UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

CORRECTED COPY
020914 HM12/1019
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON NJ 08543-4000

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/788,173	02/16/01	024	GERSTL, R 1626	10/19/01
First Named Applicant ROBL,		35 USC 154(b) term ext. =	0 Days.	

TITLE OF INVENTION CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 LA0050 NP	514-412.000	N53	UTILITY	NO	$1280.00	01/22/02

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE 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.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box 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.

PATENT AND TRADEMARK OFFICE COPY

Notice of Allowability

Application No.	Applicant(s)
09/788,173	Robl
Examiner	**Art Unit**
Robert Gerstl	1626

--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 and Issue Fee Due 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 *8/31/01*.

2. ☒ The allowed claim(s) is/are *1-24*.

3. ☐ The drawings filed on _____ are acceptable as formal drawings.

4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

   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: _____.

5. ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

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 FOR SUBMITTING NEW FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION.** ~~**This three-month period for complying with the REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL is extendable under 37 CFR 1.136(a).**~~

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS

   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No. _____.

   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.

   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☒ Information Disclosure Statement(s) (PTO-1449), Paper No(s). 2
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

ROBERT GERSTL
PRIMARY EXAMINER
ART UNIT 1626

Best Available Copy

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
LA0050 NP
APPLICATION NO.
09/788,173
APPLICANT
ROBL ET AL.
FILING DATE
FEBRUARY 16, 2001

Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	5,462,928	10/31/95	Bachovchin et al			
	AB	5,939,560	8/17/99	Jenkins et al			
	AC	6,011,155	1/4/00	Villhauer, E.B.			
	AD	6,110,949	8/29/00	Villhauer, E.G.			
	AE						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AF	WO 97/40832	11/6/01	PCT			☐	☐
	AG	WO 99/38501	8/5/99	PCT			☐	☐
	AH	WO 99/67279	12/29/99	PCT			☐	☐
	AI	WO 00/10549	3/2/00	PCT			☐	☐
	AJ	WO 00/53171	9/14/00	PCT			☐	☐
	AK	WO 00/56296	9/28/00	PCT			☐	☐
	AL	WO 00/56297	9/28/00	PCT			☐	☐
	AM	WO 00/69868	11/23/00	PCT			☐	☐
	AN	EP 1050540A2	11/8/00	Europe			☐	☐
	AO	WO 034241A1	6/15/00	PCT			☐	☐
	AP						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

AQ	Lin, J. et al, Proc. Natl. Acad. Sci, USA, Vol. 95, pp. 14020-14024, Nov. 1998
AR	Augustyns, KJL et al, Eur. J. Med. Chem. 32, 301-309, (1997)
AS	Hughes, T.E. et al, Biochemistry, 28, 11597-11603, 1999

EXAMINER	DATE CONSIDERED

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

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTY. DOCKET NO.
LA0050 NP
APPLICATION NO.
09/788,173
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ROBL ET AL.
FILING DATE
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Group

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AT	Yamada, M. et al, Bioorganic & Medicinal Chemistry Letters 8, 1537-1540 (1998)
	AU	Tanaka, S. et al, Immunopharmacology 40, 21-26 (1998)
	AV	Li, J. et al, Archives of Biochemistry and Biophysics, Vol. 323, No. 1, pp. 148-154, Oct. 20, 1995
	AW	Ashworth, D.M. et al, Bioorganic & Medicinal Chemistry Letter, Vol. 6, No. 22, pp. 2745-2748, 1996
	AX	Yamada, M. et al, Bioorganic & Medicinal Chemistry Letter 8, 1537-1540 (1998)
	AY	Ashworth, D.M. et al, Bioorganic & Medicinal Chemistry Letter, Vol. 6, No. 10, pp. 1163-1166, 1996
	AZ	Lambeir, A.-M., et al, Biochimica et Biophysica Acts, 1290, pp. 76-82 (1996)
	BA	Yoshimoto, T. et al, Agric. Biol. Chem., 55(4), pp. 1135-1136, 1991
	BB	Belyaev, A. et al, J. Med. Chem., 42, 1041-1052, 1999
	BC	Stockel, A. et al, Peptides: Chemistry, Structure and Biology, pp. 709-710, 1996
	BD	Asai, Y. et al, The Journal of Antibiotics, Vol. 50, No. 8, pp. 653-657, Aug. 1997
	BE	Demuth, H.-U. et al, FEBS LETTERS, Vol. 320, No. 1, pp. 23-27, March 1993
	BF	Ohnuki, T. et al, Drugs of the Future, 24(6): 665-670, 1999
	BG	Demuth, H-U. et al, Diabetes, 2000, Vol. 49, suppl. 1, A102
	BH	Rotherberg, P. et al, Diabetes, 2000, Vol. 49, Suppl. 1, A39

CASE LA0050 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Burton Rodney — Type or print name

Signature

Nov. 5, 2001 — Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ROBL ET AL.

APPLICATION NO: 09/788,173

FILED: FEBRUARY 16, 2001

FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Art Unit: 1626

Examiner: R. Gerstl

Batch No.: N53

Assistant Commissioner for Patents
Washington, D.C. 20231

PETITION PURSUANT TO 37 CFR §1.97(d)

Sir:

Consideration of the Information Disclosure Statement submitted concurrently herewith is requested. Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $180 for payment of the fee for filing this petition.

An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336
Date: Nov. 5, 2001

CASE LA0050 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Burton Rodney (Type or print name) — Signature — Nov. 5, 2001 (Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
ROBL ET AL.
APPLICATION NO: 09/788,173
FILED: FEBRUARY 16, 2001
FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Art Unit: 1626
Examiner: R. Gerstl
Batch No.: N53

Assistant Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

These references were cited in a search report in a corresponding PCT International application dated October 23, 2001 that is within 3 months of the filing of this information disclosure statement. Copies of these references and the search report are enclosed herewith.

A petition pursuant to 37 C.F.R. §1.97(d) is enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

12/21/2001 CCHAU1 00000059 193880 09788173
01 FC:126 180.00 CH

Certificate under 37 C.F.R. §1.97(e)(1)

I, the undersigned attorney, hereby certify that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Statement.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: Nov. 5, 2001

Burton Rodney
Attorney for Applicants
Reg. No. 22,076

FORM PTO-1449 (REV. 7-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
LA0050 NP
APPLICATION NO.
09/788,173
APPLICANT
ROBL ET AL.
FILING DATE
FEBRUARY 16, 2001

Group
1626

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	4,254,057	3/3/81	Day et al			
	AB	4,379,785	4/12/83	Weyer et al			
	AC	5,998,463	12/7/99	Hulin et al			
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AL	EP 0 007 652A1	2/6/80	EP			☐	☐
	AM	DE 33 24 263 A1	1/17/85	German			☐	☐
	AN	EP 0 219 782 A2	4/29/87	EP			☐	☐
	AO	DE 39 26 606 A1	2/14/91	German			☐	☐
	AP	WO 99/26659	6/3/99	PCT			☐	☐
	AQ	WO 99/47545	9/23/99	PCT			☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

AR	Sagnard, I. et al, Tetrahedron Letters, Vol. 36, No. 18, pp. 3149-3152, 1995.
AS	Tverezovsky, V.V. et al, Tetrahedron, Vol. 53, No. 43, pp. 14773-14792, 1997.
AT	Hanessian, S. et al, Bioorganic & Medicinal Chem. Letters, Vol. 8, No. 16, pp. 2123-2128, Aug. 18, 1998.

EXAMINER | **DATE CONSIDERED**

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

Best Available Copy

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
BRISTOL-MYERS SQUIBB CO.
Attn. Algieri, Aldo A.
P.O. Box 4000
Lawrenceville-Princeton Rd
PRINCETON, NJ 08543
UNITED STATES OF AMERICA

Date of mailing *(day/month/year)*	23/10/2001
Applicant's or agent's file reference: LA0050	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US 01/07151	International filing date *(day/month/year)*: 05/03/2001
Applicant: BRISTOL-MYERS SQUIBB CO.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chantal Meyer

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
LA0050		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 01/ 07151	05/03/2001	10/03/2000
Applicant		
BRISTOL-MYERS SQUIBB CO.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL IV, PROCESSES FOR THEIR PREPARATION, AND THEIR USE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/07151

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/52 A61K31/403 A61P3/04 A61P3/06 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 011 155 A (VILLHAUER EDWIN BERNARD) 4 January 2000 (2000-01-04) abstract; claims; examples ---	1-7,11, 23,24
Y	WO 99 47545 A (WANNAMAKER MARION W; BEMIS GUY W (US); MURCKO MARK A (US); VERTEX) 23 September 1999 (1999-09-23) page 9, formula I; page 26, especially lines 18-22; page 97, compounds 23d, 23h claims 1,6,18,19,23 ---	1-7,11, 23,24
A	WO 99 67279 A (SCHMIDT JOERN; GLUND KONRAD (DE); DEMUTH HANS ULRICH (DE); HOFFMAN) 29 December 1999 (1999-12-29) page 11 -page 17; claims 1,2,8-13 ---	1,11-13, 22-24

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2001	23/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 379 785 A (WEYER RUDI ET AL) 12 April 1983 (1983-04-12) cited in the application claims 1,5,6	1,11,23, 24
A	EP 0 219 782 A (HOECHST AG) 29 April 1987 (1987-04-29) page 1, formula (I); page 3, substructure K; page 16, line 33 to page 17, line 6 claims 1,2	1,11,23
A	DE 33 24 263 A (HOECHST AG) 17 January 1985 (1985-01-17) claims 1,19,20	1,11
A	DE 39 26 606 A (HOECHST AG) 14 February 1991 (1991-02-14) page 2, formula (I); page 3, substructure (K); page 6, lines 62-66	1
A	US 4 254 057 A (DAY JANET A ET AL) 3 March 1981 (1981-03-03) column 2, line 26 - line 38	1
A	EP 0 007 652 A (SHELL INT RESEARCH) 6 February 1980 (1980-02-06) claim 1	1
A	HANESSIAN S ET AL: "Probing the Importance of Spacial and Conformational Domains in Captopril Analogs for Angiotensin Converting Enzyme Activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 16, 18 August 1998 (1998-08-18), pages 2123-2128, XP004137231 ISSN: 0960-894X the whole document	1
A	TVEREZOVSKY V V ET AL: "Synthesis of (2S, 3R, 4S)-3,4-Methanoproline and Analogues by Cyclopropylidene Insertion" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no. 43, 27 October 1997 (1997-10-27), pages 14773-14792, XP004106307 ISSN: 0040-4020 the whole document	1

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SAGNARD I ET AL: "Enantioselective Synthesis of Cyclopropane alpha-Amino Acids: Synthesis of N-Boc-cis-(2S,3R,4S)-3,4-Methanoproline and N-Boc-(2S,3R,4S)-3,4-Methanoglutamic Acid" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 18, 1 May 1995 (1995-05-01), pages 3149-3152, XP004028212 ISSN: 0040-4039 the whole document	1
A	WO 99 26659 A (HOOVER DENNIS JAY; TREADWAY JUDITH LEE (US); HULIN BERNARD (US); P) 3 June 1999 (1999-06-03) cited in the application claims 1,6,7	12-14, 22-24
A	US 5 998 463 A (HULIN BERNARD ET AL) 7 December 1999 (1999-12-07) cited in the application claims 1,22,23	12-14, 22,23

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/07151

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23, 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/07151

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US 6011155 A	04-01-2000	US 6124305 A	26-09-2000
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		BG 104863 A	30-04-2001
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		NO	20002164 A	19-07-2000
		PL	340643 A1	12-02-2001
US 5998463 A	07-12-1999	NONE		

CASE LA0050 NP

Match & Return

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Burton Rodney		Nov. 14, 2001
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ROBL ET AL.

Art Unit: 1626

Examiner: R. Gerstl

Match and Return

APPLICATION NO: 09/788,173

FILED: FEBRUARY 16, 2001

FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Assistant Commissioner for Patents
Box Issue Fee
Washington, D.C. 20231

AMENDMENT UNDER 37 CFR 1.312

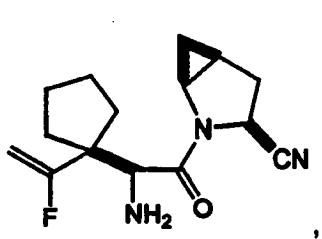
Sir:

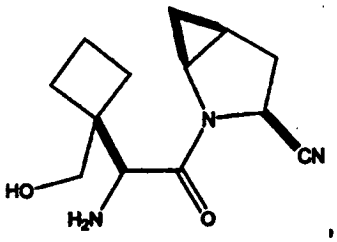
Please amend the above-identified application to read as follows:

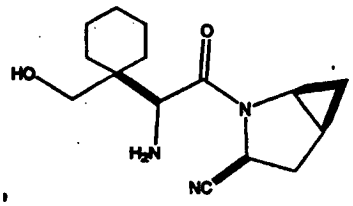
In the Claims:

Please amend Claims 8 and 10 to read as follows:

8. (Amended) A compound having the structure:







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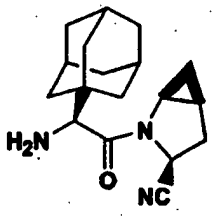
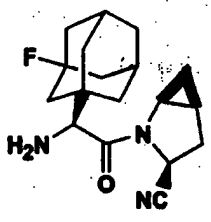
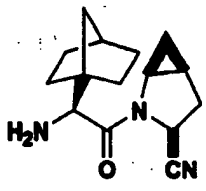
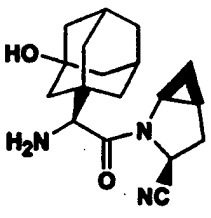
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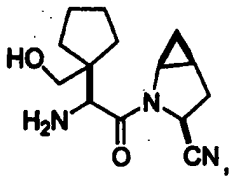
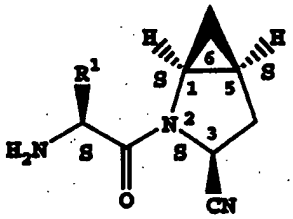


or a pharmaceutically acceptable salt thereof.

10. (Amended) A compound which is

B2

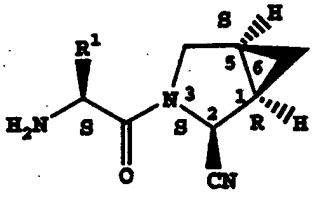


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or



B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl.

Remarks

Claims 1 to 24 are present and have been allowed in the Notice of Allowance mailed October 19, 2001.

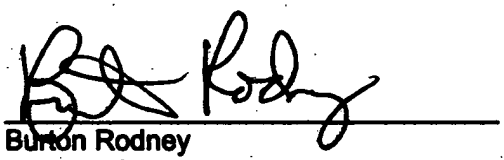
As seen above, Claims 8 and 10 have been amended to place each in independent form. No new matter has been added.

It is respectfully requested that the above amendments be entered.

A copy of Claims 8 and 10 with markings to show changes made is attached.

It is believed that this application is now in condition for issuance once the final fee has been paid.

Respectfully submitted,



Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

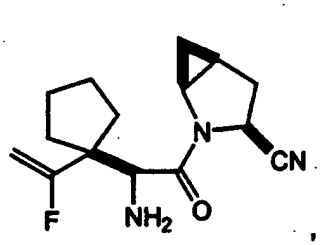
Date: Nov. 14, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 8 and 10 have been amended as follows:

-- 8. (Amended) [The] A compound [as defined in Claim 1] having the structure:



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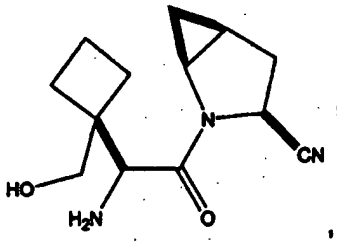

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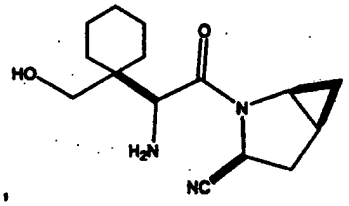

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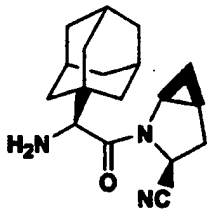

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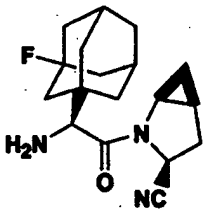

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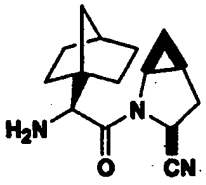

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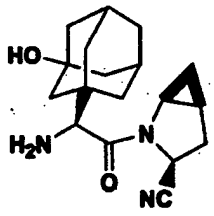

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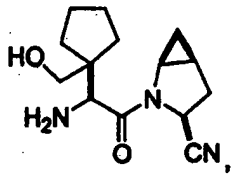
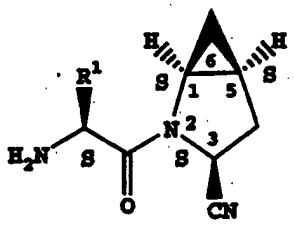


,

or a pharmaceutically acceptable salt thereof.--

--10. (Amended) [The] A compound [as defined in Claim 1] which is

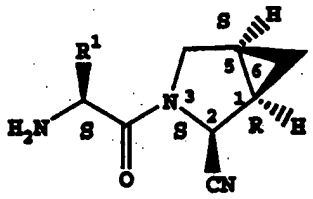


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or



B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl. --

PART B—ISSUE FEE TRANSMITTAL

Complete and mail this form, together with applicable fees, to: **Box ISSUE FEE**
Assistant Commissioner for Patents
Washington, D.C. 20231

BA

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, 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: Legibly mark-up with any corrections or use Block 1)

CORRECTED COPY
023914 HM12/1019
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON NJ 08543-4000

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee 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.

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

Burton Rodney (Depositor's name)
(Signature)
Jan. 15, 2002 (Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/788,173	02/16/01	024	GERSTL, R	1626	10/19/01

First Named Applicant: ROBL, 35 USC 154(b) term ext. = 0 Days.

TITLE OF INVENTION: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 LA0050 NP	514-412.000	N53	UTILITY	NO	$1280.00	01/22/02

1. Change of correspondence address or indication of " Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.
   - ☐ 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) attached.

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 Burton Rodney
   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. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.
   (A) NAME OF ASSIGNEE: Bristol-Myers Squibb Company
   (B) RESIDENCE: (CITY & STATE OR COUNTRY): Princeton, New Jersey
   Please check the appropriate assignee category indicated below (will not be printed on the patent)
   ☐ Individual ☒ corporation or other private group entity ☐ government

Reel: 011607
Frame: 0369

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
   - ☐ Issue Fee
   - ☐ Advance Order - # of Copies _____

4b. The following fees or deficiency in these fees should be charged to:
   DEPOSIT ACCOUNT NUMBER 19-3880
   (ENCLOSE AN EXTRA COPY OF THIS FORM)
   - ☒ Issue Fee
   - ☐ Advance Order - # of Copies _____

The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

(Authorized Signature) (Date) 1/15/02

NOTE; The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

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.

09788173
02/11/2002 CV0222 00000005 193880
1280.00 CH
01 FC:142

TRANSMIT THIS FORM WITH FEE

3

B#

CASE LA0050 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Burton Rodney
Type or print name

Signature

January 15, 2002
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
ROBL ET AL.
APPLICATION NO: 09/788,173
FILED: FEBRUARY 16, 2001
FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Art Unit: 1626
Examiner: R. Gerstl
Batch No.: N53

Box Issue Fee
Commissioner for Patents
Washington, D.C. 20231

OK to Enter

RESPONSE TO NOTICE OF PUBLICATION FEE DUE

Sir:

This is in response to the Notice of Publication Fee Due, dated November 14, 2001, a reply to which is due February 14, 2002.

Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $300.00 for the publication fee due. An additional copy of this paper is herewith enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

If this application is not published, Applicants request a refund of the publication fee paid, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Date: Jan. 15, 2002

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/788,173	02/1[illegible]/2001	Jeffrey A. Robl	LA0050 NP

CONFIRMATION NO. 4018

OC000000007066445

23914
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

Title: Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method

Date Mailed: 11/14/2001

NOTICE OF PUBLICATION FEE DUE

The above-identified application was filed (including as a Continued Prosecution Application) on or after November 29, 2000 and a non-publication request in compliance with 37 CFR 1.213 was not included with the application on filing. Since the application has been allowed, a publication fee is due.

The fee due is $300.00. No small entity discount is available. See 37 CFR 1.18(d).

The reply to this notice should be mailed to:
Box ISSUE FEE
Commissioner for Patents
Washington D.C. 20231.

The publication fee must be submitted within **THREE MONTHS** from the mailing date of this notice or the application may be regarded as abandoned. No extensions of time under 37 CFR 1.136(a) or (b) are available. A reply must be filed to this notice, even if applicant does not anticipate that the application will be published (e.g., because the patent has issued and the projected publication date is more than a month after the issue date of the patent). A proper reply to this notice in such a situation would be a statement that no fee is now due, citing 37 CFR 1.211(e). If publication of the application does not occur, any publication fee paid will be refunded, if applicant requests a refund. See 37 CFR 1.211(e).

Questions relating to this Notice should be directed to the Office of Patent Publication at (703) 305-8283.

A copy of this notice should be returned with any reply.

02/11/2002 CV0222 00000006 193880 09788173

01 FC:195 300.00 CH

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,173	02/16/2001	Jeffrey A. Robl	LA0050 NP	4018

23914 7590 04/01/2002

STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
GERSTL, ROBERT	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 04/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Response to Rule 312 Communication	Application No.	Applicant(s)	
	09/788,173	ROBL ET AL.	
	Examiner	Art Unit	
	Robert Gerstl	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *12/20/01* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

Robert Gerstl
Primary Examiner
Art Unit: 1626

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,173	02/16/2001	Jeffrey A. Robl	LA0050 NP	4018

23914 7590 04/18/2002

STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
GERSTL, ROBERT	
ART UNIT	**PAPER NUMBER**
1626	9

DATE MAILED: 04/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Response to Rule 312 Communication	Application No.	Applicant(s)	
	09/788,173	ROBL ET AL.	
	Examiner	Art Unit	
	Robert Gerstl	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *1/2/02* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

Robert Gerstl
Primary Examiner
Art Unit: 1626

cyc
4 109

CASE LA0050 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney	B Rodney	June 22, 2004
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ROBL ET AL.

PATENT NO.: 6,395,767

ISSUED: MAY 28, 2002

FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Certificate
JUN 29 2004
of Correction

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTENTION: Decision and Certificate of Correction
Branch of Patent Issue Division

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT
FOR PTO MISTAKE (37 C.F.R. §1.322(a))

Sir:

Attached, in duplicate, is PTO/SB/44 (also Form PTO-1050), with at least one copy being suitable for printing.

The exact page and line number where the errors are shown correctly in the application file are:

Claim 8 should read: --A compound having the structure:--.

Claim 10 should read: --A compound which is--.

This correction is necessary because of an error by the Office as follows.

Applicants filed an AMENDMENT UNDER 37 CFR 1.312 (copy enclosed) wherein Claim 8 is amended to place it in independent form and Claim 10 is amended to place it in independent form.

29 JUN 2004

The Examiner in his Response to Rule 312 Communication (PTO-271 (Rev. 04-01)) (copy enclosed) indicated on page 2 that:

"☒ 1. The amendment filed on 1/2/02 under 37 CFR 1.312 has been considered, and has been . . .

b). ☒ entered as directed to matters of form not affecting the scope of the invention."

The subject U.S. Patent No. 6,395,767 issued with Claim 8 and Claim 10 each being dependent on Claim 1, and without including Claim 8 and Claim 10 each being in independent form.

It is respectfully submitted that the Patent Office erred in not including Claim 8 and Claim 10 in independent form since the Examiner had entered Applicants' Amendment Under 37 CFR 1.312 to matters not affecting scope of the invention. Changing Claims 8 and 10 from dependent claims to independent claims does not change the scope of either Claim 8 or Claim 10. Either way, independent Claims 8 and 10 only cover the compounds in dependent Claims 8 and 10.

Accordingly, it is respectfully requested that the attached Certificate of Correction be approved and be included as part of the subject U.S. Patent No. 6,395,767.

Inasmuch as that this error was incurred by the Office, no fee is believed to be due. If any fee not accounted for is due in connection herewith, please charge such fee to Deposit Account No. 19-3880 of the undersigned.

Please send the Certificate to the address associated with customer account number 23914.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Date: June 22, 2004

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Burton Rodney		Nov. 14, 2001
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

"B11

IN RE APPLICATION OF

ROBL ET AL.

APPLICATION NO: 09/788,173

FILED: FEBRUARY 16, 2001

FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Art Unit: 1626

Examiner: R. Gerstl

Assistant Commissioner for Patents
Box Issue Fee
Washington, D.C. 20231

AMENDMENT UNDER 37 CFR 1.312

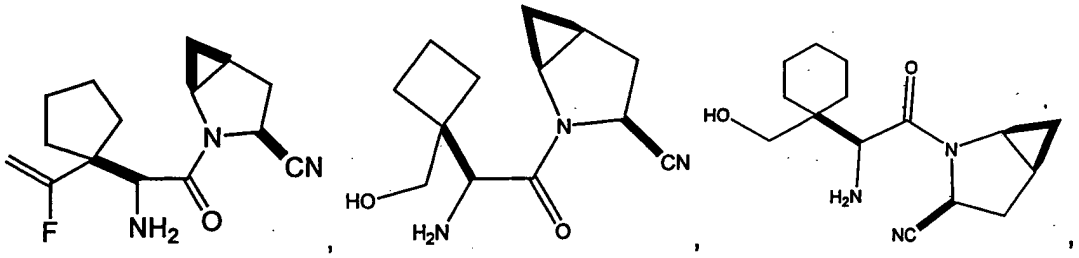
Sir:

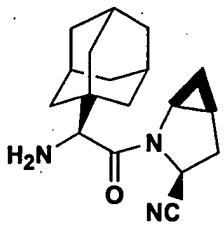
Please amend the above-identified application to read as follows:

In the Claims:

Please amend Claims 8 and 10 to read as follows:

8. (Amended) A compound having the structure:





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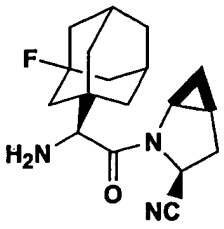

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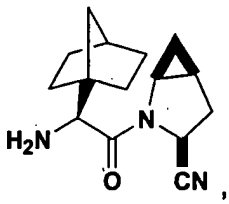

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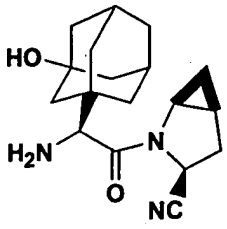
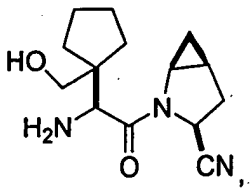


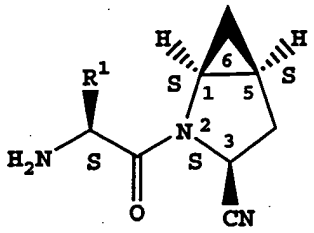
or



,

or a pharmaceutically acceptable salt thereof.

10. (Amended) A compound which is

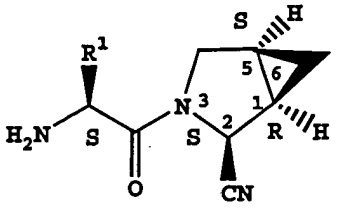


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or



B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl.

Remarks

Claims 1 to 24 are present and have been allowed in the Notice of Allowance mailed October 19, 2001.

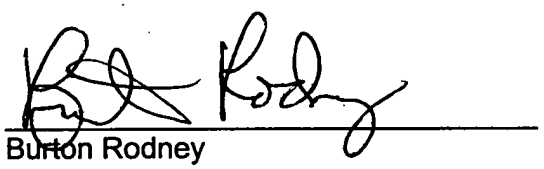
As seen above, Claims 8 and 10 have been amended to place each in independent form. No new matter has been added.

It is respectfully requested that the above amendments be entered.

A copy of Claims 8 and 10 with markings to show changes made is attached.

It is believed that this application is now in condition for issuance once the final fee has been paid.

Respectfully submitted,



Burton Rodney
Attorney for Applicants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

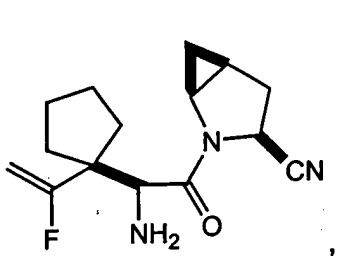
Date: Nov. 14, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 8 and 10 have been amended as follows:

-- 8. (Amended) [The] A compound [as defined in Claim 1] having the structure:



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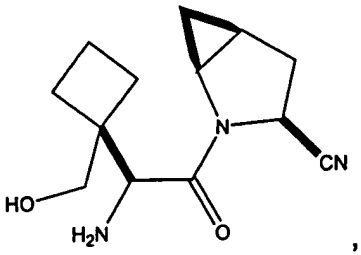

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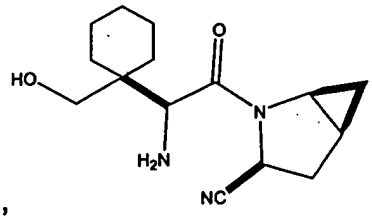

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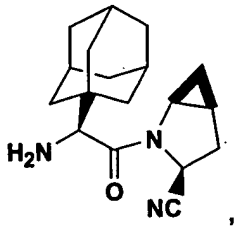

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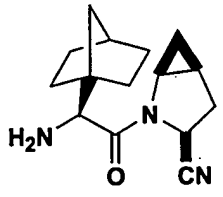

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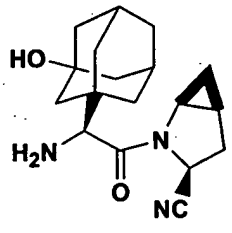

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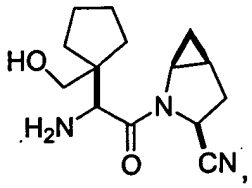
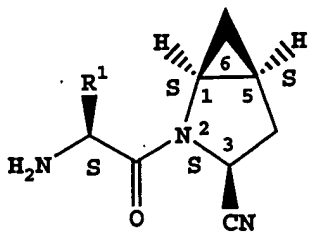


,

or a pharmaceutically acceptable salt thereof.--

--10. (Amended) [The] A compound [as defined in Claim 1] which is

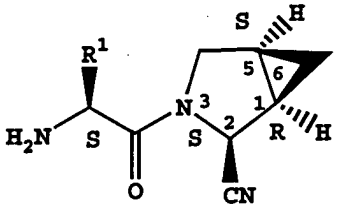


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or



B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl. –

Response to Rule 312 Communication

Application No.	Applicant(s)	
09/788,173	ROBL ET AL.	
Examiner	**Art Unit**	
Robert Gerstl	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on *12/20/01* under 37 CFR 1.312 has been considered, and has been:

   a) ☐ entered.

   b) ☒ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

Robert Gerstl
Primary Examiner 29 JUN 2004
Art Unit: 1626

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney		9 - 12 - 05
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ROBL ET AL

PATENT NO: 6,395,767

ISSUED: May 28, 2002

FOR: CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTENTION: Decision and Certificate of Correction
Branch of Patent Issue Division

REQUEST FOR SECOND CERTIFICATE OF CORRECTION FOR U.S. PATENT NO. 6,395,767 FOR PTO MISTAKE (37 C.F.R. §1.322(a))

Sir:

Attached, in duplicate, is PTO/SB/44 (also Form PTO-1050), with at least one copy being suitable for printing.

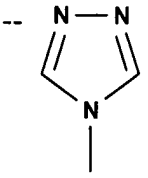
The exact page and line number where the errors are shown correctly in the application file Serial No. 09/788,173 (which issued into U.S. Patent No. 6,395,767) are as follows:

CORRECTION IN U.S. PATENT NO. 6,395,767 (basis in application)

In the Specification:

Col. 7, line 6, change "PGI" to -- PG_1 --. (page 9, line 37)

Col. 14, line 50, insert (page 18, line 14, third formula)

--  --.

Col. 14, line 56, between "refers" and "cycloheteroalkyl", insert -- to --. (page 18, line 17)

Col. 14, line 57, between "a" and "atom", insert -- C --. (page 18, line 19)

Col. 15, line 54, change "γ" to -- β --. (page 20, line 22)

Col. 20, line 59, "2,1" should be -- 2,3 --. (page 30, line 1)

Col. 29, line 23, change "w" to -- % --. (page 44, line 20)

Col. 30, line 2, after "$(M+H)^+$" and before "197", insert -- - --. (page 45, line 11)

Col. 32, line 62, after "$(M+H)^+$" and before "222", insert -- = --. (page 48, line 21)

Col. 33, line 3, change "HO" to read -- H_2O --. (page 48, line 29)

Col. 33, line 7, change "CH2cl$_2$" to read -- CH_2Cl_2 --. (page 49, line 2)

Col. 33, line 11, after "METHOD", insert -- A --. (page 49, line 6)

Col. 34, line 62, delete "15". (page 51, line 14)

Col. 41, line 43, after "was", delete "a". (page 60, line 12)

Col. 41, line 44, after "over", delete "a". (page 60, line 13)

Col. 43, line 36, delete "E". (page 63, line 18)

Col. 43, line 55, change "48.61" to -- 8.61 --. (page 63, line 31)

Col. 44, line 39, change "200" to -- 300 --. (page 65, line 5)

Col. 46, line 58, change "ter" to -- water --. (page 68, line 2)

Col. 46, line 58, after "20" and before "Detection", insert -- mL/min. --. (page 68, line 3)

Col. 46, line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --. (page 68, line 9)

Col. 52, line 64, change "25" to -- 28 --. (page 75, line 17)

Col. 53, line 31, change "OSO_4" to -- OsO4 --. (page 76, line 8)

Col. 53, line 65, after "100%" and before "Solvent A", insert -- B, --. (page 77, line 6)

Col. 53, line 66, after "vent B =" and before "MeOH", insert -- 90% --. (page 77, line 7)

Col. 62, line 67, change "549" to -- 540 --. (page 90, line 3)

Col. 66, line 24, change "CH2Cl$_2$" to -- CH_2Cl_2 --. (page 94, line 20)

Col. 69, line 21, change "9" to -- 8 --. (page 98, line 18)

Col. 69, line 30, change "Hbl" to -- HCl --. (page 98, line 28)

Col. 70, line 56, move "Step 1" to line 65. (page 101, line 10)

Col. 72, line 36, change "50°" to -- 5° --. (page 103, line 22)

Col. 72, line 65, change "2.2(" to -- 2.28 --. (page 104, line 11)

Col. 72, line 65, change "30mL2" to --30 mL --. (page 104, line 11)

Col. 73, line 25, change "the n" to -- then --. (page 104, line 29)

Col. 73, line 26, change "et her" to -- ether --. (page 104, line 30)

Col. 74, line 32, change "50°" to -- 5° --. (page 106, line 10)

Col. 79, line 61, change "100" to -- 10% --. (page 113, line 23)

Col. 82, line 65, change "10EtOAc" to -- 10% EtOAc --. (page 118, line 4)

Col. 84, line 34, change "NS" to -- MS --. (page 120, line 17)

In the Claims:

Col. 92, line 42 (Claim 15), change "APR" to -- AR --. (page 132, line 17)

The above corrections are necessary because of errors by the PTO.

Accordingly, it is respectfully requested that the attached Certificate of Correction be approved and be included as part of the subject U.S. Patent No. 6,395,767.

Inasmuch as the errors necessitating the Certificate of Correction were incurred by the Office, no fee is believed to be due. If any fee not accounted for is due in connection herewith, please charge such fee to Deposit Account No. 19-3880 of the undersigned.

Please send the Certificate to the address associated with customer account number 23914.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Burton Rodney
Attorney for Applicant
Reg. No. 22,076

Date: 9-12-05

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

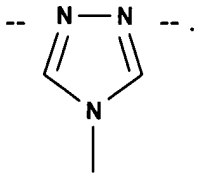
PATENT NO : 6,395,767
DATED: : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification:

Col. 7, line 6, change "PGI" to -- PG_1 --.

Col. 14, line 50, insert



Col. 14, line 56, between "refers" and "cycloheteroalkyl", insert -- to --.

Col. 14, line 57, between "a" and "atom", insert -- C --.

Col. 15, line 54, change "γ" to -- β --.

Col. 20, line 59, "2,1" should be -- 2,3 --.

Col. 29, line 23, change "w" to -- % --.

Col. 30, line 2, after "$(M+H)^+$" and before "197", insert -- - --.

Col. 32, line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Col. 33, line 3, change "HO" to read -- H_2O --.

Col. 33, line 7, change "$CH2cl_2$" to read -- CH_2Cl_2 --.

Col. 33, line 11, after "METHOD", insert -- A --.

Col. 34, line 62, delete "15".

Col. 41, line 43, after "was", delete "a".

Col. 41, line 44, after "over", delete "a".

Col. 43, line 36, delete "E".

Col. 43, line 55, change "48.61" to -- 8.61 --.

Col. 44, line 39, change "200" to -- 300 --.

Col. 46, line 58, change "ter" to -- water --.

Col. 46, line 58, after "20" and before "Detection", insert -- mL/min. --.

Col. 46, line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Col. 52, line 64, change "25" to -- 28 --.

Col. 53, line 31, change "OSO_4" to -- OsO4 --.

Col. 53, line 65, after "100%" and before "Solvent A", insert -- B, --.

