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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	SYPA-009/C02US
First Named Inventor	COMISKEY et al.
Title	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USI
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☑ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☑ **Specification** [*Total Pages* 148] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☑ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 6]
6. **Inventor's Oath or Declaration** [*Total Pages* 8] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☑ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
7. ☑ **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. ☑ Computer Readable Form (CRF)
   b. ☑ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☑ Paper
   c. ☑ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

ACCOMPANYING APPLICATION PAPERS

10. ☐ **Assignment Papers** (cover sheet & document(s)) Name of Assignee _____
11. ☐ **37 CFR 3.73(c) Statement** (*when there is an assignee*) ☐ **Power of Attorney**
12. ☐ **English Translation Document** (*if applicable*)
13. ☑ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☐ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. ☐ **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. ☐ **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☑ **Other:** Certification and Request for Prioritized Examination Under 37 CFR 1.102(e) [Form PTO/AIA/424]

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 58249 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Anne E. Fleckenstein/	Date	September 4, 2015
Name (Print/Type)	Anne E. Fleckenstein	Registration No. (Attorney/Agent)	62,951

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephen		COMISKEY	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Doylestown	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	105 Steeplechase Drive		
Address 2			
City	Doylestown	State/Province	PA
Postal Code	18902	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Rong		FENG	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Langhorne	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	74 Pine Glen Road		
Address 2			
City	Langhorne	State/Province	PA
Postal Code	19047	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	John		FOSS	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

City	Doylestown	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	525 Linden Avenue		
Address 2			
City	Doylestown	State/Province	PA
Postal Code	18901-4435	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kunwar		SHAILUBHAI	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Audubon	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	2707 Bald Eagle Circle		
Address 2			
City	Audubon	State/Province	PA
Postal Code	19403	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	58249		
Email Address	zpatdcdocketing@cooley.com	Add Email	Remove Email

Application Information:

Title of the Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE		
Attorney Docket Number	SYPA-009/C02US	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

Filing By Reference :

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	58249		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14661299	2015-03-18
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14661299	Continuation of	13421769	2012-03-15
Prior Application Status	Expired		Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13421769	Continuation in part of	PCTUS2011051805	2011-09-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61383156	2010-09-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61387636	2010-09-29
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCTUS2011051805	Claims benefit of provisional	61392186	2010-10-12
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

○ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
◉ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Synergy Pharmaceuticals Inc.		
Mailing Address Information:			
Address 1	420 Lexington Avenue		
Address 2	Suite 2012		
City	New York	**State/Province**	NY
Country [i]	US	Postal Code	10170
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SYPA-009/C02US
	Application Number	
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Anne E. Fleckenstein/			Date (YYYY-MM-DD)	2015-09-04
First Name	Anne E.	Last Name	Fleckenstein	Registration Number	62951

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

RELATED APPLICATIONS

[01] This application is a continuation of U.S. Patent Application No. 14/661,299, filed March 18, 2015, which is a continuation of U.S. Patent Application No. 13/421,769, filed March 15, 2012, which is a continuation-in-part of PCT/US2011/051805 filed on September 15, 2011, which claims the benefit of priority to U.S. Provisional Application No. 61/383,156 filed on September 15, 2010, U.S. Provisional Application No. 61/387,636 filed on September 29, 2010, and U.S. Provisional Application No. 61/392,186 filed on October 12, 2010, the contents of which are incorporated by reference in their entireties.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

[02] The contents of the text file named "SYPA_009_C02US_Sequence_Listing.txt", which was created on September 3, 2015 and is 113 KB in size, are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[03] The present invention relates to low-dose formulations of guanylate cyclase C peptide agonists useful for the treatment and prevention of various diseases and disorders.

BACKGROUND OF THE INVENTION

[04] Guanylate cyclase C is a transmembrane form of guanylate cyclase that is expressed on various cells, including gastrointestinal epithelial cells (reviewed in Vaandrager 2002 *Mol. Cell. Biochem.* 230:73-83). It was originally discovered as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria and which cause diarrhea. The ST peptides share a similar primary amino acid structure with two peptides isolated from intestinal mucosa and urine, guanylin and uroguanylin (Currie, *et al.*, *Proc. Nat'l Acad. Sci. USA 89*:947-951 (1992); Hamra, *et al.*, *Proc. Nat'l Acad. Sci. USA 90*:10464-10468 (1993); Forte, L., *Reg. Pept. 81*:25-39 (1999); Schulz, *et al.*, *Cell 63*:941-948 (1990); Guba, *et al.*, *Gastroenterology 111*:1558-1568 (1996); Joo, *et al.*, *Am. J. Physiol. 274*:G633-G644 (1998)).

[05] In the intestines, guanylin and uroguanylin act as regulators of fluid and electrolyte balance. In response to high oral salt intake, these peptides are released into the intestinal lumen where they bind to guanylate cyclase C localized on the luminal membrane of enterocytes (simple columnar epithelial cells of the small intestines and colon). The binding of the guanylin peptides to guanylate cyclase C induces electrolyte and water excretion into the intestinal lumen via a complex intracellular signaling cascade that is initiated by an increase in cyclic guanosine monophosphate (cGMP).

[06] The cGMP-mediated signaling that is initiated by the guanylin peptides is critical for the normal functioning of the gut. Any abnormality in this process could lead to gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel diseases. Inflammatory bowel disease is a general name given to a group of disorders that cause the intestines to become inflamed, characterized by red and swollen tissue. Examples include ulcerative colitis and Crohn's disease. Crohn's disease is a serious inflammatory disease that predominantly affects the ileum and colon, but can also occur in other sections of the gastrointestinal tract. Ulcerative colitis is exclusively an inflammatory disease of the colon, the large intestine. Unlike Crohn's disease, in which all layers of the intestine are involved, and in which there can be normal healthy bowel in between patches of diseased bowel, ulcerative colitis affects only the innermost lining (mucosa) of the colon in a continuous manner. Depending on which portion of the gastrointestinal tract is involved, Crohn's disease may be referred to as ileitis, regional enteritis, colitis, etc. Crohn's disease and ulcerative colitis differ from spastic colon or irritable bowel syndrome, which are motility disorders of the gastrointestinal tract. Gastrointestinal inflammation can be a chronic condition. It is estimated that as many as 1,000,000 Americans are afflicted with inflammatory bowel disease, with male and female patients appearing to be equally affected. Most cases are diagnosed before age 30, but the disease can occur in the sixth, seventh, and later decades of life.

[07] IBS and chronic idiopathic constipation are pathological conditions that can cause a great deal of intestinal discomfort and distress but unlike the inflammatory bowel diseases, IBS does not cause the serious inflammation or changes in bowel tissue and it is not thought to increase the risk of colorectal cancer. In the past, inflammatory bowel disease, celiac disease and IBS were regarded as completely separate disorders. Now, with the description of inflammation, albeit low-grade, in IBS, and of symptom overlap between IBS and celiac

disease, this contention has come under question. Acute bacterial gastroenteritis is the strongest risk factor identified to date for the subsequent development of postinfective irritable bowel syndrome. Clinical risk factors include prolonged acute illness and the absence of vomiting. A genetically determined susceptibility to inflammatory stimuli may also be a risk factor for irritable bowel syndrome. The underlying pathophysiology indicates increased intestinal permeability and low-grade inflammation, as well as altered motility and visceral sensitivity. Serotonin (5-hydroxytryptamine [5-HT]) is a key modulator of gut function and is known to play a major role in pathophysiology of IBS. The activity of 5-HT is regulated by cGMP.

[08] While the precise causes of IBS and inflammatory bowel diseases (IBD) are not known, a disruption in the process of continual renewal of the gastrointestinal mucosa may contribute to disease pathology in IBD and aggravate IBS. The renewal process of the gastrointestinal lining is an efficient and dynamic process involving the continual proliferation and replenishment of unwanted damaged cells. Proliferation rates of cells lining the gastrointestinal mucosa are very high, second only to the hematopoietic system. Gastrointestinal homeostasis depends on both the proliferation and programmed cellular death (apoptosis) of epithelial cells lining the gut mucosa. Cells are continually lost from the villus into the lumen of the gut and are replenished at a substantially equal rate by the proliferation of cells in the crypts, followed by their upward movement to the villus. The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a variety of circumstances, *e.g.*, in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone. The proliferation index is much higher in pathological states such as ulcerative colitis and other gastrointestinal disorders. Intestinal hyperplasia is a major promoter of gastrointestinal inflammation. Apoptosis and cell proliferation together regulate cell number and determine the proliferation index. Reduced rates of apoptosis are often associated with abnormal growth, inflammation, and neoplastic transformation. Thus, both increased proliferation and/or reduced cell death may increase the proliferation index of intestinal tissue, which may in turn lead to gastrointestinal inflammatory diseases.

[09] In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of gastrointestinal mucosa by maintaining the balance between proliferation and apoptosis. For example, uroguanylin and guanylin peptides appear to promote apoptosis by controlling cellular ion flux. Given the prevalence of inflammatory conditions in Western societies a need exists to improve the treatment options for inflammatory conditions, particularly of the gastrointestinal tract.

[10] Peptide agonists of guanylate cyclase C agonists ("GCC agonists") are described in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329. However, the formulation of peptides for pharmaceutical delivery presents a number of special problems. For example, peptides are subject to structural modifications by a variety of degradation mechanisms resulting in problems of chemical and physical instability of the formulation.

SUMMARY OF THE INVENTION

[11] The present invention provides low-dose formulations of peptide agonists of guanylate cyclase C ("GCC") and methods for their use in the treatment and prevention of human diseases and disorders, such as a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, inflammatory bowel disease, colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia. In certain embodiments, the formulations are stabilized against chemical degradation of the peptide. The low-dose formulations of the invention have unexpected efficacy in humans in a dosage range that was not predicted based on studies in primates. The formulations of the invention are particularly useful for the treatment or prevention of chronic idiopathic constipation. In certain embodiments, the GCC agonists are analogs of uroguanylin and bacterial ST peptides. In preferred embodiments, the analogs have superior properties compared to the naturally occurring or "wild-type" peptides. Examples of such superior properties include a high resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other

proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices. Examples of GCC agonists that can be used in the formulations and methods of the invention are described in more detail below and in U.S. Patent Nos. 7,041,786, 7,799,897, and U.S. Patent Application Publication Nos. US2009/0048175, US 2010/0069306, US 2010/0120694, US 2010/0093635, and US 2010/0221329, each of which is incorporated herein by reference in its entirety.

[12] The invention provides an oral dosage formulation comprising one or more pharmaceutically acceptable excipients and at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. In one embodiment, the GCC agonist peptide has a chromatographic purity of no less than 90%, no less than 90.5%, no less than 91%, no less than 92%, no less than 93%, no less than 94%, no less than 95%, no less than 96%, no less than 97%, no less than 98%, or no less than 99%. The chromatographic purity of the GCC agonist peptide is determined as area percent by HPLC. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 8 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg or 9.5 mg.

[13] In one embodiment, the GCC agonist peptide has a total impurity content of no greater than 10%, no greater than 9.5%, no greater than 9%, no greater than 8%, no greater than 7%, no greater than 6%, no greater than 5%, no greater than 4%, no greater than 3%, no greater than 2%, or no greater than 1%. The total impurity content is determined as total area percentages of impurities by HPLC. The impurities do not include any pharmaceutically acceptable excipient used for the formulation. In one embodiment, the formulation is substantially free of inorganic acids and carboxylic acids, e.g., HCl, phosphoric acid, or acetic acid. In this context, carboxylic acids do not include amino acids or peptides. In this context "substantially" free of acids means that the acid content of the formulation at the time of packaging is preferably less than 0.2%, less than 0.1%, less than 0.05%, less than 0.01%, less than 0.005%, or less than 0.001% of the total weight of the formulation. In one embodiment, the formulation is free of HCl.

[14] In one embodiment, the formulation is a solid formulation. In one embodiment, the formulation is in the form of a powder, granule, sachet, troche, tablet, or capsule. In another embodiment, the formulation is a liquid formulation and the GCC agonist peptide is in solution or suspension in a lipophilic liquid. In one embodiment, the liquid is a refined specialty oil or a medium chain triglyceride or related ester. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil, sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, soybean oil, Cremaphor, PG, and PG 400. In one embodiment, the unit dose is a powder, tablet, or capsule. In one embodiment, the unit dose is a liquid-filled capsule. In one embodiment, the capsule or tablet is in a blister pack or strip. Preferably, the blister pack or strip is made of a material that is impermeable to water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment the blister pack is a FOIL/FOIL blister pack. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In a preferred embodiment the desiccant is a molecular sieve. In one embodiment, the unit dose is in a high density polyethylene bottle having a seal. In one embodiment, the bottle further comprises a desiccant. In one embodiment, the bottle further comprises an oxygen scavenger or molecular sieve. In one embodiment, the bottle is nearly impermeable to oxygen and water vapor (e.g., much more impermeable than a HDPE bottle), such as an OxyGuard bottle.

[15] In one embodiment, the one or more pharmaceutically acceptable excipients include an inert carrier. In one embodiment, the inert carrier is a selected from mannitol, lactose, a microcrystalline cellulose, or starch. In one embodiment, the inert carrier has a particle size of from 50 to 900 microns, from 50 to 800 microns, from 50 to 300 microns, from 50 to 200 microns, from 75 to 150 microns, from 75 to 200 microns, or from 75 to 300 microns.

[16] In one embodiment, the GCC agonist peptide is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[17] In one embodiment, the one or more pharmaceutically acceptable excipients include a divalent cation salt such as calcium chloride. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid, such as leucine, histidine, or arginine, or an amine such TRIS or TRIS/HCl.

[18] In one embodiment, the oral dosage formulation consists of the GCC agonist peptide described herein, an inert carrier (e.g., Celphere SCP-100, Avicel PH 102, or Avicel PH 112), and a lubricant (e.g., magnesium stearate). In one embodiment, the formulation consists of the GCC agonist peptide, an inert carrier (e.g., Avicel PH 200), a divalent cation salt (e.g., calcium chloride or calcium ascorbate), an amino acid (e.g., leucine, histidine, or arginine) or a protective amine (e.g., TRIS), a coating agent (e.g., Methocel ES Premium LV) and optionally a lubricant (e.g., magnesium stearate) or another additive (e.g., trehalose). In one embodiment, the formulation consists of the GCC agonist peptide, a binder (e.g., Provsolv SMCC 90 LM), and a disintegrant (e.g., Explotab). In one embodiment, the formulation consists of the GCC agonist peptide, a diluent (e.g., Mannogem EZ), a binder (e.g., Provsolv SMCC 90 LM), a disintegrant (e.g., Explotab), a lubricant (e.g., Pruv).

[19] The invention also provides a process for making the oral dosage formulations described herein, wherein the process comprises a step of dry granulation, wet granulation, or spray coating followed by drying. In another embodiment, the process comprises a step of dry mixing. In a preferred embodiment the step of dry mixing includes geometric blending. In one embodiment, the process comprises a step of direct compression. In one embodiment, the process for making the oral dosage formulations described herein is a spray coating-drying process which includes (a) providing an aqueous solution comprising: a GCC agonist peptide selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and one or more pharmaceutically acceptable excipients, wherein the concentration of the GCC agonist peptide ranges from 10 to 60 mg/mL; and (b) applying the aqueous solution to a pharmaceutically acceptable carrier to generate a GCC agonist peptide-coated carrier.

[20] In one embodiment of the spray coating-drying process above, the one or more pharmaceutically acceptable excipients comprise a divalent cation salt wherein the divalent cation is selected from Ca^{2+}, Mg^{2+}, Zn^{2+}, and Mn^{2+}. In one embodiment, the one or more pharmaceutically acceptable excipients comprise an amino acid selected from leucine, isoleucine, and valine. In one embodiment, the one or more pharmaceutically acceptable

excipients comprise a coating agent (such as hypromellose Methocel E5 PremLV). In one embodiment, the aqueous solution has a pH greater than 4 (e.g., 4.5-5.5, 5-6, about 5, or greater than 5) or even greater than 7. In one embodiment, the aqueous solution is substantially free of inorganic acids and carboxylic acids. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, and 56. In one embodiment, the process further includes drying the GCC agonist peptide-coated carrier.

[21] The invention further provides an oral dosage formulation made by the process described herein. Preferably, the GCC agonist peptide as made is stabilized against chemical or physical degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

[22] The invention also provides a method for treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an oral dosage formulation comprising at least one GCC agonist peptide, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249. Preferably, the subject is a human subject. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56. In one embodiment, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1 and 9. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[23] In one embodiment, the disease or disorder is a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection. In a preferred embodiment, the gastrointestinal disease or disorder is chronic idiopathic constipation.

[24] In one embodiment, the method further comprises administering to the subject an effective amount of an inhibitor of a cGMP-specific phosphodiesterase. In one embodiment, the cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone, vardenifil, and suldenifil.

[25] In one embodiment, the method further comprises administering to the subject an effective amount of at least one laxative. In one embodiment, the at least one laxative is selected from the group consisting of SENNA, MIRALAX, PEG, or calcium polycarbophil.

[26] In one embodiment, the method further comprises administering to the subject an effective amount of at least one anti-inflammatory agent.

[27] The invention also provides pharmaceutical compositions comprising the formulations described herein.

[28] Other features and advantages of the invention will be apparent from and are encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[29] Figure 1: Plecanatide (SP-304) treatment reduced time to first BM following daily dose.

[30] Figure 2: Effect of daily treatment with plecanatide on spontaneous bowel movements (SBM) in chronic constipation patients.

[31] Figure 3: Effect of daily treatment with plecanatide on complete spontaneous bowel movements (CSBM) in chronic constipation patients.

[32] Figure 4: Effect of daily treatment with plecanatide on Bristol Stool Form Scores (BSFS) in chronic constipation patients.

[33] Figure 5: Effect of daily treatment with plecanatide on straining scores in chronic constipation patients

[34] Figure 6: Percentage of subjects reporting improvements in abdominal discomfort scores after 14-days of daily treatment with plecanatide.

DETAILED DESCRIPTION

[35] The invention provides pharmaceutical formulations of peptide GCC agonists. It is intended that the formulations of the invention are "pharmaceutical" formulations, meaning

that they are suitable for pharmaceutical use. Accordingly, the term "formulations" as used herein is meant to encompass pharmaceutical formulations even if "pharmaceutical" is not expressly stated. Pharmaceutical compositions comprising the formulations described herein are also provided by the invention. The formulations of the invention preferably provide stability against chemical and physical degradation of the peptide, e.g., plecanatide (i.e., SEQ ID #1).

[36] The invention is based in part upon the discovery that mannitol mixes very effectively with the GCC agonist peptides described herein and provides stability against degradation, allowing the peptides to be formulated at very low doses. The invention is also based in part on the discovery that very low doses of the GCC agonist peptides described herein are effective for the treatment of diseases and disorders in humans. The dosage range found to be effective was not predicted based on animal studies. The invention is also based in part upon the discovery that a divalent cation (e.g., Ca^{2+}) and/or an amino acid (e.g., leucine or arginine) stabilize the GCC agonist peptides described herein during a process (e.g., spray coating-drying process) of manufacturing a formulation of the GCC agonist peptides and provides stability against degradation both during the manufacturing process and storage of the formulation.

[37] Plecanatide is a charged peptide due to the presence of four carboxylic acids and single amine group with a calculated pKa of approximately 3.5. Therefore plecanatide is likely to interact with ions in solution or in the solid state. Plecanatide is a hygroscopic peptide requiring the control of water during manufacture and storage to promote long term stability. Plecanatide is prone to degradation by oxidation in the presence of residual peroxides or formaldehyde contaminants that are formed from peroxide reaction with polymeric excipients. The present invention discloses a manufacturing process and dry solid formulation compositions that minimizes water content. The formulations are comprised of components to minimize levels of residual formaldehyde and peroxides commonly found in many pharmaceutical excipients. The invention also discloses additives (i.e. $CaCl_2$) that may function as local desiccants in the formulation. Divalent cation salts such as calcium ascorbate, $MgCl_2$, $ZnCl_2$, $MnCl_2$ and $CaCl_2$ bind plecanatide and sterically hinder reactive species such as water or oxygen from causing plecanatide degradation by molecular displacement. The invention further includes scavengers of residual formaldehyde (amines such as TRIS or TRIS/HCl or amino acids such as leucine, isoleucine and valine), and

discloses packaging confirmations to minimize oxygen exposure and water vapor during storage. The invention also discloses a stable manufacturing process comprised of initially dissolving plecanatide in cold water to minimize solution degradation, followed by spray coating the peptide solution on particles and drying to remove moisture.

[38] The formulations of the invention are particularly useful for the treatment or prevention of a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, chronic idiopathic constipation, gastroparesis, heartburn, gastric cancer, and H. pylori infection.

[39] In one embodiment, the formulations of the invention are used in a method for the treatment of constipation. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining. Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics. In a preferred embodiment, the constipation is chronic idiopathic constipation.

[40] The stabilized formulations of the invention comprise at least one GCC agonist peptide formulated with one or more excipients such that the peptide is stabilized against chemical degradation. Chemical degradation of peptides results from a number of mechanisms including oxidation, water-mediated degradation, and reaction with aldehydes or reducing sugars. The ideal excipient or combination of excipients will be non-hygroscopic, have few or no reducing sugars, and be substantially free of contaminants such as iron, peroxide, and formaldehyde. The formulations of the invention are preferably substantially free of water. In this context "substantially" free of water means that the water content of the

formulation at the time of packaging is preferably less than 7%, less than 5%, less than 1%, or less than 0.5% of the total weight of the formulation. In one embodiment the amount of water is between 0.1 to 5% of the total weight of the formulation. In one embodiment, the amount of water in the formulation of the invention manuafactured through a spray-coating process is less than 0.5% (e.g., about 0.47%).

[41] In the context of the present formulations, the term "stable" or "stabilized" refers to the resistance of the peptide to chemical or physical degradation over time. Preferably, a stable formulation of the invention retains an amount of the peptide in the formulation over a period of time that is at least 90%, preferably at least 95%, and most preferably at least 99% the amount of peptide initially present in the formulation. In one embodiment, a stable formulation of the invention, over a period of time (e.g., 18 month), has an increase in the total impurity content not greater than 8%, not greater than 7%, not greater than 6%, not greater than 5%, not greater than 4%, not greater than 3%, not greater than 2%, or not greater than 1%. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 18 months, at least 20 months, or at least 24 months when stored at 2-8 degrees Celsius (2-8C). In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 12 months, 18 months and preferably 24 months when stored at 25 degrees Celsius (25C) and 60 % relative humidity. In one embodiment, the peptide is chemically stable in the formulation for a period of time that is at least 3 months, 18 months and preferably 24 months when stored at 30 degrees Celsius (30C).

[42] The low-dose formulations of the invention comprise an amount of at least one GCC agonist peptide per unit dose that is less than 10 mg. It is especially advantageous to formulate oral compositions in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage form" as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active

compound and the particular therapeutic effect to be achieved. In one embodiment, the unit dosage form is a tablet or a capsule.

[43] In one embodiment of the low-dose formulations of the invention, the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg. In one embodiment, the amount of GCC agonist peptide per unit dose is 0.1 mg, 0.3 mg, 0.6 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg, 9.5 mg, or 10 mg.

[44] In one embodiment, the low-dose formulation contains a carrier that is non-hygroscopic. In one embodiment, the carrier is selected from mannitol and maltose (e.g., ADVANTOSE 100).

[45] In one embodiment, the carrier is cellulose, preferably microcrystalline cellulose (e.g., Avicel PH 102, low moisture Avicel PH 112, Avicel PH 200, or Celphere SCP-100). In one embodiment, the carrier is calcium phosphate or calcium sulphate. In another embodiment, the carrier is a saccharide. The term "saccharide" as used herein also refers to polysaccharides. Thus, the term saccharide is meant to include polysaccharides. In one embodiment, the saccharide is selected from mannitol, trehalose, lactose, sucrose, sorbitol, and maltose. In a preferred embodiment, the saccharide is mannitol. Preferably the saccharide has a low water content, a small particle size and a narrow particle-size distribution.

[46] Carriers having small particle sizes, and/or spherical shape, and narrow size distribution are preferred. Particles of less than 20 microns have a relatively high surface area to volume ratio causing inter-particle attractive forces to dominate and resist bulk flow. Larger particles (greater than 100 microns) tend to roll or slide over one another and exhibit superior bulk flow properties compared with small particles. A narrow particle-size distribution reduces particle packing and increases flow. In one embodiment, the particles are between 20 and 500 microns in size (as measured across the largest diameter of the particle, on average). In one embodiment, a small particle size and a narrow particle size range refers to particles having a size range of from 20-300 microns, 50-200 microns, or 75-150 microns. In certain embodiments, the carrier has a substantially spherical shape such as can be obtained with a spray drying process.

[47] In one embodiment, the low-dose formulation is a solid formulation and the unit dose is in the form of a tablet or capsule. In one embodiment, the low-dose formulation is a liquid formulation and the unit dosage form is a liquid-filled capsule. In one embodiment, the liquid formulation in the form of a solution or suspension of the GCC agonist peptide in an lipophilic liquid. Examples of suitable liquids include medium chain triglycerides (e.g., LABRAFAC Lipophile), propylene glycol dicaprylocaprate (e.g., LABRAFAC PG), vitamin E (e.g., α tocopherol), PEG 400 (e.g., Polyethylene glycol low M.W. (liquid)), propylene glycol, soybean oil, and Castor oil. In one embodiment, the liquid is selected from the group consisting of medium chain triglycerides, propylene glycol dicaprylocaprate, vitamin E, and soybean oil. In one embodiment, the refined specialty oil is selected from Arachis oil, Castor oil, cottonseed oil, maize (corn) oil, olive oil, sesame oil, soybean oil, and sunflower oil. In one embodiment, the medium chain triglyceride or related ester is AKOMED E, AKOMED R, CAPTEX 355, LABRAFAC CC, LABRAFAC PG, LAUROGLYCOL FCC, MIGLYOL 810, MIGLYOL 812, MIGLYOL 829, MIGLYOL 840, and SOFTISAN 645.

[48] A formulation according to the invention may be contained in a blister pack. In a particular embodiment, the powder, tablet, or capsule comprising the formulation is contained in a blister pack. Preferably, the blister pack is made of a material that allows only minimal permeation by water vapor and oxygen. In one embodiment the blister pack is comprised of a metal foil. In one embodiment, the blister pack is comprised of ACLAR. In one embodiment, the container of the blister pack is flushed with an inert gas such as nitrogen or argon. In one embodiment, the container further includes a desiccant. In one embodiment, the desiccant is calcium chloride. In one embodiment the desiccant is a molecular sieve.

[49] While any GCC agonist known in the art can be formulated according to the present invention, analogs of uroguanylin and bacterial ST peptides are preferred. In certain embodiments, the uroguanylin and bacterial ST peptide analogs have superior properties compared to naturally occurring, or "wild-type" peptides. For example, the uroguanylin and bacterial ST peptides for use in the present invention are preferably modified to increase their resistance to degradation at the N-terminus and C-terminus from carboxypeptidases, aminopeptidases, and/or by other proteolytic enzymes present in the stimulated human intestinal juices and human gastric juices. In certain embodiments, the GCC agonist formulation comprises a peptide consisting essentially of an amino acid sequence selected from SEQ ID NOs: 1-249. In a preferred embodiment, the peptide consists essentially of an

amino acid sequence selected from SEQ ID NOs: 1, 8, 9, 55 and 56. The term "consists essentially of" refers to a peptide that is identical to the reference peptide in its amino acid sequence or to a peptide that does not differ substantially in terms of either structure or function from the reference peptide. A peptide differs substantially from the reference peptide if its primary amino acid sequence varies by more than three amino acids from the reference peptide or if its activation of cellular cGMP production is reduced by more than 50% compared to the reference peptide. Preferably, substantially similar peptides differ by no more than two amino acids and not by more than about 25% with respect to activating cGMP production. In preferred embodiments, the GCC agonist is a peptide comprising at least 12 amino acid residues, and most preferably comprising between 12 and 26 amino acids. Non-limiting examples of such analogs of uroguanylin and bacterial ST peptides are described in Section 1.2 below.

[50] The invention provides methods for treating or preventing certain diseases and disorders and methods for increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[51] In accordance with the methods of the present invention, the GCC agonist formulation can be administered alone or in combination with one or more additional therapeutic agents to prevent or treat inflammation, cancer and other disorders, particularly of the

gastrointestinal tract. In a preferred embodiment, the GCC agonist formulation is administered for the treatment of chronic constipation. In one embodiment, the GCC agonist formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA, METAMUCIL, MIRALAX, PEG, or calcium polycarbophil), a stool softener, an anti-tumor necrosis factor alpha therapy for IBD (such as REMICADE, ENBREL, or HUMAIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters.

1.1 Formulations

[52] The formulations of the invention contain one or more GCC agonist peptides described herein, in combination with one or more pharmaceutically acceptable carriers (also referred to as diluents) and/or excipients. In a preferred embodiment, the formulations of the invention include an inert carrier. The inert carrier is preferably non-hygroscopic. In one embodiment, the carrier in the formulation contains few or no reducing sugars and is substantially free of contaminants including, but not limited to, iron, peroxide, and formaldehyde. In one embodiment, the carrier is selected from the group consisting of sorbitol, mannitol, EMDEX, and starch. In one embodiment, the carrier is mannitol (e.g., MANNOGEM) or microcrystalline cellulose (e.g. PROSOLV, CELPHERE, CELPHERE beads).

[53] The low-dose formulations of the invention contain no greater than 10 mg per unit dose of a GCC agonist peptide. The remainder of the formulation is comprised of the carrier and one or more optional excipients. In one embodiment, the amount of carrier is at least 90% of the total weight of the formulation. In another embodiment, the amount of carrier is at least 95% or at least 98% of the total weight of the formulation. In one embodiment, the amount of carrier is between 90 and 99.9% of the total weight of the formulation. In one

embodiment, the one or more optional excipients comprise a disintegrant which is present at 1 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise a lubricant which is present at 0.02 to 5% of the total weight of the formulation. In one embodiment, the one or more optional excipients comprise an amino acid such as arginine, leucine, isoleucine, valine, histidine, phenylalanine, alanine, glutamic acid, aspartic acid, glutamine, methionine, asparagine, tyrosine, threonine, tryptophan, or glycine, which is present at 0.1 to 4% (e.g., 0.1-1%) of the total weight of the formulation. In one embodiment, the molar ratio between the amino acid and the GCC agonist peptide is from about 2:1 to about 30:1 or about 2:1 to about 20:1 (e.g., 5:1). In one embodiment, the one or more optional excipients comprise a stabilizer such as a divalent cation salt, more specifically, a water-soluble divalent cation salt (e.g., calcium chloride, magnesium chloride, zinc chloride, manganese chloride, or calcium ascorbate), which is present at 0.1 to 12% (e.g., 0.1-4%) of the total weight of the formulation. In one embodiment, the molar ratio between the salt and the GCC agonist peptide is from about 5:1 to about 20:1 (e.g., 10:1).

[54] The formulations may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffnose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and polypeptides and proteins, for example albumen.

[55] Further examples of pharmaceutically acceptable carriers and excipients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, antioxidant, and coating agents such as: BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (e.g., povidone, crospovidone, copovidone, etc), methyl cellulose, Methocel, pre-gelatinized starch (e.g., STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (FMC Corporation, Marcus Hook, PA, USA), Emdex, Plasdone, or mixtures thereof, FILLERS: talc, calcium carbonate (e.g., granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized

starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose,or mixtures thereof, DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate (such as Explotab), potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, ploy plasdone, or mixtures thereof, LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, compritol, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate (such as Pruv), vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Piano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof, ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof, ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, ANTOXIDANTS: ascorbic acid, BHA, BHT, EDTA, or mixture thereof, and COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum, maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

[56] The formulation can also include other excipients and categories thereof including but not limited to Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents, creams and lotions (like maltodextrin and carrageenans); materials for chewable

tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD&C Yellow No. 6 aluminum lake, FD&C Blue # 1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

[57] Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS- 1-7040), and black ink (S- 1-8 106).

[58] The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Other sustained release formulations and polymers for use in the compositions and methods of the invention are described in EP 0 467 389 A2, WO 93/24150, U.S.

5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 97/26015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of polypeptide are combined with microparticles of polymer. U.S. 6,011,0 1 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled releaseof the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224 materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4,910,021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175,003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane- coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher.

[59] The GCC peptides described herein may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents described herein may be formulated according to the methodology described in any of WO03105812 (extruded hyrdratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769

(amidated polypeptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO041 1271 1 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952,314 (biopolymer); US5,108,758 (glassy amylose matrix delivery); US 5,840,860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US 5,866,619 and US 6,368,629 (saccharide containing polymer); US 6,531,152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (e.g. hydrophobic polymer-Eudragrit)); US 6,234,464; US 6,403,130 (coating with polymer containing casein and high methoxy pectin; WO0174 175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO040 19872 (transferring fusion proteins).

[60] The GCC peptides described herein may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. The capsule shell can be a HPMC capsule shell or Gelatin capsule shell. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents described herein.

[61] The GCC peptides described herein can also be formulated using the multi matrix system technology (MMX).

[62] The GCC peptides described herein can be formulated in an osmotic device including the ones disclosed in US 4,503,030, US 5,609,590 and US 5,358,502. US 4,503,030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self- destructs and releases

all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U.S. Patent Nos. 5,609,590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (e.g., joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

[63] In one embodiment the formulation contains a GCC agonist peptide, mannitol, silicified microcrystalline cellulose, sodicum starch glycolate, and sodium stearyl fumarate. The GCC agonist is at a concentration of less than 5% w/w, less than 4%, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.23% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The mannitol is at a concentration of at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w, or at least 80% w/w. In some embodiments the mannitol is present at about 79% w/w (e.g., 79.77%). The mannitol is preferably Mannogem EZ. The silicified microcrystalline cellulose is at a concentration of at least 5% w/w, at least 10% w/w, or at least 15% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 15% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 LM. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is about 4% w/w. The sodicum starch glycolate is preferably Explotab. The sodium stearyl fumarate is at a concentration of at least 0.2% w/w, at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9, or at least 1% w/w. In some embodiments the concentration of the sodium stearyl fumarate is about 1% w/w. The sodium stearyl fumarate is preferably Pruv.

[64] In one embodiment the formulation contains a GCC agonist peptide, silicified microcrystalline cellulose, and sodicum starch glycolate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w,

less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The silicified microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, or at least 95% w/w. In some embodiments the concentration of the silicified microcrystalline cellulose is about 95.7% w/w. The silicified microcrystalline cellulose is preferably Prosolv SMCC 90 HD. The sodicum starch glycolate is at a concentration of at least 1% w/w, at least 2% w/w, at least 3% w/w, or at least 4% w/w. In some embodiments the concentration of the sodicum starch glycolate is 4% w/w. The sodicum starch glycolate is preferably Explotab.

[65] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, and hyrpomellose. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.3246% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.10% w/w. The microcrystalline cellulose is preferably Celphere SCP-100. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.2622% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.12% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.2% w/w. The hypromellose is preferably Methocel E5 PremLV.

[66] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, calcium chloride dihydrate, leucine, hypromellose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.36% w/w. The GCC peptide

is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.75% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The calcium chloride dihydrate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, at least 0.25% w/w, or at least 0.3% w/w. In some embodiments the concentration of the calcium chloride dihydrate is about 0.29% w/w. The leucine is at a concentration of at least 0.05% w/w, at least 0.1% w/w, at least 0.12% w/w, or at least 0.15% w/w. In some embodiments the concentration of leucine is about 0.13% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the hypromellose is about 0.22% w/w. The hypromellose is preferably Methocel E5 PremLV. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[67] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 99.43% w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[68] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 0.32% w/w, about 1.18% w/w. The GCC peptide is preferably SEQ

NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.57 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[69] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 97.09 % w/w. The microcrystalline cellulose is preferably Avicel PH 112. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[70] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, histidine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.18% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.48% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5%

w/w. The hypromellose is preferably Methocel ES Premium LV. The histine is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, at least 3% w/w, or at least 5% w/w. In some embodiments the concentration of the histidine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.48% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[71] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, arginine, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.31% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The arginine is a

concentration of at least 0.5% w/w, at least 1% w/w, at least 1.5% w/w, or at least 2% w/w. In some embodiments the concentration of the arginine is 1-6% w/w. In a particular embodiment, the concentration of the arginine is 1.66% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.09% w/w, or at least 0.1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[72] In one embodiment the formulation contains a GCC agonist peptide, trehalose granules, hypromellose, TRIS, calcium ascorbate, trehalose powder, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.17% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The trehalose granules are at a concentration of at least 50% w/w, at least 55% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, or at least 75% w/w. In some embodiments the concentration of the trehalose granules is 55-75% w/w. In a particular embodiment, the concentration of the trehalose granules is 70.81% w/w. The hypromellose is at a concentration of at least 0.1% w/w, at least 0.2% w/w, at least 0.3% w/w, at least 0.4% w/w, or at least 0.5% w/w. In some embodiments the concentration of the hypromellose is 0.2-2% w/w. In a particular embodiment the concentration of the hypromellose about 0.5% w/w. The hypromellose is preferably Methocel ES Premium LV. The TRIS is a concentration of at least 0.6% w/w, at least 0.8% w/w, at least 0.9% w/w, or at least 1% w/w. In some embodiments the concentration of the TRIS is 0.5-6% w/w. In a particular

embodiment, the concentration of the arginine is 1.15% w/w. The calcium ascorbate is at a concentration of at least 0.05% w/w, at least 0.07% w/w, at least 0.1% w/w, or at least 1% w/w. In some embodiments the concentration of the calcium ascorbate is 0.05-10% w/w. In a particular embodiment, the concentration of the calcium ascorbate is about 0.1% w/w. The trehalose powder is at a concentration of at least 0.5% w/w, at least 0.7% w/w, at least 0.8% w/w, at least 0.9% w/w, at least 1% w/w, or at least 1.2% w/w. In some embodiments the concentration of the trehalose powder is 0.5-4% w/w. In a particular embodiment, the concentration of the trehalose powder is 1.02% w/w. The microcrystalline cellulose is at a concentration of at least 10% w/w, at least 20% w/w, or at least 25% w/w. In some embodiments the concentration of the microcrystalline cellulose is 20-40% w/w. In a particular embodiment, the concentration of the microcrystalline cellulose is 25% w/w. The microcrystalline cellulose is preferably Avicel PH 200. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is 0.2-1% w/w. In a particular embodiment the concentration of the magnesium stearate is about 0.25% w/w.

[73] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 1.10% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO: 9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 98.64 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

[74] In one embodiment the formulation contains a GCC agonist peptide, microcrystalline cellulose, and magnesium stearate. The GCC agonist is at a concentration of less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, less than 1% w/w, less than 0.5% w/w, or less than 0.25% w/w. In some embodiments the GCC peptide is at a concentration of about 3.32% w/w. The GCC peptide is preferably SEQ NO: 1 or SEQ NO:

9. The microcrystalline cellulose is at a concentration of at least 30% w/w, at least 40% w/w, at least 50% w/w, at least 60% w/w, at least 70% w/w, at least 80% w/w, at least 90% w/w, at least 95% w/w, or at least 99% w/w. In some embodiments the concentration of the microcrystalline cellulose is about 96.43 % w/w. The microcrystalline cellulose is preferably Avicel PH 102. The magnesium stearate is at a concentration of at least 0.1% w/w, at least 0.15% w/w, at least 0.2% w/w, or at least 0.25% w/w. In some embodiments the concentration of the magnesium stearate is about 0.25% w/w.

1.2 **GCC** Agonists

[75] The GCC agonists for use in the formulations and methods of the invention bind to guanylate cyclase C and stimulate intracellular production of cGMP. Optionally, the GCC agonists induce apoptosis and inhibit proliferation of epithelial cells. The term, "guanylate cyclase C" refers to a transmembrane form of guanylate cyclase that acts as the intestinal receptor for the heat-stable toxin (ST) peptides secreted by enteric bacteria. Guanylate cyclase C is also the receptor for the naturally occurring peptides guanylin and uroguanylin. The possibility that there may be different receptors for each of these peptides has not been excluded. Hence, the term "guanylate cyclase C" may also encompass a class of transmembrane guanylate cyclase receptors expressed on epithelial cells lining the gastrointestinal mucosa.

[76] The term "GCC agonist" refers to both peptides and non-peptide compounds such as that bind to an intestinal guanylate cyclase C and stimulate the intracellular production of cGMP. Where the GCC agonist is a peptide, the term encompasses biologically active fragments of such peptides and pro-peptides that bind to guanylate cyclase C and stimulate the intracellular production of cGMP.

[77] Preferably, the GCC agonists for use in the formulations and methods of the invention stimulate intracellular cGMP production at higher levels than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists stimulate intracellular cGMP production at higher levels than the peptide designated SP-304 (SEQ ID NO:1). In specific embodiments, a GCC agonist for use in the formulations and methods of the invention stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to uroguanylin, guanylin, lymphoguanylin, linaclotide, ST

peptides, or SP-304. The terms "induce" and "stimulate"are used interchangeably throughout the specification.

[78] Preferably, the GCC agonists for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists such as uroguanylin, guanylin, and ST peptides. In some embodiments, the GCC agonists are more stable than the peptide designated SP-304. "Stability" in this context refers to resistance to degradation in gastrointestinal fluid and/or intestinal fluid (or simulated gastrointestinal or intestinal fluids) compared to the reference peptide. For example, the GCC agonists for use in the formulations and methods of the invention preferably degrade 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC angonists and/or SP-304.

[79] The GCC agonists for use in the formulations and methods of the invention are preferably peptides. In some embodiments, the GCC agonist peptide is less than 30 amino acids in length. In particular embodiments, the GCC agonist peptide is less than or equal to 30, 25, 20, 15, 14, 13, 12, 11, 10, or 5 amino acids in length. Examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in U.S. Serial Nos.: 12/133,344, filed June 4, 2008, 12/478505, filed June 4, 2009; 12/478511, filed June 4, 2009; 12/504288, filed July 16, 2009; and U.S. Provisional Application Serial Nos.: 60/933194, filed June 4, 2007; 61/058,888, filed June 4, 2008; 61/058,892, filed June 4, 2008; and 61/081,289, filed July 16, 2008, each of which is incorporated by reference herein in its entirety.

[80] Specific examples of GCC agonist peptides for use in the formulations and methods of the invention include those described in Tables I-VII below. As used Tables I-VII, the terms "PEG3" or "3PEG" refer to a polyethylene glycol such as aminoethyloxy-ethyloxy-acetic acid (AeeA), and polymers thereof. The term "X_{aa}" refers to any natural or unnatural amino acid or amino acid analogue. The term "M_{aa}" refers to a cysteine (Cys), penicillamine (Pen) homocysteine, or 3-mercaptoproline. The term "Xaa_{n1}" is meant to denote an amino acid sequence of any natural or unnatural amino acid or amino acid analogue that is one, two or three residues in length; Xaa_{n2} is meant to denote an amino acid sequence that is zero or one residue in length; and Xaa_{n3} is meant to denote an amino acid sequence zero, one, two, three, four , five or six residues in length. Additionally, any amino acid represented by Xaa,

Xaa_{n1}, $Xaa_{n2,\ or}$ Xaa_{n3} may be an L-amino acid, a D-amino acid, a methylated amino acid or any combination of thereof. Optionally, any GCC agonist peptide represented by Formulas I to XX in the tables may contain on or more polyethylene glycol residues at the the N-terminus, C-terminus or both.

[81] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide selected from SEQ ID NOs: 1-249, the sequences of which are set forth below in Tables I to VII below. In one embodiment, a GCC agonist formulation comprises the peptide designated by SEQ ID NOs:1, 8, 9, 55, or 56.

[82] In certain embodiments, a GCC agonist formulation of the invention comprises a peptide that is substantially equivalent to a peptide selected from SEQ ID NOs: 1-249. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to an intestinal guanylate cyclase receptor and stimulate fluid and electrolyte transport.

1.2.1 GCC Agonist Peptides

[83] In a preferred embodiment, the GCC agonists for use in the formulations and methods of the invention are GCC agonist peptides. In certain embodiments, the GCC agonist peptides are analogues of uroguanylin or a bacterial ST peptide. Uroguanylin is a circulating peptide hormone with natriuretic activity. An ST peptide is a member of a family of heat stable enterotoxins (ST peptides) secreted by pathogenic strains of *E. coli* and other enteric bacteria that activate guanylate cyclase receptor and cause secretory diarrhea. Unlike bacterial ST peptides, the binding of uroguanylin to guanylate cyclase receptor is dependent on the physiological pH of the gut. Therefore, uroguanylin is expected to regulate fluid and electrolyte transport in a pH dependent manner and without causing severe diarrhea.

[84] The GCC agonist peptides for use in the formulations and methods of the invention can be polymers of L-amino acids, D-amino acids, or a combination of both. For example, in various embodiments, the peptides are D retro-inverso peptides. The term "retro-inverso isomer" refers to an isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino acid residue is inverted. *See, e.g.*, Jameson *et al.*, *Nature*, 368, 744-746 (1994); Brady *et al.*, Nature, 368, 692-693 (1994). The net result of

combining D-enantiomers and reverse synthesis is that the positions of carbonyl and amino groups in each amide bond are exchanged, while the position of the side-chain groups at each alpha carbon is preserved. Unless specifically stated otherwise, it is presumed that any given L-amino acid sequence of the invention may be made into a D retro-inverso peptide by synthesizing a reverse of the sequence for the corresponding native L-amino acid sequence.

[85] The GCC agonist peptides for use in the formulations and methods of the invention are able to induce intracellular cGMP production in cells and tissues expressing guanylate cyclase C. In certain embodiments, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared to naturally occurring GCC agonists such as uroguanylin, guanylin, or ST peptides. Optionally, the GCC agonist peptide stimulates 5%, 10%, 20%, 30%, 40%, 50% , 75%, 90% or more intracellular cGMP compared SP-304 (SEQ ID NO:1). In further embodiments, the GCC agonist peptide stimulates apoptosis, *e.g.*, programmed cell death, or activate the cystic fibrosis transmembrane conductance regulator (CFTR).

[86] In some embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). For example, the GCC agonist peptide degrades 2%, 3%, 5%, 10%, 15%, 20%, 30%, 40%, 50% , 75%, 90% or less compared to naturally occurring GCC agonists and/or SP-304, SP-339 (linaclotide) or SP-340. In certain embodiments, the GCC agonist peptides for use in the formulations and methods of the invention are more stable to proteolytic digestion than naturally occurring GCC agonists and/or SP-304 (SEQ ID NO:1), SP-339 (linaclotide) (SEQ ID NO: 55) or SP-340 (SEQ ID NO: 56). In one embodiment, a GCC agonist peptide is pegylated in order to render the peptides more resistant towards protealysis by enzymes of the gastrointestinal tract. In a preferred embodiment, the GCC agonist peptide is pegylated with the aminoethyloxy-ethyloxy-acetic acid (Aeea) group at its C-terminal end, at its N-terminal end, or at both termini.

[87] Specific examples of GCC agonist peptides that can be used in the methods and formulations of the invention include a peptide selected from the group designated by SEQ ID NOs: 1-249.

[88] In one embodiment, the GCC agonist peptide is a peptide having the amino acid sequence of any one of Formulas X- XVII (*e.g.* SEQ ID NO:87-98).

[89] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula I, wherein at least one amino acid of Formula I is a D-amino acid or a methylated amino acid and/or the amino acid at position 16 is a serine. Preferably, the amino acid at position 16 of Formula I is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 of Formula I is a d-leucine or a d-serine. Optionally, one or more of the amino acids at positions 1-3 of Formula I are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula I is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula I is a leucine, serine or tyrosine.

[90] In alternative embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula II, wherein at least one amino acid of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted by Xaa_{n2} of Formula II is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula II is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula II is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula II is a leucine, a serine, or a tyrosine.

[91] In some embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula III, wherein at least one amino acid of Formula III is a D-amino acid or a methylated amino acid and/or Maa is not a cysteine. Preferably, the amino acid denoted by Xaa_{n2} of Formula III is a D-amino acid or a methylated amino acid. In some embodiments the amino acid denoted by Xaa_{n2} of Formula III is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more amino acids denoted by Xaa_{n1} of Formula III is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position Xaa^6 of Formula III is a leucine, a serine, or a tyrosine.

[92] In other embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula IV, wherein at least one amino acid of Formula IV is a D-amino acid or a methylated amino acid, and/or Maa is not a cysteine. Preferably, the Xaa_{n2} of Formula IV

is a D-amino acid or a methylated amino acid. In some embodiments, the amino acid denoted by Xaa_{n2} of Formula IV is a leucine, a d-leucine, a serine, or a d-serine. Preferably, the one or more of the amino acids denoted by Xaa_{n1} of Formula IV is a D-amino acid or a methylated amino acid. Preferably, the amino acid denoted Xaa^6 of Formula IV is a leucine, a serine, or a tyrosine.

[93] In further embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula V, wherein at at least one amino acid of Formula V is a D-amino acid or a methylated amino acid. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid. For example, the amino acid at position 16 (i.e., Xaa^{16}) of Formula V is a d-leucine or a d-serine. Optionally, one or more of the amino acids at position 1-3 of Formula V are D-amino acids or methylated amino acids or a combination of D-amino acids or methylated amino acids. For example, Asn^1, Asp^2 or Glu^3 (or a combination thereof) of Formula V is a D-amino acids or a methylated amino acid. Preferably, the amino acid denoted at Xaa^6 of Formula V is a leucine, a serine, or a tyrosine.

[94] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula VI, VII, VIII, or IX. Preferably, the amino acid at position 6 of Formula VI, VII, VIII, or IX is a leucine, a serine, or a tyrosine. In some aspects the amino acid at position 16 of Formula VI, VII, VIII, or IX is a leucine or a serine. Preferably, the amino acid at position 16 of Formula V is a D-amino acid or a methylated amino acid.

[95] In additional embodiments, GCC agonist peptides include peptides having the amino acid sequence of Formula X, XI, XII, XIII, XIV, XV, XVI or XVII. Optionally, one or more amino acids of Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. Preferably, the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-amino acid or a methylated amino acid. For example the the amino acid at the carboxy terminus of the peptides according to Formulas X, XI, XII, XIII, XIV, XV, XVI or XVII is a D-tyrosine.

[96] Preferably, the amino acid denoted by Xaa^6 of Formula XIV is a tyrosine, phenyalanine or a serine. Most preferably the amino acid denoted by Xaa^6 of Formula XIV is a phenyalanine or a serine. Preferably, the amino acid denoted by Xaa^4 of Formula XV, XVI or XVII is a tyrosine, a phenyalanine, or a serine. Most preferably, the amino acid position Xaa^4 of Formula V, XVI or XVII is a phenyalanine or a serine.

[97] In some embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XVIII. Preferably, the amino acid at position 1 of Formula XVIII is a glutamic acid, aspartic acid, glutamine or lysine. Preferably, the amino acid at position 2 and 3 of Formula XVIII is a glutamic acid, or an aspartic acid. Preferably, the amino acid at position 5 a glutamic acid. Preferably, the amino acid at position 6 of Formula XVIII is an isoleucine, valine, serine, threonine or tyrosine. Preferably, the amino acid at position 8 of Formula XVIII is a valine or isoleucine. Preferably, the amino acid at position 9 of Formula XVIII is a an asparagine. Preferably, the amino acid at position 10 of Formula XVIII is a valine or an methionine. Preferably, the amino acid at position 11 of Formula XVIII is an alanine. Preferably, the amino acid at position 13 of Formula XVIII is a threonine. Preferably, the amino acid at position 14 of Formula XVIII is a glycine. Preferably, the amino acid at position 16 of Formula XVIII is a leucine, serine or threonine

[98] In alternative embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XIX. Preferably, the amino acid at position 1 of Formula XIX is a serine or asparagine. Preferably, the amino acid at position 2 of Formula XIX is a histidine or an aspartic acid. Preferably, the amino acid at position 3 of Formula XIX is a threonine or a glutamic acid. Preferably, the amino acid at position 5 of Formula XIX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XIX is an isoleucine, leucine, valine or tyrosine. Preferably, the amino acid at position 8, 10, 11, or 13 of Formula XIX is a alanine. Preferably, the amino acid at position 9 of Formula XIX is an asparagine or a phenylalanine. Preferably, the amino acid at position 14 of Formula XIX is a glycine.

[99] In further embodiments, GCRA peptides include peptides containing the amino acid sequence of Formula XX. Preferably, the amino acid at position 1 of Formula XX is a glutamine. Preferably, the amino acid at position 2 or 3 of Formula XX is a glutamic acid or a aspartic acid. Preferably, the amino acid at position 5 of Formula XX is a glutamic acid. Preferably, the amino acid at position 6 of Formula XX is threonine, glutamine, tyrosine, isoleucine, or leucine. Preferably, the amino acid at position 8 of Formula XX is isoleucine or valine. Preferably, the amino acid at position 9 of Formula XX is asparagine. Preferably, the amino acid at position 10 of Formula XX is methionine or valine. Preferably, the amino acid at position 11 of Formula XX is alanine. Preferably, the amino acid at position 13 of Formula XX is a threonione. Preferably, the amino acid at position 1 of Formula XX is a glycine. Preferably, the amino acid at position 15 of Formula XX is a tyrosine. Optionally,

the amino acid at position 15 of Formula XX is two amino acid in length and is Cysteine (Cys), Penicillamine (Pen) homocysteine, or 3-mercaptoproline and serine, leucine or threonine.

[100] In certain embodiments, one or more amino acids of the GCC agonist peptides are replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. Such amino acids and amino acid analogs are known in the art. See, for example, Hunt, "The Non-Protein Amino Acids," in *Chemistry and Biochemistry of the Amino Acids*, Barrett, Chapman and Hall, 1985. In some embodiments, an amino acid is replaced by a naturally-occurring, non-essential amino acid, *e.g.*, taurine. Non-limiting examples of naturally occurring amino acids that can be replaced by non-protein amino acids include the following: (1) an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr); (2) Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, *e.g.*, a halogen, -CH3, -OH, -CH2NH3, -C(O)H, -CH2CH3, - CN, -CH2CH2CH3, -SH, or another group; (3) glutamine residues can be substituted with gamma-Hydroxy-Glu or gamma- Carboxy-Glu; (4) tyrosine residues can be substituted with an alpha substituted amino acid such as L-alpha-methylphenylalanine or by analogues such as: 3-Amino-Tyr; Tyr(CH3); Tyr(PO3(CH3)2); Tyr(SO3H); beta-Cyclohexyl-Ala; beta-(l-Cyclopentenyl)-Ala; beta- Cyclopentyl-Ala; beta-Cyclopropyl-Ala; beta-Quinolyl-Ala; beta-(2-Thiazolyl)-Ala; beta- (Triazole-l-yl)-Ala; beta-(2-Pyridyl)-Ala; beta-(3-Pyridyl)-Ala; Amino-Phe; Fluoro-Phe; Cyclohexyl-Gly; tBu-Gly; beta-(3-benzothienyl)-Ala; beta-(2-thienyl)-Ala; 5-Methyl-Trp; and A- Methyl-Trp; (5) proline residues can be substituted with homopro (L-pipecolic acid); hydroxy-Pro; 3,4-Dehydro-Pro; 4-fluoro-Pro; or alpha-methyl-Pro or an N(alpha)-C(alpha) cyclized amino acid analogues with the structure: n = 0, 1, 2, 3; and (6) alanine residues can be substituted with alpha-substitued or N-methylated amino acid such as alpha-amino isobutyric acid (aib), L/D-alpha-ethylalanine (L/D-isovaline), L/D-methylvaline, or L/D-alpha-methylleucine or a non-natural amino acid such as beta-fluoro-Ala. Alanine can also be substituted with: n = 0, 1, 2, 3 Glycine residues can be substituted with alpha-amino isobutyric acid (aib) or L/D-alpha- ethylalanine (L/D-isovaline).

[101] Further examples of non-natural amino acids include: an unnatural analog of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano,

halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; an amino acid that is amidated at a site that is not naturally amidated, a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (*e.g.*, an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, *e.g.*, a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β- amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2- naphthyl)alanine; a 3-methyl-phenylalanine; a ρ-acetyl-L-phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc β - serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p- benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p- iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L- phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; D- 3-(2-naphthyl)alanine (dNal); an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, 0-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine; dimethyl-Lysine; hydroxy-proline; mercaptopropionic acid; methyl-lysine; 3-nitro-tyrosine; norleucine; pyro-glutamic acid; Z (Carbobenzoxyl); ε-Acetyl-Lysine; β-alanine; aminobenzoyl derivative; aminobutyric acid (Abu); citrulline; aminohexanoic acid; aminoisobutyric acid (AIB); cyclohexylalanine; d-cyclohexylalanine; hydroxyproline; nitro-arginine; nitro-phenylalanine; nitro-tyrosine; norvaline; octahydroindole carboxylate; ornithine (Orn); penicillamine (PEN); tetrahydroisoquinoline; acetamidomethyl protected amino acids and pegylated amino acids. Further examples of unnatural amino acids and amino acid analogs can be found in U.S. 20030108885, U.S. 20030082575, US20060019347 (paragraphs 410-418) and the references cited therein. The

polypeptides of the invention can include further modifications including those described in US20060019347, paragraph 589. Exempary GCC agonist peptides which include a non-naturally occurring amino acid include for example SP-368 and SP-369.

[102] In some embodiments, the GCC agonist peptides are cyclic peptides. GCC agonist cyclic peptides can be prepared by methods known in the art. For example, macrocyclization is often accomplished by forming an amide bond between the peptide N- and C-termini, between a side chain and the N- or C-terminus [*e.g.*, with $K_3Fe(CN)_6$ at pH 8.5] (Samson *et al.*, *Endocrinology,* 137: 5182-5185 (1996)), or between two amino acid side chains, such as cysteine. See, *e.g.,* DeGrado, *Adv Protein Chem, 39*: 51-124 (1988). In various embodiments, the GCC agonist peptides are [4,12; 7,15] bicycles.

[103] In certain embodiments, one or both Cys residues which normally form a disulfide bond in a GCC agonist peptide are replaced with homocysteine, penicillamine, 3-mercaptoproline (Kolodziej *et al.* 1996 *Int. J. Pept. Protein Res.* 48:274), β, β dimethylcysteine (Hunt *et al.* 1993 *Int. J. Pept. Protein Res.* 42:249), or diaminopropionic acid (Smith *et al.* 1978 *J. Med. Chem.* 2 1:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

[104] In certain embodiments, one or more disulfide bonds in a GCC agonist peptide are replaced by alternative covalent cross-links, *e.g.*, an amide linkage ($-CH_2CH(O)NHCH_2-$ or $-CH_2NHCH(O)CH_2-$), an ester linkage, a thioester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage ($-CH_2CH_2CH_2CH_2-$), an alkenyl linkage ($-CH_2CH=CHCH_2-$), an ether linkage ($-CH_2CH_2OCH_2-$ or $-CH_2OCH_2CH_2-$), a thioether linkage ($-CH_2CH_2SCH_2-$ or $-CH_2SCH_2CH_2-$), an amine linkage ($-CH_2CH_2NHCH_2-$ or $-CH_2NHCH_2CH_2-$) or a thioamide linkage ($-CH_2CH(S)HNHCH_2-$ or $-CH_2NHCH(S)CH_2-$). For example, Ledu *et al.* (*Proc. Natl. Acad. Sci.* 100:11263-78, 2003) describe methods for preparing lactam and amide cross-links. Exemplary GCC agonist peptides which include a lactam bridge include, for example, SP-370.

[105] In certain embodiments, the GCC agonist peptides have one or more conventional polypeptide bonds replaced by an alternative bond. Such replacements can increase the stability of the polypeptide. For example, replacement of the polypeptide bond between a residue amino terminal to an aromatic residue (*e.g.* Tyr, Phe, Trp) with an alternative bond

can reduce cleavage by carboxy peptidases and may increase half-life in the digestive tract. Bonds that can replace polypeptide bonds include: a retro-inverso bond (C(O)-NH instead of NH-C(O); a reduced amide bond (NH-CH_2); a thiomethylene bond (S-CH_2 or CH_2-S); an oxomethylene bond (O-CH_2 or CH_2-O); an ethylene bond (CH_2-CH_2); a thioamide bond (C(S)-NH); a trans-olefine bond (CH=CH); a fiuoro substituted trans-olefme bond (CF=CH); a ketomethylene bond (C(O)-CHR or CHR-C(O) wherein R is H or CH_3; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH_3.

[106] In certain embodiments, the GCC agonist peptides are modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect described herein, there may be more than one type of modification on the polypeptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cys3 or Cys5. The GCC agonist peptides described herein may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl-coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-l,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-l- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The GCC agonist peptides described herein may also be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; combinations of PEG, alkyl groups and fatty acid radicals (*See*, U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110); BSA and KLH (Keyhole Limpet Hemocyanin). The addition of PEG and other polymers which can be used to modify polypeptides of the invention is described in US20060 19347 section IX.

[107] A GCC agonist peptide can also be a derivatives of a GCC agonist peptide described herein. For example, a derivative includes hybrid and modified forms of GCC agonist peptides in which certain amino acids have been deleted or replaced. A modification may also include glycosylation. Preferrably, where the modification is an amino acid substitution, it is a conservative substitution at one or more positions that are predicted to be non-essential amino acid residues for the biological activity of the peptide. A "conservative substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar

side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

[108] In one embodiment, a GCC agonist peptide described herein is subjected to random mutagenesis in order to identify mutants having biological activity.

[109] In one embodiment, the GCC agonist peptide is substantially homologous is a GCC agonist peptide described herein. Such substantially homologous peptides can be isolated by virtue of cross-reactivity with antibodies to a GCC agonist peptide described herein.

[110] Further examples of GCC agonist peptides that can be used in the methods and formulations of the invention are found in Tables I - VII below.

1.2.2 Preparation of GCC agonist peptides

[111] GCC agonist peptides can be prepared using art recognized techniques such as molecular cloning, peptide synthesis, or site-directed mutagenesis.

[112] Peptide synthesis can be performed using standard solution phase or solid phase peptide synthesis techniques or a combination of both process where segments are synthesized by solid phase and condensed in solution phase, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the first and of the carboxyl group of the second amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

[113] In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (*See*, Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of Peptide

Synthesis," 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation. Solubility considerations are also a factor. Solid phase peptide synthesis uses an insoluble polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield et al., J. Am. Chem. Soc., 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide synthesis typically utilizes either the Boc or Fmoc strategy, which are well known in the art.

[114] Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is generally most suitable when peptides are to be made on a small scale.

[115] Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

[116] Alternatively the GCC agonist peptides are produced by modern cloning techniques For example, the GCC agonist peptides are produced either in bacteria including, without limitation, E. coli, or in other existing systems for polypeptide or protein production (*e.g.*, Bacillus subtilis, baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized. If the GCC agonist peptide or variant peptide is to be produced in bacteria, *e.g.*, E. coli, the nucleic acid molecule encoding the polypeptide may also encode a leader sequence that permits the secretion of the mature polypeptide from the cell. Thus, the sequence encoding the polypeptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST polypeptide. The secreted, mature polypeptide can be purified from the culture medium.

[117] The sequence encoding a GCC agonist peptide described herein can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, E. coli, B subtilis, Pseudomonas, Salmonella. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences.

[118] A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (*e.g.*, an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during polypeptide production.

[119] The protein coding sequence that includes a GCC agonist peptide described herein can also be fused to a nucleic acid encoding a polypeptide affinity tag, *e.g.*, glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the polypeptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the polypeptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the polypeptide of interest.

[120] Genetic constructs and methods suitable for production of immature and mature forms of the GCC agonist peptides and variants described herein in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce polypeptides in a biological system.

[121] The peptides disclosed herein may be modified by attachment of a second molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

Table I. GCRA Peptides (SP-304 and Derivatives)

Name	Position of Disulfide bonds	Structure	SEQ ID NO
SP-304	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	1
SP-326	C3:C11, C6:C14	Asp[1]-Glu[2]-Cys[3]-Glu[4]-Leu[5]-Cys[6]-Val[7]-Asn[8]-Val[9]-Ala[10]-Cys[11]-Thr[12]-Gly[13]-Cys[14]-Leu[15]	2
SP-327	C2:C10, C5:C13	Asp[1]-Glu[2]-Cys[3]-Glu[4]-Leu[5]-Cys[6]-Val[7]-Asn[8]-Val[9]-Ala[10]-Cys[11]-Thr[12]-Gly[13]-Cys[14]	3
SP-328	C2:C10, C5:C13	Glu[1]-Cys[2]-Glu[3]-Leu[4]-Cys[5]-Val[6]-Asn[7]-Val[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Leu[14]	4
SP-329	C2:C10, C5:C13	Glu[1]-Cys[2]-Glu[3]-Leu[4]-Cys[5]-Val[6]-Asn[7]-Val[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	5
SP-330	C1:C9, C4:C12	Cys[1]-Glu[2]-Leu[3]-Cys[4]-Val[5]-Asn[6]-Val[7]-Ala[8]-Cys[9]-Thr[10]-Gly[11]-Cys[12]-Leu[13]	6
SP-331	C1:C9, C4:C12	Cys[1]-Glu[2]-Leu[3]-Cys[4]-Val[5]-Asn[6]-Val[7]-Ala[8]-Cys[9]-Thr[10]-Gly[11]-Cys[12]	7
SP332	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	8
SP-333	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	9
SP-334	C4:C12,C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	10
SP-335	C4:C12,C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	11
SP-336	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	12
SP-337	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-dLeu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	13
SP-338	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]	14
SP-342	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	15
SP-343	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	16
SP-344	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	17
SP-347	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	18
SP-348	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	19

SP-350	C4:C12, C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	20
SP-352	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	21
SP-358	C4:C12,C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	22
SP-359	C4:C12,C7:C15	PEG3-dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	23
SP-360	C4:C12, C7:C15	dAsn[1]-dAsp[2]-dGlu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]-PEG3	24
SP-361	C4:C12, C7:C15	dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	25
SP-362	C4:C12, C7:C15	PEG3-dAsn[1]-dAsp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	26
SP-368	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dNal[16]	27
SP-369	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-AIB[8]-Asn[9]-AIB[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	28
SP-370	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Asp[Lactam][7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Orn[15]-dLeu[1]	29
SP-371	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	30
SP-372	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	31
N1	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	32
N2	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	33
N3	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] PEG3	34
N4	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	35
N5	C4:C12,C7:C15	PEG3-dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16]	36
N6	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu[16] -PEG3	37
N7	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	38
N8	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	39
N9	C4:C12,C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	40
N10	C4:C12,C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]-PEG3	41

N11	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16} -PEG3	42
N12	C4:C12,C7:C15	PEG3-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16}	43
N13	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dSer^{16} -PEG3	44
Formula I	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	45
Formula II	C4:C12,C7:C15	Xaa$_{n1}$-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa$_{n2}$^{16}	46
Formula III	4:12,7:15	Xaa$_{n1}$-Maa^{4}-Glu^{5}-Xaa^{6}-Maa^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Maa^{12}-Thr^{13}-Gly^{14}-Maa^{15}- Xaa$_{n2}$	47
Formula IV	4:12,7:15	Xaa$_{n1}$ - Maa^{4}-Xaa^{5}-Xaa^{6}- Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}- Maa^{12}-Xaa^{13}-Xaa^{14}- Maa^{15}-Xaa$_{n2}$	48
Formula V	C4:C12,C7:C15	Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	49
Formula VI	C4:C12,C7:C15	dAsn^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-X3^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	50
Formula VII	C4:C12,C7:C15	dAsn^{1}-dGlu^{2}-Asp^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	51
Formula VII	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-Glu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Asn^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	52
Formula VIII	C4:C12,C7:C15	dAsn^{1}-dAsp^{2}-dGlu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Tyr^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	53
Formula IX	C4:C12,C7:C15	dAsn^{1}-dGlu^{2}-dGlu^{3}-Cys^{4}-Xaa^{5}-Xaa^{6}-Cys^{7}-Xaa^{8}-Tyr^{9}-Xaa^{10}-Xaa^{11}-Cys^{12}-Xaa^{13}-Xaa^{14}-Cys^{15}-d-Xaa^{16}	54

Table II. Linaclotide and Derivatives

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-339 (linaclotide)	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	55
SP-340	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	56
SP-349	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}-PEG3	57
SP-353	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	58
SP-354	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	59
SP-355	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-dTyr^{14}	60
SP-357	C1:C6, C2:C10, C5:13	PEG3-Cys^{1}-Cys^{2}-Glu^{3}-Tyr^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	61
SP-374	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	62
SP-375	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	63
SP-376	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	64
SP-377	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Ser^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	65
SP-378	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	66
SP-379	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}	67
SP-380	C3:C8, C4:C12, C7:15	dAsn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	68
SP-381	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Phe^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-dTyr^{16}	69

SP-382	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	70
SP-383	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	71
SP384	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-Tyr[14]-PEG3	72
N14	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	73
N15	C1:C6, C2:C10, C5:13	PEG3-Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]	74
N16	C1:C6, C2:C10, C5:13	Cys[1]-Cys[2]-Glu[3]-Tyr[4]-Cys[5]-Cys[6]-Asn[7]-Pro[8]-Ala[9]-Cys[10]-Thr[11]-Gly[12]-Cys[13]-PEG3	75
N17	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	76
N18	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	77
N19	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Ser[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	78
N20	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	79
N21	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	80
N22	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Phe[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	81
N23	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	82
N24	C3:C8, C4:C12, C7:15	PEG3- Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	83

N25	C3:C8, C4:C12, C7:15	Asn^{1}-Phe^{2}-Cys^{3}-Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Cys^{8}-Asn^{9}-Pro^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Tyr^{16}-PEG3	84
N26	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Ser^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	85
N27	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-Tyr^{14}	86
N28	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Ser^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}-	87
N29	C1:C6, C2:C10, C5:13	Cys^{1}-Cys^{2}-Glu3-Phe^{4}-Cys^{5}-Cys^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Cys^{10}-Thr^{11}-Gly^{12}-Cys^{13}	88
N30	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}-Tyr^{14}	89
N31	1:6, 2:10, 5:13	Pen^{1}-Pen^{2}-Glu3-Tyr^{4}-Pen^{5}-Pen^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Pen^{10}-Thr^{11}-Gly^{12}-Pen^{13}	90
Formula X	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}- Asn^{7}- Tyr^{8}-Cys^{9}-Cys^{10}-Xaa^{11}-Tyr^{12}-Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	91
Formula XI	C9:C14, C10:C18, C13:21	Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}-Asn^{7}- Phe^{8}-Cys^{9}-Cys^{10} -Xaa^{11}-Phe^{12}- Cys^{13}-Cys^{14}-Xaa^{15}-Xaa^{16}-Xaa^{17}-Cys^{18}- Xaa^{19}-Xaa^{20}-Cys^{21}-Xaa^{22}	92
Formula XII	C3:C8, C4:C12, C7:15	Asn^{1}- Phe^{2}-Cys^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Cys^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys^{12}- Xaa^{3}-Xaa^{14}-Cys^{15}-Xaa^{16}	93
Formula XIII	3:8, 4:12, C:15	Asn^{1}- Phe^{2}-Pen^{3}-Cys^{4} - Xaa^{5}-Phe^{6}-Cys^{7}-Pen^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Cys12- Xaa^{13}-Xaa^{14}-Cys^{15}-Xaa^{16}	94
Formula XIV	3:8, 4:12, 7:15	Asn^{1}- Phe^{2}-Maa^{3}-Maa^{4} - Xaa^{5}-Xaa^{6}-Maa^{7}-Maa^{8} - Xaa^{9}-Xaa^{10}- Xaa^{11}-Maa^{12}- Xaa^{13}-Xaa^{14}-Maa^{15}-Xaa^{16}	95
Formula XV	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-Tyr^{14}	96
Formula XVI	1:6, 2:10, 5:13	Maa^{1}-Maa^{2}-Glu3-Xaa^{4}- Maa^{5}-Maa^{6}-Asn^{7}-Pro^{8}-Ala^{9}-Maa^{10}-Thr^{11}-Gly^{12}-Maa^{13}-	97
Formula XVII	1:6, 2:10, 5:13	Xaa_{n3}-Maa^{1}-Maa^{2}-Xaa^{3}-Xaa^{4}-Maa^{5}-Maa^{6}-Xaa^{7}-Xaa^{8}-Xaa^{9}-Maa^{10}-Xaa^{11}-Xaa^{12}-Maa^{13}-Xaa_{n2}	98

Table III. GCRA Peptides

Name	Position of Disulfide bonds	Structure	SEQ ID NO:
SP-363	C4:C12,C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	99
SP-364	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer[16]	100
SP-365	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dSer-AMIDE[16]	101
SP-366	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	102
SP-367	C4:C12, C7:C15	dAsn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr-AMIDE[16]	103
SP-373	C4:C12, C7:C15	Pyglu[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dLeu-AMIDE[16]	104
SP-304 di PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]-PEG3	105
SP-304 N-PEG	C4:C12, C7:C15	PEG3-Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	106
SP-304 C-PEG	C4:C12, C7:C15	Asn[1]-Asp[2]-Glu[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]-PEG3	107

Table IV. SP-304 Analogs, Uroguanylin , and Uroguanylin Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XVIII	C4:C12, C7:C15	Xaa[1]- Xaa[2]- Xaa[3] -Maa[4]-Xaa[5]-Xaa[6]-Maa[7]-Xaa[8]-Xaa[9]-Xaa[10]-Xaa[11]-Maa[12]-Xaa[13]-Xaa[14]-Maa[15]-Xaa[16]	108
Uroguanylin	C4:C12, C7:C15	Asn[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	109
N32	C4:C12, C7:C15	Glu[1]-Asp[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	110
N33	C4:C12, C7:C15	Glu[1]-Asp[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	111
N34	C4:C12, C7:C15	Glu[1]-Glu[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	112
N35	C4:C12, C7:C15	Glu[1]-Glu[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	113
N36	C4:C12, C7:C15	Asp[1]-Asp[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	114
N37	C4:C12, C7:C15	Asp[1]-Asp[2]-Glu[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	115
N38	C4:C12, C7:C15	Asp[1]-Glu[2]-Asp[3] -Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]	116

N39	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	117
N40	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	118
N41	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	119
N42	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	120
N43	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	121
N44	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	122
N45	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	123
N46	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	124
N47	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	125
N48	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	126
N49	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	127
N50	C4:C12,	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	128

	C7:C15		
N51	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	129
N52	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	130
N53	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	131
N54	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	132
N55	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	133
N56	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	134
N57	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	135
N58	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	136
N59	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	137
N60	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	138
N61	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	139

N62	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	140
N63	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	141
N65	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	142
N66	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	143
N67	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	144
N68	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	145
N69	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	146
N70	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	147
N71	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	148
N72	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	149
N73	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	150
N74	C4:C12,	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	151

	C7:C15		
N75	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	152
N76	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	153
N77	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	154
N78	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	155
N79	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	156
N80	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}	157
N81	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	158
N82	C4:C12, C7:C15	Glu^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	159
N83	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	160
N84	C4:C12, C7:C15	Glu^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	161
N85	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	162

N86	C4:C12, C7:C15	Asp^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	163
N87	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	164
N88	C4:C12, C7:C15	Asp^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	165
N89	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	166
N90	C4:C12, C7:C15	Gln^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	167
N91	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	168
N92	C4:C12, C7:C15	Gln^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	169
N93	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	170
N94	C4:C12, C7:C15	Lys^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	171
N95	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	172
N96	C4:C12, C7:C15	Lys^{1}-Glu^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Ser^{16}	173

Table V. Guanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XIX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-Maa^{15}	174
Guanylin	C4:C12, C7:C15	Ser^{1}-His^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Phe^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	175
N97	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	176
N98	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	177
N99	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	178
N100	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	179
N101	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	180
N102	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	181
N103	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	182
N104	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	183
N105	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	184
N106	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	185
N107	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	186
N108	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	187

N109	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	188
N110	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	189
N111	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	190
N112	C4:C12, C7:C15	Ser^{1}- His^{2}-Thr^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	191
N113	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	192
N114	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	193
N115	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	194
N116	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	195
N117	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	196
N118	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	197
N119	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	198
N120	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	199
N121	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	200
N122	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	201
N123	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	202
N124	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	203
N125	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	204
N126	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	205

N127	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Val^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	206
N128	C4:C12, C7:C15	Asn^{1}- Asp^{2}-Glu^{3} -Cys^{4}-Glu^{5}-Tyr^{6}-Cys^{7}-Ala^{8}-Asn^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Ala^{13}-Gly^{14}-Cys^{15}	207

Table VI. Lymphoguanylin and Analogs

Name	Position of Disulfide bonds	Structure	SEQ ID NO
Formula XX	4:12,7:15	Xaa^{1}- Xaa^{2}- Xaa^{3} -Maa^{4}-Xaa^{5}-Xaa^{6}-Maa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Maa^{12}-Xaa^{13}-Xaa^{14}-$Xaa_{n1}{}^{15}$	208
Lymphoguanylin	C4:C12	Gln^{1}-Glu^{2}-Glu-$^{3}Cys^{4}$-Glu^{5}-Leu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	209
N129	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	210
N130	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	211
N131	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	212
N132	C4:C12	Gln^{1}-Glu^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Thr^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	213
N133	C4:C12	Gln^{1}-Glu^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	214
N134	C4:C12	Gln^{1}-Asp^{2}- Glu^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	215
N135	C4:C12	Gln^{1}-Asp^{2}- Asp^{3} -Cys^{4}-Glu^{5}-Glu^{6}-Cys^{7}-Ile^{8}-Asn^{9}-Met^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Tyr^{15}	216

N136	C4:C12	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	217
N137	C4:C12	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	218
N138	C4:C12	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	219
N139	C4:C12	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	220
N140	C4:C12	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	221
N141	C4:C12	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	222
N142	C4:C12	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	223
N143	C4:C12	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	224
N144	C4:C12	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Tyr[15]	225
N145	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Thr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	226
N146	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Thr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	227
N147	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Thr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	228
N148	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Thr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	229
N149	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	230

N150	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser	231
N151	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	232
N152	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Glu[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	233
N153	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	234
N154	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	235
N155	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	236
N156	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	237
N157	C4:C12, C7:C15	Gln[1]-Glu[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	238
N158	C4:C12, C7:C15	Gln[1]-Asp[2]- Glu[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	239
N159	C4:C12, C7:C15	Gln[1]-Asp[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	240

N160	C4:C12, C7:C15	Gln[1]-Glu[2]- Asp[3] -Cys[4]-Glu[5]-Ile[6]-Cys[7]-Ile[8]-Asn[9]-Met[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Ser[16]	241

Table VII. ST Peptide and Analogues

Name	Position of Disulfide bonds	Structure	SEQ ID NO
ST Peptide	C3:C8, C4:C12, C7:15	Asn[1]- Ser[2]-Ser[3]-Asn[4]-Ser[5]-Ser[6]-Asn[7]-Tyr[8]-Cys[9]-Cys[10]-Glu[11]-Lys[12]-Cys[13]-Cys[14]-Asn[15]-Pro[16]-Ala[17]-Cys[18]-Thr[19]-Gly[20]-Cys[21]-Tyr[22]	242
N161	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	243
N162	C3:C8, C4:C12, C7:15	PEG3-Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	244
N163	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Thr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]-PEG3	245
N164	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	246
N165	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	247
N166	C3:C8, C4:C12, C7:15	Asn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-dTyr[16]	248
N167	C3:C8, C4:C12, C7:15	dAsn[1]-Phe[2]-Cys[3]-Cys[4]-Glu[5]-Tyr[6]-Cys[7]-Cys[8]-Asn[9]-Pro[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Tyr[16]	249

1.3 Methods of Use

[122] The invention provides methods for treating or preventing gastrointestinal disorders and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal disorders that can be treated or prevented according to the methods of the invention include irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastroesophageal reflux disease (GERD), ileus (*e.g.*, post-operative ileus), gastroparesis, heartburn (high acidity in the GI tract), constipation (*e.g.*, constipation associated with use of medications such as opioids, osteoarthritis drugs, or osteoporosis drugs); post surgical constipation, constipation associated with neuropathic disorders, Crohn's disease, and ulcerative colitis.

[123] In one embodiment, the invention provides methods for treating or preventing gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia.

[124] In one embodiment, the invention provides methods for treating or preventing constipation and/or increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of

surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[125] In various embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is postsurgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

[126] In one embodiment, the invention provides methods for treating or preventing chronic idiopathic constipation and increasing gastrointestinal motility in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject.

[127] The term "treating" as used herein refers to a reduction, a partial improvement, amelioration, or a mitigation of at least one clinical symptom associated with the gastrointestinal disorders being treated. The term “preventing” refers to an inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorders to be prevented. The term "effective amount” as used herein refers to an amount that provides some improvement or benefit to the subject. In certain embodiments, an effective amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom of the gastrointestinal disorder to be treated. In other embodiments, the effective amount is the amount that provides some inhibition or delay in the onset or progression of at least one clinical symptom associated with the gastrointestinal disorder to be prevented. The therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. The term “subject” preferably refers to a human subject but may also refer to a non-human primate or other mammal preferably selected from among a mouse, a rat, a dog, a cat, a cow, a horse, or a pig.

[128] The invention also provides methods for treating gastrointestinal cancer in a subject in need thereof by administering an effective amount of a GCC agonist formulation to the subject. Non-limiting examples of gastrointestinal cancers that can be treated according to the methods of the invention include gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer.

[129] The invention also provides methods for treating lipid metabolism disorders, biliary disorders, inflammatory disorders, lung disorders, cancer, cardiac disorders including cardiovascular disorders, eye disorders, oral disorders, blood disorders, liver disorders, skin disorders, prostate disorders, endocrine disorders, and obesity.

[130] Lipid metabolism disorders include, but are not limited to, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, sitosterolemia, familial hypercholesterolemia, xanthoma, combined hyperlipidemia, lecithin cholesterol acyltransferase deficiency, tangier disease, abetalipoproteinemia, erectile dysfunction, fatty liver disease, and hepatitis.

[131] Billary disorders include gallbladder disorders such as for example, gallstones, gall bladder cancer cholangitis, or primary sclerosing cholangitis; or bile duct disorders such as for example,cholecystitis, bile duct cancer or fascioliasis.

[132] Inflammatory disorders include tissue and organ inflammation such as kidney inflammation (e.g., nephritis), gastrointestinal system inflammation (e.g., Crohn's disease and ulcerative colitis); necrotizing enterocolitis (NEC); pancreatic inflammation (e.g., pancreatis), lung inflammation (e.g., bronchitis or asthma) or skin inflammation (e.g., psoriasis, eczema).

[133] Lung Disorders include for example chronic obstructive pulmonary disease (COPD), and fibrosis.

[134] Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g. bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer.

[135] Cardiac disorders include for example, congestive heart failure, trachea cardia hypertension, high cholesterol, or high triglycerides. Cardiovascular disorders include for example aneurysm, angina, atherosclerosis, cerebrovascular accident (stroke), cerebrovasculardisease, congestive heart failure, coronary artery disease, myocardial infarction (heart attack), or peripheral vascular disease.

[136] Liver disorders include for example cirrhosis and fibrosis. In addition, GC-C agonist may also be useful to facilitate liver regeneration in liver transplant patients. Eye disorders include for example increased intra-ocular pressure, glaucoma, dry eyes retinal degeneration, disorders of tear glands or eye inflammation. Skin disorders include for example xerosis. Oral disorders include for example dry mouth (xerostomia), Sjögren's syndrome, gum diseases (e.g., periodontal disease), or salivary gland duct blockage or malfunction. Prostate disorders include for example benign prostatic hyperplasia (BPH). Endocrine disorders include for example diabetes mellitus, hyperthyroidism, hypothyroidism, and cystic fibrosis.

1.3.1 Therapeutically Effective Dosages

[137] Disorders are treated, prevented or alleviated by administering to a subject, *e.g.*, a mammal such as a human in need thereof, a therapeutically effective dose of a GCC agonist peptide. The present invention is based in part on the unexpected results of clinical trials in humans which demonstrated that the formulations of the invention are therapeutically effective at much lower doses than predicted based on animal studies. In accordance with one aspect of the invention, the therapeutically effective dose is between 0.01 milligrams (mg) and 10 mg per unit dose. The term "unit dose" refers to a single drug delivery entity, *e.g.*, a tablet, capsule, solution or inhalation formulation. In one embodiment, the effective dose is between 0.01 mg and 9 mg. In another embodiment, the effective dose is between 0.01 mg and 5 mg. In another embodiment, the effective dose is between 0.01 mg and 3 mg. In another embodiment, the effective dose is between 0.10 mg and 5 mg. In another embodiment, the effective dose is between 0.10 mg and 3 mg. In one embodiment, the unit dose is .01 mg, .05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 5 mg, or 10 mg. In one embodiment, the unit dose is 0.3 mg, 1.0 mg, 3.0 mg, 9.0 mg, or 9.5 mg.

[138] The GCC agonist peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient. What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art.

[139] The GCC agonists for use in the methods described above are preferably administered orally. Dosage forms include solutions, suspensions, emulsions, tablets, and capsules.

[140] The total daily dose can be administered to the patient in a single dose, or in multiple sub-doses. Typically, sub-doses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Preferably, a single daily dose is administered.

[141] The GCC agonists may be administered as either the sole active agent or in combination with one or more additional active agents. In all cases, additional active agents should be administered at a dosage that is therapeutically effective using the existing art as a guide. The GCC agonists may be administered in a single composition or sequentially with the one or more additional active agents. In one embodiment, the GCC agonist is administered in combination with one or more inhibitors of cGMP dependent phosphodiesterase such as suldinac sulfone, zaprinast, motapizone, vardenafil, or sildenifil. In another embodiment, the GCC agonist is administered in combination with one or more chemotherapeutic agents. In another embodiment, the GCC agonist is administered in combination with one or more or anti-inflammatory drugs such as steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin.

[142] Combination therapy can be achieved by administering two or more agents, *e.g.*, a GCC agonist peptide described herein and another compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a

third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[143] The GCC agonist peptides described herein may be combined with phosphodiesterase inhibitors, *e.g.*, sulindae sulfone, Zaprinast, sildenafil, vardenafil or tadalafil to further enhance levels of cGMP in the target tissues or organs.

[144] Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, *e.g.*, in the order X-Y- X, X-X-Y, Y-X-Y,Y-Y-X,X-X-Y-Y, etc.

1.3.2 Exemplary Agents for Combination Therapy

[145] The GCC agonist formulations of the invention may be administered alone or in combination with one or more additional therapeutic agents as part of a therapeutic regimen for the treatment or prevention of a gastrointestinal disease or disorder. In some embodiments, the GCC agonist formulation comprises one or more additional therapeutic agents. In other embodiments, the GCC agonist is formulated separately from the one or more additional therapeutic agents. In accordance with this embodiment, the GCC agonist is administered either simultaneously, sequentially, or at a different time than the one or more additional therapeutic agents. In one embodiment, the GCC agonist formulation is administered in combination with one or more additional therapeutic agents selected from the group consisting of phosphodiesterase inhibitors, cyclic nucleotides (such as cGMP and cAMP), a laxative (such as SENNA or METAMUCIL), a stool softner, an anti-tumor necrosis factor alpha therapy for IBD

(such as REMICADE, ENBREL, or HUMIRA), and anti-inflammatory drugs (such as COX-2 inhibitors, sulfasalazine, 5-ASA derivatives and NSAIDS). In certain embodiments, the GCC agonist formulation is administered in combination with an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said GCC agonist. cGMP-PDE inhibitors include, for example, suldinac sulfone, zaprinast, motapizone, vardenifil, and sildenafil. In another embodiment, the GCC agonist formulation is administered in combination with inhibitors of cyclic nucleotide transporters. Further examples of therapeutic agents that may be administered in combination with the GCC agonist formulations of the invention are given in the following sections.

1.3.2.1 Agents to Treat Gastrointestinal Cancers

[146] The GCC agonist formulations described herein can be used in combination with one or more antitumor agents including but not limited to alkylating agents, epipodophyllotoxins, nitrosoureas, anti-metabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular antitumor agents include tamoxifen, taxol, etoposide, and 5-fluorouracil. In one embodiment, the GCC agonist formulations are used in combination with an antiviral agent or a monoclonal antibody.

[147] Non-limiting examples of antitumor agents that can be used in combination with the GCC agonist formulations of the invention for the treatment of colon cancer include anti-proliferative agents, agents for DNA modification or repair, DNA synthesis inhibitors, DNA/RNA transcription regulators, RNA processing inhibitors, agents that affect protein expression, synthesis and stability, agents that affect protein localization or their ability to exert their physiological action, agents that interfere with protein-protein or protein-nucleic acid interactions, agents that act by RNA interference, receptor binding molecules of any chemical nature (including small molecules and antibodies), targeted toxins, enzyme activators, enzyme inhibitors, gene regulators, HSP-90 inhibitors, molecules interfering with microtubules or other cytoskeletal components or cell adhesion and motility, agents for phototherapy, and therapy adjuncts.

[148] Representative anti-proliferative agents include N-acetyl-D-sphingosine (C.sub.2 ceramide), apigenin, berberine chloride, dichloromethylenediphosphonic acid disodium salt, loe-emodine, emodin, HA 14-1, N-hexanoyl-D-sphingosine (C.sub.6 ceramide), 7b-hydroxycholesterol, 25-hydroxycholesterol, hyperforin, parthenolide, and rapamycin.

Representative agents for DNA modification and repair include aphidicolin, bleomycin sulfate, carboplatin, carmustine, chlorambucil, cyclophosphamide monohydrate, cyclophosphamide monohydrate ISOPAC.RTM., cis-diammineplatinum(II) dichloride (Cisplatin), esculetin, melphalan, methoxyamine hydrochloride, mitomycin C, mitoxantrone dihydrochloride, oxaliplatin, and streptozocin.

[149] Representative DNA synthesis inhibitors include (.+-.)amethopterin (methotrexate), 3-amino-1,2,4-benzotriazine 1,4-dioxide, aminopterin, cytosine b-D-arabinofurdnoside (Ara-C), cytosine b-D-arabinofuranoside (Ara-C) hydrochloride, 2-fluoroadenine-9-b-D-arabinofuranoside (Fludarabine des-phosphate; F-ara-A), 5-fluoro-5'-deoxyuridinc, 5-fluorouracil, ganciclovir, hydroxyurea, 6-mercaptopurine, and 6-thioguanine.

[150] Representative DNA/RNA transcription regulators include actinomycin D, daunorubicin hydrochloride, 5,6-dichlorobenzimidazole 1-b-D-ribofuranoside, doxorubicin hydrochloride, homoharringtonine, and idarubicin hydrochloride.

[151] Representative enzyme activators and inhibitors include forskolin, DL-aminoglutethimide, apicidin, Bowman-Birk Inhibitor, butein, (S)-(+)-camptothecin, curcumin, (-)-deguelin, (-)-depudecin, doxycycline hyclate, etoposide, formestane, fostriecin sodium salt, hispidin, 2-imino-1-imidazolidineacetic acid (Cyclocreatine), oxamflatin, 4-phenylbutyric acid, roscovitine, sodium valproate, trichostatin A, tyrphostin AG 34, tyrphostin AG 879, urinary trypsin inhibitor fragment, valproic acid (2-propylpentanoic acid), and XK469.

[152] Representative gene regulators include 5-aza-2'-deoxycytidine, 5-azacytidine, cholecalciferol (Vitamin D3), ciglitizone, cyproterone acetate, 15-deoxy-D.sup.12,14-prostaglandin J.sub.2, epitestosterone, flutamide, glycyrrhizic acid ammonium salt (glycyrrhizin), 4-hydroxytamoxifen, mifepristone, procainamide hydrochloride, raloxifene hydrochloride, all trans-retinal (vitamin A aldehyde), retinoic acid (vitamin A acid), 9-cis-

retinoic acid, 13-cis-retinoic acid, retinoic acid p-hydroxyanilide, retinol (Vitamin A), tamoxifen, tamoxifen citrate salt, tetradecylthioacetic acid, and troglitazone.

[153] Representative HSP-90 inhibitors include 17-(allylamino)-17-demethoxygeldanamycin and geldanamycin.

[154] Representative microtubule inhibitors include colchicines, dolastatin 15, nocodazole, taxanes and in particular paclitaxel, podophyllotoxin, rhizoxin, vinblastine sulfate salt, vincristine sulfate salt, and vindesine sulfate salt and vinorelbine (Navelbine) ditartrate salt.

[155] Representative agents for performing phototherapy include photoactive porphyrin rings, hypericin, 5-methoxypsoralen, 8-methoxypsoralen, psoralen and ursodeoxycholic acid.

[156] Representative agents used as therapy adjuncts include amifostine, 4-amino-1,8-naphthalimide, brefeldin A, cimetidine, phosphomycin disodium salt, leuprolide (leuprorelin) acetate salt, luteinizing hormone-releasing hormone (LH-RH) acetate salt, lectin, papaverine hydrochloride, pifithrin-a, (-)-scopolamine hydrobromide, and thapsigargin.

[157] The agents can also be anti-VEGF (vascular endothelial growth factor) agents, as such are known in the art. Several antibodies and small molecules are currently in clinical trials or have been approved that function by inhibiting VEGF, such as Avastin (Bevacizumab), SU5416, SU11248 and BAY 43-9006. The agents can also be directed against growth factor receptors such as those of the EGF/Erb-B family such as EGF Receptor (Iressa or Gefitinib, and Tarceva or Erlotinib), Erb-B2, receptor (Herceptin or Trastuzumab), other receptors (such as Rituximab or Rituxan/MabThera), tyrosine kinases, non-receptor tyrosine kinases, cellular serine/threonine kinases (including MAP kinases), and various other proteins whose deregulation contribute to oncogenesis (such as small/Ras family and large/heterotrimeric G proteins). Several antibodies and small molecules targeting those molecules are currently at various stages of development (including approved for treatment or in clinical trials).

[158] In a preferred embodiment, the invention provides a method for treating colon cancer in a subject in need thereof by administering to the subject a GCC agonist formulation in combination with one or more antitumor agent selected from the group consisting of paclitaxel,

docetaxel, tamoxifen, vinorelbine, gemcitabine, cisplatin, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclophosphamide, gentuzumab, carboplatin, interferons, and doxorubicin. In a particular embodiment the antitumor agent is paclitaxel. In a further embodiment, the method further comprises an antitumor agent selected from the group consisting of 5-FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

1.3.2.2 Agents that Treat Crohn's Disease

[159] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of Crohn's disease. Non-limiting examples of the one or more additional therapeutic agents include sulfasalazine and other mesalamine-containing drugs, generally known as 5-ASA agents, such as Asacol, Dipentum, or Pentasa, or infliximab (REMICADE). In certain embodiments, the one or more additional agents is a corticosteroid or an immunosuppressive agent such as 6-mercaptopurine or azathioprine. In another embodiment, the one or more additional agents is an antidiarrheal agent such as diphenoxylate, loperamide, or codeine.

1.3.2.3 Agents that Treat Ulcerative Colitis

[160] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of ulcerative colitis. The agents that are used to treat ulcerative colitis overlap with those used to treat Chrohn's Disease. Non-limiting examples of the one or more additional therapeutic agents that can be used in combination with a GCC agonist formulation of the invention include aminosalicylates (drugs that contain 5-aminosalicyclic acid (5-ASA)) such as sulfasalazine, olsalazine, mesalamine, and balsalazide. Other therapeutic agents that can be used include corticosteroids, such as prednisone and hydrocortisone, immunomodulators, such as azathioprine, 6-mercapto-purine (6-MP), cytokines, interleukins, and lymphokines, and anti-TNF-alpha agents, including the thiazolidinediones or glitazones such as rosiglitazone and pioglitazone. In one emobidment, the one or more additional therapeutic agents includes both cyclosporine A and 6-MP or azathioprine for the treatment of active, severe ulcerative colitis.

1.3.2.4 Agents that Treat Constipation/Irritable Bowel Syndrome

[161] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of constipation, such as that associated with irritable bowel syndrome. Non-limiting examples of the one or more additional therapeutic agents include laxatives such as SENNA, MIRALAX, LACTULOSE, PEG, or calcium polycarbophil), stool softeners (such as mineral oil or COLACE), bulking agents (such as METAMUCIL or bran), agents such as ZELNORM (also called tegaserod), and anticholinergic medications such as BENTYL and LEVSIN.

1.3.2.5 Agents for the Treatment of Postoperative Ileus

[162] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of postoperative ileus. Non-limiting examples of the one or more additional therapeutic agents include ENTEREG (alvimopan; formerly called ado lor/ ADL 8-2698), conivaptan, and related agents describes in US 6,645,959.

1.3.2.6 Anti-obesity agents

[163] In one embodiment, a GCC agonist formulation of the invention is administered as part of a combination therapy with one or more additional therapeutic agents for the treatment of obesity. Non-limiting examples of the one or more additional therapeutic agents include 1 lβ HSD-I (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(l-adamantyl)-4-ethyl-5-(ethylthio)- 4H-l,2,4-triazole, 3-(l-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-l,2,4-triazole, 3- adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-l,2,4-triazolo[4,3-a][l l]annulene, and those compounds disclosed in WO01/90091, WOO 1/90090, WOO 1/90092 and WO02/072084; 5HT antagonists such as those in WO03/037871, WO03/037887, and the like; 5HTIa modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like; 5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010,

WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; 5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like; acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al, Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190; anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769; CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700, WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546; CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A- 71378, A-71623 and SR146131 (Sanofi), and those described in US5739106; CNTF (Ciliary neurotrophic factors), such as GI- 181771 (Glaxo-SmithKline), SRl 46131 (Sanofi Synthelabo), butabindide, PD 170,292, and PD 149164 (Pfizer); CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-l,2,3,4-tetrahydroisoquinoline-3- carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2- cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476; growth hormone secretagogue

receptor agonists/antagonists, such as NN703, hexarelin, MK- 0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L- 163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888; H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(lH-imidazol-4- yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(lH-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N- phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929; leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WRl 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453; lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267; Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME- 10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WOO 1/991752, WOO 1/25192, WOO 1/52880, WOO 1/74844, WOO 1/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410; Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041; melanin-concentrating hormone 1

receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WOO 1/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059; mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like; serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl- alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WOO 1/27068, and WOO 1/62341; NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI- 264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW- 587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WOO 1/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al, J. Med. Chem. 43:4288-4312 (2000); opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone,

methylnaltrexone, naloxone, and naltrexone (e.g. PT901; Pain Therapeutics, Inc.) and those disclosed in US20050004155 and WO00/21509; orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847; PDE inhibitors (e.g. compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I- XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562,

EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra™)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500; Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344- 000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD- 57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L- 686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®); Neuropeptide Y2 (NPY2) agonists include but are not limited to: polypeptide YY and fragments and variants thereof (e.g. YY3-36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO:XXX)) and PYY agonists such as those disclosed in WO02/47712, WO03/026591, WO03/057235, and WO03/027637; serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WOO 1/27060, and WOO 1/162341; thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190; UCP-I (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5, 6,7,8- tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-l-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123; β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-

37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881; noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1- propanone, 2-(diethylamino)-l -phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H- imidazo[2,l-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(l-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-lH-imidazol-2-yl)ethyl](4-methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)- tartrate (1 :1)) such as Metra® (Forest) , Plegine® (Wyeth- Ay erst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9- Tetrahydro-2-methyl-9-phenyl-lH-indenol[2,l-c]pyridine L-(+)-tartrate (1 :1)), Hoffmann- LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)-N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate); fatty acid oxidation upregulator/inducers such as Famoxin® (Genset); monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGATl (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors,

ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), polypeptide hormones and variants thereof which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory polypeptide (GIP)/vasoactive intestinal polypeptide (VIP)/pituitary adenylate cyclase activating polypeptide (PACAP)/glucagon-like polypeptide II (GLP- II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related polypeptide (CGRP) gene family includingGLP-1 (glucagon- like polypeptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-I molecules described in US20050130891 including GLP- 1(7-34), GLP-l(7-35), GLP-l(7-36) or GLP-l(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-I polypeptides and modifications thereof including those described in paragraphs 17-44 of US20050130891, and derivatives derived from GLP-l-(7- 34)COOH and the corresponding acid amide are employed which have the following general formula: R-NH-HAEGTFTSDVSYLEGQAAKEFIAWLVK-$CONH_2$ wherein R=H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert- butyl.) and glp-1 (glucagon-like polypeptide- 1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L- carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-I (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase- 1 inhibitors (β -HSD-I), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™,

indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs 20-26.

1.3.2.7 Phosphodiesterase inhibitors

[164] In certain embodiments, the regimen of combination therapy includes the administration of one or more phosphodiesterase ("PDE") inhibitors. PDE inhibitors slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibiting phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and/or cGMP. Non-limiting examples of PDE inhibitors that can be used in combination with the GCC agonists of the invention include PDE3 inhibitors, PDE4 inhibitors and/or PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. Non-limiting examples of such PDE inhibitors are described in the following patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EPOl 12987, EPOl 16948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DEl 116676, DE2162096,

EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543, US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF- 107806, PICLAMILAST, RS- 17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN, ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include: cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®), zaprinast (PDE5 specific). GCC AGONIST

1.3.2.8 Analgesic Agents

[165] In certain embodiments, the regimen of combination therapy includes the administration of one or more analgesic agents, *e.g.*, an analgesic compound or an analgesic polypeptide. In some embodiments, the GCC agonist formulation is administered simultaneously or sequentially with one or more analgesic agents. In other embodiments, the GCC agonist is covalently linked or attached to an analgesic agent to create a therapeutic conjugate. Non-limiting examples of

analgesic agents that can be used include calcium channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HTl receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NKl receptor antagonists, CCK receptor agonists (*e.g.*, loxiglumide), NKl receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Further examples of analgesic agents in the various classes are known in the art.

[166] In one embodiment, the analgesic agent is an analgesic polypeptide selected from the group consisting of sialorphin-related polypeptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO: 239), including: VQHNPR (SEQ ID NO: 240); VRQHNPR (SEQ ID NO: 241); VRGQHNPR (SEQ ID NO: 242); VRGPQHNPR (SEQ ID NO: 243); VRGPRQHNPR (SEQ ID NO: 244); VRGPRRQHNPR (SEQ ID NO: 245); and RQHNPR (SEQ ID NO: 246). Sialorphin-related polypeptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or polypeptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the GCC agonists described herein or covalently linked to a GCC agonist to form a therapeutic conjugate. Sialorphin and related polypeptides are described in U.S. Patent 6,589,750; U.S. 20030078200 Al; and WO 02/051435 A2.

[167] In another embodiment, a GCC agonist formulation of the invention is administered as part of a regimen of combination therapy with an opioid receptor antagonist or agonist. In one embodiment, the GCC agonist and the opioid receptor antagonist or agonist are linked via a covalent bond. Non-limiting examples of opioid receptor antagonists include naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, nor-binaltorphimine, enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine), trimebutine, vasoactive intestinal polypeptide, gastrin, glucagons. Non-limiting examples of opioid receptor agonists include fedotozine, asimadoline, and ketocyclazocine, the compounds described in WO03/097051 and WO05/007626, morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH 2; WO 01/019849 Al), and loperamide.

[168] Further non-limiting examples of analgesic agents that can be used in a regimen of combination therapy along with the GCC agonist formulations of the invention include the

dipeptide Tyr-Arg (kyotorphin); the chromogranin-derived polypeptide (CgA 47-66; *See, e.g.*, Ghia et al. 2004 Regulatory polypeptides 119:199); CCK receptor agonists such as caerulein; conotoxin polypeptides; peptide analogs of thymulin (FR Application 2830451); CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R- isomer of loxiglumide) (WO 88/05774); 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride; calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6087,091, US 6,136,786, WO 93/13128 Al, EP 1336409 Al, EP 835126 Al, EP 835126 Bl, US 5,795,864, US 5,891,849, US 6,054,429, WO 97/01351 Al; NK-I, receptor antagonists such as aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 Al, US 20010006972 Al, US 20030109417 Al, WO 01/52844 Al (for a review see Giardina et al. 2003.Drugs 6:758); NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc); NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 Al, WO 97/21680 Al, US 6,277,862, WO 98/1 1090, WO 95/28418, WO 97/19927, and Boden et al. (J Med Chem. 39:1664-75, 1996); norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897; and vanilloid receptor antagonists such as arvanil and related compouds described in WO 01/64212 Al.

[169] In addition to sialorphin-related polypeptides, analgesic polypeptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

1.3.2.9 Insulin and Insulin Modulating Agents

[170] The GCC agonist peptides described herein can be used in combination therapy with insulin and related compounds including primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in

recombinant form. Sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin). See, the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins).

[171] The GCC peptides described herein can also be used in combination therapy with agents that can boost insulin effects or levels of a subject upon administration, e.g. glipizide and/or rosiglitazone. The polypeptides and agonistsdescribed herein can be used in combitherapy with SYMLIN® (pramlintide acetate) and Exenatide® (synthetic exendin-4; a 39 aa polypeptide).