Col. 53, line 66, after "vent B =" and before "MeOH", insert -- 90% --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,395,767
DATED: : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 62, line 67, change "549" to -- 540 --.
Col. 66, line 24, change "CH2Cl$_2$" to -- CH_2Cl_2 --.
Col. 69, line 21, change "9" to -- 8 --.
Col. 69, line 30, change "Hbl" to -- HCl --.
Col. 70, line 56, move "Step 1" to line 65.
Col. 72, line 36, change "50°" to -- 5° --.
Col. 72, line 65, change "2.2(" to -- 2.28 --.
Col. 72, line 65, change "30mL2" to --30 mL --.
Col. 73, line 25, change "the n" to -- then --.
Col. 73, line 26, change "et her" to -- ether --.
Col. 74, line 32, change "50°" to -- 5° --.
Col. 79, line 61, change "100" to -- 10% --.
Col. 82, line 65, change "10EtOAc" to -- 10% EtOAc --.
Col. 84, line 34, change "NS" to -- MS --.

In the Claims:
Col. 92, line 42 (Claim 15), change "APR" to -- AR --.

MAILING ADDRESS OF SENDER:
Burton Rodney
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

PATENT NO. 6,395,767

SEP 2 6 2005

FORM PTO-1050

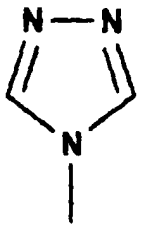
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,
Line 6, change "PGI" to -- PG_1 --.

Column 14,
Line 50, insert --  --.

Line 56, between "refers" and "cycloheteroakyl", insert -- to --.
Line 57, between "a" and "atom", insert -- C --.

Column 15,
Line 54, change "γ" to -- β --.

Column 20,
Line 59, "2,1" should be -- 2,3 --.

Column 29,
Line 23, change "w" to -- % --.

Column 30,
Line 2, after "$(M+H)^+$" and before "197", insert -- - --.

Column 32,
Line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Column 33,
Line 3, change "HO" to read -- H_2O --.
Line 7, change "$CH2cl_2$" to read -- CH_2Cl_2 --.
Line 11, after "METHOD", insert -- A --.

Column 34,
Line 62, delete "15".

Column 41,
Line 43, after "was", delete "a".
Line 44, after "over", delete "a".

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 43,
Line 36, delete "E".
Line 55, change "48.61" to -- 8.61 --.

Column 44,
Line 39, change "200" to -- 300 --.

Column 46,
Line 58, change "ter" to -- water --.
Line 58, after "20" and before "Detection", insert -- mL/min. --.
Line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Column 52,
Line 64, change "25" to -- 28 --.

Column 53,
Line 31, change "OSO_4" to -- OsO4 --.
Line 65, after "100%" and before "Solvent A", insert -- B, --.
Line 66, after "vent B =" and before "MeOH", insert -- 90% --.

Column 62,
Line 67, change "549" to -- 540 --.

Column 66,
Line 24, change "$CH2Cl_2$" to read -- CH_2Cl_2 --.

Column 69,
Line 21, change "9" to -- 8 --.
Line 30, change "Hbl" to -- HCl --.

Column 70,
Line 56, move "Step 1" to line 65.

Column 72,
Line 36, change "50°" to -- 5° --.
Line 65, change "2.2(" to -- 2.28 --.
Line 65, change "30mL2" to -- 30 mL --.

Column 73,
Line 25, change "the n" to -- then --.
Line 26, change "et her" to -- ether --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 74,
Line 32, change "50°" to -- 5° --.

Column 79,
Line 61, change "100" to -- 10% --.

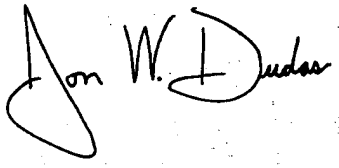
Column 82,
Line 65, change "10EtOAc" to -- 10% EtOAc --.

Column 84,
Line 34, change "NS" to -- MS --.

Column 92,
Line 42, change "APR" to -- AR --.

Signed and Sealed this

Twenty-ninth Day of November, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

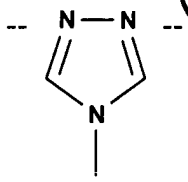
PATENT NO : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

~~In the Specification:~~

Col. 7, line 6, change "PGI" to -- PG_1 --.

Col. 14, line 50, insert



Col. 14, line 56, between "refers" and "cycloheteroalkyl", insert -- to --.

Col. 14, line 57, between "a" and "atom", insert -- C --.

Col. 15, line 54, change "γ" to -- β --.

Col. 20, line 59, "2,1" should be -- 2,3 --.

Col. 29, line 23, change "w" to -- % --.

Col. 30, line 2, after "$(M+H)^+$" and before "197", insert -- - --.

Col. 32, line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Col. 33, line 3, change "HO" to read -- H_2O --.

Col. 33, line 7, change "$CH2cl_2$" to read -- CH_2Cl_2 --.

Col. 33, line 11, after "METHOD", insert -- A --.

Col. 34, line 62, delete "15".

Col. 41, line 43, after "was", delete "a".

Col. 41, line 44, after "over", delete "a".

Col. 43, line 36, delete "E".

Col. 43, line 55, change "48.61" to -- 8.61 --.

Col. 44, line 39, change "200" to -- 300 --.

Col. 46, line 58, change "ter" to -- water --.

Col. 46, line 58, after "20" and before "Detection", insert -- mL/min. --.

Col. 46, line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Col. 52, line 64, change "25" to -- 28 --.

Col. 53, line 31, change "OSO_4" to -- OsO4 --.

Col. 53, line 65, after "100%" and before "Solvent A", insert -- B, --.

Col. 53, line 66, after "vent B =" and before "MeOH", insert -- 90% --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,395,767 B2
DATED: : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 62, line 67, change "549" to -- 540 --.
Col. 66, line 24, change "CH2Cl$_2$" to -- CH_2Cl_2 --.
Col. 69, line 21, change "9" to -- 8 --.
Col. 69, line 30, change "Hbl" to -- HCl --.
Col. 70, line 56, move "Step 1" to line 65.
Col. 72, line 36, change "50°" to -- 5° --.
Col. 72, line 65, change "2.2(" to -- 2.28 --.
Col. 72, line 65, change "30mL2" to --30 mL --.
Col. 73, line 25, change "the n" to -- then --.
Col. 73, line 26, change "et her" to -- ether --.
Col. 74, line 32, change "50°" to -- 5° --.
Col. 79, line 61, change "100" to -- 10% --.
Col. 82, line 65, change "10EtOAc" to -- 10% EtOAc --.
Col. 84, line 34, change "NS" to -- MS --.

In the Claims:
Col. 92, line 42 (Claim 15), change "APR" to -- AR --.

MAILING ADDRESS OF SENDER:
Burton Rodney
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

PATENT NO. 6,395,767

SEP 2 6 2005

FORM PTO-1050

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 91,
Lines 9-10, should read -- A compound having the structure: --
Line 54, should read -- A compound which is --.

Issued

Signed and Sealed this

Twenty-seventh Day of July, 2004

Jon W. Dudas

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

Case: LA0050 NP

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,395,767 B2
DATED: : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, David A. Betebenner

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Claim 8, line 1 should read --A compound having the structure:--.

Claim 10, line 1 should read --A compound which is--.

Issued

MAILING ADDRESS OF SENDER:
Burton Rodney
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

PATENT NO. 6,395,767

FORM PTO-1050

29 JUN 2004

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 07-1293)

U.S. Patent No.:	**6,395,767**	)
		)
Granted:	**May 28, 2002**	)
		)
Inventors:	**Robl *et al.***	)
		)
Serial No.:	**09/788,173**	)
		)
Filed:	**February 6, 2001**	)
		)
For:	**Cyclopropyl-fused Pyrrolidine-based Inhibitors of Dipeptidyl Peptidase IV and Method**	)

TRANSMITTAL LETTER

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22303-1450

Dear Sir:

In regard to the above-identified patent application:

1. We are transmitting herewith the attached:
   a. Request for Patent Term Extension and Exhibits (1 Original and two copies)
   b. Postcard
2. With respect to additional fees:
   ____ A. No additional fee is required.
   X B. Attached is a check in the amount of $1,120.00.
3. Please charge any additional fees or credit over-payments to the Deposit Account No.13-2490.
4. x The undersigned hereby certifies that this Transmittal Letter and this paper, as described in paragraph 1 hereinabove, are being hand-delivered, in an envelope addressed to: Office of Patent Legal Administration, Room MDW 7D55, 600 Dulany Street (Madison Building), Alexandria, VA 22314 on September 22, 2009.

Dated: September 21, 2009

By: _____
Kevin E. Noonan
Reg. No. 46,375

McDonnell Boehnen Hulbert & Berghoff, LLP
300 South Wacker Drive
Chicago, Illinois 60606
Tel: (312)913-0001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 07-1293)

U.S. Patent No.:	**6,395,767**	)
		)
Granted:	**May 28, 2002**	)
		)
Inventors:	**Robl *et al.***	)
		)
Serial No.:	**09/788,173**	)
		)
Filed:	**February 6, 2001**	)
		)
For:	**Cyclopropyl-fused Pyrrolidine-based Inhibitors of Dipeptidyl Peptidase IV and Method**	)

APPLICATION FOR PATENT TERM EXTENSION PURSUANT TO 35 U.S.C. §156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22303-1450

Dear Sir:

Applicant, Bristol-Myers Squibb Company, the owner of record of U.S. Patent No. 6,395,767 ("the '767 patent"; *attached hereto* as Exhibit A) submits this Application for Patent Term Extension pursuant to the provisions of 35 U.S.C. §156. In making this application for patent term extension, Applicant has received regulatory approval of a new human anti-diabetic drug as disclosed below and claimed in the '767 patent.

I. Eligibility

Applicant is entitled to patent term extension for this patent on the grounds that

the circumstances fulfill the requirements of 35 U.S.C. §156. Specifically:

a) U.S. Patent 6,395,767 claims a product according to the provisions of §156(a);

b) The term of this patent has not expired before submission of this application for patent term extension pursuant to §156(a)(1);

c) The term of this patent has never been extended, pursuant to §156(a)(2);

d) Applicant is the owner of record of the patent according to the assignment documents appended to this application, pursuant to §156(a)(3);

e) The product has been subject to a regulatory review period before commercial marketing and use pursuant to §156(a)(4); and

f) Permission for commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provisions of the law under which the regulatory review period was conducted pursuant to §156(a)(5).

Applicant, Bristol-Myers Squibb Company, is the owner of all right, title and interest in U.S. Patent 6,395,767, as recorded by assignment in the U.S. Patent and Trademark Office at reel 11607 and frame 0369 (attached hereto as **Exhibit B**).

Bristol-Myers Squibb Company received regulatory approval for the approved product on July 31, 2009.

The term of U.S. Patent No. 6,395,767 has not expired prior to submission of this application.

II. Requirements

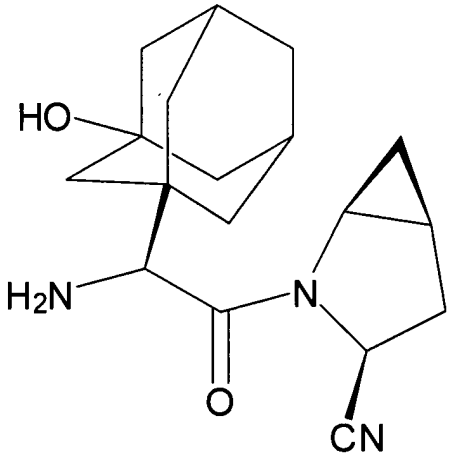
Applicant provides the following information, pursuant to the requirements of 35 U.S.C. §156(d) and 37 C.F.R. 1.740 *et seq.*:

(a) An application for extension of patent term must be made in writing to the Commissioner. A formal application for the extension of patent term must include:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is ONGLYZA® (generic name: saxagliptin), an anti-diabetic drug having the chemical name (1S,3S,5S)-2-[(2S)-amino(3-hydroxytricyclo[3.3.1.$1^{3,7}$]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

This compound has the structural formula:



(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

The approved product was subject to regulatory review pursuant to 21 U.S.C. §355(a) and Title 505(b)(1) of the Federal Food, Drug and Cosmetic Act, *codified at* 21 U.S.C. §355(b)(1).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

The product received permission for commercial marketing or use on July 31, 2009, pursuant to NDA 22-350 by the letter of that date from Curtis J. Rosebraugh, M.D.,

M.P.H., Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research, Food and Drug Administration, Public Health Services, Department of Health and Human Services (attached hereto as **Exhibit C**).

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of the approved drug product is (1S,3S,5S)-2-[(2S)-amino(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, generic name saxagliptin This active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

The product has been approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The product has been approved pursuant to 21 U.S.C. §355(a) and Title 505(b)(1) of the Federal Food, Drug and Cosmetic Act, *codified at* 21 U.S.C. §355(b)(1).

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § l.720(f) and an identification of the date of the last day on which the application could be submitted;

This application is submitted within 60 days of the date that the product first received permission for commercial marketing or use under the provisions of law under which the regulatory review period occurred, the last day for such submission being

September 28, 2009.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

This application is made for U.S. Patent No. 6,395,767, issued May 28, 2002 to Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, and David A. Betebenner, and will expire on February 16, 2021.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A copy of this patent is attached hereto as **Exhibit A**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

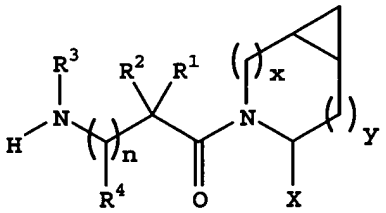
A copy of a receipt for payment of the first maintenance fee, paid November 4, 2005, is attached hereto as **Exhibit D**.

A copy of Certificates of Correction, filed July 27, 2004 and November 29, 2005 are attached hereto as **Exhibit E**.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

This patent claims the approved product and methods for using the approved product. Specifically, the approved product and methods for using the approved product are claimed in the following claims of U.S. Patent No. 6,395,767:

Claim 1. A compound having the structure



wherein x is 0 or 1 and y is 0 or 1, provided that

x = 1 when y = 0 and

x = 0 when y = 1; and wherein

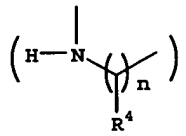
n is 0 or 1;

X is H or CN;

R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl, arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl or cycloheteroalkylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfinyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

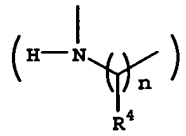
and R^1 and R^3 may optionally be taken together to form $-(CR^5R^6)_m-$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, H, alkyl, alkenyl, alkynyl, cycloalkyl, halo, amino, substituted amino, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R^4 may optionally be taken together to form –

$(CR^7R^8)_p$- wherein p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, halo, amino, substituted amino, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together with



form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2;

or optionally R^1 and R^3 together with



form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

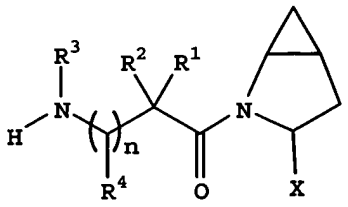
with the proviso that where x is 1 and y is 0, X is H, n is 0, and one of R^1 and R^2 is H and the other is alkyl, then R^3 is other than pyridyl or substituted pyridyl;

including all stereoisomers thereof;

and a pharmaceutically acceptable salt thereof, or a prodrug ester thereof, and all stereoisomers thereof.

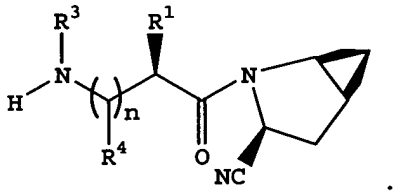
Claim 1 reads on the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 2. The compound as defined in claim 1 having the structure:



Claim 2 reads on the approved product when: n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 4. The compound as defined in claim 1 having the structure:



Claim 4 reads on the approved product when: n is 0; R^1 is hydroxytricycloalkyl; and R^3 is hydrogen.

Claim 6. The compound as defined in claim 1 wherein:

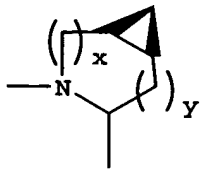
R^3 is H, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

R^2 is H or alkyl, n is 0,

X is CN.

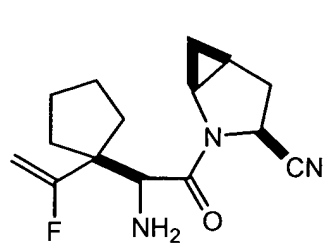
Claim 6 reads on the approved product when: x is 0; y is 1; R^1 is hydroxytricycloalkyl; and R^2 is H.

Claim 7. The compound as defined in claim 1 wherein the cyclopropyl fused to the pyrrolidine has the configuration:



Claim 7 reads on the approved product when; x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 8. The compound as defined in claim 1 having the structure: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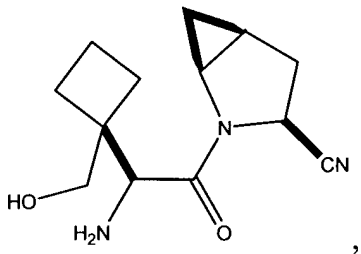
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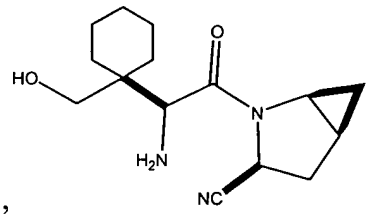
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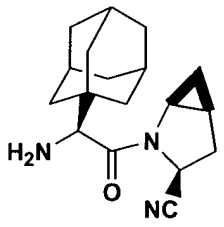
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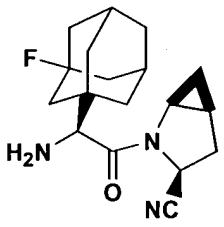
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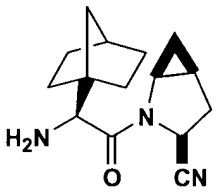
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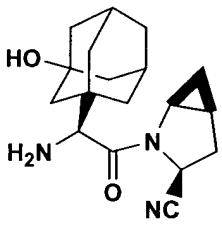
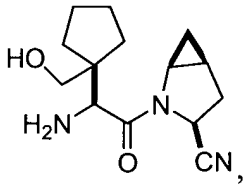
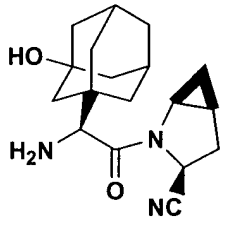

or


,

or a pharmaceutically acceptable salt thereof.

Claim 8 reads on the claimed product because it includes the structure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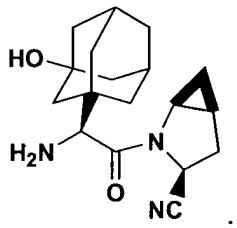
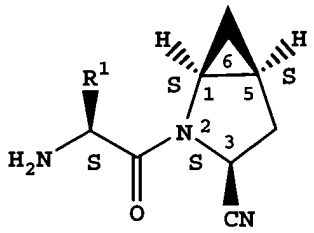
Claim 9. The compound as defined in claim 8 wherein the pharmaceutically acceptable salt is the hydrochloride salt or the trifluoroacetic acid salt.

Claim 9 reads on the approved product because it includes the structure



Claim 10. The compound as defined in claim 1 which is

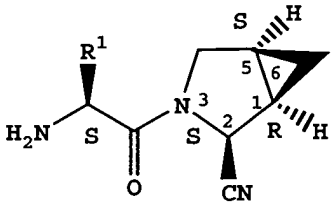


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or

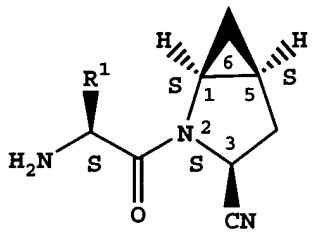


B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl.

Claim 10 reads on the approved product when the structure is



A

and R^1 is hydroxytricycloalkyl.

Claim 11. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

Claim 11 reads on a composition comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 12. A pharmaceutical combination comprising a DP4 inhibitor compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent.

Claim 12 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 13. The pharmaceutical combination as defined in claim 12 comprising said DP4 inhibitor compound and an antidiabetic agent.

Claim 13 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 14. The combination as defined in claim 13 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, an aP2 inhibitor, a glycogen phosphorylase

inhibitor, an AGE inhibitor, an insulin sensitizer, a glucagon-like peptide-l (GLP-l) or mimetic thereof, insulin and/or a meglitinide.

Claim 14 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 15. The combination as defined in claim 14 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, and/or LY315902.

Claim 15 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 16. The combination as defined in claim 13 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.0l to about l00:l.

Claim 16 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 17. The combination as defined in claim 12 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, an anorectic agent, and/or a fatty acid oxidation upregulator.

Claim 17 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 18. The combination as defined in claim 17 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, famoxin, and/or mazindol.

Claim 18 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 19. The combination as defined in claim 12 wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, an ACAT inhibitor, a cholesteryl ester transfer protein inhibitor, or an ATP citrate lyase inhibitor.

Claim 19 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 20. The combination as defined in claim 19 wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, implitapide, CP-529,414, avasimibe, TS-962, MD-700, and/or LY295427.

Claim 20 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 21. The combination as defined in claim 19 wherein the DP4 inhibitor is present in a weight ratio to the lipid-modulating agent within the range from about 0.01 to about 100:1.

Claim 21 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 22. A pharmaceutical combination comprising a DP4 inhibitor compound as defined in claim 1 and an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty, an anti-arthritis agent, an agent for preventing inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent and/or an anti-obesity agent.

Claim 22 reads on a combination comprising the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 23. A method for treating diabetes, insulin resistance, hyperglycemia, hyperisulinemia, or elevated blood levels of free fatty acids or glycerol, obesity, Syndrome X, dysmetabolic syndrome, diabetic complications, hypertriglyceridemia, hyperinsulinemia, atherosclerosis, impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases, AIDS, intestinal diseases, inflammatory bowel syndrome, nervosa, osteoporosis, or an immunomodulatory disease or a chronic inflammatory bowel disease, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in claim 1.

Claim 23 reads on a method for using the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Claim 24. The method as defined in claim 23 for treating type II diabetes and/or obesity.

Claim 24 reads on a method for using the approved product when: x is 0; y is 1; n is 0; X is CN; R^1 is hydroxytricycloalkyl; and R^2 and R^3 are hydrogen.

Thus,

Claim 1 reads on the approved product.

Claim 2 reads on the approved product.

Claim 4 reads on the approved product.

Claim 6 reads on the approved product.

Claim 7 reads on the approved product.

Claim 8 reads on the approved product.

Claim 9 reads on the approved product.

Claim 10 reads on the approved product.

Claim 11 reads on the approved product.

Claim 12 reads on the approved product.

Claim 13 reads on the approved product.

Claim 14 reads on the approved product.

Claim 15 reads on the approved product.

Claim 16 reads on the approved product.

Claim 17 reads on the approved product.

Claim 18 reads on the approved product.

Claim 19 reads on the approved product.

Claim 20 reads on the approved product.

Claim 21 reads on the approved product.

Claim 22 reads on the approved product.

Claim 23 reads on a method for using the approved product.

Claim 24 reads on a method for using the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

The following dates are relevant for a determination of the length of the Patent Term Extension available to applicant:

An Investigational New Drug (IND) application, No. 63,634 was filed November 8, 2001 (copy of FDA letter acknowledgment attached hereto as **Exhibit F**).

A New Drug Application (NDA), No. 22-350 was filed June 30, 2008 (copy of FDA letter acknowledgment attached hereto as **Exhibit G**).

An Approval letter for NDA No. 22-350 was signed July 31, 2009 (copy of FDA letter attached hereto as **Exhibit C**).

(11) A brief description beginning on a new page of the significant activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

Applicant submits its log of activities before the FDA as **Exhibit H**. The following provides a brief description of significant activities undertaken by the applicant during the regulatory review period with respect to the approved product, with significant dates:

- The original IND submission (IND 63,634) for ONGLYZA® (Saxagliptin) was submitted on **November 8, 2001**.

- Letter and telephonic correspondence between Applicant and FDA regarding protocol changes and ophthalmological data on **November 21, 2001**, **December 7, 2001**, **December 10, 2001** and **December 17, 2001**.

- In **2002**, protocol and information amendments submitted on **February 20**, **March 13**, **March 27**, and **November 12**; information submitted by Applicant on pharmacology/toxicology and safety on **March 4**, **June 7**, **August 9**, **November 18** and **December 18**; letter from FDA regarding clinical trials database on **April 11**.

- In **2003**, protocol and information amendments submitted on **January 31**, **March 26**, **April 21**, **June 3**, **June 25**, **July 17**, **July 31**, **August 6**, **August 26**, **September 15**, **September 30**, **October 7**, **October 9**, **October 30**, **November 17**, **December 2**, **December 12**, and **December 23**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 24**, **January 31**, **February 21**, **May 6**, **May 21**, **July 29**, **August 11**, **September 30**, and **December 18**; telephone, facsimile and e-mail communications between Applicant and FDA on **April 1**, **April 3**, **April 4**, **April 8**, **April 9**, **April 16**, **April 18**, **April 23**, **April 28**, **August 13**, **October 15** (multiple), **October 29**, and **November 10**; FDA letter to Applicant with comments and request regarding

preclinical pharmacology review of IND on **July 7**; FDA letter regarding FDA review of Applicant September 30th submission on **October 6th**; Applicant submitted an IND annual report for period December 1, 2001 through November 20, 2002 on **April 14**.

- In **2004**, protocol amendments submitted on **February 27**, **March 18**, **May 19**, **June 28**, **July 16**, **August 6**, **August 25**, **September 14**, and **September 23**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 8**, **January 16**, **February 25**, and **June 15**; telephone, facsimile and e-mail communications between Applicant and FDA on **February 3**, and **October 22**; Applicant submitted response to FDA CAC review of rat and mouse carcinogenicity study on **January 29th**; Applicant submitted an initial safety report on **February 11**; IND annual report Applicant submitted an IND annual report for period December 1, 2002 through November 20, 2003 on **February 12**; Applicant submitted letters requesting Type B End of Phase 2 meeting on **August 26**, **September 13**, and **December 20**, with FDA responses on **September 22** and **December 29** and telephone communication regarding cancellation of End of Phase 2 meeting on **October 21** (multiple).

- In **2005**, protocol amendments submitted on **June 16**, **June 23**, **July 20**, **August 24**, **August 25**, **September 8**, **September 9**, **September 27**, **October 5**, **October 13**, **October 25**, **November 7**, **November 16**, **December 12**, **December 14**, **December 16**, and **December 19**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 14**, **February 22**, **March 2**, **May 11**, **June 20**, **July 22**, **August 30**, **October 10**, **October 14**, **November 30**, **December 1**, and **December 7**, including a final study report on **July 8** and **October** 14, a response to request for additional analysis of nonclinical saxagliptin exposure on **July 19**, and background briefing package for End of Phase 2 meeting on **August 22**; telephone, facsimile and e-mail communications between Applicant and FDA on **April 28**, **May 13**, **May 17**, **July 19**, **July 26**, **August 1**, **August 29**, **September 27**, **October 13** (multiple), **October 18** (multiple), **December 28** and **December 29**; Applicant submitted an

IND annual report for period December 1, 2003 through November 20, 2003 on **February 7**.

- On **July 15, 2005**, Applicant submitted a request for End of Phase 2 meeting. FDA letters providing details for End of Phase 2 meeting scheduled for July 27th, on **May 19**, official minutes of End of Phase 2 meeting on **August 23**, and comments and recommendations for June 5, 2005 submission on **August 24**. Applicant submitted briefing book for End of Phase 2 meeting and response to request for desk copy of protocol on **June 27**, an IND amendment submitted to provide drug products information to support Phase III clinical studies on **April 21** and an IND safety report regarding expedited investigator brochure on **October 13**. On **December 14, 2005**, FDA issued a letter providing comments and recommendations upon completion of review of November 7th submission. Applicant submitted a request for FDA review and comment on draft protocol for combination of saxagliptin and metformin on **December 22**.

- In **2006**, protocol amendments submitted on **January 12, January 27, February 14, March 7, March 13, March 17, March 23, March 30, April 24, April 27, April 28, May 11, May 17, May 24, June 2, June 19, July 7, July 12, August 15, August 17, September 6, September 18, September 22, September 27, October 3, October 18, October 19, November 3, November 16**, and **December 8**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 13, February 24, March 23, June 2, June 29, August 4, September 18, September 19, November 3, November 17**, and **December 8**; telephone, facsimile and e-mail communications between Applicant and FDA on **January 30, January 31, February 3, April 26**, and **November 13**; Applicant submitted an IND annual report for period December 1, 2004 through November 20, 2005 on **February 3**.

- FDA issued letter regarding completion of review of December 14, 2005 amendment on **January 19** and **January 30, 2006**. Applicant submitted e-mail

response to FDA inquiry regarding saxagliptin combination questions on **January 25**.

- On **February 1, 2006**, telephone contact with FDA to clarify Applicant 's interest on Dr. Misbin's (Clinical Reviewer) comments on Protocol 013 (TZD study), as well as Applicant's decision to accept Dr. El-Hage's suggestion regarding control group in the rat carcinogenicity study.

- On **February 3, 2006**, Applicant submitted results of 1 to 3-month Monkey Toxicity Study.

- On **February 13, 2006**, FDA issued a draft statement for ESR.

- On **February 15, 2006**, Applicant submitted an IND safety report.

- On **April 20, 2006**, FDA issued letter regarding saxagliptin Capsules and Amendment dated 01/12-05 (New Protocol CV181033: Pharmacokinetic Drug Interaction Study with Saxagliptin and Simvastatin in Healthy Subjects), completed review with comments and recommendations. On **April 28** and **May 17, 2006**, FDA issued letters denying Applicant's Request for a Teleconference to discuss Saxagliptin progress and written responses to questions included in meeting request.

- On **May 26, 2006** Applicant submitted Request for FDA Review and Comment regarding The Planned Core Statistical Analysis Plan (CSAP)(BMS Doc. #930014584 v1.0) for the short-term periods of the Phase # Clinical Superiority Studies, and requests FDA input on the following protocols CV181011, CV181013, and CV181014. On **June 9**, **June 30, September 13**, **September 14**, and **October 30, 2006**, Applicant submitted IND safety reports regarding Supraventricular tachycardia. Report No. 1332659 and Anemia).

- In **2007**, protocol amendments submitted on **January 5**, **January 12**, **January 19**, **March 1**, **March 13**, **April 5**, **May 3**, **May 8**, **June 7**, **June 11**, **June 15**, **July 2**, **August 14**, **August 30**, **October 1**, **October 3**, **November 15**, **November 16**,

and **November 27**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 12**, **March 5**, **March 12**, **April 19**, **May 3**, **May 30**, **June 7**, **September 5**, **September 12**, **September 14**, **September 26**, **October 2**, **October 16**, **October 18**, **October 19**, **October 23**, **October 24**, **November 6**, **November 8**, **November 12**, **November 15**, **November 16**, **December 14**, **December 20**, and **December 21**; telephone, facsimile and e-mail communications between Applicant and FDA on **April 11**, **May 3**, **May 9** through **June 22** (multiple) regarding denial of Applicant request for meeting, and **June 12** through **June 19**, regarding Applicant submission of Monkey Comparator test result from EMEA; Applicant submitted an IND annual report for period December 1, 2005 through November 20, 2006 on **February 5**.

- On **January 24, 2007**, telephone request from FDA for a revisit target submission date with an explanation for the Saxagliptin NDA. FDA also requested that Applicant submit to the Docket a revised target date for NDA submission with an explanation for submission timing.

- On **March 7, 2007**, FDA issued a letter regarding data indicating that the administration of dipeptidyl peptidase-4 (DPP-4) inhibitors to monkeys results in dose and duration-dependent increases in necrotizing cutaneous lesions of the periphery, including the tail, digits, hands/feet, ears, nose, and scrotum.

- On **March 15, 2007**, FDA issued a letter regarding FDA approval for a Type C meeting with Applicant, to discuss the quality portion of the upcoming NDA, as part of the CMC pilot program, to which Applicant responded with a Briefing Document on **April 11** for a meeting scheduled for **April 26**. FDA provided letter with official minutes of meeting on **May 25**.

- On **April 19, 2007**, FDA issued a letter regarding the amendment dated **January 22, 2007** (serial #0011), containing proposed QTc evaluation plan. QTc Team has completed their review of submission and has comments and recommendations.

- On **June 5, 2007**, Applicant provided additional data request by FDA relating to IND.

- On **September 14, 2007**, Applicant submitted a request for type B Pre-NDA Meeting to discuss several issues related to the format and content of the saxagliptin NDA, proposing a meeting date of **November 12, 14 or 16, 2007**.

- On **September 28, 2007**, Applicant submitted a Response to Agency Comments, Request for Review and Comment. Applicant are now providing for the Agency's review and comment Protocol D1680C00007 CV181-062 dated 20-Sept-2007 (DCN 930023980 v2.0) and (DCN 930023982 v1.0).

- On **October 15, 2007**, Applicant submitted a Pre-NDA Briefing Document as requested by the FDA, including a final agenda and set of questions that Applicant planned to discuss at the meeting.

- On **December 27, 2007**, Applicant submitted CMC-Correspondence to the IND in reference to minutes from April 26, 2007 meeting, included with this correspondence two CMC questions related to Applicant upcoming NDA for Saxagliptin tablets.

- In **2008**, protocol amendments submitted on **January 16**, **January 18**, **February 8**, **February 11**, **February 27**, **March 14**, **March19**, **June 5**, and **June 18**; information submitted by Applicant on stability, safety and pharmacology/toxicology on **January 8**, **January 17**, **February 14**, **February 25**, **March 6**, **March 11**, **March 27**, **April 23**, **April 25**, **April 30**, and **May 8**; telephone, facsimile and e-mail communications between Applicant and FDA on **April 11**; Applicant submitted an IND annual report for period December 1, 2006 through November 20, 2007 on **February 5**.

- On **January 8, 2008**, FDA issued a letter providing comments and recommendations on amendment submitted by Applicant on September 28, 2007, containing protocol d1680c00007.

- On **February 15, 2008**, Applicant submitted a Response to request for information regarding entire submission dated Oct 23, 2007; IB submitted on June 20, 2007; study rpt. for CV181001 submitted on Feb 22, 2005; study report for CV181002 submitted on Jul 8, 2005 and study report for CV181010 submitted on Oct 19, 2007.

- On **March 16, 2008**, FDA issued a letter regarding FDA's comments and request for a written response upon completion of FDA review of Applicant 's responses to FDA's comments in a letter dated Jan 3, 2008 with regards to Protocol D1680C00007. This is in reference to the amendment dated **Feb 29, 2008**.

- On **June 19, 2008**, Applicant provided a response to FDA request for information regarding the Agency's comment (no. 7), requesting a justification for the plan to submit results from the study (Protocol D1680C00007) after the planned action date of the saxagliptin NDA.

- On **June 30, 2008**, Applicant submitted a New Drug Application (NDA 22-350) for ONGLYZA® as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus to the United States Food and Drug Administration (FDA).

- On **August 28, 2008**, Applicant provided datasets for carcinogenicity studies DN03100 and DN05004 for saxagliptin.

- On **September 26, 2008**, Applicant resubmitted corrected datasets for CV 181-013 LT.

- On **October 15, 2008**, Applicant responded to CMC question in FDA letter dated September 12, 2008.
- On **October 24, 2008**, Applicant responded to FDA request for information dated September 12 2008 specifically questions 1, 3, 4, 6, 7, 8, 9 & 10.

- On **October 28, 2008**, Applicant provided 120-day safety update for saxagliptin, including clinical safety update on several clinical protocols.

- On **October 29, 2008**, Applicant provided case report forms in support of 120-day clinical safety update.

- On **November 3, 2008**, Applicant provided responses to clinical questions 2 and 5, biostatistics questions 11 and 12 and CMC questions 16(c) and 16(f) from FDA letter dated September 12, 2008.

- On **November 14, 2008**, Applicant provided final responses for all Serious Adverse Events for subjects in control groups for Clinical Question #3.

- On **November 19, 2008**, Applicant provided responses to Clinical Pharmacology request for data sets used for the population pK analysis (for both parent and metabolite) and exposure-response analysis with regard to HbA1c, plasma fasting glucose and lympholysis.

- On **November 24, 2008**, Applicant proposed pediatric study and request for partial pediatric waiver.

- On **December 2, 2008**, Applicant provided a response to FDA request for clinical pharmacology information.

- On **December 15, 2008**, Applicant provided a response to FDA request for additional information.

- On **December 16, 2008**, Applicant provided response to FDA CMC request.

- On **December 23, 2008**, Applicant provided response to FDA questions issued December 19, 2008, regarding clarification of potential statistical errors.

- On **December 24, 2008**, Applicant reviewed FDA request for additional information regarding "ST" and "UP TO WEEK 24" relating to clinical information requests dated **December 19, 2008** and provided additional long term stability study date during the review process.

- On **January 21, 2009**, Applicant provided a response to information request dated **January 11, 2009** and CMC request for information dated **December 1, 2008**.

- On **January 22, 2009**, Applicant provided response to FDA request for additional information contained in e-mail communication dated December 19, 2008.

- On **January 23, 2009**, Applicant provided a timeline for submission of responses to FDA request for clinical IR questions and provided response to FDA request for additional information.

- On **January 26, 2009**, Applicant provided response to FDA request for additional information and submitted final Clinical Study Report for CV181059.

- On **February 3, 2009**, Applicant provided response to FDA request for additional information contained in e-mail communication dated December 11, 2008.

- On **February 19, 2009**, Applicant provided corrections to response for information contained in FDA letter dated September 12, 2008, provided amended replacement response to clinical question 6 and provided response to FDA request for information dated January 28, 2009

- On **February 24, 2009**, Applicant provided response to FDA request for additional information contained in e-mail communication dated January 30, 2009.