1.3.2.10 Anti-Hypertensive Agents

[172] The GCC agonist peptides described herein can be used in combination therapy with an anti-hypertensive agent including but not limited to: (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; carbonic anhydrase inhibitors, osmotics(such as glycerin) and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; ceranapril; cilazapril; delapril; enalapril; enalopril; fosinopril; imidapril; lisinopril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8)

angiotensin II receptor antagonists such as aprosartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/β adrenergic blockers such as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, and XENOlO, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12) aldosterone inhibitors, and the like; and (13) angiopoietin-2 -binding agents such as those disclosed in WO03/030833. Specific anti-hypertensive agents that can be used in combination with polypeptides and agonists described herein include, but are not limited to: diuretics, such as thiazides (e.g., chlorthalidone, cyclothiazide (CAS RN 2259-96-3), chlorothiazide (CAS RN 72956-09-3, which may be prepared as disclosed in US2809194), dichlorophenamide, hydroflumethiazide, indapamide, polythiazide, bendroflumethazide, methyclothazide, polythiazide, trichlormethazide, chlorthalidone, indapamide, metolazone, quinethazone, althiazide (CAS RN 5588-16-9, which may be prepared as disclosed in British Patent No. 902,658), benzthiazide (CAS RN 91-33-8, which may be prepared as disclosed in US3108097), buthiazide (which may be prepared as disclosed in British Patent Nos. 861 ,367), and hydrochlorothiazide), loop diuretics (e.g. bumetanide, ethacrynic acid, furosemide, and torasemide), potassium sparing agents (e.g. amiloride, and triamterene (CAS Number 396-01-O)), and aldosterone antagonists (e.g. spironolactone (CAS Number 52-01-7), epirenone, and the like); β-adrenergic blockers such as Amiodarone (Cordarone, Pacerone), bunolol hydrochloride (CAS RN 31969-05-8, Parke-Davis), acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(l methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide), acebutolol hydrochloride (e.g. Sectral®, Wyeth-Ayerst), alprenolol hydrochloride (CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692), atenolol (e.g. Tenormin®, AstraZeneca), carteolol hydrochloride (e.g. Cartrol® Filmtab®, Abbott), Celiprolol hydrochloride (CAS RN 57470-78-7, also see in US4034009), cetamolol hydrochloride (CAS RN 77590-95-5, see also US4059622), labetalol hydrochloride (e.g. Normodyne®, Schering), esmolol hydrochloride (e.g. Brevibloc®, Baxter), levobetaxolol hydrochloride (e.g. Betaxon™ Ophthalmic Suspension, Alcon), levobunolol hydrochloride (e.g. Betagan® Liquifilm® with C CAP® Compliance Cap, Allergan), nadolol (e.g. Nadolol, Mylan), practolol (CAS RN 6673-35-4, see also US3408387), propranolol hydrochloride (CAS RN 318-

98-9), sotalol hydrochloride (e.g. Betapace AF™,Berlex), timolol (2-Propanol,l-[(l,l-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-l,2,5-thiadiazol-3-yl]oxy]-, hemihydrate, (S)-, CAS RN 91524-16-2), timolol maleate (S)-I -[(1,1 -dimethylethyl) amino]-3-[[4- (4-morpholinyl)-l,2,5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1 :1) salt, CAS RN 26921-17-5), bisoprolol (2-Propanol, l-[4-[[2-(l-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(l-meth- ylethyl)amino]-, (±), CAS RN 66722-44-9), bisoprolol fumarate (such as (±)-l-[4-[[2-(l-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(l-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), e.g., Zebeta™ , Lederle Consumer), nebivalol (2H-l-Benzopyran-2-methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also U.S. Pat. No. 4,654,362), cicloprolol hydrochloride, such 2-Propanol, l-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[l-methylethyl)amino]-, hydrochloride, A.A.S. RN 63686-79-3), dexpropranolol hydrochloride (2-Propanol,l-[l-methylethy)-amino]-3-(l-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9), diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(l-methyl-ethyl)amino]propoxy] [phenyl]-, monohydrochloride CAS RN 69796-04-9), dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[l-hydroxy-2-[l-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride, CAS RN 75659-08-4), exaprolol hydrochloride (2-Propanol, 1 -(2-cyclohexylphenoxy)-3 - [(1 -methylethyl)amino] -, hydrochloride CAS RN 59333-90-3), flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]- - dimethylethyl]amino]-2-hydroxypropyl ester, (+)- sulfate (1 :1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[l-hydroxy-2-(methylamino)propyl]phenyl]-, monohydrochloride CAS RN 7701-65-7), metoprolol 2-Propanol, l-[4-(2- methoxyethyl)phenoxy]-3-[l-methylethyl)amino]-; CAS RN 37350-58-6), metoprolol tartrate (such as 2-Propanol, l-[4-(2-methoxyethyl)phenoxy]-3-[(l-methylethyl)amino]-, e.g., Lopressor®, Novartis), pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(l- methylethyl)amino]propoxyl]phenyl]-ethyl]-, methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7), penbutolol sulfate (2-Propanol, l-(2-cyclopentylphenoxy)-3-[l,l-dimethyle- thyl)amino] 1 , (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5), practolol (Acetamide, N-[4-[2- hydroxy-3-[(l-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, l-[(l-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4), tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl] amino] ethoxyl]-, CAS RN 38103-61-6), bopindolol, indenolol, pindolol, propanolol,

tertatolol, and tilisolol, and the like; calcium channel blockers such as besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-l ,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, e.g., Norvasc®, Pfizer), clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-cis)-, (Z)-2-butenedioate (1 :1), see also US4567195), isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-l,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)- 1 ,4-dihydro-2,6-dimethyl-3 ,5 -pyridinedicarboxylate, see also US4466972); nimodipine (such as is isopropyl (2- methoxyethyl) 1, 4- dihydro -2,6- dimethyl -4- (3-nitrophenyl) -3,5- pyridine - dicarboxylate, e.g. Nimotop®, Bayer), felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-l,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate- , e.g. Plendil® Extended-Release, AstraZeneca LP), nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-l,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(l-methylethyl) ester, also see US3799934), nifedipine (such as 3, 5 -pyridinedicarboxylic acid,l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, e.g., Procardia XL® Extended Release Tablets, Pfizer), diltiazem hydrochloride (such as l,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., e.g., Tiazac®, Forest), verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)-(1 -methylethyl) hydrochloride, e.g., Isoptin® SR, Knoll Labs), teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]4-[2-[(lE)-3-(l,l-dimethylethoxy)-3-oxo- l-propenyl]phenyl]-l,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4), belfosdil (Phosphonic acid, [2-(2-phenoxy ethyl)- 1,3 -propane- diyl]bis-, tetrabutyl ester CAS RN 103486-79-9), fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2), aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, efonidipine, gallopamil, lacidipine, lemildipine, lercanidipine, monatepil maleate (1-Piperazinebutanamide, N-(6, 11 -dihydrodibenzo(b,e)thiepin- 11 -yl)4-(4-fluorophenyl)-, (+)-, (Z)-2-butenedioate (1 :1) (±)-N-(6,l l-Dihydrodibenzo(b,e)thiep- in-l l-yl)-4-(p- fluorophenyl)-l-piperazinebutyramide maleate (1 :1) CAS RN 132046-06-1), nicardipine, nisoldipine, nitrendipine, manidipine, pranidipine, and the like; T-channel calcium antagonists such as mibefradil; angiotensin converting enzyme (ACE) inhibitors such as benazepril, benazepril hydrochloride (such as 3-[[l-(ethoxycarbonyl)-3- phenyl-(1 S)-propyl]amino]-2,3

,4,5-tetrahydro-2-oxo- 1 H - 1 -(3 S)-benzazepine- 1 -acetic acid monohydrochloride, e.g., Lotrel®, Novartis), captopril (such as l-[(2S)-3-mercapto-2- methylpropionyl]-L-proline, e.g., Captopril, Mylan, CAS RN 62571-86-2 and others disclosed in US4046889), ceranapril (and others disclosed in US4452790), cetapril (alacepril, Dainippon disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986)), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987), indalapril (delapril hydrochloride (2H-1,2,4- Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1- dioxide CAS RN 2259-96-3); disclosed in US4385051), enalapril (and others disclosed in US4374829), enalopril, enaloprilat, fosinopril, ((such as L-proline, 4-cyclohexyl-l-[[[2-methyl- l-(l-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl]acetyl]-, sodium salt, e.g., Monopril, Bristol-Myers Squibb and others disclosed in US4168267), fosinopril sodium (L- Proline, 4-cyclohexyl-l-[[(R)-[(lS)-2-methyl-l-(l-ox- opropoxy)propox), imidapril, indolapril (Schering, disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983)), lisinopril (Merck), losinopril, moexipril, moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(lS)- 1 -(ethoxycarbonyl)-3-phenylpropyl]amino]- 1 -oxopropyl]- 1 ,- 2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5), quinapril, quinaprilat, ramipril (Hoechsst) disclosed in EP 79022 and Curr. Ther. Res. 40:74 (1986), perindopril erbumine (such as 2S,3aS,7aS- 1 -[(S)-N-[(S)- 1 -Carboxybutyljalanyljhexahydro^-indolinecarboxylic acid, 1 -ethyl ester, compound with tert-butylamine (1 :1), e.g., Aceon®, Solvay), perindopril (Servier, disclosed in Eur. J. clin. Pharmacol. 31 :519 (1987)), quanipril (disclosed in US4344949), spirapril (Schering, disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5): 173 (1986)), tenocapril, trandolapril, zofenopril (and others disclosed in US4316906), rentiapril (fentiapril, disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983)), pivopril, YS980, teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7), BRL 36,378 (Smith Kline Beecham, see EP80822 and EP60668), MC-838 (Chugai, see CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986), CGS 14824 (Ciba-Geigy, 3-([l-ethoxycarbonyl-3-phenyl-(lS)-propyl]amino)-2,3,4,5-tetrahydro-2-ox- o-l-(3S)-benzazepine-l acetic acid HCl, see U.K. Patent No. 2103614), CGS 16,617 (Ciba- Geigy, 3(S)-[[(lS)-5-amino-l-carboxypentyl]amino]-2,3,4,- 5-tetrahydro-2-oxo-lH-l- benzazepine-1-ethanoic acid, see US4473575), Ru 44570 (Hoechst, see Arzneimittelforschung 34:1254 (1985)), R 31-2201 (Hoffman-LaRoche see FEBS Lett. 165:201 (1984)), CI925 (Pharmacologist 26:243, 266 (1984)), WY-44221 (Wyeth, see J. Med. Chem. 26:394 (1983)), and those disclosed in

US2003006922 (paragraph 28), US4337201, US4432971 (phosphonamidates); neutral endopeptidase inhibitors such as omapatrilat (Vanlev®), CGS 30440, cadoxatril and ecadotril, fasidotril (also known as aladotril or alatriopril), sampatrilat, mixanpril, and gemopatrilat, AVE7688, ER4030, and those disclosed in US5362727, US5366973, US5225401, US4722810, US5223516, US4749688, US5552397, US5504080, US5612359, US5525723, EP0599444, EP0481522, EP0599444, EP0595610, EP0534363, EP534396, EP534492, EP0629627; endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; vasodilators such as hydralazine (apresoline), clonidine (clonidine hydrochloride (1H-Imidazol- 2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-, monohydrochloride CAS RN 4205-91-8), catapres, minoxidil (loniten), nicotinyl alcohol (roniacol), diltiazem hydrochloride (such as 1,5- Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4- methoxyphenyl)-, monohydrochloride, (+)-cis, e.g., Tiazac®, Forest), isosorbide dinitrate (such as l,4:3,6-dianhydro-D-glucitol 2,5-dinitrate e.g., Isordil® Titradose®, Wyeth- Ayerst), sosorbide mononitrate (such as l,4:3,6-dianhydro-D-glucito- 1,5-nitrate, an organic nitrate, e.g., Ismo®, Wyeth-Ayerst), nitroglycerin (such as 2,3 propanetriol trinitrate, e.g., Nitrostat® Parke- Davis), verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3-[[2-(3,4 dimethoxypheny l)ethyl]methylamino]propyl] -3 ,4-dimethoxy-(alpha)- (1 -methylethyl) hydrochloride, e.g., Covera HS® Extended-Release, Searle), chromonar (which may be prepared as disclosed in US3282938), clonitate (Annalen 1870 155), droprenilamine (which may be prepared as disclosed in DE2521113), lidoflazine (which may be prepared as disclosed in US3267104); prenylamine (which may be prepared as disclosed in US3152173), propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113), mioflazine hydrochloride (1 -Piperazineacetamide, 3-(aminocarbonyl)4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6- dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3), mixidine (Benzeneethanamine, 3,4- dimethoxy-N-(l-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-[(3,4-dimethoxyphenethyl)imino]- 1 -methyl- l-Methyl-2- [(3, 4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), isosorbide mononitrate (D-Glucitol, l,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7), erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel-CAS RN 7297-25-8), clonitrate(l,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1), dipyridamole Ethanol, 2,2',2",2'"-[(4,8-di-l-piperidinylpyrimido[5,4-d]pyrimidine-2,6-

diyl)dinitrilo]tetrakis- CAS RN 58-32-2), nicorandil (CAS RN 65141-46-0 3-), pyridinecarboxamide (N-[2-(nitrooxy)ethyl]-Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9), nifedipine3,5-Pyridinedicarboxylic acid, l,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4), perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1 :1) CAS RN 6724-53-4), oxprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9), pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6), verapamil (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]- methylamino]propyl]-3, 4-dimethoxy-α-(l -methylethyl)- CAS RN 52-53-9) and the like; angiotensin II receptor antagonists such as, aprosartan, zolasartan, olmesartan, pratosartan, FI6828K, RNH6270, candesartan (1 H-Benzimidazole-7-carboxylic acid, 2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)[l,l'-biphenyl]4-yl]methyl]- CAS RN 139481-59-7), candesartan cilexetil ((+/-)-l-(cyclohexylcarbonyloxy)ethyl-2-ethoxy-l-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl]-lH-benzimidazole carboxylate, CAS RN 145040-37-5, US5703110 and US5196444), eprosartan (3-[l-4-carboxyphenylmethyl)-2-n-butyl-imidazol-5-yl]-(2-thienylmethyl) propenoic acid, US5185351 and US5650650), irbesartan (2-n-butyl-3- [[2'-(lh-tetrazol-5-yl)biphenyl-4-yl]methyl] 1 ,3-diazazspiro[4,4]non-l-en-4-one, US5270317 and US5352788), losartan (2-N-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole, potassium salt, US5138069, US5153197 and US5128355), tasosartan (5,8-dihydro-2,4-dimethyl-8-[(2'-(lH-tetrazol-5-yl)[l,r-biphenyl]4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(6H)-one, US5149699), telmisartan (4'-[(1 ,4-dimethyl-2'-propyl-(2,6'-bi-lH-benzimidazol)-r-yl)]-[1 , 1 '-biphenyl]-2-carboxylic acid, CAS RN 144701-48-4, US5591762), milfasartan, abitesartan, valsartan (Diovan® (Novartis), (S)-N-valeryl-N-[[2'-(lH-tetrazol-5-yl)biphenyl-4-yl)methyl]valine, US5399578), EXP-3137 (2-N-butyl-4-chloro-l-[(2'-(lH-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazole-5-carboxylic acid, US5138069, US5153197 and US5128355), 3-(2'-(tetrazol-5-yl)-l,r-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine, 4'[2-ethyl-4-methyl-6-(5,6,7,8-tetrahydroimidazo[l,2-a]pyridin-2-yl]-benzimidazol-l-yl]-methyl]-l,r-biphenyl]-2- carboxylic acid, 2-butyl-6-(l-methoxy-l-methylethyl)-2-[2'-)IH-tetrazol-5-yl)biphenyl-4-ylmethyl] guinazolin-4(3H)-one, 3 - [2 ' -carboxybiphenyl-4-yl)methyl] -2-cyclopropyl-7-methyl- 3H-imidazo[4,5-b]pyridine, 2-butyl-4-chloro-l-[(2'-tetrazol-5-

yl)biphenyl-4-yl)methyl]imidazole-carboxylic acid, 2-butyl-4-chloro-l-[[2'-(lH-tetrazol-5- yl) [1 , 1 ' -biphenyl] -4-yl]methyl]- 1 H-imidazole-5 -carboxylic acid- 1 -(ethoxycarbonyl-oxy)ethyl ester potassium salt, dipotassium 2-butyl-4-(methylthio)-l-[[2-[[[(propylamino)carbonyl]amino]-sulfonyl](l,l '-biphenyl)-4-yl]methyl]-l H-imidazole-5 -carboxylate, methyl-2-[[4-butyl-2-methyl-6-oxo-5-[[2'-(lH-tetrazol-5-yl)-[l,l '-biphenyl]-4-yl]methyl]-l-(6H)- pyrimidinyl]methyl]-3-thiophencarboxylate, 5-[(3,5-dibutyl-lH-l,2,4-triazol-l-yl)methyl]-2-[2- (1 H-tetrazol-5 -ylphenyl)]pyridine, 6-butyl-2-(2-phenylethyl)-5 [[2'-(I H-tetrazol-5 -yl)[1,1 '- biphenyl]-4-methyl]pyrimidin-4-(3H)-one D,L lysine salt, 5-methyl-7-n-propyl-8-[[2'-(lH- tetrazol-5-yl)biphenyl-4-yl]methyl]-[1 ,2,4]-triazolo[1 ,5-c]pyrimidin-2(3H)-one, 2,7-diethyl-5- [[2'-(5-tetrazoly)biphenyl-4-yl]methyl]-5H-pyrazolo[l,5-b][l,2,4]triazole potassium salt, 2-[2- butyl-4,5-dihydro-4-oxo-3-[2'-(lH-tetrazol-5-yl)-4-biphenylmethyl]-3H-imidazol[4,5- c]pyridine-5-ylmethyl]benzoic acid, ethyl ester, potassium salt, 3-methoxy-2,6-dimethyl-4- [[2'(lH-tetrazol-5-yl)-l,l '-biphenyl-4-yl]methoxy]pyridine, 2-ethoxy-l-[[2'-(5-oxo-2,5-dihydro- 1 ,2,4-oxadiazol-3 -yl)biphenyl-4-yl]methyl] - 1 H-benzimidazole-7-carboxylic acid, 1 - [N-(2 ' -(1 H- tetrazol-5-yl)biphenyl-4-yl-methyl)-N-valerolylaminomethyl)cyclopentane- 1 -carboxylic acid, 7- methyl-2n-propyl-3-[[2' lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-3H-imidazo[4,5-6]pyridine, 2- [5-[(2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridine-3-yl)methyl]-2-quinolinyl]sodium benzoate, 2-butyl-6-chloro-4-hydroxymethyl-5 -methyl-3 -[[2'-(I H-tetrazol-5 -yl)biphenyl-4-yl]methyl]pyridine, 2- [[[2-butyl- 1 - [(4-carboxyphenyl)methyl] - 1 H-imidazol-5 -yl]methyl]amino]benzoic acid tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-6-one, 4(S)- [4-(carboxymethyl)phenoxy]-N-[2(R)-[4-(2-sulfobenzamido)imidazol- 1 -yl]octanoyl]-L-proline, 1 - (2,6-dimethylphenyl)-4-butyl-l,3-dihydro-3-[[6-[2-(lH-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl]-2H-imidazol-2-one, 5 ,8-ethano-5 ,8-dimethyl-2-n-propyl-5 ,6,7,8-tetrahydro-1 - [[2'(lH-tetrazol-5-yl)biphenyl-4-yl]methyl]-lH,4H-l,3,4a,8a-tetrazacyclopentanaphthalene-9-one, 4-[l-[2'-(l,2,3,4-tetrazol-5-yl)biphen-4-yl)methylamino]-5,6,7,8-tetrahydro-2-trifylquinazoline, 2-(2-chlorobenzoyl)imino-5-ethyl-3-[2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl-l,3,4-thiadiazoline, 2-[5-ethyl-3-[2-(lH-tetrazole-5-yl)biphenyl-4-yl]methyl-l,3,4-thiazoline-2-ylidene]aminocarbonyl-l-cyclopentencarboxylic acid dipotassium salt, and 2-butyl-4-[N-methyl-N-(3 -methylcrotonoyl)amino] - 1 - [[2 ' -(1 H-tetrazol-5 -yl)biphenyl-4-yl]methyl]- 1 H- imidzole-5 -carboxylic acid 1-ethoxycarbonyloxyethyl ester, those disclosed in patent publications EP475206, EP497150, EP539086, EP539713, EP535463, EP535465,

EP542059, EP497121, EP535420, EP407342, EP415886, EP424317, EP435827, EP433983, EP475898, EP490820, EP528762, EP324377, EP323841, EP420237, EP500297, EP426021, EP480204, EP429257, EP430709, EP434249, EP446062, EP505954, EP524217, EP514197, EP514198, EP514193, EP514192, EP450566, EP468372, EP485929, EP503162, EP533058, EP467207 EP399731, EP399732, EP412848, EP453210, EP456442, EP470794, EP470795, EP495626, EP495627, EP499414, EP499416, EP499415, EP511791, EP516392, EP520723, EP520724, EP539066, EP438869, EP505893, EP530702, EP400835, EP400974, EP401030, EP407102, EP411766, EP409332, EP412594, EP419048, EP480659, EP481614, EP490587, EP467715, EP479479, EP502725, EP503838, EP505098, EP505111 EP513,979 EP507594, EP510812, EP511767, EP512675, EP512676, EP512870, EP517357, EP537937, EP534706, EP527534, EP540356, EP461040, EP540039, EP465368, EP498723, EP498722, EP498721, EP515265, EP503785, EP501892, EP519831, EP532410, EP498361, EP432737, EP504888, EP508393, EP508445, EP403159, EP403158, EP425211, EP427463, EP437103, EP481448, EP488532, EP501269, EP500409, EP540400, EP005528, EP028834, EP028833, EP411507, EP425921, EP430300, EP434038, EP442473, EP443568, EP445811, EP459136, EP483683, EP518033, EP520423, EP531876, EP531874, EP392317, EP468470, EP470543, EP502314, EP529253, EP543263, EP540209, EP449699, EP465323, EP521768, EP415594, WO92/14468, WO93/08171, WO93/08169, WO91/00277, WO91/00281, WO91/14367, WO92/00067, WO92/00977, WO92/20342, WO93/04045, WO93/04046, WO91/15206, WO92/14714, WO92/09600, WO92/16552, WO93/05025, WO93/03018, WO91/07404, WO92/02508, WO92/13853, WO91/19697, WO91/11909, WO91/12001, WO91/11999, WO91/15209, WO91/15479, WO92/20687, WO92/20662, WO92/20661, WO93/01177, WO91/14679, WO91/13063, WO92/13564, WO91/17148, WO91/18888, WO91/19715, WO92/02257, WO92/04335, WO92/05161, WO92/07852, WO92/15577, WO93/03033, WO91/16313, WO92/00068, WO92/02510, WO92/09278, WO9210179, WO92/10180, WO92/10186, WO92/10181, WO92/10097, WO92/10183, WO92/10182, WO92/10187, WO92/10184, WO92/10188, WO92/10180, WO92/10185, WO92/20651, WO93/03722, WO93/06828, WO93/03040, WO92/19211, WO92/22533, WO92/06081, WO92/05784, WO93/00341, WO92/04343, WO92/04059, US5104877, US5187168, US5149699, US5185340, US4880804, US5138069, US4916129, US5153197, US5173494, US5137906, US5155126, US5140037, US5137902, US5157026, US5053329, US5132216, US5057522, US5066586, US5089626,

US5049565, US5087702, US5124335, US5102880, US5128327, US5151435, US5202322, US5187159, US5198438, US5182288, US5036048, US5140036, US5087634, US5196537, US5153347, US5191086, US5190942, US5177097, US5212177, US5208234, US5208235, US5212195, US5130439, US5045540, US5041152, and US5210204, and pharmaceutically acceptable salts and esters thereof; α/β adrenergic blockers such as nipradilol, arotinolol, amosulalol, bretylium tosylate (CAS RN: 61-75-6), dihydroergtamine mesylate (such as ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(α))-, monomethanesulfonate, e.g., DHE 45® Injection, Novartis), carvedilol (such as (±)-l-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl] amino] -2-propanol, e.g., Coreg®, SmithKline Beecham), labetalol (such as 5-[l-hydroxy-2-[(l-methyl-3-phenylpropyl) amino] ethyljsalicylamide monohydrochloride, e.g., Normodyne®, Schering), bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1 :1) CAS RN 61-75-6), phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-lH-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1), solypertine tartrate (5H-l,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-l-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1 :1) CAS RN 5591-43-5), zolertine hydrochloride (Piperazine, l-phenyl4-[2-(lH-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3) and the like; α adrenergic receptor blockers, such as alfuzosin (CAS RN: 81403-68-1), terazosin, urapidil, prazosin (Minipress®), tamsulosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHP 164, XENOlO, fenspiride hydrochloride (which may be prepared as disclosed in US3399192), proroxan (CAS RN 33743-96-3), and labetalol hydrochloride and combinations thereof; α 2 agonists such as methyldopa, methyldopa HCL, lofexidine, tiamenidine, moxonidine, rilmenidine, guanobenz, and the like; aldosterone inhibitors, and the like; renin inhibitors including Aliskiren (SPPlOO; Novartis/Speedel); angiopoietin-2-binding agents such as those disclosed in WO03/030833; anti-angina agents such as ranolazine (hydrochloride 1-Piperazineacetamide, N-(2,6- dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635- 56-6), betaxolol hydrochloride (2-Propanol, l-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(l- methylethyl)amino]-, hydrochloride CAS RN 63659-19-8), butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3), cinepazet maleatel-Piperazineacetic acid, 4-[l-oxo-3-(3,4,5- trimethoxyphenyl)-2-

propenyl]-, ethyl ester, (2Z)-2-butenedioate (1 :1) CAS RN 50679-07-7), tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184), verapamilhydrochloride (Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3 ,4-dimethoxy-α-(1 -methylethyl)-, monohydrochloride CAS RN 152-114), molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0), and ranolazine hydrochloride (1 -Piperazineacetamide, N-(2,6-dimethylphenyl)4-[2-hydroxy-3-(2-meth-oxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(lS)-l-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-184); adrenergic stimulants such as guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, e.g., Tenex® Tablets available from Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2H -l,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide, e.g., the combination as, e.g., Aldoril® Tablets available from Merck), methyldopa-chlorothiazide (such as 6-chloro-2H-l, 2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and methyldopa as described above, e.g., Aldoclor®, Merck), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(l-hydroxy-3-oxo-l-isoindolinyl) benzenesulfonamide), e.g., Combipres®, Boehringer Ingelheim), clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride, e.g., Catapres®, Boehringer Ingelheim), clonidine (lH-Imidazol-2-amine, N-(2,6-dichlorophenyl)4,5-dihydro-CAS RN 4205-90-7), Hyzaar (Merck; a combination of losartan and hydrochlorothiazide), Co-Diovan (Novartis; a combination of valsartan and hydrochlorothiazide, Lotrel (Novartis; a combination of benazepril and amlodipine) and Caduet (Pfizer; a combination of amlodipine and atorvastatin), and those agents disclosed in US20030069221.

1.3.2.11 Agents for the Treatment of Respiratory Disorders

[173] The GCC agonist peptides described herein can be used in combination therapy with one or more of the following agents useful in the treatment of respiratory and other disorders including but not limited to: (1) β-agonists including but not limited to : albuterol (PRO VENTIL® , S ALBUT AMOl® , VENTOLIN®), bambuterol, bitoterol, clenbuterol, fenoterol,

formoterol, isoetharine (BRONKOSOL®, BRONKOMETER®), metaproterenol (ALUPENT®, METAPREL®), pirbuterol (MAXAIR®), reproterol, rimiterol, salmeterol, terbutaline (BRETHAIRE®, BRETHINE®, BRICANYL®), adrenalin, isoproterenol (ISUPREL®), epinephrine bitartrate (PRIMATENE®), ephedrine, orciprenline, fenoterol and isoetharine; (2) steroids, including but not limited to beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methyl prednisone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetonide; (3) β2-agonist-corticosteroid combinations [e.g., salmeterol-fluticasone (AD V AIR®), formoterol-budesonid (S YMBICORT®)] ; (4) leukotriene D4 receptor antagonists/leukotriene antagonists/LTD4 antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafhiukast, montelukast, montelukast sodium (SINGULAIR®), pranlukast, iralukast, pobilukast, SKB-106,203 and compounds described as having LTD4 antagonizing activity described in U.S. Patent No. 5,565,473; (5) 5 -lipoxygenase inhibitors and/or leukotriene biosynthesis inhibitors [e.g., zileuton and BAY1005 (CA registry 128253-31-6)]; (6) histamine Hl receptor antagonists/antihistamines (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: astemizole, acrivastine, antazoline, azatadine, azelastine, astamizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chloropheniramine maleate, cimetidine clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylarnine, ebastine, efletirizine, epinastine, famotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norasternizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; (7) an anticholinergic including but not limited to: atropine, benztropine, biperiden, flutropium, hyoscyamine (e.g. Levsin®; Levbid®; Levsin/SL®, Anaspaz®, Levsinex timecaps®, NuLev®), ilutropium, ipratropium, ipratropium bromide, methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium; (8) an anti-tussive

including but not limited to: dextromethorphan, codeine, and hydromorphone; (9) a decongestant including but not limited to: pseudoephedrine and phenylpropanolamine; (10) an expectorant including but not limited to: guafenesin, guaicolsulfate, terpin, ammonium chloride, glycerol guaicolate, and iodinated glycerol; (11) a bronchodilator including but not limited to: theophylline and aminophylline; (12) an anti-inflammatory including but not limited to: fluribiprofen, diclophenac, indomethacin, ketoprofen, S-ketroprophen, tenoxicam; (13) a PDE (phosphodiesterase) inhibitor including but not limited to those disclosed herein; (14) a recombinant humanized monoclonal antibody [e.g. xolair (also called omalizumab), rhuMab, and talizumab]; (15) a humanized lung surfactant including recombinant forms of surfactant proteins SP-B, SP-C or SP-D [e.g. SURFAXIN®, formerly known as dsc-104 (Discovery Laboratories)], (16) agents that inhibit epithelial sodium channels (ENaC) such as amiloride and related compounds; (17) antimicrobial agents used to treat pulmonary infections such as acyclovir, amikacin, amoxicillin, doxycycline, trimethoprin sulfamethoxazole, amphotericin B, azithromycin, clarithromycin, roxithromycin, clarithromycin, cephalosporins(ceffoxitin, cefmetazole etc), ciprofloxacin, ethambutol, gentimycin, ganciclovir, imipenem, isoniazid, itraconazole, penicillin, ribavirin, rifampin, rifabutin,amantadine, rimantidine, streptomycin, tobramycin, and vancomycin; (18) agents that activate chloride secretion through Ca++ dependent chloride channels (such as purinergic receptor (P2Y(2) agonists); (19) agents that decrease sputum viscosity, such as human recombinant DNase 1, (Pulmozyme®); (20) nonsteroidal anti-inflammatory agents (acemetacin, acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid , oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxican, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin,

zomepirac, and zomepirac); and (21) aerosolized antioxidant therapeutics such as S-Nitrosoglutathione.

1.3.2.12 Anti-Diabetic Agents

[174] The GCC agonist peptides described herein can be used in therapeutic combination with one or more anti-diabetic agents, including but not limited to: PPARγ agonists such as glitazones (e.g., WAY-120,744, AD 5075, balaglitazone, ciglitazone, darglitazone (CP-86325, Pfizer), englitazone (CP-68722, Pfizer), isaglitazone (MIT/J&J), MCC- 555 (Mitsibishi disclosed in US5594016), pioglitazone (such as such as Actos™ pioglitazone; Takeda), rosiglitazone (Avandia™;Smith Kline Beecham), rosiglitazone maleate, troglitazone (Rezulin®, disclosed in US4572912), rivoglitazone (CS-Ol 1, Sankyo), GL-262570 (Glaxo Welcome), BRL49653 (disclosed in WO98/05331), CLX-0921, 5-BTZD, GW-0207, LG- 100641, JJT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/Pfizer), NN-2344 (Dr. Reddy/NN), YM-440 (Yamanouchi), LY-300512, LY-519818, R483 (Roche), T131 (Tularik), and the like and compounds disclosed in US4687777, US5002953, US5741803, US5965584, US6150383, US6150384, US6166042, US6166043, US6172090, US6211205, US6271243, US6288095, US6303640, US6329404, US5994554, W097/10813, WO97/27857, WO97/28115, WO97/28137,WO97/27847, WO00/76488, WO03/000685,WO03/027112,WO03/035602, WO03/048130, WO03/055867, and pharmaceutically acceptable salts thereof; biguanides such as metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride, such as Glucophage™, Bristol-Myers Squibb); metformin hydrochloride with glyburide, such as Glucovance™, Bristol-Myers Squibb); buformin (Imidodicarbonimidic diamide, N-butyl-); etoformine (l-Butyl-2-ethylbiguanide, Schering A. G.); other metformin salt forms (including where the salt is chosen from the group of, acetate, benzoate, citrate, ftimarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutarnate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate), and phenformin; protein tyrosine phosphatase- IB

(PTP-IB) inhibitors, such as A-401,674, KR 61639, OC- 060062, OC-83839, OC-297962, MC52445, MC52453, ISIS 113715, and those disclosed in WO99/585521, WO99/58518, WO99/58522, WO99/61435, WO03/032916, WO03/032982, WO03/041729, WO03/055883, WO02/26707, WO02/26743, JP2002114768, and pharmaceutically acceptable salts and esters thereof; sulfonylureas such as acetohexamide (e.g. Dymelor, Eli Lilly), carbutamide, chlorpropamide (e.g. Diabinese®, Pfizer), gliamilide (Pfizer), gliclazide (e.g. Diamcron, Servier Canada Inc), glimepiride (e.g. disclosed in US4379785, such as Amaryl , Aventis), glipentide, glipizide (e.g. Glucotrol or Glucotrol XL Extended Release, Pfizer), gliquidone, glisolamide, glyburide/glibenclamide (e.g. Micronase or Glynase Prestab, Pharmacia & Upjohn and Diabeta, Aventis), tolazamide (e.g. Tolinase), and tolbutamide (e.g. Orinase), and pharmaceutically acceptable salts and esters thereof; meglitinides such as repaglinide (e.g. Pranidin®, Novo Nordisk), KAD1229 (PF/Kissei), and nateglinide (e.g. Starlix®, Novartis), and pharmaceutically acceptable salts and esters thereof; α glucoside hydrolase inhibitors (or glucoside inhibitors) such as acarbose (e.g. Precose™, Bayer disclosed in US4904769), miglitol (such as GLYSET™, Pharmacia & Upjohn disclosed in US4639436), camiglibose (Methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2- (hydroxymethyl)piperidino]-alpha-D-glucopyranoside, Marion Merrell Dow), voglibose (Takeda), adiposine, emiglitate, pradimicin-Q, salbostatin, CKD-711, MDL-25,637, MDL- 73,945, and MOR 14, and the compounds disclosed in US4062950, US4174439, US4254256, US4701559, US4639436, US5192772, US4634765, US5157116, US5504078, US5091418, US5217877, US51091 and WOO 1/47528 (polyamines); α-amylase inhibitors such as tendamistat, trestatin, and Al -3688, and the compounds disclosed in US4451455, US4623714, and US4273765; SGLT2 inhibtors including those disclosed in US6414126 and US6515117; an aP2 inhibitor such as disclosed in US6548529; insulin secreatagogues such as linogliride, A-4166, forskilin, dibutyrl cAMP, isobutylmethylxanthine (IBMX), and pharmaceutically acceptable salts and esters thereof; fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and pharmaceutically acceptable salts and esters thereof; A2 antagonists, such as midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan, and pharmaceutically acceptable salts and esters thereof; insulin and related compounds (e.g. insulin mimetics) such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-I (1-36) amide, GLP-I (73-7) (insulintropin, disclosed in US5614492), LY-315902 (Lilly), GLP-I (7-36)-NH2), AL-401

(Autoimmune), certain compositions as disclosed in US4579730, US4849405, US4963526, US5642868, US5763396, US5824638, US5843866, US6153632, US6191105, and WO 85/05029, and primate, rodent, or rabbit insulin including biologically active variants thereof including allelic variants, more preferably human insulin available in recombinant form (sources of human insulin include pharmaceutically acceptable and sterile formulations such as those available from Eli Lilly (Indianapolis, Ind. 46285) as Humulin™ (human insulin rDNA origin), also see the THE PHYSICIAN'S DESK REFERENCE, 55.sup.th Ed. (2001) Medical Economics, Thomson Healthcare (disclosing other suitable human insulins); non-thiazolidinediones such as JT-501 and farglitazar (GW-2570/GI- 262579), and pharmaceutically acceptable salts and esters thereof; PPARα/γ dual agonists such as AR-HO39242 (Aztrazeneca), GW-409544 (Glaxo-Wellcome), BVT-142, CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297 (Kyorin Merck; 5-[(2,4-Dioxo thiazolidinyl)methyl] methoxy-N-[[4-(trifluoromethyl)phenyl] methyljbenzamide), L-796449, LR-90, MK-0767 (Merck/Kyorin/Banyu), SB 219994, muraglitazar (BMS), tesaglitzar (Astrazeneca), reglitazar (JTT-501) and those disclosed in WO99/16758, WO99/19313, WO99/20614, WO99/38850, WO00/23415, WO00/23417, WO00/23445, WO00/50414, WO01/00579, WO01/79150, WO02/062799, WO03/004458, WO03/016265, WO03/018010, WO03/033481, WO03/033450, WO03/033453, WO03/043985, WO 031053976, U.S. application Ser. No. 09/664,598, filed Sep. 18, 2000, Murakami et al. Diabetes 47, 1841-1847 (1998), and pharmaceutically acceptable salts and esters thereof; other insulin sensitizing drugs; VPAC2 receptor agonists; GLK modulators, such as those disclosed in WO03/015774; retinoid modulators such as those disclosed in WO03/000249; GSK 3β/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-lH-imidazol-5- yl]pyridine and those compounds disclosed in WO03/024447, WO03/037869, WO03/037877, WO03/037891, WO03/068773, EP1295884, EP1295885, and the like; glycogen phosphorylase (HGLPa) inhibitors such as CP-368,296, CP-316,819, BAYR3401, and compounds disclosed in WOO 1/94300, WO02/20530, WO03/037864, and pharmaceutically acceptable salts or esters thereof; ATP consumption promotors such as those disclosed in WO03/007990; TRB3 inhibitors; vanilloid receptor ligands such as those disclosed in WO03/049702; hypoglycemic agents such as those disclosed in WO03/015781 and WO03/040114; glycogen synthase kinase 3 inhibitors such as those disclosed in WO03/035663 agents such as those disclosed in WO99/51225, US20030134890, WO01/24786, and

WO03/059870; insulin-responsive DNA binding protein-1 (IRDBP-I) as disclosed in WO03/057827, and the like; adenosine A2 antagonists such as those disclosed in WO03/035639, WO03/035640, and the like; PPARδ agonists such as GW 501516, GW 590735, and compounds disclosed in JP10237049 and WO02/14291; dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, NVP-DPP728A (1- [[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999), P32/98, NVP-LAF-237, P3298, TSL225 (tryptophyl-l,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), valine pyrrolidide, TMC-2A/2B/2C, CD- 26 inhibitors, FE999011, P9310/K364, VIP 0177, DPP4, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) ,and the compounds disclosed in US6395767, US6573287, US6395767 (compounds disclosed include BMS-477118, BMS-471211 and BMS 538,305), WO99/38501, WO99/46272, WO99/67279, WO99/67278, WO99/61431WO03/004498, WO03/004496, EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; GLP-I agonists such as exendin-3 and exendin-4 (including the 39 aa polypeptide synthetic exendin-4 called Exenatide®), and compounds disclosed in US2003087821 and NZ 504256, and pharmaceutically acceptable salts and esters thereof; peptides including amlintide and Symlin® (pramlintide acetate); and glycokinase activators such as those disclosed in US2002103199 (fused heteroaromatic compounds) and WO02/48106 (isoindolin-1-one-substituted propionamide compounds).

EXAMPLES

Example 1: Clinical Study for safety and efficacy in humans for the treatment of chronic idiopathic constipation

[175] A randomized, double-blind, placebo-controlled, 14-day repeat oral, dose ranging study was conducted in patients with chronic idiopathic constipation (CIC). The primary objective of this study was to evaluate the safety of SP-304 (1.0 mg, 3.0 mg, 9.0 mg and 0.3 mg) for 14 days in patients with CIC. One secondary objective was to assess the pharmacokinetic profile of

SP-304 in plasma. Other secondary objectives included evaluations of pharmacodynamic effects (efficacy) on parameters such as the time to first bowel movement after daily dosing with SP-304, bowel habits over time – for example, spontaneous bowel movements (SBMs), complete spontaneous bowel movements (CSBMs), and stool consistency [using Bristol Stool Form Scale (BSFS)] – and other patient reported outcomes such as abdominal discomfort.

[176] The study included five arms with assigned interventions as indicated in the table below.

Arms	Interventions
SP-304 1.0 mg: Experimental	Subjects receiving SP-304 1.0 mg for 14 consecutive days
SP-304 3.0 mg: Experimental	Subjects receiving SP-304 3.0 mg for 14 consecutive days
SP-304 9.0 mg: Experimental	Subjects receiving SP-304 9.0 mg for 14 consecutive days
Placebo: Placebo Comparator	Subjects receiving Placebo for 14 consecutive days
SP-304 0.3 mg: Experimental	Subjects receiving SP-304 0.3 mg for 14 consecutive days

[177] Subjects diagnosed with CIC were screened for the anticipated 4 cohorts to yield 80 randomized subjects for enrollment. There were four dose cohorts (1.0 mg, 3.0mg, 9.0 mg and 0.3 mg) with 20 subjects per dose cohort [randomization ratio 3:1 (15 receive SP-304:5 receive placebo)]. Subjects who continued to meet all the entry criteria and complete the pre-treatment bowel movement (BM) diary received, in a double-blind, randomized fashion, SP-304 or matching placebo. The entry criteria included (1) meeting modified ROME III criteria for chronic constipation (CC); (2) no significant finding in colonoscopy within past 5 years; (3) good health as determined by physical examination, medical history, vital signs, ECG, clinical chemistry, hematology, urinalysis, drug screen and serology assessments; and (4) during 14-day pre-treatment period, subjects reporting < 6 SBM and < 3 CSBM in each pre-treatment week. All subjects receiving at least one dose of SP-304 or matching placebo were considered evaluable for the safety endpoints (78 total). If a subject did not have a major protocol deviation, had at least 5 days of study treatment each week and corresponding entries for bowel habits, he/she was considered evaluable for efficacy parameters (54-55 total).

[178] The demographics of the subjects in the study are summarized in the table below.

	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
			Age		
	47.7 (14.6)	51.1 (12.0)	50.5 (10.6)	48.5 (16.1)	47.3 (12.7)
			Gender		
Female	18 (90.0%)	12 (85.7%)	14 (100%)	13 (86.7)	12 (80%)
Male	2 (10.0%)	2 (14.3%)	0	2 (13.3%)	3 (20%)
			Race		
White	17 (85.0%)	13 (92.9%)	12 (85.7%)	14 (93.3%)	12 (80.0%)
African American	1 (5.0%)	0	1 (7.1%)	0	2 (13.3%)
Asian	1 (5.0%)	1 (7.1%)	1 (7.1%)	0	1 (6.7%)
American Indian	1 (5.0%)	0	0	0	0
Other	0	0	0	1 (6.7%)	0

Values for age are the mean (standard deviation); values for gender and race are the number (percentage of experimental arm).

Results

[179] Pharmacokinetics and Safety:

[180] There was no detectable systemic absorption of plecanatide (assay sensitivity $\geq$ 10 ng/mL). No serious adverse events (SAE) were reported in subjects receiving plecanatide and no deaths reported in this study. 10% (2/20) subjects who received placebo and 17.2% (10/58) subjects who received SP-304 reported adverse events considered as related to the treatment. The majority of adverse events were mild / moderate and transient in nature. 10% (2/20) subjects who received placebo and 5.2% (3/58) subjects who received SP-304 reported GI-related adverse events considered as related to treatment. There was no diarrhea reported for any subject receiving SP-304. The table below is a GI-related adverse event (AE) summary.

	Placebo n=20	0.3 mg n=14	1.0 mg n=14	3.0 mg n=15	9.0 mg n=15
Abdominal Cramping	1 (5.0%)	0	0	0	0
Abdominal Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)		0	0
Upset Stomach	0	0	0	1 (6.7%)	0

Values are the number (percentage of experimental arm).

[181] Efficacy:

[182] SP-304 (plecanatide) treatment decreased the time to first bowel movement, increased stool frequency (SBM and CSBM), improved stool consistency, and reduced straining and abdominal discomfort. See Figures 1-6.

Example 2: Composition of Wet Granulation batch 10005

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.23
2	Mannogem EZ, USP/EP (Mannitol)	Diluent	79.77
3	PROSOLV SMCC 90 LM (silicified microcrystalline cellulose)	Binder	15.0
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a
6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0

7	Pruv (sodium stearyl fumarate)	Lubricant	1.0
	Total		100

Example 3: Composition of Wet Granulation batch 10007

Item No.	Ingredient	Use	Concentration % w/w
1	SP304		0.3
3	PROSOLV SMCC 90 HD (silicified microcrystalline cellulose)	Binder	95.7
4	Purified Water (chilled to 5°C), USP	vehicle	n/a
5	Purified Water (chilled to 5°C), USP		n/a
6	Explotab (Sodium Starch Glycolate)	Disintregant	4.0
	Total		100

Example 4: EXCIPIENT COMPATIBILITY

[183] Binary mixtures of SP-304 were prepared and stored in glass vials. For solid excipients the binary mixtures were comprised of 9.1% or 50% excipient. Glass vials were stored at 40C/75RH open or closed. The percent purity (measured by HPLC) of the GCC agonist peptide (SP-304) after storage for the time indicated in each column (i.e., 1, 2, or 3 months for the closed vial and 0.5, 1, 2, or 3 months for the open vials) is indicated by numerical values.

		Closed			Open			
PURPOSE	EXCIPIENT	1M	2M	3M	0.5M	1M	2M	3M
None	None	91.4	88.2	84.1	93.7	91.2	88.2	84.8
Diluent	Sorbitol	92.4	90.1	87.2	92.2	90.8	87.1	80.9
	Mannitol	91.9	88.4	85.1	92.6	90.5	87.9	83.8
	Prosolv	92.2	89.6	86.3	93	90.5	87.8	83.7
	Starch	91.4	88.7	85.4	92.5	90.5	87.9	83.7
Binder	Emdex	91.3	88.7	85.2	91.8	90.7	87.9	81.9

	Plasdone	92.8	90.6	85.6	93.1	90.4	87.3	83
Disintegrant	Explotab	91.9	89.4	87.1	92.2	90.3	84.7	78.3
	Polyplasdone	92	89	85.6	93.5	90.3	87.4	83.1
Glidant	Cabosil	92.1	88.3	85.6	92.6	90.5	87.3	84
Lubricant	Mg stearte	91.5	87.7	84.6	92.6	90.6	87.6	83.8
	PRUV	92	88.3	85.7	92.2	90.5	87.5	83.8
	compritol	90.8	87.1	84.4	92	90.5	86.7	84.1
Excipient	PEG 3350	90.9	87	83.3	91.5	89.4	84.4	77.5
Antioxidant	Ascorbic acid	91.3	86.9	83	92.8	90	85.7	83.8
	BHA	91.9	88.9	85.9	93.5	90.8	87.4	85.8
	BHT	90.8	87.2	84.6	92.4	90.3	86.6	83.6
	EDTA	90.9	87.5	84.1	92.3	90.4	86.7	84.6
Capsule	HPMC capsule	92.2	89	85.2	92.3	90.2	86.4	83.5
	Gelatin capsule	91.5	88.3	84.3	84.3	90.5	86.7	83.6
Liquid for liquid filled capsule	Medium chain trig		90.4					
	PG dicaprylocaprate		89.3					
	Vit E		90					
	Soybean oil		89.6					
	Cremaphor		79.7					
	PG		3.4					
	PG 400		0.7					

Example 5: Geometric dry mix for 0.3mg capsule

[184] Place 12g mannitol in mortar. Add 4g SP-304 and gently mix until a visually uniform powder is obtained. Transfer to Turbula mixer. Rinse mortar with mannitol and transfer to Turbula mixer and mix at high speed for 10 minutes. Add about 150g of mannitol to 4 quart V-shell mixer. Transfer the contents of the Turbula mixer to the V-shell and add 150g of mannitol mix. Discharge v-shell contents and screen through 40 mesh and return to mixer. Add 586g of mannitol to mixer and mix for 20 minutes.

Example 6: Wet granulation process:

[185] Batch 017-10005 comprised of mannitol and low-moisture (2.4%) PROSOLV LM90 (0.33 g/mL) was sprayed with SP-304 solution and fluid bed dried resulted in granulation water content of 0.35%. The final blend contained 1% water, flowed well, and filled capsules well. The 2nd prototype 017-1006 comprised of the same components was adjusted to obtain a target capsule fill weight of 100 mg based on the results of the 1st batch. Water was sprayed onto powder blend with SP-304. The inlet temperature was 50C and the granulation was dried for 1.5 hours and stopped when the product temperature reached 36C. The 3rd (batch017-10006) and 4th (batch 017-10007) capsule prototypes will use PROSOLV HD90, which is a higher density material with superior flow properties and higher moisture content of 5.5% than the PROSOLV LM90. The moisture content of the PROSOLV HD90 is readily removed by fluid bed drying. The density of PROSOLV HD90 is about 0.55 g/mL. The PRUV lubricant will be removed for these batches.

Example 7: Wet granulation stability

[186] SP-304 was extracted from the capsules by sonication at either at room temperature (RT) or cold temperature and the amount of peptide was determined by HPLC. Initial percentages are based on the amount stated on the label.

Batch	% peptide (initial)	% peptide (1 mos at RT)
017-10006	101.1 (sonicated RT)	97.6 (sonicated cold)
017-10008	97.5 (sonicated RT)	108.2 (sonciated cold)

Example 8: 1M capsule stability in HDPE Bottles

[187] Capsules contained 0.3 mg SP-304 with the remainder of the fill weight (up to 5 mg) made up by mannitol (Perlitol 300 DC). Each capsule contained 1.5% by weight SP-304 and 98.5% mannitol. The capsule shell was composed of HPMC. Amounts are relative to the amount specified on the label (i.e., 0.30 mg peptide). The indicated number of capsules was placed in a high density polyethylene bottle with an induction seal and molecular sieve desiccant for 1 month at either 2-8C (first two columns) or 25C and 60% relative humidity (last two columns). The initial amount of peptide present was 101% of the label claim. The last row gives

the amount of peptide remaining after 1 month storage at the indicated temperature as determined by HPLC.

2-8C	2-8C	25C/60RH	25C/60RH
1-capsule per bottle	6-capsules per bottle	1-capsule per bottle	6-capsules per bottle
100%	92%	92%	98%

Example 9: Composition of batch 1528-2855-RD (capsules) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3246
2	Microcrystalline cellulose (Celphere SCP-100)	99.10	99.10
3	Calcium chloride dihydrate	0.2622	0.2622
4	Leucine USP	0.1171	0.1171
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2000
6	Purified Water, USP	7.2 mL*	n/a
	Total	100	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[188] The spray drying process of making the batch 2855-RD is described below.

Preparation of Coating Dispersion:

[189] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well

dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[190] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Celphere SCP-100 beads. After loading the Wurster column with Celphere SCP-100 beads, bed temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Celphere SCP-100 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) 2.399%.

Example 10: Composition of batch 1528-2851-RD (tablets) and spray coating and drying process

Item No.	Ingredient	Amount per unit (mg)	Concentration % w/w
1	SP-304	0.3246	0.3607
2	Microcrystalline	88.88	98.75

	cellulose (Avicel PH 102)		
3	Calcium chloride dihydrate	0.2622	0.2913
4	Leucine USP	0.1171	0.1301
5	Hypromellose (Methocel E5 PremLV)	0.2000	0.2222
6	Magnesium stearate	0.225	0.2500
7	Purified Water, USP	7.2 mL*	n/a
	Total	90.0	100

*: The amount of water is calculated based on use of 119.0 mL purified water for the whole batch containing 5.356 g SP-304.

[191] The spray coating and drying process of making the batch 2851-RD is described below.

Preparation of Coating Dispersion:

[192] Purified water was added to a glass container and stirred such that a liquid vortex was produced without introducing air. Then calcium chloride dihydrate was slowly added into the water. The mixture was stirred until the salt was dissolved or well dispersed. Next, leucine was slowly added and the resulting mixture was stirred until the amino acid was dissolved or well dispersed. Afterward, methocel was slowly added and the mixture was stirred until methocel was completely dissolved. The solution could be warmed up to dissolve methocel, if necessary. The resulting excipient solution was allowed to cool to room temperature and pass through 80 mesh screen. Then, 127.9g of screened excipient solution was added to a glass container and placed in an ice bath for 0.5 to 1 hour until the solution reached 0 °C. Next, SP-304 was added into the cold excipient solution. The mixture was stir vigorously to allow the peptide to dissolve in the cold solution. The resulting peptide solution was kept cold in the ice bath as a spraying/coating solution.

Drug Layering

[193] A Glatt GPCG-2 fluid bed processor (with top spray tower) with a Wurster insert was set up for drug layering onto Avicel PH 102 beads. After loading the Wurster column with Avicel

PH 102 beads, temperature was raised to 35 °C and maintained for 30 minutes with minimum fluidization of the beads. The bed temperature was reduced until an exhaust temperature of 35 °C was achieved. The pump tubing of the peristaltic pump used was primed by circulating the spraying solution mentioned above. After the spraying apparatus was adjusted to obtain a satisfactory spray pattern, the coating solution was sprayed onto Avicel PH 102 beads until all coating solution was sprayed. Operating parameters were recorded. The bed temperature and fluidization were maintained until the beads were sufficiently dry. The fluidization was then reduced while the bed temperature was maintained at 35 °C for 10 minutes. 2g of beads were sampled for moisture analysis when the bed temperature was kept at 35 °C. When the moisture of the sampled beads reached < 5% moisture, the coated beads were discharged and loaded into a dry container. LOD (loss on drying) <5%.

[194] The net weight of the coated blend was determined for calculation of the amount of magnesium stearate needed to lubricate the blend. Then the magnesium stearate was added to the coated blend and the mixture was blended for 1 minute.

Compression

[195] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and hardness to be 4-6 Kp. The weight, hardness and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 11: Composition of batch 1528-2850-RD (capsules) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH 102)	99.43
3	Magnesium stearate	0.2500
4	HPMC capsule shells	n/a

	Total	100

[196] The dry blend process of making the batch 2850-RD is described below.

Blending:

[197] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to the 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Encapsulation

[198] A MG2 Planeta capsule filler was set up. Average weight of the empty capsule shells was determined and target capsule fill weight was calculated (±5%). The blend from the above process was added into the hopper of the capsule filler and encapsulation was started. Run weight parameters were manually adjusted. Resulting capsules were then sorted according to the target fill weight.

Example 12: Composition of batch 1528-2850B-RD (tablets) and process

Item No.	Ingredient	Concentration % w/w
1	SP-304	0.3246
2	Microcrystalline cellulose (Avicel PH 102)	99.43
3	Magnesium stearate	0.2500
	Total	100

[199] The dry blend process of making the batch 2850B-RD is described below.

Blending:

[200] Avicel PH 102 was screened through a 60 mesh screen. V-blenders (1 Qt, 4Qt, and 16 Qt) were then dusted by the screened Avicel PH 102. SP-304 was screened through a 200 mesh screen and loaded into the 1-Qt V-blender. Then, about 80 g Avicel PH 102 was added into the 1-Qt blender and the mixture was blended for 10 minutes at 25 rpm. The mixture was then transferred to the 4-Qt V-blender which was pre-dusted by the screened Avicel PH 102. The 1-Qt blender was rinsed with Avicel and the rinse material was transferred to the 4-Qt blender. The rinsing was repeated until all SP-304 was transferred to the 4-Qt blender. About 200g Avicel was added to 4-Qt V-blender and the mixture was blended for 10 minutes. The resulting blend was then screened through a 60 mesh screen and then transferred into the pre-dusted 16-Qt blender (dusted with 1500g Avicel). The 4-Qt blender was rinsed with Avicel and the rinse material was transferred to the 16-Qt blender. The remaining Avicel was added to the 16-Qt blender and the mixture was blended for 10 minutes. The resulting blend was passed through Comil and then returned to the 16-Qt blender and was further blended for 5 minutes. Proper amount of magnesium stearate was weighed, screened through a 60 mesh screen, and added into the 16-Qt blender. The resulting mixture was blended for 2 minutes.

Compression

[201] A Fette tablet press was set up. Then the blend mixture was loaded into the powder hopper and tooling was installed. The weight of each tablet was set to be 90 mg±5% and

hardness to be 4-6 Kp. The weight, hardness, and thickness of tablets were measured and recorded every 5 to 10 minutes. Friability measurement was also performed to ensure satisfactory product.

Example 13: Composition of dry blend tablet formulation 1528-3161-RD, 1mg for vacuum drying

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 102)	98.57
3	Magnesium stearate	0.2500
	Total	100

Example 14: Composition of dry blend tablet formulation 1528-3162-RD, 1mg with low-moisture cellulose

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Microcrystalline cellulose (Avicel PH 112)	97.09
3	Magnesium stearate	0.2500
	Total	100

Example 15: Composition of spray coated trehalose granules tablet formulation 1528-3170-RD, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.176
2	Trehalose granules	70.48
3	Methocel ES Premium LV	0.50
4	Histidine (in coating solution)	0.9225
5	Calcium ascorbate	0.100
6	Purified water	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Histidine	0.5535
10	Magnesium stearate	0.2500
	Total	100

The process for making spray coated trehalose Granules tablet formulation 1528-3170-RD is described below.

Preparation of the Coating Dispersion

[202] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50 °C). Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Adjust pH to 7.0 with 1N NaOH solution if pH >7.0. Record adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.107 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Add Histidine to solution. Stir not more than 10min to dissolve the material. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution. Coating Solution must be used within 30min to avoid coloration.

Drug Layering

[203] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column. Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20 psi. Air flow: 60cmh and adjust for fluidization. Prepare double polyethylene bags large enough to hold drug layered Granules. Load column with Trehalose. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing by circulating spraying solution; must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Coating Solution Weight after priming

should > 317g. Record initial weight below before spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 297.2 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray (Save bags). Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Record final Moisture (<1%). Calculate net weight of dried Granules.

Blending

[204] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender per SOP EQP-OCM-00056. Weigh amount of Histidine needed and blend with small amount of Avicel weighed. Charge into 4 qt. V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Rinse 2-3 times the Lyoguard tray from Step 24 with adequate amount of Weighed Avicel .Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 15 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes.

Compression

[205] Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP. Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range and record on form QRA-DOC-00011-F6. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic

weight check. Continue to compress acceptable tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 16: Composition of spray coated trehalose granules tablet formulation 1528-3171-RD, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.31
3	Methocel ES Premium LV	0.50
4	Arginine	1.657
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[206] The process for making spray coated trehalose Granules tablet formulation 1528-3171-RD is described below.

Preparation of Coating Solution

Add purified water (Item 6) to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50 °C). Record appearance of solution. Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add Arginine to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Adjust solution pH to pH 8.5 - 8.6 with concentrated HCl followed by adjust pH to 8.3 – 8.4 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~360.3 g). Coating Solution must be used within as soon as possible.

Drug Layering

[207] Setup Glatt GPCG2 with Wurster insert according to SOP EQP-OCM-064 for drug layering onto Trehalose Granules with coating dispersion. Use Glatt GPCG2 In-process form, "EQP-OCM-064-F1," to record in-process information. Turn unit on and preheat column.

Fluid Bed Processor: Glatt GPCG-2. Filter: 200 micron screen. Product Container: 4" wurster, stainless steel. Insert height from bottom: 1". Spray direction: Top Spray. Fluid Nozzle Size/ Type: 1mm. Pump: Peristaltic, Master Flex LS. Tubing: Nalge #14 Silicon. Bed Temperature: ≤ 40°C. Inlet air temperature: Adjust to meet bed temperature target. Outlet air temperature: Monitor & record. Spray rate: initial rate 4-6g/min, adjust as required. Atomizing air pressure: 20psi. Air flow: 60cmh and adjust for fluidization. Load column with Trehalose G. Increase bed temperature to 35°C and maintain for 30 minutes with minimum fluidization of the

Granules. Reduce bed temperature until an exhaust temperature of 35 °C is achieved. Prime pump tubing with coating solution. Must not use more than 40g for tubing priming. Adjust the spraying apparatus to obtain satisfactory spray pattern. Record initial weight below before spraying onto trehalose. Start spraying the coating solution onto Trehalose Granules. Record operating parameters on fluid bed processing form. Stop spraying when 300.3 g of coating solution has been sprayed. Maintain bed temperature and continue fluidization until Granules are sufficiently dry. Reduce fluidization and maintain bed temperature at 35°C for 10 minutes. Do not cool down the Granules. Sample 2g for moisture analysis until moisture is below 1%. Discharge coated Granules into pre-prepared and labeled container (with tare weight) lined with double polyethylene bag. Calculate net weight of drug layered Granules. If moisture is > 1%, vacuum dry blend as follows: Setup Lyophilizer per SOP EQP-OCM-00002. Load drug layered granules into a Lyoguard tray. Use recipe 3 to dry blend overnight. Discharge dried blend into saved polyethylene bags. Obtain final moisture of the dried granules. Calculate net weight of dried Granules.

Blending

[208] Screen required Avicel and pass through 60 mesh screen. Setup 4 qt V-blender. Transfer Plecanatide Dried Granules into the V-Blender. Save bag for discharging final blend. Rinse 2-3 times the Lyoguard tray and bag with adequate amount of Weighed Avicel. Transfer rinses into 4 qt. V-b;ender. Transfer all remaining Pre-weighed/screened Avicel into the V-Blender. Mix for 20 minutes. Weigh and screen Magnesium Stearate through a 60 mesh screen. Charge Magnesium Stearate to the 4 qt V-Blender. Ensure the cover is securely closed with no potential powder leakage during blending. Blend for 2 minutes. Sample 3 x 350 mg of blend at three locations. Obtain exact weight of each sample that has been transferred into the sampling bottle.

Compression

Set-up Korsch press per SOP EQP-OCM-00087. Install 0.250" Standard Concave Round Plain tolling. Obtain blend Assay results and calculate Target Tablet Weight. Acceptable weight range of tablets is ± 5.0%. Load the Final Blend into the powder hopper. Refill as necessary. Adjust fill weight to obtain tablets in the range of 95.0 - 105.0mg and hardness in the range of 4-6kP.

Verify friability is NMT 1.0%. Check 5 tablet weights periodically every 5-10min to ensure tablet weight is within the range. After tablet weights are recorded, obtain and record 3 tablet hardness and thickness during the periodic weight check. Continue to compress acceptable tablets until the blend is used up. Once press is running properly to achieve specifications above, perform final Friability test and record results (Spec: NMT 1.0%).

Example 17: Composition of spray coated trehalose granules tablet formulation 1528-3172, 1mg

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.167
2	Trehalose granules	70.81
3	Methocel ES Premium LV	0.50
4	TRIS	1.1524
5	Calcium ascorbate	0.100
6	Water for injection	N/A
7	Trehalose powder (in coating solution)	1.0176
8	Microcrystalline cellulose (Avicel PH 200)	25.00
9	Magnesium stearate	0.2500
	Total	100

[209] The process for making spray coated trehalose granules tablet formulation 1528-3172-RD is described below.