- On **February 26, 2009**, FDA proposed new dates for FDA inspection in Canada, and Applicant provided response to FDA request for information in letter dated December 11, 2008.

- On **March 11, 2009**, Applicant provided responses to FDA's request for information regarding additional CMC information and to FDA request that dissolution testing be performed on every batch of saxagliptin tablets.

- On **March 16, 2009**, Applicant provided correction for handling localized edema Adverse Events.

- On **April 2, 2009**, Applicant provided response to FDA request for additional information contained in e-mail communication dated March 18, 2009.

- On **April 6, 2009**, Applicant provided response to request for information regarding location for laboratory shift tables for pooled monotherapy studies.

- On **April 15, 2009**, Applicant provided response to request for information regarding report of rat embryo-fetal development.

- On **April 20, 2009**, Applicant provided response to request for information providing tables to relevant literature and study report references in DN08072.

- On **April 23, 2009**, Applicant provided response to request for cardiovascular outcomes study design concept.

- On **May 19, 2009**, FDA and Applicant correspondence regarding request for change in timelines for cardiovascular outcomes study design concept.

- On **May 27, 2009**, Applicant submitted response to FDA request dated May 12, 2009 for information regarding analysis of pancreatitis cases after saxagliptin administration and comparators in controlled Phase II/III clinical trials.

- On **June 3, 2009**, Applicant submitted response to e-mail communication from FDA dated May 11, 2009 regarding requests for additional information relating suspension from Russia.

- On **June 17, 2009**, Applicant submitted response to FDA letter dated March 25, 2009 regarding requests for additional information and e-mail communication dated June 12, 2009.

- On **June 23, 2009**, Applicant provided response to request for additional information in e-mail communication from FDA dated June 4, 2009.

- On **July 6, 2009**, Applicant submitted response to FDA request for revised carton and container labels.

- On **July 17, 2009**, Applicant submitted responses to multiple FDA requests for information contained in e-mails dated June 26 and June 28, 2009.

- On **July 17, 2009**, Applicant submitted responses to FDA requests for additional label revisions for 5mg strength on physician sample pack.

- On **July 22, 2009**, Applicant submitted case report forms for 18 hypersensitivity cases, and responses to requests dated July 7 and 8, 2009 for incidence of fracture and renal analysis on 120-day safety update.

- On **July 22, 2009**, Applicant submitted response to FDA request dated July 10, 2009, providing narratives for cases of "Alt" and "Hy's Law" in clinical trials since DB lock for 120-day safety update.

- On **July 27, 2009**, Applicant submitted response to request for additional information regarding narratives for 18 hypersensitivity cases to determine whether reactions had signs and symptoms of anaphylaxis.

- On **July 28, 2009**, Applicant provided chemical name of saxagliptin major metabolite and simplified variation thereof.

- On **July 28, 2009**, Applicant submitted response to request for information providing 2-hr. postprandial glucose excursions for Phase III clinical trials.

- On **July 29, 2009**, Applicant submitted response to request for information providing 2-hr. postprandial glucose excursions for Phase III clinical trials.

- ONGLYZA® NDA 22-350 was approved by the FDA on **July 31, 2009** following multiple interactions with the Agency regarding the content of final product

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

Applicant submits that U.S. Patent No. 6,395,767 is entitled to patent term extension according to the provisions of 35 U.S.C. §156. Applicant believes that the length of the extension of the patent term is equal to 896 days, pursuant to the provisions of 35 U.S.C. §§156(c) and (g).

The length of the patent term extension requested in this application is 896 days, comprising half of the period from November 8, 2001 until June 30, 2008 (a total of 2,426/2 = 1,213 days) plus the period from June 30, 2008 until July 31, 2009 (396 days), for a total of 1,609 days, as limited by the proviso of 35 U.S.C. §156(g)(6) that the total patent term extension is limited to be no longer than five (5) years (1,825 days), and further limited by the proviso of 35 U.S.C. §156(c)(3) that the total patent term is limited to be no longer than fourteen (14) years from the date of marketing approval, calculated as follows:

Length of regulatory review period under IND:

November 8, 2001 - November 7, 2002	=	365 days
November 8, 2002 - November 7, 2003	=	365 days
November 8, 2003 - November 7, 2004	=	366 days
November 8, 2004 - November 7, 2005	=	365 days
November 8, 2005 - November 7, 2006	=	365 days
November 8, 2006 - November 7, 2007	=	365 days
November 8, 2007 - June 30, 2008	=	235 days
Total	=	2,426 days

Length of regulatory review under NDA:

June 30, 2008 - June 29, 2009	=	365 days
June 30, 2009 - July 31, 2009	=	32 days
Total	=	396 days

Length of time from current expiration date of U.S. Patent No. 6,395,767 and fourteen years from July 31, 2009:

February 16, 2021 - February 15, 2022	= 365 days
February 16, 2022 - February 15, 2023	= 365 days
February 15, 2023 - July 31, 2023	= 166 days
Total	= 896 days

Applicant is applying for a patent term extension to the fullest extent that the patent deserves under the circumstances of regulatory delay set forth herein. Applicant believes the length of the patent term extension determined above is the appropriate length pursuant to the statute. Despite Applicant's diligent efforts, if the total number of days to which U.S. Patent No. 6,395,767 is greater than the number of days (896) requested here, Applicant requests the U.S. Patent and Trademark Office recalculate the correct length of patent term extension and award a patent term extension to U.S. Patent No. 6,395,767 for the correct number of days.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought;

Applicant and its undersigned agent acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the patent term extension sought in this application.

(14) The prescribed fee for receiving and acting upon the application for extension pursuant to 37 C.F.R. § 120(j)

The prescribed fee of one thousand one hundred twenty dollars ($1,120.00) as set forth in 37 C.F.R. §1.20(j) accompanies this application. The U.S. Patent and

Trademark Office is authorized to charge Deposit Account 13-2490 for the full amount of any deficiency in this fee.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Inquiries and correspondence relating to this patent term extension application should be addressed to:

Kevin E. Noonan
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606
(312) 913-2145 (direct)
(312) 913-0002 (facsimile)
noonan@mbhb.com

A Power of Attorney from applicant and a Rule 3.73(b) document are appended hereto as **Exhibit I**.

If the Examiner or other Patent Office official reviewing this application believes it to be helpful, he or she is invited to contact the undersigned attorney by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: September 21, 2009

By: _____
Kevin E. Noonan
Reg. No. 35,303

LIST OF EXHIBITS

Exhibit A: U.S. Patent No. 6,395,767

Exhibit B: U.S. Patent and Trademark Office assignment record for U.S. Patent No. 6,395,767

Exhibit C: ONGLYZA® FDA approval letter

Exhibit D: Copy of a receipt for payment of the first maintenance fee, paid **November 4, 2005**

Exhibit E1: Copy of a Certificates of Correction, filed **July 27, 2004** and **November 29, 2005**

Exhibit F: FDA acknowledgement letter for filing an New Drug (IND) application, No. **63,634**

Exhibit G: FDA acknowledgment letter for filing a New Drug Application (NDA), No. 22-350

Exhibit H: FDA Log

Exhibit I: Power of Attorney and Rule 3.73(b) document

US006395767B2

(12) **United States Patent**
Robl et al.

(10) **Patent No.: US 6,395,767 B2**
(45) **Date of Patent: May 28, 2002**

Exhibit A

(54) **CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD**

(75) Inventors: **Jeffrey A. Robl**, Newtown, PA (US); **Richard B. Sulsky**, West Trenton, NJ (US); **David J. Augeri**, Princeton, NJ (US); **David R. Magnin**, Hamilton, NJ (US); **Lawrence G. Hamann**, Cherry Hill, NJ (US); **David A. Betebenner**, Lawrenceville, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/788,173**

(22) Filed: **Feb. 16, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/188,555, filed on Mar. 10, 2000.

(51) **Int. Cl.**[7] **C07D 209/07**; A61K 31/403

(52) **U.S. Cl.** **514/412**; 548/452

(58) **Field of Search** 548/452; 514/412

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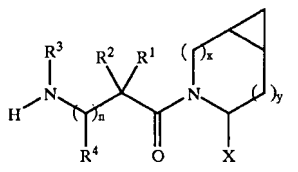
Primary Examiner—Robert Gerstl
(74) *Attorney, Agent, or Firm*—Burton Rodney

(57) **ABSTRACT**

Dipeptidyl peptidase IV (DP 4) inhibiting compounds are provided having the formula



where

x is 0 or 1 and y is 0 or 1 (provided that x=1 when y=0 and x=0 when y=1);

n is 0 or 1; X is H or CN;

and wherein R^1, R^2, R^3 and R^4 are as described herein.

A method is also provided for treating diabetes and related diseases, especially Type II diabetes, and other diseases as set out herein, employing such DP 4 inhibitor *or a combination of such DP 4 inhibitor and one or more of another antidiabetic agent such as metformin, glyburide, troglitazone, pioglitazone, rosiglitazone and/or insulin and/or one or more of a hypolipidemic agent and/or anti-obesity agent and/or other therapeutic agent.

24 Claims, No Drawings

CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD

This application takes priority from U.S. provisional application No. 60/188,555, filed Mar. 10, 2000.

FIELD OF THE INVENTION

The present invention relates to cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV (DP-4), and to a method for treating diabetes, especially Type II diabetes, as well as hyperglycemia, Syndrome X, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as various immunomodulatory diseases and chronic inflammatory bowel disease, employing such cyclopropyl-fused pyrrolidines alone or in combination with another type antidiabetic agent and/or other type therapeutic agent.

BACKGROUND OF THE INVENTION

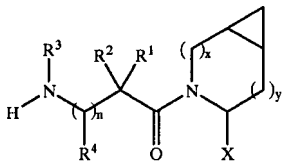
Depeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1(7-36), glucagon) in vivo and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) in vitro.

GLP-1(7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine. GLP-1(7-36) has multiple actions in vivo including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying. Based on its physiological profile, the actions of GLP-1(7-36) are expected to be beneficial in the prevention and treatment of type II diabetes and potentially obesity. To support this claim, exogenous administration of GLP-1(7-36) (continuous infusion) in diabetic patients has demonstrated efficacy in this patient population. Unfortunately GLP-1(7-36) is degraded rapidly in vivo and has been shown to have a short half-life in vivo (t1/2≈1.5 min). Based on a study of genetically bred DP-4 KO mice and on in vivo/in vitro studies with selective DP-4 inhibitors, DP-4 has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo. GLP-1(7-36) is degraded by DP-4 efficiently to GLP-1(9-36), which has been speculated to act as a physiological antagonist to GLP-1(7-36). Thus, inhibition of DP-4 in vivo should potentiate endogenous levels of GLP-1(7-36) and attenuate formation of its antagonist GLP-1(9-36) and thus serve to ameliorate the diabetic condition.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, cyclopropyl-fused pyrrolidine-based compounds are provided which inhibit DP-4 and have the structure

I



wherein

x is 0 or 1 and y is 0 or 1 (provided that

x=1 when y=0 and

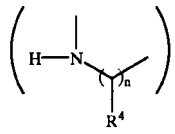
x=0 when y=1);

n is 0 or 1;

X is H or CN (that is cyano);

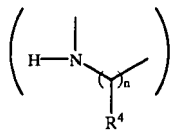
R^1, R^2, R^3 and $R^4$are the same or different and are independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl, arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl and cycloheteroalkylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

and R^1 and R^3 may optionally be taken together to form $—(CR^5R^6)_m—$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, halo, amino, substituted amino, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R^4 may optionally be taken together to form $—(CR^7R^8)_p—$ where p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, halo, amino, substituted amino, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together with



form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2;

or optionally R^1 and R^3 together with

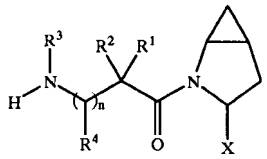


form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

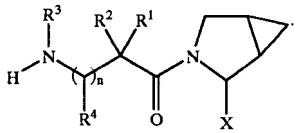
and including pharmaceutically acceptable salts thereof, and prodrug esters thereof, and all stereoisomers thereof.

Thus, the compounds of formula I of the invention include the following structures

IA



IB



In addition, in accordance with the present invention, a method is provided for treating diabetes, especially Type II diabetes, as well as impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases (such as scleroderma and multiple sclerosis), various immunomodulatory diseases (such as lupus erythematosis or psoriasis), AIDS, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease), inflammatory bowel syndrome, chemotherapy-induced intestinal mucosal atrophy or injury, anorexia nervosa, osteoporosis, Syndrome X, dysmetabolic syndrome, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), wherein a therapeutically effective amount of a compound of structure I (which inhibits DP 4) is administered to a human patient in need of treatment.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727–734 (1997).

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter as well as any of the other disease states mentioned above, wherein a therapeutically effective amount of a combination of a compound of structure I and one, two, three or more of other types of antidiabetic agent(s) (which may be employed to treat diabetes and related diseases) and/or one, two or three or more other types of therapeutic agent(s) is administered to a human patient in need of treatment.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications, dysmetabolic syndrome, and hyperinsulinemia.

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

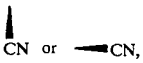
The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than DP4 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-modulating agents (including anti-atherosclerosis agents), and/or one or more infertility agents, one or more agents for treating polycystic ovary syndrome, one or more agents for treating growth disorders, one or more agents for treating frailty, one or more agents for treating arthritis, one or more agents for preventing allograft rejection in transplantation, one or more agents for treating autoimmune diseases, one or more anti-AIDS agents, one or more anti-osteoporosis agents, one or more agents for treating immunomodulatory diseases, one or more agents for treating chronic inflammatory bowel disease or syndrome and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

In the above methods of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent or other type therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 500:1, preferably from about 0.1:1 to about 100:1, more preferably from about 0.2:1 to about 10:1.

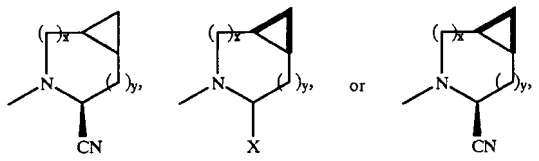
Preferred are compounds of formula I wherein R^3 is H or alkyl, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxytricycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxyalkylcycloalkyl, R^2 is H or alkyl, n is 0, X is CN, x is 0 or 1 and y is 0 or 1.

Most preferred are preferred compounds of formula I as described above where X is



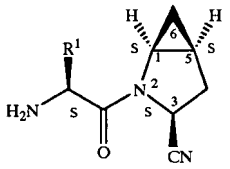
and/or wherein the fused cyclopropyl group is identified as

Thus, preferred compounds of formula I of the invention will include the moiety:



Particularly preferred are the following compounds:

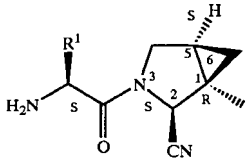
A)



[1S, 2(2S), 3S, 5S]

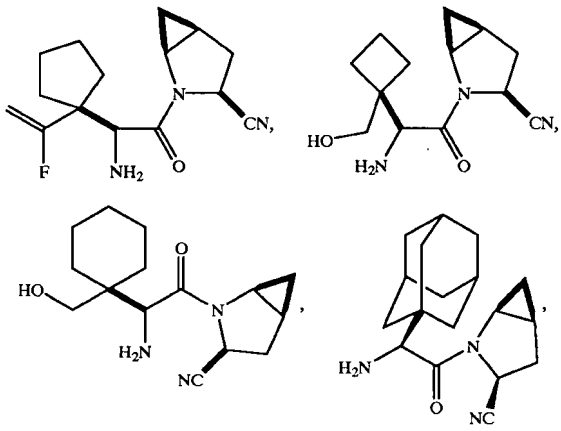
wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl or hydroxytricycloalkyl;

B)



[1R, 2S, 3(2S), 5S]

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl or hydroxyalkylcycloalkyl as well as the following:



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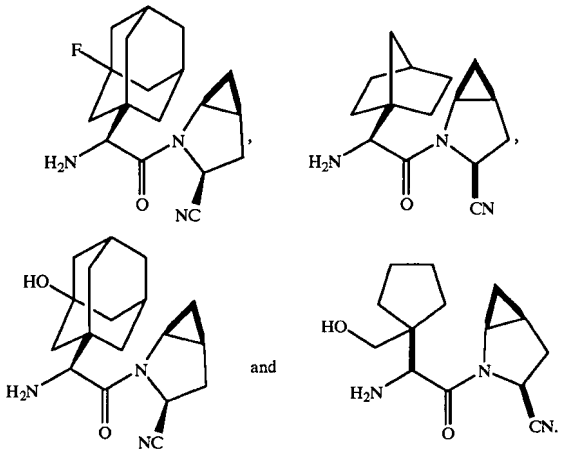


DETAILED DESCRIPTION OF THE INVENTION

Compounds of the structure I may be generated by the methods as shown in the following reaction schemes and the description thereof.

Referring to Reaction Scheme 1, compound 1, where PG_1 is a common amine protecting group such as Boc, Cbz, or FMOC and X^1 is H or CO_2R^9 as set out below, may be generated by methods as described herein or in the literature (for example see Sagnard et al, Tet-Lett., 1995, 36, pp. 3148–3152, Tverezovsky et al, Tetrahedron, 1997, 53, pp. 14773–14792, Hanessian et al, Bioorg. Med. Chem. Lett., 1998, 8, p. 2123–2128). Removal of the PG_1 group by conventional methods (e.g. (1) TFA or HCl when PG_1 is Boc, or (2) H_2/Pd/C, TMSI when PG_1 is Cbz, or (3) Et_2NH when PG_1 is (FMOC) affords the free amine 2. Amine 2 may be coupled to various protected amino acids such as 3 (where PG_2 can be any of the PG_1 protecting groups) using standard peptide coupling conditions (e.g. EDAC/HOAT, i-BuCOCOC1/TEA, PyBop/NMM) to afford the corresponding dipeptide 4. Removal of the amine protecting group PG_2 provides compound Ia of the invention where X=H.

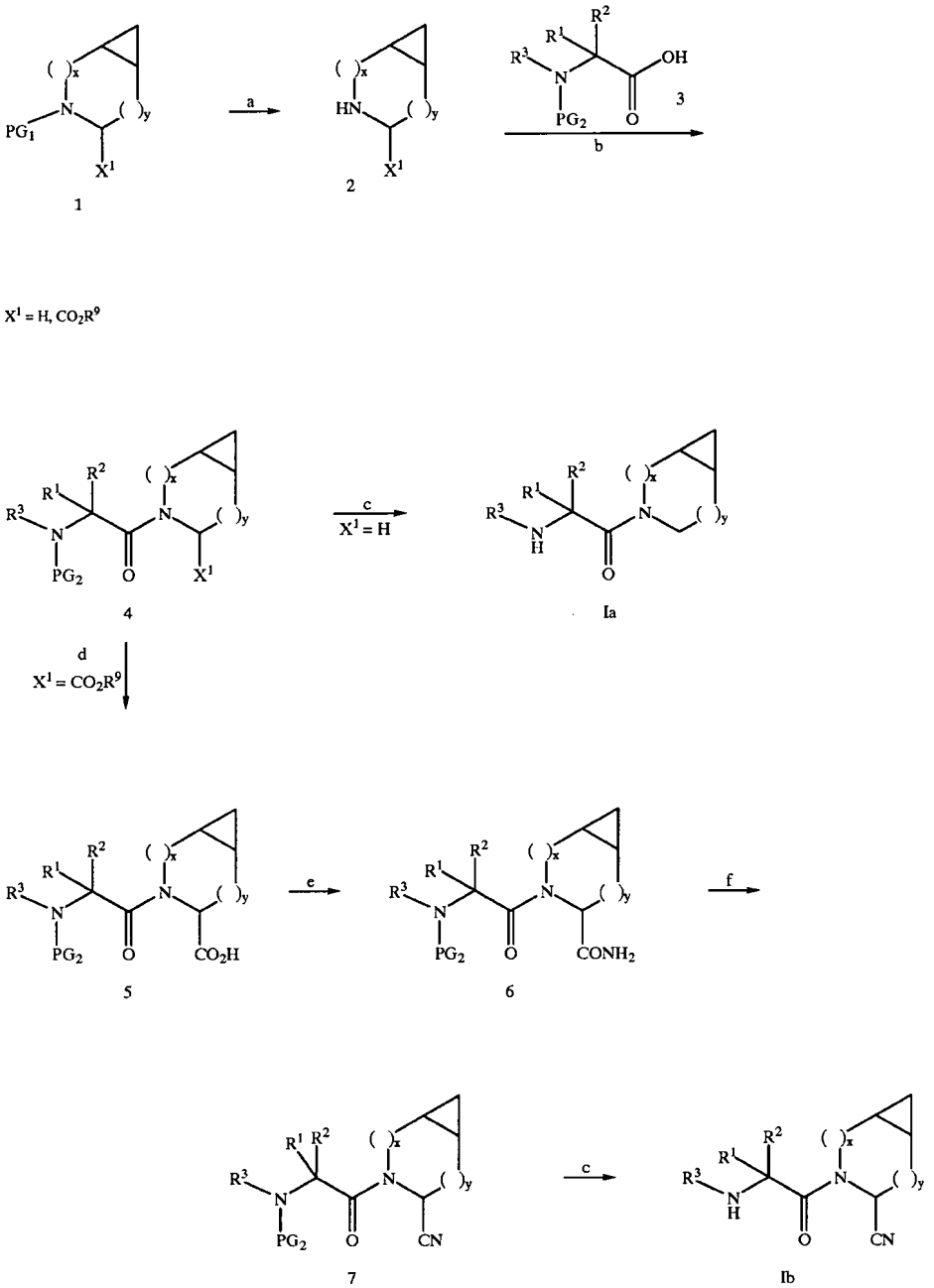
In the case where X^1=CO_2R^9 (where R^9 is alkyl or aralkyl groups such as methyl, ethyl, t-butyl, or benzyl), the ester may be hydrolyzed under a variety of conditions, for example with aqueous NaOH in a suitable solvent such as methanol, THF, or dioxane, to provide the acid 5. Conversion of the acid group to the primary carboxamide, affording 6, may be effected by activation of the acid group (e.g. employing i-BuOCOC1/TEA or EDAC) followed by treatment with NH_3 or an ammonia equivalent in a solvent such as dioxane, ether, or methanol. The amide functionality may be converted to the nitrile group by a variety of standard conditions (e.g. $POCl_3$/pyridine/imidazole or cyanuric chloride/DMF or trifluoroacetic anhydride, THF, pyridine) to give 7. Finally, removal of the PG_2 protecting group similar to above provides compound of the invention Ib.

In a different sequence (Scheme 2), compound 1 where X^1 is CO_2R^9 may be saponified to the acid and subsequently

amidated as described above to give amide 8. Removal of the PG_1 group followed by peptide coupling to 3 affords compound 6, an intermediate in the synthesis of Ib.

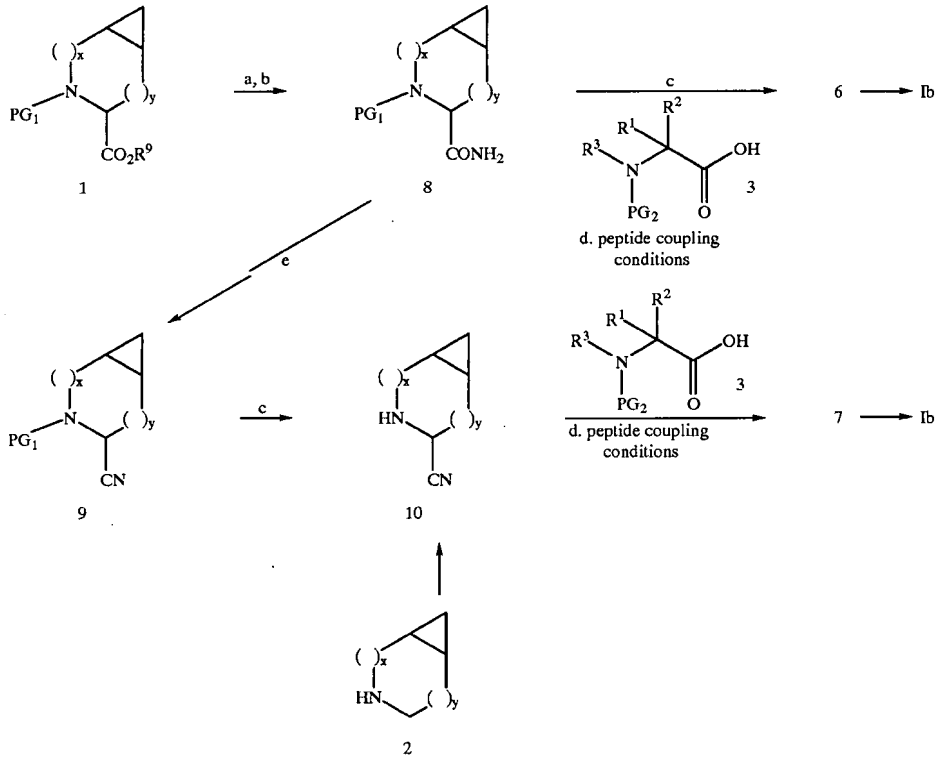
Alternately, the carboxamide group in 8 may be converted to the nitrile as described above to give compound 9. Deprotection of PGI affords 10 which may be subject to standard peptide coupling conditions to afford 7, an intermediate in the synthesis of Ib. Compound 10 may also be generated by oxidation of the amine 2 (e.g. NCS) followed by hydrolysis and subsequent cyanide treatment. Compound 10 may be obtained as a mixture of stereoisomers or a single isomer/diastereomer which may be epimerized (employing conventional procedures) to afford a mixture of stereoisomers.

Scheme 1



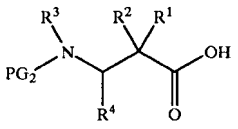
a. PG_1 = Boc, TFA or HCl; PG_1 = Cbz, H_2/Pd/C or TMSI; PG_1 = FMOC, Et_2NH b. EDAC, HOBT, DMF or i-BuOCOCl/TEA or PyBop, NMM c. $PG_2 = PG_1$, (see conditions for a) d. LiOH or NaOH MeOH or THF/H_2O or dioxane e. i-BuOCOCl/NMM or i-BuOCOCl/TEA or EDAC, then NH_3 in dioxane or Et_2O f. $POCl_3$, pyridine, imidazole or cyanuric chloride, DMF or TFAA, THF, pyridine.

Scheme 2



a. LiOH or NaOH in MeOH or THF/H_2O or dioxane b. i-BuOCOCl/NMM or i-BuOCOCl/TEA or EDAC, then NH_3 in dioxane or Et_2O c. PG_1 = Boc, TFA or HCl; PG_1 = Cbz, H_2/Pd/C or TMSI; PG_1 = FMOC, Et_2NH d. EDAC, HOBT, DMF or i-BuOCOCl/TEA or PyBop, NMM e. $POCl_3$, pyridine, imidazole or cyanuric chloride, DMF.

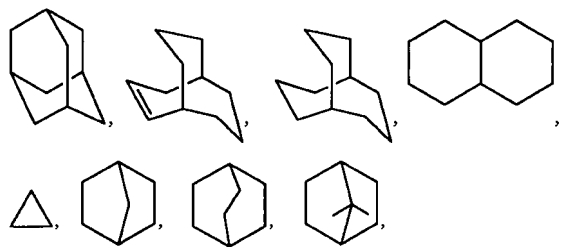
In a like manner, β-amino acids such as,



may be coupled with 2, the free amine of 8, or 10 to give the corresponding amides which may be converted to the β-amino acid derivatives of compound Ia or Ib following the same chemistry.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl) and tricyclic alkyl (tricycloalkyl), containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl, adamantyl,

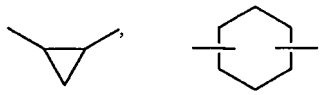


any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl,

aryloxy, arylalkyl, cycloalkyl, hydroxyalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "cycloalkylene" as employed herein refers to a "cycloalkyl" group which includes free bonds and thus is a linking group such as



and the like, and may optionally be substituted as defined above for "cycloalkyl".

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octenyl, 3-nonenyl, 4-decenyl,3-undecenyl, 4-dodecenyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

The terms "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

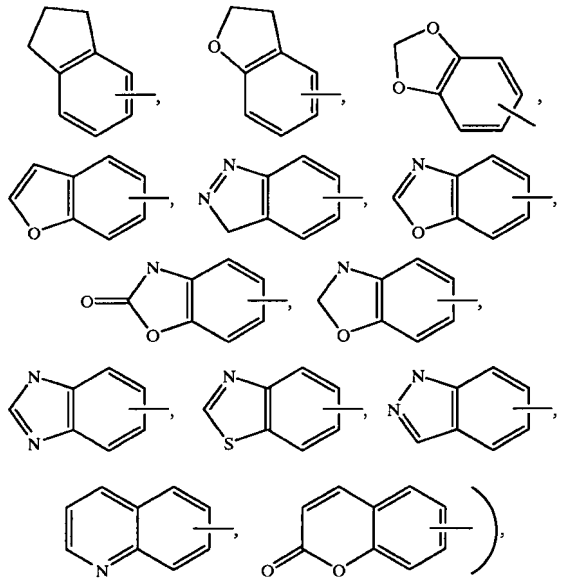
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with any of the R^1 groups or substituents for R^1 as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

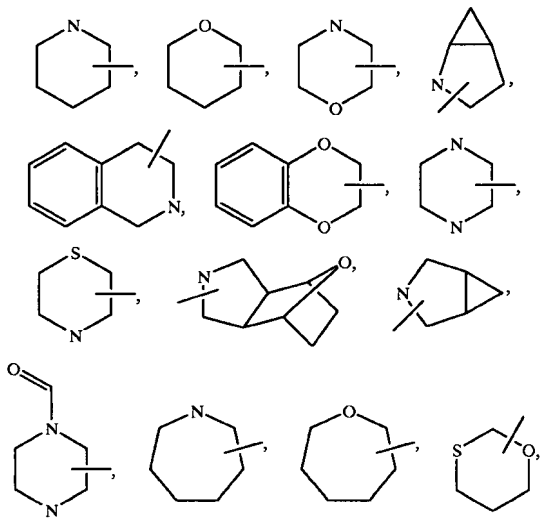
Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl

group; examples of acyl groups include any of the R^1 groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_r$ (where r is 1, 2 or 3), such as:



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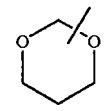
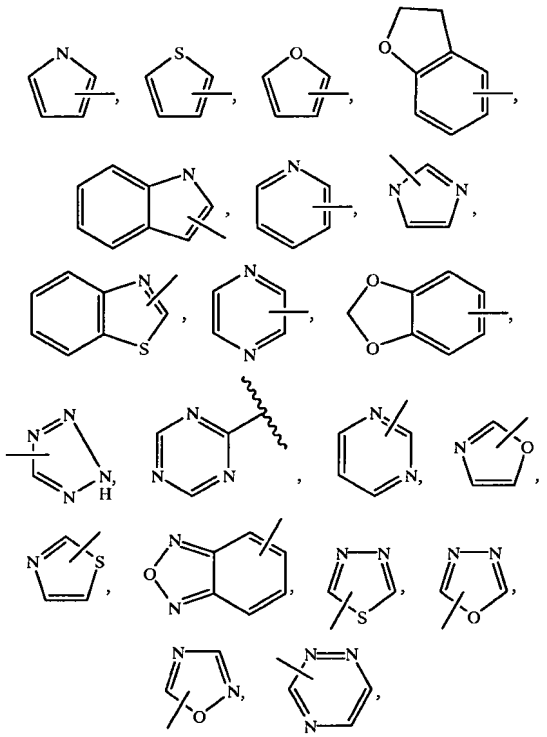


and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the substituents set out above for alkyl. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers cycloheteroalkyl groups as defined above linked through a atom or heteroatom to a $(CH_2)_r$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_r-$ chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

The term "polyhaloalkoxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Where desired, the compounds of structure I may be used in combination with one or more other types of antidiabetic agents (employed to treat diabetes and related diseases) and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The other type of antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from DP4 inhibition and may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, SGLT2 inhibitors, PPAR α/γ dual agonists, aP2 inhibitors, glycogen phosphorylase inhibitors, advanced glycosylation end (AGE) products inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1) or mimetics thereof.

It is believed that the use of the compounds of structure I in combination with 1, 2, 3 or more other antidiabetic agents produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive antihyperglycemic effects produced by these medicaments.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the other antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Pat. No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the γ-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Pat. No. 4,904,769) or miglitol (disclosed in U.S. Pat. No. 4,639, 436), which may be administered in the same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 50:1.

The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Pat. No. 4,572,912), rosiglitazone (en), pioglitazone (Takeda), Mitsubishi MCC-555 (disclosed in U.S. Pat. No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(**1-36**) amide, GLP-1(7-36) amide, GLP-1(**7-36**) (as disclosed in U.S. Pat. No. 5,614,492 to Habener, disclosure of which is incorporated herein by reference), or a GLP-1 mimic such as AC2993 or Exendin-4 (Amylin) and LY-315902 or LY-307167 (Lilly) and NN2211 (Novo-Nordisk), which may be administered via injection, intranasal, or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration (for example inhalation spray) or parenterally as described in U.S. Pat. Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631, 224 which are incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation—Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841–1847 (1998), and in U.S. application Ser. No. 09/664, 598, filed Sep. 18, 2000, (attorney file LA29NP) the disclosure of which is incorporated herein by reference, employing

dosages as set out therein, which compounds designated as preferred are preferred for use herein.

The other antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. application Ser. No. 09/679,027, filed Oct. 4, 2000 (attorney file LA49NP), which is incorporated herein by reference, employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be an aP2 inhibitor such as disclosed in U.S. application Ser. No. 09/391,053, filed Sep. 7, 1999, and U.S. application Ser. No. 09/519,079, filed Mar. 6, 2000 (attorney file LA27NP), which is incorporated herein by reference, employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be a glycogen phosphorylase inhibitor such as disclosed in WO 96/39384, WO 96/39385, EP 978279, WO 2000/47206, WO 99/43663, and U.S. Pat. Nos. 5,952,322 and 5,998,463, WO 99/26659 and EP 1041068.

The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The DP4 inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, SGLT2 inhibitor, aP2 inhibitor, or glycogen phosphorylase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 10:1.

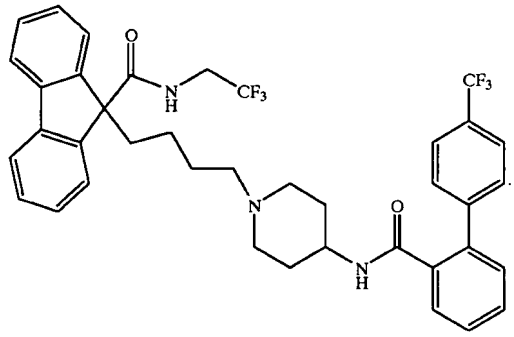
The hypolipidemic agent or lipid-modulating agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, ATP citrate lyase inhibitors, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Pat. No. 5,595,872, U.S. Pat. No. 5,739, 135, U.S. Pat. No. 5,712,279, U.S. Pat. No. 5,760,246, U.S. Pat. No. 5,827,875, U.S. Pat. No. 5,885,983 and U.S. application Ser. No. 09/175,180 filed Oct. 20, 1998, now U.S. Pat. No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Pat. Nos. 5,739,135 and 5,712, 279, and U.S. Pat. No. 5,760,246 as well as implitapide (Bayer).

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl] butyl]-N-(2, 2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Pat. No. 3,983, 140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Pat. No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Pat. No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Pat. Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Pat. No. 5,354, 772, cerivastatin disclosed in U.S. Pat. Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Pat. Nos. 4,681, 893, 5,273,995, 5,385,929 and 5,686,104, atavastatin (Nissan/Sankyo nisvastatin (NK-104)) disclosed in U.S. Pat. No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Pat. No. 5,260,440.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Pat. No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 11, No. 10, pp 1869–1871, including isoprenoid (phosphinyl-methyl) phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Pat. Nos. 4,871,721 and 4,924,024 and in Biller, S. A., Neuenschwander, K., Ponpipom, M. M., and Poulter, C. D., Current Pharmaceutical Design, 2, 1–40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243–249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291–1293, phosphinylphosphonates reported by McClard, R. W. et al, J.A.C.S., 1987, 10, 5544 and cyclopropanes reported by Capson, T. L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstracts Table of Contents, pp 16, 17, 40–43, 48–51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Pat. No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox,

acifran, neomycin, p-aminosalicylic acid, aspirin, poly (diallylmethylamine) derivatives such as disclosed in U.S. Pat. No. 4,759,923, quaternary amine poly (diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Pat. No. 4,027,009, and other known serum cholesterol lowering agents.

The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9–15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77–85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16–30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47–50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173–98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204–25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359–62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis 115, 45–63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425–430 (1999).

The lipid-modulating agent may be a cholesteryl ester transfer protein (CETP) inhibitor such as Pfizer's CP 529, 414 (WO/0038722 and EP 818448) and Pharmacia's SC-744 and SC-795.

The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Pat. No. 5,447,954.

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199–1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11–20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

The other type of therapeutic agent which may be optionally employed with the DP4 inhibitor of formula I may be 1, 2, 1 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug, an anorectic agent and/or a fatty acid oxidation upregulator.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Pat. Nos. 5,541,204, 5,770,615, 5,491,134,

5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopoamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor beta compound which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO099/00353 (KaroBio) and GB98/284425 (KaroBio), with compounds of the KaroBio applications being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The fatty acid oxidation upregulator which may be optionally employed in combination with the compound of formula I can be famoxin (Genset).

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

The infertility agent which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of clomiphene citrate (Clomid®, Aventis), bromocriptine mesylate (Parlodel®, Novartis),LHRH analogs, Lupron (TAP Pharm.), danazol, Danocrine (Sanofi), progestogens or glucocorticoids, which may be employed in amounts specified in the PDR.

The agent for polycystic ovary syndrome which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of gonadotropin releasing hormone (GnRH), leuprolide (Lupron®), Clomid®, Parlodel®, oral contraceptives or insulin sensitizers such as PPAR agonists, or other conventional agents for such use which may be employed in amounts specified in the PDR.

The agent for treating growth disorders and/or frailty which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of a growth hormone or growth hormone secretagogue such as MK-677 (Merck), CP-424,391 (Pfizer), and compounds disclosed in U.S. Ser. No. 09/506,749 filed Feb. 18, 2000 (attorney docket LA26), as well as selective androgen receptor modulators (SARMs), which is incorporated herein by reference, which may be employed in amounts specified in the PDR, where applicable.

The agent for treating arthritis which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of aspirin, indomethacin, ibuprofen, diclofenac sodium, naproxen, nabumetone (Relafen®, SmithKline Beecham), tolmetin sodium (Tolectin®, Ortho-McNeil), piroxicam (Feldene®, Pfizer), ketorolac tromethamine (Toradol®, Roche), celecoxib (Celebrex®, Searle), rofecoxib (Vioxx®, Merck) and the like, which may be employed in amounts specified in the PDR.

Conventional agents for preventing allograft rejection in transplantation such as cyclosporin, Sandimmune (Novartis), azathioprine, Immuran (Faro) or methotrexate may be optionally employed in combination with the DP4 inhibitor of the invention, which may be employed in amounts specified in the PDR.

Conventional agents for treating autoimmune diseases such as multiple sclerosis and immunomodulatory diseases such as lupus erythematosis, psoriasis, for example, azathioprine, Immuran, cyclophosphamide, NSAIDS such as ibuprofen, cox 2 inhibitors such as Vioxx and Celebrex, glucocorticoids and hydroxychloroquine, may be optionally employed in combination with the DP4 inhibitor of the invention, which may be employed in amounts specified in the PDR.

The AIDS agent which may be optionally employed in combination with the DP4 inhibitor of the invention may be a non-nucleoside reverse transcriptase inhibitor, a nucleoside reverse transcriptase inhibitor, a protease inhibitor and/or an AIDS adjunct anti-infective and may be 1, 2, or more of dronabinol (Marinol®, Roxane Labs), didanosine (Videx®, Bristol-Myers Squibb), megestrol acetate (Megace®, Bristol-Myers Squibb), stavudine (Zerit®, Bristol-Myers Squibb), delavirdine mesylate (Rescriptor®, Pharmacia), lamivudine/zidovudine (Combivir™, Glaxo), lamivudine (Epivir™, Glaxo), zalcitabine (Hivid®, Roche), zidovudine (Retrovir®, Glaxo), indinavir sulfate (Crixivan®, Merck), saquinavir (Fortovase™, Roche), saquinovir mesylate (Invirase®, Roche), ritonavir (Norvir®, Abbott), nelfinavir (Viracept®, Agouron).

The above anti-AIDS agents may be employed in amounts specified in the PDR.

The agent for treating inflammatory bowel disease or syndrome which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of sulfasalazine, salicylates, mesalamine (Asacol®, P&G) or Zelmac®, (Bristol-Myers Squibb), which may be employed in amounts specified in the PDR or otherwise known in the art.

The agent for treating osteoporosis which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of alendronate sodium (Fosamax®, Merck, tiludronate (Skelid®, Sanofi), etidronate disodium (Didronel®, P&G), raloxifene HCl (Evista®, Lilly), which may be employed in amounts specified in the PDR.

In carrying our the method of the invention, a pharmaceutical composition will be employed containing the compounds of structure I, with or without another antidiabetic agent and/or other type therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 10 and 1,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1–4 times per day.

A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

DP4 inhibitor activity of the compounds of the invention may be determined by use of an in vitro assay system which

measures the potentiation of inhibition of DP4. Inhibition constants (Ki values) for the DP4 inhibitors of the invention may be determined by the method described below.

Purification of Porcine Dipeptidyl Peptidase IV

Porcine enzyme was purified as previously described (1), with several modifications. Kidneys from 15–20 animals were obtained, and the cortex was dissected away and frozen at –80° C. Frozen tissue (2000 –2500 g) was homogenized in 12 L of 0.25 M sucrose in a Waring blender. The homogenate then was left at 37° C. for 18 hours to facilitate cleavage of DP-4 from cell membranes. After the cleavage step, the homogenate was clarified by centrifugation at 7000×g for 20 min at 4° C., and the supernatant was collected. Solid ammonium sulfate was added to 60% saturation, and the precipitate was collected by centrifugation at 10,000×g and was discarded. Additional ammonium sulfate was added to the supernatant to 80% saturation, and the 80% pellet was collected and dissolved in 20 mM Na_2HPO_4, pH 7.4.

After dialysis against 20 mM Na_2HPO_4, pH 7.4, the preparation was clarified by centrifugation at 10,000×g. The clarified preparation then was applied to 300 mL of ConA Sepharose that had been equilibrated in the same buffer. After washing with buffer to a constant A_{280}, the column was eluted with 5% (w/v) methyl α-D-mannopyranoside. Active fractions were pooled, concentrated, and dialyzed against 5 mM sodium acetate, pH 5.0. Dialyzed material then was flowed through a 100 mL Pharmacia Resource S column equilibrated in the same buffer. The flow through material was collected and contained most of the enzyme activity. Active material again was concentrated and dialyzed into 20 mM Na_2HPO_4, pH 7.4. Lastly, the concentrated enzyme was chromatographed on a Pharmacia S-200 gel filtration column to removed low molecular weight contaminants. Purity of column fractions was analyzed by reducing SDS-PAGE, and the purest fractions were pooled and concentrated. Purified enzyme was stored in 20% glycerol at –80° C.

Assay of Porcine Dipeptidyl Peptidase IV

Enzyme was assayed under steady-state conditions as previously described (2) with gly-pro-p-nitroanilide as substrate, with the following modifications. Reactions contained, in a final volume of 100 μl, 100 mM Aces, 52 mM TRIS, 52 mM ethanolamine, 500 μM gly-pro-p-nitroanilide, 0.2 % DMSO, and 4.5 nM enzyme at 25° C., pH 7.4. For single assays at 10 μM test compound, buffer, compound, and enzyme were added to wells of a 96 well microtiter plate, and were incubated at room temperature for 5 min. Reactions were started by addition of substrate, The continuous production of p-nitroaniline was measured at 405 nM for 15 min using a Molecular Devices Tmax plate reader, with a read every 9 seconds. The linear rate of p-nitroaniline production was obtained over the linear portion of each progress curve. A standard curve for p-nitroaniline absorbance was obtained at the beginning of each experiment, and enzyme catalyzed p-nitroaniline production was quantitated from the standard curve. Compounds giving greater than 50% inhibition were selected for further analysis.

For analysis of positive compounds, steady-state kinetic inhibition constants were determined as a function of both substrate and inhibitor concentration. Substrate saturation curves were obtained at gly-pro-p-nitroanilide concentrations from 60 μM to 3600 μM. Additional saturation curves also were obtained in the presence of inhibitor. Complete inhibition experiments contained 11 substrate and 7 inhibitor concentrations, with triplicate determinations across plates. For tight binding inhibitors with K_is less than 20 nM, the enzyme concentration was reduced to 0.5 nM and reaction times were increased to 120 min. Pooled datasets from the three plates were fitted to the appropriate equation for either competitive, noncompetitive or uncompetitive inhibition.

(1) Rahfeld, J. Schutkowski, M., Faust, J., Neubert., Barth, A., and Heins, J. (1991) Biol. Chem. Hoppe-Seyler, 372, 313–318.

(2) Nagatsu, T., Hino, M., Fuyamada, H., Hayakawa, T., Sakakibara, S., Nakagawa, Y., and Takemoto, T. (1976) Anal. Biochem., 74, 466–476.

The following abbreviations are employed in the Examples and elsewhere herein:

Ph=phenyl
Bn=benzyl
i-Bu=iso-butyl
Me=methyl
Et=ethyl
Pr=propyl
Bu=butyl
TMS=trimethylsilyl
FMOC=fluorenylmethoxycarbonyl
Boc or BOC=tert-butoxycarbonyl
Cbz=carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
HOAc or AcOH=acetic acid
DMF=N,N-dimethylformamide
EtOAc=ethyl acetate
THF=tetrahydrofuran
TFA=trifluoroacetic acid
Et_2NH=diethylamine
NMM=N-methyl morpholine
n-BuLi=n-butyllithium
Pd/C=palladium on carbon
PtO_2=platinum oxide
TEA=triethylamine
EDAC=3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-[(3-(dimethyl)amino)propyl])-3-ethylcarbodiimide hydrochloride)
HOBT or HOBT.H_2O=1-hydroxybenzotriazole hydrate
HOAT=1-hydroxy-7-azabenzotriazole
PyBOP reagent=benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate
min=minute(s)
h or hr=hour(s)
L=liter
mL=milliliter
μL=microliter
g=gram(s)
mg=milligram(s)
mol=mole(s)
mmol=millimole(s)
meq=milliequivalent
rt=room temperature
sat or sat'd=saturated
aq.=aqueous

TLC=thin layer chromatography

HPLC=high performance liquid chromatography

LC/MS=high performance liquid chromatography/mass spectrometry

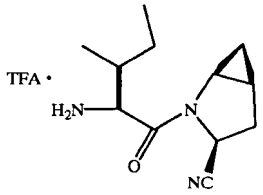
MS or Mass Spec=mass spectrometry

NMR=nuclear magnetic resonance

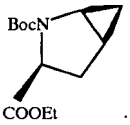
mp=melting point

The following Examples represent preferred embodiments of the invention.

EXAMPLE 1



Step 1

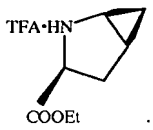


Step 1 title compound was synthesized by following the literature procedure [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128] or with the following modifications. L-pyroglutamic acid ethyl ester was N-protected as the t-butylcarbamate (Boc_{20}, DMAP or NaH) and then dehydrated to the 4,5-dehydroproline ethyl ester in one pot by carbonyl reduction (triethylborohydride, toluene, −78° C.) followed by dehydration (TFAA, lutidine). The title compound was obtained by cyclopropanation of the 4,5-dehydroproline ethyl ester (Et_2Zn, $ClCH_2I$, 1,2-dichloroethane, −15° C.). A more detailed protocol is as follows;

Synthesis of 4,5-dehydro-L-proline ethyl ester: L-pyroglutamic acid ethyl ester (200 g, 1.27 mol) was dissolved in 1.2 liters of methylene chloride and treated sequentially with di-tert-butyldicarbonate (297 g, 1.36 mol) and a catalytic DMAP (1.55 g, 0.013 mol) at ambient temperature. After 6 h, the mixture was quenched with saturated brine and the organic phase was dried (Na_2SO_4) and filtered through a short silica gel column to give 323 g (100%) of N-Boc- L-pyroglutamic acid ethyl ester. N-Boc-L-pyroglutamic acid ethyl ester (160 g, 0.62 mol) was dissolved in 1 liter of toluene, cooled to −78° C. and treated with lithium triethylborohydride (666 mL of a 1.0 M soln in THF) and added dropwise over 90 minutes. After 3 h, 2,6-lutidine (423 mL, 3.73 mol) was added dropwise followed by DMAP (0.2 g, 0.0016 mol). To this mixture was added TFAA (157 g, 0.74 mol) and the reaction was allowed to come to ambient temperature over 2 h. The mixture was diluted with EtOAc and water and the organics were washed with 3 N HCl, water, aqueous bicarbonate and brine and dried (Na_2SO_4) and filtered through a silica gel plug to give 165 g of the crude 4,5-dehydroproline ethyl ester that was purified by flash column chromatography on silica gel with 1:5 ethyl acetate:hexanes to give 120 g, 75% of the olefin.

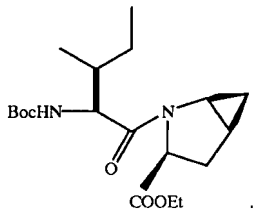
Cyclopropanation of 4,5-dehydro-L-proline ethyl ester: 4,5-Dehydro-L-proline ethyl ester (35.0 g, 0.145 mol) was added to a solution of neat Et_2Zn (35.8 g, 0.209 mol) in 1 liter of 1,2-dichloroethane at −15° C. To this mixture was added a dropwise addition of $ClCH_2I$ (102 g, 0.58 mol) over 1 h and the mixture stirred at −15° C. for 18 h. The reaction was quenched with saturated aqueous bicarbonate and the solvent was evaporated and the reaction was taken up in EtOAc, washed with brine and purified by silica gel chromatography using a stepwise gradient of from 20% EtOAc/hexanes to 50% EtOAc/hexanes to give 17.5 g (50%) of diastereomerically pure step 1 title compound.

Step 2



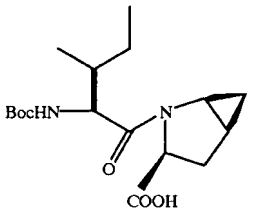
To a stirred solution of Step 1 compound (411 mg, 1.61 mmol) in CH_2Cl_2 (1.5 mL) at rt was added TFA (1.5 mL). The reaction mixture was stirred at rt for 2 h and evaporated. The residue was diluted with CH_2Cl_2 and then evaporated and re-evaporated three times to give the title compound as a colorless oil, 433 mg, 100% yield,

Step 3



To a stirred solution of (S)-N-tert-butoxycarbonyl-isoleucine (372.6 mg, 1.61 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.25 g, 2.42 mmol) in CH_2Cl_2 (6 mL) under nitrogen at rt was added 4-methylmorpholine (NMM) (0.36 mL, 3.2 mmol). After 5 min, a solution of Step 2 compound (433 mg, 1.61 mmol) and NMM (0.27 mL, 2.4 mmol) in CH_2Cl_2 (1 mL) was added. After addition, the reaction mixture was stirred under nitrogen at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 4% $KHSO_4$(10 mL), aqueous $NaHCO_3$(10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography (1:4 EtOAc/hexane) gave the title compound as a colorless oil, 530 mg, 89% yield.

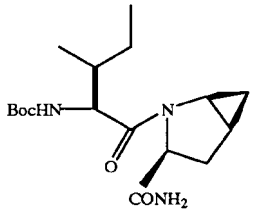
Step 4



To a stirred solution of Step 3 compound (530 mg, 1.44 mmol) in MeOH (4 mL) and H_2O (4 mL) at rt was added LiOH—H_2O (91 mg, 2.16 mmol). The reaction mixture was stirred at rt overnight and evaporated. Water (10 mL) was

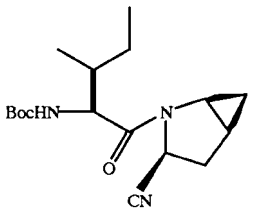
added to the residue and extracted with Et_2O (2×10 mL). The aqueous layer was acidified to ~pH 4 by adding 4% $KHSO_4$ dropwise. The milky solution was extracted with EtOAc (15 mL×3). Combined EtOAc layers were washed with brine, dried over Na_2SO_4 and evaporated to give the title compound as a white solid, 440 mg, 90% yield.

Step 5



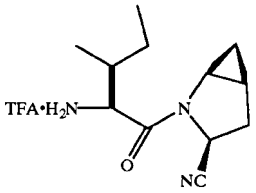
To a stirred solution of Step 4 compound (300 mg, 0.88 mmol) in THF (6 mL) at −15° C. under nitrogen, was added 4-methylmorpholine (0.12 mL, 1.06 mmol) and then isobutyl chloroformate (0.13 mL, 0.97 mmol) over 2 min. White precipitate was formed. The reaction mixture was stirred at −15° C. under nitrogen for 25 min and a solution of NH_3 in dioxane (8.8 mL, 4.4 mmol) was added. The reaction mixture was stirred at −15° C. for 30 min, warmed to rt and stirred at rt overnight. The reaction mixture was quenched by 4% $KHSO_4$ to ~pH 4 and extracted with EtOAc (20 mL×3). The extracts were combined, washed with brine (10 mL) dried (Na_2SO_4) and evaporated. Purification by flash column chromatography (1:1 EtOAc/hexane) gave the title compound as a white foam, 268 mg, 90% yield.

Step 6



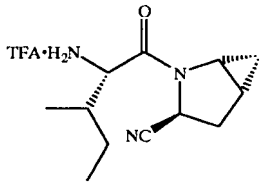
To a stirred solution of Step 5 compound (248 mg, 1.38 mmol) and imidazole (94 mg, 1.38 mmol) in dry pyridine (12 mL) at −35° C. under nitrogen was added $POCl_3$ (0.26 mL, 2.76 mmol) dropwise. The reaction mixture was stirred between −35° C. to −20° C. for 1 h and evaporated. CH_2Cl_2 (10 mL) was added and white precipitates were formed. After filtration, the filtrate was concentrated and purified by flash chromatography (2:5 EtOAc/hexane) to give the title compound as a colorless oil, 196 mg, 88% yield.

Step 7

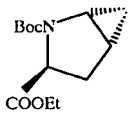


To a stirred solution of Step 6 compound (130 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) at rt was added TFA (2 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a pre-cooled slurry of $NaHCO_3$ (3.8 g) in H_2O (3 mL). The mixture was extracted with CH_2Cl_2 (6 mL×5), and the. combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compound as a white powder, 77 mg. 57% yield, mp=141–143° C. LC/MS gave the correct molecular ion $[(M+H)^+=222]$ for the desired compound.

EXAMPLE 2

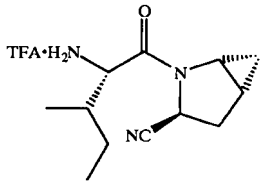


Step 1



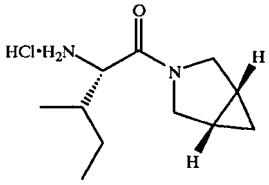
Step 1 title compound was synthesized by following the literature procedure. [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128.]

Step 2

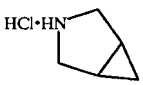


The title compound was prepared from Step 1 compound, employing the same procedure as that described for Example 1, Steps 2–6. LC/MS gave the correct molecular ion $[(M+H)^+=222]$ for the desired compound.

EXAMPLE 3

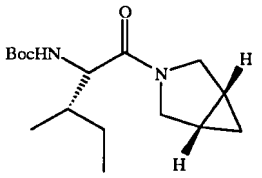


Step 1



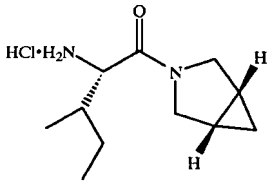
Step 1 title compound was prepared by following the literature procedure. [Willy D. Kollmeyer, U.S. Pat. No. 4,183,857.].

Step 2



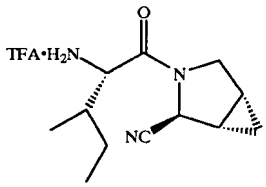
To a stirred solution of (S)-N-tert-butoxycarbonyl-isoleucine (231 mg, 1 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (780 mg, 1.5 mmol) in CH_2Cl_2 (6 mL) under nitrogen at rt was added 4-methylmorpholine (0.33 mL, 3 mmol). After 5 min, Step 1 compound (120 mg, 1 mmol) was added in one portion. The reaction mixture was stirred under nitrogen at rt overnight and then diluted with CH_2Cl_2 (30 mL), washed with 4.1w $KHSO_4$ (10 mL)), aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4x20 cm column, 1:3 EtOAc/hexane) gave the title compound as a colorless oil, 290 mg, 90% yield. LC/MS gave the correct molecular ion [$(M+H)^+$=297] for the desired compound.

Step 3

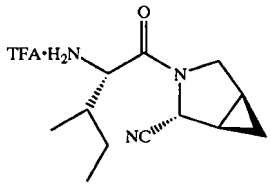


The reaction mixture of Step 2 compound (220 mg, 0.74 mmol) and 4 M HCl in dioxane (1.5 mL, 6 mmol) was stirred at rt for 2 h and evaporated under reduced pressure. Et_2O was added to the residue and a precipitate was formed. Et_2O was decanted and this was done three times. The precipitate was dried in vacuo to give the title compound as a white powder, 130 mg (76% yield), mp 205–206° C. LC/MS gave the correct molecular ion [$(M+H)^+$197] for the desired compound.

EXAMPLES 4–4A

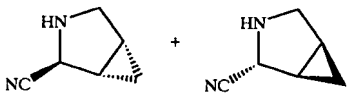


(Example 4)



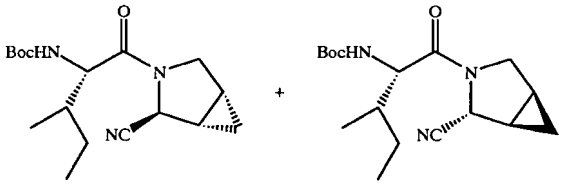
(Example 4A)

Step 1



Step 1 title compound, as a 1:1 ratio of enantiomers, was prepared by following the literature procedure. [Willy D. Kollmeyer, U.S. Pat. No. 4,183,857.]

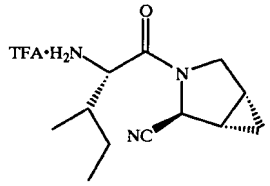
Step 2



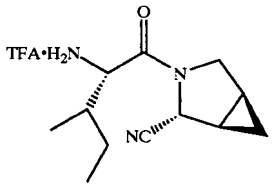
A slurry of (S)-N-tert-butoxycarbonyl-isoleucine (92.5 mg, 0.4 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (77 mg, 0.4 mmol) and HOAT (54.4 mg, 0.4 mmol) in $ClCH_2CH_2Cl$ (0.3 mL) was stirred under nitrogen at rt for 1 h, then Step 1 compound (22 mg, 0.2 mmol) was added, followed by Et_3N (0.015 mL, 0.1 mmol). The reaction mixture was stirred under nitrogen at rt over

night and then diluted with CH_2Cl_2 (3 mL), washed with H_2O (1 mL), aqueous $NaHCO_3$(1 mL) and brine (1 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4×12 cm column, 2:7 EtOAc/hexane) gave the title compound as a colorless oil, 33 mg, 51% yield. LC/MS gave the correct molecular ion [$(M+H)^+$ 322] for the desired compound.

Step 3



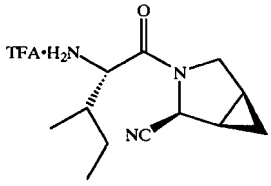
(Example 4)



(Example 4A)

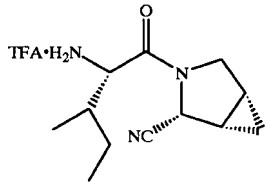
To a stirred solution of Step 2 compound (30 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL) at rt was added TFA (0.5 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a precooled slurry of $NaHCO_3$ (0.8 g) in H_2O (1 mL). The mixture was extracted with CH_2Cl_2 (2 mL×5), and combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compounds as a 1:1 ratio of diastereomers, 22 mg, 73% yield. LC/MS gave the correct molecular ion [$(M+H)^+$=222] for the desired compounds.

EXAMPLES 5–5A



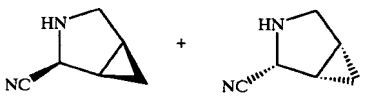
and

(Example 5)



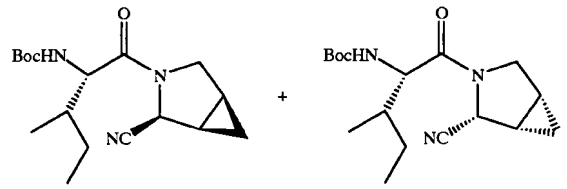
(Example 5A)

Step 1



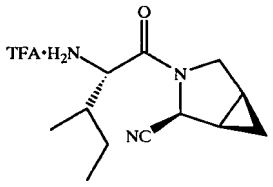
To a solution of Example 4, Step 1 compound (150 mg, 1.39 mmol) in 2-propanol (0.8 mL), was added NaCN (40 mg, 1.0 mmol). The reaction mixture was heated to reflux for 3 h. After cooling to rt, the reaction mixture was evaporated and then slurried in Et_2O (5 mL). After filtration, the filtrate was evaporated to give Example 4 Step 1 compounds and Example 5 Step 1 compounds (140 mg, 93%) as a 2:1 mixture of diastereomers, each as a racemic mixture.

Step 2



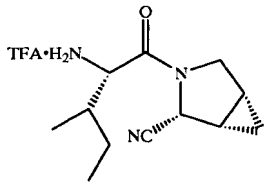
A slurry of (S)-N-tert-butoxycarbonyl-isoleucine (595 mg, 2.57 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (493 mg, 2.57 mmol) and 1-hydroxy-7-azabenzotriazole (350 mg, 2.57 mmol) in $ClCH_2CH_2Cl$ (2 mL) was stirred under nitrogen at rt for 1 h, then Step 1 compound mixture (139 mg, 1.28 mmol) was added. The reaction mixture was stirred under nitrogen at rt overnight and then diluted with CH_2Cl_2 (30 mL), washed with H_2O (10 mL) , saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4×20 cm column, 1:3 EtOAc/hexane) gave the Example 4, Step 2 compound (260 mg), and the title compounds (105 mg) as a ratio of 1:1 diastereomers. LC/MS gave the correct molecular ion [$(M+H)^+$=322] for the desired compounds.

Step 3



and

(Example 5)



(Example 5A)

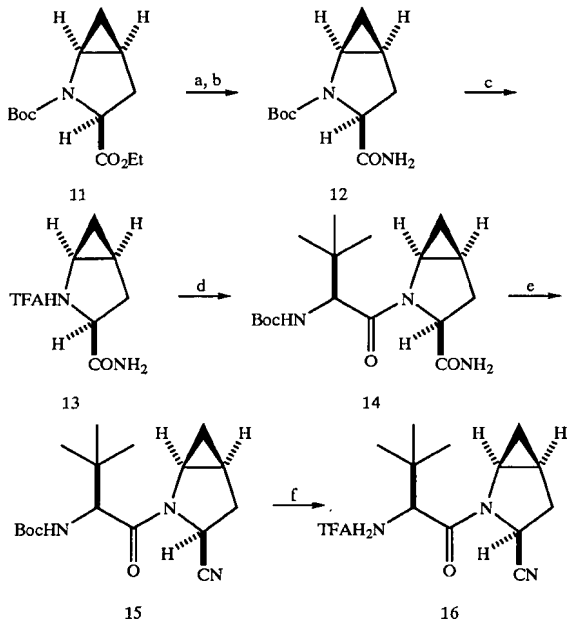
To a stirred solution of Step 2 compounds (104 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) at rt was added TFA (1 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a precooled slurry of $NaHCO_3$ (2 g) in H_2O (2 mL). The mixture was extracted with CH_2Cl_2 (4 mL×4), and combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compound Example 5 (36 mg) and Example 5A (36 mg). LC/MS gave the correct molecular ion [$(M+H)^+$222] for the desired compounds.

EXAMPLE 6

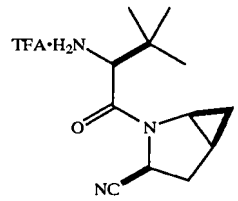
General Method A: Parallel array synthesis methods for preparation of inhibitors from commercially available amino

acids. As shown in Scheme 3, the ester 11, described in Example 1 Step 1, was saponified to the acid with LiOH in THF/HO and converted to the amide 12 by treatment with isobutyl chloroformate/NMM followed by ammonia in dioxane. The Boc protecting group was removed under acidic conditions using TFA in methylene chloride to give 13. The TFA salt was coupled to Boc-t-butylglycine using either EDAC/HOBT/DMF or EDAC/DMAP/CH2cl$_2$ to give 14. The amide was dehydrated to the nitrile 15 using $POCl_3$/imidazole in pyridine at −20° C. and finally deprotected with TFA in CH_2Cl_2 at ambient temperature to afford the target 16. SCHEME 3, GENERAL METHOD (EXAMPLES 6–27)

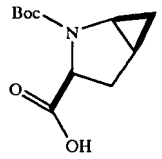
Scheme 3
General Method A (Examples 6–27)



a. LiOH in THF/H_2O or MeOH/H_2O b. i-BuOCOCl/NMM or i-BuOCOCl/TEA at -30 C or EDAC, then NH_3 in dioxane or Et_2O at RT c. TFA, CH_2Cl_2, RT d. Boc-t-butylglycine and PyBop/NMM or EDAC, DMAP, CH_2Cl_2 e. $POCl_3$, pyridine, imidazol, -20 C f. TFA, CH_2Cl_2, RT

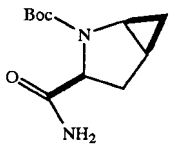


Step 1



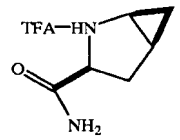
To a stirred solution of Example 1 Step 1 compound (1.40 g, 5.49 mmol) in 40 mL of a 1:1 methanol:water solution at rt was added lithium hydroxide (0.20 g, 8.30 mmol). The reaction mixture was stirred at rt for 18 h and then heated to 50° C. for 2 h. The mixture was diluted with equal volumes of ether and water (50 mL) and then acidified with $KHSO_4$ to pH 3. The milky solution was extracted with ether (3×20 mL). The combined ether layers were dried over Na_2SO_4 and evaporated. The residue was stripped from toluene (2×10 mL) and dried under reduced pressure to give the title compound as a thick syrup, 1.20 g, 96%.

Step 2



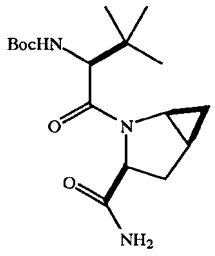
To a stirred solution of Step 1 compound (1.20 g, 5.28 mmol) in THF (20 mL) at −15° C. under nitrogen was added 4-methylmorpholine (0.71 mL, 6.50 mmol) and then isobutyl chloroformate (0.78 mL, 6.00 mmol) over 5 min. The reaction was stirred at −15° C. for 30 min, cooled to −30° C. and treated with a solution of NH_3 in dioxane (50 mL, 25 mmol). The reaction mixture was stirred at −30° C. for 30 min, warmed to rt and stirred overnight. The reaction mixture was quenched with citric acid solution (pH 4) and extracted with ether (3×50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel with EtOAc gave the Step 2 compound, 1.00 g, 84%.

Step 3



To a stirred solution of Step 2 compound (0.90 g, 4.00 mmol) in CH_2Cl_2 (3 mL) at 0° C. was added TFA (3 mL). The reaction mixture was stirred at 0° C. for 18 h. The reaction mixture was concentrated under reduced pressure to produce title compound in the form of a thick oil, 0.98 g, 100%. The oil gradually solidified upon prolonged standing.

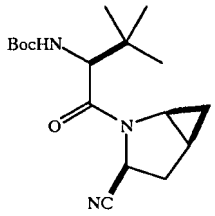
Step 4



An oven-dried 15-mL test tube was charged with Step 3 compound (56 mg, 0.22 mmol), N-tert-butoxycarbonyl-(L)-tert-leucine (53 mg, 0.23 mmol), dimethylaminopyridine (0.11 g, 0.88 mmol), and CH_2Cl_2 (4 mL). The tube was 15 sealed under nitrogen atmosphere and treated with 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (84 mg, 0.44 mmol). The mixture was placed in a shaker and vortexed overnight. The product was purified by solid phase extraction using a United Technology SCX column (2 g of sorbent

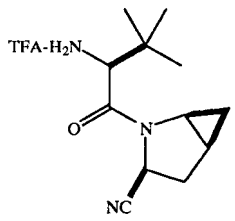
in a 6 mL column) by loading the material on a SCX ion exchange column and successively washing with CH_2Cl_2 (5 mL), 30% methanol in CH_2Cl_2 (5 mL), 50% methanol in CH_2Cl_2 (5 mL) and methanol (10 mL). The product containing fractions were concentrated under reduced pressure to give the desired amide. Further purification by reverse phase preparative column chromatography on a YMC S5 ODS 20×250 mm column gave the title compound, 50 mg (68% yield). Purification conditions: Gradient elution from 30% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 15 min. 5 min. hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time: 14 min.

Step 5



An oven-dried 15-mL test tube was charged with Step 4 compound (50 mg, 0.15 mmol), imidazole (31 mg, 0.46 mmol), and pyridine (1 mL). The tube was sealed under nitrogen atmosphere and cooled to −30° C. Slow addition of $POCl_3$ (141 mg, 88 uL, 0.92 mmol) gave after mixing a thick slurry. The tube was mixed at −30° C. for 3 h and the volatiles evaporated. The product was purified by solid phase extraction using a United Technology silica extraction column (2 g of sorbent in a 6 mL column) by loading the material on a silica column and successively washing with CH_2Cl_2 (5 mL), 5% methanol in CH_2Cl_2 (5 mL), 7% methanol in CH_2Cl_2 (5 mL) and 12% methanol in CH_2Cl_2 (10 mL). The product containing fractions were pooled and concentrated under reduced pressure to give the title compound, 46 mg, 96%.

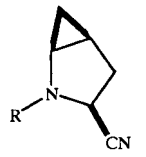
Step 6



An oven-dried 15-mL test tube was charged with Step 5 compound (0.45 mg, 0.14 mmol), CH_2Cl_2 (1 mL), and TFA (1 mL). The reaction mixture was vortexed for 40 min at rt, diluted with toluene (4 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20×250 mm column to give the Example 6 compound, 14 mg, 35%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 18 min; 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time: 10 min.

Examples 7–27 were prepared from amino acids available from commercial sources according to the procedure in Example 6.

TABLE 1



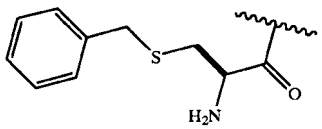
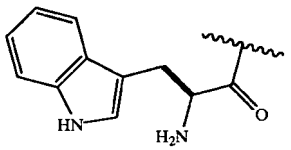
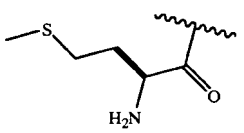
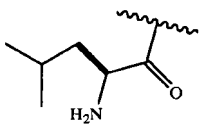
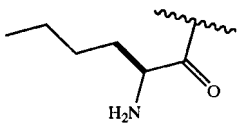
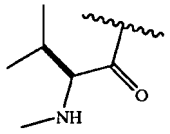
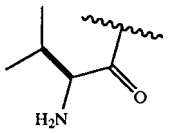
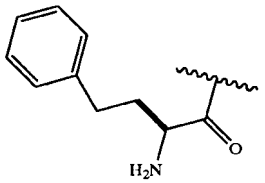
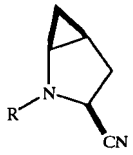
Example	R	[M + H]
7		302
8		295
9		240
10		222
11		222
12		222
13		208
14		270

TABLE 1-continued



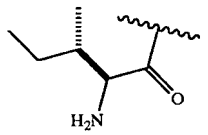
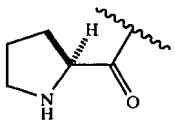
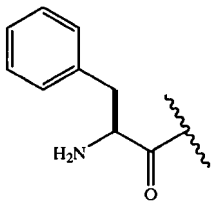
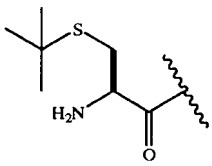
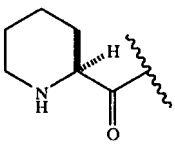
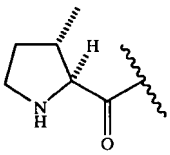
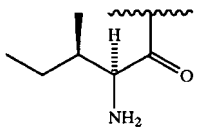
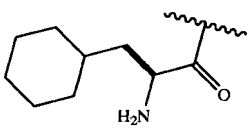
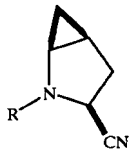
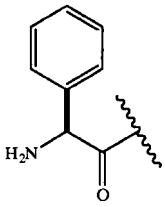
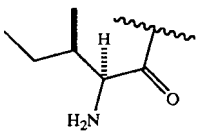
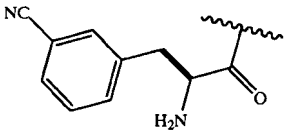
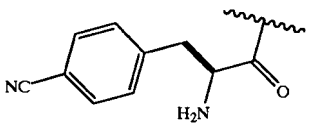
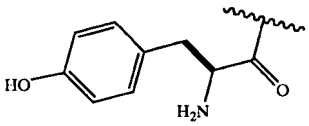
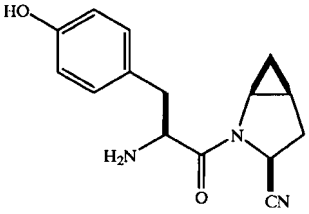
Example	R	[M + H]
15		222
16		206
17		256
18		268
19		220
20		220
21		210
22		262

TABLE 1-continued



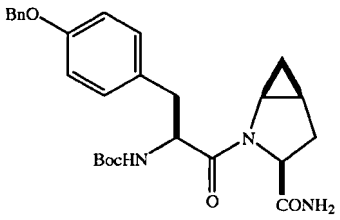
Example	R	[M + H]
23		242
24		210
25		281
26		281
27		272

EXAMPLE 27



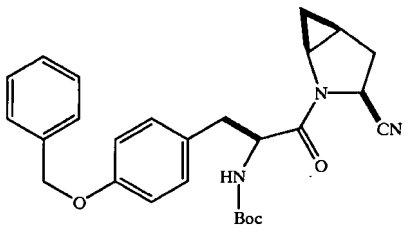
-continued

Step 1



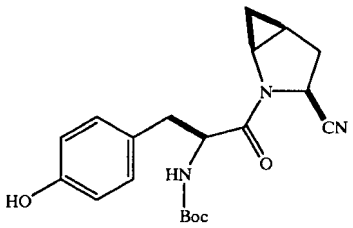
(2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt (53 mg, 0.22 mmol) was coupled to N-Boc-L-Tyrosine-benzyl ether (82 mg, 0.22 mmol) using PyBop (172 mg, 0.33 mmol) and N-methylmorpholine (67 mg, 0.66 mmol) in 4 mL CH_2Cl_2. The reaction stirred for 16 h, was taken up in EtOAc, washed with H_2O, 1N aqueous HCl, brine, then evaporated and purified by silica gel flash chromatography to give the coupled product (FAB MH+480).