Preparation of Coating Solution

[210] Add purified water to labeled container and begin stirring. Stir such that a liquid vortex is produced without introducing air into liquid. Slowly add Methocel to solution. Stir until methocel is completely dissolved. Warm the solution if necessary to dissolve Methocel (≤ 50°C). Record appearance of solution.

[211] Solution must be cooled before adding other materials. Add Trehalose to solution. Stir until materials are dissolved. Record appearance of solution. Add TRIS to solution. Stir until materials are dissolved. Record appearance of solution. Add Calcium Ascorbate to solution. Stir until materials are dissolved. Record appearance of solution. Obtain solution pH: Adjust pH to pH 7.8 – 7.9 with concentrated HCl followed by adjust pH to 7.7 – 7.6 with 10N HCl. Record final adjusted pH. Place the Coating Solution in an ice bath and allow it stay in the batch for 0.5 to 1 hour until it reaches the ice temperature. Check with a thermometer to ensure at ice temperature. Weigh portions of required amount of API on a weighing boat and add each portion carefully to the cold Excipient Solution. Stir vigorously to allow peptide wetting and dissolving in the cold solution. Total amount of peptide must equal 14.006 g. Continue stirring solution such that a liquid vortex is produced without introducing air into liquid. Stir until PLECANATIDE is completely dissolved. Keep peptide solution cold all the time in the ice bath. Weigh 5.0g of WFI to rinse API container. Carefully rinse the side of coating solution container and completely transfer the rinse back to the coating solution container. Obtain final pH of the Coating Solution. Obtain net weight of the Coating Solution (~354.2 g). Coating Solution must be used as soon as possible.

The blending and compression processes for batch 1528-3172-RD are similar to that described above for batch 1528-3171-RD.

Example 18: Composition of 1mg dry blend tablet formulation 1528-2925-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	1.106
2	Microcrystalline cellulose (Avicel PH	98.64

	102)	
3	Magnesium stearate	0.2500
	Total	100

Example 19: Composition of 3mg dry blend tablet formulation 1528-2926-RD

Item No.	Ingredient	Concentration % w/w
1	SP-304	3.318
2	Microcrystalline cellulose (Avicel PH 102)	96.43
3	Magnesium stearate	0.2500
	Total	100

[212] Other batches were prepared by the processes similar to those described in Examples 9-12. Their compositions are listed below.

[213] Batch 500-55: 0.33% plecanatide, 95.17% microcyrstalline cellulose, 4.0% sodium starch glycolate, and 0.5% magnesium stearate.

[214] Batches 1528-2907-RD and 2010F100A: 3.318% plecanatide, 96.43% Avicel, and 0.25% Mg stearate.

[215] Batches 1528-2906-RD and 2010F099A: 1.106% plecanatide, 98.65% Avicel, and 0.25% Mg stearate.

[216] Batches 1528-2890-RD and 2010F101A: 0.3246% plecanatide, 99.43% Avicel, and 0.25% Mg stearate.

[217] Formula compositions for batches 11H141, 11H152, and 11H140 in this table below (not previously disclosed) are the same as the formula compositions for GMP stability batches 2010F101A, 2010F099A, and 2010F100A, respectively.

Example 20: Plecanatide tablet and capsule stability

[218] Capsules and tablets of different batches were tested for their stability and the results were provided. Unless otherwise specified, 1M, 2M, 3M, or 4M in the tables below denotes that the measurements were carried out at the end of 1, 2, 3, or 4 month(s) of the storage period.

Potency Summary: This test was performed by taking a composite sample of about 5 units to determine the average potency of the sample. The table below shows the stability of capsules or tablets in terms of potency (% of label claim).

Lot (description)	Potency (% Label Claim)																		
	Bulk*	Package	Storage Condition																
		Package	Initial	40C/75RH			30C/65RH			25C/60RH					5C				
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD (0.3mg dry blend capsules)	88	HDPE bottle		89		87			89			91		80				89.3		89
		Oxyguard bottle		91		91			92			91		79				88.9		90
		Blister strip	90	90		85			88			91		79						90
1528-2855-RD (0.3mg coated bead capsule)	94	HDPE bottle		101		100			96			102		88						98
		Oxyguard bottle		101		96			99			104		87						100
		Blister strip		97		103			99			98		87						97
500-55 (0.3mg dry blend capsule)	97	HDPE bottle		97		94			95			96		84						98
		Oxyguard bottle		98		96			96			102		83						97
		Blister strip	93	97		93			95			106		83						96
1528-2850B-RD (0.3mg dry blend tablet)	76	HDPE bottle		85		88			94			83		67						70
		Oxyguard bottle		84		84			88			74		74						80
1528-2851-RD (0.3mg coated particle tablet)	96	HDPE bottle		115		72			90			99		99						78
		Oxyguard bottle		81		88			83			111		85						96
2010F100A (3mg dry blend capsule)	101	Blister strip	97	95	94	91	95	95	92	97	95	93			97	94	94			
2010F101A (0.3mg dry blend capsule)	97	Blister strip	92	91	91	86	94	92	85	95	93	88			95	95	92			
2010F099A (1mg dry blend capsule)	98	Blister srtip	94	92	91	89	93	94	89	94	94	91			95	94	92			
11H141 (0.3mg dry blend	103	Blister strip	101	95	92	87	98	93	92	96	92	95			100	97	97			

capsule)																				
11H152 (1mg dry blend capsule)	102	Blister strip	97	91	91	93	94	95	96	96	95	96			97	95	97			
11H140 (3mg dry blend capsule)	105	Blister strip	99	94	95	94	95	94	97	99	95	97			99	97	97			
1528-2925-RD (1mg dry blend tablet)	99	Oxyguard 40cc with PharnaKeep											99						103	
1528-2926-RD (3mg dry blend tablet)	100	Oxyguard 40cc with PharnaKeep											94						93	
1528-2907-RD (3mg dry blend capsule)	98																			
1528-2906-RD (1mg dry blend capsule)	98																			
1528-2890-RD (0.3mg dry blend capsule)	93																			

*Blend

[219] As demonstrated by the table above, there was little or no appreciable loss in potency after storage under accelerated conditions (40C/75RH or 30C/65RH), which suggests that these capsules or tablets could be stable at room temperature for 18 months or for longer times if refrigerated or stored at 25C.

[220] Water content summary: The table below shows that the water content was stable over the testing period in the packages evaluated for various capsule/tablet compositions. This further demonstrated that products were stable.

[221]

Lot	Water	Packaging	Water packaged product

	(in-process)		Initial	40C/75RH			30C/65RH			25C/60RH					5C					
				1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD 0.3mg dry blend capsule		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		5.03		5.64			3.00			2.22		2.39				5.48		1.8
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.07		5.24			4.28			5.33		4.08				5.31		3.7
		Blister, N2	4.21	4.87		5.80			4.76			4.31		4.09						2.8
1528-2855-RD 0.3mg coated bead capsule	2.40	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		0.57		0.47			1.63			0.68		0.42						0.2
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		2.10		1.05			1.29			2.07		0.30						0.8
		Blister strip		0.73		2.11			0.54			0.58		0.32						0.3
500-55 0.3mg dry blend capsule		HDPE bottle		5.63		4.19			5.51			5.79		2.98						2.7
		Oxyguard bottle		5.78		4.69			5.90			5.66		2.99						2.8
		Blister strip	4.09	5.78		4.17			5.53			6.16		3.12						2.9
1528-2850B-RD 0.3mg dry blend tablet		32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.09		4.03			6.28			6.10		2.86						2.1
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		4.81		4.91			6.15			6.30		4.05						3.4
1528-2851-RD 0.3mg coated particle tablet	3.32	32-count, HDPE bottle, 60cc, N2, 2g mol. sieve		4.33		4.50			5.09			5.90		2.55						1.5
		32-count, Oxyguard bottle, 40cc, PharmaKeep KD-20		5.15		4.88			5.82			6.02		4.34						3.0
2010F100A (3mg dry blend capsule)		Blister strip	4.7	4.5	4.6	4.4	4.5	4.7	4.4	4.5	4.8	4.4			4.5	4.8	4.5			
2010F101A (0.3mg dry blend capsule)		Blister strip	4.5	4.8	4.7	4.7	4.5	4.7	4.3	4.4	4.7	4.3			4.5	4.7	4.2			
2010F099A (1mg dry blend capsule)		Blister strip	4.6	4.4	4.6	4.4	4.5	4.5	4.3	4.4	4.6	4.4			4.2	4.7	4.3			

11H141 (0.3mg dry blend capsule)		Blister strip	5	4.8	4.9	4.9	5.1	4.9	4.8	5.0	5.0	4.9			5.0	4.9	4.9			
11H152 (1mg dry blend capsule)		Blister strip	5.2	4.8	4.9	4.8	4.8	4.8	4.9	4.8	4.8	4.9			5.0	4.9	4.8			
11H140 (3mg dry blend capsule)		Blister strip	5.2	5.0	5.0	5.0	4.9	5.0	5.0	4.9	5.0	4.9			4.9	4.9	4.8			
1528-2925-RD (1mg dry blend tablet)		Oxyguard 40cc with PharnaKeep											4.9						4.0	
1528-2926-RD (3mg dry blend capsule)		Oxyguard 40cc with PharnaKeep											4.0						4.0	
1528-2907-RD 3mg dry blend capsule		Bulk capsule	4.78																	
1528-2906-RD 1m dry blend capsule		Bulk capsule	4.84																	
1528-2890-RD		Bulk capsule	4.8																	

[222]

Impurity summary: The table below shows the product stability in terms of HPLC or UPLC of total impurities as a function of time and storage condition. The data in the table suggest that the increase in total impurities in tested batches except batch 500-55 be no greater than 7% at room temperature after 18 months. It also suggest that the increase in total impurities in all tested 1528-2855-RD batche in different packages be no greater than 7% at 30 °C for 18 months. It was also observed that the 1528-2855-RD batch had less impurity increase than the 1528- 2850-RD batch or was more stable than the 1528-2850-RD batch.

Batch	Package	Total impurities % area																	
		Initial	40C/75RH			30C/65RH			25C/60RH					5C					
			1M	2M	3M	1M	2M	3M	1M	2M	3M	7M	10M	1M	2M	3M	4M	7M	8.5M
1528-2850-RD	HDPE bottle	3.2	5.1		5.9			4.4			3.8		4.8				3.1		3.7
	Oxyguard bottle		5.7		7.4			5.3			4.3		5.3				3.1		3.5
	Blister strip		5.5		7.0			5.0			4.3		5.5						3.7
1528-2855-RD	HDPE bottle	3.5	3.6		5.1			3.8			3.4		4.4						3.4
	Oxyguard bottle		3.9		4.4			4.1			3.7		4.0						3.7
	Blister strip		4.0		5.2			4.0			3.6		4.2						3.8
500-55	HDPE bottle	3.2	5.7		8.4			5.4			4.4		6.0						3.5
	Oxyguard bottle		5.6		7.0			5.1			4.3		5.6						3.5
	Blister strip		6.5		8.0			5.7			4.8		6.5						3.6
1528-2850B-RD	HDPE bottle	3.6	5.0		6.5			4.5			3.9		4.7						3.7
	Oxyguard bottle		5.6		7.3			4.7			4.1		4.9						3.6
1528-2851-RD	HDPE bottle	3.7	4.2		5.1			4.0			3.8		3.9						3.7
	Oxyguard bottle		4.9		6.8			4.7			4.4		4.3						3.9
2010F101A (0.3mg dry blend capsule)	Blister strip	2.1	4.4	3.9	4.7	2.9	3.2	3.4	3.1	2.7	3.2			2.0	1.3	2.0			
2010F099A (1mg dry blend capsule)	Blister strip	2.9	3.7	3.8	4.3	3.1	3.1	3.6	2.7	2.9	3.2			2.4	2.4	2.4			
2010F100A (3mg dry blend capsule)	Blister strip	2.4	3.2	3.6	4.2	2.8	2.8	3.0	2.6	2.7	2.9			2.4	2.5	2.7			

11H141 (0.3mg dry blend capsule)	Blister strip	1.3	3.3	4.2	4.5	2.5	3.6	3.3	2.0	2.8	2.9			1.4	1.5	1.8			
11H152 (1mg dry blend capsule)	Blister strip	2.4	3.6	4.2	4.1	2.6	3.2	3.1	2.6	3.1	2.9			2.3	2.3	2.1			
11H140 (3mg dry blend capsule)	Blister strip	2.1	3.5	3.7	4.5	2.6	2.7	3.3	2.5	2.7	2.9			2.3	2.2	1.8			
1528-2925-RD (1mg dry blend tablet)	Oxyguard 40cc with PharnaKeep											2.7						1.7	
1528-2926-RD (3mg dry blend capsule)	Oxyguard 40cc with PharnaKeep											2.6							
1528-2906-RD	HDPE bottle	1.83		5.18															
1528-2907-RD	HDPE bottle	1.85		4.58															
1528-2890-RD	Bulk	1.9																	

Content uniformity: This test was performed by placing 10 individual capsule/tablet units in 10 individual bottles and potency of each unit was measured to show whether individual capsules or tablets have uniform potency (% label claim or %LC).

0.3mg Dry blend tablet 1528-2850B-RD	
	%LC
Sample	**1528-2850B-RD (dry tabs)**
1	78.62
2	91.43
3	86.52
4	90.9
5	84.83
6	95.29
7	75.69
8	76.87
9	84.92
10	86.9
Mean	**85.2**
std. dev	6.51
% RSD	**7.64**

0.3mg Coated particle tablet 1528-2851-RD		
Sample	**Weight (mg)**	**% Label Claim**
1	88.86	69.55
2	89	94.41
3	88.89	94.34
4	88.6	72.18
5	88.37	142.52
6	88.76	149.44

7	89.42	78.8
8	88.56	131.08
9	89.08	102.55
10	88.78	99.13
Mean		103.4
St. Dev		28.53
%RSD		27.59

0.3mg Dry blend capsule 1528-2890			3mg Dry blend capsule 1528-2907-RD			1mg Dry blend capsule 1528-2906-RD	
Sample	%LC		Sample	%LC		Sample	%LC
1	87.2		1	94.5		1	98.1
2	94.6		2	101.2		2	101.8
3	92.6		3	97.9		3	93.1
4	94.2		4	94.5		4	97.5
5	93.5		5	95.9		5	97.9
6	91.7		6	95.2		6	97.1
7	91.6		7	96.1		7	94.5
8	99		8	99		8	100.1
9	91.8		9	93.8		9	98.1
10	92.1		10	93.4		10	97.9
Mean	92.8		Mean	96.2		Mean	97.6
RSD	3.20%		RSD	2.60%		RSD	2.50%
AV(10)***	12.8		AV(10)	8.4		AV(10)	6.8

***AV = acceptance value used for UPS <905> content uniformity. Idealy AV should be less than 15 to pass USP <905> content uniformity.

0.3mg dry blend capsule 1528-2850-RD		
Sample	Original %LC	Re -preparation %LC
1	82.73	85.87
2	84.57	89.45
3	80.29	91.39
4	84.88	88.45
5	85.2	86.96
6	82.9	84.84
7	84.75	86.21
8	86.58	91.37
9	84.34	88.79
10	88.82	84.75
Mean	84.51	87.81
std. dev	2.288445	2.467121
% RSD	2.7	2.8

Conte1528-2855-RD Sample	**%LC**		**1528-2850B-RD Sample**	**%LC**
1	88.82		1	78.62
2	93.73		2	91.43
3	89.06		3	86.52
4	84.94		4	90.9
5	89.93		5	84.83
6	88.7		6	95.29
7	88.71		7	75.69
8	86.85		8	76.87
9	86.92		9	84.92
10	91.33		10	86.9
Mean	**88.9**		**Mean**	**85.2**
std. dev	2.45		std. dev	6.51
% RSD	**2.76**		**% RSD**	**7.64**

500-55	
Sample	% label claim
1	96.90%
2	99.40%
3	103.20%
4	96.90%
5	100.00%
6	99.60%
7	96.90%
8	102.80%
9	96.80%
10	93.90%
Mean	98.60%
SD	2.91
RSD	3.00%
AV	7.1 (PASS)

[223] The data in the tables above show that all of the batches yield very good content uniformity acceptable for commercial product.

[224] Dissolution 50-rpm summary: The tables below are summaries of the dissolution of drug from capsules or tablets in an unconventional small-volume apparatus needed to measure the small amount of drug in the units using slow stirring to look for changes in dissolution over time. The test was performed by placing one unit into a very small volume of water at 37C with a paddle stirring at 50-rpm (which is slow) and data were collected at 15, 30 45, and 60 minutes to show the drug release rate over time. These tested products are "immediate release" oral solid dosage forms and a conventional requirement is to have about 75% released in about 45 minutes. The tables summarize the results at 45 minutes and indicate that dissolution was stable over time.

		Dissolution (% label claim at 45 minutes)						
		Initial		40C/75RH	30C/65RH		25C	5C
Lot (description)		bulk	0M	1M	2M	3M	3M	4M
1528-2850-RD (dry blend V-Cap capsule HDPE bottle)	Vessel 1	85		78	84	81	86	83
	Vessel 2	87		73	90	82	84	85
	Vessel 3	88		79	85	79	91	87
	Vessel 4	84		86	87	78	83	85
	Vessel 5	89		72	89	80	79	90
	Vessel 6	88		81	85	82	88	83
	Average	87		78	87	80	85	85
	RSD	2		6.4	2.7	2.1	5.0	2.9
1528-2850-RD (dry blend Vcap capsule OxyGuard bottle)	Vessel 1	85		69	89	79	88	82
	Vessel 2	87		75	89	87	81	85
	Vessel 3	88		77	87	86	84	86
	Vessel 4	84		80	87	83	83	80
	Vessel 5	89		71	88	89	84	84
	Vessel 6	88		76	88	79	86	89
	Average	87		75	88	84	84	84
	RSD	2		5.3	1.2	5.2	3.1	3.6
1528-2850-RD (dry blend V-cap capsule blister strip)	Vessel 1	85	75	59	86	73	83	
	Vessel 2	87	89	77	79	81	81	
	Vessel 3	88	88	83	87	74	84	
	Vessel 4	84	89	67	93	85	83	
	Vessel 5	89	93	75	82	82	84	
	Vessel 6	88	90	82	90	67	87	
	Average	87	87	74	86	77	84	
	RSD	2	7	12.5	6.3	8.6	2.4	

	Dissolution (% label claim at 45 minutes)					
		Initial	40C/75RH	30C/65RH		25C
Lot (description)		bulk	1M	2M	3M	3M
1528-2855-RD (coated bead V-Cap capsule HDPE bottle)	Vessel 1	104	85	100	79	83
	Vessel 2	89	90	97	83	88
	Vessel 3	91	84	71	91	50

	Vessel 4	88	64	73	94	88
	Vessel 5	94	75	72	75	92
	Vessel 6	93	80	39	96	94
	Average	93	**80**	**75**	**86**	**83**
	RSD	6	**12**	**29**	9.7	20
1528-2855RD (coated bead V-cap capsule OxyGuard bottle)	Vessel 1	104	88	80	87	78
	Vessel 2	89	79	91	86	94
	Vessel 3	91	84	63	92	74
	Vessel 4	88	92	98	90	98
	Vessel 5	94	89	81	81	93
	Vessel 6	93	44	99	81	78
	Average	93	**79**	**85**	**86**	**86**
	RSD	6	**23**	**16**	5.3	12.1
1528-2855-RD (coated bead V-cap capsule blister strip)	Vessel 1	104	85	98	100	81
	Vessel 2	89	84	94	63	80
	Vessel 3	91	97	96	82	87
	Vessel 4	88	94	96	55	74
	Vessel 5	94	64	75	95	66
	Vessel 6	93	96	102	89	82
	Average	93	**87**	**93**	**81**	**78**
	RSD	6	**14**	**10**	22.4	9.2

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M
1528-2851-	Vessel 1	58%	67	68	89

RD (coated particle tablet HDPE bottle)	Vessel 2	77%	84	78	124
	Vessel 3	57%	62	68	70
	Vessel 4	96%	110	84	105
	Vessel 5	95%	65	107	61
	Vessel 6	64%	103	76	51
	Average	74%	**82**	**80**	**83**
	RSD	24%	**26**	**18**	33
1528-2851-RD (coated particle tablet OxyGuard bottle)	Vessel 1	58%	89	54	118
	Vessel 2	77%	73	101	69
	Vessel 3	57%	75	82	80
	Vessel 4	96%	68	67	73
	Vessel 5	95%	76	162	96
	Vessel 6	64%	97	82	95
	Average	74%	**80**	**91**	**89**
	RSD	24%	**14**	42	**21**

	Dissolution (% label claim at 45 minutes)				
		Initial	40C/75RH	30C/65RH	
Lot (description)		bulk	1M	2M	3M
1528-2850B-RD (dry blend tablet HDPE bottle)	Vessel 1	90%	88	96	92
	Vessel 2	69%	79	82	92
	Vessel 3	83%	76	100	85
	Vessel 4	94%	96	86	94
	Vessel 5	88%	89	89	83
	Vessel 6	92%	83	97	83
	Average	86%	**85**	**92**	**88**
	RSD	11%	**8.2**	**8**	**5.6**
1528-2850B-RD (dry blend tablet OxyGuard bottle)	Vessel 1	90%	74	80	91
	Vessel 2	69%	97	87	95
	Vessel 3	83%	91	86	90
	Vessel 4	94%	94	91	90
	Vessel 5	88%	83	91	89
	Vessel 6	92%	91	76	84
	Average	86%	**88**	**85**	**90**
	RSD	11%	**9.6**	7	**4.0**

	Dissolution (% label claim at 45 minutes)					
		Initial		40C/75RH	30C/65RH	25C
Lot (description)		bulk	0M	1M	2M	3M	3M
500-55 (dry blend V-Cap Plus capsule HDPE bottle)	Vessel 1	95		90	92	91	89
	Vessel 2	98		85	98	97	98
	Vessel 3	69		85	96	94	76
	Vessel 4	94		89	95	100	97
	Vessel 5	99		89	97	98	86
	Vessel 6	104		100	99	94	92
	Average	93		**89**	**96**	**96**	**90**
	RSD	13.1		**6.2**	**2.4**	**3.6**	**9.1**
500-55 (dry blend V-Cap Plus capsule OxyGuard bottle)	Vessel 1	95		84	103	99	94
	Vessel 2	98		97	101	95	103
	Vessel 3	69		97	99	98	97
	Vessel 4	94		92	97	92	96
	Vessel 5	99		91	100	95	101
	Vessel 6	104		96	95	93	91
	Average	93		**93**	**99**	**95**	**97**
	RSD	13.1		**5.3**	**2.7**	**2.7**	**4.3**
500-55 (dry blend V-Cap Plus capsule foil blister)	Vessel 1	95	98	99		89	98
	Vessel 2	98	101	88		94	87
	Vessel 3	69	107	90		89	96
	Vessel 4	94	96	90		86	87
	Vessel 5	99	99	68		89	94
	Vessel 6	104	99	90		82	89
	Average	93	**100**	**87**		**88**	**92**
	RSD	13.1	**3.8**	**11.8**		**4.3**	**5.5**

Dry blend 3mg lot 1528-2907-RD 500-mL				
	15 min	30 min	45 min	60 min
Vessel 1	91	96	97	96
Vessel 2	96	95	97	96
Vessel 3	96	97	97	97
Vessel 4	95	102	100	100
Vessel 5	97	96	96	97
Vessel 6	92	99	98	98

Average	94	97	98	97
RSD	2.7	2.5	1.1	1.4

Dry blend 1mg lot 1528-2906-RD 150-mL				
	15 min	30 min	45 min	60 min
Vessel 1	65	92	96	99
Vessel 2	49	91	95	96
Vessel 3	46	88	96	97
Vessel 4	44	96	101	102
Vessel 5	39	78	93	99
Vessel 6	57	90	95	96
Average	50	89	96	98
RSD	18.8	7	2.8	2.4

Dry blend 0.3mg lot 1528-2890-RD 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	57	94	100	105
Vessel 2	60	96	100	105
Vessel 3	86	93	94	95
Vessel 4	76	90	91	101
Vessel 5	69	90	97	106
Vessel 6	68	95	97	97
Average	69	93	97	102
RSD	15.6	2.8	3.4	4.5

	Capsule Dissolution at 45 minutes												
		5C			**25C**			**30C**			**40C**		
Lot (strength)	COA	1M	2M	3M	1M	2M	3M	1M	2M	3M	1M	2M	3M
2011F101 A (0.3mg)	98%	99%	95%	95%	95%	92%	95%	94%	93%	97%	93%	90%	92%
2011F099 A (1mg)	96%	95%	95%	95%	91%	93%	94%	93%	90%	95%	95%	92%	93%
2011F100 A (3mg)	99%	101%	97%	97%	100 %	95%	95%	98%	95%	95%	96%	93%	95%
11H141 (0.3mg)	101%	102%	101 %	101 %	105 %	96%	106 %	102 %	97%	103 %	99%	96%	98%
11H152 (1mg)	96%	96%	99%	97%	96%	99%	97%	96%	96%	98%	96%	96%	98%
11H140 (3mg)	102%	102%	102 %	101 %	105 %	100%	97%	102 %	99%	102 %	101 %	99%	96%

[225] Dissolution 75-rpm: The tables below show a few examples where the stirring rate was increased slightly to 75-rpm to give more consistent results and indicates stable dissolution after accelerated storage of 1 or 2 months at 40C 75% relative humidity.

Dry blend 0.3mg lot 1528-2850-RD 1M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	75	80	80	81
Vessel 2	61	75	80	82
Vessel 3	65	81	83	84
Vessel 4	78	86	84	85
Vessel 5	66	79	83	84
Vessel 6	62	79	84	86
Average	68	80	82	84
RSD	10.3	4.5	2.3	2.2

Dry blend 1mg lot 1528-2906A-RD 2M 40C/75RH 75-rpm 50-mL				
	15 min	30 min	45 min	60 min
Vessel 1	69	84	88	88
Vessel 2	62	82	84	85
Vessel 3	65	82	85	85
Vessel 4	58	70	80	79
Vessel 5	59	77	82	81
Vessel 6	68	80	83	84
Average	64	79	84	84
RSD	7.2	6.4	3.3	3.8

[226] 2855-RD dissolution: The tables below are all the dissolution profiles of batch 1528-2850-RD and indicate stable drug release over time.

	Initial Percent Dissolved			
Vessel	**15**	**30**	**45**	**60**
1	84%	99%	104%	104%
2	28%	80%	89%	92%
3	68%	83%	91%	95%
4	56%	79%	88%	98%

5	29%	83%	94%	98%
6	74%	85%	93%	96%
Mean	57%	85%	93%	97%
RSD	41.20%	8.50%	6.00%	4.20%

1M 40C/75RH OxyGuard Packaging					2M 30C/65RH OxyGuard				3M 30C/65RH OxyGuard				3M 25C/60RH OxyGuard			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	35	74	88	93	47	67	80	90	76	83	87	88	44	62	78	85
2	46	74	79	85	57	80	91	95	65	79	86	91	70	89	94	97
3	39	78	84	88	43	55	63	71	64	84	92	97	48	62	74	79
4	59	82	92	94	753	92	98	101	71	85	90	94	65	92	98	103
5	22	82	89	92	38	64	81	92	60	75	81	87	72	86	93	96
6	4	20	44	61	54	94	99	101	55	74	81	87	53	74	78	84
Average	**34**	**68**	**79**	**86**	**52**	**75**	**85**	**92**	**65**	**80**	**86**	**91**	**59**	**78**	**86**	**91**
RSD	**57**	**35**	**23**	**14**	**25**	**21**	**16**	**12**	11.7	5.7	5.3	4.6	20.1	17.4	12.1	10.4

1M 40C/75RH HDPE Bottle					2M 30C/65RH HDPE				3M 30C/65RH HDPE				3M 25C/60RH HDPE			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	61	78	85	89	78	97	100	103	58	72	79	85	54	70	83	92
2	63	83	90	92	77	93	97	98	51	72	83	90	66	81	88	92
3	66	79	84	91	41	59	71	78	53	84	91	94	10	29	50	66
4	25	44	64	77	50	65	73	78	66	89	94	95	69	81	88	92
5	47	67	75	80	37	59	72	83	48	66	75	81	68	83	92	97
6	57	71	80	85	6	21	39	52	85	94	96	99	82	91	94	97
Average	**53**	**70**	**80**	**86**	**48**	**66**	**75**	**82**	**60**	**80**	**86**	**91**	**58**	**73**	**83**	**89**
RSD	**28**	**20**	**12**	**7**	**56**	**42**	**29**	**22**	22.6	14	9.7	7.3	43	30.6	19.6	13.3

1M 40C/75RH Blister Packaging					2M 30C/65RH Blister				3M 30C/65RH Blister				3M 25C/60RH Blister			
Vessel	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	36	69	85	90	61	91	98	100	82	95	100	102	53	71	81	90
2	41	69	84	88	57	82	94	100	31	48	63	74	27	57	80	87

3	67	96	97	98	63	87	96	100	69	77	82	85	70	78	87	92
4	54	83	94	104	36	80	96	100	29	41	55	69	52	66	74	87
5	10	46	64	79	45	61	75	83	84	94	95	97	25	48	66	80
6	70	91	96	100	87	100	102	104	74	84	89	82	50	74	82	84
Average	**47**	**76**	**87**	**93**	**58**	**83**	**93**	**98**	**62**	**73**	**81**	**85**	**46**	**66**	**78**	**87**
RSD	**48**	**25**	**14**	**10**	**30**	**16**	**10**	**8**	40.5	32.1	22.4	14.9	37.0	17.0	9.2	5.3

[227] Bathes 2850-RD, 2850B-RD, 2851-RD, and 500-55 were also tested in the similar fashion and all showed stable drug release over time.

We claim:

1. A method for treating chronic constipation in a patient comprising orally administering to said patient a composition comprising a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle and one or more pharmaceutically acceptable excipients.

2. The method of claim 1, wherein the constipation is associated with irritable bowel syndrome or chronic idiopathic constipation.

3. A method of treating or alleviating a symptom associated with chronic idiopathic constipation or irritable bowel syndrome in a patient comprising orally administering to said patient a composition comprising a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle and one or more pharmaceutically acceptable excipients.

4. The method of claim 3, wherein the symptom is constipation or abdominal pain.

5. The method of claim 1, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

6. The method of claim 5, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

7. The method of claim 1, further comprising administering to said patient an effective dose of a laxative.

8. The method of claim 3, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

9. The method of claim 8, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

10. The method of claim 3, further comprising administering to said patient an effective dose of a laxative.

ABSTRACT OF THE DISCLOSURE

The invention provides low-dose formulations of guanylate cyclase-C ("GCC") agonist peptides and methods for their use. The formulations of the invention can be administered either alone or in combination with one or more additional therapeutic agents, preferably an inhibitor of cGMP-dependent phosphodiesterase or a laxative.

Median time to first BM (hours)
25
20
15
10
5
0
placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
all
n= 16
n= 12
n=14
n= 13
n=15
n=54

Fig. 1

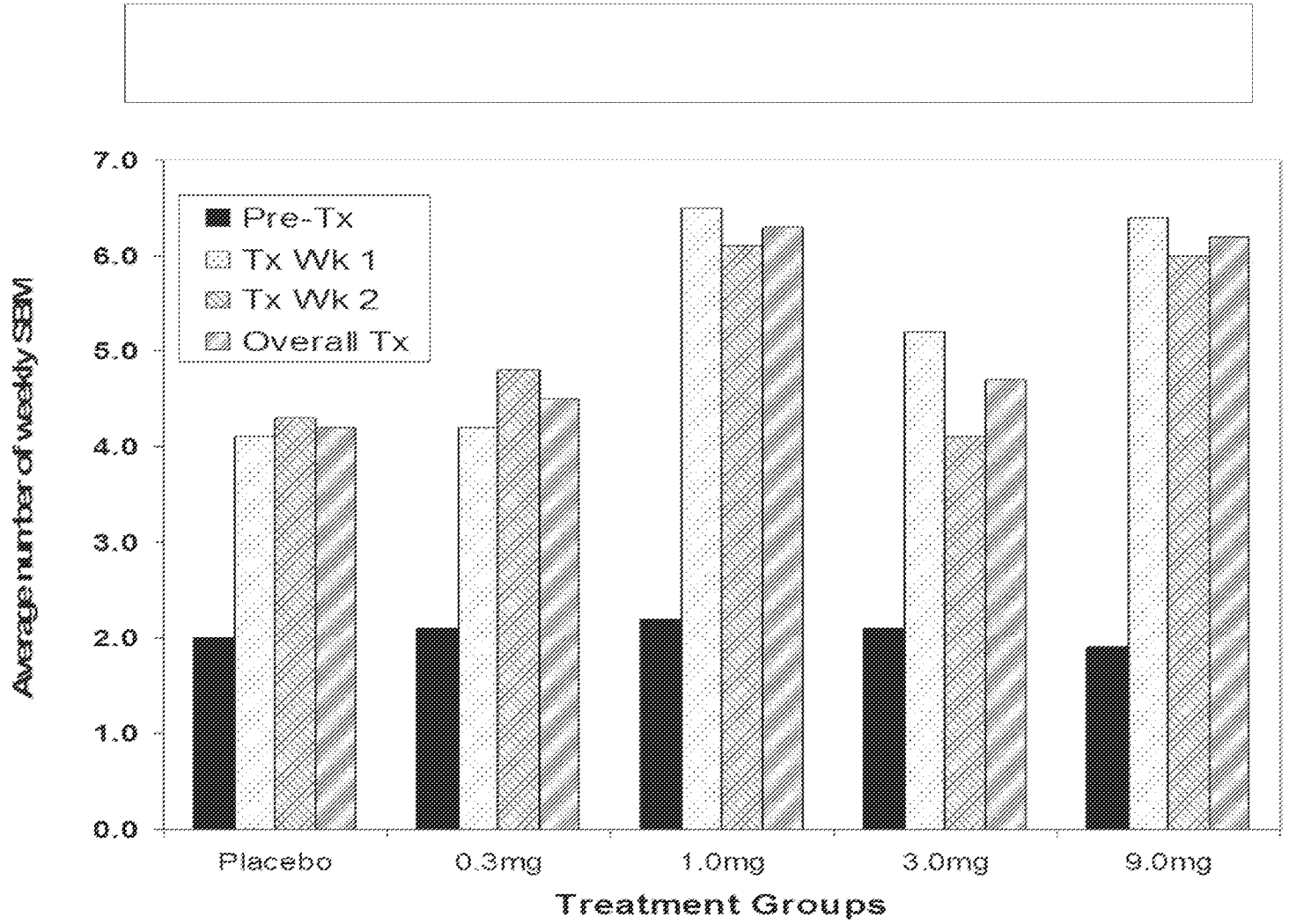
Pre-Tx
Tx Wk 1
Tx Wk 2
Overall Tx
Average number of weekly SEM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Treatment Groups

Fig. 2

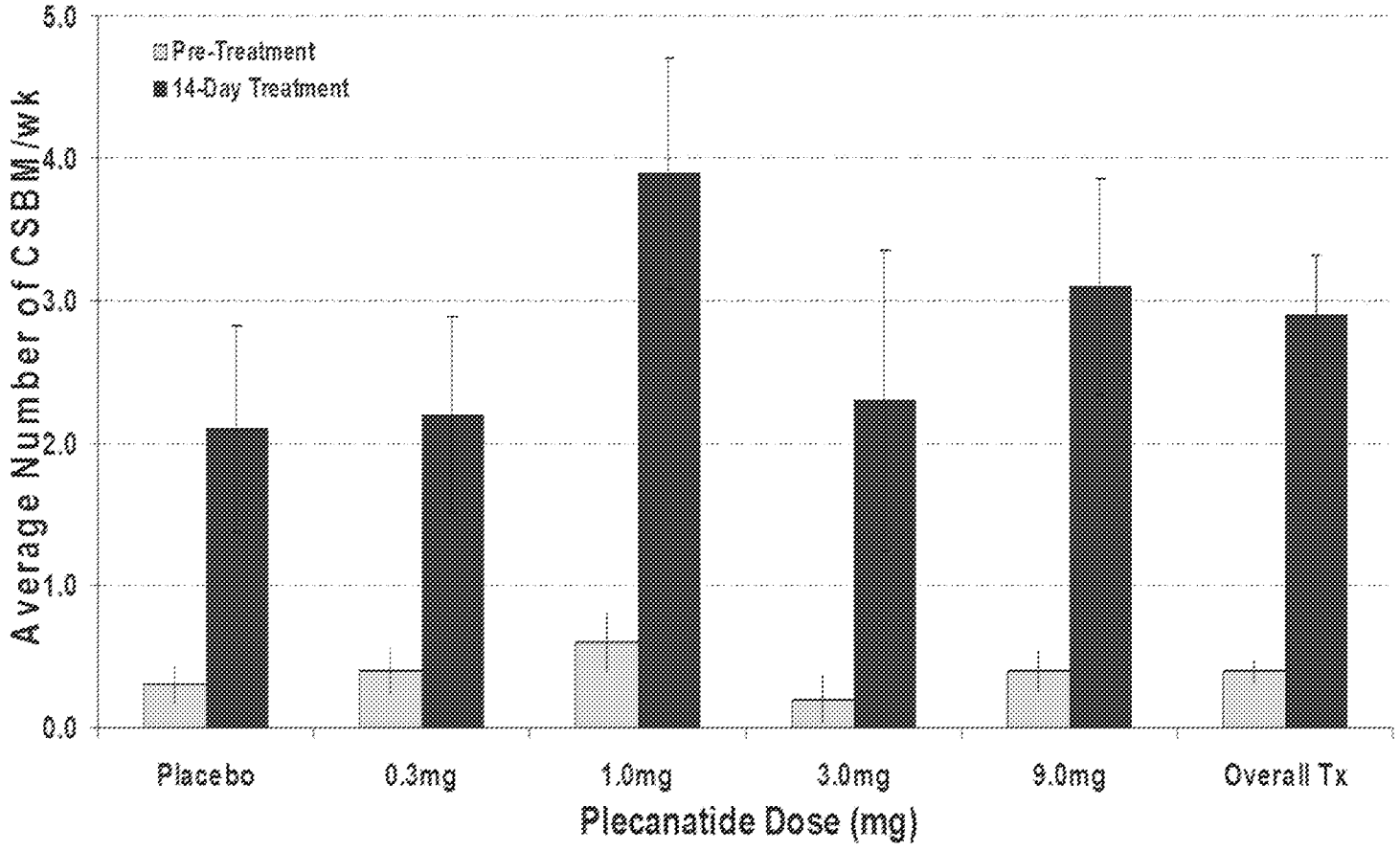
5.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Average Number of CSBM/wk
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 3

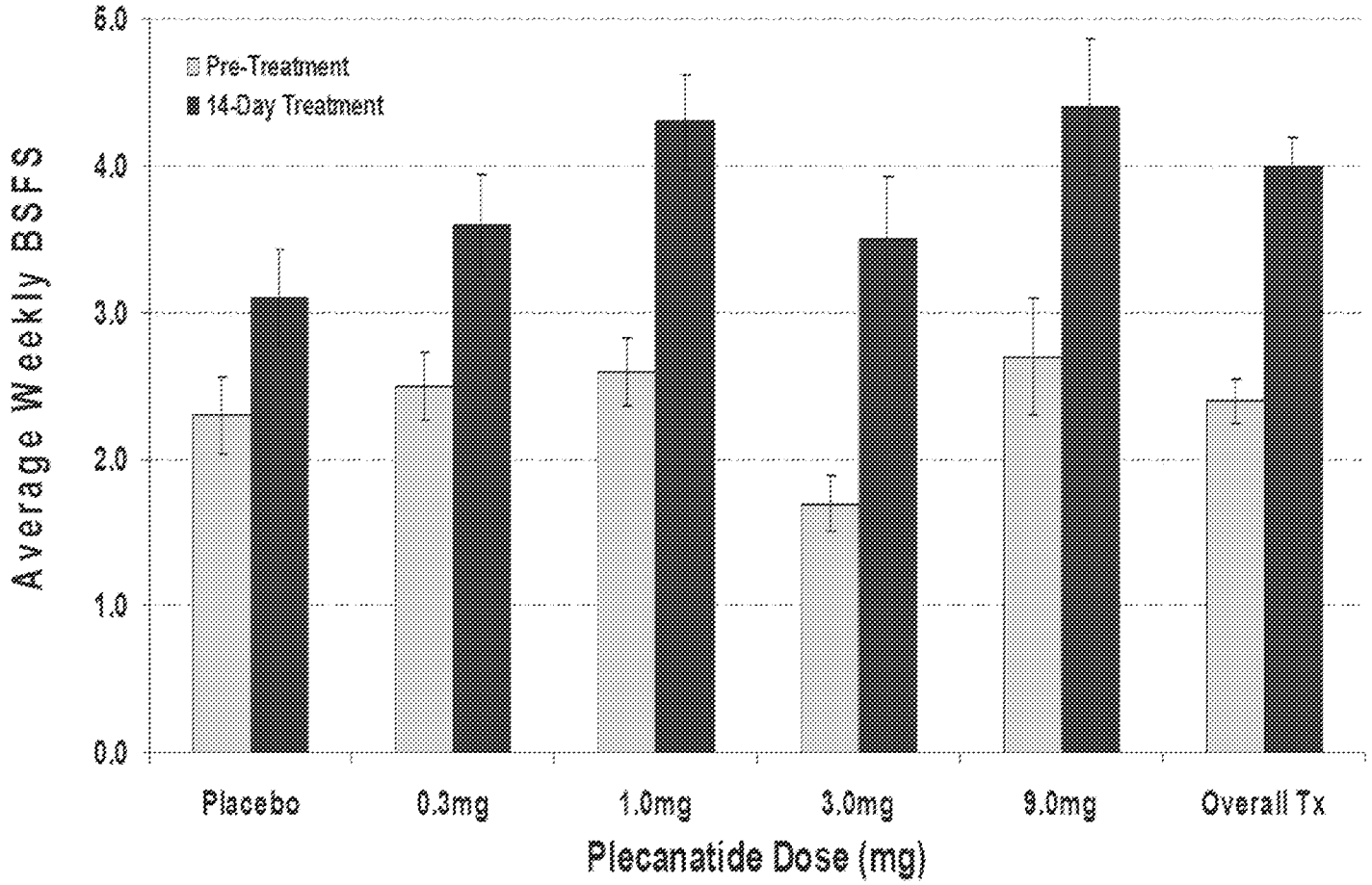
Average Weekly BSFS
6.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Placebo
0.3mg
1.0mg
3.0mg
9.0mg
Overall Tx
Plecanatide Dose (mg)

Fig. 4

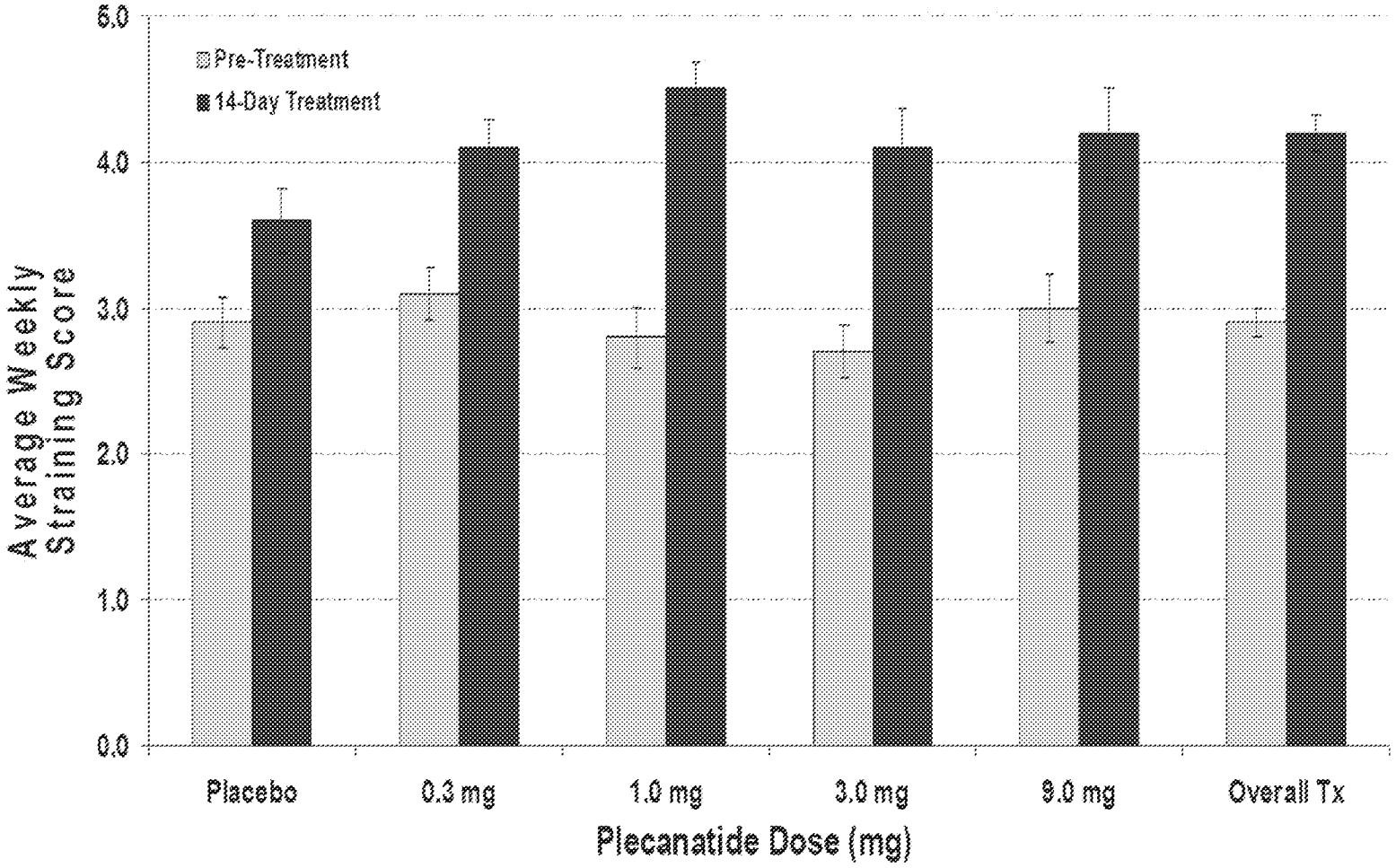
6.0
4.0
3.0
2.0
1.0
0.0
Pre-Treatment
14-Day Treatment
Average Weekly Straining Score
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Plecanatide Dose (mg)

Fig. 5

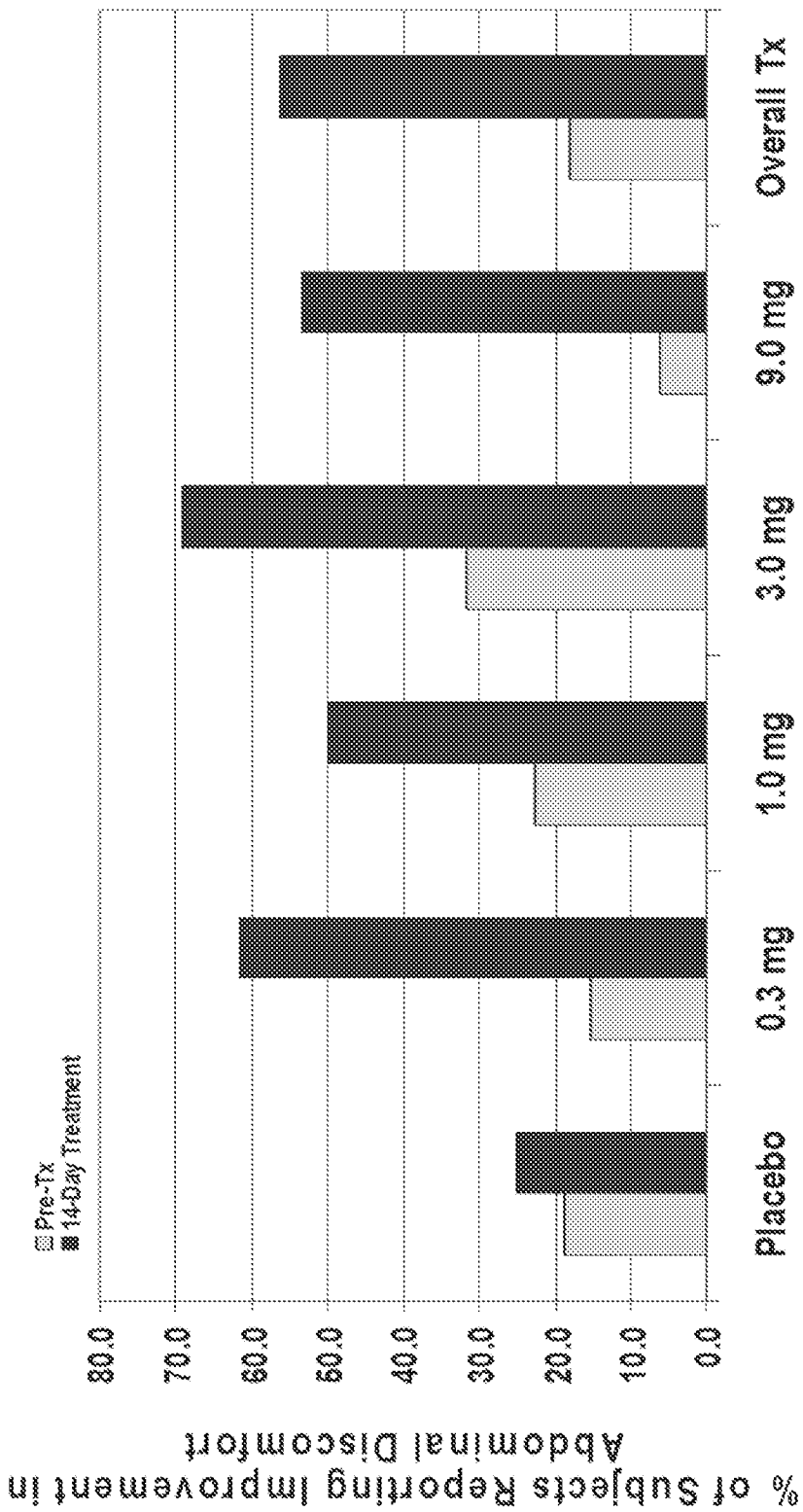
% of Subjects Reporting Improvement in Abdominal Discomfort
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Pre-Tx
14-Day Treatment
Placebo
0.3 mg
1.0 mg
3.0 mg
9.0 mg
Overall Tx
Treatment Groups

Fig. 6

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Stephen Comiskey Date (Optional): 2/10/2015

Signature: S. Comiskey

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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LEGAL NAME OF INVENTOR

Inventor: Rong Feng Date (Optional): 10 Feb 2015

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: John Foss Date (Optional): 09 Feb 2015

Signature: John Foss

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Kunwar Shailubhai Date (Optional): 02/10/2015

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Stephen COMISKEY *et al.*	Confirmation No.: *To Be Assigned*
Application No.: *To Be Assigned*	Group Art Unit: *To Be Assigned*
Filed: September 4, 2015	Examiner: *To Be Assigned*

For: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant(s) hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98.

☐ Pursuant to 37 C.F.R. §1.98, a copy of each non-US patent document cited in the attached Form PTO/SB/08 is enclosed.

☒ No copies of the publications listed on the attached Form PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in prior **Application Serial No. 14/661,299** to which the above-identified application claims priority under 35 U.S.C. §120.

☒ No copies of any U.S. patents or U.S. patent application publications listed on the attached Form PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98.

☐ Publication(s) listed on the attached Form PTO/SB/08 were cited in a foreign search or examination report corresponding to _____ Patent Application Serial No. _____ and mailed on _____.

☐ Enclosed is a copy of a non-English publication(s) _____ Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s).

☐ Enclosed is a copy of a non-English publication(s) _____ English language publication _____ (copy enclosed) claims priority from this non-English publication.

☐ Enclosed is an explanation of non-English publication(s) _____ for which an English translation is not available.

☐ Enclosed is an English translation of non-English publication(s) _____ cited in the attached Form PTO/SB/08.

☐ Enclosed is a copy of pending patent Application Serial No. _____.

This Information Disclosure Statement is filed within any one of the following time periods:

☐ within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);

☐ within three months from the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in this international application;

☒ before the mailing date of a first office action on the merits; or

☐ before the mailing of a first office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form PTO/SB/08 to the undersigned.

Dated: **September 4, 2015**

Respectfully submitted,
COOLEY LLP

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By: /Anne E. Fleckenstein/
Anne E. Fleckenstein
Reg. No. 62,951

INFORMATION DISCLOSURE STATEMENT LIST

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Complete if Known	
Application Number	*To Be Assigned*
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Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	SYPA-009/C02US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2002/0128176 A1	09-12-2002	Forssmann et al.	
	2.	2002/0078683	06-27-2002	Katayama et al.	
	3.	2002/0133168	09-19-2002	Smeldley et al.	
	4.	2002/0143015	10-03-2002	Fryburg et al.	
	5.	2003/0073628	04-17-2003	Shailubhai et al.	
	6.	2004/0015140 A1	01-22-2004	Shields	
	7.	2005/0016244	01-27-2005	Hergemoller	
	8.	2005/0032684 A1	02-10-2005	Cetin et al.	
	9.	2005/0107734	05-19-2005	Coroneo	
	10.	2005/0266047	12-01-2005	Tu et al	
	11.	005/0267297	12-01-2005	Berlin	
	12.	2006/0086653	04-27-2006	St. Germain	
	13.	2006/0094658	05-04-2006	Currie	
	14.	2007/0101158	05-03-2007	Elliott	
	15.	2008/0137318	06-12-2008	Rangaraj et al.	
	16.	2008/0151257	06-26-2008	Yasuda et al.	
	17.	2009/0048175 A1	02-19-2009	Shailubhai et al.	
	18.	2009/0192083 A1	07-30-2009	Currie	
	19.	2009/0253634 A1	10-08-2009	Currie et al.	
	20.	2010/0069306 A1	03-18-2010	Shailubhai et al.	

Examiner Signature:		**Date Considered**	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

121042409v1

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	21.	2010/0093635 A1	04-15-2010	Shailubhai	
	22.	2010/0120694 A1	05-13-2010	Shailubhai et al.	
	23.	2010/0152118 A1	06-17-2010	Shailubhai	
	24.	2010/0221329 A1	09-02-2010	Shailubhai et al.	
	25.	2012/0196797 A1	08-02-2012	Currie et al.	
	26.	2012/0237593 A1	09-20-2012	Comiskey et al.	
	27.	2012/0289460 A1	11-15-2012	Shailubhai	
	28.	2013/0274204 A1	10-17-2013	Shailubhai et al.	
	29.	2014/0024605 A1	01-23-2014	Shailubhai et al.	
	30.	2014/0121169 A1	05-01-2014	Shailubhai et al.	
	31.	2014/0135274 A1	05-15-2014	Shailubhai	
	32.	2014/0287002 A1	09-25-2014	Shailubhai	
	33.	2014/0329738 A1	11-06-2014	Shailubhai et al.	
	34.	5,106,834	04-21-1992	Bovy et al.	
	35.	5,130,333	07-14-1992	Pan et al.	
	36.	5,489,670	02-06-1994	Currie et al.	
	37.	5,518,888	05-21-1996	Waldman et al.	
	38.	5,578,709	11-26-1996	Woiszwillo et al.	
	39.	5,601,990	02-11-1997	Waldman et al.	
	40.	5,731,159	03-24-1998	Waldman et al.	

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	41.	5,721,238	02-24-1998	Heiker et al.	
	42.	5,879,656	03-9-1999	Waldman et al.	
	43.	5,928,873	07-29-1999	Waldman et al.	
	44.	5,969,097	10-19-1999	Wiegand et al.	
	45.	6,060,037	05-09-2000	Waldman et al.	
	46.	6,235,782 B2	05-22-2001	Pamukcu et al.	
	47.	7,041,786 B2	05-09-2006	Shailubhai et al.	
	48.	7,375,083 B2	05-20-2008	Mickle et al.	
	49.	7,494,979 B2	02-24-2009	Currie et al.	
	50.	7,799,897 B2	09-21-2010	Jacob et al.	
	51.	7,879,802 B2	02-01-2011	Shailubhai et al.	
	52.	8,034,782 B2	10-11-2011	Shailubhai	
	53.	8,114,831 B2	02-14-2012	Shailubhai et al.	
	54.	8,207,295 B2	06-26-2012	Shailubhai et al.	
	55.	8,357,775 B2	01-22-2013	Shailubhai et al.	
	56.	8,367,800 B2	02-05-2013	Shailubhai	
	57.	8,497,348 B2	07-30-2013	Shailubhai et al.	
	58.	8,637,451 B2	01-28-2014	Shailubhai et al.	
	59.	8,716,224 B2	05-06-2014	Shailubhai et al.	