Step 2



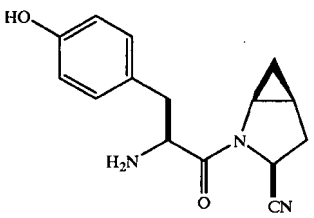
The Step 1 amide was dehydrated to the nitrile using the general method C (which follows Example 29) (FAB MH+462).

Step 3



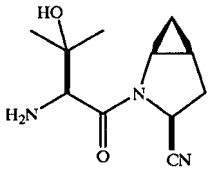
The Step 2 benzyl ether was cleaved by catalytic hydrogenolysis using 10% palladium on carbon and 1 atmosphere hydrogen gas in MeOH at rt for 1.5 h. The reaction was filtered through celite and concentrated to an oil and taken on without further purification (FAB MH+372).

Step 4



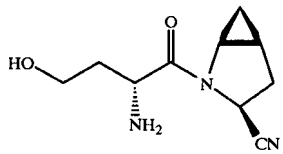
Step 3 N-[N-Boc-L-Tyrosine-]-(2S,4S,5S)-2-cyano-4,5-methano-L-prolylamide was dissolved in CH_2Cl_2 and TFA was added at rt. The reaction stirred for 1 h and was evaporated and purified by preparative HPLC as described in general method B (set out following Example 29) to afford the title compound (FAB MH+272).

EXAMPLE 28

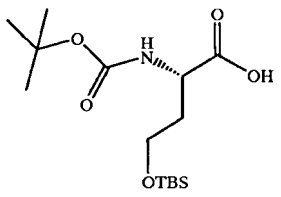


The title compound was prepared by coupling (2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt described in Example 6 Step 3 compound with N-(tert-butyloxy-carbonylhydroxyvaline. After hydroxyl protection with triethylsilyl chloride and dehydration of the amide with $POCl_3$/imidazole in pyridine and deprotection (N-terminal nitrogen and valine hydroxyl) with TFA using general method C (FAB MH+224), the title compound was obtained.

EXAMPLE 29

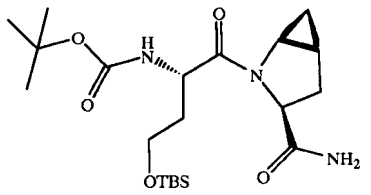


Step 1



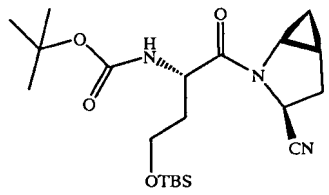
N-Boc-L-homoserine (1.20 g, 5.47 mmol) upon treatment with tert-butyldimethylsilyl chloride (1.67 g, 11.04 mmol) and imidazole (938 mg, 13.8 mmol) in THF (17 mL) was stirred as thick slurry for 48 h under N_2. The solvent was evaporated, and the crude material was dissolved in MeOH (10 mL). The resulting solution was stirred at rt for 2 h. The solvent was evaporated, and the crude material was diluted with CH_2Cl_2 (50 mL) and treated with 0.1N HCl (2×10 mL). The CH_2Cl_2 layer was washed with brine and dried over $MgSO_4$. Removal of the volatiles gave title compound as an oil (1.8 g), which was used without further purification (LC/Mass, + ion): 334 (M+H).

Step 2



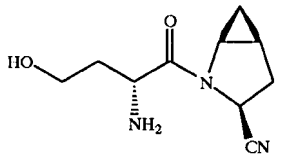
To a stirred solution of Step 1 compound (333 mg, 1.0 mmol) in 6 mL of CH_2Cl_2 was added 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (256 mg, 1.32 mmol). The solution was then stirred at rt for 30 min, followed by addition with Example 6 Step 3 amine TFA salt (160 mg, 0.66 mmol) and 4-(dimethylamino)pyridine (244 mg, 2.0 mmol). The solution was then stirred at rt overnight. The mixture was diluted with CH_2Cl_2 (5 mL) and washed sequentially with H_2O, 10% citric acid, brine, then dried over Na_2SO_4 and evaporated to give the title compound (350 mg) which was used without further purification (LC/Mass, + ion): 442 (M+H).

Step 3



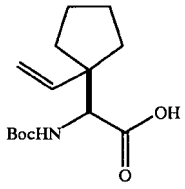
An oven-dried 10-mL round bottomed flask was charged with Step 2 compound (350 mg, 0.79 mmol), imidazole (108 mg, 1.58 mmol), pyridine (3 mL). The flask under argon was cooled to −30° C. Slow addition of $POCl_3$ (0.30 mL, 3.16 mmol) gave after mixing a thick slurry. The slurry was mixed at −30° C. for 3 h and the volatiles evaporated. Dichloromethane (5 mL) was then added and the insoluble solid was removed by filtration. The organic layer was a washed with H_2O, 10% citric acid, brine and dried over a Na_2SO_4. Removal of solvent gave crude desired nitrile (330 mg) (LC/Mass, + ion): 424 (M+H).

Step 4



Trifluoroacetic acid (3.3 mL) was added to a stirred solution of Step 3 compound (330 mg, 0.58 mmol) in 3.3 mL CH_2Cl_2. The solution was then stirred at rt for 30 min, a few drops of water were added and the mixture mixture stirred for 0.5 h. The mixture was diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20×100 mm column to give the title compound, 59 mg, 17%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/ 0.1 TFA over 15 min; 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time 10 Min. (LC/Mass, + ion): 210 (M+H).

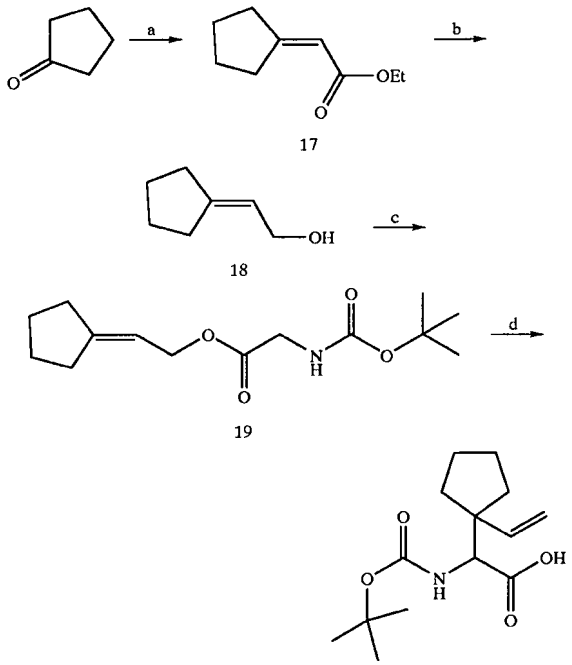
General Method B: Claisen rearrangement sequence to Boc-protected amino acids.



General method B affords the quaternary Boc-protected amino acids. Examples 30–47 contain the vinyl sidechain by coupling amino acids of which Scheme 4, compound 20 is representative. Cyclopentanone was olefinated under Horner-Emmons conditions to afford 17 which was reduced to the allylic alcohol 18 using DIBAL-H in toluene −78° C. to rt. Allylic alcohol 18 was esterified with N-Boc glycine using DCC/DMAP in CH_2Cl_2 to give 19. Glycine ester 19 was subjected to a Lewis acid mediated Claisen rearrangement by complexation with anhydrous zinc chloride and deprotonation at −78° C. with lithium diisopropylamide followed by warming to ambient temperature to afford 20.

Scheme 4

General Method B, Examples 30–47



a. Triethylphosphonoacetate, NaH, THF O C to RT b. DIBAL-H, toluene, -78 C. to RT c. N-Boc glycine, DCC, DMAP, CH_2Cl_2, RT
d. $ZnCl_2$, THF, LDA, -78 C. to RT

Step 1

Cyclopentylideneacetic Acid Ethyl Ester

To a flame-dried 500-mL round-bottomed flask containing NaH (5.10 g of a 60% dispersion in mineral oil, 128

mmol, 1.10 equiv) in 120 mL anhydrous THF at 0° C. under argon was added triethylphosphonoacetate (25.6 mL, 128 mmol, 1.10 equiv) dropwise through an addition funnel. The mixture was allowed to warm to rt, stirring for an additional 1 h. A solution of cyclopentanone (10.3 mL, 116 mmol) in 10 mL anhydrous THF was added dropwise over 20 min through an addition funnel, and the mixture was allowed to stir at rt for 2.5 h. Ether (200 mL) and water (100 mL) were then added, and the layers were separated. The organic phase was washed successively with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure, giving 17.5 g (98%) of the desired ester as a colorless oil.

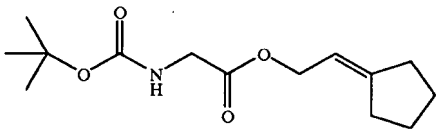
Step 2

2-Cyclopentylideneethanol

To a flame-dried 500-mL round-bottomed flask containing cyclopentylideneacetic acid ethyl ester (17.5 g, 113 mmol) in 100 mL anhydrous toluene at −78° C. under argon was added DIBAL-H (189 mL of a 1.5 M solution in toluene, 284 mmol, 2.50 equiv) dropwise over a 30 min period through an addition funnel, and the mixture was then allowed to warm to rt, stirring for 18 h. The reaction mixture was then recooled to −78° C., and quenched by the careful addition of 30 mL anhydrous MeOH. Upon warming to rt, 1 N Rochelle's salt (100 mL) was added, and the mixture was stirred 90 min. The biphasic reaction mixture was then diluted with Et_2O (200 mL) in a separatory funnel, and the layers were separated. The organic layer was then washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column E chromatography (silica gel, CH_2Cl_2/EtOAc, 10:1) gave 11.6 g (92%) of the desired allylic alcohol as a colorless oil.

Step 3

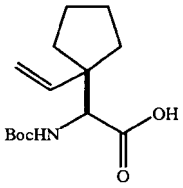
(2-Cyclopentylideneethyl)-N-(tert-Butyloxycarbonyl) glycinate



To a flame-dried 500-mL round-bottomed flask containing N-(tert-butyloxycarbonyl)glycine (13.45 g, 76.75 mmol) in 100 mL CH_2Cl_2 at rt was added Step 2 compound 48.61 g, 76.75 mmol, 1.00 equiv) in 20 mL CH_2Cl_2, followed by dicyclohexylcarbodiimide (16.63 g, mmol, 1.05 equiv) in 80 mL CH_2Cl_2. To this reaction mixture was then added 4-dimethylaminopyridine (0.94 mg, mmol, 0.10 equiv), and the mixture was allowed to stir overnight. The reaction mixture was then filtered through a medium sintered-glass funnel, rinsing with 100 mL CH_2Cl_2, and concentrated under reduced pressure. The crude product was then purified by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 1:1 gradient) to give 19.43 g (94%) of the desired glycinyl ester as a colorless oil.

Step 4

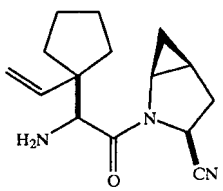
N-(tert-Butyloxycarbonyl)(1'vinylcyclopentyl)-glycine



A flame-dried 500-mL round-bottomed flask under argon was charged with $ZnCl_2$ (11.8 g, mmol, 1.20 equiv) and 20 mL toluene. The mixture was heated under vacuum with vigorous stirring to azeotrope off any traces of moisture with the distilling toluene, repeating this process (2 ×). The flask was then cooled to rt under argon, (2-cyclopentylideneethyl) N-(tert-butyloxycarbonyl)glycinate (19.36 g, 71.88 mmol) was added via cannula as a solution in 180 mL THF, and the mixture was then cooled to −78° C. In a separate flame-dried 200-mL round-bottomed flask containing diisopropylamine (26.3 mL, mmol, 2.60 equiv) in 90 mL THF at −78° C. was added n-butyllithium (71.89 mL of a 2.5 M solution in hexanes, mmol, 2.5 equiv), and the mixture was allowed to warm to 0° C. for 30 min before recooling to −78° C. The lithium diisopropylamine thus generated was then added via cannula to the $ZnCl_2$ ester mixture dropwise at a steady rate over 40 min, and the resultant reaction mixture was allowed to slowly warm to rt and stir overnight. The yellow reaction mixture was then poured into a separatory funnel, diluted with 300 mL Et_2O, and the resultant organic solution was washed successively with 200 mL 1N HCl and 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 3% MeOH in CH_2Cl_2 with 0.5% HOAc) gave 17.8 g (92%) of the desired amino acid product as a white solid. (FAB MH+270).

EXAMPLE 30

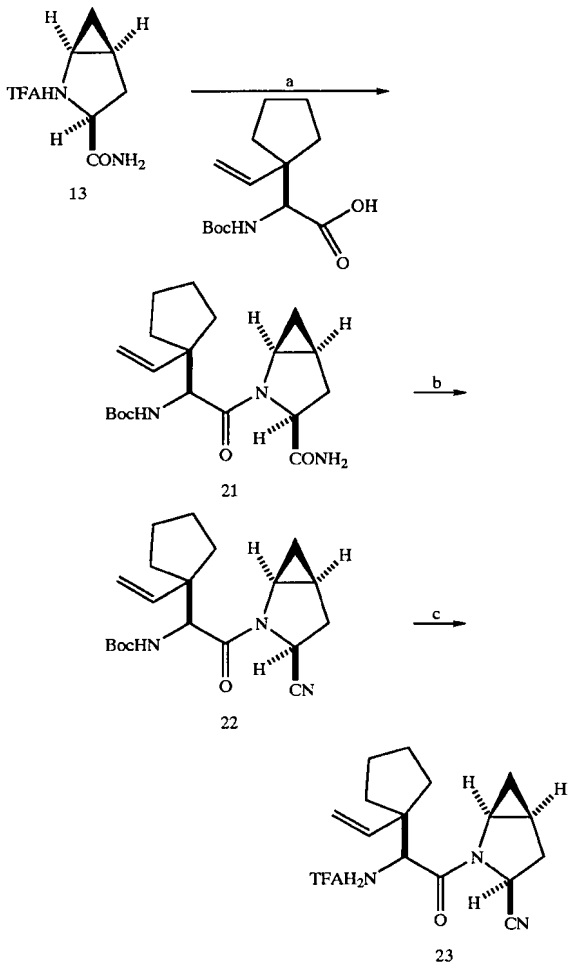
General Method C: Peptide coupling to 4,5-methano-prolinamide, amide dehydration and final deprotection.



The TFA salt of amide 13 was coupled to a variety of racemic quaternary protected amino acids using HOBT/

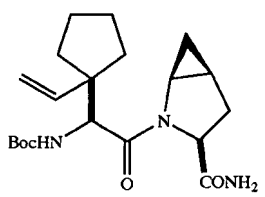
EDC in DMF at rt to give a D/L mixture of diastereomers at the N-terminal amino acid. The desired L diastereomer was chromatographically isolated either as the amide 21 or as the nitrile 22. Nitrile 22 was obtained by treatment of the amide with $POCl_3$/imidazole in pyridine at −20° C. The final target 23 was obtained by deprotection under acidic conditions using TFA in CH_2Cl_2.

Scheme 5
General Method C



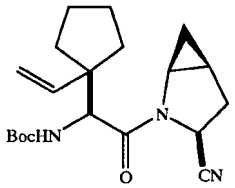
a. EDAC, HOBT, DMF b. $POCl_3$, pyridine, imidazole, -20 C c. TFA, CH_2Cl_2, RT

Step 1



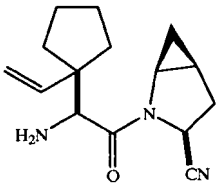
Example 6 Step 3 compound (877 mg, 3.65 mmol) and N-Boc cyclopentylvinylamino acid, described in Step 4 of general method B (1.13 g, 4.20 mmol) were dissolved in 20 mL anhydrous DMF, cooled to 0° C. and to this mixture was added EDAC (1.62 g, 8.4 mmol), HOBT hydrate (2.54 g, 12.6 mmol, and TEA (1.27 g, 12.6 mmol) and the reaction was allowed to warm to rt and stirred for 24 h. The reaction mixture was taken up in EtOAc (100 mL), washed with H_2O (3×20 mL), dried (Na_2SO_4), and purified by silica gel flash column chromatography (100% EtOAc) to give 1.38 g (86%) of Step 1 compound (MH+, 378).

Step 2



Step 1 compound (1.38 g, 3.65 mmol) and imidazole (497 mg, 7.30 mmol) were dried by toluene azeotrope (5 mL×2), dissolved in 10 mL anhydrous pyridine, cooled to −30° C. under nitrogen gas and $POCl_3$ (2.23 g, 14.60 mmol) was added by syringe. The reaction was complete after 1 h and was evaporated to dryness and the remainder purified by two sequential flash column chromatographies over silica gel. The first column (100% EtOAc) was used to isolate the mixture of diastereomers (1.15 g, 88%) from the by-products of the reaction. The second column (gradient of 25% EtOAC/hexanes to 50% EtOAc/hexanes) was run to resolve the mixture of diastereomers and provided 504 mg of the desired Step 2 nitrile (MH+360).

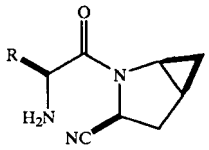
Step 3



Step 2 compound (32 mg, 0.09 mmol) was dissolved in 1 mL of CH_2Cl_2 and 1 mL of TFA was added and the reaction stirred for 30 min at rt and was evaporated to dryness. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20×250 mm column to give 12 mg of the TFA salt (lyophilized from water or isolated after evaporation of eluent and trituration with ether) the title compound. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 18 min; 5 min. hold at 90% ter/0.1 trifluoroacetic acid. Flow rate: 20 Detection wavelength: 220.

Examples 30–39 were prepared by the methods outlined in General Method B and General Method C starting from cyclopentanone, cyclobutanone, cyclohexanone, cycloheptanone, cyclooctanone, cis-3,4-dimethylcylopentanonc, and 4-pyranone, cyclopropaneethylhemiacetal, acetone, and 3-pentanone respectively.

TABLE 2



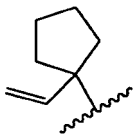
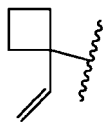
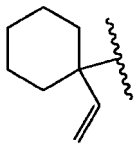
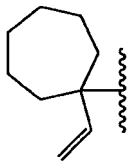
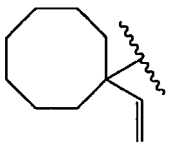
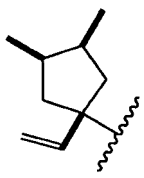
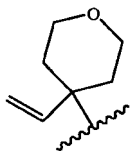
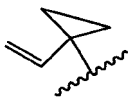
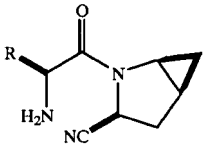
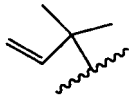
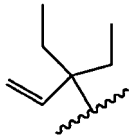
Example	R	MS [M + H]
30		260
31		246
32		274
33		288
34		302
35		288
36		276
37*		232

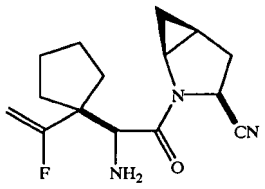
TABLE 2-continued



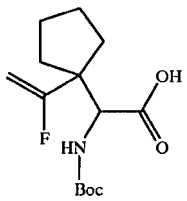
Example	R	MS [M + H]
38		234
39		262

*Step 3 compound was prepared by the method described in Tetrahedron Letters 1986, 1281–1284.

EXAMPLE 40

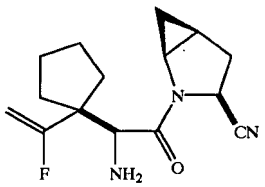


Step 1



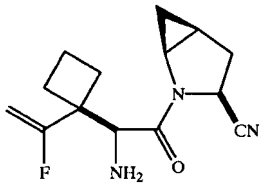
Step 1 compound was prepared employing general method B starting from cyclopentanone and 2-fluoro-triethylphos-phonoacetate instead of triethylphosphonoacetate.

Step 2

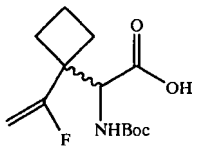


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C [MS (M+H) 278].

EXAMPLE 41

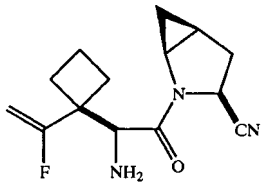


Step 1



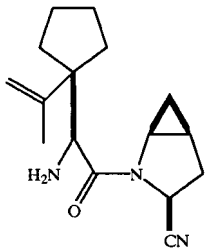
Step 1 compound was prepared employing general method B starting from cyclobutanone and 2-fluoro-triethylphos-phonoacetate instead of triethylphosphonoacetate.

Step 2

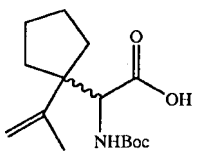


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 264.

EXAMPLE 42

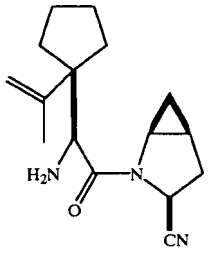


Step 1



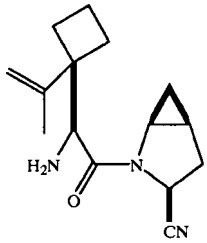
Step 1 compound was prepared employing general method B starting from cyclopentanone and triethylphosphono propionate instead of triethylphosphonoacetate.

Step 2

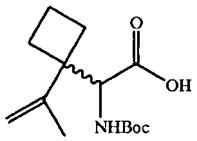


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 274

EXAMPLE 43

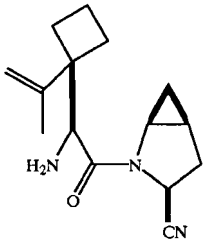


Step 1



Step 1 compound was prepared employing general method B starting from cyclobutanone and triethylphosphono propionate instead of triethylphosphonoacetate.

Step 2

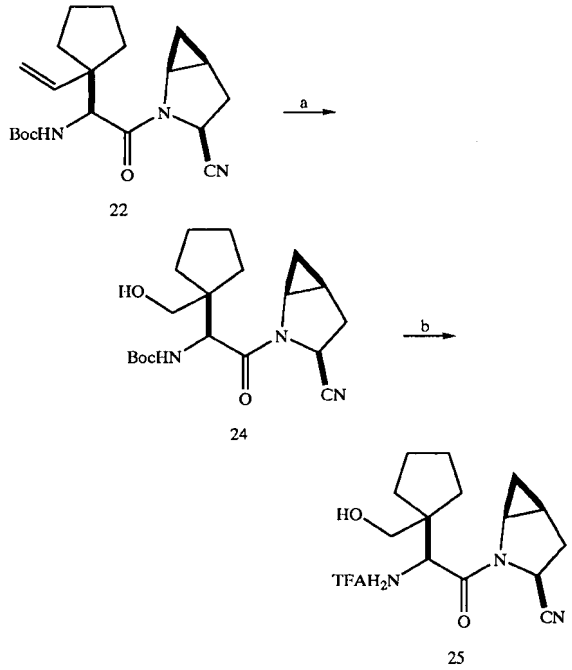


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 260.

EXAMPLE 44

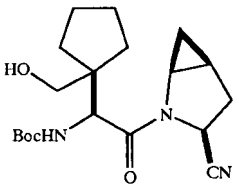
General Method D: Oxidative cleavage of vinyl substituent by ozonolysis. The protected cyclopentylvinyl nitrile 22 was treated with ozone for 6–8 min and subjected to a reductive quench with sodium borohydride to furnish the hydroxymethyl analog 24 directly. This compound was deprotected under acidic conditions with TFA in CH_2Cl_2 at 0° C. to give the target compound 25.

Scheme 6
General Method D, Examples 44, 46, 48



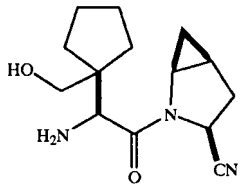
a. O_3, MeOH:CH_2Cl_2, 10:4, -78 C; then $NaBH_4$, -78 C to 0 C, 79%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C.

Step 1



Cyclopentylvinyl compound prepared in Step 2 of general method C (1.28 g, 3.60 mmol) was dissolved in 56 mL of a 2:5 mixture of CH_2Cl_2:methanol, cooled to −78° C. and was treated with a stream of ozone until the reaction mixture took on a blue color, at which time, $NaBH_4$ (566 mg, 15.0 mmol, 4.2 equiv) was added and the reaction was warmed to 0° C. After 30 min, the reaction was quenched with 2 mL saturated aqueous $NaHCO_3$ and then warmed to rt. The reaction mixture was evaporated to dryness and taken up in EtOAc. A small amount of water was added to dissolve the inorganics and the layers separated. The EtOAc layer was dried (Na_2SO_4), filtered and evaporated to an oil that was purified by flash column chromatography on silica gel with EtOAc to give 922 mg (71%) of Step 1 compound. MS(M+H)364.

Step 2

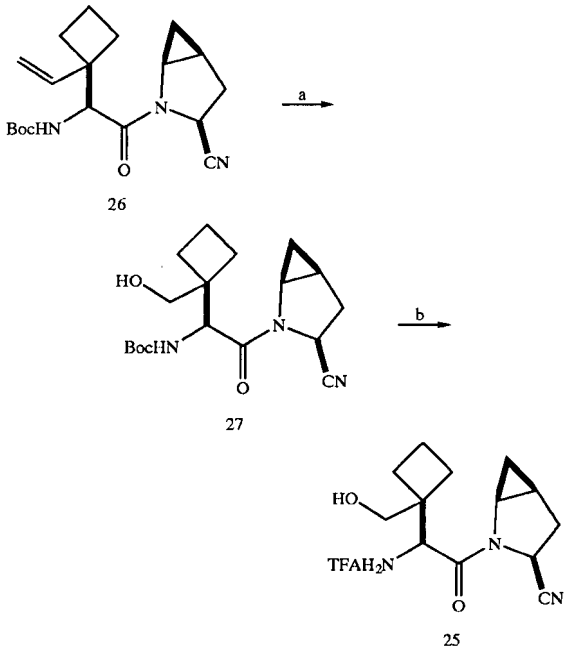


Step 1 compound (900 mg, 2.48 mmol) was dissolved in 60 mL of CH_2Cl_2, cooled to 0° C. and treated with 20 mL of freshly distilled TFA. The reaction was complete in 80 min and the mixture was evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30x100 mm, 18 minute gradient 80% Solv A:Solv B to 100% Solv B, Solvent A=10% MeOH-90%H_2O-0.1% TFA, Solvent B=90% MeOH-10% H_2O -0.1% TFA, collected product from 5.1–6.5 min) to give, after lyophillization from water, 660 mg (71%) of title compound, TFA salt as a white lyophillate. (MH+264).

EXAMPLE 45

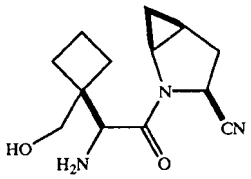
General Method E: Oxidative cleavage of vinyl substituent by osmium tetroxide-sodium periodate followed by sodium borohydride reduction to alcohol. The cyclobutylolefin 26 was treated with osmium tetroxide and sodium periodate in THF:water, 1:1, and the intermediate aldehyde was isolated crude and immediately reduced with sodium borohydride to give 27 in 56% yield. Standard deprotection conditions using TFA afforded the target compound 28.

Scheme 7
General Method E, Examples 45, 47

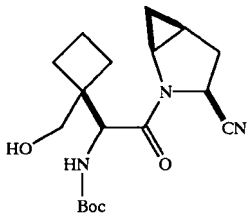


a. OsO_4, THF:H_2O; 1:1; $NaIO_4$; workup, then $NaBH_4$, MeOH, RT. 56%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C to RT.

-continued

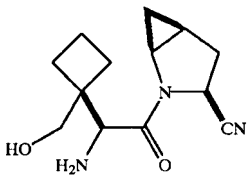


Step 1



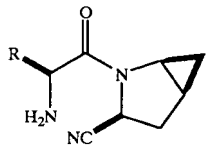
N-Boc protected cyclobutylvinyl compound (Example 31, prepared by general method C) (0.16 g, 0.46 mmol) was dissolved in 10 mL of a 1:1 mixture of THF:water and treated with OSO_4 (12 mg, catalyst) and $NaIO_4$ (0.59 g, 2.76 mmol, 6 equiv). After 2 h, the reaction mixture was diluted with 50 mL of ether and 10 mL of water. The layers were equilibrated and the organic fraction was washed one time with $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give a dark oil. The oil was diluted with 10 mL of methanol and treated with $NaBH_4$ (0.08 g, 2.0 mmol). The mixture turned very dark and after 30 min was diluted with ether and the reaction was quenched with aqueous $NaHCO_3$ solution. The mixture was equilibrated and layers separated. The organic fraction was washed with solutions of $NaHCO_3$ and 0.1 M HCl. The organics were dried ($MgSO_4$) and concentrated to give 90 mg (56%) of the Step 1 compound as a dark oil.

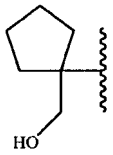
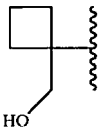
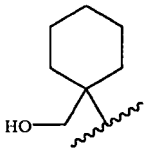
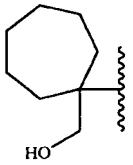
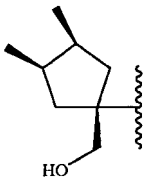
Step 2



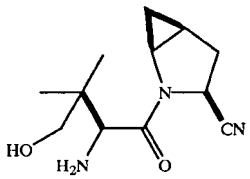
Step 1 compound (90 mg, 0.26 mmol) was dissolved in 3 mL of CH_2Cl_2, cooled to 0° C. and treated with 3 mL of freshly distilled TFA. The reaction was complete in 80 min and evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30x100 mm, 10 minute gradient 100%A to 100% Solvent A=10% MeOH-90%H2OO-0.1% TFA, Solvent B=MeOH-10% H_2O-0.1% TFA, to give, after removal of water, 50 mg (60%) of title compound. (MH+250).

TABLE 3

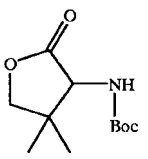


Example	R	Method of Preparation	[M + H]
44		Ozonolysis/ borohydride	264
45		Osmium/periodate/ borohydride	250
46		Ozonolysis/ borohydride	278
47		Osmium/periodate/ borohydride	292
48		Ozonolysis/ borohydride	292

EXAMPLE 49



Step 1

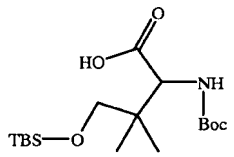


Part A. A 50-mL flask was charged with dihydro-4,4-dimethyl-2,3-furandione (5.0 g, 39.0 mmol), acetic acid (10 mL), sodium acetate (3.82 g, 39.0 mmol) and hydroxylamine hydrochloride (2.71 g, 39.0 mmol). The reaction mixture was stirred for 2 h at rt and concentrated under reduced pressure to remove most of the acetic acid. The remainder was poured into water (100 mL) and the aqueous phase extracted with EtOAc (3×40 mL). The organics were dried over Na_2SO_4 and concentrated to a colorless oil which solidified on standing.

Part B. A 200-mL round bottomed flask was charged with Part A solid (@ 39 mmol) and diluted with 80 mL of ethanol and 39 mL of 2N HCl (78 mmol). The mixture was treated with 1.0 g of 5% Pd/carbon and the mixture degassed. The flask was placed under an atmosphere of H_2 for 8 h. The mixture was filtered through celite and the filtrate concentrated to an off white solid.

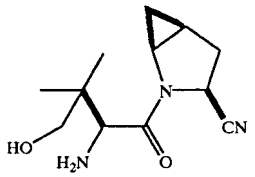
Part C. A 250-mL round bottomed flask was charged with Part B solid and diluted with THF (50 mL) and water (15 mL). The mixture was treated with di-tert-butyldicarbonate (12.7 g, 117 mmol) and sodium bicarbonate (10.0 g, 117 mmol). After 4 h of stirring the mixture was diluted with 50 mL of ether and 50 mL of water. The layers were separated and the organic fraction dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel with 30% EtOAc in hexanes to give 2.00 g (22% overall) of Step 1 compound as a white solid.

Step 2



To a stirred solution of Step 1 compound (1.00 g, 3.80 mmol) in THF (20 mL) at rt under nitrogen was added LiOH hydrate (0.16 g, 3.80 mmol) and then water (5 mL). The reaction was stirred at 40° C. for 0.5 h and then cooled to rt. The mixture was concentrated to dryness and the remainder was stripped from THF (2×), toluene (2×) and THF (1×). The remaining glass was diluted with 5 mL of THF and treated with imidazole (0.63 g, 9.19 mmol) followed by t-butyl-dimethylsilyl chloride (1.26 g, 8.36 mmol). The reaction was stirred overnight and quenched with 10 mL of methanol. After 1 h of stirring the mixture was concentrated. An additional portion of methanol was added and the mixture concentrated. The oil was diluted with ether and 0.1 N HCl (pH 2). The layers were equilibrated and aqueous drawn off. The organic fraction was dried over $MgSO_4$ and concentrated to give 1.25 g (83%) of Step 2 compound as a colorless glass.

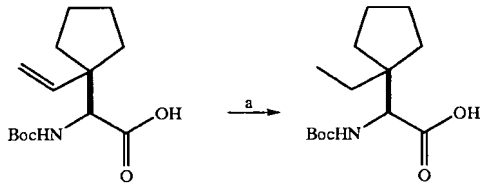
Step 3



The Title compound was prepared by the peptide coupling of Step 2 carboxylic acid with Example 6 Step 3 amine, followed by dehydration and deprotection as outlined in General Method C. MS (M+H) 238.

General Method F: Catalytic Hydrogenation of vinyl substituent. As shown in Scheme 8, the protected vinyl substituted amino acid 20 was transformed to the corresponding saturated analog 29 by catalytic hydrogenation using 10% Pd/C and hydrogen at atmospheric pressure.

Scheme 8
General Method F, Examples 50–56



20 29

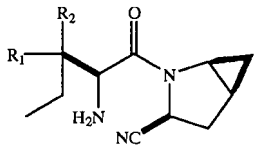
a. 10% Pd/C, 1atm H_2, MeOH, 12h, 100%

Step 1.

The N-(tert-Butyloxycarbonyl)(1'vinylcyclopentyl) glycine (2.23 g, 8.30 mmol) was dissolved in 50 mL MeOH and placed in a hydrogenation vessel purged with argon. To this mixture was added 10% Pd-C (224 mg, 10% w/w) and the reaction stirred under 1 atm H_2 at rt for 12 h. The reaction was filtered through celite and concentrated and purified by flash column chromatography on silica gel with 1:9 methanol:CH_2Cl_2 to give the Step 1 compound as a glass. (FAB MH+272)

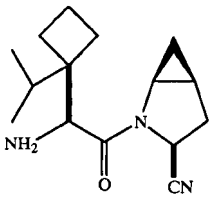
Examples 50–56 were prepared by the peptide coupling of amino acids (where the vinyl substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C.

TABLE 4



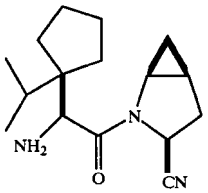
Example	R1, R2	MS [M + H]
50	Cyclopentyl	262
51	cyclobutyl	248
52	cycloheptyl	290
53	4-pyranyl	278
54	methyl, methyl	236
55	ethyl, ethyl	264
56	methyl, ethyl	250

EXAMPLE 57



The title compound in Example 57 was prepared by the peptide coupling of the isopropyl cyclobutane amino acid (where the olefin substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C.

EXAMPLE 58

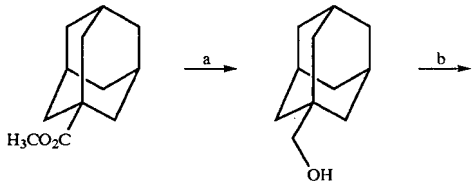


The title compound in Example 58 was prepared by the peptide coupling of the isopropyl cyclopentane amino acid (where the olefin substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C. MS (M+H) 276

General Method G: L-Amino acids synthesized by Asymmetric Strecker Reaction. Commercially available adamantyl carboxylic acid was esterified either in MeOH with HCl at reflux or using trimethylsilyldiazomethane in Et_2O/methanol to give 30. The ester was reduced to the alcohol 31 with LAH in THF and then subjected to a Swern oxidation to give aldehyde 32. Aldehyde 32 was transformed to 33 under asymmetric Strecker conditions with KCN, $NaHSO_3$ and R-(−)-2-phenylglycinol. The nitrile of 33 was hydrolyzed under strongly acidic conditions using 12M HCl in HOAc to give 34. The chiral auxiliary was removed by catalytic reduction using Pearlman's catalyst in acidic methanol under 50 psi hydrogen to give 35 and the resulting amino group was protected as the t-butylcarbamate to give 36.