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	60.	DE 19744027	04-08-1999	Hoechst Marion Rouseel Deutschland GmbH		
	61.	WO 88/05306	07-28-1988	The General Hospital Corporation		
	62.	WO 93/12068 A1	06-24-1993	Brigham and Women's Hospital		
	63.	WP 1999/026567 A1	06-03-1999	Optonol Ltd		
	64.	WO 01/25266 A1	04-12-2001	Pharmacia Corporation		
	65.	WO 02/062369 A2	08-15-2002	Pharmacia Corporation		
	66.	WO 2002/078683 A1	10-10-2002	Synergy Pharmaceuticals, Inc.		
	67.	WO 2002/098912 A3	12-12-2002	Cetin		
	68.	WO 2004/069165	08-19-2004	Microbia Inc. et al.		
	69.	WO 2005/016244 A2	02-24-2005	Microbia, Inc. et al.		
	70.	WO 2005/087797	09-22-2005	Microbia, Inc. et al.		
	71.	WO 2006/086653 A2	08-17-2006	Microbia, Inc. et al.		
	72.	WO 2007/101158 A2	09-07-2007	Microbia, Inc. et al.		
	73.	WO 2007/022531	02-22-2007	Microbia, Inc. et al.		
	74.	WO 2008/106429	09-04-2008	Microbia, Inc. et al.		
	75.	WO 2008/137318 A1	11-13-2008	Ironwood Pharmaceuticals, Inc. et al.		

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	76.	WO 2008/151257 A2	12-11-2008	Synergy Pharmaceuticals Inc. et al.		
	77.	WO 2009/149278 A1	12-10-2009	Synergy Pharmaceuticals Inc. et al.		
	78.	WO 2009/149279 A2	12-10-2009	Synergy Pharmaceuticals Inc. et al.		
	79.	WO 2010/009319 A2	01-21-2010	Synergy Pharmaceuticals Inc. et al.		
	80.	WO 2010/027404 A2	03-11-2010	Ironwood Pharmaceuticals Inc. et al.		
	81.	WO 2010/065751 A2	06-10-2010	Synergy Pharmaceuticals Inc. et al.		
	82.	WO 2011/020054 A1	02-17-2011	Ironwood Pharmaceuticals Inc. et al.		
	83.	WO 2012/037380 A2	03-22-2012	Synergy Pharmaceuticals Inc. et al.		

NON PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	84.	Advisory Committee Briefing document for Merida [sibutramine hydrochloride monohydrate], Abbott, August 13, 2010 (205 pages)	
	85.	Alrefai et al., "Cholesterol modulates human intestinal sodium-dependent bile acid transporter," Am. J. Physiol. Gastrointest. Liver Physiol. 288:G978-G985 (2005)	

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	86.	Askling et al. "Colorectal cancer rates among first degree relatives of patients with inflammatory bowel disease: A population-based cohort study" Lancet 357:262-266 (2001).	
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Applicants :	Stephen COMISKEY *et al.*		
Serial Number :	*To Be Assigned*	Examiner :	*To Be Assigned*
Filing Date :	September 4, 2015	Art Unit :	*To Be Assigned*
For :	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE		

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I hereby state that the contents of the computer readable form of the Sequence Listing, submitted in the above-identified application in accordance with 37 C.F.R. § 1.821 (e) do not include any new matter that goes beyond the disclosure of the application as filed. The Sequence Listing is supported by the specification and references incorporated therein. Therefore, no new matter is added.

Dated: **September 4, 2015**

Respectfully submitted,
COOLEY LLP

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Anne E. Fleckenstein
Reg. No. 62,951

SEQUENCE LISTING

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Feng, Rong

Foss, John

Shailubhai, Kunwar

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Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

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<212> PRT
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<220>
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<223> wherein ASN is a D-amino acid

<220>
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<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 9

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 10
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<220>
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<223> wherein ASN is a D-amino acid

<220>
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<223> wherein ASP is a D-amino acid

<220>
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<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 10

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1 5 10 15

<210> 11
<211> 16
<212> PRT
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<220>
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<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 11

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1   5   10   15

<210> 12
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<400> 12

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1   5   10   15

<210> 13
<211> 16
<212> PRT
<213> Artificial Sequence

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<220>
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<223> wherein ASN is a D-amino acid

<220>
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<222> (6)..(6)
<223> wherein LEU is a D-amino acid

<220>

<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 13

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 14
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 14

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys
1 5 10 15

<210> 15
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
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<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 15

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1 5 10 15

<210> 16
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<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 16

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1 5 10 15

<210> 17
<211> 16
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<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 17

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu

1 5 10 15

<210> 18
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 18

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1 5 10 15

<210> 19
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 19

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 20
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<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
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<223> wherein LEU is a D-amino acid

<400> 20

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1 5 10 15

<210> 21
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<213> Artificial Sequence

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<220>
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<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 21

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 22
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 22

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 23
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE

<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 23

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1   5   10   15

<210> 24
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 24

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1   5   10   15

<210> 25
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 25

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 26
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 26

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 27
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is 3-(2-naphthyl)alanine

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is a D-amino acid

<400> 27

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Xaa
1 5 10 15

<210> 28
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MOD_RES
<222> (8)..(8)
<223> wherein the x is a 2-aminoisobutyric acid, Aib

<220>
<221> MOD_RES
<222> (10)..(10)
<223> wherein the x is a 2-aminoisobutyric acid, Aib

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 28

Asn Asp Glu Cys Glu Leu Cys Xaa Asn Xaa Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 29
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
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<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> wherein ASP at position 7 is attached to a Lactam bridge

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> wherein x at position 15 is ornithine

<220>
<221> MOD_RES
<222> (15)..(15)
<223> wherein x is an ornithine, Orn

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 29

Asn Asp Glu Cys Glu Leu Asp Val Asn Val Ala Cys Thr Gly Xaa Leu
1 5 10 15

<210> 30
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 30

Asn Asp Glu Cys Glu Tyr Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 31
<211> 16
<212> PRT

<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
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<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 31

Asn Asp Glu Cys Glu Ser Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 32
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 32

Asn Asp Glu Cys Glu Tyr Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 33
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Chemically Synthesized

<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
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<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 33

Asn Asp Glu Cys Glu Tyr Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 34
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN is a D-amino acid

<220>
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<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 34

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1 5 10 15

<210> 35
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<400> 35

Asn Asp Glu Cys Glu Ser Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 36
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 36

Asn Asp Glu Cys Glu Ser Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 37
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 37

Asn Asp Glu Cys Glu Ser Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 38
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 38

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 39
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER at position 16 is attached to polyethylene glycol

<400> 39

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 40

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
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<223> wherein ASN at position 1 is attached to polyethylene glycol

<400> 40

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 41
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER at position 16 is attached to polyethylene glycol

<400> 41

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 42
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER at position 16 is attached to polyethylene glycol

<400> 42

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 43
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is a D-amino acid

<400> 43

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 44
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER at position 16 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is a D-amino acid

<400> 44

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1 5 10 15

<210> 45
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 45

Asn Asp Glu Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 46
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)

<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(11)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 46

Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 47
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 47

Xaa Xaa Xaa Xaa Glu Xaa Xaa Val Asn Val Ala Xaa Thr Gly Xaa Xaa
1 5 10 15

<210> 48
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (8)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>

<221> MISC_FEATURE
<222> (15)..(15)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue that is zero or one residue in length and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 48

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 49
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 49

Asn Asp Asp Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 50
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 50

Asn Glu Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 51
<211> 16

<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 51

Asn Glu Asp Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 52
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 52

Asn Asp Glu Cys Xaa Xaa Cys Xaa Asn Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 53
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein ASP is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 53

Asn Asp Glu Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 54
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein GLU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (10)..(11)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid, or amino acid analogue and may be an L-amino acid, or a D-amino acid, a methylated or an unmethylated amino acid

<400> 54

Asn Glu Glu Cys Xaa Xaa Cys Xaa Tyr Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 55
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 55

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10

<210> 56
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 56

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys
1   5   10

<210> 57
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein CYS at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> wherein TYR at position 14 is attached to polyethylene glycol

<400> 57

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10

<210> 58
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 58

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10   15

<210> 59
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 59

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 60
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> wherein TYR is a D-amino acid

<400> 60

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10

<210> 61
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein CYS at position 1 is attached to polyethylene glycol

<400> 61

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10

<210> 62
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 62

Asn Phe Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 63
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 63

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 64
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<400> 64

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 65
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 65

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 66
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 66

Asn Phe Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 67
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<400> 67

Asn Phe Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 68
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE

<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 68

Asn Phe Cys Cys Glu Thr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10   15

<210> 69
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 69

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10   15

<210> 70
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<400> 70

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1   5   10   15

<210> 71
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 71

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 72
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> wherein TYR at position 14 is attached to polyethylene glycol

<400> 72

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10

<210> 73
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein CYS at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein CYS at position 13 is attached to polyethylene glycol

<400> 73

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys
1 5 10

<210> 74
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein CYS at position 1 is attached to polyethylene glycol

<400> 74

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys
1 5 10

<210> 75
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein CYS at position 13 is attached to polyethylene glycol

<400> 75

Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys
1 5 10

<210> 76
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 76

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 77
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<400> 77

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 78
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 78

Asn Phe Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 79
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 79

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 80
<211> 16
<212> PRT

<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<400> 80

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 81
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 81

Asn Phe Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 82
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 82

Asn Phe Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 83

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN at position 1 is attached to polyethylene glycol

<400> 83

Asn Phe Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 84
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR at position 16 is attached to polyethylene glycol

<400> 84

Asn Phe Cys Cys Glu Tyr Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 85
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 85

Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10

<210> 86
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 86

Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys Tyr
1 5 10

<210> 87
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 87

Cys Cys Glu Ser Cys Cys Asn Pro Ala Cys Thr Gly Cys
1 5 10

<210> 88
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 88

Cys Cys Glu Phe Cys Cys Asn Pro Ala Cys Thr Gly Cys
1 5 10

<210> 89
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein x is penicillamine

<400> 89

Xaa Xaa Glu Tyr Xaa Xaa Asn Pro Ala Xaa Thr Gly Xaa Tyr
1   5   10

<210> 90
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein x is penicillamine

<400> 90

Xaa Xaa Glu Tyr Xaa Xaa Asn Pro Ala Xaa Thr Gly Xaa
1   5   10

<210> 91
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid
       analogue and may be an L-amino acid, or a D-amino acid, or a
       methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid
       analogue and may be an L-amino acid, or a D-amino acid, or a
       methylated or an unmethylated amino acid

<220>

<221> MISC_FEATURE
<222> (15)..(17)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (19)..(20)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 91

Xaa Xaa Xaa Xaa Xaa Xaa Asn Tyr Cys Cys Xaa Tyr Cys Cys Xaa Xaa
1 5 10 15

Xaa Cys Xaa Xaa Cys Xaa
20

<210> 92
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (15)..(17)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (19)..(20)

<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 92

Xaa Xaa Xaa Xaa Xaa Xaa Asn Phe Cys Cys Xaa Phe Cys Cys Xaa Xaa
1 5 10 15

Xaa Cys Xaa Xaa Cys Xaa
20

<210> 93
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (9)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 93

Asn Phe Cys Cys Xaa Phe Cys Cys Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 94
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> wherein x is penicillamine

<220>
<221> MISC_FEATURE
<222> (9)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 94

Asn Phe Xaa Cys Xaa Phe Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa
1 5 10 15

<210> 95
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (3)..(4)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(8)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (9)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 95

Asn Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 96
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<400> 96

Xaa Xaa Glu Xaa Xaa Xaa Asn Pro Ala Xaa Thr Gly Xaa Tyr
1 5 10

<210> 97
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(2)
<223> wherein x is a cysteine, or penicillamine, homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is a cysteine, or penicillamine, homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> wherein x is a cysteine, or penicillamine, homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> wherein x is a cysteine, or penicillamine, homocysteine, or 3-mercaptoproline

<400> 97

Xaa Xaa Glu Xaa Xaa Xaa Asn Pro Ala Xaa Thr Gly Xaa
1 5 10

<210> 98
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an

unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(8)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (9)..(10)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (11)..(12)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(15)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (17)..(18)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (19)..(19)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (20)..(20)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be zero or one residue in length, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 98

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa
20

<210> 99
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is conjugated to an AMIDE

<400> 99

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 100
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>

<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is a D-amino acid

<400> 100

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1   5   10   15

<210> 101
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein SER is conjugated to an AMIDE

<400> 101

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Ser
1   5   10   15

<210> 102
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<400> 102

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Tyr
1   5   10   15

<210> 103
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is a D-amino acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein TYR is conjugated to an AMIDE

<400> 103

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Tyr
1 5 10 15

<210> 104
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein x is Pyroglutamic acid

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is conjugated to an AMIDE

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is a D-amino acid

<400> 104

Xaa Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 105

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is attached to polyethylene glycol

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is attached to polyethylene glycol

<400> 105

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 106
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> wherein ASN is attached to polyethylene glycol

<400> 106

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 107
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein LEU is attached to polyethylene glycol

<400> 107

Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 108
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<220>
<221> MISC_FEATURE
<222> (1)..(3)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (5)..(6)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (8)..(11)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> wherein x is a cysteine, penicillamine homocysteine, or 3-mercaptoproline

<220>

<221> MISC_FEATURE
<222> (16)..(16)
<223> wherein x is any natural, or unnatural amino acid or amino acid analogue, and may be an L-amino acid, or a D-amino acid, or a methylated or an unmethylated amino acid

<400> 108

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 109
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 109

Asn Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 110
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 110

Glu Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 111
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 111

Glu Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 112
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 112

Glu Glu Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 113
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 113

Glu Glu Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 114
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 114

Asp Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 115
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 115

Asp Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 116
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 116

Asp Glu Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 117
<211> 16

<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 117

Asp Glu Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 118
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 118

Gln Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 119
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 119

Gln Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 120
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 120

Gln Glu Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 121
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 121

Gln Glu Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 122
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 122

Lys Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 123
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 123

Lys Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 124
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Chemically Synthesized

<400> 124

Lys Glu Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
1 5 10 15

<210> 125
<211> 16
<212> PRT
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<222> (16)..(16)
<223> wherein TYR is attached to polyethylene glycol

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Arg Tyr

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<223> wherein LYS is conjugated to an AMIDE

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<210> 253
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<210> 260
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<222> (4)..(4)
<223> wherein PHE is attached to an AMINE

<400> 261

Tyr Ala Phe Phe
1

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009/C02US

Filed as Small Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Utility Appl Size fee per 50 sheets >100	2081	1	200	200
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70

Petition:	
Patent-Appeals-and-Interference:	
Post-Allowance-and-Post-Issuance:	
Extension-of-Time:	
Miscellaneous:	
Total in USD ($)	**3000**

Electronic Acknowledgement Receipt

EFS ID:	23404344
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US
Receipt Date:	04-SEP-2015
Filing Date:	
Time Stamp:	13:08:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$3000
RAM confirmation Number	13000
Deposit Account	501283
Authorized User	COOLEY LLP

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	SYPA_009_C02US_FastTrackRequest.pdf	114222 1863ba0bed4f1b01d491796c120867a41242334e	no	2
Warnings:					
Information:					
2	Transmittal of New Application	SYPA_009_C02US_UtlityTransmittal.pdf	277691 fa71b1641c81b3b38a4593ea276167f587cc9b20	no	2
Warnings:					
Information:					
3	Application Data Sheet	SYPA_009_C02US_ADS.pdf	1561920 c0c8efab6b5ad28ece6aff2d24d527484d2af83b	no	8
Warnings:					
Information:					
4		SYPA_009_C02US_Specification.pdf	785882 b8d9f107607dc40efc848008b851650c8658f4a7	yes	148

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	145
Claims	146	147
Abstract	148	148

Warnings:					
Information:					
5	Drawings-only black and white line drawings	SYPA_009_C02US_Figures.pdf	1069916 23dfeb11a6a7a9fe17538d06d13450cafc3bc1c9	no	6
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Information:					
6	Oath or Declaration filed	SYPA_009_C02US_Declaration.pdf	529790 97851888210539 2a9ae6413d0d08d96d0b6851c5	no	8

Warnings:					
Information:					
7	Transmittal Letter	SYPA_009_C02US_IDSTransmittal.pdf	95083 a5875ee26d7b142adcd641045f71eb39956a2da6	no	2
Warnings:					
Information:					
8	Information Disclosure Statement (IDS) Form (SB08)	SYPA_009_C02US_SB08.pdf	363336 8673abad84539074866c2901100833c234ab6d4f	no	19
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Information:					
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9	CRF Statement Paper and CRF are the same	SYPA_009_C02US_StatementCRF.pdf	94000 62e08f04f4e01ccd726e1ea9d009c8beba87e15e	no	1
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Warnings:					
Information:					
		Total Files Size (in bytes):	5137712		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Stephen COMISKEY	Nonprovisional Application Number (if known):	
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Anne E. Fleckenstein/	Date September 4, 2015
Name (Print/Typed) Anne E. Fleckenstein	Practitioner Registration Number 62,951

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

SCORE Placeholder Sheet for IFW Content

Application Number: 14845644 Document Date: 09/04/2015

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Form Revision Date: September 30, 2013

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).
Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2015; month=9; day=9; hr=10; min=15; sec=49; ms=866;]
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Validated By CRFValidator v 1.0.4

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Finished: 2015-09-09 10:15:41.965
Elapsed: 0 hr(s) 0 min(s) 6 sec(s) 246 ms
Total Warnings: 293
Total Errors: 0
No. of SeqIDs Defined: 261
Actual SeqID Count: 261

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/845,644	09/04/2015	1675	930	SYPA-009/C02US	10	2

CONFIRMATION NO. 8164

FILING RECEIPT

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Suite 700
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OC000000077385687

Date Mailed: 09/14/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Stephen COMISKEY, Doylestown, PA;
Rong FENG, Langhorne, PA;
John FOSS, Doylestown, PA;
Kunwar SHAILUBHAI, Audubon, PA;

Applicant(s)

SYNERGY PHARMACEUTICALS INC., NEW YORK, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/661,299 03/18/2015
which is a CON of 13/421,769 03/15/2012
which is a CIP of PCT/US2011/051805 09/15/2011
which claims benefit of 61/383,156 09/15/2010
and claims benefit of 61/387,636 09/29/2010
and claims benefit of 61/392,186 10/12/2010

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 09/11/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/845,644**

Projected Publication Date: 12/24/2015

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/845,644

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	10 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			200			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	930		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US

CONFIRMATION NO. 8164

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

PUBLICATION NOTICE

OC000000079559886

Title:FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Publication No.US-2015-0366935-A1
Publication Date:12/24/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	14/845,644
Filing Date	September 4, 2015
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/C02US 321994-2242

NON PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	1.	FMC BioPolymer of Avicel PH Production Instruction, 21 pages (2005).	
	2.	LAI and TOPP, "Solid-State Chemical Stability of Proteins and Peptides", Journal of Pharmaceutical Sciences, MiniReview, 88(5): 489-500 (1999).	
	3.	MIHRANYAN et al., "Moisture sorption by cellulose powders of varying crystallinity", International Journal of Pharmaceutics, 269(2): 433-442 (2004).	

Examiner Signature:	125824976 v1	Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	24496184
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein/Sandra Laramore
Filer Authorized By:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009/C02US
Receipt Date:	30-DEC-2015
Filing Date:	04-SEP-2015
Time Stamp:	19:47:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS.pdf	79274 0ed16d4cf8b504ac57b423d84e81aa354d41aa6b	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	167270 6ddc3802bf4762ebf16b5bdc86edb3a1adcaae9c	no	1

Warnings:	
Information:	
This is not an USPTO supplied IDS fillable form	
Total Files Size (in bytes):	246544

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

VIA EFS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant(s) hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98.

☐ Pursuant to 37 C.F.R. §1.98, a copy of each non-US patent document cited in the attached Form PTO/SB/08 is enclosed.

☒ Copies of the publications listed on the attached Form PTO/SB/08 are **not** being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in prior Application Serial No. **13/421,769** to which the above-identified application claims priority under 35 U.S.C. §120.

☐ No copies of any U.S. patents or U.S. patent application publications listed on the attached Form PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98.

☐ Publication(s) _____ listed on the attached Form PTO/SB/08 were cited in a foreign search or examination report corresponding to _____ application serial no. _____ and mailed on _____.

☐ Enclosed is a copy of a non-English publication(s) _____ Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s).

☐ Enclosed is a copy of a non-English publication(s) _____ English language publication _____ (copy enclosed) claims priority from this non-English publication.

☐ Enclosed is an explanation of non-English publication(s) _____ for which an English translation is not available.

☐ Enclosed is an English translation of non-English publication(s) _____ cited in the attached Form PTO/SB/08.

☐ Enclosed is a copy of pending patent Application Serial No. _____.

This Information Disclosure Statement is filed within any one of the following time periods:

☐ within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);

☐ within three months from the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in this international application;

☒ before the mailing date of a first office action on the merits; or

☐ before the mailing of a first office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form PTO/SB/08 to the undersigned.

Dated: December 30, 2015

Respectfully submitted,
COOLEY LLP

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (202) 728-7030
Fax: (202) 842-7899

By: /Anne E. Fleckenstein/
Anne E. Fleckenstein
Reg. No. 62951

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US	8164

58249 7590 01/29/2016

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
01/29/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

Office Action Summary	Application No. 14/845,644	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/04/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *12/30/2015, 09/04/2015*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claim Status

Claims 1-10 are pending.

Claims 1-10 have been examined.

Priority

This application is a CON of 14/661,299 filed on 03/18/2015 (abandoned), which is a CON of 13/421,769 filed on 03/15/2012, which is a CIP of PCT/US2011/051805 filed on 09/15/2011, which claims the benefits of 61/383,156 filed on 09/15/2010, 61/387,636 filed on 09/29/2010, and 61/392,186 filed on 10/12/2010.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 09/04/2015 and 12/30/2015 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described

> as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 2008/151257 A2, IDS #76 dated 9/4/2015) in view of Business Wire News (April 07, 2008).

Claim 1 is drawn to a method for treating a patient (intended use for treating chronic constipation) comprising orally administering to a patient a composition comprising a per unit dose of 3 mg or 6 mg of a [4,12; 7,15] bicyclic peptide consisting the peptide sequence of SEQ ID NO: 1 and a pharmaceutically acceptable excipient.

Shailubhai et al. shows a [4,12; 7,15] bicyclic peptide of guanylate cyclase receptor agonist (GCRA) of SP-304 as follows (p11, Table 1, SEQ ID NO: 1/SP-304; Fig 3) is able to enhance intracellular levels of cGMP (Fig 5). Shailubhai's SP-304/GCRA is

SP304

NDECELCVNVACTGCL SEQ ID NO: 1

identical to the [4,12; 7,15] bicyclic peptide of this instant SEQ ID NO: 1 as claimed. Shailubhai et al. suggests the use of a guanylate cyclase agonist SP-304/GCRA peptide to treat any condition that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. suggests a SP-304/GCRA peptide can be formulated in a pharmaceutical composition in unit dose form typically between 100 µg and 3g together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25). Shailubhai et al. suggests the SP-304/GCRA peptide formulated for oral composition includes an inert diluent or an edible carrier (p41, line 19-30). Shailubhai et al. shows the oral dosage of SP-304/GCRA peptide via gavage administration for the phase I trial of cynomolgus monkeys was about 1 mg/kg (p92, Example 7, line 15-20). The weight range of cynomolgus monkeys was known to be 1.7 kg – 8.0 kg according to a supplier's web page of (http://www.wwprimates.com/?q=cynomolgus-monkeys). Thus, a unit dose form of SP-304/GCRA peptide ranged from 1.7 mg to 8.0 mg was used for the phase I trial of cynomolgus monkeys.

Shailubhai et al. teaches the use of SP-304/GCRA peptide to increase intracellular levels of cGMP to treat constipation and irritable bowel syndrome (p5, line 8-21, Fig 5), but does not show the use of SP-304/GCRA peptide to treat chronic constipation.

Business Wire News 2008 reported SP-304 (Guanilib) was under clinical trial for

the treatment of chronic constipation and constipation-predominant irritable bowel syndrome because nonclinical animal studies had shown SP-304 to be well tolerated (p1, para 1-2).

One of ordinary skill in the art would be motivated to use SP-304 (Guanilib) for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome as stated by Dr. Jacob “There are only two compounds presently in this class, our drug, and linaclotide, a drug that is currently being developed by Microbia and Forest Laboratories to treat GI disorders. We believe that SP-304 has the potential to be the best in class.” (p1, para 3), reading on the use of SP-304/GCRA (Guanilib) for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome in claim 1.

With respect to claim 2, Shailubhai et al. suggests the use of a guanylate cyclase agonist of SP-304/GCRA peptide to treat any condition or disease symptom that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders of irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Business Wire News 2008 reported SP-304/GCRA (Guanilib) was under clinical trial for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome (p1, para 1).

With respect to claim 3, Shailubhai et al. shows a peptide of guanylate cyclase receptor agonist SP-304/GCRA (p11, Table 1, SEQ ID NO: 1/SP-304) able to enhance intracellular levels of cGMP and suggests the use of SP-304/GCRA peptide to treat any condition that responds to enhanced intracellular levels of cGMP, including

gastointestinal disorders include for example, irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. suggests the SP-304/ GCRA peptide can be in a pharmaceutical composition in unit dose form typically between 100 µg and 3g, e.g., 1.7 mg to 8 mg (1 mg/kg) for cynomolgus monkeys (p92, Example 7, line 15-20), together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25). Shailubhai et al. teaches a SP-304/GCRA peptide formulated for oral compositions generally include an inert diluent or an edible carrier (p41, line 19-30). With respect to claim 4, Shailubhai et al. suggests the use of a guanylate cyclase agonist of SP-304/GCRA to treat any condition that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders of irritable bowel syndrome (IBS) and constipation (p5, line 8-21).

With respect to claim 5, Shailubhai et al. suggests administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32).

With respect to claim 6, Shailubhai et al. suggests a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33).

With respect to claim 7, Shailubhai et al. suggests additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

With respect to claim 8, Shailubhai et al. suggests administration to said patient

an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32).

With respect to claim 9, Shailubhai et al. suggests a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33).

With respect to claim 10, Shailubhai et al. suggests additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*,

686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 4 of copending Application No.

14/301,812 ('812 application) in view of Shailubhai et al. (WO 2008/151257 A2). The GCC agonist peptide sequence of SEQ ID NO: 1 in claims 1 and 4 of the '812 application is identical to 1) the peptide comprising SEQ ID NO: 1 wherein the peptide is a [4,12; 7,15] bicycle in this instant claim 1 and also identical to 2) Shailubhai's GCRA SEQ ID NO: 1/SP-304 (p11, SEQ ID NO: 1). Claims 1 and 4 of the '812 application is drawn to a GCC agonist formulation comprising the instant SEQ ID NO: 1 wherein the peptide is a [4,12; 7,15] bicycle as claimed and a pharmaceutically acceptable excipient of a pH-dependent polymer. Shailubhai et al. teaches a method of using a unit dose of a GCC agonist peptide (SP-304) between 100 µg and 3g (p6, line 21-25; p38, line 21-25) for oral administration (p41, line 19-30) to treat any condition that responds to enhanced intracellular levels of cGMP comprising constipation (intrinsically including chronic constipation able to respond to enhanced intracellular levels of cGMP) or irritable bowel syndrome (p5, line 8-21), satisfying this instant claim 1.

With respect to the instant claims 2-4, Shailubhai et al. suggests the use of SEQ ID NO: 1 (SP-304) of claim 1 in the '812 application to treat any condition that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. suggests a GCRA peptide can be in a pharmaceutical composition in unit dose form typically between 100 µg and 3g together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25). Shailubhai et al. teaches a GCRA peptide formulated for oral compositions generally include an inert diluent or an edible carrier (p41, line 19-30), satisfying the instant claims 2-4.

With respect to the instant claims 5-6 and 8-9, Shailubhai et al. suggests administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist, SEQ ID NO: 1 (SP-304) of claim 1 in the '812 application, (p6, line 30-32). Shailubhai et al. further suggests a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33), satisfying the instant claims 5-6 and 8-9.

With respect to the instant claims 7 and 10, Shailubhai et al. suggests additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3 of copending Application No. 14/001,638 ('638 application) in view of Shailubhai et al. (WO 2008/151257 A2). Claim 1-3 of the '638 application is drawn to a method of making a GCC agonist peptide of SEQ ID NO: 1/SP304 (specification p15, para 54 and p17, scheme 4). Shailubhai et al. teaches the use of a unit dose of the GCC agonist peptide SP-304 between 100 µg and 3g (p6, line 21-25; p38, line 21-25) for oral administration (p41, line 19-30) to treat constipation or irritable bowel syndrome. (p5, line 8-21). Thus, this instant claim 1 is obvious to claims 1-3 of the '638 application in view of Shailubhai et al. (WO 2008/151257 A2).

With respect to the instant claims 2-4, Shailubhai et al. suggests the use of SEQ ID NO: 1 (SP-304) of claims 1-3 in the '638 application to treat any condition that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. suggests a GCRA peptide can be in a pharmaceutical composition in unit dose form typically between 100 µg and 3g together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25). Shailubhai et al. teaches a GCRA peptide formulated for oral compositions generally include an inert diluent or an edible carrier (p41, line 19-30), satisfying the instant claims 2-4.

With respect to the instant claims 5-6 and 8-9, Shailubhai et al. suggests administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32). Shailubhai et al. further suggests a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33), satisfying the instant claims 5-6 and 8-9.

With respect to the instant claims 7 and 10, Shailubhai et al. suggests additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2-9 and 42-43 (an oral dosage formulation

of SEQ ID NO: 1/SP-304), 26 and 32 (a process of making SP-304), and 36-40 (a method of using SP-304 to treat disease) of copending Application No. 13/421,769 ('769 application) in view of Shailubhai et al. (WO 2008/151257 A2). Claims 2-9 and 42-43 of the '769 application are drawn to an oral dosage formulation of comprising the peptide sequence of SEQ ID NO: 1/SP-304 (p44, Table 1, SEQ ID NO: 1) and an inert low moisture carrier. Claims 36-40 are drawn to a method of treating a disease or a disorder (e.g., irritable bowel syndrome or chronic idiopathic constipation) by administering an oral dosage of GCC agonist peptide from 0.01 mg to 10 mg and an inert low moisture carrier. Shailubhai et al. teaches a method of using a unit dose of the GCC agonist peptide SP-304 between 100 µg and 3 g (p6, line 21-25; p38, line 21-25) for oral administration (p41, line 19-30) to treat constipation or irritable bowel syndrome. (p5, line 8-21). Thus, this instant claim 1 is obvious to claims 2-9 and 42-43 of the '769 application in view of Shailubhai et al. Furthermore, this instant claim 1 is also obvious to claims 26 and 32 of the '769 application (drawn to a process of making SP-304) in view of Shailubhai's teaching of using a unit dose of the GCC agonist peptide SP-304 between 100 µg and 3g (p6, line 21-25; p38, line 21-25) for oral administration (p41, line 19-30) to treat constipation or irritable bowel syndrome (p5, line 8-21).

Claims 36-38 of the '769 application are drawn to a method of using the SEQ ID NO: 1 (SP-304) to treat a disease comprising irritable bowel syndrome and chronic idiopathic constipation. Shailubhai et al. suggests the use of the SEQ ID NO: 1 (SP-304) of claims 2-9 and 42-43 in the '769 application to treat any condition that responds to enhanced intracellular levels of cGMP, including gastointestinal disorders comprising

irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. suggests a GCRA peptide of SP-304 can be in a pharmaceutical composition in unit dose form typically between 100 µg and 3g together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25), satisfying the instant claims 2-4

Claim 39 of the '769 application is drawn to a combination of the SEQ ID NO: 1 (SP-304) and an inhibitor of a cGMP-specific phosphodiesterase. Similarly, Shailubhai et al. suggests administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32). Shailubhai et al. further suggests a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33), satisfying the instant claims 5-6 and 8-9.

Claim 40 of the '769 application is drawn to a combination of the SEQ ID NO: 1 (SP-304) and an effective amount of at least one laxative. Similarly, Shailubhai et al. suggests additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28), satisfying the instant claims 7 and 10.

These are provisional nonstatutory double patenting rejections.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-

1691. The examiner can normally be reached on Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

16-January-2016

Notice of References Cited	Application/Control No. 14/845,644	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Business Wire. Callisto Pharmaceuticals Files IND for SP-304 (Guanilib) in Chronic Constipation and Irritable Bowel Syndrome. April 07, 2008. http://www.businesswire.com/news/home/20080407005383/en/Callisto-Pharmaceuticals-F.
	V	Cynomolgus monkeys. Worldwide Primates Inc. http://www.wwprimates.com/?q=cynomolgus-monkeys.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

(FILE 'HOME' ENTERED AT 00:14:57 ON 05 JAN 2016)

FILE 'REGISTRY' ENTERED AT 00:15:34 ON 05 JAN 2016

L1 77 SEA SPE=ON ABB=ON PLU=ON NDECELCVNVACTGCL/SQSP AND SQL<=20

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 00:16:33 ON 05 JAN 2016

L2 71 SEA SPE=ON ABB=ON PLU=ON L1

L3 6 SEA SPE=ON ABB=ON PLU=ON L2 AND DISULFIDE

L4 11 SEA SPE=ON ABB=ON PLU=ON L2 AND CYCLIC

L5 50082 SEA SPE=ON ABB=ON PLU=ON (CHRONIC CONSTIPATION) OR (CHRONIC IDIOPATHIC CONSTIPATION) OR (IRRITABLE BOWEL SYNDROME)

L6 45 SEA SPE=ON ABB=ON PLU=ON L2 AND L5

L7 22 SEA SPE=ON ABB=ON PLU=ON (GUANYLATE CYCLASE RECEPTOR AGONIST)

L8 10 SEA SPE=ON ABB=ON PLU=ON L2 AND L7

L9 5754 SEA SPE=ON ABB=ON PLU=ON (CGMP-DEPENDENT PHOSPHODIESTERASE) OR (SULINDAC SULFONE) OR ZAPRINAST OR MOTAPIZONE

L10 12 SEA SPE=ON ABB=ON PLU=ON L7 AND L9

L11 29030 SEA SPE=ON ABB=ON PLU=ON LAXATIVE

L12 1794 SEA SPE=ON ABB=ON PLU=ON L5 (L) L11

L13 28 SEA SPE=ON ABB=ON PLU=ON L2 AND L11

L14 58 SEA SPE=ON ABB=ON PLU=ON L6 OR L8 OR L10 OR L13

L15 54 DUP REM L14 (4 DUPLICATES REMOVED)

L*** DEL 22 S L6 OR L8 OR L10 OR L13

L*** DEL 32 S L6 OR L8 OR L10 OR L13

L*** DEL 4 S L6 OR L8 OR L10 OR L13

L*** DEL 4 S L6 OR L8 OR L10 OR L13

L16 10 SEA SPE=ON ABB=ON PLU=ON L15 AND (AY<2010 OR PY<2010 OR PRY<2010)

E COMISKEY STEPHE?/AU

L17 40 SEA SPE=ON ABB=ON PLU=ON ("COMISKEY STEPHEN"/AU OR "COMISKEY STEPHEN DR"/AU OR "COMISKEY STEPHEN J"/AU OR "COMISKEY STEPHEN JOHN"/AU OR "COMISKEY STEPHEN W"/AU)

E FENG RON?/AU

L18 117 SEA SPE=ON ABB=ON PLU=ON "FENG RONG"/AU

E FOSS JOH?/AU

L19 45 SEA SPE=ON ABB=ON PLU=ON "FOSS JOHN"/AU

E SHAILUBHAI KUNWA?/AU

L20 116 SEA SPE=ON ABB=ON PLU=ON ("SHAILUBHAI KUNWAR"/AU OR "SHAILUBHAI KUNWAR DR"/AU)

L21 249 SEA SPE=ON ABB=ON PLU=ON L17 OR L18 OR L19 OR L20

L22 18 SEA SPE=ON ABB=ON PLU=ON L21 AND L2

L23 17 DUP REM L22 (1 DUPLICATE REMOVED)

L*** DEL 17 S L21 AND L2

L*** DEL 17 S L21 AND L2

L*** DEL 17 S L21 AND L2

L*** DEL 17 S L21 AND L2

L24 6 SEA SPE=ON ABB=ON PLU=ON L23 AND (AP<2010 OR PY<2010 OR PRY<2010)

L25 12 SEA SPE=ON ABB=ON PLU=ON L24 OR L16

D L25 1-12 IBIB ABS HITIND

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	1/5/2016	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	1/5/2016	JL
PALM Inventor Search	1/5/2016	JL
STIC search, results available on SCORE	10/28/2015	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/J.L./ Examiner.Art Unit 1676	

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CONFIRMATION NO. 8164

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/845,644	09/04/2015	514	1676	SYPA-009/C02US

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Kunwar SHAILUBHAI, Audubon, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/661,299 03/18/2015 ABN
which is a CON of 13/421,769 03/15/2012
which is a CIP of PCT/US2011/051805 09/15/2011
which claims benefit of 61/383,156 09/15/2010
and claims benefit of 61/387,636 09/29/2010
and claims benefit of 61/392,186 10/12/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
09/11/2015

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /J.L. / Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	6	10	2

ADDRESS

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UNITED STATES

TITLE

FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

FILING FEE RECEIVED		
930	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	221	(guanylate near cyclase) and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:09
L2	59	(guanylate near cyclase) same (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:09
L3	13	L2 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:13
L4	43234	(guanylate near cyclase) or (GCC near agonist) or (chronic near constipation) or (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L5	26	(guanylate near cyclase) and (GCC near agonist) and (chronic near constipation) and (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L6	1794	L4 and laxative	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L7	288	L6 and phosphodiesterase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L8	135	L7 and cGMP	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L9	32	L8 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L10	107	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26

L11	259	(Rong near3 FENG).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L12	131	(John near3 FOSS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L13	188	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L14	618	L10 or L11 or L12 or L13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L15	30	L14 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L16	42	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26
L17	17	L16 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/01/03 21:26

EAST Search History (Interference)

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1/3/2016 9:28:06 PM
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INFORMATION DISCLOSURE STATEMENT LIST

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Complete if Known	
Application Number	14/845,644
Filing Date	September 4, 2015
First Named Inventor	Stephen Comiskey
Art Unit	1676
Examiner Name	Jia-Hai Lee
Attorney Docket Number	SYPA-009/C02US 321994-2242

NON PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
/J.L/	1.	FMC BioPolymer of Avicel PH Production Instruction, 21 pages (2005).	
/J.L/	2.	LAI and TOPP, "Solid-State Chemical Stability of Proteins and Peptides", Journal of Pharmaceutical Sciences, MiniReview, 88(5): 489-500 (1999).	
/J.L/	3.	MIHRANYAN et al., "Moisture sorption by cellulose powders of varying crystallinity", International Journal of Pharmaceutics, 269(2): 433-442 (2004).	

Examiner Signature:	125824976 v1 /JIA-HAI LEE/	Date Considered	01/02/2016

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	1.	2002/0128176 A1	09-12-2002	Forssmann et al.	
	2.	2002/0078683	06-27-2002	Katayama et al.	
	3.	2002/0133168	09-19-2002	Smeldley et al.	
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Attorney Docket Number	SYPA-009/C02US

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	21.	2010/0093635 A1	04-15-2010	Shailubhai	
	22.	2010/0120694 A1	05-13-2010	Shailubhai et al.	
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	40.	5,731,159	03-24-1998	Waldman et al.	

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	41.	5,721,238	02-24-1998	Heiker et al.	
	42.	5,879,656	03-9-1999	Waldman et al.	
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First Named Inventor	Stephen COMISKEY
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	SYPA-009/C02US

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	60.	DE 19744027	04-08-1999	Hoechst Marion Rouseel Deutschland GmbH		
	61.	WO 88/05306	07-28-1988	The General Hospital Corporation		
	62.	WO 93/12068 A1	06-24-1993	Brigham and Women's Hospital		
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	76.	WO 2008/151257 A2	12-11-2008	Synergy Pharmaceuticals Inc. et al.		
	77.	WO 2009/149278 A1	12-10-2009	Synergy Pharmaceuticals Inc. et al.		
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	85.	Alrefai et al., "Cholesterol modulates human intestinal sodium-dependent bile acid transporter," Am. J. Physiol. Gastrointest. Liver Physiol. 288:G978-G985 (2005)	

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	97.	Camilleri et al. "Management of the irritable bowel syndrome" Gastroentrerol. 120:652-668 (2001)	
	98.	Carrithers et al., "Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues" Proc. Natl. Acad. Sci. USA 93:14827-14832. (1996)	

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Examiner Name	*To Be Assigned*
Attorney Docket Number	SYPA-009/C02US

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Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: **14/845644**

1. THE REQUEST FILED September 4, 2015 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination
A. ☒ for an original nonprovisional application (Track I). ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Jose' G. Dees at 571-272-1569.

/Jose' G. Dees/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

This amendment and response is submitted in response to the non-final Office Action mailed on January 29, 2016 in the above-identified application. This response is due on or before April 29, 2016.

Prior to examination of the above-identified application, please amend the application as follows:

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough and underlining. This listing also reflects any cancellation and/or addition of claims.

1. (Currently Amended) A method for treating chronic constipation in a human subject ~~patient~~ comprising orally administering to said human subject ~~patient~~ a composition comprising a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle and one or more pharmaceutically acceptable excipients.

2. The method of claim 1, wherein the constipation is associated with irritable bowel syndrome or chronic idiopathic constipation.

3. (Currently Amended) A method of treating or alleviating a symptom associated with chronic idiopathic constipation or irritable bowel syndrome in a human subject ~~patient~~ comprising orally administering to said human subject ~~patient~~ a composition comprising a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle and one or more pharmaceutically acceptable excipients.

4. The method of claim 3, wherein the symptom is constipation or abdominal pain.

5. The method of claim 1, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

6. The method of claim 5, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

7. The method of claim 1, further comprising administering to said patient an effective dose of a laxative.

8. The method of claim 3, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

9. The method of claim 8, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

10. The method of claim 3, further comprising administering to said patient an effective dose of a laxative.

REMARKS

Claim 1-10 are pending. Claims 1 and 3 have been amended. Support for the amendment can be found at paragraph [22] of the specification as filed. No new matter is added.

Claim Rejections under 35 U.S.C. § 103

Claims 1-10 are rejected under 35 U.S.C. 103 as being unpatentable over Shailubhai et al. (WO 2008/151257) ("Shailubhai") in view of Business Wire News (April 7, 2008) ("Buinsess Wire") (Office Action at page 3). Applicants traverse.

Applicants assert, that the combination Shailubhai and Business Wire fail to support a *prima facie* case of obviousness. The consistent criterion for determination of obviousness is whether the prior art would suggest to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, when viewed in the light of the prior art.[1] Moreover, the mere fact that these references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art.[2] Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel.[3] Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of unexpected results.[4]

As a preliminary matter, independent claims 1 and 3, from which all the remaining pending claims depend, have been amended to clarifying the differences between the cited art and the claimed invention. Specifically, independent claims 1 and 3, have been amended to require that the compositions are administered to a human subject. Accordingly, the claimed methods are now directed to treating chronic constipation or alleviating a symptom of chronic idiopathic constipation or irritable bowel syndrome by administering to a human subject a 3 mg or a 6 mg unit dose of a peptide consisting of SP-304.

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1 *See In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir.1988).
2 *See* MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007).
3 *See Graham* v. *John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966).

According to the Examiner, Shailubhai teaches a peptide consisting of SEQ ID NO: 1 (also known as SP-304) and that the peptide could be used to treat any condition that responds to enhanced intracellular cGMP, including constipation and irritable bowel syndrome. The Examiner further asserts that Shailubhai teaches a unit dose form typically between 100 μg and 3 g. Moreover, the Examiner asserts that Shailubhai, discloses administering a dose of 1 mg/kg to cynomolgus monkeys and concludes that since cynomolgus monkeys weigh between 1.7 kg to 8.0 kg, Shailubhai teaches a 1.7 mg to a 8 mg unit dose form of SP-304. The Examiner relies on Business Wire to show that one of ordinary skilled would be motivated to use SP-304 for the treatment of treatment of chronic constipation and constipation-predominate irritable bowel syndrome.

The Examiner's rationale for combining and modifying the references is deeply flawed. The rationale is based upon an incorrect reading of the reference on which it is based, Shailubhai. The Examiner relies on Shailubhai for providing both the reasoned basis and the expectation of success in combining and modifying Shailubhai and Buisness Wire to arrive at a composition consisting of a unit dosage form of 3 mg or 6 mg for treating constipation and irritable bowel syndrome. But the Examiner's rationale is flawed and Shailubhai fails to provide any such reasonable expectation of success in arriving at a unit dosage form for the treatment of constipation and irritable bowel syndrome, as urged by the Examiner.

Applicants submit herewith a §1.132 declaration of Kunwar Shailubhai ("Shailubhai Decl.") demonstrating that a 3 mg or 6 mg unit dose of SP-304 for a human subject, as expressly required by the amended claims, would equate to approximately a 0.05 mg/kg or a 0.1 mg/kg respectively —a 10 and 20 fold lower dose per kg than the 1 mg/kg dose administered to the cynomolgus monkeys in Shailubhai. ("Decl." at ¶5) As described by Dr. Shailubhai, using the Examiners logic, Shailubhai teaches a unit dose form of 60 mg not a 1.7 mg to a 8 mg unit dose form of as the Examiner suggests. ("Decl." at ¶6).

In summary, the combination of Shailubhai, and Business Wire fails to support a *prima facie* case of obviousness at least because both a reasoned basis and a reasonable expectation of success are lacking for making the combination and modifying the

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4 *Id.*

references. The Examiner's conclusion of obviousness is based on flawed reasoning coupled with impermissible hindsight reconstruction and should be reversed.

Even assuming, *arguendo*, that the Examiners reasoning is not flawed and the skilled person would find a reason to combine Shailubhai, and Business Wire as proffered by the Examiner, she would nevertheless lack a reasonable expectation of success with predictable results.

There is no evidence that the resultant combination of Shailubhai and Business Wire would lead the skilled artisan to arrive at the claimed invention with predictable results. These references, when considered in their entirety, fail to provide the skilled artisan with a reasonable expectation that chronic constipation could be treated or a symptom of chronic idiopathic constipation of irritable bowl syndrome could be alleviated in a human subject by administering unit dose of either 3 mg or 6 mg of SP-304. This is especially true given the accompanying Shailubhai Decl as discussed in detail below.

Shailubhai fails to disclose a composition comprising the specific unit 3 mg or 6 mg unit dose form of SP-304 as required by the instant claims. Moreover, Shailubhai fails to describe any specific disorders for which these expressly recited unit dose forms can be used to treat. In particular, Shailubhai fails to teach or suggest that any disorder, let alone chronic constipation or irritable bowel syndrome, could be treated in a human subject with a unit dose form of 3 mg or 6 mg of SP-304.

Shailubhai discloses a long list guanylate cyclase receptor agonists and disorders that could be treated therewith. Shailubhai discloses an equally broad ranges of unit dosage forms, between 100 μg and 3 g, in which the long list of guanylate cyclase receptor agonists can be formulated to treat a long list of disorders. Nowhere in Shailubhai is the specific combination of SP-304 at a unit dose of 3 mg or 6 mg to treat constipation or irritable bowel syndrome suggested. To arrive at the present invention, one of skill in the art would first have had to pick the specific combination of SP-304 and constipation or irritable bowel syndrome from the variety of combinations generally disclosed by Shailubhai and second, pick the specific 3 mg or 6 mg unit dosage form from the broad range of disclosed unit dosage forms. The combination of Shailubhai with Business Wire does not overcome the deficiencies of Shailubhai. Business Wire

does not provide any guidance for the skilled artisan to arrive at the expressly recited dosage forms of SP-304 to treat constipation and irritable bowel syndrome.

Furthermore, as described by Dr. Shailubhai, animals studies described in Shailubhai were performed to determine the safety and toxicity not to determine optimal human dosing. (Shailubhai Decl. at ¶7 and ¶10). Moreover, Shailubhai does not provide the results of the described study. Thus one of ordinary skill could not make any conclusion with respect to toxicity, let alone an appropriate therapeutic dose for humans. (Shailubhai Decl. at ¶8)

As described by Dr. Shailubhai, additional toxicity studies were performed in cynomolgus monkeys. Surprisingly, toxicity was not dose dependent, further indicating that monkey data would not be able to predict an optimal therapeutics dose. ("Decl." at ¶10) Moreover, SP304 was well tolerated at extremely high doses --with a safe high level dose of 75mg/kg/day, which is 150 and 75 times higher than the claimed 3 mg and 6 mg dose. ("Decl." at ¶10 and ¶12).

Notably, even after a dose escalation study in humans, no prediction as to an effective therapeutic dose could be determined as there was no correlation between dose and clinical effect. (Shailubhai Decl. at ¶13)

The as-filed specification and the Shailubhai Decl unequivocally demonstrate that the claimed invention yielded unexpected results. Example 1 of the as-filed specification describes a human safety and efficacy study. As shown in Figures 1-6, SP-304 treatment at all doses decreased the time to first bowel movement, increased stool frequency (SBM and CSBM), improved stool consistency, and reduced straining and abdominal discomfort. As shown in Figure 6, the 3 mg dose had a greater number of subjects report improvement in abdominal discomfort than the other doses. Based on this result and the results of a Phase 1 study showing that the efficacy of SP-304 plateaued at about 9 mg, a 3 mg and a 6 mg unit dose form was chosen for future studies. As stated by Shailubhai, these findings were surprising and unexpected. (Shailubhai Decl. at ¶14) Clinical studies confirmed the safety and efficacy of the 3 mg and 6 mg dosage form. (Shailubhai Decl.at ¶15)

Thus, the claimed invention possesses unexpected properties that could not have been predicted. Accordingly, the pending claims are non-obvious. Reconsideration and withdrawal of the rejection is requested.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: April 29, 2016

Respectfully submitted,
COOLEY LLP

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By: /Cynthia Kozakiewicz/
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Reg. No. 42764

130393727 v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF KUNWAR SHAILUBHAI UNDER 37 CFR 1.132

I, the undersigned Kunwar Shailubhai hereby declare and state as that:

1. I am the Executive Vice President and Chief Scientific Officer of Synergy Pharmaceuticals, Inc. (referred to herein as "Synergy"), the assignee of the above referenced patent application. I received my Ph.D. in Microbiology from the University of Baroda.

2. I understand that the present claims are directed to methods of treating chronic constipation or irritable bowel syndrome by administering to a human subject a per unit dose of 3 mg or 6 mg of SP-304.

3. I have reviewed the Office Action mailed January 29, 2016. I understand that the pending claims are rejected under 35 U.S.C. 103(a) as being obvious over Shailubhai et al. (WO 2008/151257) ("Shailubhai") in view of Business Wire News (April 7, 2008) ("Business Wire").

4. I make this declaration to rebut the Examiner's rejection, with which I do not agree.

5. As an initial matter, I would like to note that a 3 mg or 6 mg unit dose form of SP-304 in an average 60 kg human would equal about 0.05 mg/kg or 0.1 mg/kg respectively. This is 10 to 20 fold lower dose that the 1 mg/kg dose administered to cynomolgus monkeys in Shailubhai.

6. I would also like to point out that administering the 1 mg/kg dose of Shailubhai, in humans would amounts to a 60 mg dose form not a 1.7 mg -8 mg dose as stated by the Examiner.

7. We conducted animal studies like the one described in Shailubhai to determine the toxicity of SP-304 not to optimize human dosing

8. As described in Shailubhai Example 7, cynomolgus monkeys were first to be given a dose of 1 mg/kg, a 60 mg human unit dose form, and observed for 33 days. After the observation the cynomolgus monkeys were to be given a second dose of 10 mg/kg, a 600 mg human unit dose form, and observed for 7 days. Clinical observation of the cynomolgus monkeys were to be made, with particular attention as to the stools. As Shailubhai does not describe any actual clinical observations of the treated monkeys, one of ordinary skill could not make a conclusion with respect to toxicity, let alone an appropriate therapeutic dose for humans.

9. In fact, animal studies rarely, if at all, provide any guidance as to what would be a clinically effective dose in humans. Animal models only provide information with respect to toxicity, which serves as a guide for human safety and efficacy studies. Only after human safety and efficacy studies, like the one described in the instant specification, can a determination of a therapeutic dose be made. This is especially true for SP-304 as extremely high doses were well tolerated in monkeys, as described in detail below.

10. We completed the Shailubhai toxicity study. In summary, cynomolgus monkeys were given a daily dose of 1 mg/kg, 10 mg/ kg, 25 mg/kg and 50 mg/kg SP-304. The 1 mg/kg and the 25 mg/kg was well tolerated and did not result in any overt signs of toxicity. The 10 mg/kg and the 50 mg/kg produced mild diarrhea. Since toxicity was not dose dependent in monkeys, these data indicate that monkeys could not be used to predict human therapeutic doses.

11. In a further toxicity study, cynomolgus monkeys were given a daily dose of 100 mg/kg and 250 mg/kg SP-304. Both 100 mg/kg and the 250 mg/kg produced severe diarrhea.

12. Based upon the results of these two toxicity studies, a high level dose of 75 mg/kg/day was established. This high dose is 150 and 75 times higher than the claimed 3 mg and 6 mg human unit dose respectively

13. We then conducted a dose escalation study in humans. In this study, heathy human volunteers were administered 9 dose levels of SP-304 including 0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3 and 48.6 mg. This equates to a dose range of between about 0.0015 to 0.7 mg/kg. Pharmacodynamic assessments include time to first stool, stool frequency and stool consistency using the Bristol Stool Form Scale (BSFS). There was no correlation between BSFS and SP-304 dose. As such no prediction as to an effective therapeutic dose could be determines from this study. However, as adverse abdominal events were observed at the two highest doses (i.e. 24.3 and 48.6 mg) future human doses we limited future human doses to 9 mg or less.

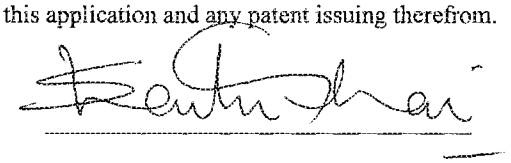
14. In the instant application, Example 1 describes a safety and efficacy study in human patients having chronic idiopathic constipation. Patients received 0.1, 1.0, 3.0 or 9.0 mg of SP-304 for 14 days. No serious adverse effects were reported for any subject. Importantly, and unexpectedly no diarrhea was reported for any subject. As shown in Figure 1-6, SP-304 treatment at all doses decreased the time to first bowel movement, increases stool frequency (SBM and CSBM), improved stool consistency, and reduced straining and abdominal discomfort. Surprising and unexpectedly, the 3 mg dose had a greater number of subjects report improvement in abdominal discomfort. (Figure 6) Based on this result and the results of a Phase 1 study showing that the efficacy of SP-304 plateaued at about 9 mg, a 3 mg and a 6 mg unit dose form was chosen for future studies. These results could not have been predicted.

15. We then conducted a Phase 3 clinical trial to evaluate the safety and efficacy study of a 3 mg and 6 mg dose in in human patients having chronic idiopathic constipation. Based upon the previous safety and efficacy studies described above, SP-304 was safe and well tolerated at both these doses.

16. A similar Phase 3 clinical trial to evaluate the safety and efficacy study of a 3 mg and 6 mg dose in in human patients having irritable bowel syndrome with constipation (IBS-C) is ongoing.

17. Accordingly, it is my opinion that that a person of ordinary skill in the art would not have selected a 3 mg or 6 mg unit dose to treat constipation or irritable bowel with constipation in humans based upon the dosages described Shailubhai.

18. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.



Signed, April 29, 2016

130586087 v1

Electronic Acknowledgement Receipt

EFS ID:	25639627
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US
Receipt Date:	29-APR-2016
Filing Date:	04-SEP-2015
Time Stamp:	16:05:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	SYPA-009_C02US_Resp_to_Office_Action.pdf	134930 45ff53bb21276e79cb3745e7f9737d2c9665ed6e	no	9

Warnings:	
Information:	

2	Oath or Declaration filed	SYPA-009_C02US_Shailubhai_Dec.pdf	3088318 57ac02012c8aa2e8d42a3cf744d5592455e88be5	no	4

Warnings:	
Information:	
Total Files Size (in bytes):	3223248

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/845,644	Filing Date 09/04/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **04/29/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/GLORIA ANTHONY/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009C02US 321994-2242	8164

58249 7590 06/03/2016

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EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
06/03/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

Office Action Summary	Application No. 14/845,644	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/29/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Claim Status

Claims 1-10 are pending.

Claims 1-10 have been examined.

Priority

This application is a CON of 14/661,299 filed on 03/18/2015 (abandoned), which is a CON of 13/421,769 filed on 03/15/2012, which is a CIP of PCT/US2011/051805 filed on 09/15/2011, which claims the benefits of 61/383,156 filed on 09/15/2010, 61/387,636 filed on 09/29/2010, and 61/392,186 filed on 10/12/2010.

Affidavit or Declaration Under 37 CFR 1.132

The affidavit under 37 CFR 1.132 filed 04/29/2016 is insufficient to overcome the rejection of claims 1-10 based upon the new ground of rejection Shailubhai et al. (WO 2008/151257 A2, IDS #76 dated 9/4/2015) in view of Shailubhai's conference abstract (Digestive Disease Week. San Diego: 2008, referred as D2) because D2 suggests the safe and most effective unit dosage of SP304 for human use is within a very narrow range between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) in the data chart (col 3, last chart), reading on 3 mg or 6 mg in claim 1. Furthermore, any dosage unit between the very narrow range of 2,7 mg and 8.1

mg is fully expect to be well-tolerated and highly effective for human use to treat the diseases as demonstrated in the data chart of SP-304 Single-dose data in volunteers (col 3, last chart). MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

Withdrawn Rejection

The rejection of claims 1-10 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 2008/151257 A2, IDS #76 in the parent application dated 9/4/2015) in view of Business Wire News (April 07, 2008) is withdrawn in view of applicant’s amendments to the claims.

The provisional rejection of claims 1-10 on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 4 of copending Application No. 14/301,812 (‘812 application) in view of Shailubhai et al. (WO 2008/151257 A2) is withdrawn in view of applicant’s amendments to the claims.

The provisional rejection of claims 1-10 on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 4 of copending Application No. 14/001,638 (‘638 application) in view of Shailubhai et al. (WO 2008/151257 A2) is withdrawn in view of applicant’s amendments to the claims.

New ground of rejection

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

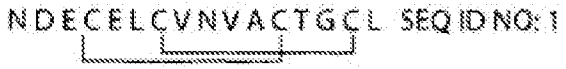
4. Considering objective evidence present in the application indicating obviousness or nonobviousness. Shailubhai et al. (WO 2008/151257 A2, IDS #76 cited in the parent application dated 9/4/2015) in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008, referred as D2).

Claim 1 is drawn to a method for treating a patient (intended use for treating chronic constipation) comprising orally administering to a human patient a composition comprising a per unit dose of 3 mg or 6 mg of a [4,12; 7,15] bicyclic peptide consisting the peptide sequence of SEQ ID NO: 1 and a pharmaceutically acceptable excipient.

Shailubhai et al. suggest the use of a guanylate cyclase agonist SP-304/GCRA peptide to treat gastrointestinal disorders comprising irritable bowel syndrome (IBS) and

constipation (p5, line 8-21). Shailubhai et al show the peptide compound of SP304 has the structure as follows (p11, Table 1; Fig 3).

SP304



Shailubhai et al. suggest the SP304 peptide can be formulated in a pharmaceutical composition in unit dose form between 100 µg and 3g together with one or more pharmaceutically acceptable excipients (p6, line 21-25; p38, line 21-25). Shailubhai et al. further suggest the administration of SP304 to treat human diseases (Abstract; p38, 19-20).

Shailubhai et al. do not specify a unit dose suitable for administration to human.

D2 teaches the use of a compound SP-304 for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract). D2 suggests the safe and most effective unit dosage for human use is between 2.7 mg and 8.1 mg, such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg), in the data chart (col 3, last chart), reading on 3 mg or 6 mg in claim 1. MPEP 2144.05 states “In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

With respect to claim 2, Shailubhai et al. suggest the use of a guanylate cyclase agonist of SP-304 peptide to treat gastrointestinal disorders of irritable bowel syndrome (IBS) and constipation (p5, line 8-21). D2 teaches the use of the same compound SP-

304 for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract).

With respect to claim 3, Shailubhai et al. suggest the use of SP-304 to treat human gastrointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Similarly, D2 teaches the use of the same SP-304 for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract). D2 further suggests the most effective unit dosage for human use is between 2.7 mg and 8.1 mg, such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg), in the data chart (col 3, last chart), reading on unit dosage of 3 mg or 6 mg.

With respect to claim 4, Shailubhai et al. suggest the use of a guanylate cyclase agonist of SP304 to treat gastrointestinal disorders of irritable bowel syndrome (IBS) and constipation (p5, line 8-21). D2 teaches the use of a compound SP-304 for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract).

With respect to claim 5, Shailubhai et al. suggest administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32).

With respect to claim 6, Shailubhai et al. suggest a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33).

With respect to claim 7, Shailubhai et al. suggest additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

With respect to claim 8, Shailubhai et al. suggest administration to said patient an effective dose of an inhibitor of cGMP-specific phosphodiesterase (cGMP-PDE) either concurrently or sequentially with said guanylate cyclase receptor agonist (p6, line 30-32).

With respect to claim 9, Shailubhai et al. suggest a cGMP-dependent phosphodiesterase inhibitor can be sulindac sulfone, zaprinast, and motapizone (p6, line 32-33).

With respect to claim 10, Shailubhai et al. suggest additional therapeutic agents to treat gastrointestinal disorders and constipation with a laxative of commercial products comprising Plantago Ovata® or Equalactin® and others (p51, line 17-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Shailubhai's SP304 peptide with D2's teaching of safe and effective dosage of SP304 because D2 suggests Shailubhai's SP304 is safe and most effective at 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) for human use in the data chart (col 3, last chart; col 4, conclusion). The combination would have reasonable expectation of success.

Response to Arguments

Applicant's arguments of the unit dosage of the therapeutic peptide of SEQ ID NO: 1 (SP304) is nonobvious to Shailubhai et al. (WO 2008/151257 A2) in view of

Business Wire News filed 04/29/2016 have been fully considered but they are not persuasive because this instant rejection is based on Shailubhai et al. (WO 2008/151257 A2) in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008, referred as D2) whereas applicant argues the different combination of Shailubhai et al. in view of Business Wire News.

Applicant argues 1) the unit dosage is limited to human use not taught by the primary reference of Shailubhai et al., 2) Shailubhai's therapeutic unit dosage for monkey is not suitable unit dosage for human, 3) Shailubhai fails to disclose a composition comprising the specific unit 3 mg or 6 mg unit dose form of SP-304 and fails to show a specific disease of treatment, 4) Shailubhai fails to address toxicity.

With respect to applicant's arguments 1-4, D2 teaches the use of a compound SP-304 for treatment of human chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract). D2 suggests the safe and best effective unit dosage for human use is between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) in the data chart (col 3, last chart), reading on 3 mg or 6 mg in claim 1. D2 further suggests SP304 was safe and well-tolerated without severe diarrhea as well as no systemic absorption via oral administration (col 4, conclusion). Thus, one of ordinary skill in the art would be taught and motivated to optimize the unit dosage of SP304 between 2.7 mg and 8.1 mg, such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg), according the human clinical trial results in D2 (col 3, last chart). Furthermore, applicant argues the primary reference alone; whereas, the rejection is based on Shailubhai et al.

(WO 2008/151257 A2) in view of a second reference Shailubhai et al. (Digestive Disease Week. San Diego: 2008, referred as D2). It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091,231 USPQ 375 (Fed. Cir. 1986).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-5, 7-8, and 10 are provisionally rejected on the ground of nonstatutory double patenting as being obvious over claims 1 and 4 of copending Application No. 14/301,812 (‘812 application) in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008, referred as D2). The GCC agonist peptide sequence of SEQ ID NO: 1 in claims 1 and 4 of the ‘812 application is identical to the peptide comprising SEQ ID NO: 1 wherein the peptide is a [4,12; 7,15] bicycle in this instant claim 1 and also identical to Shailubhai’s SP304 in the second reference. Claims 1 and 4 of the ‘812 application are drawn to a GCC agonist formulation comprising the instant SEQ ID NO: 1 wherein the

peptide is a [4,12; 7,15] bicycle as claimed and a pharmaceutically acceptable excipient of a pH-dependent polymer. D2 suggests a method of using a unit dose of a GCC agonist peptide (SP-304) between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) in the data chart (col 3, last chart) for oral administration to human treat chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract), satisfying this instant claim 1.

With respect to the instant claims 2-4, D2 suggests the use of SP-304 of claim 1 in the '812 application to treat human chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases via oral administration (Abstract). D2 suggests a method of using a unit dose of a GCC agonist peptide (SP-304) between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) via oral administration (Abstract; col 3, last chart).

With respect to the instant claims 5 and 8, claim 34 in the '812 application teaches the composition further comprising an inhibitor of cGMP-dependent phosphodiesterase.

With respect to the instant claims 7 and 10, claim 36 in the '812 application teaches the composition further comprising an effective dose of a laxative.

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2-9 and 42-43 (an oral dosage formulation of SEQ ID NO: 1/SP-304), 26 and 32 (a process of making SP-304), and 36-40 (a

method of using SP-304 to treat disease) of copending Application No. 13/421,769 ('769 application) in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008, referred as D2). Claims 2-9 and 42-43 of the '769 application are drawn to an oral dosage formulation of comprising the peptide sequence of SEQ ID NO: 1/SP-304 (p44, Table 1, SEQ ID NO: 1) and an inert low moisture carrier. Claims 36-40 are drawn to a method of treating a disease or a disorder (e.g., irritable bowel syndrome or chronic idiopathic constipation) by administering an oral dosage of GCC agonist peptide from 0.01 mg to 10 mg and an inert low moisture carrier. D2 teaches a method of using a unit dose of the GCC agonist peptide SP-304 between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) for oral administration to treat chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases (Abstract). Thus, this instant claim 1 is obvious to claims 2-9 and 42-43 of the '769 application in view of D2. Furthermore, this instant claim 1 is also obvious to claims 26 and 32 of the '769 application (drawn to a process of making SP-304) in view of D2's teaching of using a unit dose of SP-304 between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg) for oral administration to treat chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other GI diseases (Abstract).

Claims 36-38 of the '769 application are drawn to a method of using the SEQ ID NO: 1 (SP-304) to treat a disease comprising irritable bowel syndrome and chronic idiopathic constipation. D2 teaches the use of a compound SP-304 for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C), and other

GI diseases via oral administration (Abstract). D2 further suggests the most effective unit dosage for human use is between 2.7 mg and 8.1 mg such as 2.7 mg (rounding up to 3 mg) or 5.4 mg (rounding up to 6 mg), satisfying the instant claims 2-4

Claim 39 of the '769 application is drawn to a combination of the SEQ ID NO: 1 (SP-304) and an inhibitor of a cGMP-specific phosphodiesterase, satisfying the instant claims 5 and 8.

Claim 40 of the '769 application is drawn to a combination of the SEQ ID NO: 1 (SP-304) and an effective amount of at least one laxative, satisfying the instant claims 7 and 10.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

/SATYANARAYANA R GUDIBANDE/
Primary Examiner, Art Unit 1676

Notice of References Cited	Application/Control No. 14/845,644	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Shailubhai, K.; Gerson, W.; Talluto, C.; Jacob, G. Digestive Disease Week. San Diego: 2008. A randomized, double-blind, placebo-controlled, single-, ascending-, oral-dose safety, tolerability and pharmacokinetic study of SP-304 in healthy adult human male and female volunteers.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

(FILE 'HOME' ENTERED AT 21:51:41 ON 21 MAY 2016)

FILE 'REGISTRY' ENTERED AT 21:51:58 ON 21 MAY 2016

L1 77 S NDECELCVNVACTGCL/SQSP AND SQL<=20

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 21:52:31 ON 21 MAY 2016

L2 76 S L1

L3 13 S L2 AND CYCLIC

L4 52042 S (CHRONIC CONSTIPATION) OR (CHRONIC IDIOPATHIC CONSTIPATION) OR (IRRITABLE BOWEL SYNDROME)

L5 49 S L2 AND L4

L6 5800 S (CGMP-DEPENDENT PHOSPHODIESTERASE) OR (SULINDAC SULFONE) OR ZAPRINAST OR MOTAPIZONE

L7 10 S L5 AND L6

L8 29976 S LAXATIVE

L9 31 L2 AND L8

L10 44 S L3 OR L7 OR L9

L11 41 DUP REM L10 (3 DUPLICATES REMOVED)

L12 9 S L11 AND (AD<2011 OR PD<2011 OR PRD<2011)

E COMISKEY STEPHE?/AU

L13 40 S E4-E8

E FENG RON?/AU

L14 123 S FENG RONG/AU

E FOSS JOH?/AU

L15 115 S E28-E34

E SHAILUBHAI KUNWA?/AU

L16 119 S E40-E41

=> S L13 or L14 or L15 or L16

L17 318 L13 OR L14 OR L15 OR L16

=> S L17 and L2

L18 19 L17 AND L2

=> S L18 and L4

L19 11 L18 AND L4

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	232	(guanylate near cyclase) and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L2	60	(guanylate near cyclase) same (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L3	13	L2 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L4	44348	(guanylate near cyclase) or (GCC near agonist) or (chronic near constipation) or (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L5	27	(guanylate near cyclase) and (GCC near agonist) and (chronic near constipation) and (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L6	1843	L4 and laxative	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L7	298	L6 and phosphodiesterase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L8	138	L7 and cGMP	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L9	32	L8 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L10	109	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38

L11	263	(Rong near3 FENG).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L12	134	(John near3 FOSS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L13	194	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L14	629	L10 or L11 or L12 or L13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L15	32	L14 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L16	44	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L17	19	L16 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L18	151	SP304 or SP-304 pr (SP near "304")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L19	24	L18 same unit	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L20	0	L18 same constipation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L21	32	L18 and constipation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38
L22	31	L21 and unit	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2016/05/21 21:38

EAST Search History (Interference)

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	5/21/2016	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	5/21/2016	JL
PALM Inventor Search	5/21/2016	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/J.L./ Examiner.Art Unit 1676	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

This amendment and response is submitted in response to the Final Office Action mailed on June 3, 2016 in the above-identified application. This response is timely filed by September 3, 2016. As September 3, 2016 is a Saturday, and the following Monday, September 5, 2016, is a federal holiday, this response is timely filed by September 6, 2016 per the next-business-day rule.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough and underlining. This listing also reflects any cancellation and/or addition of claims.

1. (Currently Amended) A method for treating chronic constipation in a human subject comprising orally administering to said human subject a composition ~~comprising~~ consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months ~~and one or more pharmaceutically acceptable excipients~~.

2. (Original) The method of claim 1, wherein the constipation is associated with irritable bowel syndrome or chronic idiopathic constipation.

3. (Currently Amended) A method of treating or alleviating a symptom associated with chronic idiopathic constipation or irritable bowel syndrome in a human subject comprising orally administering to said human subject a composition ~~comprising~~ consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months ~~and one or more pharmaceutically acceptable excipients~~.

4. (Original) The method of claim 3, wherein the symptom is constipation or abdominal pain.

5. (Original) The method of claim 1, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

6. (Original) The method of claim 5, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

7. (Original) The method of claim 1, further comprising administering to said patient an effective dose of a laxative.

8. (Original) The method of claim 3, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

9. (Original) The method of claim 8, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

10. (Original) The method of claim 3, further comprising administering to said patient an effective dose of a laxative.

REMARKS

Claims 1-10 are pending. Claims 1 and 3 are amended herein to recite the composition comprises a low-moisture inert carrier and a lubricant, and the peptide has a chromatographic purity of no less than 91% after storage for at least three months. Support for these amendments can be found throughout the application as filed, and specifically for example, in Example 14 and paragraph [040]. No new matter is added.

The Examiner rejected claims 1-10 under 35 U.S.C. § 103(a) as allegedly being obvious over Shailubhai *et al.* (WO 2008/151257' "the '257 publication") in view of Shailubhai *et al.* (2008; "Shailubhai Abstract"). Office Action at page 4. Specifically, the Examiner alleges the '257 publication teaches the use of a guanylate cyclase agonist SP-304 to treat gastrointestinal disorders including irritable bowel syndrome and constipation. *Id.* at pages 4-5. The Examiner further asserts the '257 publication teaches the SP-304 peptide can be formulated in a pharmaceutical composition in unit dose form between 100 μg and 3g together with one or more pharmaceutically acceptable excipients. *Id.* at page 5. While the Examiner concedes that the '257 publication does not specify a unit dose suitable for administration to humans, the Examiner contends the Shailubhai Abstract teaches the use of SP-304 for the treatment of chronic constipation, irritable bowel syndrome with constipation, and other GI disease via oral administration. *Id.* The Examiner thus argues that it would have been obvious to the skilled artisan to have combined the SP-304 peptide disclosed in the '257 publication with the Shailubhai Abstract's teaching of safe and effective administration of 2.7 mg or 5.4 mg of SP-304 with a reasonable expectation of success. *Id.* at page 7.

Applicants respectfully disagree. A *prima facie* case of "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The present claims are amended to recite the formulation consists of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. This is neither taught nor suggested in the cited art. The '257 publication does not teach or suggest a formulation consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle,

an inert low moisture carrier, and a lubricant where the peptide has a chromatographic purity of no less than 91% after storage for at least three months. Nothing in the '257 publication teaches or suggests a formulation with such characteristics. The Examiner has therefore failed to make a *prima facie* case of obviousness.

Nor does the Shailubhai Abstract cure the deficiencies of the '257 publication. Neither of these references teaches or suggests a formulation consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. The rejection fails for this reason alone.

Even assuming, arguendo, that the skilled person would find a reason to combine the '257 publication with the teaching of the Shailubhai Abstract, such combination still would not have led one to arrive at the instant claims. For a determination of obviousness the prior art must suggest to one of ordinary skill in the art that this method should be carried out and that one of ordinary skill would have a reasonable likelihood of success, when viewed in the light of the prior art. Moreover, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of unexpected results.

Applicants submit herewith that a §1.132 declaration of Dr. Comiskey ("Comiskey Decl.") demonstrating that formulation having a low-moisture inert carrier as recited in the amended claims shows superior results compared with formulations taught in the art, and are more stable than expected compared to formulations comprising a regular-grade carrier. *See* Comiskey Decl. at ¶ 7. Formulations containing a low-moisture carrier demonstrate unexpectedly dramatically decreased amounts of impurities. *See* Comiskey Decl. at ¶ 7-8. These data demonstrate that the formulation required by the claimed methods provides an unexpectedly superior result relative to formulations taught in the art. As noted by Dr. Comiskey, stability of the active ingredient, the peptide of SEQ ID NO: 1, is essential to insure proper dosing in the treatment of chronic constipation or irritable bowel syndrome. *See* Comiskey Decl. at ¶ 9

The cited art therefore does not provide a suggestion of all elements of the pending claims. Nor does it teach or predict the surprising stability demonstrated by the instantly claimed formulations. Accordingly the claimed formulations are not obvious, and Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: September 6, 2016

Respectfully submitted,
COOLEY LLP

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By: /Anne E. Fleckenstein/
Anne E. Fleckenstein, Ph.D.
Reg. No. 62,951

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

U.S. Patent and Trademark Office
Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned Stephen Comiskey, declare and as follows:

1. I am the Vice President of Product Development of Synergy Pharmaceutical's the assignee of the above reference patent application I received him B.S. in Biochemistry, M.S. in Food Chemistry, and Ph.D. in Pharmaceutics from the University of Wisconsin-Madison.

2. I understand that the present claims are directed to directed to methods of treating chronic constipation or irritable bowel syndrome by administering to a human subject a composition consisting of a per unit dose of 3 mg or 6 mg of SP-304 (SEQ ID NO: 1), an inert low moisture carrier, and a lubricant, and wherein the SP-304 in the composition has a chromatographic purity of no less than 91% after storage for at least three months.

3. I have reviewed the Office Action mailed June 3, 2016. I understand that the pending claims are rejected under 35 U.S.C. 103(a) as being obvious over Shailubhai *et al.* (WO

2008/151257; "the '257 publication) in view of Shailubhai *et al.* (2008; "the Shailubhai Abstract").

4. I make this declaration to rebut the Examiner's rejection, with which I do not agree.

5. At the time of filing, those working in the field would not have found the presently formulation recited in the claims obvious based on the teachings of the '257 publication in view of the Shailubhai Abstract. It is my opinion that the claimed methods are not obvious over the above cited references, for at least the following reasons.

6. We conducted studies to test the stability and purity of various formulations comprising the peptide of SEQ ID NO:1 (SP-304) and discovered that a low-moisture carrier improved the stability of a GCC agonist peptide compared to a regular grade carrier.

7. Appendix A shows total impurities and impurities with relative retention time (RRT) of 0.97 and 1.33 at both 25°C and 40°C in formulations of GCC agonist peptides comprising the low-moisture carrier (Avicel PH112) compared with the regular grade carrier (Avicel PH102). Formulations of plecanatide (a GCC agonist peptide of SEQ ID NO: 1) tablet with low moisture Avicel PH112 shows improved stability compared to regular grade Avicel.

8. This reduction in total impurities and impurities with relative retention time (RRT) of 0.97 and 1.33 with the low-moisture carrier (Avicel PH112) is surprising. Other than the low-moisture element of Avicel PH112, the two carriers are the same, but the reduced moisture content of the low-moisture carrier (~1.5%)[1] had a greater effect on peptide stability than expected. As shown in Appendix A, a 1.5% reduction in the water content resulted in approximately a 37% decrease in total impurities at 9 months at 25°C (2.733±0.289 for Avicel PH102; 1.7±0.00 for Avicel PH112) and approximately a 29% decrease in total impurities at 6 months at 40°C (4.767±0.322 for Avicel PH102;

[1] http://www.fmcbiopolymer.com/Portals/bio/content/Docs/PS-Section%2011.pdf, at page 9.

3.36±0.207 for Avicel PH112). This dramatic reduction in impurities was surprising unexpected.

9. In my opinion the superior stability of the formulation as required by the claims is not without consequence. As without stability of the active ingredient (i.e., the peptide of SEQ ID NO:1) accurate dosing to treat chronic constipation or irritable bowel syndrome could not be accomplished.

10. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

S. Comiskey

Stephen Comiskey

Signed, September 6, 2016

APPENDIX A

Improved Plecanatide Tablet Stability (reduced impurity levels) using low moisture Avicel PH112 compared to regular Avicel PH102
Created July 10, 2014

		Sum of Total Impurities (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	2.4	2.6	2.6	2.9	2.9	2.9	3.2	3.3	2.4	3.2	3.6	4.2	4.9
11H140 (3mg capsule)	PH102	2.1	2.5	2.7	2.6	2.8	2.9	3.4	3.6	2.1	3.5	3.6	4.0	5.0
12G080 (3mg tablet)	PH102	1.9	2.7	2.2	2.3	2.4	2.4	2.7		1.9	3.0	2.8	3.2	4.4
13C049 (3mg tablet)	PH112	1.2	1.2	1.4	1.4	1.7	1.7			1.2	1.7	2.1	3.1	3.2
13C050 (3mg tablet)	PH112	1.2	1.2	1.3	1.4	1.7	1.7			1.2	1.7	2.1	2.3	3.4
13C051 (6mg tablet)	PH112	1.1	1.2	1.3	1.4	1.5	1.7			1.1	1.7	2.5	2.2	3.2
13E090 (3mg tablet)	PH112	1.3	1.2	1.2	1.4	1.6				1.3	1.8	2.5	2.6	3.3
13F106 (6mg tablet)	PH112	1.7	1.6	1.5	1.9	2.1				1.7	1.9	2.6	2.8	3.7

		Impurity RRT 0.97 (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	0.48	0.26	0.34	0.00	0.43	0.33	0.38	0.20	0.48	0.29	0.31	0.31	0.33
11H140 (3mg capsule)	PH102	0.11	0.20	0.26	0.00	0.31	0.36	0.63	0.15	0.11	0.22	0.25	0.24	0.25
12G080 (3mg tablet)	PH102	0.00	0.30	0.00	0.30	0.00	0.00	0.00		0.00	0.34	0.00	0.00	0.00
13C049 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00	0.00	0.00
13C050 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00	0.00			0.00	0.00	0.00	0.00	0.00
13C051 (6mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00
13E090 (3mg tablet)	PH112	0.00	0.00	0.00	0.00	0.00				0.00	0.00	0.00	0.00	0.00
13F106 (6mg tablet)	PH112	0.00	0.12	0.00	0.15	0.19				0.00	0.00	0.18	0.00	0.12

		Impurity RRT 1.33 (Area%)												
		25C								40C				
Batch (dosage form)	Months→ Avicel↓	0	1	2	3	6	9	12	18	0	1	2	3	6
2011F100A (3mg capsule)	PH102	0.29	0.49	0.54		0.69	0.92	1.10	1.32	0.29	1.00	1.36	1.73	2.49
11H140 (3mg capsule)	PH102	0.31	0.45	0.54	0.60	0.79	0.95	1.04	1.48	0.31	1.10	1.48	1.84	2.77
12G080 (3mg tablet)	PH102	0.12	0.21	0.29	0.34	0.50	0.57	0.61		0.12	0.54	0.83	0.97	1.53
13C049 (3mg tablet)	PH112	0.22	0.29	0.36	0.38	0.56	0.58			0.22	0.65	0.82	1.54	1.45
13C050 (3mg tablet)	PH112	0.21	0.32	0.33	0.39	0.54	0.58			0.21	0.62	0.84	0.95	1.42
13C051 (6mg tablet)	PH112	0.22	0.26	0.35	0.38	0.50				0.22	0.66	1.15	0.90	1.39
13E090 (3mg tablet)	PH112	0.25	0.31	0.37	0.43	0.51				0.25	0.65	0.94	1.11	1.43
13F106 (6mg tablet)	PH112	0.20	0.26	0.29	0.43	0.47				0.20	0.59	0.76	1.03	1.38

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
SYPA-009C02US 321994-2242	14/845,644	09-04-2015
First Named Inventor:	**Title:**	
Stephen COMISKEY	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Anne E. Fleckenstein/	September 6, 2016
Name (Print/Typed) Anne E. Fleckenstein	**Practitioner Registration No.** 62,951

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☑ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	26838955
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009C02US 321994-2242
Receipt Date:	06-SEP-2016
Filing Date:	04-SEP-2015
Time Stamp:	16:13:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	SYPA_009_C02US_ResponseOA.pdf	125496 72c348ec586e55ba891030af2c5b19a5c05deb51	no	6

Warnings:

Information:					
2	Miscellaneous Incoming Letter	SYPA_009_C02US_Declaration.pdf	688557 733f13cf815d265db532e6ac15feada231363967	no	5
Warnings:					
Information:					
3	After Final Consideration Program Request	SYPA_009_C02US_AFCP.pdf	227059 6224a2937f2a45074e99fcfd7d260f73a39a2b82	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1041112	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
14/845,644	09/04/2015	

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

09/06/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
HENRIETT K. DENDY

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/845,644
Filing Date	September 4, 2015
First Named Inventor	Stephen COMISKEY
Title	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/C02US 321994-2242

SIGNATURE of Applicant or Patent Practitioner

Signature	/Anne E. Fleckenstein/	Date (Optional)	September 15, 2016
Name	Anne E. Fleckenstein	Registration Number	62,951
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/82B(07-13)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

58249

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

SYNERGY PHARMACEUTICALS INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	Oct. 6, 2014
Name	Gary S. Jacob, Ph.D.		
Title	President and Chief Executive Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

Electronic Acknowledgement Receipt

EFS ID:	26939762
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009C02US 321994-2242
Receipt Date:	15-SEP-2016
Filing Date:	04-SEP-2015
Time Stamp:	16:50:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	SYPA_009_C02US_POA.pdf	346333 942b5bbdb6a08efc1aa05b9e319f641be415710f	no	2

Warnings:

Information:	
Total Files Size (in bytes):	346333

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224

CONFIRMATION NO. 8164

POA ACCEPTANCE LETTER

58249
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000085961880

Date Mailed: 09/22/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/15/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ylueng/

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	14845644
Filing Date	04-Sep-2015
First Named Inventor	Stephen COMISKEY
Attorney Docket Number	SYPA-009/C02US 321994-224
Title of Invention	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Synergy Pharmaceuticals, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

13421769 filed on 03/15/2012

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ◉ Small Entity ○ Micro Entity ○ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 62951 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request

Signature	/Anne E Fleckenstein/
Name	Anne E Fleckenstein

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14845644
Filing Date:	04-Sep-2015
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009/C02US 321994-224

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14845644

Filing Date: 04-Sep-2015

Applicant/Patent under Reexamination: COMISKEY et al.

Electronic Terminal Disclaimer filed on September 22, 2016

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	27002725
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US 321994-224
Receipt Date:	22-SEP-2016
Filing Date:	04-SEP-2015
Time Stamp:	15:53:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	2502
Deposit Account	501283
Authorized User	Fleckenstein, Anne

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	33988 b77af4c01dbf369a335f9fb23dca00fb0924645a	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30382 438cc7141a08135a0c636cfbb8d4067117f6f92e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64370		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224	8164

58249 7590 09/29/2016

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
09/29/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zpatdcdocketing@cooley.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/845,644	COMISKEY ET AL.	
	Examiner	Art Unit	
	JIA-HAI LEE	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JIA-HAI LEE*.

(2) *Satyanarayana R. Gudibande*.

(3) *Ivor Elirifi*.

(4) *Cynthia Kozakiewicz*.

Date of Interview: *15 September 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Shailubhai et al. (SP-304 poster, D2 reference) and Shailubhai et al. (WO 2008/151257 A2)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

No agreement was reached. Applicant's amendment may overcome the prior art rejection on record if the amendment is entered. However, the amended claims, if entered, would be subjec to the new ground of rejection of Currie et al. (WO 2005/016244 A2) in view of FMC biopolymer product (2005), in view of Fretzen et al. (US 2010/0048489 A1) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, recited). The same rejection has been applied to the copending application 13/421,769.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J. L./ Examiner, Art Unit 1676	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 14/845,644	**Applicant(s)** COMISKEY ET AL.	
	Examiner JIA-HAI LEE	**Art Unit** 1676	**AIA (First Inventor to File) Status** No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 September 2016 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;

(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

14. ☒ Other: PTO-2323, A.NE., PTO413, PTO-892.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: 1-10.
Claim(s) withdrawn from consideration: .

/KARLHEINZ R SKOWRONEK/ Supervisory Patent Examiner, Art Unit 1676	/J. L./ Examiner, Art Unit 1676

Continuation of 3. NOTE: The amended claims raise new issues that requiring new search and examination. The priority date of this application would be also changed by the proposed amendment.

Continuation of 12. does NOT place the application in condition for allowance because: The argument is based on the amended claims, but the amended claims have not been entered. If the amended claims were entered, the claims would be subjec to at least the new ground of rejection of Currie et al. (WO 2005/016244 A2) in view of FMC biopolymer product (2005), in view of Fretzen et al. (US 2010/0048489 A1) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, recited). The same rejection has been applied to the copending application 13/421,769.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/845,644	COMISKEY ET AL.	
	Examiner	Art Unit	
	JIA-HAI LEE	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JIA-HAI LEE*.

(2) *Satyanarayana R. Gudibande*.

(3) *Ivor Elirifi*.

(4) *Cynthia Kozakiewicz*.

Date of Interview: *15 September 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Shailubhai et al. (SP-304 poster, D2 reference) and Shailubhai et al. (WO 2008/151257 A2)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

No agreement was reached. Applicant's amendment may overcome the prior art rejection on record if the amendment is entered. However, the amended claims, if entered, would be subjec to the new ground of rejection of Currie et al. (WO 2005/016244 A2) in view of FMC biopolymer product (2005), in view of Fretzen et al. (US 2010/0048489 A1) and in view of Shailubhai et al. (Digestive Disease Week. San Diego, 2008, recited). The same rejection has been applied to the copending application 13/421,769.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J. L./ Examiner, Art Unit 1676	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

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Notice of References Cited	Application/Control No. 14/845,644	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2010/0048489 A1	02-2010	Fretzen; Angelika	A61K9/1611	514/1.1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2005016244A2	02-2005	US	Currie et al.	A61K
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	FMC BioPolymer Catalog. 2005.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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24 February 2005 (24.02.2005)

PCT

(10) International Publication Number
WO 2005/016244 A2

(51) International Patent Classification[7]: A61K

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PCT/US2004/018751

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(25) Filing Language: English

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(30) Priority Data:

60/478,492	13 June 2003 (13.06.2003)	US
60/532,361	23 December 2003 (23.12.2003)	US
60/571,386	14 May 2004 (14.05.2004)	US

(71) Applicant *(for all designated States except US)*: **MICROBIA, INC.** [US/US]; 320 Bent Street, Cambridge, MA 02141 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CURRIE, Mark, G.** [US/US]; 18 Hall Avenue, Sterling, MA 01564 (US). **MAHAJAN-MIKLOS, Shalina** [IN/US]; 14 Holland Street, Needham, MA 02492 (US). **LI, Jing, Sun** [US/US]; 41 Fenno Street, Cambridge, MA 02138 (US).

(74) Agent: **MEIKLEJOHN, Anita, L.**; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys

Human Guanylin (SEQ ID NO:)

--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

(57) Abstract: Compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudoobstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders are described. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

WO 2005/016244 A2

ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

TECHNICAL FIELD

This invention relates to methods and compositions for treating gastrointestinal disorders, obesity, congestive heart failure, benign prostatic hyperplasia and other disorders.

BACKGROUND

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that affects 20 to 60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable Bowel Syndrome Industry Update, September 1999). IBS is the most common disorder diagnosed by gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care physicians (Camilleri 2001 *Gastroenterology* 120:652-668). In the US, the economic impact of IBS is estimated at $25 billion annually, through direct costs of health care use and indirect costs of absenteeism from work (Talley 1995 Gastroenterology 109:1736-1741). Patients with IBS have three times more absenteeism from work and report a reduced quality of life. Sufferers may be unable or unwilling to attend social events, maintain employment, or travel even short distances (Drossman 1993 *Dig Dis Sci* 38:1569-1580). There is a tremendous unmet medical need in this population since few prescription options exist to treat IBS.

Patients with IBS suffer from abdominal pain and a disturbed bowel pattern. Three subgroups of IBS patients have been defined based on the predominant bowel habit: constipation-predominant (c-IBS), diarrhea-predominant (d-IBS) or alternating between the two (a-IBS). Estimates of individuals who suffer from c-IBS range from 20-50% of the IBS patients with 30% frequently cited. In contrast to the other two subgroups that have a similar gender ratio, c-IBS is more common in women (ratio of 3:1) (Talley et al. 1995 *Am J Epidemiol* 142:76-83).

The definition and diagnostic criteria for IBS have been formalized in the "Rome Criteria" (Drossman et al. 1999 *Gut* 45:Suppl II:1-81), which are well accepted in clinical practice. However, the complexity of symptoms has not been explained by anatomical abnormalities or

metabolic changes. This has led to the classification of IBS as a functional GI disorder, which is diagnosed on the basis of the Rome criteria and limited evaluation to exclude organic disease(Ringel et al. 2001 *Annu Rev Me*d 52: 319-338). IBS is considered to be a "biopsychosocial" disorder resulting from a combination of three interacting mechanisms: altered bowel motility, an increased sensitivity of the intestine or colon to pain stimuli (visceral sensitivity) and psychosocial factors (Camilleri 2001 *Gastroenterology* 120:652-668). Recently, there has been increasing evidence for a role of inflammation in the etiology of IBS. Reports indicate that subsets of IBS patients have small but significant increases in colonic inflammatory and mast cells, increased inducible nitric oxide (NO) and synthase (iNOS) and altered expression of inflammatory cytokines (reviewed by Talley 2000, Medscape Coverage of DDW Week).

SUMMARY OF THE INVENTION

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudoobstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

The present invention also features compositions and related methods for treating obesity, congestive heart failure and benign prostatic hyperplasia (BPH).

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful because they can increase gastrointestinal motility.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful, in part, because they can decrease inflammation.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are also useful because they can decrease gastrointestinal pain or visceral pain.

The invention features pharmaceutical compositions comprising certain peptides that are capable of activating the guanylate-cyclase C (GC-C) receptor. Also within the invention are pharmaceutical compositions comprising a peptide of the invention as well as combination compositions comprising a peptide of the invention and one or more additional therapeutic agents, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of additional therapeutic agents include: acid reducing agents such as proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole), H2 receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemcinal fumarate), 5HT receptor agonists (e.g. 5HT4 receptor agonists such as Zelnorm®; 5HT3 receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT1, 5HT2, 5HT3 (e.g., alosetron), 5HT4 receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN™ (ChemoCentryx, Inc.; San Carlos, CA)), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (e.g., motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be used in combination with agents such as tianeptine (Stablon®) and other agents described in U.S. 6,683,072, (E)-4 (1,3bis(cyclohexylmethyl)-1,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can also be used in combination with treatments entailing the administration of microorganisms useful in the treatment of gastrointestinal disorders such as IBS. Probactrix®

(The BioBalance Corporation; New York, NY) is one example of a formulation that contains microorganisms useful in the treatment of gastrointestinal disorders. The peptides can also be used in combination with purgatives that draw fluids to the intestine (e.g., Visicol®, a combination of sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate.

In addition, the pharmaceutical compositions can include one or more agents selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3 (e.g., alosetron, ATI-7000; Aryx Thearpeutics, Santa Clara CA), 5HT4, 5HT2, and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT2, 5HT4 (e.g., tegaserod, mosapride and renzapride), 5HT1 receptor agonists, CRF receptor agonists (NBI-34041), β-3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, peptide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774). These peptides and compounds can be administered with the peptides of the invention (simultaneously or sequentially). They can also be covalently linked to a peptide of the invention to create therapeutic conjugates.

The invention includes methods for treating various gastrointestinal disorders by administering a peptide that acts as a partial or complete agonist of the GC-C receptor. The peptide contains up to four cysteines that form one or two disulfide bonds. In certain embodiments the disulfide bonds are replaced by other covalent cross-links and in some cases the cysteines are substituted by other residues to provide for alternative covalent cross-links. The peptides may also include at least one trypsin or chymotrypsin cleavage site and/or a carboxy-terminal analgesic peptide or small molecule, e.g., AspPhe or some other analgesic peptide. When present within the peptide, the analgesic peptide or small molecule may be preceded by a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide or small molecule. The peptides and methods of the invention are also useful for treating pain and inflammation associated with various disorders, including gastrointestinal disorders. Certain peptides include a functional chymotrypsin or trypsin cleavage site located so as to allow inactivation of the peptide upon cleavage. Certain peptides having a functional cleavage site undergo cleavage and gradual inactivation in the digestive tract, and this is desirable in some circumstances. In certain peptides, a functional chymotrypsin site is altered, increasing the stability of the peptide *in vivo*(e.g., guanylin).

The invention includes methods for treating other disorders such as congestive heart failure and benign prostatic hyperplasia by administering a peptide or small molecule (parenterally or orally) that acts as an agonist of the GC-C receptor. Such agents can be used in combination with natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

The invention features methods and compositions for increasing intestinal motility. Intestinal motility involves spontaneous coordinated distentions and contractions of the stomach, intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process.

The peptide can contain additional carboxy terminal or amino terminal amino acids or both. For example, the peptide can include an amino terminal sequence that facilitates recombinant production of the peptide and is cleaved prior to administration of the peptide to a patient. The

peptide can also include other amino terminal or carboxy terminal amino acids. In some cases the additional amino acids protect the peptide, stabilize the peptide or alter the activity of the peptide. In some cases some or all of these additional amino acids are removed prior to administration of the peptide to a patient. The peptide can include 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70 80, 90, 100 or more amino acids at its amino terminus or carboxy terminus or both. The number of flanking amino acids need not be the same. For example, there can be 10 additional amino acids at the amino terminus of the peptide and none at the carboxy terminus.

In certain embodiments the peptides include either one or two or more contiguous negatively charged amino acids (e.g., Asp or Glu) or one or two or more contiguous positively charged residues (e.g., Lys or Arg) or one or two or more contiguous positively or negatively charged amino acids at the carboxy terminus. In these embodiments all of the flanking amino acids at the carboxy terminus are either positively or negatively charged. In other embodiments the carboxy terminal charged amino acids are preceded by a Leu. For example, the following amino acid sequences can be added to the carboxy terminus of the peptide: Asp; Asp Lys; Lys Lys Lys Lys Lys Lys; Asp Lys Lys Lys Lys Lys Lys; Leu Lys Lys; and Leu Asp. It is also possible to simply add Leu at the carboxy terminus.

In a first aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In some embodiments, Xaa_1 is preceded by Lys or Tyr.

In certain embodiments, a Cys is replaces by any amino acid other than Cys. Certain such polypeptides will have fewer disulfide bonds.

In a related aspect the invention features a composition comprising a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein: Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu; Xaa_5 is Asp, Ile or Glu; Xaa_6 is Ile, Trp or Leu; Xaa_7 is Cys, Ser, or Tyr; Xaa_8 is Ala, Val, Thr, Ile, Met or is missing; Xaa_9 is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing; Xaa_{10} is Ala, Val, Met, Thr or Ile; Xaa_{11} is Ala or Val; Xaa_{13} is Ala or Thr; Xaa_{14} is Gly, Ala or Ser; Xaa_{15} is Cys, Tyr or is missing; and Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser and a pharmaceutically acceptable carrier. In related aspects, the invention features a pharmaceutically acceptable tablet, pill, capsule comprising the peptide.

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Asn, any amino acid or is missing;

Xaa_2 is Asp, Glu, any amino acid or is missing;

Xaa_3 is Asp or Glu;

Xaa_5 is any amino acid or Glu;

Xaa_6 is any amino acid or Leu;

Xaa_7 is Cys;

Xaa_8 is any amino acid or Val;

Xaa_9 is Asn, Gln, Tyr;

Xaa_{10} is is any amino acid or Val;

Xaa_{11} is any amino acid or Ala;

Xaa_{13} is is any amino acid or Thr;

Xaa_{14} is is any amino acid or Gly;

Xaa_{15} is Cys;

Xaa_{16} is any amino acid, Leu or missing

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Asn_1 Xaa_2 Xaa_3 Xaa_4 Glu_5 Leu_6 Xaa_7 Val_8 Asn_9 Xaa_{10} Xaa_{11} Xaa_{12} Thr_{13} Xaa_{14} Xaa_{15} Leu_{16} (SEQ ID NO:__)

Xaa_2 is Asp or Glu;

Xaa_3 is Asp or Glu;

Xaa_4 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_7 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{10} is Val or Pro;

Xaa_{11} is Ala or Aib (alpha-aminoisobutyric acid);

Xaa_{12} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and

In certain embodiments, where Xaa_{15} is other than Cys or is missing, Xaa_7 is Ser or an amino acid other than Cys.

In certain embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of Xaa_1, Xaa_2,Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{13}, Xaa_{14}, and Xaa_{16} are any amino acid other than Cys.

In certain embodiments, Xaa_9 is any amino acid other than Gln. In other embodiments where Xaa_2 and Xaa_3 are Glu, Xaa_9 is any amino acid other than Gln.

In certain embodiments Xaa_1 and Xaa_2 are missing; Xaa_3 is Thr; Xaa_5 is Glu; Xaa_6 is Ile or Leu; Xaa_8 is Ala, Val, or Ile; Xaa_9 is Phe or Tyr; Xaa_{10} is Ala or Val; Xaa_{11} is Ala; Xaa_{13} is Ala or Thr; Xaa_{14} is Gly; and Xaa_{16} is Trp, Tyr, Phe, Lys, Arg or is missing.

In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) is not cleaved after Xaa_9 by chymotrypsin. In these embodiments wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is either: a) any amino acid other than Phe and Tyr, b) any amino acid other than Phe, Tyr, and Trp, c) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; d) any non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In addition, the invention features variants of Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin due to the addition of an amino terminal lysine. An example of such a molecule is a human guanylin variant having an amino terminal lysine: KPGTCEICAYAACTGC (SEQ ID NO:).

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin, Xaa_7 and Xaa_{15} are both Cys.

Also within the invention are variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:) wherein Y is substituted by any amino acid other than a) Phe; b) any amino acid other than Phe and Trp; c) any amino acid other than Phe, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Trp, Ile, Leu, Val and His; e) any non-aromatic amino acid or f) is missing.

In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) is not cleaved after Xaa_9 by either chymotrypsin or trypsin. In these embodiments wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is either: a) any amino acid other than Lys, Arg, Phe and Tyr, b) any amino acid other than Lys, Arg, Phe, Tyr, and Trp, c) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) that is not cleaved after Xaa_9 by chymotrypsin or trypsin, Xaa_7 and Xaa_{15} are both Cys.

Useful variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:) that should not be cleaved by chymotrypsin include:

PGTCEICASAACTGC (SEQ ID NO:)

PGTCEICATAACTGC (SEQ ID NO:)

PGTCEICANAACTGC (SEQ ID NO:)

PGTCEICAQAACTGC (SEQ ID NO:)

PGTCEICARAACTGC (SEQ ID NO:)

PGTCEICAEAACTGC (SEQ ID NO:)

PGTCEICADAACTGC (SEQ ID NO:)

PGTCEICAGAACTGC (SEQ ID NO:)

PGTCEICAAAACTGC (SEQ ID NO:)

PGTCEICAMAACTGC (SEQ ID NO:).

Additional variants which are not likely to be cleaved by chymotrypsin under certain conditions include:

PGTCEICAIAACTGC (SEQ ID NO:)

PGTCEICALAACTGC (SEQ ID NO:)

PGTCEICAVAACTGC (SEQ ID NO:)

PGTCEICAHAACTGC (SEQ ID NO:)

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids, other than a Cys, are deleted. Where two (or more) amino acids are deleted and the peptide comprises the sequence: Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d, in some embodiments two or more deletions can be located between Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. Thus, there can be two or more deletions between two Cys. However, in other embodiments there is at most one deletion between each Cys, i.e., there is no more than one deletion between each of Cys_a and Cys_b, Cys_b and Cys_c, and Cys_c and Cys_d. Thus, the invention includes any of the peptides described herein comprising the sequence Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d wherein: a) one amino acid between Cys_a and Cys_b is deleted; b) one amino acid between Cys_b and Cys_c is deleted; c) one amino acid between Cys_c and Cys_d is deleted; d) one amino acid between Cys_a and Cys_b is deleted and one amino acid between Cys_b and Cys_c is deleted; e) one amino acid between Cys_a and Cys_b is deleted and one amino acid between Cys_c and Cys_d is deleted; f) one amino acid between Cys_b and Cys_c is deleted and one amino acid between Cys_c and Cys_d is deleted; or g) one amino acid between Cys_a and Cys_b is deleted, one amino acid between Cys_b and Cys_c is deleted, and one amino acid between Cys_c and Cys_d is deleted. In addition, one or more amino acids preceding Cys_a and/or one or more amino acids following Cys_d can be deleted. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids (or non-natural amino acids or natural or non-natural amino acid analogs), other than a Cys (or an amino acid substituted for Cys, e.g., an amino acid capable of forming a covalent bond to another amino acid) is deleted. Thus, additional variants include those in which a Cys is substituted by an amino acid capable of forming a covalent linkage with another amino acid (e.g., a Cys or a substitute therefore). Such amino acids include: Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid).

FIG. 1 includes deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a.

The invention also features insertion variants of any of the peptides described herein in which one, two, three or four amino acids are inserted.

Where two (or more) amino acids are inserted and the peptide comprises the sequence: Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d, in some embodiments two or more insertions can be located between Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. However, in other embodiments there is at most one insertion between each of Cys_a and Cys_b or between Cys_b and Cys_c or between Cys_c and Cys_d. Thus, the invention includes any of the peptides described herein comprising the sequence Cys_a Xaa Xaa Cys_b Xaa Xaa Xaa Xaa Cys_c Xaa Xaa Cys_d wherein: a) one amino acid is inserted between Cys_a and Cys_b; b) one amino acid is inserted between Cys_b and Cys_c; c) one amino acid is inserted between Cys_c and Cys_d; d) one amino acid is inserted between Cys_a and Cys_b and one amino acid is inserted between Cys_b and Cys_c; e) one amino acid is inserted between Cys_a and Cys_b and one amino acid is inserted between Cys_c and Cys_d; f) one amino acid is inserted between Cys_b and Cys_c and one amino acid is inserted between Cys_c and Cys_d or g) one amino acid is inserted between Cys_a and Cys_b, one amino acid is inserted between Cys_b and Cys_c, and one amino acid is inserted between Cys_c and Cys_d . In addition, one or more amino acids can be inserted preceding Cys_a and/or one or more amino acids can be inserted following Cys_d. The insertions can be any natural or non-natural occurring amino acid (e.g., Gly or Ala) or amino acid analog and where there are more than one insertions present, they can be the same or different. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

For example, the invention includes the following insertion variants of PGTCGEICAYAACTGC (human guanylin) (SEQ ID NO:) include:

PGTCEGICAYAACTGC (SEQ ID NO:)
PGTCEIGCAYAACTGC (SEQ ID NO:)

PGTCEICGAYAACTGC (SEQ ID NO:)
PGTCEICAGYAACTGC (SEQ ID NO:)
PGTCEICAYGAACTGC (SEQ ID NO:)
PGTCEICAYAGACTGC (SEQ ID NO:)
PGTCEICAYAAGCTGC (SEQ ID NO:)
PGTCEICAYAACGTGC (SEQ ID NO:)
PGTCEICAYAACTGGC (SEQ ID NO:)
PGTCAEICAYAACTGC (SEQ ID NO:)
PGTCEAICAYAACTGC (SEQ ID NO:)
PGTCEIACAYAACTGC (SEQ ID NO:)
PGTCEICAAYAACTGC (SEQ ID NO:)
PGTCEICAYAAACTGC (SEQ ID NO:)
PGTCEICAYAACATGC (SEQ ID NO:)
PGTCEICAYAACTAGC (SEQ ID NO:)
PGTCEICAYAACTGAC (SEQ ID NO:)
PGTCAEICAAYAACTGC (SEQ ID NO:)
PGTCEAICAAYAACTGC (SEQ ID NO:)
PGTCEIACAAYAACTGC (SEQ ID NO:)

Other insertion variants of human guanylin can have up to four amino acids (i.e., 0, 1, 2, 3 or 4 natural or non-natural amino acids) inserted after each of the 15 amino acids in human guanylin. Thus, the invention includes peptides having the sequence: Pro $Xaa_{(0-4)}$ Gly $Xaa_{(0-4)}$ Thr $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Glu $Xaa_{(0-4)}$ Ile $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Tyr $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Ala $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ Thr $Xaa_{(0-4)}$ Gly $Xaa_{(0-4)}$ Cys $Xaa_{(0-4)}$ (SEQ ID NO:). The inserted amino acids can be any amino acid and can be the same or different. In certain embodiments the inserted amino acids are all Gly or all Ala or a combination of Gly and Ala.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a and carboxy terminal to Cys_d.

The invention also features variants of peptides having the sequence Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1), e.g., variants of PGTCEICAYAACTGC human guanylin (SEQ ID NO:) in which up to four amino acids are deleted and/or up to four amino acids are inserted. The insertions and deletions can be between Cys4 and Cys12 in SEQ ID NO:1 or they can be amino terminal to Cys4 and/or carboxy terminal to Cys12 in SEQ ID NO:1

When Xaa_{16} is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide carboxy-terminal to Xaa_{16}. When Xaa_{16} is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide carboxy-terminal to Xaa_{16}. Thus, if the peptide includes an analgesic peptide carboxy-terminal to Xaa_{16}, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P and other analgesic peptides described herein.

When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa_1 (or Xaa_2 or Xaa_3) along with Xaa_1, Xaa_2 or Xaa_3. When Xaa_1 or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa_2 or Xaa_3) is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide amino-terminal to Xaa_1 along with Xaa_1, Xaa_2 or Xaa_3). Thus, for example, if the peptide includes an analgesic peptide amino-terminal to Xaa_1, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance p and other analgesic peptides described herein.

The peptides can linked, e.g., covalently linked to any of a variety of other analgesic peptides or analgesic compounds. Thus, a peptide described herein can be linked to a second therapeutic

agent, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of a second therapeutic agent include: acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole), H2 receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemcinal fumarate), 5HT receptor agonists (e.g., 5HT4 receptor agonists such as Zelnorm®; 5HT3 receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT1, 5HT2, 5HT3 (e.g., alosetron), 5HT4 receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN™ (ChemoCentryx, Inc.; San Carlos, CA), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be linked to agents such a tianeptine (Stablon®) and other agents described in U.S. 6,683,072; (E)-4 (1,3bis(cyclohexylmethyl)-1,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can be linked to an agent selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3 (e.g., alosetron, ATI-7000; Aryx Thearpeutics, Santa Clara CA), 5HT4, 5HT2, and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT2, 5HT4 (e.g., tegaserod, mosapride and renzapride) and 5HT1 receptor agonists, CRF receptor agonists (NBI-34041), β-3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabanoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides

comprising the amino acid sequence QHNPR (SEQ ID NO:) for example, VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, pepetide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) and other analgesic peptides or compounds.

Amino acid, non-amino acid, peptide and non-peptide spacers can be interposed between a peptides of the invention and a peptide that has some other biological function, e.g., an analgesic peptide or a peptide used to treat obesity. The linker can be one that is cleaved from the flanking peptides *in vivo* or one that remains linked to the flanking peptides *in vivo*. For example, glycine, beta-alanine, glycyl-glycine, glycyl-beta-alanine, gamma-aminobutyric acid, 6-aminocaproic acid, L-phenylalanine, L-tryptophan and glycil-L-valil-L-phenylalanine can be used as a spacer (Chaltin et al. 2003 Helvetica Chimica Acta 86:533-547; Caliceti et al. 1993 FARMCO 48:919-32) as can polyethylene glycols (Butterworth et al. 1987 J. Med. Chem 30:1295-302) and maleimide derivatives (King et al. 2002 Tetrahedron Lett. 43:1987-1990). Various other linkers are described in the literature (Nestler 1996 Molecular Diversity 2:35-42; Finn et al. 1984 Biochemistry 23:2554-8; Cook et al. 1994 Tetrahedron Lett. 35:6777-80; Brokx et al. 2002 Journal of Controlled Release 78:115-123; Griffin et al. 2003 J. Am. Chem. Soc. 125:6517-6531; Robinson et al. 1998 Proc. Natl. Acad. Sci. USA 95:5929-5934.

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides. Also within the invention are peptidomimetics corresponding to the peptides of the invention.

When fully folded, disulfide bonds are present between the first and third cysteines and between the second and fourth cysteines, e.g., there is a disulfide bond between Cys_4 and Cys_{12} and a

disulfide bond between Xaa_7 and Xaa_{15} (when Xaa_7 is a Cys and Xaa_{15} is a Cys). In some embodiments, the peptide has only one disulfide bond, e.g., between the first and third cysteines (i.e., Cys_4 and Cys_{12}; corresponds to the first and second cysteines when Xaa_7 is other than Cys). In certain embodiments one or more Cys can be replaced by Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or some other amino acid that can covalently link to another amino acid (e.g., Cys, Mpt, Pen or Dpr). In some embodiments, one or both members of a pair of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274); β, β dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, e.g., an amide bond, an ester linkage, an alkyl linkage, a thio ester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl linkage, and alkenyl linkage, an ether, a thioether linkage, or an amino linkage. For example, Ledu et al. (Proceedings Nat'l Acad. Sci. 100:11263-78, 2003) described methods for preparing lactam and amide cross-links. Schafmeister et al. (J. Am. Chem. Soc. 122:5891, 2000) describes stable, all carbon cross-links. In some cases, the generation of such alternative cross-links requires replacing the Cys residues with other residues such as Lys or Glu or non-naturally occurring amino acids.

In certain embodiments one or more amino acids can be replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and other amino acids including Phe and Tyr can be substituted by, e.g., a halogen, -CH3, -OH, -CH_2NH_3, -C(O)H, -CH_2CH_3, -CN, -$CH_2CH_2CH_3$, -SH, or another group.