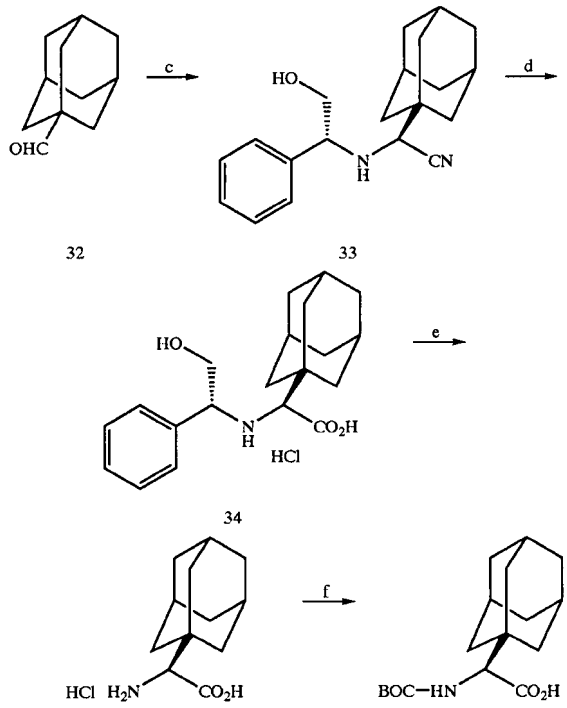
Scheme 9

General Method G, Examples 59–64



30 31

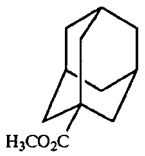
-continued



32 33 34 35 36

a. LAH, THF, 0 C TO RT, 96% b. ClCOCOCl, DMSO, CH_2Cl_2, -78 C, 98% c. R-(-)-2-Phenylglycinol, $NaHSO_3$, KCN d. 12M HCl, HOAc, 80 C, 16h, 78% e. 20% $Pd(OH)_2$, 50 psi H_2, MeOH:HOAc, 5:1 f. $(Boc)_2O$, K_2CO_3, DMF, 92%, 2 steps

Step 1



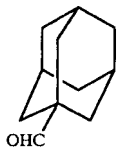
Adamantane-1-carboxylic acid (10.0 g, 55 mmol, 1 equiv) was dissolved in a mixture of Et_2O (160 mL) and MeOH (40 mL), and was treated with trimethylsilyl diazomethane (2.0 M in hexane, 30 mL, 60 mmol, 1.1 equiv) and stirred at rt for 3 h. The volatiles were then removed by rotary evaporation and the product purified by flash column chromatography on silica gel (5×15 cm) with 40% CH_2Cl_2/hexanes to give the product as a white crystalline solid (10.7 g, 100%).

Step 2

Step 1 compound (10.7 g, 0.055 mmol, 1 equiv) was dissolved in anhydrous THF (150 mL) under argon and was treated with a solution of $LiAlH_4$ (1 M in THF, 69 mL, 69 mmol, 1.25 equiv). After stirring at rt for 1.5 h, the reaction was cooled to 0° C. and quenched sequentially with H_2O (5.1 mL), 15% aq NaOH (5.1 mL), and H_2O (10.2 mL). After stirring at rt for 15 min, the slurry was vacuum filtered, and the solids washed with EtOAc (2×100 mL). The filtrate

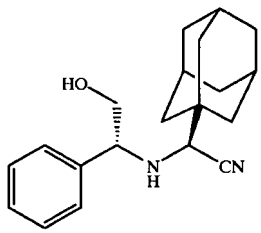
was concentrated by rotary evaporation and the resulting solid purified by flash column chromatography on silica gel (5×15 cm) with 10% EtOAc/CH_2Cl_2. This afforded the Step 2 product as a white solid (8.74 g, 96%).

Step 3



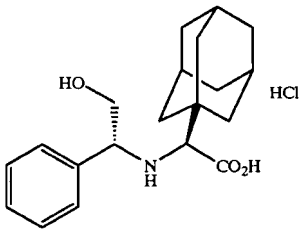
An oven-dried 3-neck flask equipped with 125-mL addition funnel was charged with anhydrous CH_2Cl_2 (150 mL) and anhydrous DMSO (10.3 mL, 0.145 mol, 2.5 equiv) under argon atmosphere and cooled to −78° C. Slow dropwise addition of oxalyl chloride (6.7 mL, 0.0768 mol, 1.32 equiv) followed by stirring for 15 min provided an activated DMSO adduct. This was treated with a solution of Step 2 compound (9.67 g, 58.2 mmol, 1 equiv) in dry CH_2Cl_2 (75 mL) and the reaction allowed to stir for 1 h. The resulting white mixture was then treated dropwise with triethylamine (40.5 mL, 0.291 mol, 5 equiv). After 30 min, the cooling bath was removed, and the reaction quenched sequentially with cold 20% aq KH_2PO_4 (25 mL) and cold H_2O (150 mL). After stirring at rt for 15 min the mixture was diluted with Et_2O (400 mL)and the layers were separated. The organics were washed organic with cold 10% aq KH_2PO_4 (3×150 mL) and satd aq NaCl (100 mL). The organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography on silica gel (5×10 cm) with CH_2Cl_2 to give the Step 3 compound as a white solid (9.40 g, 98%).

Step 4



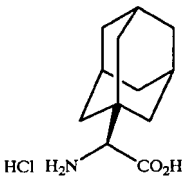
Step 3 compound (9.40 g, 57 mmol, 1 equiv) was suspended in H_2O (145 mL) and cooled to 0° C. The mixture was treated with $NaHSO_3$ (5.95 g, 57 mmol, 1 equiv), KCN (4.0 g, 59 mmol, 1.04 equiv), and a solution of (R)-(−)-phenylglycinol (8.01 g, 57 mmol, 1 equiv) in MeOH (55 mL). The resulting mixture was stirred at rt for 2 h, then refluxed for 16 h. The mixture was cooled to rt, and 200 mL of EtOAc added. After mixing for 15 min the layers were separated. The aqueous fraction was extracted with EtOAc. The combined EtOAc extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated. The product was purified by flash column chromatography on silica gel (6.4×20 cm) with 20% EtOAc/hexanes to give the desired (R,S) product as a white solid (11.6 g, 37.4 mmol, 65%): MS m/e 311 $(M+H)^+$.

Step 5



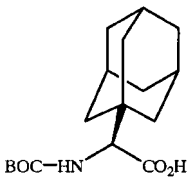
The Step 4 nitrile (5.65 g, 18 mmol) was heated in conc. HCl (120 mL) and HOAc (30 mL) at 80° C. for 18 h, at which time the reaction was cooled in an ice bath. Vacuum filtration of the resulting precipitate afforded the desired product as a white solid (5.21 g, 14 mmol, 78%). MS m/e 330 $(m+H)^+$.

Step 6



The Step 6 compound (5.21 g, 14 mmol) was dissolved in MeOH (50 mL) and HOAc (10 mL), and hydrogenated with H_2 (50 psi) and Pearlman's catalyst (20% $Pd(OH)_2$, 1.04 g, 20% w/w) for 18 h. The reaction was filtered through a PTFE membrane filter and the catalyst washed with MeOH (3×25 mL). The filtrate was concentrated by rotary evaporation to afford a white solid. The product was used in Step 7 without further purification.

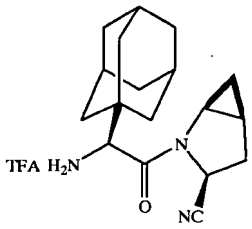
Step 7



The crude Step 6 compound (@ 14 mmol) was dissolved in anhydrous DMF (50 mL) under argon and treated with K_2CO_3 (5.90 g, 42 mmol, 3 equiv) and di-tert-butyldicarbonate (3.14 g, 14 mmol, 1 equiv) under argon at rt. After 19 h, the DMF was removed by rotary evaporation (pump) and the residue dried further under reduced pressure. The residue was mixed with H_2O (100 mL) and Et_2O (100 mL), the layers separated, and the alkaline aqueous with Et_2O (2×100 mL) to remove the by-product from the hydrogenolysis step. The aqueous was cooled to 0° C., diluted with EtOAc (200 mL), and stirred vigorously while care

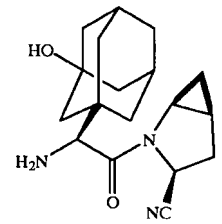
fully acidifying the aqueous to pH 3 with 1N aq HCl. The layers separated and the aqueous extracted with EtOAc (100 mL). The combined EtOAc extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and the filtrate concentrated by rotary evaporation. The residue was purified by SiO_2 flash column (5×12 cm) with 5% MeOH/CH_2Cl_2+0.5% HOAc. The product was chased with hexanes to afford the product as a white foam (4.07 g, 13 mmol, 92%): MS m/e 310 $(m+H)^+$.

EXAMPLE 59

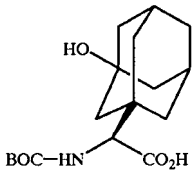


The title compound in Example 59 was prepared by the peptide coupling of the Step 7 compound in general method G followed by dehydration and deprotection as described in general method C.MS m/e 300 $(m+H)^+$.

EXAMPLE 60

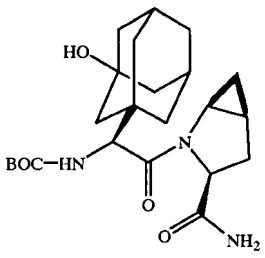


Step 1



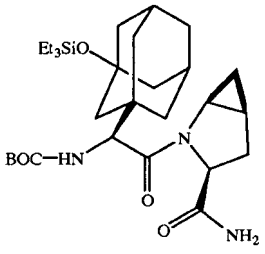
A solution of $KMnO_4$ (337 mg, 2.13 mmol, 1.1 equiv) in 2% aq KOH (6 mL) was heated to 60° C. and Step 7 compound in general method G (600 mg, 1.94 mmol, 1 equiv) was added in portions, and heating increased to 90° C. After 1.5 h, the reaction was cooled to 0° C., EtOAc (50 mL) was added, and the mixture was carefully acidified to pH 3 with 1N HCl. The layers were separated and the aqueous was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (3.8×15 cm) with 2% (200 mL), 3% (200 mL), 4% (200 mL), and 5% (500 mL) MeOH/CH_2Cl_2+0.5% HOAc. After isolation of the product, the material was chased with hexanes to afford a white solid (324 mg, 51%): MS m/e 326 $(m+H)^+$.

Step 2



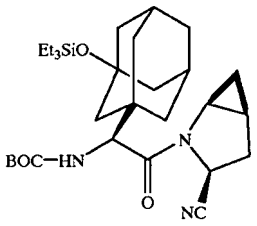
The Step 1 compound (404 mg, 1.24 mmol, 1 equiv) was dissolved in anhydrous DMF (10 mL) under argon and cooled to 0° C. The following were added in order: Example 6 Step 3 salt (328 mg, 1.37 mmol, 1.1 equiv), HOBT (520 mg, 3.85 mmol, 3.1 equiv), EDAC (510 mg, 2.61 mmol, 2.1 equiv), and TEA (0.54 mL, 3.85 mmol, 3.1 equiv). The reaction mixture was allowed to warm to rt overnight and the DMF removed by rotary evaporation (pump). The remainder was dried further under vacuum. The residue was dissolved in EtOAc (100 mL), washed with satd aq $NaHCO_3$ (50 mL) and satd aq NaCl (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation. The product was purified flash column chromatography on silica gel (3.8×15 cm) with a gradient of 6% (200 mL), 7% (200 mL), and 8% (500 mL) MeOH/CH_2Cl_2 to give the product as a white solid (460 mg, 1.06 mmol, 85%): MS m/e 434 $(m+H)^+$.

Step 3



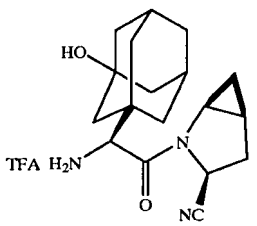
The Step 2 compound (95 mg, 0.22 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) under argon and cooled to −78° C. The mixture was treated with diisopropylethylamine (65 μL, 0.37 mmol, 1.7 equiv), and triethylsilyl triflate (75 μL, 0.33 mmol, 1.5 equiv), and stirred at 0° C. for 1.5 h. The reaction was mixed with MeOH (0.5 mL), silica gel (200 mg) and H_2O (2 drops) and stirred at rt for 18 h. The solvent was removed by rotary evaporation and the residue purified flash column chromatography on silica gel(2.5×10 cm) with 4% MeOH/CH_2Cl_2 to afford the product (92 mg, 0.17 mmol, 77%): Ms m/e 549 $(m+H)^+$.

Step 4



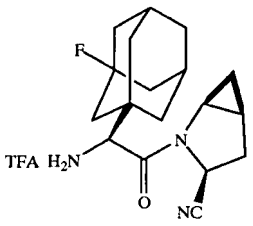
The Step 3 compound (90 mg, 0.16 mmol, 1 equiv) was dissolved in anhydrous pyridine (2 mL) under argon and cooled to −30° C. Treatment with imidazole (24 mg, 0.35 mmol, 2.1 equiv) and phosphorous oxychloride (66 μL, 0.67 mmol, 4.1 equiv), and continued stirring at −30° C. for 45 min gave a thick slurry. Volatiles were by rotary evaporation and the cake dried further under reduced pressure. The product was purified by flash column chromatography on silica gel (2.5×10 cm) with 7% EtOAc/CH_2Cl_2 to afford the product as a white foam (76 mg, 87%): MS m/e 530 $(m+H)^+$

Step 5



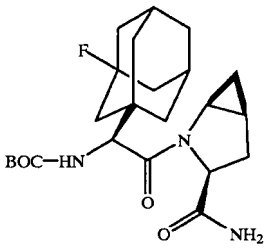
The Step 4 compound (76 mg, 0.14 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0° C. and treated with TFA (1 mL) and H_2O (2 drops) and stirred for 1.5 hr at 0° C. The solvents were removed by rotary evaporation and the residue was chased with toluene (5 mL) and dried under reduced pressure. Trituration with Et_2O afforded the title compound as a white solid (54 mg, 88%): MS m/e 316 $(m+H)^+$.

EXAMPLE 61



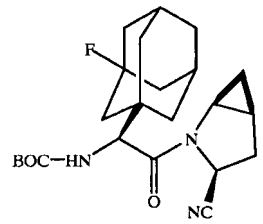
-continued

Step 1



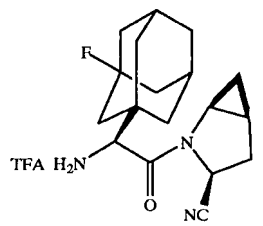
An oven-dried flask purged with argon was charged with anhydrous CH_2Cl_2 (3 mL) and cooled to −78° C. Treatment with diethylaminosulfur trifluoride (DAST, 60 μL, 0.45 mmol, 1.5 equiv), followed by a solution of the Example 60 Step 2 compound (131 mg, 0.30 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL). After 15 min, the reaction was poured into a separatory funnel containing satd aq $NaHCO_3$ (25 mL) and the layers were separated. The aqueous fraction was extracted with CH_2Cl_2 (25 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (2.5×10 cm) with 5% MeOH/CH_2Cl_2 to give Step 1 compound (124 mg, 0.29 mmol, 94%): MS m/e 436 $(m+H)^+$.

Step 2



The fluorinated amide from Step 1 (161 mg, 0.37 mmol, 1 equiv) was dissolved in anhydrous pyridine (4 mL) under argon and cooled to −30° C. The mixture was treated with imidazole (54 mg, 0.77 mmol, 2.1 equiv) and phosphorous oxychloride (143 μL, 1.52 mmol, 4.1 equiv) and stirred at −30° C. for 40 min. The solvent was removed by rotary evaporation and dried further under reduced pressure. The product was purified by flash column chromatography on silica gel (2.5×10 cm) with 5% EtOAc/CH_2Cl_2 to give the Step 2 compound as a white foam (126 mg, 82%): MS m/e 418 $(m+H)^+$.

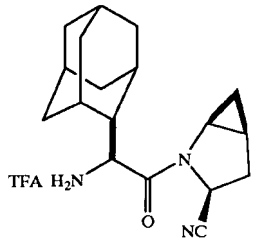
Step 3



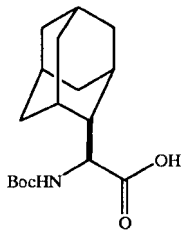
The Step 2 compound (125 mg, 0.30 mmol) was dissolved in TFA/CH_2Cl_2 (1:1 v/v, 2 mL), and stirred at rt. After 30 min, the solvents were removed by rotary evaporation, the

remainder was chased with toluene (2×5 mL), and the solid dried under reduced pressure. Trituration with Et_2O afforded the title compound as a white solid (93 mg, 0.21 mmol, 72%): MS m/e 318 $(m+H)^+$.

EXAMPLE 62

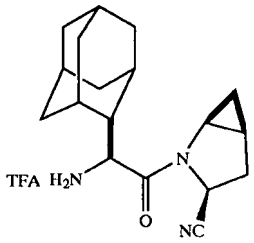


Step 1



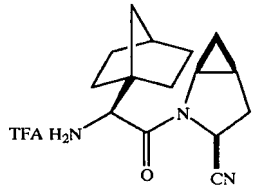
The Step 1 compound was prepared beginning with 2-adamantanal and elaborated to the homochiral Boc-amino acid by an asymmetric Strecker synthesis according to general method G.

Step 2



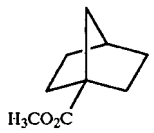
The title compound in Example 62 was prepared by the peptide coupling of the 2-adamantyl amino acid described in Step 1 followed by dehydration and deprotection as described in general method C.MS (M+H) 300.

EXAMPLE 63

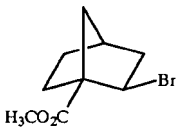


-continued

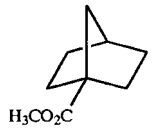
Step 1



An oven-dried flask equipped with a condenser and drying tube was charged with norbornane-2-carboxylic acid (4.92 g, 35 mmol, 1 equiv) and treated with bromine (2.1 mL, 41 mmol, 1.15 equiv) and phosphorous trichloride (0.153 mL, 1.8 mmol, 0.05 equiv). The mixture was heated at 85° C. for 7 h protected from light. Additional bromine (0.4 mL, 7.8 mmol, 0.22 equiv) was added with continued heating for 1 h. The mixture was cooled to rt, and Et_2O (100 mL) was added. The mixture was washed with 10% aq $NaHSO_3$ (50 mL), H_2O (2×50 mL), and brine (25 mL). The ether fraction was dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The product was purified by flash column chromatography on silica gel (5×15 cm) with 2% to 4% MeOH/CH2Cl_2+0.5% HOAc. The product was chased with hexanes to remove residual HOAc. The isolated material consists of two inseparable materials (4.7 g), which was used without further purification in the next step.

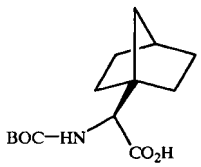


The crude product from above, exo-2-bromonorbornane-1-carboxylic acid (4.7 g, impure) in Et_2O (80 mL) and MeOH (20 mL), was mixed with trimethylsilyldiazomethane (2.0 M in hexane, 11.8 mL, 23.6 mol), and stirred at rt for 1 h. Solvent was removed by rotary evaporation, and purification of the oil by flash column chromatography on silica gel (5×18 cm) with a gradient of CH_2Cl_2/hexanes (600 mL each of 20% and 30%) followed by CH_2Cl_2 afforded the product as a white solid (3.97 g, 0.017 mol, 79% for 2 steps): MS m/e 233/235 $(m+H)^+$.



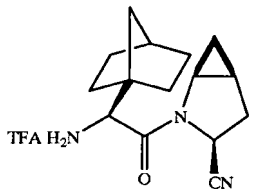
Methyl exo-2-bromonorbornane-1-carboxylate (2.0 g, 8.58 mmol, 1 equiv) was dissolved in anhydrous THF (50 mL) in an oven-dried 3-neck flask equipped with a condenser, and purged with argon. The mixture was treated with AIBN (288 mg, 1.71 mmol, 0.2 equiv) and tributyltin hydride (3.6 mL, 12.87 mmol, 1.5 equiv), and then heated to reflux for 2 h. The flask was cooled to rt, and the THF was removed by rotary evaporation to give the crude product. The product was purified by flash column chromatography on silica gel(5×10 cm) with 5% EtOAc/hexanes. The resulting material was used in the next step without further purification.

Step 2



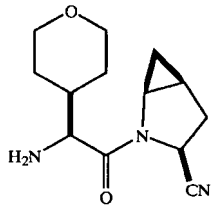
The Step 1 compound was prepared beginning with 1-norbonyl methyl carboxylate and elaborated to the homochiral Boc amino acid by an asymmetric Strecker synthesis according to general method G.

Step 3

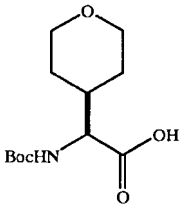


The title compound in Example 63 was prepared by the peptide coupling of the 1-norbonyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 260.

EXAMPLE 64

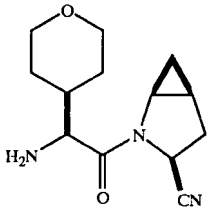


Step 1



The Step 1 compound was prepared beginning with 4-formylpyran and elaborated to the homochiral Boc amino acid by an asymmetric Strecker synthesis according to general method G.

Step 2

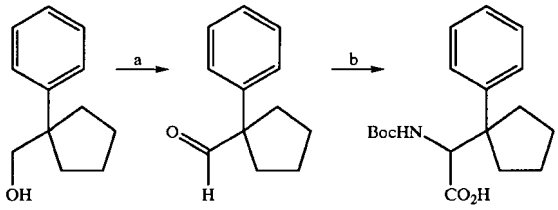


The title compound in Example 64 was prepared by the peptide coupling of the 4-pyranyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 250.

General Method H: Strecker Synthesis of Racemic Amino Acids.

Scheme 10

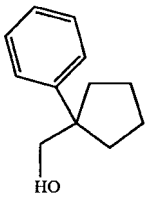
General Method H, Examples 65–66



37 38 39

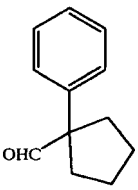
a. celite, PCC, CH_2Cl_2, RT, 91% b. NH_4Cl, NaCN, MeOH; 12M HCl, HOAc; $(Boc)_2O$, TEA, DMF.

Step 1



To a stirred solution of 1-phenylcyclo-1-pentanecarboxylic acid (5.00 g, 26.3 mmol) in 25 mL of THF at 0° C. was added LAH (52 mL , 52 mmol, 1M) in THF. The reaction mixture was slowly warmed to rt and then refluxed for 18 h. The reaction was quenched according to the Fieser procedure: careful addition of 2 mL of water; 6 mL of 15% NaOH in water; and 2 mL of water. The biphasic mixture was diluted with 100 mL of ether and the granular white solid filtered off. The ether fraction was dried over Na_2SO_4 and evaporated to give 4.30 g (93%) of the Step 1 compound.

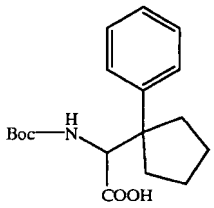
Step 2



To a stirred solution of Step 1 compound (0.80 g, 4.50 mmol) in 15 mL of CH_2Cl_2 at rt was added celite (5 g)

followed by PCC (1.95 g, 5.00 mmol). After stirring for 3 h the reaction mixture was diluted with 40 mL of CH_2Cl_2 and filtered through celite. The filtrate was filtered an additional time through silica gel resulting in a colorless filtrate. The CH_2Cl_2 fraction was evaporated to give 0.72 g (91%) of the aldehyde as a colorless oil.

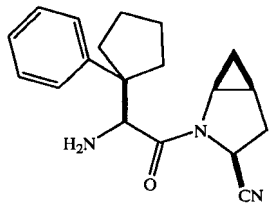
Step 3



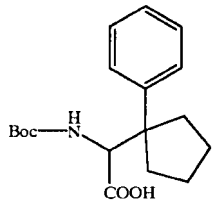
To a 50-mL round-bottomed flask containing Step 2 compound (0.72 g, 4.20 mmol) in 9 mL of water at rt was added NaCN (0.20 g, 4.20 mmol) followed by NH_4Cl (0.20 g, 5.00 mmol). To this reaction mixture was then added methanol (8 mL) and the mixture was allowed to stir overnight. The reaction mixture was then extracted with ether (2×15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude Strecker product.

To a 100-mL round-bottomed flask containing the crude Strecker product was added 10 mL of HOAc and 10 mL of conc. Hbl. The mixture was refluxed overnight. The mixture was concentrated under reduced pressure to give a yellow solid. The solid was triturated with 5 mL of 1:1 mixture of ether and hexanes. The white solid was treated with triethylamine (1.4 mL, 9.99 mmol) and di-tert-butyldicarbonate (1.00 g, 4.60 mmol) in 50 mL DMF. After 4 h the pH of the mixture was adjusted to 9 with saturated Na_2CO_3 soln. After an additional 3 h of stirring the mixture was extracted with 1:1 ether and hexanes and the aqueous fraction acidified to pH 2 with 5% $KHSO_4$ solution. The aqueous phase was washed with ether (2×40 mL), the organics dried ($MgSO_4$), and evaporated to an oil that was purified by silica gel flash chromatography with 8:92 methanol:CH_2Cl_2 to give 0.3 g (23%) of the Boc-protected amino acid as a light oil (M-H, 318).

EXAMPLE 65

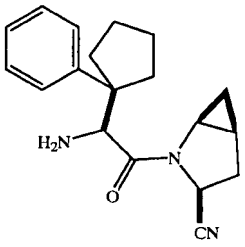


Step 1



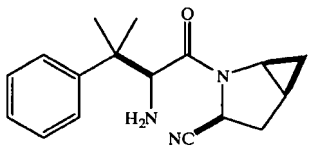
The synthesis of the Step 1 compound was described in general method H for the Strecker synthesis of racemic amino acids.

Step 2

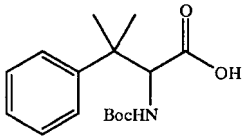


The title compound in Example 65 was prepared by the peptide coupling of the cyclopentylphenyl amino acid described in Step 1 and general method H followed by dehydration and deprotection as described in general method C. MS (M+H) 310.

EXAMPLE 66

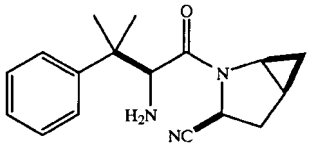


Step 1



Step 1 compound was prepared using racemic Strecker synthesis according to general method H starting from 2,2-dimethyl-phenylacetic acid.

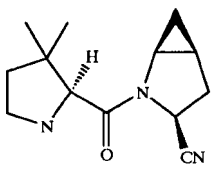
Step 2



The title compound in Example 66 was prepared by the peptide coupling of the dimethylphenyl amino acid described in step 1 followed by dehydration and deprotection as described in general method C. MS (M+H) 284.

EXAMPLE 67

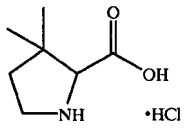
Step 1



N-(Benzyloxycarbonyl)succinimide (5.6 g, 22.4 mmol) was dissolved in CH_2Cl_2 (25 mL) and the solution was

added to a cooled (0° C.) and stirred solution of diethyl aminomalonate hydrochloride (5.0 g, 23.6 mmol) and triethylamine (13.4 mL, 95 mmol) in CH_2Cl_2 (125 ml). The resulting solution was stirred at 0° C. for 10 min and then at rt for 1 h. The solution was washed with 10% citric acid (2x50 mL),10% sodium hydrogen carbonate (2x50 mL), and water (50 mL) and was then dried (Na_2SO_4) and evaporated to afford diethyl N-benzyloxycarbonylaminomalonate as a colorless oil, which crystallized upon standing at 0° C. (6.3 g) (LC/Mass + ion): 310 (M+H).

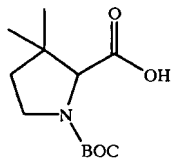
Step 2



Step 1 compound (6.18 g, 20 mmol) was dissolved in dry ethanol (30 mL) and added to a solution of sodium ethoxide (2.85 g, 8.8 m mol; 21% w/w solution in ethanol (6 mL). A solution of 3-methyl-2-butenal (1.68 g, 20 mmol) in ethanol (12 mL) was added, and the solution stirred at 25° C. for 24 h. Acetic acid (0.56 mL) was then added the solution hydrogenated at 50 psi for 24 h using 10% Pd/C (2.0 g) as catalyst. The solution was filtered, evaporated and the residue chromatographed on silica with CH_2Cl_2 /EtOAc (9:1) to give 2,2-dicarboethoxy-3,3-dimethyl-pyrrolidine (1.6 g) (LC/Mass, +ion): 244 (M+H).

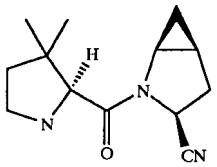
This diester (850 mg) was refluxed in 5 M hydrochloric acid (10 mL)/TFA (1 mL) for 8 h to give, after evaporation, a powdery white solid. Crystallization from methanol/ether gave 3,3-dimethyl-dl-proline hydrochloride (190 mg) as white crystals mp 110–112° C.

Step 3



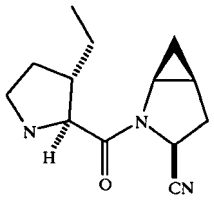
Step 2 compound (173 mg, 0.97 mmol) was dissolved in DMF (3 mL)/water (3 mL). To this clear solution was added triethylamine (0.46 mL, 3.18 mmol) and di-t-butyl dicarbonate (0.23 g, 1.06 mmol), and the reaction mixture was stirred at rt for 5 h. The solution was evaporated and the residue chromatographed on silica column using CH_2Cl_2/methanol (9:1) as eluent to yield t-butyloxy-carbonyl-3,3-dimethyl-dl-proline (200 mg) as an oil (LC/Mass, + ion): 244 (M+H).

Step 4

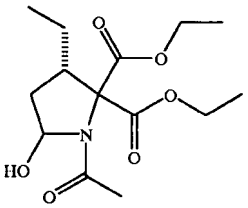


The title compound in Example 67 was prepared by the peptide coupling of the t-butyloxycarbonyl-3,3-dimethyl-dl-proline amino acid described in Step 3 followed by dehydration and deprotection as described in general method C. MS (M+H) 220.

EXAMPLE 68

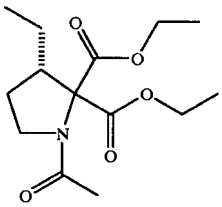


Step 1



Sodium ethoxide (940 mg of 21 wt % solution in ethanol, 2.9 mmol) in ethanol (2 mL) was added to a stirred solution of diethyl acetamidomalonate (4.31 g, 19,8 mmol) in EtOH (23 mL) at rt under argon. The reaction mixture was cooled to 0° C.; and trans-2-pentenal (1.51 g, 18.0 mmol) was added dropwise maintaining the reaction temperature at <50° C. After the addition, the reaction was allowed to warm to rt, stirred for 4 h, then quenched with acetic acid (460 μl). The solution was concentrated in vacuo, and the residue dissolved in EtOAc (25 mL), washed with 10% $NaHCO_3$ solution (2x5 mL), brine and dried ($MgSO_4$). The solution was filtered and concentrated to a 10 mL volume, then heated to reflux and diluted with hexane (20 mL). Upon cooling to rt, the title compound precipitated and was collected to give 3.0 g (50%) of the Step 1 compound (mp 106–109° C.; LC/Mass: + ions, 324 M+Na).

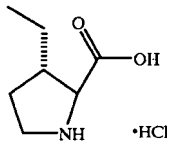
Step 2



To a solution of Step 1 compound (2.87 g, 9.5 mmol) and triethylsilane (2.2(mL, 14.3 mmol) in CH_2Cl_2 (30 mL2 under argon was added TFA (7.35 mL, 95.3 mmol) dropwise with stirring while maintaining the internal temperature at

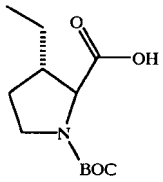
25° C. by means of an ice bath. After stirring for 4 h at rt, the solution was concentrated. The residue was diluted with CH_2Cl_2 (100 mL), then treated with H_2O (50 mL) and solid Na_2CO_3 with vigorous stirring until the mixture was basic. The organic layer was separated, dried (Na_2SO_4), filtered, then concentrated to give the Step 2 compound as a yellow oil which was used without further purification (LC/Mass: + ions, 308 M+Na).

Step 3



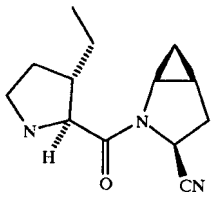
Step 2 compound (3.73 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was then cooled, washed with EtOAc (20 mL), the n concentrated to give an oil which crystallized upon trituration with et her to give the title compound (1.2 g, 70.6%) (LC/Mass, + ion): 144 (M+H).

Step 4



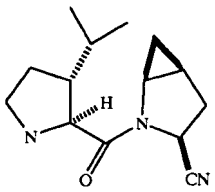
Step 3 compound (692 mg, 3.76 mmol) was dissolved in acetone (12 mL)/ water (12 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-t-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solvents were evaporated and the residue chromatographed on silica with 1:9 methanol:CH_2Cl_2 to give the Step 4 compound as an oil (LC/Mass: + ions, 266 M+Na).

Step 5

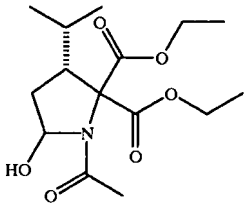


Example 68 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 234).

EXAMPLE 69

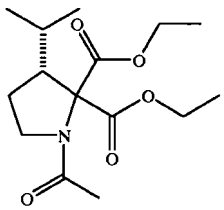


Step 1



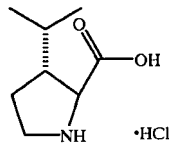
Sodium ethoxide (940 mg, 2.9 mmol; 21% w/w solution in ethanol) in ethanol (2 mL) was added to a stirred solution of diethyl acetamidomalonate (4.31 g, 19.8 mmol) in EtOH (23 mL) at rt under argon. The reaction mixture was cooled to 0° C.; and 4-methyl-2-pentenal (1.77 g, 18.0 mmol)was added dropwise maintaining the reaction temperature at <50° C. After the addition, the reaction was allowed to warm to rt, stirred for 4 h, then quenched with acetic acid (460 μl). The solution was concentrated and the remainder dissolved in EtOAc (25 mL). The organics were washed with 10% $NaHCO_3$ solution (2×5 mL), brine and dried ($MgSO_4$). The solution was filtered and concentrated to 10 mL volume, then heated to reflux and treated with hexane (20 mL). On cooling, the Step 1 compound precipitated and was collected (3.3 g) (LC/Mass, + ion): 338 (M+Na).

Step 2



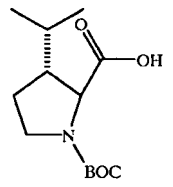
To a solution of Step 1 compound (3.0g, 9.5 mmol) and triethylsilane (2.28 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) under argon was added TFA (7.35 mL, 95.3 mmol) dropwise with stirring while maintaining the internal temperature at 25° C., by means of an ice bath. After stirring for 4 h at rt, the solution was concentrated, the residue diluted with CH_2Cl_2 (100 mL), then treated with H_2O (50 mL) and solid Na_2CO_3 with vigorous stirring until the mixture was basic. The organic layer was separated, dried (Na_2SO_4), filtered, then concentrated to give the title compound as an oil which was used without further purification (LC/Mass:+ ions, 300 M+H).

Step 3



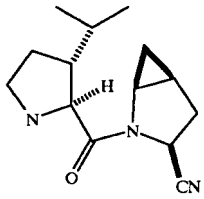
Step 2 compound (3.8 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (20 mL), then concentrated to give an oil which crystallized upon trituration with ether to give the step 3 compound (1.4 g, 76.0%). LC/Mass: + ions, 158 (M+H).

Step 4



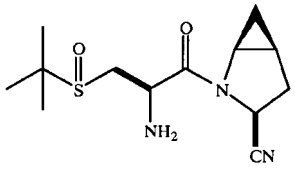
Step 3 compound (728 mg, 3.76 mmol) was dissolved in a 1:1 acetone/water solution (24 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-t-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solution was evaporated and the residue chromatographed on silica column using CH_2Cl_2/methanol (9:1) as eluent to give the title compound as an oil (LC/Mass, + ion): 258 (M+H).

Step 5



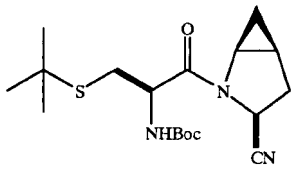
Example 69 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 248).

EXAMPLE 70



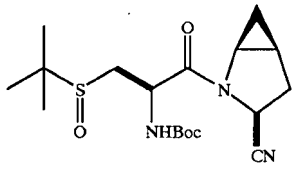
-continued

Step 1



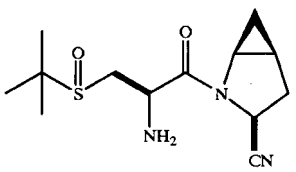
Step 1 compound was prepared by the procedure described in General Method C starting from N-Boc-S-t-butylcysteine.

Step 2



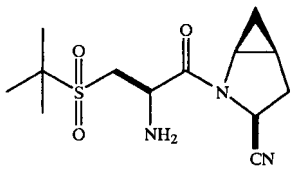
A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with Step 1 compound (78 mg, 0.21 mmol) and chloroform (3 mL). The mixture was cooled to 0° C. and treated with m-chloroperoxybenzoic acid (85 mg, 0.44 mmol) in $CHCl_3$ (2 mL). After 3 h the solution was diluted with $CHCl_3$ (7 mL), washed with 5% $NaHCO_3$ (2×5 mL), H_2O and dried over Na_2SO_4. Removal of solvent gave crude sulfoxide (100 mg), which was used without further purification (LC/Mass, + ions): 384 (M+H).