Further examples of unnatural amino acids include: an unnatural analogue of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue

of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (e.g., an amino acid containing deuterium, tritium, ^{13}C, ^{15}N, or ^{18}O); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, e.g., a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an α.-hydroxy containing acid; an amino thio acid containing amino acid; an α, α disubstituted amino acid; a β-amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2-naphthyl)alanine; a 3-methyl-phenylalanine; a *p*-acetyl-L-phenylalanine; an 0-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAcβ-serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a p-azido-L-phenylalanine; a p-acyl-L-phenylalanine; a p-benzoyl-L-phenylalanine; an L-phosphoserine; a phosphonoserine; a phosphonotyrosine; a p-iodo-phenylalanine; a 4-fluorophenylglycine; a p-bromophenylalanine; a p-amino-L-phenylalanine; a isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, O-methyl-L-tyrosine; a glycosylated amino acid; a p-(propargyloxy)phenylalanine, dimethyl-Lysine, hydroxy-proline, mercaptopropionic acid, methyl-lysine, 3-nitro-tyrosine, norleucine, pyro-glutamic acid, Z (Carbobenzoxyl), ε-Acetyl-Lysine, β-alanine, aminobenzoyl derivative, aminobutyric acid (Abu), citrulline, aminohexanoic acid, aminoisobutyric acid, cyclohexylalanine, d-cyclohexylalanine, hydroxyproline, nitro-arginine, nitro-phenylalanine, nitro-tyrosine, norvaline, octahydroindole carboxylate, ornithine, penicillamine, tetrahydroisoquinoline, acetamidomethyl protected amino

acids and a pegylated amino acid. Further examples of unnatural amino acids can be found in U.S. 20030108885, U.S. 20030082575, and the references cited therein.

In some embodiments, an amino acid can be replaced by a naturally-occurring, non-essential amino acid, e.g., taurine.

Methods to manufacture peptides containing unnatural amino acids can be found in, for example, U.S. 20030108885, U.S. 20030082575, Deiters et al., J Am Chem Soc. (2003) 125:11782-3, Chin et al., Science (2003) 301:964-7, and the references cited therein.

Peptides that include non-natural amino acids can also be prepared using the methods described in WO02086075.

The peptides of the invention can be modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceeding. In one aspect of the invention, there may be more than one type of modification on the peptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cy3 or Cy5. The peptides of the invention may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysin, modification by 7-Amino-4-methyl-coumarin (AMC), flourescein, NBD (7-Nitrobenz-2-Oxa-1,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-1- sulfonic acid), dabcyl, dabsyl, dansyl, texas red, FMOC, and Tamra (Tetramethylrhodamine). The peptides of the invention may also be conjugated to, for example, BSA or KLH (Keyhole Limpet Hemocyanin).

The invention also features a purified polypeptide comprising, consisting of or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys;

Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing;

Xaa_9 is any of the 20 naturally-occurring amino acids;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any of the 20 naturally-occurring amino acids;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys; and

Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

In various embodiments: Xaa_9 is Asn; Xaa_{11} is Ala or Thr; Xaa_8 is missing; and Xaa_{16} is Tyr.

In other embodiments Xaa_4 is immediately preceded by an amino acid sequence seleted from: Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His Thr; Ile Ala Gln Asp Pro Ser Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp Asn Asp Glu; Arg Thr Ile Ala Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu; Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

The invention further features a purified polypeptide comprising, consisting of or consisting essentially the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b)

preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa_2 is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

Xaa_3 is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa_4 is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

Xaa_5 is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa_6 is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa_7 is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

Xaa_8 is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa_9 is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa_{10} is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa_{11} is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

Xaa_{12} is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa_{13} is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa_{14} is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa_{15} is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or is missing; and

Xaa_{16} is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

Also featured is purified polypeptide comprising, consiting of or consisting essentially of the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_4 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_8 is any amino acid other than Cys or is missing;

Xaa_9 is any amino acid;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any amino acid;

Xaa_{12} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; and

Xaa_{16} is any amino acid or is missing.

The various peptides can be present with a counterion. Useful counterions include salts of: acetate, benzenesulfonate, benzoate, calcium edetate, camsylate, carbonate, citrate, edetate (EDTA), edisylate, embonate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, iodide, bromide, chloride, hydroxynaphthoate, isethionate, lactate, lactobionate, estolate, maleate, malate, mandelate, mesylate, mucate, napsylate, nitrate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tartarate, theoclate, acetamidobenzoate, adipate, alginate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, camphorate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate, formate, gentisate, glucuronate, glycerophosphate, glycolate, hippurate, fluoride, malonate, napadisylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate polymer, phenylethylbarbiturate, picrate, propionate, pidolate, sebacate, rhodanide, tosylate, tannate

In a second aspect, the invention also features a therapeutic or prophylactic method comprising administering a composition comprising a purified peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. For the treatment of gastrointestinal disorders, the peptide can be administered orally, by rectal suppository or parenterally.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction, obesity, congestive heart failure, or benign prostatic hyperplasia; the composition is administered orally; the peptide comprises 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, or 30 or fewer amino acids. In other embodiments, the peptide comprises 20 or fewer amino acids, and the peptide comprises no more than 5 amino acids prior to Cys_4. In other embodiments the peptide comprises no more than 20, 15, 10, or 5 peptides subsequent to Cys_{15}. In certain embodiments Xaa_{16} is a chymotrypsin or trypsin cleavage site and an analgesic peptide is present immediately following Xaa_{16}.

Among the useful peptides are those comprising, consisting of or consisting essentially of any of the following amino acid sequences:

SHTCEICAFAACAGC (opossum guanylin) (SEQ ID NO:);

PGTCEICAYAACTGC (human guanylin) (SEQ ID NO:);

PSTCEICAYAACAGC (pig guanylin) (SEQ ID NO:);

PNTCEICAYAACTGC (rat guanylin) (SEQ ID NO:);

PDPCEICANAACTGCL (European eel guanylin, inferred) (SEQ ID NO:);

NDDCELCVNVACTGCL (human uroguanylin) (SEQ ID NO:);

QEECELCINMACTGY (opossum lymphoguanylin) (SEQ ID NO:);

GDDCELCVNVACTGCS (pig uroguanylin) (SEQ ID NO:);

NDECELCVNIACTGC (guinea pig uroguanylin) (SEQ ID NO:);

TDECELCINVACTGC (rat uroguanylin) (SEQ ID NO:);

QEDCELCINVACTGC (opossum uroguanylin) (SEQ ID NO:);

MPSTQYIRRPASSYASCIWCTTACASCHGRTTKPSLAT (EAST 1) (SEQ ID NO:);

MPSTQYIRRPASSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPTSSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPTSSYASCIWCATVCASCHGRTTKPSLAT (SEQ ID NO:);

MPSTQYIRRPASSYASCIWYATACASCHGRTTEPSLAT (SEQ ID NO:);

QEECELSINMACTGY (opossum lymphoguanylin analog) (SEQ ID NO:);

YDECEICMFAACTGC (Japanese eel guanylin) (SEQ ID NO:);

VCEICAFAACTGC (Zebrafish guanylin, inferred) (SEQ ID NO:);

ADLCEICAFAACTGCL (Japenese eel renoguanylin, inferred) (SEQ ID NO:);

PGTCEICAYAACTGCL (SEQ ID NO:);

PGTCEICAYAACTGCLKK (SEQ ID NO:);

PNTCEICAYAACTGCKKKKKK (SEQ ID NO:);

PNTCEICAYAACTGCD (SEQ ID NO:);

PNTCEICAYAACTGCDK (SEQ ID NO:);

YPNTCEICAYAACTGC (SEQ ID NO:);

KNTCEICAYAACTGC (SEQ ID NO:);

KPNTCEICAYAACTGC (SEQ ID NO:);

EDPGTCEICAYAACTGC (SEQ ID NO:);

VTVQDG NFSFSLESVK KLKDLQEPQE PRVGKLRNFA PIPGEPVVPI LCSNPNFPEE LKPLCKEPNA QEILQRLEEIAEDPGTCEICAYAACTGC (SEQ ID NO:);

DPGTCEICAYAACTGC (SEQ ID NO:);

MNAFLLSALC LLGAWAALAG GVTVQDGNFS FSLESVKKLK DLQEPQEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKP LCKEPNAQEI LQRLEEIAED PGTCEICAYAACTGC (SEQ ID NO:);

MNAFLLFALC LLGAWAALAG GVTVQDGNFS FSLEPRVGKL RNFAPIPGEP VVPILCSNPN FPEELKPLCK EPNAQEILQR LEEIAEDPGTCEICAYAACTGC (SEQ ID NO:);

TGSMNAFLLF ALCLLGAWAA LAGGVTVQDG NFSFSLEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKP LCKEPNAQEI LQRLEEIAEDPGTCEICAYAACTGCLEG (SEQ ID NO:);

NDECELCVNVACTGCL (SEQ ID NO:); line 17

ECELCVNVACTGCL (SEQ ID NO:);

EDCELCINVACTGC (SEQ ID NO:);

NDDCELCVACTGCL (SEQ ID NO:);

FKTLRTIANDDCELCVNVACTGCL (SEQ ID NO:);

FKTLRTIANDDCLCVNVACTGCL (SEQ ID NO:);

DDCELCVNVACTGCL (SEQ ID NO:);

DCELCVNVACTGCL (SEQ ID NO:);

CELCVNVACTGCL (SEQ ID NO:);

KDDCELCVNVACTGCL (SEQ ID NO:);

PNTCEICANPACTGC (SEQ ID NO.).

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides.

In a third aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 *Aliment Pharmacol Ther* 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In various embodiments, the constipation is associated with use of a therapeutic agent; the constipation is associated with a neuropathic disorder; the constipation is post-surgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated

with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a fourth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, Inflammatory bowel disease , colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia.

In a fifth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a sixth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a seventh aspect, the invention features a method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In an eighth aspect, the invention features an isolated nucleic acid molecule comprising a nucleotide sequence encoding a peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a ninth aspect, the invention features a composition comprising a purified polypeptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. In an embodiment, the composition is a pharmaceutical composition.

In a tenth aspect, the invention features a method for treating obesity, the method comprising administering a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of obesity, for example, gut hormone fragment peptide YY_{3-36} (PYY_{3-36}) (*N. Engl. J. Med.* 349:941, 2003; ikpeapge daspeelnry yaslrhylnl vtrqry) or a variant thereof, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (focus vesiculosus), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (teucrium chamaedrys), B-hydroxy-β-methylbutyrate, ATL-962 (Alizyme PLC), and pyruvate. A peptide useful for treating obesity can be administered as a co-therapy with a peptide of the invention either as a distinct molecule or as part of a fusion protein with a peptide of the invention. Thus, for example, PYY_{3-36} can be fused to the carboxy or amino terminus of a peptide of the invention. Such a fusion protein can include a chymostrypsin or trypsin cleavage site that can permit cleavage to separate the two peptides. A peptide useful for treating obesity can be administered as a co-therapy with electrostimulation (U.S. 20040015201).

In an eleventh aspect, the invention features a method for treating congestive heart failure, the method comprising: administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In a twelfth aspect, the invention features a method for treating benign prostatic hyperplasia, the method comprising: administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a thirteenth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor. In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, and colonic pseudo-obstruction.

In a fourteenth aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.

In a fifteenth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

In a sixteenth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

In a seventeenth aspect, the invention features a method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists can act in the kidney and adrenal gland to control natriuresis, kaliuresis, and diuresis thereby reducing the build-up of fluid associated with congestive heart failure (Lorenz et al. *J Clin Invest* 112:1138, 2003; Carrithers et al. *Kidney Int* 65:40, 2004). The agonist can be administered in combination with one or more agents for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In an eighteenth aspect, the invention features a method for treating BPH, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists acting in the prostate can reduce cellular hypertrophy and complications associated with cellular hypertrophy. The agonist can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a nineteenth aspect, the invention features a method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor. The agonist can be administered in combination with one or more agents for treatment of obesity, for example, sibutramine.

The peptides and agonists of the GC-C receptor can be used to treat constipation or decreased intestinal motility, slow digestion or slow stomach emptying. The peptides can be used to relieve one or more symptoms of IBS (bloating, pain, constipation), GERD (acid reflux into the esophagus), duodenogastric reflux, functional dyspepsia, or gastroparesis (nausea, vomiting, bloating, delayed gastric emptying) and other disorders described herein.

Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001, Aliment Pharmacol Ther 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a twentieth aspect, the invention features isolated nucleic acid molecules comprising or consisting of a sequence encoding a peptide of the invention. The invention also features vectors, e.g., expression vectors that include such nucleic acid molecules and can be used to express a peptide of the invention in a cultured cell (e.g., a eukaryotic cell or a prokaryotic cell). The vector can further include one or more regulatory elements, e.g., a heterologous promoter or elements required for translation operably linked to the sequence encoding the peptide. In some cases the nucleic acid molecule will encode an amino acid sequence that includes the amino acid sequence of a peptide of the invention. For example, the nucleic acid molecule can encode a preprotein or a preproprotein that can be processed to produce a peptide of the invention.

A vector that includes a nucleotide sequence encoding a peptide of the invention or a peptide or polypeptide comprising a peptide of the invention may be either RNA or DNA, single- or double-stranded, prokaryotic, eukaryotic, or viral. Vectors can include transposons, viral vectors, episomes, (e.g., plasmids), chromosomes inserts, and artificial chromosomes (e.g. BACs or YACs). Suitable bacterial hosts for expression of the encode peptide or polypeptide include, but are not limited to, *E. coli*. Suitable eukaryotic hosts include yeast such as *S. cerevisiae*, other fungi, vertebrate cells, invertebrate cells (e.g., insect cells), plant cells, human cells, human tissue cells, and whole eukaryotic organisms. (e.g., a transgenic plant or a transgenic animal). Further, the vector nucleic acid can be used to generate a virus such as vaccinia or baculovirus.

As noted above the invention includes vectors and genetic constructs suitable for production of a peptide of the invention or a peptide or polypeptide comprising such a peptide. Generally, the genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art and may be functional in, but are not limited to, a bacterium, yeast, plant, or animal cell. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, a poly A addition site, or an internal ribosome entry site), a splicing sequence or splicing regulatory sequence, and a transcription termination sequence. The vector can be capable of autonomous replication or it can integrate into host DNA.

The invention also includes isolated host cells harboring one of the forgoing nucleic acid molecules and methods for producing a peptide by culturing such a cell and recovering the peptide or a precursor of the peptide. Recovery of the peptide or precursor may refer to collecting the growth solution and need not involve additional steps of purification. Proteins of the present invention, however, can be purified using standard purification techniques, such as, but not limited to, affinity chromatography, thermaprecipitation, immunoaffinity chromatography, ammonium sulfate precipitation, ion exchange chromatography, filtration, electrophoresis and hydrophobic interaction chromatography.

In a twenty first aspect, the invention features a method of increasing the level of cyclic guanosine 3'-monophosphate (cGMP) in an organ, tissue (e.g, the intestinal mucosa), or cell (e.g., a cell bearing GC-A receptor) by administering a composition that includes a peptide of the invention.

The details of one or more embodiments of the invention are set forth in the accompanying description and claims. The publications and patents referenced herein are incorporated by reference.

DRAWINGS

FIG.1 depicts deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys_a and Cys_d as well as amino terminal to Cys_a and carboxy terminal to Cys_d.

FIG. 3 depicts various polypeptides which include the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein: Xaa_1 is any amino acid or is missing; Xaa_2 is any amino acid or is missing; Xaa_3 is any amino acid or is missing; Xaa_5 is Glu; Xaa_6 is Tyr, Trp, Phe or Leu; Xaa_7 is Cys; Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing; Xaa_9 is any of the 20 naturally-occurring amino acids; Xaa_{10} is Pro or Gly; Xaa_{11} is any of the 20 naturally-occurring amino acids; Xaa_{13} is Thr, Val or Gly; Xaa_{14} is Gly or Ala; Xaa_{15} is Cys; and Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

DETAILED DESCRIPTION

The peptides of the invention bind to the guanylate cyclase (GC-C) receptor, a key regulator of fluid and electrolyte balance in the intestine and kidney. When stimulated, this receptor, which is located on the apical membrane of the intestinal epithelial surface, causes an increase in intestinal epithelial cyclic GMP (cGMP). This increase in cGMP is believed to cause a decrease in water and sodium absorption and an increase in chloride and potassium ion secretion, leading to changes in intestinal fluid and electrolyte transport and increased intestinal motility. The

intestinal GC-C receptor possesses an extracellular ligand binding region, a transmembrane region, an intracellular protein kinase-like region and a cyclase catalytic domain. Proposed functions for the GC-C receptor are the fluid and electrolyte homeostasis, the regulation of epithelial cell proliferation and the induction of apoptosis (Shaibhubhai 2002 *Curr Opin Drug Dis Devel* 5:261-268).

In addition to being expressed in gastrointestinal epithelial cells, GC-C is expressed in extra-intestinal tissues including kidney, lung, pancreas, pituitary, adrenal, developing liver, heart and male and female reproductive tissues (reviewed in Vaandrager 2002 *Mol Cell Biochem* 230:73-83). This suggests that the GC-C receptor agonists can be used in the treatment of disorders outside the GI tract, for example, congestive heart failure and benign prostatic hyperplasia.

Ghrelin, a peptide hormone secreted by the stomach, is a key regulator of appetite in humans. Ghrelin expression levels are regulated by fasting and by gastric emptying. (Kim et al., 2003, Neuroreprt 14:1317-20; Gualillo et al., 2003, FEBS Letts 552: 105-9). Thus, by increasing gastrointestinal motility, GC-C receptor agonists may also be used to regulate obesity.

In humans, the GC-C receptor is activated by guanylin (Gn) (U.S. Patent 5,96,097), uroguanylin (Ugn) (U.S. Patent 5,140,102) and lymphoguanylin (Forte et al. 1999 *Endocrinology* 140:1800-1806).

Many gastrointestinal disorders, including IBS, are associated with abdominal or visceral pain. Certain of the peptides of the invention include the analgesic or anti-nociceptive tags such as the carboxy-terminal sequence AspPhe immediately following a Trp, Tyr or Phe (i.e., a chymotrypsin cleavage site) or following Lys or Arg (a trypsin cleavage site). Chymotrypsin in the intestinal tract will cleave such peptides immediately carboxy terminal to the Trp, Phe or Tyr residue, releasing the dipeptide, AspPhe. This dipeptide has been shown to have analgesic activity is animal models (Abdikkahi et al. 2001 *Fundam Clin Pharmacol* 15:117-23; Nikfar et al 1997, 29:583-6; Edmundson et al 1998 *Clin Pharmacol Ther* 63:580-93). In this manner such peptides can treat both pain and inflammation. Other analgesic peptides can be present at the carboxy terminus of the peptide (following a cleavage site) including: endomorphin-1,

endomorphin-2, nocistatin, dalargin, lupron, and substance P. As described in greater detail below, various analgesic peptides and compounds can be covalently linked to or used in combination therapy with the therapeutic peptides described herein.

In the human body an inactive form of chymotrypsin, chymotrypsinogen is produced in the pancreas. When this inactive enzyme reaches the small intestine it is converted to active chymotrypsin by the excision of two di-peptides. Active chymotrypsin will cleave peptides at the peptide bond on the carboxy-terminal side of Trp, Tyr or Phe. The presence of active chymotrypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned chymotrypsin cleavage site. Certain of the peptides of the invention include a Trp, Tyr or Phe immediately followed by a carboxy-terminal analgesic peptide. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned chymotrypsin cleavage site as the peptide passes through the intestinal tract.

Trypsinogen, like chymotrypsin, is a serine protease that is produced in the pancreas and is present in the digestive tract. The active form, trypsin, will cleave peptides having a Lys or Arg. The presence of active trypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned trypsin cleavage site. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned trypsin cleavage site as the peptide passes through the intestinal tract.

In some cases, the peptides of the invention are produced as a prepro protein. The prepro protein can include any suitable prepro sequence, including, for example, mnafllsalc llgawaalag gvtvqdgnfs fslesvkklk dlqepqeprv gklrnfapip gepvvpilcs npnfpeelkp lckepnaqei lqrleeiaed (SEQ ID NO:) and mgcraasgll pgvavvllll lqstqsvyiq yqgfrvqles mkklsdleaq wapsprlqaq sllpavchhp alpqdlqpvc asqeassifk tlrtia (SEQ ID NO:) or a bacterial leader sequence such as: mkksilfiflsvlsfspfaqdakpvesskekitleskkcniakksnksgpesmn. Where the peptide is produced by a bacterial cell, e.g., *E. coli*, the forgoing leader sequence will be cleaved and the mature peptide will be efficiently secreted from the bacterial cell. U.S. Patent No. 5,395,490 describes vectors,

expression systems and methods for the efficient production of certain mature peptides having disulfide bonds in bacterial cells and methods for achieving efficient secretion of such mature peptides. The vectors, expression systems and methods described in U.S. Patent No. 5,395,490 can be used to produce the polypeptides of the present invention.

Variant Peptides

The invention includes variant peptides that can include one, two, three, four, or five or more (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) amino acid substitutions compared to any of the peptides described above. The substitution(s) can be conservative or non-conservative. The naturally-occurring amino acids can be substituted by D-isomers of any amino acid, non-natural amino acids, natural and non-natural amino acid analogs, and other groups. A conservative amino acid substitution results in the alteration of an amino acid for a similar acting amino acid, or amino acid of like charge, polarity, or hydrophobicity. At some positions, even conservative amino acid substitutions can reduce the activity of the peptide. A conservative substitution can substitute a naturally-occurring amino acid for a non-naturally-occurring amino acid. Among the naturally occurring amino acid substitutions generally considered conservative are:

For Amino Acid	Code	Replace with any of
Alanine	Ala	Gly, Cys, Ser
Arginine	Arg	Lys, His
Asparagine	Asn	Asp, Glu, Gln,
Aspartic Acid	Asp	Asn, Glu, Gln
Cysteine	Cys	Met, Thr, Ser
Glutamine	Gln	Asn, Glu, Asp
Glutamic Acid	Glu	Asp, Asn, Gln
Glycine	Gly	Ala
Histidine	His	Lys, Arg
Isoleucine	Ile	Val, Leu, Met
Leucine	Leu	Val, Ile, Met
Lysine	Lys	Arg, His
Methionine	Met	Ile, Leu, Val
Phenylalanine	Phe	Tyr, His, Trp
Proline	Pro	
Serine	Ser	Thr, Cys, Ala
Threonine	Thr	Ser, Met, Val
Tryptophan	Trp	Phe, Tyr
Tyrosine	Tyr	Phe, His
Valine	Val	Leu, Ile, Met

In some circumstances it can be desirable to treat patients with a variant peptide that binds to and activates intestinal GC-C receptor, but is less active or more active than the non-variant form of the peptide. Reduced activity can arise from reduced affinity for the receptor or a reduced ability to activate the receptor once bound or reduced stability of the peptide. Increased activity can arise from increased affinity for the receptor or an increased ability to activate the receptor once bound or increased stability of the peptide.

In some peptides one or both members of one or both pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274); β, β dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

Production of peptides

Useful peptides can be produced either in bacteria including, without limitation, *E. coli*, or in other existing systems for peptide or protein production (e.g., *Bacillus subtilis,* baculovirus expression systems using Drosophila Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized.

If the peptide or variant peptide is to be produced in bacteria, e.g., *E. coli*, the nucleic acid molecule encoding the peptide may also encode a leader sequence that permits the secretion of the mature peptide from the cell. Thus, the sequence encoding the peptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST peptide. The secreted, mature peptide can be purified from the culture medium.

The sequence encoding a peptide of the invention is can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, *E. coli,* B *subtilis*, *Pseudomonas*, *Salmonella*. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during peptide production.

The protein coding sequence that includes a peptide of the invention can also be fused to a nucleic acid encoding a polypeptide affinity tag, e.g., glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the peptide of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the peptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the peptide of interest.

Genetic constructs and methods suitable for production of immature and mature forms of the peptides and variants of the invention in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce peptides in a biological system.

Mature peptides and variants thereof can be synthesized by the solid-phase method using an automated peptide synthesizer. For example, the peptide can be synthesized on Cyc(4-CH_2 Bxl)-OCH_2-4-(oxymethyl)-phenylacetamidomethyl resin using a double coupling program. Protecting groups must be used appropriately to create the correct disulfide bond pattern. For example, the following protecting groups can be used: t-butyloxycarbonyl (alpha-amino groups); acetamidomethyl (thiol groups of Cys residues B and E); 4-methylbenyl (thiol groups of Cys residues C and F); benzyl (y-carboxyl of glutamic acid and the hydroxyl group of threonine, if present); and bromobenzyl (phenolic group of tyrosine, if present). Coupling is effected with symmetrical anhydride of t-butoxylcarbonylamino acids or hydroxybenzotriazole ester (for asparagine or glutamine residues), and the peptide is deprotected and cleaved from the solid support in hydrogen fluoride, dimethyl sulfide, anisole, and p-thiocresol using 8/1/1/0.5 ratio (v/v/v/w) at 0°C for 60 min. After removal of hydrogen fluoride and dimethyl sulfide by reduced pressure and anisole and p-thiocresol by extraction with ethyl ether and ethyl acetate sequentially, crude peptides are extracted with a mixture of 0.5M sodium phosphate buffer, pH 8.0 and N,N-dimethylformamide using 1/1 ratio, v/v. The disulfide bond for Cys residues B and E is the formed using dimethyl sulfoxide (Tam et al. (1991) *J. Am. Chem. Soc.* 113:6657-62). The resulting peptide is the purified by reverse-phase chromatography. The disulfide bond

between Cys residues C and F is formed by first dissolving the peptide in 50% acetic acid in water. Saturated iodine solution in glacial acetic acid is added (1 ml iodine solution per 100 ml solution). After incubation at room temperature for 2 days in an enclosed glass container, the solution is diluted five-fold with deionized water and extracted with ethyl ether four times for removal of unreacted iodine. After removal of the residual amount of ethyl ether by rotary evaporation the solution of crude product is lyophilized and purified by successive reverse-phase chromatography.

Intestinal GC-C Receptor Binding and Activity Assays

The ability of peptides, variant peptides and other compounds to bind to and activate the intestinal GC-C receptor can be tested using the T84 human colon carcinoma cell line (American Type Culture Collection (Bethesda, Md.).

Briefly, cells are grown to confluency in 24-well culture plates with a 1:1 mixture of Ham's F12 medium and Dulbecco's modified Eagle's medium (DMEM), supplemented with 5% fetal calf serum and are used at between passages 54 and 60.

Monolayers of T84 cells in 24-well plates are washed twice with 1 ml/well DMEM, then incubated at 37°C for 10 min with 0.45 ml DMEM containing 1 mM isobutylmethylxanthine (IBMX), a cyclic nucleotide phosphodiesterase inhibitor. Test peptides (50µl) are then added and incubated for 30 minutes at 37°C. The media is aspirated and the reaction is terminated by the addition of ice cold 0.5 ml of 0.1N HCl. The samples are held on ice for 20 minutes and then evaporated to dryness using a heat gun or vacuum centrifugation. The dried samples are resuspended in 0.5ml of phosphate buffer provided in the Cayman Chemical Cyclic GMP EIA kit (Cayman Chemical, Ann Arbor, MI). Cyclic GMP is measured by EIA according to procedures outlined in the Cayman Chemical Cyclic GMP EIA kit.

For the binding assay, T84 cell monolayers in 24-well plates are washed twice with 1 ml of binding buffer (DMEM containing 0.05% bovine serum albumin and 25 mM HEPES, pH 7.2), then incubated for 30 min at 37°C in the presence of mature radioactively labeled *E. coli* ST

peptide and the test material at various concentrations. The cells are then washed 4 times with 1 ml of DMEM and solubilized with 0.5 ml/well 1N NaOH. The level of radioactivity in the solubilized material is then determined using standard methods.

Murine gastrointestinal transit (GIT) assay

In order to determine whether a test compound or a peptide, increases the rate of gastrointestinal transit, the test compound can be tested in the murine gastrointestinal transit (GIT) assay (Moon et al. *Infection and Immunity* 25:127, 1979). In this assay, charcoal, which can be readily visualized in the gastrointestinal tract is administered to mice after the administration of a test compound. The distance traveled by the charcoal is measured and expressed as a percentage of the total length of the colon.

Mice are fasted with free access to water for 12 to 16 hours before the treatment with peptide or control buffer. The peptides are orally administered at 1μg/kg – 1mg/kg of peptide in buffer (20mM Tris pH 7.5) seven minutes before being given an oral dose of 5% Activated Carbon (Aldrich 242276-250G). Control mice are administered buffer only before being given a dose of Activated Carbon. After 15 minutes, the mice are sacrificed and their intestines from the stomach to the cecum are dissected. The total length of the intestine as well as the distance traveled from the stomach to the charcoal front is measured for each animal and the results are expressed as the percent of the total length of the intestine traveled by the charcoal front. Results are reported as the average of 10 mice ± standard deviation. A comparison of the distance traveled by the charcoal between the mice treated with peptide versus the mice treated with vehicle alone is performed using a Student's t test and a statistically significant difference is considered for $P<0.05$. Positive controls for this assay may include commercially available wild-type ST peptide (Sigma-Aldrich, St Louis, MO) and Zelnorm®, a drug approved for IBS that is an agonist for the serotonin receptor 5HT4.

Suckling mouse model of intestinal secretion (SuMi assay)

The peptides of the invention can be tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a test compound is administered to

suckling mice that are between seven and nine days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected ("guts"). The remains ("carcass") as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion. Controls for this assay may include wild-type ST peptide and Zelnorm®

Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of the peptides and GC-C receptor agonists of the invention. This model is described by Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g., a peptide, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5^{th} to the 10^{th} minute after PBQ injection, and can also be counted between the 35^{th} and 40^{th} minute and between the 60^{th} and 65^{th} minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Colonic hyperalgesia animal models

Hypersensitivity to colorectal distension is a common feature in patients with IBS and may be responsible for the major symptom of pain. Both inflammatory and non-inflammatory animal models of visceral hyperalgesia to distension have been developed to investigate the effect of compounds on visceral pain in IBS.

I. Trinitrobenzenesulphonic acid (TNBS)-induced rectal allodynia model

Male Wistar rats (220-250 g) are premedicated with 0.5 mg/kg of acepromazine injected intraperitoneally (IP) and anesthetized by intramuscular administration of 100 mg/kg of

ketamine. Pairs of nichrome wire electrodes (60 cm in length and 80 μm in diameter) are implanted in the striated muscle of the abdomen, 2 cm laterally from the white line. The free ends of electrodes are exteriorized on the back of the neck and protected by a plastic tube attached to the skin. Electromyographic (EMG) recordings are started 5 days after surgery. Electrical activity of abdominal striated muscle is recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz).

Ten days post surgical implantation, trinitrobenzenesulphonic acid (TNBS) is administered to induce rectal inflammation. TNBS (80 mg kg^{-1} in 0.3 ml 50 % ethanol) is administered intrarectally through a silicone rubber catheter introduced at 3 cm from the anus under light diethyl-ether anesthesia, as described (Morteau et al. 1994 Dig Dis Sci 39:1239). Following TNBS administration, rats are placed in plastic tunnels where they are severely limited in mobility for several days before colorectal distension (CRD). Experimental compound is administered one hour before CRD which is performed by insertion into the rectum, at 1 cm of the anus, a 4 cm long balloon made from a latex condom (Gue et al, 1997 *Neurogastroenterol. Motil.* 9:271). The balloon is fixed on a rigid catheter taken from an embolectomy probe (Fogarty). The catheter attached balloon is fixed at the base of the tail. The balloon, connected to a barostat is inflated progressively by step of 15 mmHg, from 0 to 60 mmHg, each step of inflation lasting 5 min. Evaluation of rectal sensitivity, as measured by EMG, is performed before (1-2 days) and 3 days following rectal instillation of TNBS.

The number of spike bursts that corresponds to abdominal contractions is determined per 5 min periods. Statistical analysis of the number of abdominal contractions and evaluation of the dose-effects relationships is performed by a one way analysis of variance (ANOVA) followed by a post-hoc (Student or Dunnett tests) and regression analysis for ED50 if appropriate.

II. Stress-induced hyperalgesia model

Male Wistar Rats (200-250 g) are surgically implanted with nichrome wire electrodes as in the TNBS model. Ten days post surgical implantation, partial restraint stress (PRS), is performed as

described by Williams et al. for two hours (Williams et al. 1988 Gastroenterology 64:611). Briefly, under light anaesthesia with ethyl-ether, the foreshoulders, upper forelimbs and thoracic trunk are wrapped in a confining harness of paper tape to restrict, but not prevent body movements. Control sham-stress animals are anaesthetized but not wrapped. Thirty minutes before the end of the PRS session, the animals are administered test-compound or vehicle. Thirty minutes to one hour after PRS completion, the CRD distension procedure is performed as described above for the TNBS model with barostat at pressures of 15, 30, 45 and 60mm Hg. Statistical analysis on the number of bursts is determined and analyzed as in the TNBS model above.

Administration of peptides and GC-C receptor agonists

For treatment of gastrointestinal disorders, the peptides and agonists of the invention are can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The peptides and agonists can be co-administered with other agents used to treat gastrointestinal disorders including but not limited to acid suppressing agents such as Histamine-2 receptor agonists (H2As) and proton pump inhibitors (PPIs). The peptides and agonists can also be administered by rectal suppository. For the treatment of disorders outside the gastrointestinal tract such as congestive heart failure and benign prostatic hypertrophy, peptides and agonists can be administered parenterally or orally.

The peptides described herein can be used alone or in combination with other agents. For example, the peptides can be administered together with one or more analgesic peptides or compounds. The analgesic peptide and/or compound can be covalently attached to a peptide

described herein or it can be a separate agent that is administered together with or sequentially with a peptide described herein in a combination therapy.

Combination therapy can be achieved by administering two or more agents, e.g., a peptide described herein and an analgesic peptide or compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation.

The composition may contain other additives as needed, including for exanple lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof,

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof,

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose,

croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof,

LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and

COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, or mixtures thereof.

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO

01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a peptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations and polymers for use in such formulations are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and. US20020019446. In such sustained release formulations microparticles of peptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1,U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasaly (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other

form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115-124)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal adminisitration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranassaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a

gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccaride are advantageous in that some of them also reportedly enhance absorption of the peptide in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means.

The agent can be fused to immunoglobulins or albumin, or incorporated into a lipsome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The peptides of the invention may also be conjugated to, for example, alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations of PEG, alkyl groups and fatty acid radicals (see U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110). The agent

can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Company, 1995).

The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

Methods to increase chemical and/or physical stability of the agents the described herein are found in U.S. 6,541,606, U.S. 6,068,850, U.S. 6,124,261, U.S. 5,904,935, and WO 00/15224, U.S. 20030069182 (via the additon of nicotinamide), U.S. 20030175230A1, U.S. 20030175230A1, U.S. 20030175239A1, U.S. 20020045582, U.S. 20010031726, WO 02/26248, WO 03/014304, WO 98/00152A1, WO 98/00157A1, WO 90/12029, WO 00/04880, and WO 91/04743, WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 6,008,187, U.S. 5,424,289, U.S. 20030198619, WO 90/01329, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAl) and UEAI mimetics which may be used to target the agents of the invention to the GI tract.

Analgesic Agents

The peptides described herein can be used in combination therapy with an analgesic agent, e.g., an analgesic compound or an analgesic peptide. The analgesic agent can optionally be covalently attached to a peptide described herein. Among the useful analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic peptides are sialorphin-related peptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO:), including: VQHNPR (SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:). Sialorphin-related peptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or peptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the peptides of the invention in a co-therapy or linked to the peptides of the invention, e.g., by a covalent bond. Sialophin and related peptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the peptides of the invention in co-therapy or linked to the peptide of the invention, e.g., by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility (Eur. J. Pharm. 219:445, 1992), and this peptide can be used in conjunction with the peptides of the invention. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal peptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, ketocyclazocine, and compounds described in WO 03/097051 A2 can be used with or linked to the peptides of the invention. In addition, mu opioid receptor agonists such as morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (J. Biol. Chem. 262:8165, 1987). Kyotorphin can be used with or linked to the peptides of the invention.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the peptides of the invention.

Conotoxin peptides represent a large class of analgesic peptides that act at voltage gated Ca channels, NMDA receptors or nicotinic receptors. These peptides can be used with or linked to the peptides of the invention.

Peptide analogs of thymulin (FR 2830451) can have analgesic activity and can be used with or linked to the peptides of the invention.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the peptides of the invention.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod/zelnorm and lirexapride. Such agonists are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, U.S. 5,510,353, EP 507672 A1, EP 507672 B1, and U.S. 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP 625162B1, U.S. 5,364,842, U.S. 5,587,454, U.S. 5,824,645, U.S. 5,859,186, U.S. 5,994,305, U.S. 6,087,091, U.S. 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126 B1, U.S. 5,795,864, U.S. 5,891,849, U.S. 6,054,429, WO 97/01351 A1, can be used with or linked to the peptides of the invention.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003 *Drugs* 6:758) can be can be used with or linked to the peptides of the invention.

NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-14033 and related compounds described in, for example, EP 873753 A1, U.S. 20010006972 A1, U.S. 20030109417 A1, WO 01/52844 A1, can be used with or linked to the peptides of the invention.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the peptides of the invention.

NK3 receptor antagonists such as osanetant (Sanofi-Synthelabo), talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, U.S. 6,277,862, WO 98/11090, WO 95/28418, WO 97/19927, and Boden et al. (*J Med Chem.* 39:1664-75, 1996) can be used with or linked to the peptides of the invention.

Norepinephrine-serotonin reuptake inhibitors such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the peptides of the invention.

Vanilloid receptor antagonists such as arvanil and related compounds described in WO 01/64212 A1 can be used with or linked to the peptides of the invention.

Where the analgesic is a peptide and is covalently linked to a peptide described herein the resulting peptide may also include at least one trypsin or chymotrypsin cleavage site. When present within the peptide, the analgesic peptide may be preceded by (if it is at the carboxy terminus) or followed by (if it is at the amino terminus) a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide.

In addition to sialorphin-related peptides, analgesic peptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, zicnotide, and substance P.

Methods of Treatment

The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of cancer, pre-cancerous growths, or metastatic growths. For example, they can be used for the prevention or treatment of: colorectal/local metastasized colorectal cancer, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma, carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal carcinoma, Ehrlich tumor, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (e.g., B-

cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytonia, histiocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchionia, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondrorna, cylindroma, cystadenocarcinoma, cystadenoma, cystosarconia phyllodes, dysgenninoma, ependymoma, Ewing sarcoma, fibroma, fibrosarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphaugioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma,, osteosarcoma, papilloma, paraganglioma, paraganglionia. nonchroinaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of: Familial Adenomatous Polyposis (FAP) (autosomal dominant syndrome) that precedes colon cancer, hereditary nonpolyposis colorectal cancer (HNPCC), and inherited autosomal dominant syndrome.

For treatment or prevention of cancer, pre-cancerous growths and metastatic growths, the peptides can be used alone or in combination therapy with radiation or chemotherapeutic agents, an inhibitor of a cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor (a number of selective cyclooxygenase-2 inhibitors are described in WO02062369, hereby incorporated by reference).

The peptides can be for treatment or prevention of inflammation. Thus, they can be used alone or in combination with inhibitors of cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor for treatment of: organ inflammation, IBD (e.g, Crohn's disease, ulcerative colitis), asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis, ischemic bowel diseases, intestinal inflammations/allergies, coeliac disease, proctitis, eosnophilic gastroenteritis, mastocytosis, and other inflammatory disorders.

The peptides can also be used alone or in combination therapy to treat or prevent insulin-related disorders, for example: II diabetes mellitus, hyperglycemia, obesity, disorders associated with disturbances in glucose or electrolyte transport and insulin secretion in cells, or endocrine disorders. They can be also used in insulin resistance treatment and post-surgical and non-post surgery decrease in insulin responsiveness.

The peptides can be used alone or in combination therapy to prevent or treat respiratory disorders, including, inhalation, ventilation and mucus secretion disorders, pulmonary hypertension, chronic obstruction of vessels and airways, and irreversible obstructions of vessels and bronchi.

The peptides can be used in combination therapy with a phosphodiesterase inhibitor (examples of such inhibitors can be found in U.S. 6,333,354, hereby incorporated by reference).

The peptides can also be used alone or in combination therapy to prevent or treat: retinopathy, nephropathy, diabetic angiopathy, and edema formation

The peptides can also be used alone or in combination therapy to prevent or treat neurological disorders, for example, headache, anxiety, movement disorders, aggression, psychosis, seizures, panic attacks, hysteria, sleep disorders, depression, schizoaffective disorders, sleep apnea, attention deficit syndromes, memory loss, and narcolepsy. They may also be used as a sedative.

The peptides and detectabley labeled peptides can be used as markers to identify, detect, stage, or diagnosis diseases and conditions of the small intestine, including:
Crohn's disease, colitis, inflammatory bowel disease, tumors, benign tumors, such as benign stromal tumors, adenoma, angioma, adenomatous (pedunculated and sessile) polyps, malignant, carcinoid tumors, endocrine cell tumors, lymphoma, adenocarcinoma, foregut, midgut, and hindgut carcinoma, gastroinstestinal stromal tumor (GIST), such as leiomyorna, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma, gastrointestinal autonomic nerve tumor, malabsorption syndromes, celiac diseases, diverticulosis, Meckel's diverticulurn, colonic diverticula, megacolon, Hirschsprung's disease, irritable bowel syndrome, mesenteric ischemia, ischemic colitis, colorectal cancer, colonic polyposis, polyp syndrome, intestinal adenocarcinoma, Liddle syndrome, Brody myopathy, infantile convulsions, and choreoathetosis

The peptides can be conjugated to another molecule (e.g, a diagnostic or therapeutic molecule) to target cells bearing the GCC receptor, e.g., cystic fibrosis lesions and specific cells lining the intestinal tract. Thus, they can be used to target radioactive moieties or therapeutic moieties to the intestine to aid in imaging and diagnosing or treating colorectal/metastasized or local colorectal cancer and to deliver normal copies of the p53 tumor suppressor gene to the intestinal tract.

The peptides can be used alone or in combination therapy to treat erectile dysfunction.

The peptides can be used alone or in combination therapy to treat inner ear disorders, e.g., to treat Meniere's disease, including symptoms of the disease such as vertigo, hearing loss, tinnitus, sensation of fullness in the ear, and to maintain fluid homeostasis in the inner ear.

The peptides can be used alone or in combination therapy to treat disorders associated with fluid and sodium retention, e.g., diseases of the electrolyte-water/electrolyte transport system within the kidney, gut and urogenital system, congestive heart failure, hypertension, hypotension, liver cirrhosis, and nephrotic syndrome. In addition they can be used to facilitate diuresis or control intestinal fluid.

The peptides can be used alone or in combination therapy to treat disorders associated with chloride or bicarbonate secretion, e.g., Cystic Fibrosis.

The peptides can be used alone or in combination therapy to treat disorders associated with bile secretion. In addition, they can be used to facilitate or control chloride and bile fluid secretion in the gall bladder.

The peptides can be used alone or in combination therapy to treat disorders associated with liver cell regeneration.

What is claimed is:

1. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr;

Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing; and

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

2. The purified polypeptide of claim 1 wherein Xaa_1 is preceded by Lys or Tyr.

3. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

4. A composition comprising a polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa_2 is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing;

Xaa_3 is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa_5 is Asp, Ile or Glu;

Xaa_6 is Ile, Trp or Leu;

Xaa_7 is Cys, Ser, or Tyr;

Xaa_8 is Ala, Val, Thr, Ile, Met or is missing;

Xaa_9 is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing;

Xaa_{10} is Ala, Val, Met, Thr or Ile;

Xaa_{11} is Ala or Val;

Xaa_{13} is Ala or Thr; Xaa_{14} is Gly, Ala or Ser;

Xaa_{15} is Cys, Tyr or is missing;

Xaa_{16} is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser

and a pharmaceutically acceptable carrier.

5. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is Asn, any amino acid or is missing;

Xaa_2 is Asp, Glu, any amino acid or is missing;

Xaa_3 is Asp or Glu;

Xaa_5 is any amino acid or Glu;

Xaa_6 is any amino acid or Leu;

Xaa_7 is Cys;

Xaa_8 is any amino acid or Val;

Xaa_9 is Asn, Gln, Tyr;

Xaa_{10} is is any amino acid or Val;

Xaa_{11} is any amino acid or Ala;

Xaa_{13} is is any amino acid or Thr;

Xaa_{14} is is any amino acid or Gly;

Xaa_{15} is Cys;

Xaa_{16} is any amino acid, Leu or missing

6. A purified polypeptide comprising the amino acid sequence: Asn_1 Xaa_2 Xaa_3 Xaa_4 Glu_5 Leu_6 Xaa_7 Val_8 Asn_9 Xaa_{10} Xaa_{11} Xaa_{12} Thr_{13} Xaa_{14} Xaa_{15} Leu_{16} (SEQ ID NO:__)

Xaa_2 is Asp or Glu;

Xaa_3 is Asp or Glu;

Xaa_4 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_7 is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{10} is Val or Pro;

Xaa_{11} is Ala or Aib (alpha-aminoisobutyric acid);

Xaa_{12} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and

7. The polypeptide of claim 1 wherein Xaa_{15} is other than Cys or is missing and Xaa_7 is Ser or an amino acid other than Cys.

8. The polypeptide of claim 1 wherein at least 5 of Xaa_1, Xaa_2,Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{13}, Xaa_{14}, and Xaa_{16} are any amino acid other than Cys.

9. The polypeptide of claim 1 wherein: Xaa_9 is any amino acid other than Gln.

10. The polypeptide of claim 1 wherein Xaa_2 and Xaa_3 are Glu.

11. A polypeptide comprising the amino acid sequence of claim 1 wherein the polypeptide is not cleaved after Xaa_9 by chymotrypsin.

12. The polypeptide of claim 1 wherein the polypeptide does not comprise the amino acid sequence PGTCEICAYAACTGC.

13. A purified polypeptide comprising the amino acid sequence KPGTCEICAYAACTGC.

14. A purified polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe;

b) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe and Trp;

c) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu and Val;

d) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu, Val and His;

e) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any non-aromatic amino acid or

f) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is missing.

15. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

PGTCEICASAACTGC (SEQ ID NO:)
PGTCEICATAACTGC (SEQ ID NO:)
PGTCEICANAACTGC (SEQ ID NO:)
PGTCEICAQAACTGC (SEQ ID NO:)
PGTCEICARAACTGC (SEQ ID NO:)
PGTCEICAEAACTGC (SEQ ID NO:)
PGTCEICADAACTGC (SEQ ID NO:)
PGTCEICAGAACTGC (SEQ ID NO:)
PGTCEICAAAACTGC (SEQ ID NO:)
PGTCEICAMAACTGC (SEQ ID NO:)
PGTCEICAIAACTGC (SEQ ID NO:)
PGTCEICALAACTGC (SEQ ID NO:)
PGTCEICAVAACTGC (SEQ ID NO:) and

PGTCEICAHAACTGC (SEQ ID NO:)

16. A purified polypeptide comprising an amino acid sequence shown in Figure 1.

17. A purified polypeptide comprising an amino acid sequence shown in Figure 2 wherein Xaa is any amino acid.

18. The purified polypeptide of claim 17 wherein Xaa is any amino acid other than Cys.

19. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:
PGTCEGICAYAACTGC (SEQ ID NO:)
PGTCEIGCAYAACTGC (SEQ ID NO:)
PGTCEICGAYAACTGC (SEQ ID NO:)
PGTCEICAGYAACTGC (SEQ ID NO:)
PGTCEICAYGAACTGC (SEQ ID NO:)
PGTCEICAYAGACTGC (SEQ ID NO:)
PGTCEICAYAAGCTGC (SEQ ID NO:)
PGTCEICAYAACGTGC (SEQ ID NO:)
PGTCEICAYAACTGGC (SEQ ID NO:)
PGTCAEICAYAACTGC (SEQ ID NO:)
PGTCEAICAYAACTGC (SEQ ID NO:)
PGTCEIACAYAACTGC (SEQ ID NO:)
PGTCEICAAYAACTGC (SEQ ID NO:)
PGTCEICAYAAACTGC (SEQ ID NO:)
PGTCEICAYAACATGC (SEQ ID NO:)
PGTCEICAYAACTAGC (SEQ ID NO:)
PGTCEICAYAACTGAC (SEQ ID NO:)
PGTCAEICAAYAACTGC (SEQ ID NO:)
PGTCEAICAAYAACTGC (SEQ ID NO:) and

PGTCEIACAAYAACTGC (SEQ ID NO:).

20. The polypeptide of claim 1 further comprising an amino acid sequence selected from: Asp Phe, the amino acid sequence of endomorphin-1, the amino acid sequence of endomorphin-2, the amino acid sequence of nocistatin, the amino acid sequence of dalargin, the amino acid sequence of lupron, and the amino acid sequence of substance P.

21. A method for treating a gastrointestinal disorder comprising administering a composition comprising the purified polypeptide of claim 1.

22. The method of claim 21 wherein the gastrointestinal disorder is: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or colonic pseudo-obstruction.

23. A method for treating obesity comprising administering a composition comprising the purified polypeptide of claim 1.

24. A method for treating congestive heart failure comprising administering a composition comprising the purified polypeptide of claim 1.

25. A method for treating benign prostatic hyperplasia comprising administering a composition comprising the purified polypeptide of claim 1.

26. A method for treating constipation comprising administering a composition comprising the purified polypeptide of claim 1

27. The method of claim 21 wherein the polypeptide does not comprise the amino acid sequence PGTCEICAYAACTGC or the amino acid sequence

NDDCELCVNVACTGCL.

28. A method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient the polypeptide of claim 1.

29. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient the polypeptide of claim 1.

30. A method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient the polypeptide of claim 1.

31. A method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

32. A method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.

33. A method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

34. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

35. A method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the GC-C receptor.

36. A method for treating benign prostatic hyperplasia, the method comprising administering a complete or partial agonist of the GC-C receptor.

37. A method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor.

38. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys;

Xaa_8 is any of the 20 naturally-occurring amino acids other than Cys or is missing;

Xaa_9 is any of the 20 naturally-occurring amino acids;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any of the 20 naturally-occurring amino acids;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys; and

Xaa_{16} is any of the 20 naturally-occurring amino acids or is missing.

39. The purified polypeptide of claim 38 wherein Xaa_9 is Asn.

40. The purified polypeptide of claim 38 wherein Xaa_{11} is Ala or Thr.

41. The purified polypeptide of claim 38 wherein Xaa_8 is missing.

42. The purified polypeptide of claim 38 wherein Xaa_{16} is Tyr.

43. The purified polypeptide of claim 38 wherein Xaa_4 is immediately preceded by an amino acid sequence seleted from: Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His

Thr; Ile Ala Gln Asp Pro Ser Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp Asn Asp Glu; Arg Thr Ile Ala Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu; Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

44. A pharmaceutical composition comprising the polypeptide of claim 38 and a pharmaceutically acceptable carrier.

45. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Cys_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Cys_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b) preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa_2 is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

Xaa_3 is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa_4 is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

Xaa_5 is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa_6 is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any

amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa_7 is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

Xaa_8 is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa_9 is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa_{10} is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa_{11} is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

Xaa_{12} is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa_{13} is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa_{14} is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa_{15} is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or is missing; and

Xaa_{16} is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

46. A composition comprising the polypeptide of claim 45 and a pharmaceutically acceptable carrier.

47. A purified polypeptide comprising the amino acid sequence: Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} (SEQ ID NO:1) wherein:

Xaa_1 is any amino acid or is missing;

Xaa_2 is any amino acid or is missing;

Xaa_3 is any amino acid or is missing;

Xaa_4 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_5 is Glu;

Xaa_6 is Tyr, Trp, Phe or Leu;

Xaa_7 is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_8 is any amino acid other than Cys or is missing;

Xaa_9 is any amino acid;

Xaa_{10} is Pro or Gly;

Xaa_{11} is any amino acid;

Xaa_{12} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;

Xaa_{13} is Thr, Val or Gly;

Xaa_{14} is Gly or Ala;

Xaa_{15} is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; and

Xaa_{16} is any amino acid or is missing.

FIG. 1 (sheet 1 of 13)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys

Human Guanylin (SEQ ID NO:)

--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 2 of 13)

--- Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 3 of 13)

--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)

FIG. 1 (Sheet 4 of 13)

--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
--- Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 5 of 13)

Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 6 of 13)

Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG 1 (sheet 7 of 13)

Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro --- Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 8 of 13)

Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)

FIG.1 (sheet 9 of 13)

Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly --- Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 10 of 13)

Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 11 of 13)

Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys --- Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 12 of 13)

Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly --- Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu --- Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)

FIG. 1 (sheet 13 of 13)

Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO:)

Pro Gly Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Xaa' Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Xaa' Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)

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Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Xaa' Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Xaa' Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Xaa' Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Xaa' Cys Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Xaa' Ala Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Xaa' Tyr Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Xaa' Ala Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Xaa' Ala Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys (SEQ ID NO:)
Pro Gly Xaa' Xaa' Thr Cys Gly Glu Ile Xaa' Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
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Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Xaa' Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Xaa' Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Xaa' Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Xaa' Cys Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Xaa' Thr Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Xaa' Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Xaa' Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Xaa' Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Xaa' Gly Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Xaa' Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Xaa' Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Xaa' Xaa' Cys (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Xaa' Cys Xaa' Xaa' (SEQ ID NO:)

FIG. 2 (sheet 91 of 91)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO:)
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' Xaa' (SEQ ID NO:)

FIGURE 3 (sheet 1 of 68)

Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 2 of 68)

Cys Glu Tyr Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 3 of 68)

Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Ala Cys Val Gly Cys Tyr

FIGURE 3 (sheet 4 of 68)

Cys Glu Tyr Cys His Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 5 of 68)

Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 6 of 68)

Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr

Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Gly Cys Tyr

FIGURE 3 (sheet 8 of 68)

Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 9 of 68)

Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Ala Cys Tyr
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Cys Glu Tyr Cys --- Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ala Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Gly Cys Tyr

Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Ala Cys Tyr

Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Glu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Gly Cys Tyr

FIGURE 3 (sheet 12 of 68)

Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys His Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys His Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr

Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr
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Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr

Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr
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Cys Glu Trp Cys Met Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr
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Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr
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Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr
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Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr
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Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr
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Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr
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Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 17 of 68)

Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr
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Cys Glu Trp Cys Val Asn Gly Ala Cys Val Gly Cys Tyr
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Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys Tyr
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Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Trp Cys --- Asn Pro Ala Cys Thr Gly Cys Tyr
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Cys Glu Trp Cys --- Asn Pro Ala Cys Val Gly Cys Tyr
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Cys Glu Trp Cys --- Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys --- Asn Pro Thr Cys Val Ala Cys Tyr
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Cys Glu Trp Cys --- Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Trp Cys --- Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Trp Cys --- Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Gly Cys Tyr

Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Gly Cys Tyr
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Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Ala Cys Tyr
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Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr
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Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Pro Thr Cys Gly Ala Cys Tyr
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Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr

Cys Glu Phe Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Asn Asn Gly Thr Cys Gly Ala Cys Tyr
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Cys Glu Phe Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr
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Cys Glu Phe Cys Asp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr
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Cys Glu Phe Cys Asp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Ala Cys Tyr
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Cys Glu Phe Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr
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Cys Glu Phe Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr
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Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr
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Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr
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Cys Glu Phe Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr
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Cys Glu Phe Cys His Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys His Asn Pro Ala Cys Val Gly Cys Tyr
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Cys Glu Phe Cys His Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 21 of 68)

Cys Glu Phe Cys His Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys His Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys His Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys His Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 22 of 68)

Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Met Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 23 of 68)

Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr

FIGURE 5 (sheet 24 of 68)

Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 25 of 68)

Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 26 of 68)

Cys Glu Phe Cys --- Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys --- Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys --- Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Phe Cys --- Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 27 of 68)

Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Gly Cys Tyr

FIGURE 3 (sheet 28 of 68)

Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Glu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 29 of 68)

Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys His Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr
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Cys Glu Leu Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr

Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr
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Cys Glu Leu Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr
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Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr
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Cys Glu Leu Cys Met Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Met Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr
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Cys Glu Leu Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr
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Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr
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Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr
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Cys Glu Leu Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 33 of 68)

Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr
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Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Val Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Val Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Val Asn Pro Thr Cys Val Gly Cys Tyr

Cys Glu Leu Cys Val Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr
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Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Gly Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Ala Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Val Ala Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Gly Cys Tyr
Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Ala Cys Tyr
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Cys Glu Leu Cys --- Asn Pro Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys --- Asn Pro Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Ala Cys Tyr
Cys Glu Leu Cys --- Asn Gly Ala Cys Thr Gly Cys Tyr
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Cys Glu Leu Cys --- Asn Gly Ala Cys Val Gly Cys Tyr
Cys Glu Leu Cys --- Asn Gly Ala Cys Val Ala Cys Tyr
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Cys Glu Leu Cys --- Asn Gly Ala Cys Gly Ala Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Gly Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Ala Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Val Gly Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Val Ala Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Gly Cys Tyr
Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Ala Cys Tyr
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 35 of 68)

Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Asn Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Asn Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 36 of 68)

Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Gln Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Ala Cys

Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys His Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 38 of 68)

Cys Glu Tyr Cys His Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Ala Cys

FIGURE 3 (sheet 39 of 68)

Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Gly Cys

FIGURE 3 (sheet 40 of 68)

Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 41 of 68)

Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 42 of 68)

Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Val Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys Val Asn Gly Ala Cys Gly Ala Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Ala Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Gly Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Ala Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Gly Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Ala Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Gly Cys
Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Ala Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Gly Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Ala Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Gly Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Ala Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Gly Cys
Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Ala Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Gly Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Ala Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Gly Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Ala Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Gly Cys
Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 43 of 68)

Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Gly Cys
Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Ala Cys
Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Gly Cys
Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Ala Cys
Cys Glu Tyr Cys --- Asn Gly Thr Cys Gly Gly Cys
Cys Glu Tyr Cys --- Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ala Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Arg Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 44 of 68)

Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Asp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 45 of 68)

Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Glu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Glu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Glu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Glu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Gly Cys

Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys His Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys His Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys His Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys His Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Ala Cys

FIGURE 3 (sheet 47 of 68)

Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Leu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Met Asn Gly Ala Cys Val Gly Cys

FIGURE 3 (sheet 48 of 68)

Cys Glu Trp Cys Met Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Met Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Met Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Phe Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Pro Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 49 of 68)

Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ser Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Ser Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Thr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 50 of 68)

Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Trp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Trp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Trp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys Val Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 51 of 68)

Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Thr Gly Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Thr Ala Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Val Gly Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Val Ala Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Gly Gly Cys
Cys Glu Trp Cys --- Asn Pro Ala Cys Gly Ala Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Thr Gly Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Thr Ala Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Val Gly Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Val Ala Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Gly Gly Cys
Cys Glu Trp Cys --- Asn Pro Thr Cys Gly Ala Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Thr Gly Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Thr Ala Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Val Gly Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Val Ala Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Gly Gly Cys
Cys Glu Trp Cys --- Asn Gly Ala Cys Gly Ala Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Thr Gly Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Thr Ala Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Val Gly Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Val Ala Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Gly Cys
Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 52 of 68)

Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Asn Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Asn Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Asp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Asp Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 53 of 68)

Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Asp Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Asp Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Asp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Asp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Gln Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Gln Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Gln Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Gln Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Glu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Glu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Glu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Glu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Glu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Glu Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 54 of 68)

Cys Glu Phe Cys Glu Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Glu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Glu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Gly Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Gly Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys His Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys His Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys His Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Ala Cys

FIGURE 3 (sheet 55 of 68)

Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Gly Cys

FIGURE 3 (sheet 56 of 68)

Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Met Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 57 of 68)

Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 58 of 68)

Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Trp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 59 of 68)

Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Ala Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Gly Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Ala Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Gly Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Ala Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Gly Cys
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Ala Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Gly Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Ala Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Val Gly Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Val Ala Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Gly Gly Cys
Cys Glu Phe Cys --- Asn Pro Thr Cys Gly Ala Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Thr Gly Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Thr Ala Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Val Gly Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Val Ala Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Gly Gly Cys
Cys Glu Phe Cys --- Asn Gly Ala Cys Gly Ala Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Thr Gly Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Thr Ala Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Val Gly Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Val Ala Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Gly Gly Cys
Cys Glu Phe Cys --- Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 60 of 68)

Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Arg Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 61 of 68)

Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 62 of 68)

Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Glu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Glu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Ala Cys

FIGURE 3 (sheet 63 of 68)

Cys Glu Leu Cys His Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys His Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys His Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys His Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys His Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ile Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Leu Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Leu Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Leu Asn Gly Ala Cys Val Gly Cys

FIGURE 3 (sheet 64 of 68)

Cys Glu Leu Cys Leu Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Leu Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Lys Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Lys Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Met Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Met Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Met Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Met Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 65 of 68)

Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Pro Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 66 of 168)

Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 67 of 68)

Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Val Gly Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Ala Cys
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Gly Cys
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Ala Cys
Cys Glu Leu Cys --- Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 68 of 68)

Cys Glu Leu Cys --- Asn Pro Ala Cys Val Ala Cys
Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Gly Cys
Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Ala Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Thr Gly Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Thr Ala Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Val Gly Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Val Ala Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Gly Cys
Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Ala Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Thr Gly Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Thr Ala Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Val Gly Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Val Ala Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Gly Gly Cys
Cys Glu Leu Cys --- Asn Gly Ala Cys Gly Ala Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Gly Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Ala Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Val Gly Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Val Ala Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Gly Cys
Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Ala Cys

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DO NOT ENTER: /J.L/
09/23/2016

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

This amendment and response is submitted in response to the Final Office Action mailed on June 3, 2016 in the above-identified application. This response is timely filed by September 3, 2016. As September 3, 2016 is a Saturday, and the following Monday, September 5, 2016, is a federal holiday, this response is timely filed by September 6, 2016 per the next-business-day rule.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AFCP 2.0 Decision	Application No.	Applicant(s)
	14/845,644	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

This is in response to the After Final Consideration Pilot request filed 06 September 2016.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ A proper AFCP 2.0 request was submitted in response to the most recent final rejection.

   ☐ Other:

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☐ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action. See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☒ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other:

Examiner Note: Please attach an interview summary when necessary as described above.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14/845,644	Filing Date	2015-09-04	Docket Number (if applicable)	SYPA-009/C02US 321994-22	Art Unit	1676
First Named Inventor	Stephen COMISKEY			Examiner Name	LEE, Jia-Hai		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☒ Other Certification and Request For Prioritized Examination Under 37 CFR 1.102(e)

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

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X Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-09)
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Signature of Registered U.S. Patent Practitioner			
Signature	/Anne E. Fleckenstein/	Date (YYYY-MM-DD)	2016-12-05
Name	Anne E. Fleckenstein	Registration Number	62951

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	COMISKEY, Stephen, et al.	Confirmation No.:	8164
Application No.:	14/845,644	Group Art Unit:	1676
Filed:	September 4, 2015	Examiner:	Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION AND ADVISORY ACTION AND REQUEST FOR CONTINUED EXAMINATION

This amendment and response is submitted in response to the Final Office Action mailed on June 3, 2016 and the Advisory Action mailed September 29, 2016 in the above-identified application. The fee for a three-month extension of time is submitted herewith, making this response timely filed by December 3, 2016. As December 3, 2016 is a Saturday, this response is timely filed by Monday, December 5, 2016 per the next-business-day rule. This response is being filed with a Request for Continued Examination.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough and underlining. This listing also reflects any cancellation and/or addition of claims.

1. (Currently Amended) A method for treating chronic constipation in a human subject comprising orally administering to said human subject a composition ~~comprising~~ consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months ~~and one or more pharmaceutically acceptable excipients~~.

2. (Original) The method of claim 1, wherein the constipation is associated with irritable bowel syndrome or chronic idiopathic constipation.

3. (Currently Amended) A method of treating or alleviating a symptom associated with chronic idiopathic constipation or irritable bowel syndrome in a human subject comprising orally administering to said human subject a composition ~~comprising~~ consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months ~~and one or more pharmaceutically acceptable excipients~~.

4. (Original) The method of claim 3, wherein the symptom is constipation or abdominal pain.

5. (Original) The method of claim 1, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

6. (Original) The method of claim 5, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

7. (Original) The method of claim 1, further comprising administering to said patient an effective dose of a laxative.

8. (Original) The method of claim 3, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

9. (Original) The method of claim 8, wherein said inhibitor of cGMP-dependent phosphodiesterase is selected from the group consisting of sulindac sulfone, zaprinast, and motapizone.

10. (Original) The method of claim 3, further comprising administering to said patient an effective dose of a laxative.

11. (New) The method of claim 1, wherein the inert low moisture carrier is microcrystalline cellulose.

12. (New) The method of claim 1, wherein the lubricant is magnesium stearate.

13. (New) The method of claim 1, wherein the inert low moisture carrier is microcrystalline cellulose and the lubricant is magnesium stearate.

14. (New) The method of claim 3, wherein the inert low moisture carrier is microcrystalline cellulose.

15. (New) The method of claim 3, wherein the lubricant is magnesium stearate.

16. (New) The method of claim 3, wherein the inert low moisture carrier is microcrystalline cellulose and the lubricant is magnesium stearate.

REMARKS

Claims 1-16 are pending. Claims 11-16 are new. Claims 1 and 3 are amended herein to recite the composition comprises a low-moisture inert carrier and a lubricant, and the peptide has a chromatographic purity of no less than 91% after storage for at least three months. Support for these amendments can be found throughout the application as filed, and specifically for example, in Example 14 and paragraph [040]. Support for new claims 11 and 14 can be found throughout the application as filed, and specifically for example at paragraph [015]. Support for new claims 12 and 15 can be found throughout the application as filed, and specifically for example at paragraph [015]. Support for new claims 13 and 16 can be found throughout the application as filed, and specifically for example at paragraph [067]. No new matter is added.

Claims 1-10 are not obvious

The Examiner rejected claims 1-10 under 35 U.S.C. § 103(a) as allegedly being obvious over Shailubhai *et al.* (WO 2008/151257' "the '257 publication") in view of Shailubhai *et al.* (2008; "Shailubhai Abstract"). Office Action mailed June 3, at page 4. Specifically, the Examiner alleges the '257 publication teaches the use of a guanylate cyclase agonist SP-304 to treat gastrointestinal disorders including irritable bowel syndrome and constipation. *Id.* at pages 4-5. The Examiner further asserts the '257 publication teaches the SP-304 peptide can be formulated in a pharmaceutical composition in unit dose form between 100 μg and 3g together with one or more pharmaceutically acceptable excipients. *Id.* at page 5. While the Examiner concedes that the '257 publication does not specify a unit dose suitable for administration to humans, the Examiner contends the Shailubhai Abstract teaches the use of SP-304 for the treatment of chronic constipation, irritable bowel syndrome with constipation, and other GI disease via oral administration. *Id.* The Examiner thus argues that it would have been obvious to the skilled artisan to have combined the SP-304 peptide disclosed in the '257 publication with the Shailubhai Abstract's teaching of safe and effective administration of 2.7 mg or 5.4 mg of SP-304 with a reasonable expectation of success. *Id.* at page 7.

Applicants respectfully disagree. A *prima facie* case of "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333,

1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The present claims are amended to recite the formulation consists of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. This is neither taught nor suggested in the cited art. The '257 publication does not teach or suggest a formulation consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant where the peptide has a chromatographic purity of no less than 91% after storage for at least three months. Nothing in the '257 publication teaches or suggests a formulation with such characteristics. The Examiner has therefore failed to make a *prima facie* case of obviousness.

Nor does the Shailubhai Abstract cure the deficiencies of the '257 publication. Neither of these references teaches or suggests a formulation consisting of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. The rejection fails for this reason alone.

Even assuming, arguendo, that the skilled person would find a reason to combine the '257 publication with the teaching of the Shailubhai Abstract, such combination still would not have led one to arrive at the instant claims. For a determination of obviousness the prior art must suggest to one of ordinary skill in the art that this method should be carried out and that one of ordinary skill would have a reasonable likelihood of success, when viewed in the light of the prior art. Moreover, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of unexpected results.

Applicants previously submitted a §1.132 declaration of Dr. Comiskey ("Comiskey Decl.") on September 6, 2016 demonstrating that formulations having a low-moisture inert carrier as recited in the amended claims shows superior results compared with formulations taught in the art, and are more stable than expected compared to formulations comprising a

regular-grade carrier. *See* Comiskey Decl. at ¶ 7. Formulations containing a low-moisture carrier demonstrate unexpectedly dramatically decreased amounts of impurities. *See* Comiskey Decl. at ¶ 7-8. These data demonstrate that the formulation required by the claimed methods provides an unexpectedly superior result relative to formulations taught in the art. As noted by Dr. Comiskey, stability of the active ingredient, the peptide of SEQ ID NO: 1, is essential to ensure proper dosing in the treatment of chronic constipation or irritable bowel syndrome. *See* Comiskey Decl. at ¶ 9

The cited art therefore does not provide a suggestion of all elements of the pending claims. Nor does it teach or predict the surprising stability demonstrated by the instantly claimed formulations. Accordingly the claimed formulations are not obvious, and Applicants respectfully request withdrawal of the instant rejection.

Advisory Action mailed September 29, 2016

In the Advisory Action mailed September 29, 2016 the Examiner indicated that the proposed claim amendments have not been entered, and if they were, they are subject to a new ground of rejection. *See* Advisory Action, "Continuation of 12". Specifically, the Examiner contends the claims would be rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Currie *et al.* (WO 2005/016244; "Currie") in view of FMC biopolymer (2005; "FMC"), Fretzen (US 2010/0048489; "Fretzen"), and Shailubhai (Digestive Disease Week; 2008; "Shailubhai Abstract"). *Id.* The Examiner made the same rejection in co-pending US Application No. 13/421,769. *Id.* The Examiner argues Currie discloses bicyclic GC-C receptor agonist peptides in formulations that can include binders, lubricants, inert diluents, or microcrystalline cellulose purchased from FMC Corporation. *See* Office Action mailed October 5, 2016 in co-pending US Appln. No. 13/421,769, pages 6-7. The Examiner argues FMC shows a range of low moisture Avicel PH grades. *Id.* at page 7. The Examiner contends Fretzen *et al.* teaches an orally administered formulation of a GC-C receptor agonist polypeptide comprising microcrystalline cellulose, and a lubricant. *Id.* at page 8. The Examiner further argues Fretzen *et al.* "shows the chromatographic purity of the GC-C receptor agonist polypeptide decreases by less than 9%....". *Id.* The Examiner states the Shailubhai Abstract teaches a dose range for SP-304 of 2.7mg-5.4mg. *Id.* at page 9. Thus, the Examiner contends the skilled artisan would have been motivated

by Fretzen to store Currie's therapeutic in a sealed container containing a desiccant to achieve the chromatographic purity as claimed by Fretzen. *Id.* Applicants respectfully disagree.

A *prima facie* case of "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The present claims are amended to recite the formulation ***consists of*** a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91% after storage for at least three months. This is neither taught nor suggested in the cited art. None of the cited art teaches or suggests a formulation ***consisting*** of a per unit dose of 3 mg or 6 mg of a peptide consisting of SEQ ID NO:1 wherein the peptide is a [4,12; 7,15] bicycle, an inert low moisture carrier, and a lubricant where the peptide has a chromatographic purity of no less than 91% after storage for at least three months. For these reasons alone, Applicants assert that the claims are non-obvious over the cited references. This is especially true given the unexpected superior stability of the formulation recited in the amended claims. *See* Comiskey Decl. at ¶ 7-8.

Furthermore, there is no objective reason provided by the teachings of Currie in view of view of FMC, Fretzen *et al.*, and the Shailubhai Abstract that would lead the skilled artisan to combine these references, nor is there any evidence that the resultant combination of these references would lead the skilled artisan to arrive at the claimed invention with predictable results. These references, when considered in their entirety, fail to provide the skilled artisan with a reasonable expectation of success.

Currie is cited as teaching bicyclic GC-C receptor agonist peptides in formulations that can include binders, lubricants, inert diluents, or microcrystalline cellulose purchased from FMC Corporation. *See* Office Action in '769 application, pages 6-7. Currie teaches thousands of different GC-C receptor agonist peptides, one of which is the claimed peptide. Currie teaches an equally long list of binders, lubricants, inert diluents, or microcrystalline cellulose, one of which is a low moisture carrier. There is no teaching in Currie that SEQ ID NO:1 is a preferred GC-C receptor agonist. There is therefore no motivation to select SEQ ID NO: 1 in particular from the list of GC-C receptor agonists. There is no teaching in Currie that an inert low moisture carrier and a lubricant are preferred excipients, and therefore there is no motivation to select those

particular excipients from the list of excipients. Furthermore, there is certainly no motivation to select SEQ ID NO:1, an inert low moisture carrier, and a lubricant for use in a pharmaceutical composition, let alone a pharmaceutical composition having a per unit dose of 3 mg or 6 mg to treat chronic constipation or irritable syndrome as required by the claims. Accordingly, the teachings of Currie fail to establish a *prima facie* case of obviousness against the current claims.

Given the fatal deficiency of Currie, one of ordinary skill would have had no motivation to combine the teachings of Currie with FMC, Fretzen, and the Shailubhai Abstract either alone or in combination to reach the claimed invention with a reasonable expectation of success. The mere fact that something is possible does not, standing alone, support an obviousness rejection. Rather, an objective reason to combine the references is required. *See* MPEP § 2143.01 (IV). Here, the Examiner has not provided the required articulated reasoning and, in fact, nothing in the cited art provides any reason to arrive at the formulation recited claim 1 to treat constipation or irritable bowel syndrome. The Examiner has therefore failed to make a *prima facie* case of obviousness.

FMC merely discloses a range of low moisture Avicel PH grades. Fretzen teaches GC-C receptor agonist formulations with the claimed chromatographic purity[1]. Specifically, the Examiner points to the chromatographic purity of the formulations disclosed in Table 7 of Fretzen. However, as shown in the table below, none of these formulations ***consist*** of a GC-C receptor agonist peptide an inert low moisture carrier and a lubricant.

Example	**Formulation Components**	**% Linaclotide (taken from Table 7 of Fretzen)**
1	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***99.13***
3	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***99.42***
4	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***97.83***
5	$CaCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	***98.68***
6	$MgCl_2$, leucine, hypromellose, linaclotide, celphere CP-305	95.51
7	ZnAc, leucine, hypromellose, linaclotide, celphere CP-305	95.36
8	Leucine, hypromellose, linaclotide, celphere CP-305	94.90
9	$CaCl_2$, hypromellose, linaclotide, celphere CP-305	96.55

1 *See* Office Action mailed October 5, 2016 in the '769 application, at page 8.

10	hypromellose, linaclotide, celphere CP-305	**87.77**
11	hypromellose, linaclotide, celphere CP-305	**91.63**
12	$CuCl_2$, hypromellose, linaclotide, celphere CP-305	**43.15**
13	ZnAc, hypromellose, linaclotide, celphere CP-305	94.01
14	$MgCl_2$, hypromellose, linaclotide, celphere CP-305	92.70
15	Methionine, hypromellose, linaclotide, celphere CP-305	93.24
17	$CaCl_2$, hypromellose, linaclotide, celphere CP-305	95.16

Moreover, all of the formulations disclosed in Fretzen contain components in addition to a GC-C receptor agonist, an inert low moisture carrier, and a lubricant. Importantly, as shown in the table above, the most stable formulations (e.g. those from examples 1, 3, 4, and 5) all contain $CaCl_2$ and leucine, while the least stable (e.g. those from examples 10, 11, and 12) all lack an amino acid and/or a cation. Given the chromatographic purities demonstrated by the formulations disclosed in Fretzen, the skilled artisan would not have been motivated to alter the Fretzen formulations to remove components. Moreover, the skilled artisan would not have done so with a reasonable expectation of success of obtaining the claimed chromatographic purity.

Finally and of critical importance, Fretzen fails to disclose any formulation with the claimed GC-C receptor agonist peptide. There are three different families of GC-C receptor agonist peptides— Uroguanylin, Guanylin and heat-stable enterotoxin. Although, each of these family of peptide share the common function of binding the GC-C receptor they all have different physiological purposes.

Uroguanylin is secreted by enterochromaffin cells in the duodenum and proximal small intestine. Uroguanylin acts as an agonist of the guanylyl cyclase receptor GC-C and regulates electrolyte and water transport in intestinal and renal epithelia. Guanylin is secreted by goblet cells in the colon and induces chloride secretion and decreases intestinal fluid absorption. Both uroguanylin and guanylin are *endogenous* peptide hormones that physiologically regulate R-GC signaling proteins in target cells. In contrast, heat-stable enterotoxins are *bacterial* enterotoxins, which have greater potency than the endogenous peptides, and induce excessive fluid secretion into intestinal lumen leading to secretory diarrhea (i.e., Travellers' Diarrhea)

The claimed peptide is structurally related to the endogenous hormone uroguanylin. In contrast, the Fretzen peptides are structurally related to *bacterial* heat-stable enterotoxin. Thus one skilled in the art would not have been motivated to alter the Fretzen formulations to replace a bacterially derived peptide with a endogenous human derived peptides. Moreover, the skilled artisan would not have done so with a reasonable expectation of success of obtaining the claimed chromatographic purity.

Further, as explained above, Applicants have surprisingly discovered that formulations consisting of just a uroguanylin derived GC-C receptor agonist, an inert low moisture carrier, and a lubricant show superior results compared with formulations taught in the art, and are more stable than expected compared to formulations comprising a regular-grade carrier. *See* Comiskey Decl. at ¶ 7.

The cited art therefore does not provide a suggestion of all elements of the pending claims. Nor does it teach or predict the surprising stability demonstrated by the instantly claimed formulations. Accordingly the claimed formulations are not obvious, and Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: December 5, 2016

Respectfully submitted,
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Anne E. Fleckenstein, Ph.D.
Reg. No. 62,951

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Stephen COMISKEY	Nonprovisional Application Number (if known):	14/845,644
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Anne E. Fleckenstein/	Date December 5, 2016
Name (Print/Typed) Anne E. Fleckenstein	Practitioner Registration Number 62,951

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	14845644
Filing Date:	04-Sep-2015
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009/C02US 321994-224

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 1st Request	2801	1	600	600
OTHER PUBLICATION PROCESSING FEE	2808	1	130	130
		Total in USD ($)		**3500**

Electronic Acknowledgement Receipt

EFS ID:	27692257
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US 321994-224
Receipt Date:	05-DEC-2016
Filing Date:	04-SEP-2015
Time Stamp:	15:32:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	SYPA_009_C02US_RCETransmittal.pdf	697704 702af07c0a7d56d9eb62072b7ef659c245171525	no	3

Warnings:

Information:					
2	Amendment Submitted/Entered with Filing of CPA/RCE	SYPA-009_C02US_response_FOA_and_AA.pdf	165339 30bf3856264b930ce67f87a15025dced78105a7b	no	12
Warnings:					
Information:					
3	TrackOne Request	SYPA_009_C02US_RCETrackOne.pdf	141020 c8b3024ef47de3d408a2667b7f73894f56c3892c	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	37475 203e1454aaa493441b6dc6813a7911dc553a2e70	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1041538	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/845,644	Filing Date 09/04/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **12/05/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 16	Minus	** 20	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
CORALIA BETANCOURT

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DEC 05 2016

PTO/SB/17 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL

Complete if known	
Application Number	14/845,644
Filing Date	September 4, 2015
First Named Inventor	Stephen COMISKEY
Examiner Name	LEE, Jia-Hai
Art Unit	1676
Practitioner Docket No.	SYPA-009/C02US 321894-22

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 3,500.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-1283 Deposit Account Name: Cooley LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	_____	_____	_____
_____	_____	_____	_____

3 APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number)	x _____ =	_____

4 OTHER FEE(S) Fees Paid ($)

Non-English specification, $130 fee (no small or micro entity discount) _____

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity) _____

Other (e.g., late filing surcharge): Fee Codes: 2830; 2253; 2808; 2801; 2817 $3,500.00

SUBMITTED BY

Signature	/Anne E. Fleckenstein/	Registration No. (Attorney/Agent) 62,951	Telephone (202) 728-7030
Name (Print/Type)	Anne E. Fleckenstein		Date December 5, 2016

RECEIVED
CENTRAL FAX CENTER
DEC 05 2016

Electronic Acknowledgement Receipt

EFS ID:	27692257
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE 12/06/2016 [illegible] 00000024 501283 14845644 Sale Ref: 00000026 DA#: 501283 14845644 01 FC:2253 700.00 DA 02 FC:2830 70.00 DA 03 FC:2808 130.00 DA 04 FC:2801 600.00 DA 05 FC:2817 2000.00 DA
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US 321994-224
Receipt Date:	05-DEC-2016
Filing Date:	04-SEP-2015
Time Stamp:	15:32:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	SYPA_009_C02US_RCETransmittal.pdf	697704 [illegible]	no	3

Warnings:

Information:					
2	Amendment Submitted/Entered with Filing of CPA/RCE	SYPA-009_C02US_response_FOA_and_AA.pdf	165339 [illegible]	no	12
Warnings:					
Information:					
3	TrackOne Request	SYPA_009_C02US_RCETrackOne.pdf	141020 [illegible]	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	37475 [illegible]	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1041538		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

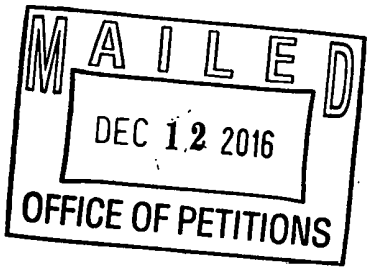
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington DC 20004



Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/845,644

1. THE REQUEST FILED December 5, 2016 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

58249 7590 02/10/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER
LEE, JIA-HAI

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 02/10/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224	8164

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/10/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 02/10/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224	8164

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/10/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224	8164

58249 7590 02/10/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

EXAMINER	
LEE, JIA-HAI	

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 02/10/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/845,644	Applicant(s) COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *12/05/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-16*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J. L./
Examiner, Art Unit 1676

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/05/2016 has been entered including the new claims 11-16.

Withdrawn Rejection

The prior rejection of claims 1-10 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 2008/151257 A2, IDS #76) in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008) has been withdrawn because the combined references did not teach or suggest a composition consisting of . a per unit dose of 3 mg or 6 mg of a [4, 12; 7, 15] bicyclic peptide consisting of SEQ ID NO: 1, an inert low moisture carrier, and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months in the amended claims.

The provisional rejection of claims 1-5, 7-8, and 10 on the ground of nonstatutory

double patenting as being obvious over claims 1 and 4 of copending Application No. 14/301,812 in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008) has been withdrawn because the amendments to the claims overcome the rejection.

The provisional rejection of claims 1-10 on the ground of nonstatutory double patenting as being unpatentable over claims 2-9 and 42-43 (an oral dosage formulation of SEQ ID NO: 1/SP-304), 26 and 32 (a process of making SP-304), and 36-40 (a method of using SP-304 to treat disease) of copending Application No. 13/421,769 in view of Shailubhai et al. (Digestive Disease Week. San Diego: 2008) has been withdrawn in view of the approved terminal disclaimer dated 9/22/2016.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

The closest prior art reference Shailubhai et al. (Digestive Disease Week. San Diego: 2008) taught the use of a per unit dose of a [4, 12; 7, 15] bicyclic peptide consisting of SEQ ID NO: 1 (named SP-304) at substantially the same dosage of 2.7, 5.4, and 8.1 mg in a clinical trial, but the reference did not teach or suggest the composition further comprising an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

The other closest reference Shailubhai et al. (WO 2008/151257 A2, IDS #76) suggest the use of SP-304 to treat gastrointestinal disorders comprising irritable bowel syndrome (IBS) and constipation (p5, line 8-21). Shailubhai et al. further suggest the

oral composition comprising a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or com starch and/or a lubricant such as magnesium stearate or Sterotes (p41, line 19-30). However, Shailubhai et al. did not teach the composition consisting of SP-304, an inert low moisture carrier and a lubricant, and wherein the peptide has a chromatographic purity of no less than 91 % after storage for at least three months as claimed.

For the reasons described above, the amended claims are allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri from 9:00 A.M. to 5:30 P.M..

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./
Examiner, Art Unit 1676

26-January-2017

(FILE 'HOME' ENTERED AT 20:22:20 ON 05 JAN 2017)

FILE 'REGISTRY' ENTERED AT 20:23:34 ON 05 JAN 2017

L1 79 SEA SPE=ON ABB=ON PLU=ON NDECELCVNVACTGCL/SQSP

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 20:24:12 ON 05 JAN 2017

L2 93 SEA SPE=ON ABB=ON PLU=ON L1

L3 4 SEA SPE=ON ABB=ON PLU=ON INERT (L) (LOW MOISTURE) (L) CARRIER

L4 29258 SEA SPE=ON ABB=ON PLU=ON (MICROCRYSTALLINE CELLULOSE)

L5 205762 SEA SPE=ON ABB=ON PLU=ON LUBRICANT OR (MAGNESIUM STEARATE)

L6 169554 SEA SPE=ON ABB=ON PLU=ON CONSTIPATION OR (IRRITABLE BOWEL SYNDROME)

L7 0 SEA SPE=ON ABB=ON PLU=ON L2 AND L4 AND L5

L8 74 SEA SPE=ON ABB=ON PLU=ON L2 AND L6

L9 0 SEA SPE=ON ABB=ON PLU=ON L8 AND L4

L10 5 SEA SPE=ON ABB=ON PLU=ON L8 AND L5

L11 27 SEA SPE=ON ABB=ON PLU=ON COMISKEY STEPHEN/AU

L12 129 SEA SPE=ON ABB=ON PLU=ON FENG RONG/AU

L13 45 SEA SPE=ON ABB=ON PLU=ON FOSS JOHN/AU

L14 124 SEA SPE=ON ABB=ON PLU=ON SHAILUBHAI KUNWAR/AU

L15 261 SEA SPE=ON ABB=ON PLU=ON L11 OR L12 OR L13 OR L14

L16 53 SEA SPE=ON ABB=ON PLU=ON L15 AND L6

L17 16 SEA SPE=ON ABB=ON PLU=ON L16 AND L2

L18 6 SEA SPE=ON ABB=ON PLU=ON L17 AND (AD<2012 OR PD<2012 OR PRD<2012)

L19 8 SEA SPE=ON ABB=ON PLU=ON L18 OR L10

L20 8 DUP REM L19 (0 DUPLICATES REMOVED)

D L20 1-8 IBIB ABS HITIND

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	Art Unit
	JIA-HAI LEE	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	1/26/2017	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	1/5/2017	JL
PALM Inventor Search	1/26/2017	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	EAST, Database: USPATFUL, USPGPUB,	1/26/2017	JL
	STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	1/5/2017	JL
	PALM Inventor Search	1/26/2017	JL

/J.L./ Examiner.Art Unit 1676	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	254	(guanylate near cyclase) and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L2	66	(guanylate near cyclase) same (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L3	13	L2 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L4	47025	(guanylate near cyclase) or (GCC near agonist) or (chronic near constipation) or (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L5	31	(guanylate near cyclase) and (GCC near agonist) and (chronic near constipation) and (irritable near bowel near syndrome)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L6	1946	L4 and laxative	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L7	331	L6 and phosphodiesterase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L8	159	L7 and cGMP	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L9	32	L8 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L10	121	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53

L11	290	(Rong near3 FENG).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L12	138	(John near3 FOSS).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L13	235	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L14	690	L10 or L11 or L12 or L13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L15	38	L14 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L16	52	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L17	22	L16 and (chronic near constipation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L18	167	SP304 or SP-304 pr (SP near "304")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L19	28	L18 same unit	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L20	0	L18 same constipation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L21	37	L18 and constipation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L22	36	L21 and unit	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53

L23	3	(microcrystalline celloluse)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L24	2	(microcrystalline near3 celloluse)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L25	964766	(magnesium with stearate) or lubricant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L26	160993	(microcrystalline with celloluse) or (inert with carrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L27	551	(SP near3 "304") or NDECELCVNVACTGCL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L28	0	L25 same L26 same L27	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L29	70	L25 and L26 and L27	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53
L30	20	L29 and @py<"2012"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2017/01/26 22:53

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L31	14	NDECELCVNVACTGCL	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L32	69923	low with moisture	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L33	0	L31 and L32	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L34	575	SP304 or SP-304 or uroguanylin	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L35	4	L34 and L32	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L36	22	(Stephen near3 COMISKEY).in.	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L37	74	(Rong near3 FENG).in.	US-PGPUB;	WITH	ON	2017/01/26

			USPAT			22:53
L38	41	(John near3 FOSS).in.	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L39	66	(Kunwar near3 SHAILUBHAI).in.	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L40	38	(SYNERGY near3 PHARMACEUTICALS).asn.	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L41	194	L36 or L37 or L38 or L39 or L40	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L42	2	L41 and L32	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L43	2	L41 and L32	US-PGPUB; USPAT	WITH	ON	2017/01/26 22:53
L45	128	inert same low same moisture same carrier	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:01
L46	226842	lubricanr or (magnesium near3 stearate)	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:02
L47	114207	microcrystalline same cellulose	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:03
L48	0	L34 same L45 same L46	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:04
L49	0	L34 and L45 and L46	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:05
L50	6036	chromatographic purity	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:05
L51	0	L34 same L50	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:06
L52	11	L34 and L50	US-PGPUB; USPAT	WITH	ON	2017/01/26 23:06

1/26/2017 11:08:43 PM
C:\Users\jlee24\Documents\EAST\Workspaces\14845644.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

CPC						
Symbol					**Type**	**Version**
A61K		38	/	12	F	2013-01-01
C07K		7	/	54	I	2013-01-01
C12Y		406	/	01002	A	2013-01-01
A61K		9	/	1623	I	2013-01-01
A61K		9	/	1652	I	2013-01-01
A61K		9	/	1676	I	2013-01-01
A61K		9	/	2054	I	2013-01-01
A61K		9	/	4858	I	2013-01-01
A61K		9	/	4866	I	2013-01-01
A61K		38	/	10	I	2013-01-01
A61K		45	/	06	I	2013-01-01
A61K		31	/	192	I	2013-01-01
A61K		31	/	501	I	2013-01-01
A61K		31	/	519	I	2013-01-01
A61K		31	/	53	I	2013-01-01
A61K		31	/	765	I	2013-01-01
A61K		31	/	78	I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	192	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	519	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	501	I	3	1	2013-01-01
A61K		2300	/	00	A	3	2	2013-01-01
A61K		31	/	53	I	4	1	2013-01-01
A61K		2300	/	00	A	4	2	2013-01-01
A61K		31	/	765	I	5	1	2013-01-01
A61K		2300	/	00	A	5	2	2013-01-01

/J.L./ Examiner.Art Unit 1676	01/26/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/06/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	N/A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

A61K		31	/	78	I	6	1	2013-01-01
A61K		2300	/	00	A	6	2	2013-01-01

/J.L./ Examiner.Art Unit 1676	01/26/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/06/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	N/A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED							
424	451	A	6	1	K	38 / 10 (2006.01.01)								
CROSS REFERENCE(S)		A	6	1	K	9 / 48 (2006.01.01)								
		A	6	1	K	9 / 00 (2006.01.01)								
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)													

/J.L./ Examiner.Art Unit 1676	01/26/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/06/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	N/A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14845644	COMISKEY ET AL.
	Examiner	**Art Unit**
	JIA-HAI LEE	1676

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/J.L./ Examiner.Art Unit 1676	01/26/2017	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/SATYANARAYANA R GUDIBANDE/ Primary Examiner.Art Unit 1676	02/06/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	N/A

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

58249 7590 02/10/2017
COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224	8164

TITLE OF INVENTION: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/10/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, JIA-HAI	1676	424-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Cynthia Kozakiewicz
2 Ivor Elrifi
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SYNERGY PHARMACEUTICALS, INC.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): NEW YORK, NEW YORK

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ● Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ● Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ● The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-1283 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Anne E. Fleckenstein/ Date February 16, 2017

Typed or printed name Anne E. Fleckenstein Registration No. 62,951

Electronic Patent Application Fee Transmittal

Application Number:	14845644
Filing Date:	04-Sep-2015
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Filer:	Anne Elizabeth Fleckenstein
Attorney Docket Number:	SYPA-009/C02US 321994-224

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**480**

Electronic Acknowledgement Receipt

EFS ID:	28373378
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Anne Elizabeth Fleckenstein
Filer Authorized By:	
Attorney Docket Number:	SYPA-009/C02US 321994-224
Receipt Date:	16-FEB-2017
Filing Date:	04-SEP-2015
Time Stamp:	14:07:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$480
RAM confirmation Number	021717INTEFSW00000428501283
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	SYPA_009_C02US_IssueFeeTransmittal.pdf	354423 a1101b11d3466de7c4203a2bbb2a8e9d80d6e31c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30469 af74c0d4ec33fdf7c90d56fe75362ce8fafad3c4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	384892		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Change(s) applied to document, /S.R.R./ 2/16/2017 **Notice of References Cited**	Application/Control No. 14/845,644	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2010/0048489 A1	02-2010	Fretzen; Angelika	A61K9/1611	514/1.1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO2005016244A2	02-2005	~~US~~ WO	Currie et al.	A61K
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	FMC BioPolymer Catalog. 2005.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	*To Be Assigned*
Filing Date	September 4, 2015
First Named Inventor	Stephen COMISKEY
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	SYPA-009/C02US

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	60.	DE 19744027	04-08-1999	Hoechst Marion Rouseel Deutschland GmbH		
	61.	WO 88/05306	07-28-1988	The General Hospital Corporation		
	62.	WO 93/12068 A1	06-24-1993	Brigham and Women's Hospital		
Change(s) applied to document, /S.R.R./ 2/16/2017	63.	~~WO~~ 1999/026567 A1 WO	06-03-1999	Optonol Ltd		
	64.	WO 01/25266 A1	04-12-2001	Pharmacia Corporation		
	65.	WO 02/062369 A2	08-15-2002	Pharmacia Corporation		
	66.	WO 2002/078683 A1	10-10-2002	Synergy Pharmaceuticals, Inc.		
	67.	WO 2002/098912 A3	12-12-2002	Cetin		
	68.	WO 2004/069165	08-19-2004	Microbia Inc. et al.		
	69.	WO 2005/016244 A2	02-24-2005	Microbia, Inc. et al.		
	70.	WO 2005/087797	09-22-2005	Microbia, Inc. et al.		
	71.	WO 2006/086653 A2	08-17-2006	Microbia, Inc. et al.		
	72.	WO 2007/101158 A2	09-07-2007	Microbia, Inc. et al.		
	73.	WO 2007/022531	02-22-2007	Microbia, Inc. et al.		
	74.	WO 2008/106429	09-04-2008	Microbia, Inc. et al.		
	75.	WO 2008/137318 A1	11-13-2008	Ironwood Pharmaceuticals, Inc. et al.		

Examiner Signature:		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

121042409v1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Change(s) applied to document, /S.R.R./ 2/16/2017

PTO/SB/08a (09-08)
Approved for use through 10/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT LIST

(Use as many sheets as necessary)

Complete if Known	
Application Number	*To Be Assigned*
Filing Date	September 4, 2015
First Named Inventor	Stephen COMISKEY
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	SYPA-009/C02US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code2 (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2002/0128176 A1	09-12-2002	Forssmann et al.	
	2.	2002/0078683	06-27-2002	Katayama et al.	
	3.	2002/0133168	09-19-2002	Smeldley et al.	
	4.	2002/0143015	10-03-2002	Fryburg et al.	
	5.	2003/0073628	04-17-2003	Shailubhai et al.	
	6.	2004/0015140 A1	01-22-2004	Shields	
	7.	2005/0016244	01-27-2005	Hergemoller	
	8.	2005/0032684 A1	02-10-2005	Cetin et al.	
	9.	2005/0107734	05-19-2005	Coroneo	
	10.	2005/0266047	12-01-2005	Tu et al	
	11.	~~005/0267297~~	12-01-2005	Berlin	2005/0267197
	12.	2006/0086653	04-27-2006	St. Germain	
	13.	2006/0094658	05-04-2006	Currie	
	14.	2007/0101158	05-03-2007	Elliott	
	15.	2008/0137318	06-12-2008	Rangaraj et al.	
	16.	2008/0151257	06-26-2008	Yasuda et al.	
	17.	2009/0048175 A1	02-19-2009	Shailubhai et al.	
	18.	2009/0192083 A1	07-30-2009	Currie	
	19.	2009/0253634 A1	10-08-2009	Currie et al.	
	20.	2010/0069306 A1	03-18-2010	Shailubhai et al.	

Examiner Signature:		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/845,644	04/04/2017	9610321	SYPA-009/C02US 321994-224	8164

58249 7590 03/15/2017

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Stephen COMISKEY, Doylestown, PA;
SYNERGY PHARMACEUTICALS INC., NEW YORK, NY
Rong FENG, Langhorne, PA;
John FOSS, Doylestown, PA;
Kunwar SHAILUBHAI, Audubon, PA;

PTO/AIA/81A (02-15)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	9,610,321
Issue Date	April 4, 2017
First Named Inventor	Stephen Comiskey
Title	Formulations of Guanylate Cyclase C Agonists and Methods of Use
Attorney Docket No.	376464-2005US3 (00110)

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

162421

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Patent Owner

Signature		Date	August 22, 2018
Name	Robert Comeau	Telephone	
Title and Company	VP and Assistant General Counsel @ Bausch Health Ireland Limited		

NOTE: Signatures of all the applicants or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☐ A total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Synergy Pharmaceuticals Inc.

Application No./Patent No.: 9,610,321 Filed/Issue Date: April 4, 2017

Titled: FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE

Bausch Health Ireland Limited, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: inventors To: Synergy Pharmaceuticals, Inc.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 041258, Frame 0280, or for which a copy thereof is attached.

2. From: Synergy Pharmaceuticals, Inc. To: Bausch Health Ireland Limited

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Domingos J. Silva/	September 28, 2020
Signature	Date
Domingos J. Silva	64197
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT ASSIGNMENT AGREEMENT – UNITED STATES

THIS PATENT PROPERTY ASSIGNMENT AGREEMENT – UNITED STATES, dated as of March 6, 2019 (this "Agreement"), is made by and among Bausch Health Ireland Limited, a private limited company organized under the laws of Ireland (the "Assignee"), and Synergy Pharmaceuticals Inc., a Delaware corporation (the "Parent"), and its wholly-owned subsidiary, Synergy Advanced Pharmaceuticals, Inc., a Delaware corporation ("SF Sub") (each of the Parent and SF Sub, an "Assignor" and collectively, the "Assignors"). Each of the Assignee and the Assignors are referred to individually herein as a "Party" and collectively as the "Parties." Capitalized terms used herein and not otherwise defined shall have the respective meanings set forth in the Asset Purchase Agreement (as defined below).

RECITALS:

WHEREAS, the Assignee and the Assignors have entered into that certain Asset Purchase Agreement, dated as of December 11, 2018, as amended and restated on January 4, 2019 (as further amended, restated, supplemented or otherwise modified from time to time, the "Asset Purchase Agreement"); and

WHEREAS, this Agreement is made and delivered pursuant to the terms and subject to the conditions set forth in the Asset Purchase Agreement.

AGREEMENT:

NOW, THEREFORE, subject to the terms and conditions of the Asset Purchase Agreement, and in consideration of the representations, warranties, covenants and agreements set forth therein, the Parties hereto agree as follows:

1. Acquired Patents. For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Assignors hereby irrevocably and unconditionally sell, transfer, assign, convey, and deliver to the Assignee and its successors and permitted assigns, forever, and the Assignee accepts and acquires from the Assignors all of the Assignors' right, title, and interest (of every nature, kind, and description, tangible or intangible (including goodwill), whether real, personal, or mixed, whether accrued, contingent, or otherwise, wherever located), in each case free and clear of any and all Encumbrances (other than Permitted Post-Closing Encumbrances) in, to, and under all of Seller's right, title and interest in and to those patents and patent applications set forth on Schedule I hereto (the "Acquired Patents"), including (i) all of Assignors' rights in and to all income, royalties, damages and payments now or hereafter due or payable with respect thereto, (ii) all causes of action (whether in law or in equity) with respect thereto, and (iii) the right to sue, counterclaim, and recover for past, present and future infringement of the Acquired Patents.

2. Further Assurances. This Agreement has been executed and delivered by the Assignors with the agreement that the same may be recorded with the United States Patent and Trademark Office and with other applicable governmental entity or registrar in other jurisdictions outside the United States. From time to time hereafter, and without further consideration, each of the Assignors, the Assignee, and their respective successors and permitted

assigns, covenant and agree that each of the Assignors, the Assignee, and their respective successors and permitted assigns shall execute and deliver, or shall cause to be executed and delivered, such further instruments of conveyance and transfer and take such additional action as the other Party may reasonably request to effect, consummate, confirm, or evidence the transfer to the Assignee, its successors, and permitted assigns of the Acquired Patents in accordance with the foregoing. Assignor shall provide Assignee and its successors and assigns reasonable cooperation and assistance at Assignee's request and expense (including the execution and delivery of any and all country specific forms of assignment, affidavits, declarations, oaths, exhibits, powers of attorney or other documentation) as are reasonably requested by Assignee to effect, record, register or maintain this Assignment and/or the rights assigned herein. The Parties hereby authorize the relevant authority at the United States Patent and Trademark Office and respective foreign patent and trademark offices to record this Agreement and record Assignee as the owner of the Acquired Patents and to issue any and all Acquired Patents to Assignee, as assignee of Assignor's entire right, title and interest in, to and under the same.

3. Power of Attorney. The Assignors hereby constitute and appoint the Assignee as the Assignors' true and lawful attorney in fact, with full power of substitution in the Assignors' name and stead, to take any and all steps, including proceedings at law, in equity or otherwise, to execute, acknowledge and deliver any and all instruments and assurances necessary or expedient in order to vest or perfect the aforesaid rights more effectively in the Assignee or to protect the same or to enforce any claim or right of any kind with respect thereto. The Assignors hereby declare that the foregoing power is coupled with an interest and as such is irrevocable.

4. Notices. All notices, requests, claims, demands or other communications hereunder to any Party shall be given in the manner set forth in the Asset Purchase Agreement. Any Party may change its address for receiving notices, requests, and other documents by giving written notice of such change to the other Parties in accordance with the Asset Purchase Agreement.

5. Severability. If any provision of this Agreement or the application thereof to any Person or circumstance is held invalid or unenforceable, the remainder of this Agreement, and the application of such provision to other Persons or circumstances, shall not be affected thereby, and to such end, the provisions of this Agreement are agreed to be severable.

6. Effectiveness. This Agreement shall be effective as of the Closing Date pursuant to the terms of the Asset Purchase Agreement.

7. Amendments; Waivers. This Agreement may not be waived, altered, amended or modified except by an instrument in writing signed by, or on behalf of each of the Parties hereto.

8. Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed to be an original but all of which shall constitute one and the same agreement.

9. Governing Law; Submission of Jurisdiction; Waiver of Jury Trial. With regard to patent, trademark and copyright issues, this Agreement shall be governed by and construed in accordance with the federal Laws of the United States. For all other matters, this Agreement shall be governed by and construed in accordance with the Laws of the State of Delaware

without regard to the rules of conflict of Laws of the State of Delaware or any other jurisdiction. Each of the Parties irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the Bankruptcy Court for any litigation arising out of or relating to this Agreement and the transactions contemplated thereby (and agrees not to commence any litigation relating thereto except in the Bankruptcy Court), provided, however, that if the Chapter 11 Case has been closed and/or the Bankruptcy Court declines jurisdiction, each of the Parties agree to and hereby irrevocably and unconditionally consents to submit to the exclusive jurisdiction of the United States District Court sitting in Wilmington, Delaware. Each of the Parties irrevocably and unconditionally waives any objection to the laying of venue of any such litigation in any such court. Each Party hereby consents to service of process in the manner set forth in Section 4. EACH PARTY HERETO IRREVOCABLY AND UNCONDITIONALLY WAIVES ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN RESPECT OF ANY LITIGATION ARISING OUT OF OR RELATING TO THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY.

10. Third Parties. This Agreement will be binding upon, inure to the benefit of and be enforceable by the Parties hereto and their respective successors and permitted assigns and shall not be binding upon, inure to the benefit of, or be enforceable by any other party.

[*Signature Pages Follow*]

IN WITNESS WHEREOF, the Parties have caused this Assignment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNORS:

SYNERGY PHARMACEUTICALS INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

SYNERGY ADVANCED PHARMACEUTICALS, INC.

By: _____
Name: Gary G. Gemignani
Title: EVP and Chief Financial Officer

STATE OF Connecticut)
: ss.: Darien
COUNTY OF Fairfield)

On this 4th day of March 2019, before me personally appeared Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Pharmaceuticals Inc., and Gary G Gemignani, in his/her capacity as EVP and CFO of Synergy Advanced Pharmaceuticals, Inc.., who each proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is subscribed to or who executed the foregoing instrument in his authorized capacity, and who duly acknowledged to me that execution of the same is his/her own free act and deed and made with appropriate authority.

_____
Notary Public

MICHAEL HENRY BERGMANN
Notary Public
Connecticut
My Commission Expires Mar 31, 2019

My Commission Expires: 03/31/2019

[Notary Seal]

[Signature Page to Patent Assignment – United States]

IN WITNESS WHEREOF, the Parties have caused this Assigment to be executed by their respective officers thereunto duly authorized as of the date first above written.

ASSIGNEE:

BAUSCH HEALTH IRELAND LIMITED

By: _____
Name: Graham Jackson
Title: Director

[Signature Page to Patent Assignment – United States]

Schedule I

Acquired Patents

Title/Mark	Application No.	Application Date	Registration No.	Registration Date	Case Status	Country
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	10/107,814	3/28/2002	7,041,786	5/9/2006	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	11/347,115	2/2/2006	7,799,897	9/21/2010	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	12/763,707	4/20/2010	8,114,831	2/14/2012	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	13/339,785	12/29/2011	8,637,451	1/28/2014	Granted	United States of America
GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	14/137,256	12/20/2013			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/133,344	6/4/2008	7,879,802	2/1/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	12/630,654	12/3/2009	8,969,514	3/3/2015	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/010,267	1/20/2011	8,716,224	5/6/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/857,283	4/5/2013	8,901,075	12/2/2014	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/528,257	10/30/2014	9,266,926	2/23/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA, ATHEROSCLEROSIS, CORONARY HEART DISEASE, GALLSTONE, OBESITY AND OTHER CARDIOVASCULAR DISEASES	14/742,456	6/17/2015	9,814,752	11/14/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/049,740	2/22/2016	9,914,752	3/13/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/471,462	3/28/2017			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	15/918,047	3/12/2018			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/228,843	3/28/2014	9,238,677	1/19/2016	Granted	United States of America

METHOD OF INHIBITING BILE ACID ABSORPTION BY ADMINISTERING AN AGONIST OF A GUANYLATE CYCLASE RECEPTOR	13/513,224	12/3/2010	9,089,612	7/28/2015	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/478,505	6/4/2009	8,207,295	6/26/2012	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/467,703	5/9/2012	8,357,775	1/22/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/716,874	12/17/2012	8,497,348	7/30/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/831,293	8/20/2015	9,920,095	3/20/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	12/504,288	7/16/2009	8,034,782	10/11/2011	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	14/632,314	2/26/2015	9,505,805	11/29/2016	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/226,300	9/6/2011	8,367,800	2/5/2013	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/731,483	12/31/2012	8,569,246	10/29/2013	Granted	United States of America

AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS, INFLAMMATION, CANCER AND OTHER DISORDERS	13/955,710	7/31/2013	8,664,354	3/4/2014	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/301,812	6/11/2014	10,034,836	7/31/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	16/018,278	6/26/2018			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	15/405,787	1/13/2017			Pending	United States of America
PROCESS OF PREPARING GUANYLATE CYCLASE C AGONIST	14/001,638	3/1/2012	9,580,471	2/28/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	14/845,644	9/4/2015	9,610,321	4/4/2017	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,631	3/23/2017	9,925,231	3/27/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/467,648	3/23/2017	9,919,024	3/20/2018	Granted	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	15/924,940	3/19/2018			Pending	United States of America
FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE	13/421,769	3/15/2012	9,616,097	4/11/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR DOWNREGULATION OF PRO-INFLAMMATORY CYTOKINES	15/026,560	10/9/2014			Pending	United States of America
COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	14/207,749	3/13/2014	9,486,494	11/8/2016	Granted	United States of America

COMPOSITIONS USEFUL FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS	15/272,873	9/22/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/189,645	2/25/2014	9,545,446	1/17/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/381,680	12/16/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	14/207,753	3/13/2014	9,708,367	7/18/2017	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	15/622,526	6/14/2017	10,118,946	11/6/2018	Granted	United States of America
AGONISTS OF GUANYLATE CYCLASE AND THEIR USES	16/150,703	10/3/2018			Pending	United States of America
FORMULATIONS AND METHODS FOR TREATING ULCERATIVE COLITIS	16/069,313	1/11/2017			Pending	United States of America
COMPOSITIONS AND METHOD FOR THE TREATMENT AND DETECTION OF COLON CANCER	15/777,273	11/18/2016			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	15/026,563	10/10/2014			Pending	United States of America
AGONISTS OF GUANYLATE CYCLASE USEFUL FOR THE TREATMENT OF OPIOID INDUCED DYSFUNCTIONS	14/944,499	11/18/2015			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	16/000,251	6/5/2018			Pending	United States of America
ULTRA-PURE AGONISTS OF GUANYLATE CYCLASE C, METHOD OF MAKING AND USING SAME	14/896,019	6/5/2014	10,011,637	7/3/2018	Granted	United States of America

INTER PARTES REVIEW OF USP 8,101,579 ENTITLED METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS (IPR 2018-01363)			8,101,579		Pending	United States of America

Electronic Acknowledgement Receipt

EFS ID:	40687250
Application Number:	14845644
International Application Number:	
Confirmation Number:	8164
Title of Invention:	FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen COMISKEY
Customer Number:	58249
Filer:	Domingos J. Silva/Catherine Rose
Filer Authorized By:	Domingos J. Silva
Attorney Docket Number:	SYPA-009/C02US 321994-224
Receipt Date:	28-SEP-2020
Filing Date:	04-SEP-2015
Time Stamp:	14:11:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Executed_General_BauschHealthPatentPOA.pdf	302929 12eec354c05916892a8a5300cc83a2cc847bd67a	no	2

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

2	Assignee showing of ownership per 37 CFR 3.73	Statement_373c_Assignment.pdf	309297 0da13deef1468046c04875544679d953d4e9db2c	no	14

Warnings:

Information:

Total Files Size (in bytes):	612226

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
14/845,644	09/04/2015	Synergy Pharmaceuticals Inc.	376464-2005US3 (00110)	122074

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 09/29/2020 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Domingos J. Silva/
Name:	DOMINGOS J. SILVA
Registration Number:	64197

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/845,644	09/04/2015	Stephen COMISKEY	SYPA-009/C02US 321994-224

CONFIRMATION NO. 8164

POWER OF ATTORNEY NOTICE

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

OC000000120277105

Date Mailed: 10/01/2020

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/28/2020.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/845,644	09/04/2015	Stephen COMISKEY	376464-2005US3 (00110)

CONFIRMATION NO. 8164

POA ACCEPTANCE LETTER

162421
SAUL EWING ARNSTEIN & LEHR LLP (Bausch Health)
Attn: Patent Docket Clerk, Centre Square West,
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186

OC000000120277172

Date Mailed: 10/01/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/28/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,041,786	5/9/2006	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	7,799,897	9/21/2010	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	8,637,451	1/28/2014	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4	9,610,321	4/4/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
5	9,616,097	4/11/2017	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
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	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,919,024	3/20/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
2	9,925,231	3/27/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
3	10,011,637	7/3/2018	Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

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DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino		5-6-2021

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
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Page 2 of 2

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
21-611-LPS	4/29/2021	for the District of Delaware

PLAINTIFF	DEFENDANT
BAUSCH HEALTH IRELAND LIMITED and SALIX PHARMACEUTICALS, INC.	MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. - a VIATRIS COMPANY

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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAUSCH HEALTH IRELAND LIMITED, and SALIX PHARMACEUTICALS, INC. Plaintiffs, v. MYLAN LABORATORIES LTD., AGILA SPECIALTIES INC., MYLAN API US LLC, MYLAN INC., VIATRIS INC. and MYLAN PHARMACEUTICALS INC. — a VIATRIS COMPANY, Defendants.	C.A. No. 1:21-cv-00611-LPS

NOTICE OF VOLUNTARY DISMISSAL WITHOUT PREJUDICE

Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc., pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), hereby voluntarily dismiss this action, without prejudice.

GIBBONS P.C.

By: */s/ Christopher Viceconte*
Christopher Viceconte (No. 5568)
Jennifer M. Rutter (No. 6200)
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Wilmington, Delaware 19801
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Attorneys for Plaintiffs Bausch Health Ireland Limited and Salix Pharmaceuticals, Inc.

OF COUNSEL:

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Tel: (202) 408-4000

Dated: May 5, 2021