Step 3

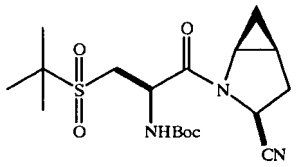


Trifluoroacetic acid (1.5 mL) was added to a cooled (0° C.) solution of Step 2 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was then stirred at 0° C. for 1.5 h, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20×100 mm column to give the title compound of Example 70 , 17 mg, 16%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 15 min 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time 10 Min (LC/Mass, + ion): 284 (M+H).

EXAMPLE 71

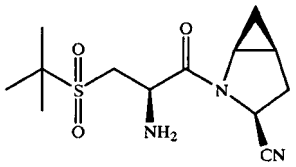


Step 1



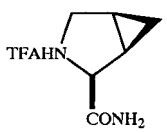
A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with compound from Example 70, Step 1 (78 mg, 0.21 mmol) in chloroform (3 mL). The mixture was cooled to 0° C. and treated with m-chloroperoxybenzoic acid (144 mg, 0.84 mmol) in $CHCl_3$ (2 mL). After 30 min at rt, the solution was diluted with $CHCl_3$ (7 mL), washed with 5% $NaHCO_3$ (2×10 mL), H_2O and dried over Na_2SO_4. Removal of solvent gave the crude sulfone (100 mg), which was used without further purification (LC/Mass, + ion): 344 (M+H–Bu).

Step 2



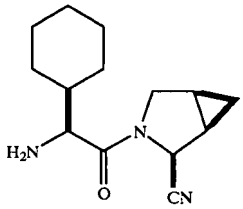
Trifluoroacetic acid (1.5 mL) was added to a cooled (0° C.) and stirred solution of Step 1 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was stirred at 0° C. for 30 min, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20×100 mm column to give the title compound, 14 mg, 17%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 15 min. 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time 10 Min. (LC/Mass, + ion): 300 (M+H).

EXAMPLE 72



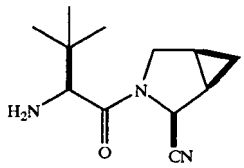
The title compound was prepared following a published procedure (Sasaki et al, Tetrahedron Lett. 1995, 36, 3149, Sasaki et al. Tetrahedron 1994, 50, 7093) used to synthesize (2S,3R,4S)-N-Boc-3,4-methano-L-proline carboxylate. The corresponding amide was prepared by general method A and deprotected with TFA to give the TFA salt also as described in general method A.

EXAMPLE 73



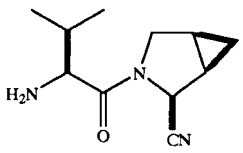
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-cyclohexylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+248).

EXAMPLE 74



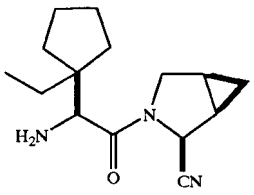
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-tert-butylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+222).

EXAMPLE 75



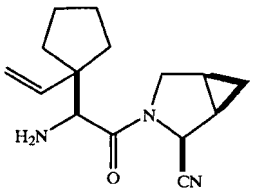
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-valine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+207).

EXAMPLE 76



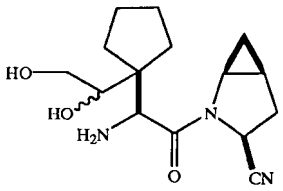
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(tert-butyloxycarbonyl)-(1'ethylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+262).

EXAMPLE 77



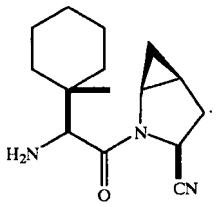
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(tert-butyloxycarbonyl)-(1'vinylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using General Method C (FAB MH+260).

EXAMPLE 78



N-[((S)-cyclopentylvinyl)-N-tert-butoxycarbonylglycinyl]-(2S,4S,5S)-2-cyano-4,5-methano-L-prolylamide (70 mg, 0.19 mmol) described in General Method C, Step 2 was dissolved in a mixture of 2 mL t-BuOH/3 mL THF and N-methylmorpholine-N-oxide (33mg, 0.28 mmol) was added followed by osmium tetroxide (0.1 mmol, 50 mol %). The reaction was quenched with 1 mL of 100 aqueous Na_2SO_3 and was taken up in EtOAc and washed with H_2O 5 mL, dried (Na_2SO_4), filtered, evaporated and purified by silica gel flash chromatography (5% MeOH/CH_2Cl_2) to give 41 mg (55%) of the protected diol as an oil. The title compound was obtained by deprotection of the amine functionality with TFA according to General Method C (FAB MH+294).

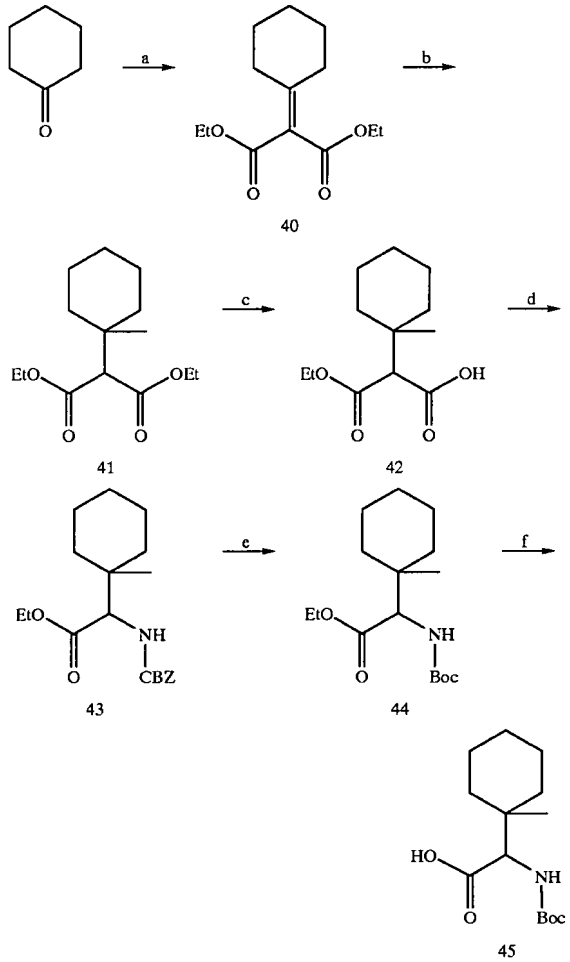
EXAMPLE 79



General Procedure I: Synthesis of Quaternary Amino Acids Via Michael Addition to Malonates followed by Selective Hydrolysis and Curtius Rearrangement. Examples 79–84.

Cyclohexanone and diethylmalonate underwent Knoevenagel condensation mediated by titanium tetrachloride in THF and CCl_4 to give 40. Copper (I) mediated Grignard addition of methylmagnesium bromide gave 41 which was selectively saponified to 42. Curtius rearrangement with trapping by benzyl alcohol gave 43 which was converted to 44 by a standard deprotection-protection protocol. Ester 44 was saponified to give the quaternary amino acid 45.

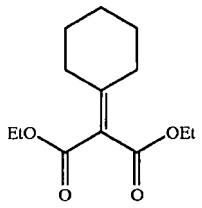
Scheme 11
General Method I



-continued

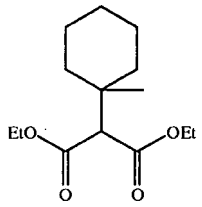
a. THF, CCl_4, $TiCl_4$, diethylmalonate, 0 C; pyridine, THF, 0 to RT 72 h b. MeMgBr, CuI, Et_2O, 0 C c. 1N NaOH, EtOH, RT 6 days d. Ph_2PON_3, TEA, RT to reflux to RT, BnOH e. 10% $Pd(OH)_2/C$, EtOAc; $(Boc)_2O$, K_2CO_3, THF f. IN NaOH, dioxane

Step 1



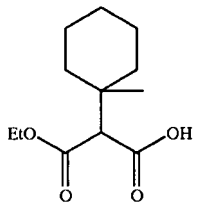
According to literature procedure (Tetrahedron 1973, 29, 435), a mixture of dry tetrahydrofuran (400 mL) and dry carbon tetrachloride (50 mL) was cooled to 0° C. (ice-salt bath) and treated with titanium tetrachloride (22.0 mL, 0.2 mole). The resulting yellow suspension was stirred at 0° C. for 5 min, treated sequentially with cyclohexanone (10.3 mL, 0.1 mole) and distilled diethylmalonate (15.2 mL, 0.1 mole) then stirred at 0° C. for 30 min. The reaction mixture was then treated with a solution of dry pyridine (32 mL, 0.40 mole) in dry THF (60 mL), stirred at 0° C. for 1.0 h, then at rt for 72 h. The reaction mixture was quenched with water (100 mL), stirred for 5 min then extracted with ether (2×200 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), saturated sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography using 5% EtOAc in hexane gave step 1 compound as a light yellow oil. Yield: 5.25 g (22%). MS (M+Na) 263.

Step 2



According to literature (Org. Syn. VI, 442, 1988; Liebigs Ann. Chem. 1981, 748) a mixture of 3.0 M methylmagnesium iodide (3.1 mL, 9.36 mmol) and cuprous chloride (9.0 mg) was stirred at 0° C. (ice-salt water bath), treated with a solution of Step 1 compound (1.5 g, 6.24 mmol) in dry ether (1.8 mL) over 5 min and stirred at 0° C. for 1 h, then at rt for 40 min. The mixture was slowly added to a slurry of ice and water (15 mL), treated dropwise with 10% HCl (3.7 mL) then extracted with EtOAc (3×25 mL). The combined organic extracts were washed with 1% sodium thiosulfate (2.0 mL) and saturated sodium chloride (2.0 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography on a silica gel column using 5% ether in hexane (1.0 L) gave step 2 compound as a clear syrup. Yield: 1.09 g,(68%). MS (M+H)257.

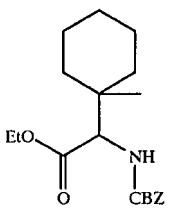
Step 3



A solution of Step 2 compound (1.09 g, 4.03 mmol) in a mixture of methanol (5.4 mL) and water (2.7 mL) was treated with 1N sodium hydroxide (4.84 mL, 4.84 mmol or 1.2 equiv) and stirred at rt for 6 days. The reaction mixture still showed the presence of starting material, so THF (4.0 mL) was added and the entire mixture stirred for another 2 days. The solution was evaporated to dryness and the resulting syrup partitioned between water (8.0 mL) and ether (15 mL). The aqueous phase was acidified with 1N hydrochloric acid (4.8 mL) to pH 2–3 and extracted with EtOAc (3 ×25 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give step 3 compound as a thick syrup. Yield: 875 mg, (95.1%). MS (M+H) 229.

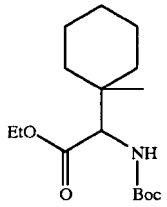
Or alternately: solutions of the diester in a mixture of ethanol, THF, dioxane and water or mixtures thereof may be hydrolyzed with sodium hydroxide.

Step 4



According to literature (J. Org. Chem 1994, 59, 8215), a solution of Step 3 compound (0.875 g, 3.83 mmol) in dry benzene (4.0 mL) was treated with triethylamine (0.52 mL, 3.83 mmol) and diphenylphosphoryl azide (0.85 mL, 3.83 mmol), refluxed under nitrogen for 1 h and cooled to rt. The solution was treated with benzyl alcohol (0.60 mL, 5.75 mmol or 1.5 equiv), refluxed for 17 h, cooled then diluted with ether (40 mL). The solution was washed with 10% aqueous citric acid (2×3 mL), back-extracting the citric acid wash with ether (40 mL). The combined organic extracts were washed with 5% sodium bicarbonate (2×3 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of the crude product with 10EtOAc in hexane (1.0 L) gave step 4 compound as a clear thick syrup. Yield: 1.15 g (90%). MS(M+H) 334.

Step 5



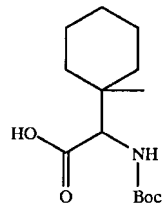
A solution of Step 4 compound (1.15 g, 3.46 mmol) in EtOAc (60 mL) was treated with palladium hydroxide on carbon (298 mg) and hydrogenated at rt for 20 h. The mixture was filtered through a celite pad and then washing the pad well with EtOAc (3×25 mL) then the filtrate was concentrated to give the free amine. A solution of the amine in tetrahydrofuran (12 mL) and water (12 mL) was treated with di-t-butyl dicarbonate (1.0 g, 4.58 mmol or 1.48 equiv) and potassium carbonate (854 mg, 6.18 mmol or 2.0 equiv), then stirred at rt for 20 h. The reaction mixture was partitioned between water (8 mL) and diethyl ether (3×40 mL) and the combined organic extracts were washed with brine (8 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the crude product with 10% EtOAc in hexane (1 L) gave step 5 compound as a clear thick syrup. Yield: 1.18 g (100%). MS:(M+H) 300.

Other methods can also be employed, for example:

According to Tetrahedron Lett. 1988, 29, 2983, where a solution of the benzylcarbamate in ethanol may be treated with triethylsilane (2 equiv), di-t-butyldicarbonate (1.1 equiv), catalytic palladium acetate and triethylamine (0.3 equiv) to give the BOC-protected amine in a "one-pot" manner.

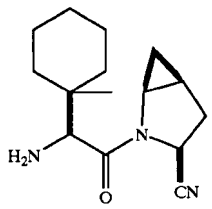
Or alternately: Solutions of the benzylcarbamate in methanol may be subjected to hydrogenolysis in the present of di-t-butyldicarbonate to give the BOC-protected amine in a "one-pot" manner.

Step 6



A solution of Step 5 compound (1.18 g, 3.09 mmol) in dioxane (8.0 mL) was treated with 1N sodium hydroxide (9.1 mL, 9.1 mmol or 3.0 equiv) and stirred at 60° C. (oil bath) for 28 h. The reaction mixture was concentrated to a syrup which was dissolved in water (15 mL) and extracted with ether (25 mL). The aqueous phase was acidified to pH 2–3 with 1N hydrochloric acid (9.2 mL) then extracted with EtOAc (3×50 mL). The combined organic extracts were washed with saturated sodium chloride (10 mL), dried ($MgSO_4$), filtered, and concentrated to give Step 6 compound as an off-white solid. Yield: 808 mg (96%). MS (M+H) 272.

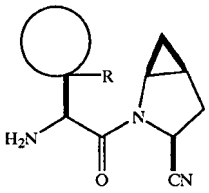
Step 7



The title compound was prepared from Step 6 compound according to the procedure in General Method C where the amino acid was coupled, the amide was dehydrated, and the protecting group removed to give the title compound. MS (M+H) 262.

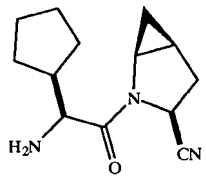
Compounds 90–100 were prepared by General Method I and General Method C starting from cyclohexanone, cyclopentanone and cyclobutanone, and employing methyl-, ethyl-, allyl- and propylmagnesium halides as Grignard reagents.

TABLE 5

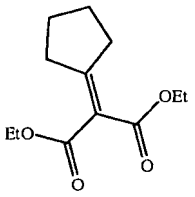


Example #	Cycloalkane	R	NS Data M + H
79	cyclohexane	Methyl	262
80	cyclohexane	Ethyl	276
81	cyclopentane	Methyl	248
82	cyclopentane	Allyl	274
83	cyclopentane	Propyl	276
84	cyclobutane	Methyl	234

EXAMPLE 85



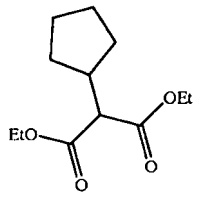
Step 1



According to Example 79: A mixture of dry carbon tetrachloride (50 mL) was cooled to 0° C. (ice-salt bath) and treated with titanium tetrachloride (11.0 mL, 0.1 mol). The resulting yellow suspension was stirred at 0° C. for 5 min, treated sequentially with cyclopentanone (4.42 mL, 0.05

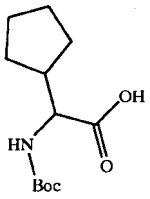
mol) and distilled diethylmalonate (7.6 mL, 0.05 mol) then stirred at 0° C. for 30 min. The reaction mixture was then treated with a solution of dry pyridine (16 mL, 0.20 mol) in dry THF (30 mL), stirred at 0° C. for 1.0 h, then at rt for 20 h. The reaction mixture was quenched with water (50 mL), stirred for 5 min then extracted with ether (2×100 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography using 5% EtOAc in hexane gave Step 1 compound as a light yellow oil. Yield: 7.67 g (68%). MS (M+H) 226.

Step 2



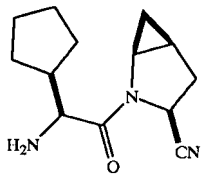
A solution of Step 1 compound (1.00 g 4.42 mmol) in methanol (50 mL) was treated with 10% Pd/C (0.20 g, 10 mol %) and hydrogenated (balloon pressure) at rt for 20 h. The mixture was diluted with methanol and filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography on silica gel with 7% EtOAc in hexanes to give 0.84 g (91%) of Step 2 compound. MS (M+H) 229.

Step 3



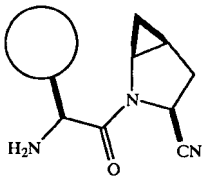
The Step 3 compound was prepared by the process outlined in General Method H, where the ester underwent hydrolysis, Curtius Rearrangement, protecting group exchange, and again final ester hydrolysis.

Step 4



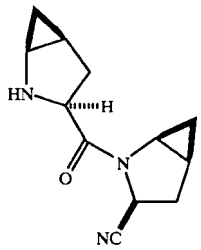
The title compound was prepared from Step 3 compound according to the procedure in General Method C where the amino acid was coupled, the amide was dehydrated, and the protecting group removed to give the title compound. MS (M+H) 234.

Examples 86 and 87 were prepared by the procedures used for Example 85 starting from cyclohexanone and cyclobutanone respectively

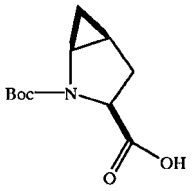


Example #	Cycloalkane	Mass Spec M + H
85	cyclopentyl	234
86	cyclohexyl	248
87	cyclobutyl	220

EXAMPLE 89

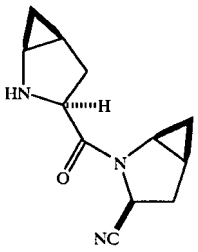


Step 1



Step 1 compound was prepared in Example 6 Step 1.

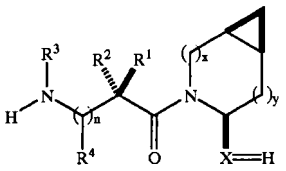
Step 2

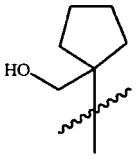
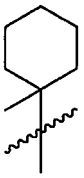
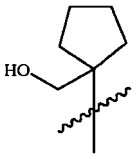
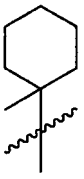


The title compound was prepared from Step 1 compound according to General Method C, where the carboxylic acid underwent a peptide coupling, the amide dehydration and protecting group removal. MS (M+H) 218.

EXAMPLES 90 TO 99

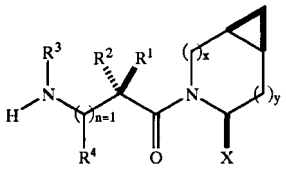
Examples of compounds where X=H include the following compounds which may be prepared employing procedures as described hereinbefore.

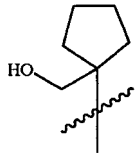
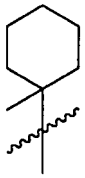
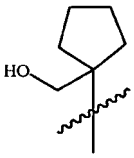
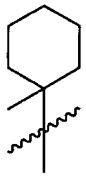


Ex. #	n	x	y	R^1	R^2	R^3	R^4
90	0	0	1	t-Bu	H	H	—
91	0	0	1	adamantyl	H	H	—
92	0	0	1		H	H	—
93	0	0	1		H	Me	—
94	0	1	0	t-Bu	H	H	—
95	0	1	0	adamantyl	H	H	—
96	0	1	0		H	H	—
97	0	1	0		H	Me	—
98	1	0	1	H	H	H	t-Bu
99	1	1	0	Me	H	H	t-Bu

EXAMPLES 100 TO 109

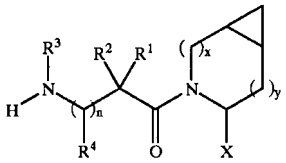
Examples of compounds where n=1 include the following compounds which may be prepared employing procedures as described hereinbefore.



Ex. #	X	x	y	R^1	R^2	R^3	R^4
100	CN	0	1	H	H	H	t-Bu
101	CN	0	1	H	H	H	adamantyl
102	CN	0	1	H	Me	H	
103	CN	0	1		H	Me	H
104	CN	1	0	t-Bu	H	H	H
105	CN	1	0	adamantyl	H	H	Me
106	CN	1	0		Et	H	H
107	CN	1	0	H	H	Me	
108	H	0	1	t-Bu	H	H	H
109	H	1	0	Me	H	H	t-Bu

What is claimed is:

1. A compound having the structure



wherein x is 0 or 1 and y is 0 or 1, provided that

x=1 when y=0 and

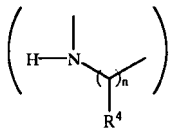
x=0 when y=1; and wherein

n is 0 or 1;

X is H or CN;

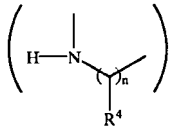
R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl, arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl or cycloheteroalkylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfinyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

and R^1 and R^3 may optionally be taken together to form $-(CR^5R^6)_m-$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, H, alkyl, alkenyl, alkynyl, cycloalkyl, halo, amino, substituted amino, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R4 may optionally be taken together to form $-(CR^7R^8)_p-$ wherein p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, halo, amino, substituted amino, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together with



form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2;

or optionally R^1 and R^3 together with



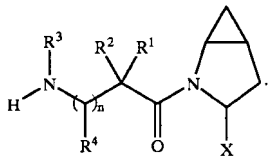
form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

with the proviso that where x is 1 and y is 0, X is H, n is o, and one of R^1 and R^2 is H and the other is alkyl, then R^3 is other than pyridyl or substituted pyridyl;

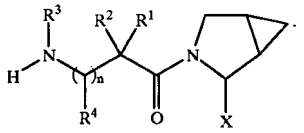
including all stereoisomers thereof;

and a pharmaceutically acceptable salt thereof, or a prodrug ester thereof, and all stereoisomers thereof.

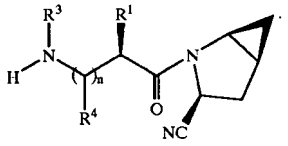
2. The compound as defined in claim **1** having the structure:



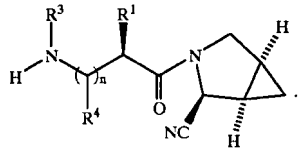
3. The compound as defined in claim **1** having the structure:



4. The compound as defined in claim **1** having the structure:



5. The compound as defined in claim **1** having the structure:



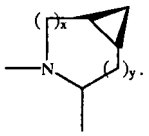
6. The compound as defined in claim **1** wherein:

R^3 is H, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl hydroxybicycloalkyl, or hydroxytricycloalkyl,

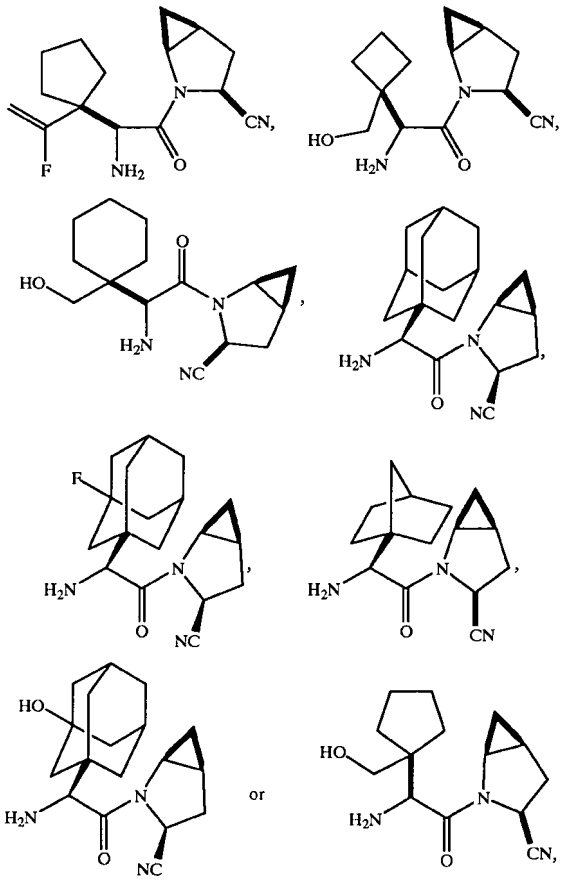
R^2 is H or alkyl, n is 0,

X is CN.

7. The compound as defined in claim **1** wherein the cyclopropyl fused to the pyrrolidine has the configuration:



8. The compound as defined in claim 1 having the structure:

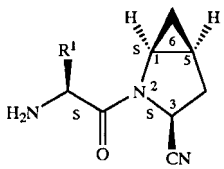


or a pharmaceutically acceptable salt thereof.

9. The compound as defined in claim 8 wherein the pharmaceutically acceptable salt is the hydrochloride salt or the trifluoroacetic acid salt.

10. The compound as defined in claim 1 which is

A

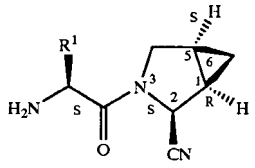


(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl,

or

B



(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl.

11. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

12. A pharmaceutical combination comprising a DP4 inhibitor compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent.

13. The pharmaceutical combination as defined in claim 12 comprising said DP4 inhibitor compound and an antidiabetic agent.

14. The combination as defined in claim 13 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, an aP2 inhibitor, a glycogen phosphorylase inhibitor, an AGE inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1) or mimetic thereof, insulin and/or a meglitinide.

15. The combination as defined in claim 14 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI -262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, APR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, and/or LY315902.

16. The combination as defined in claim 13 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 100:1.

17. The combination as defined in claim 12 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, an anorectic agent, and/or a fatty acid oxidation upregulator.

18. The combination as defined in claim 17 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, famoxin, and/or mazindol.

19. The combination as defined in claim 12 wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, an ACAT inhibitor, a cholesteryl ester transfer protein inhibitor, or an ATP citrate lyase inhibitor.

20. The combination as defined in claim 19 wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin,

fenofibrate, gemfibrozil, clofibrate, implitapide, CP-529, 414, avasimibe, TS-962, MD-700, and/or LY295427.

21. The combination as defined in claim **19** wherein the DP4 inhibitor is present in a weight ratio to the lipid-modulating agent within the range from about 0.01 to about 100:1.

22. A pharmaceutical combination comprising a DP4 inhibitor compound as defined in claim **1** and an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty, an anti-arthritis agent, an agent for preventing inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent and/or an anti-obesity agent.

23. A method for treating diabetes, insulin resistance, hyperglycemia, hyperisulinemia, or elevated blood levels of free fatty acids or glycerol, obesity, Syndrome X, dysmetabolic syndrome, diabetic complications, hypertriglyceridemia, hyperinsulinemia, atherosclerosis, impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases, AIDS, intestinal diseases, inflammatory bowel syndrome, nervosa, osteoporosis, or an immunomodulatory disease or a chronic inflammatory bowel disease, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in claim **1**.

24. The method as defined in claim **23** for treating type II diabetes and/or obesity.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

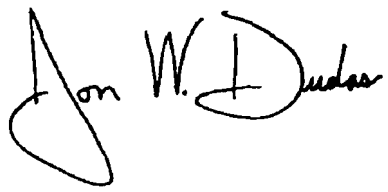
PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 91,
Lines 9-10, should read -- A compound having the structure: --
Line 54, should read -- A compound which is --.

Signed and Sealed this

Twenty-seventh Day of July, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

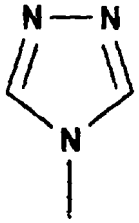
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,
Line 6, change "PGI" to -- PG_1 --.

Column 14,
Line 50, insert --  --.

Line 56, between "refers" and "cycloheteroakyl", insert -- to --.
Line 57, between "a" and "atom", insert -- C --.

Column 15,
Line 54, change "γ" to -- β --.

Column 20,
Line 59, "2,1" should be -- 2,3 --.

Column 29,
Line 23, change "w" to -- % --.

Column 30,
Line 2, after "$(M+H)^+$" and before "197", insert -- - --.

Column 32,
Line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Column 33,
Line 3, change "HO" to read -- H_2O --.
Line 7, change "CH2cl$_2$" to read -- CH_2Cl_2 --.
Line 11, after "METHOD", insert -- A --.

Column 34,
Line 62, delete "15".

Column 41,
Line 43, after "was", delete "a".
Line 44, after "over", delete "a".

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 43,
Line 36, delete "E".
Line 55, change "48.61" to -- 8.61 --.

Column 44,
Line 39, change "200" to -- 300 --.

Column 46,
Line 58, change "ter" to -- water --.
Line 58, after "20" and before "Detection", insert -- mL/min. --.
Line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Column 52,
Line 64, change "25" to -- 28 --.

Column 53,
Line 31, change "OSO_4" to -- OsO4 --.
Line 65, after "100%" and before "Solvent A", insert -- B, --.
Line 66, after "vent B =" and before "MeOH", insert -- 90% --.

Column 62,
Line 67, change "549" to -- 540 --.

Column 66,
Line 24, change "$CH2Cl_2$" to read -- CH_2Cl_2 --.

Column 69,
Line 21, change "9" to -- 8 --.
Line 30, change "Hbl" to -- HCl --.

Column 70,
Line 56, move "Step 1" to line 65.

Column 72,
Line 36, change "50º" to -- 5º --.
Line 65, change "2.2(" to -- 2.28 --.
Line 65, change "30mL2" to -- 30 mL --.

Column 73,
Line 25, change "the n" to -- then --.
Line 26, change "et her" to -- ether --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 74,
Line 32, change "50º" to -- 5º --.

Column 79,
Line 61, change "100" to -- 10% --.

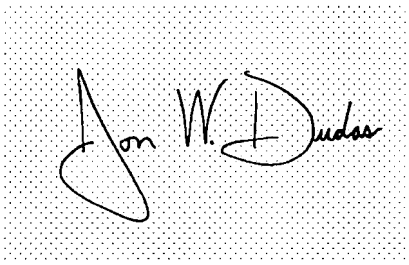
Column 82,
Line 65, change "10EtOAc" to -- 10% EtOAc --.

Column 84,
Line 34, change "NS" to -- MS --.

Column 92,
Line 42, change "APR" to -- AR --.

Signed and Sealed this

Twenty-ninth Day of November, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

Exhibit B

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6395767 **Issue Dt:** 05/28/2002 **Application #:** 09788173 **Filing Dt:** 02/16/2001

Publication #: 20020019411 **Pub Dt:** 02/14/2002

Inventors: Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin et al

Title: Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method

Assignment: 1

Reel/Frame: 011607/0369 **Recorded:** 02/16/2001 **Pages:** 5

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:

ROBL, JEFFREY A.	**Exec Dt:** 02/13/2001
SULSKY, RICHARD B.	**Exec Dt:** 02/13/2001
AUGERI, DAVID J.	**Exec Dt:** 01/14/2001
MAGNIN, DAVID R.	**Exec Dt:** 02/13/2001
HAMANN, LAWRRENCE G.	**Exec Dt:** 02/13/2001
BETEBENNER, DAVID A.	**Exec Dt:** 02/13/2001

Assignee: BRISTOL-MAYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
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Correspondent: BRISTOL-MYERS SQUIBB COMPANY
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P.O. BOX 4000
PRINCETON, NJ 08543-4000

Search Results as of: 09/16/2009 03:30 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.2

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-350

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated and received on June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg.

We acknowledge receipt of your submissions dated June 30, August 28, September 26, October 15, 24, 28, and 29, November 3, 14, 19, and 24, and December 2, 15, 16, 23, and 24, 2008, and January 21(2), 22, 23, and 26, February 3, 19(2), 24, and 26, March 12 and 16, April 2, 6, 15, 20, and 23, May 19 and 27, June 3, 17, and 22, and July 6, 17 (2), 22 (3), 27, 28, and 30 (3), 2009.

This new drug application provides for the use of Onglyza (saxagliptin) Tablets, 2.5 mg and 5 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm , that is identical to the enclosed labeling text for the package insert and patient package insert submitted July 30, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-350**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on June 30, 2008 and July 6 and 17, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-350.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impracticable (there are too few children in this age range with type 2 diabetes mellitus to study).

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

PMR 1493-1: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of saxagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years.

Final Report Submission: by June 30, 2015

Submit all final reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess: a signal of a serious risk of embryofetal toxicity observed in a previously submitted study of saxagliptin plus metformin in rats, a signal of a serious risk of cardiovascular events, and the serious risks of severe hepatic events and hypersensitivity reactions associated with saxagliptin treatment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

PMR 1493-2 Embryofetal development study of saxagliptin and metformin in combination in rats. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-3 Embryofetal development study with of saxagliptin and metformin in combination in rabbits. Include saxagliptin monotherapy and metformin monotherapy treatment arms.

The timetable you submitted via email on June 29, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by July 31, 2010
Study Completion:	by September 30, 2010
Final Report Submission:	by April 30, 2011

PMR 1493-4 An epidemiologic study to compare the risk of severe hepatic events among patients with type 2 diabetes exposed to saxagliptin to the risk in patients exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by May 30, 2015
Final Report Submission:	by November 30, 2015

PMR 1493-5 An epidemiologic study to compare severe hypersensitivity and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin and those exposed to other antidiabetic medications.

The timetable you submitted by email on July 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by January 31, 2010
Study Completion:	by November 30, 2016
Final Report Submission:	by June 30, 2017

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes and available data have not definitively excluded the potential for this serious risk with saxagliptin. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-diabetic medications, including saxagliptin, to definitively exclude unacceptable cardiovascular toxicity. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1493-6 A randomized, double-blind, controlled trial evaluating the effect of saxagliptin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with saxagliptin to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of saxagliptin on lymphocyte counts, infections, hypersensitivity reactions, liver, bone fracture, pancreatitis, skin reactions, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging study reports should be included in the narratives.

Because renal impairment is an important complication of diabetes, you must ensure that there is a minimum of 1 year of exposure for at least 200 saxagliptin-treated patients with moderate renal impairment and at least 100 saxagliptin-treated patients with severe renal impairment.

The timetable you submitted on July 15, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by November 30, 2009
Study Completion:	by July 31, 2015
Final Report Submission:	by January 31, 2016

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing,

Advertising, and Communications (DDMAC), see
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

In addition to the standard reporting requirements for an approved NDA, we request that you submit as 15-day expedited reports, all postmarketing cases of (1) liver test abnormalities accompanied by jaundice or hyperbilirubinemia, (2) opportunistic infections associated with the use of saxagliptin, and (3) pancreatitis, regardless of whether these reports are classified as serious or unexpected.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Patient Package Insert
Container Label – 2.5mg, 30 tablet bottle
Container Label – 2.5mg, 90 tablet bottle
Container Label – 5mg, 10 tablet blister card
Container Label – 5mg, 30 tablet bottle
Container Label – 5mg, 30 tablet bottle (sample)
Container Label – 5mg, 90 tablet bottle
Container Label – 5mg, 500 tablet bottle
Carton Label – 5mg, 28 tablet, contains 4 of the 7 tablet wallets (sample)
Carton Label – 5mg, 30 tablet bottle (sample)
Carton Label – 5mg, 100 tablet, 10 blister cards with 10 tablets each
Container/Carton Label – 5mg, 7 tablet wallet (sample)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONGLYZA safely and effectively. See full prescribing information for ONGLYZA.

ONGLYZA (saxagliptin) tablets
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ONGLYZA is a dipeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important limitations of use:

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.2)
- Has not been studied in combination with insulin. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dose is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)
- 2.5 mg daily is recommended for patients with moderate or severe renal impairment, or end-stage renal disease (CrCl ≤50 mL/min). Assess renal function prior to initiation of ONGLYZA and periodically thereafter. (2.2)
- 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole). (2.3, 7.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg and 2.5 mg (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- When used with an insulin secretagogue (e.g., sulfonylurea), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. (5.1)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug. (5.2)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with placebo are: upper respiratory tract infection, urinary tract infection, and headache. (6.1)
- Peripheral edema was reported more commonly in patients treated with the combination of ONGLYZA and a thiazolidinedione (TZD) than in patients treated with the combination of placebo and TZD. (6.1)
- Hypoglycemia was reported more commonly in patients treated with the combination of ONGLYZA and sulfonylurea than in patients treated with the combination of placebo and sulfonylurea. (6.1)
- Hypersensitivity-related events (e.g., urticaria, facial edema) were reported more commonly in patients treated with ONGLYZA than in patients treated with placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- Coadministration with strong CYP3A4/5 inhibitors (e.g., ketoconazole) significantly increases saxagliptin concentrations. Recommend limiting ONGLYZA dose to 2.5 mg once daily. (2.3, 7.2)

USE IN SPECIFIC POPULATIONS

- There are no adequate and well-controlled studies in pregnant women. (8.1)
- Safety and effectiveness of ONGLYZA in pediatric patients below the age of 18 have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies (14)*.]

1.2 Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in combination with insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals.

2.2 Patients with Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min).

The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dose of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease formula. [See *Clinical Pharmacology (12.3)*.]

2.3 Strong CYP3A4/5 Inhibitors

The dose of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). [See *Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*.]

3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the reverse side, in blue ink.
- ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA. [See *Adverse Reactions (6.1)*.]

5.2 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Monotherapy and Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	Placebo N=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Adverse Reactions Associated with ONGLYZA Coadministered with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Table 2: Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

	Number (%) of Patients	
	ONGLYZA 5 mg + Metformin* N=320	Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count $\leq$750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

7 DRUG INTERACTIONS

7.1 Inducers of CYP3A4/5 Enzymes

Rifampin significantly decreased saxagliptin exposure with no change in the area under the time-concentration curve (AUC) of its active metabolite, 5-hydroxy saxagliptin. The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin. Therefore, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology (12.3)*.]

7.2 Inhibitors of CYP3A4/5 Enzymes

Moderate Inhibitors of CYP3A4/5

Diltiazem increased the exposure of saxagliptin. Similar increases in plasma concentrations of saxagliptin are anticipated in the presence of other moderate CYP3A4/5 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil); however, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology (12.3)*.]

Strong Inhibitors of CYP3A4/5

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

8.3 Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many

drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

8.5 Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3).*]

10 OVERDOSAGE

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

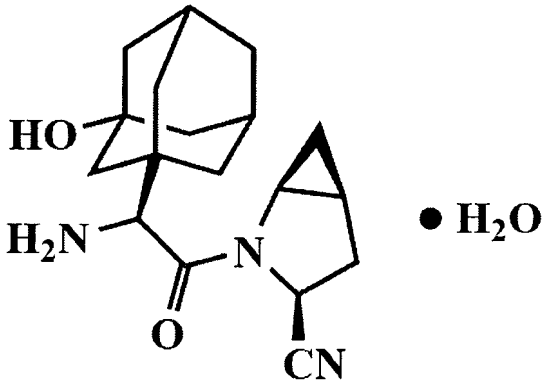
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-

azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their

bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7)*.]

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group) compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

The degree of renal impairment did not affect the C_{max} of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Pediatric

Studies characterizing the pharmacokinetics of saxagliptin in pediatric patients have not been performed.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant

difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

In Vivo Assessment of Drug Interactions

Effects of Saxagliptin on Other Drugs

In studies conducted in healthy subjects, as described below, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, ONGLYZA is not an inhibitor of hOCT-2-mediated transport.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the plasma C_{max} of glyburide by 16%; however, the AUC of glyburide was unchanged. Therefore, ONGLYZA does not meaningfully inhibit CYP2C9-mediated metabolism.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of digoxin. Therefore, ONGLYZA is not an inhibitor or inducer of P-gp-mediated transport.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, did not alter the pharmacokinetics of simvastatin. Therefore, ONGLYZA is not an inhibitor or inducer of CYP3A4/5-mediated metabolism.

Diltiazem: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the plasma C_{max} of diltiazem by 16%; however, the AUC of diltiazem was unchanged.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, decreased the plasma C_{max} and AUC of ketoconazole by 16% and 13%, respectively.

Effects of Other Drugs on Saxagliptin

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the C_{max} of saxagliptin by 8%; however, the AUC of saxagliptin was unchanged.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} of saxagliptin by 63% and the AUC by 2.1-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 44% and 36%, respectively.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, increased the C_{max} for saxagliptin by 62% and the AUC by 2.5-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 95% and 91%, respectively.

In another study, coadministration of a single dose of saxagliptin (20 mg) and ketoconazole (200 mg every 12 hours at steady state), increased the C_{max} and AUC of saxagliptin by 2.4-fold and 3.7-fold, respectively. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 96% and 90%, respectively.

Rifampin: Coadministration of a single dose of saxagliptin (5 mg) and rifampin (600 mg QD at steady state) decreased the C_{max} and AUC of saxagliptin by 53% and 76%, respectively, with a corresponding increase in C_{max} (39%) but no significant change in the plasma AUC of the active metabolite.

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin.

Aluminum hydroxide + magnesium hydroxide + simethicone: Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminum hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged.

Famotidine: Administration of a single dose of saxagliptin (10 mg) 3 hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

13.2 Animal Toxicology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy. ONGLYZA has not been studied in combination with insulin.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated a saxagliptin dose of 10 mg daily. The 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. Treatment with ONGLYZA at all doses produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

14.1 Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C $\geq$7% to $\leq$10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 3). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group.

Table 3: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	ONGLYZA 2.5 mg N=102	ONGLYZA 5 mg N=106	Placebo N=95
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	−0.4	−0.5	+0.2
Difference from placebo (adjusted mean†)	−0.6‡	−0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=78**	**N=84**	**N=71**
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo

§ p-value <0.05 compared to placebo

¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA.

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo.

Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of –0.4% and –0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of –0.4%).

14.2 Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 4). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

Table 4: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	ONGLYZA 2.5 mg + Metformin N=192	ONGLYZA 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

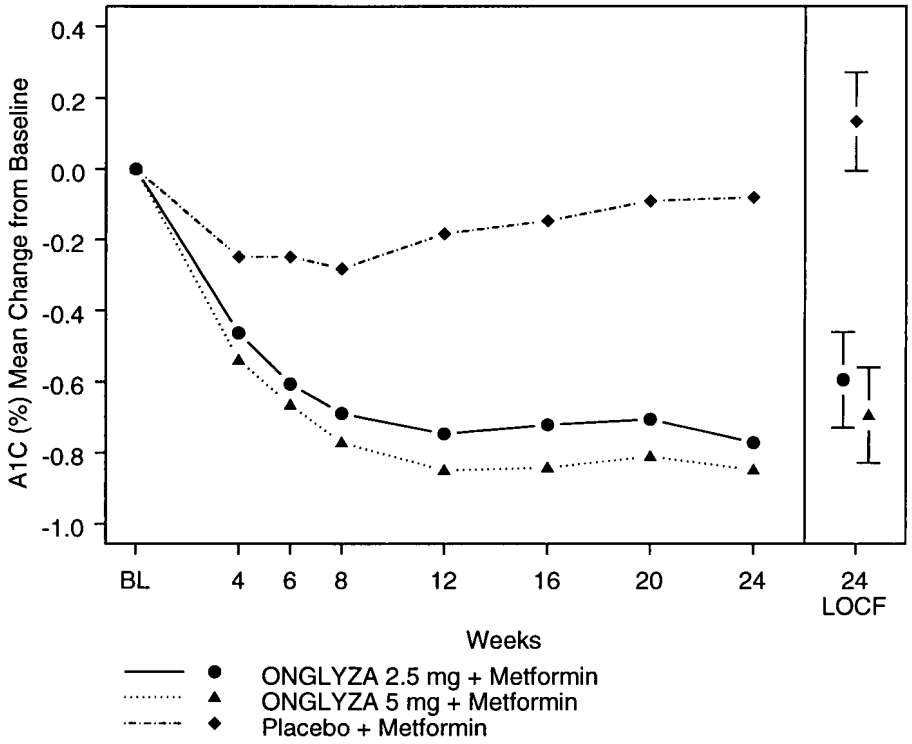
* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

Figure 1: **Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin***



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to

existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 5). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA 2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	**ONGLYZA 2.5 mg + TZD N=195**	**ONGLYZA 5 mg + TZD N=186**	**Placebo + TZD N=184**
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.4§	−0.6‡	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%§ (81/192)	42%§ (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean†)	−14	−17	−3
Difference from placebo (adjusted mean†)	−12§	−15§	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean†)	−55	−65	−15
Difference from placebo (adjusted mean†)	−40§	−50§	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + TZD

§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 6). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248	ONGLYZA 5 mg + Glyburide 7.5 mg N=253	Placebo + Up-Titrated Glyburide N=267
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean†)	−0.5	−0.6	+0.1
Difference from up-titrated glyburide (adjusted mean†)	−0.6‡	−0.7‡	
95% Confidence Interval	(−0.8, −0.5)	(−0.9, −0.6)	
Percent of patients achieving A1C <7%	22%§ (55/246)	23%§ (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean†)	−7	−10	+1
Difference from up-titrated glyburide (adjusted mean†)	−8§	−10§	
95% Confidence Interval	(−14, −1)	(−17, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean†)	−31	−34	+8
Difference from up-titrated glyburide (adjusted mean†)	−38§	−42§	
95% Confidence Interval	(−50, −27)	(−53, −31)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + up-titrated glyburide

§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA

5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 7).

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−41§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA™ (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 8.

Table 8: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	pink biconvex, round	"5" on one side and "4215" on the reverse, in blue ink	Bottles of 30	0003-4215-11
			Bottles of 90	0003-4215-21
			Bottles of 500	0003-4215-31
			Blister of 100	0003-4215-41
2.5 mg	pale yellow to light yellow biconvex, round	"2.5" on one side and "4214" on the reverse, in blue ink	Bottles of 30	0003-4214-11
			Bottles of 90	0003-4214-21

Storage and Handling

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be

instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

17.2 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1256316
1256317

Iss July 2009

PATIENT INFORMATION
ONGLYZA (on-GLY-zah)
(saxagliptin)
tablets

Read the Patient Information that comes with ONGLYZA before you start taking it and each time you get a refill. There may be new information. This patient leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is ONGLYZA?

ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.

ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.

ONGLYZA is unlikely to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low.

ONGLYZA has not been studied in children younger than 18 years old.

What should I tell my healthcare provider before taking ONGLYZA?

Before you take ONGLYZA, tell your healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes. ONGLYZA should not be used to treat people with type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). ONGLYZA should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems
- are taking insulin. ONGLYZA has not been studied with insulin.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- During periods of stress on the body, such as:
  - fever
  - trauma
  - infection
  - surgery

  Contact your healthcare provider right away as your medication needs may change.
- Your healthcare provider should test your blood to measure how well your kidneys work. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Your healthcare provider may prescribe ONGLYZA along with other medicines that lower blood sugar.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who already take another medication to treat diabetes, such as sulfonylureas. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

Allergic (hypersensitivity) reactions, such as rash, hives, and swelling of the face, lips, and throat. If you have these symptoms, stop taking ONGLYZA and call your healthcare provider right away.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68° to 77°F (20° to 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in patient leaflets. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.

This patient leaflet summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals. For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

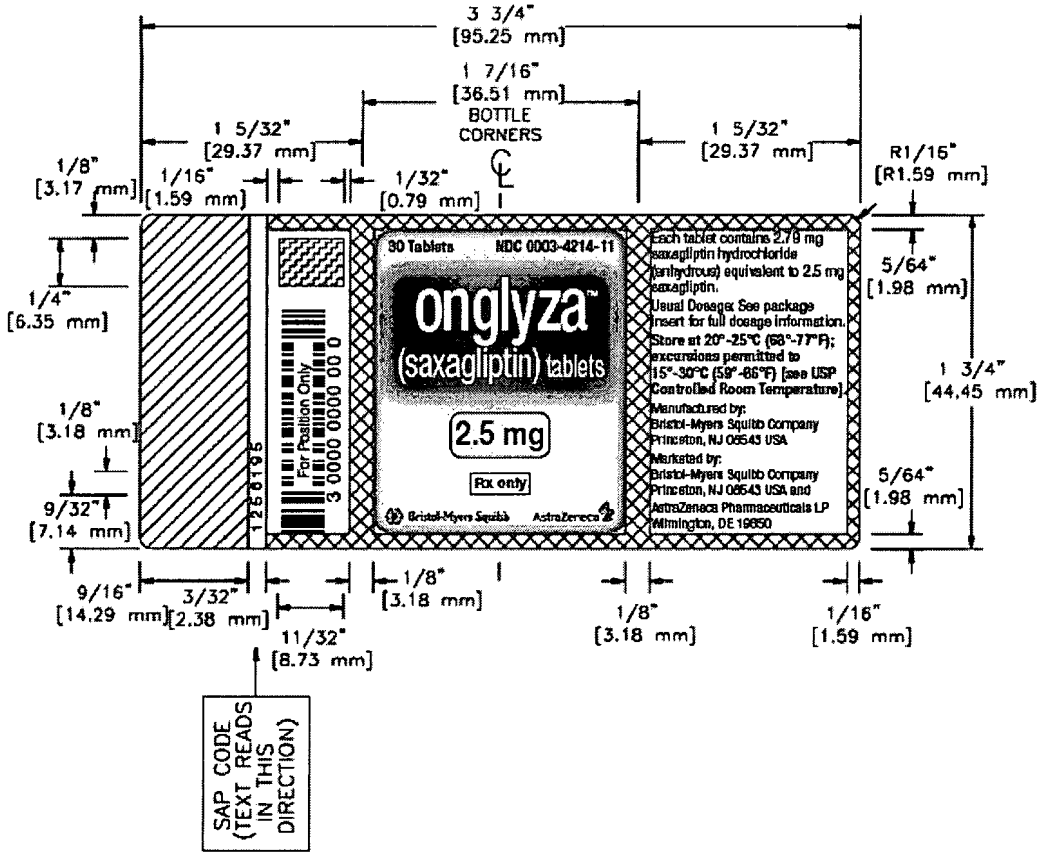
ONGLYZA (saxagliptin) tablets

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1256316
1256317

Iss July 2009



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300 KERNING

NO TEXT AREA

COLOR SHIFTING INK AREA
1/4" x 11/32"

PMS
Pantone Black

PMS
3295 Green

PMS
1205 Gradient
100%-0%-100%

Color Shifting Ink
Placeholder

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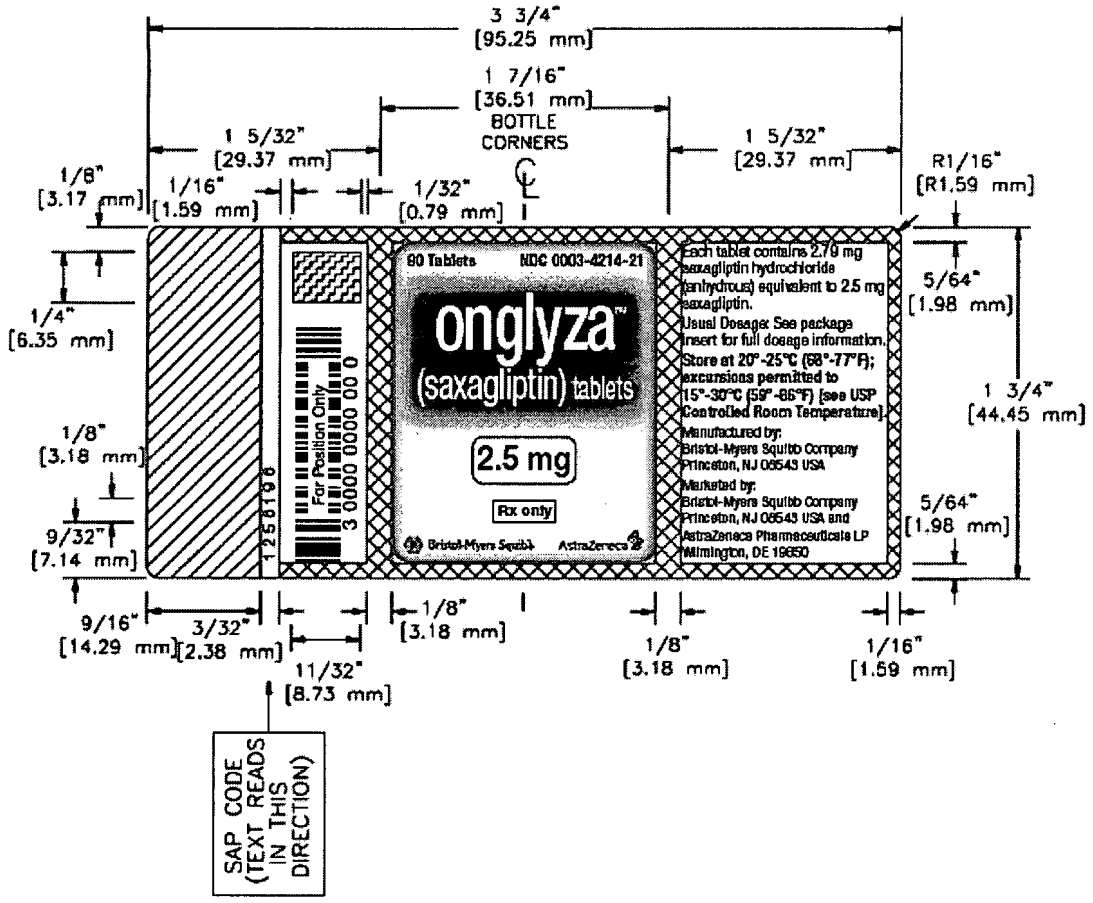

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COLOR SHIFTING INK AREA
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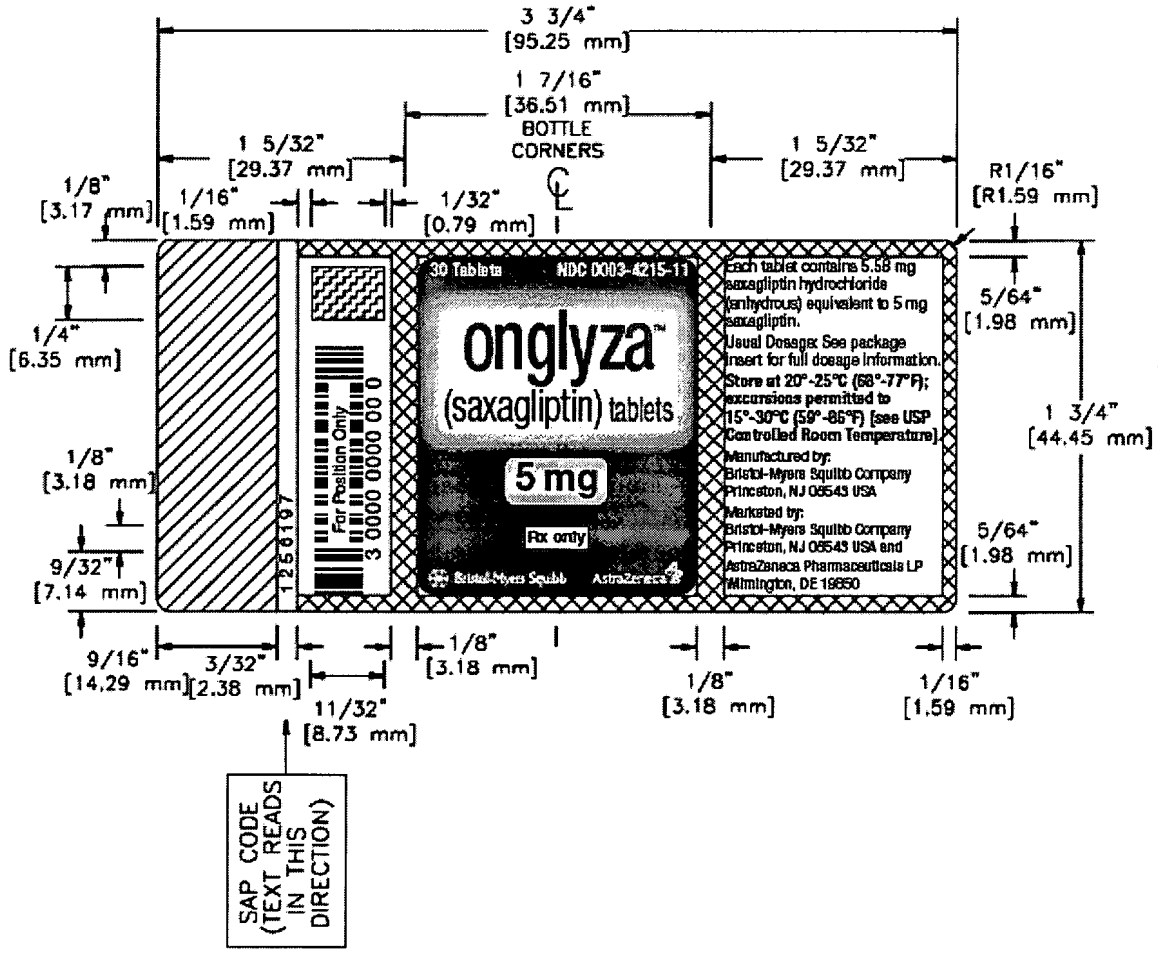
Special UPC Barcode Value:

3 0003 4214 21


onglyza®
(saxagliptin) tablet
5 mg



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NO TEXT AREA

COLOR SHIFTING INK AREA
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PMS
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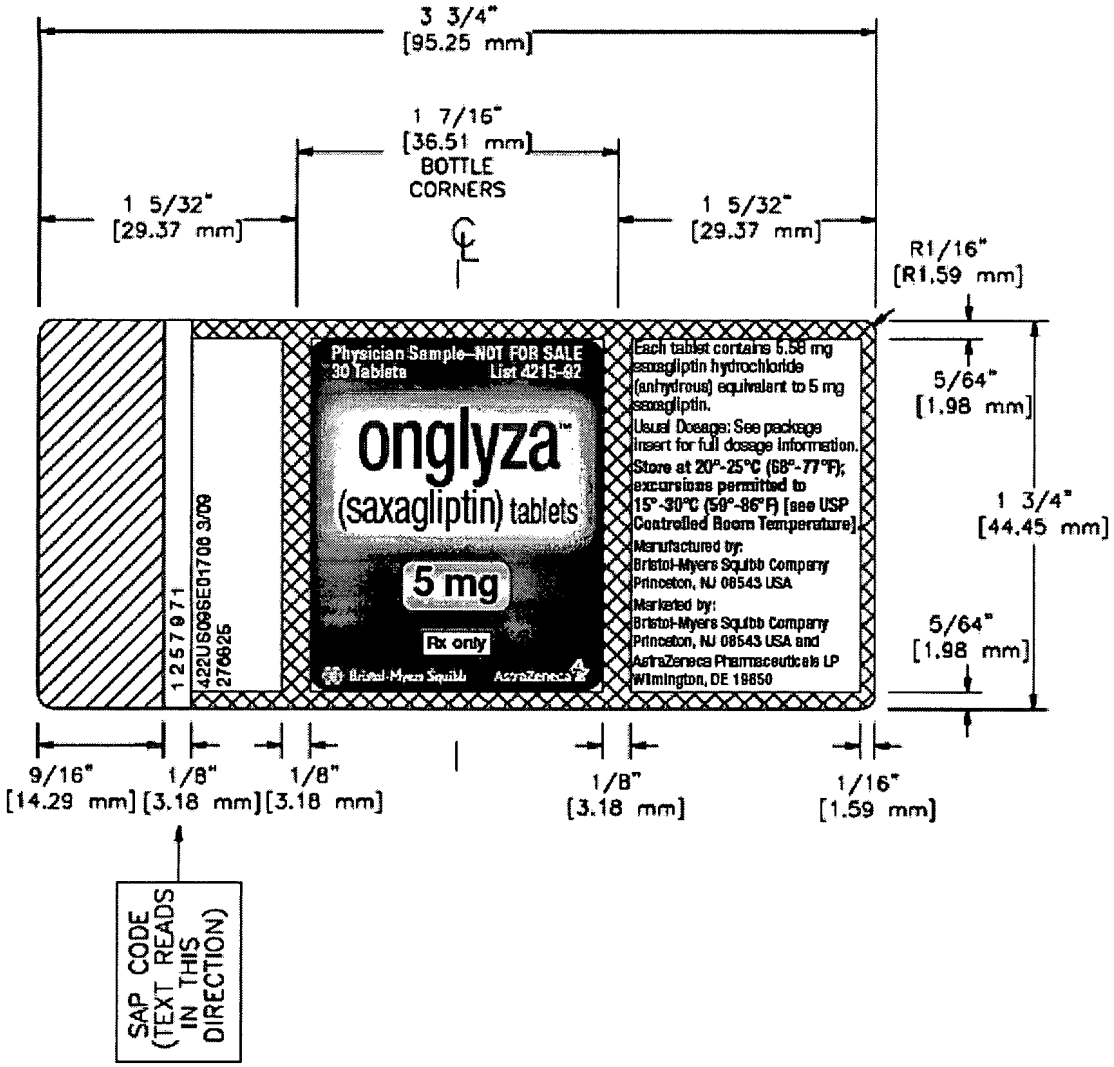

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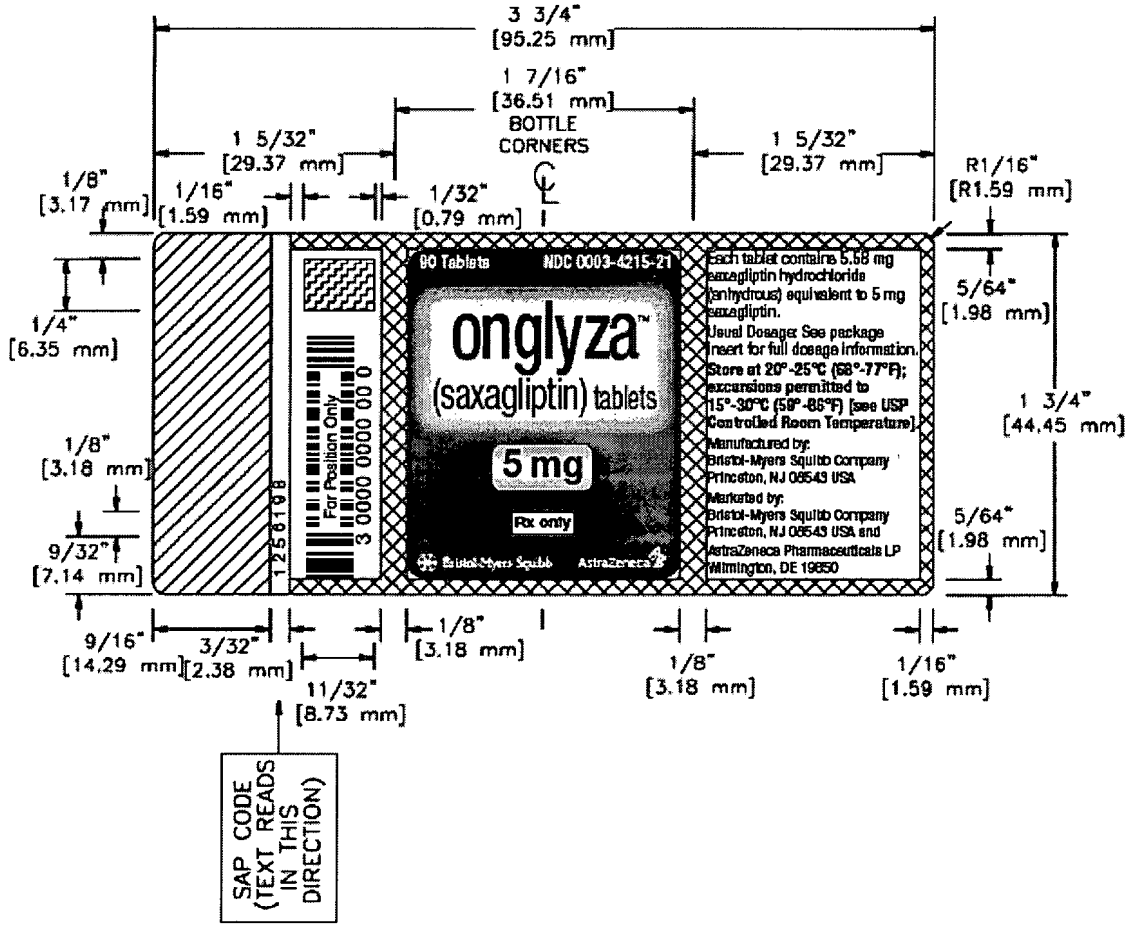
100%-0%-100%



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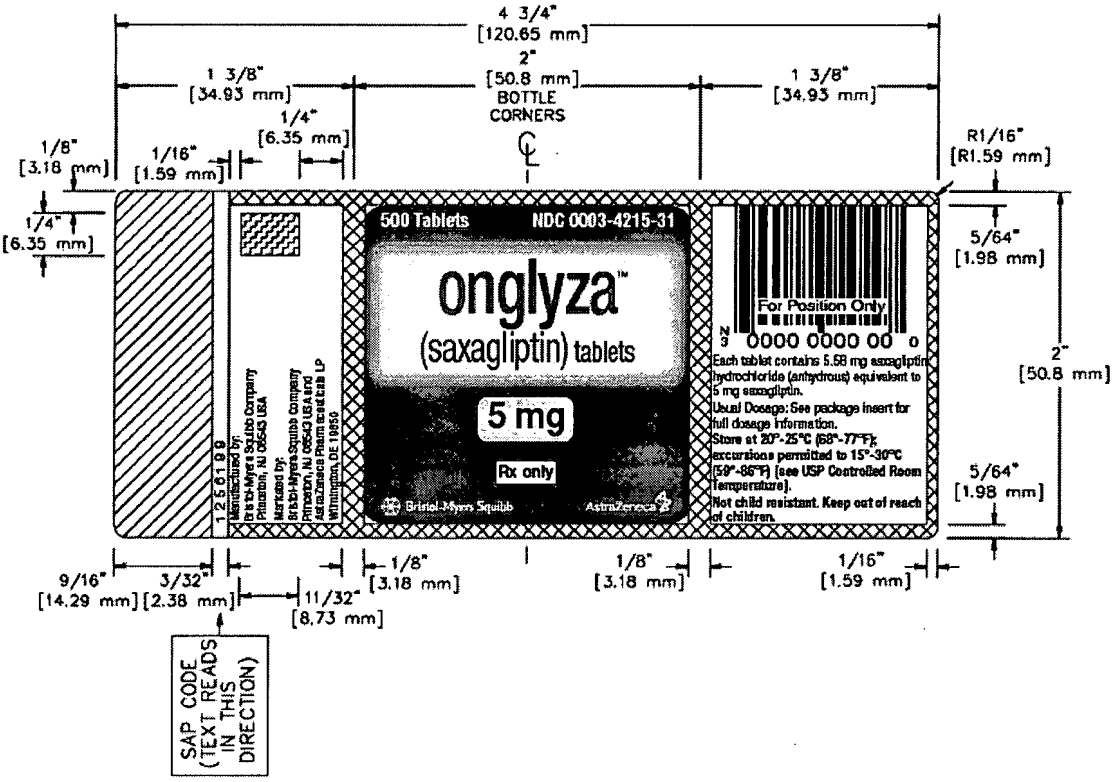

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(COPY FREE)

NO TEXT AREA

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PMS
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100%-0%-100%

Color Shifting Ink
Placeholder

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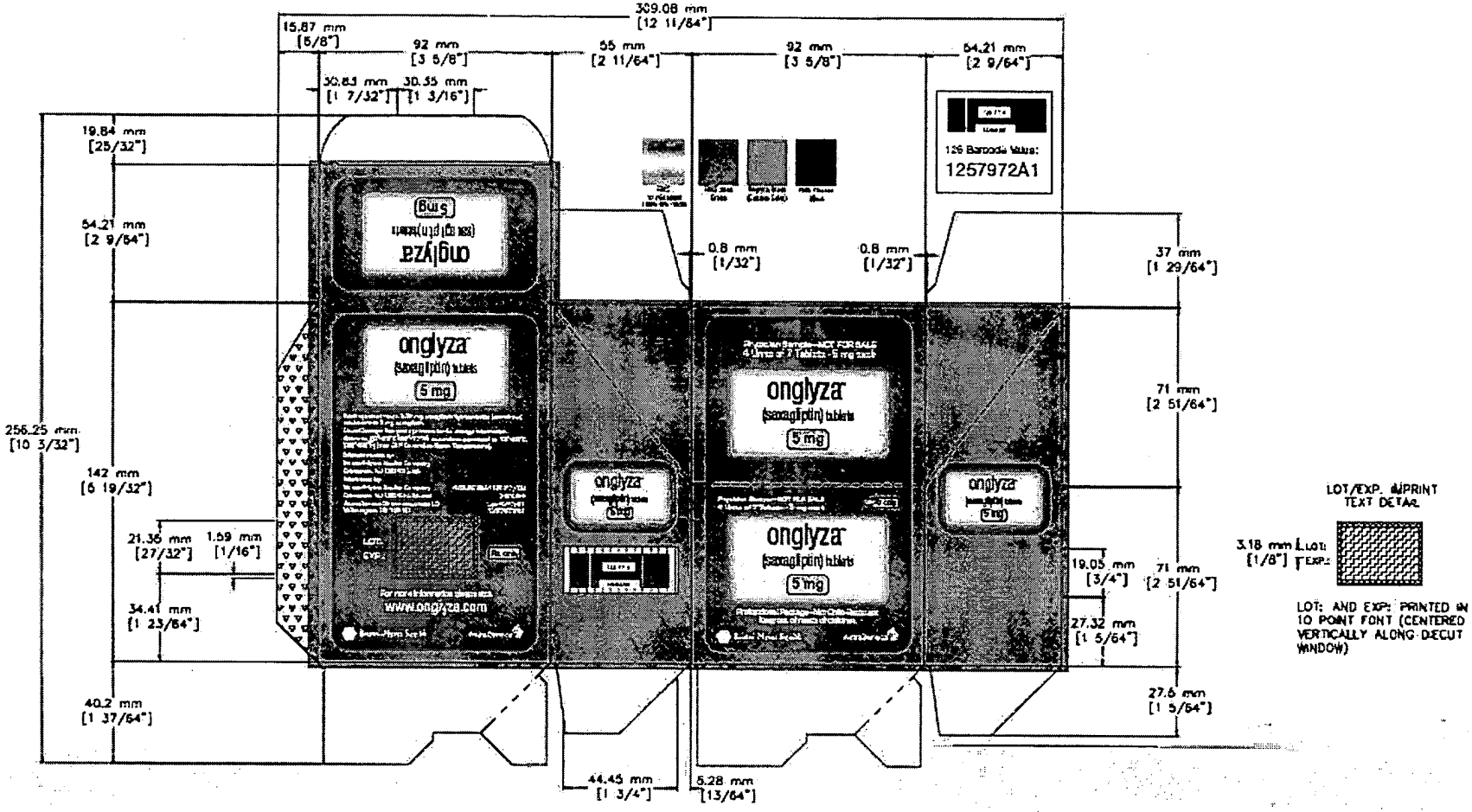
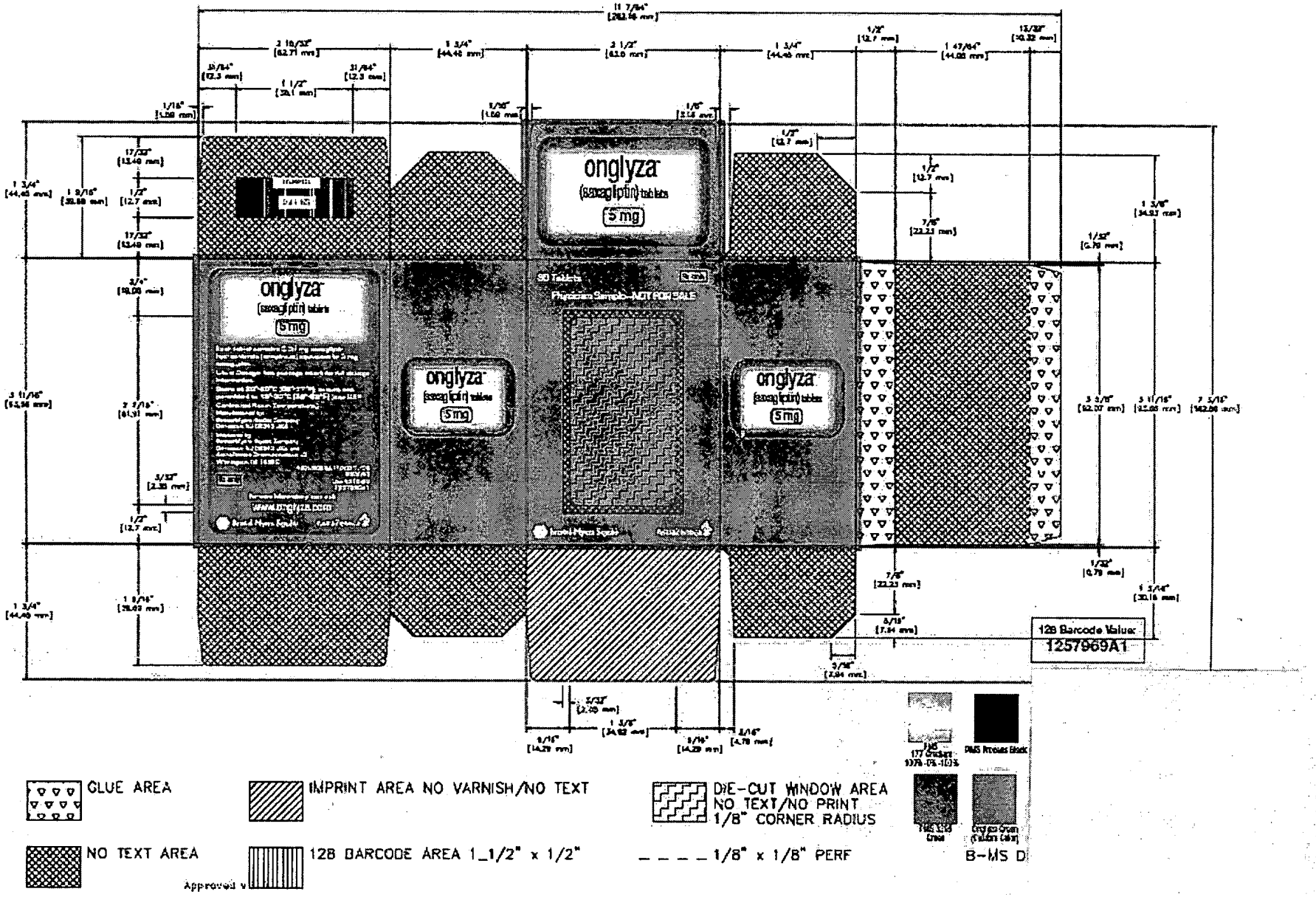
~~Approved v2.~~0





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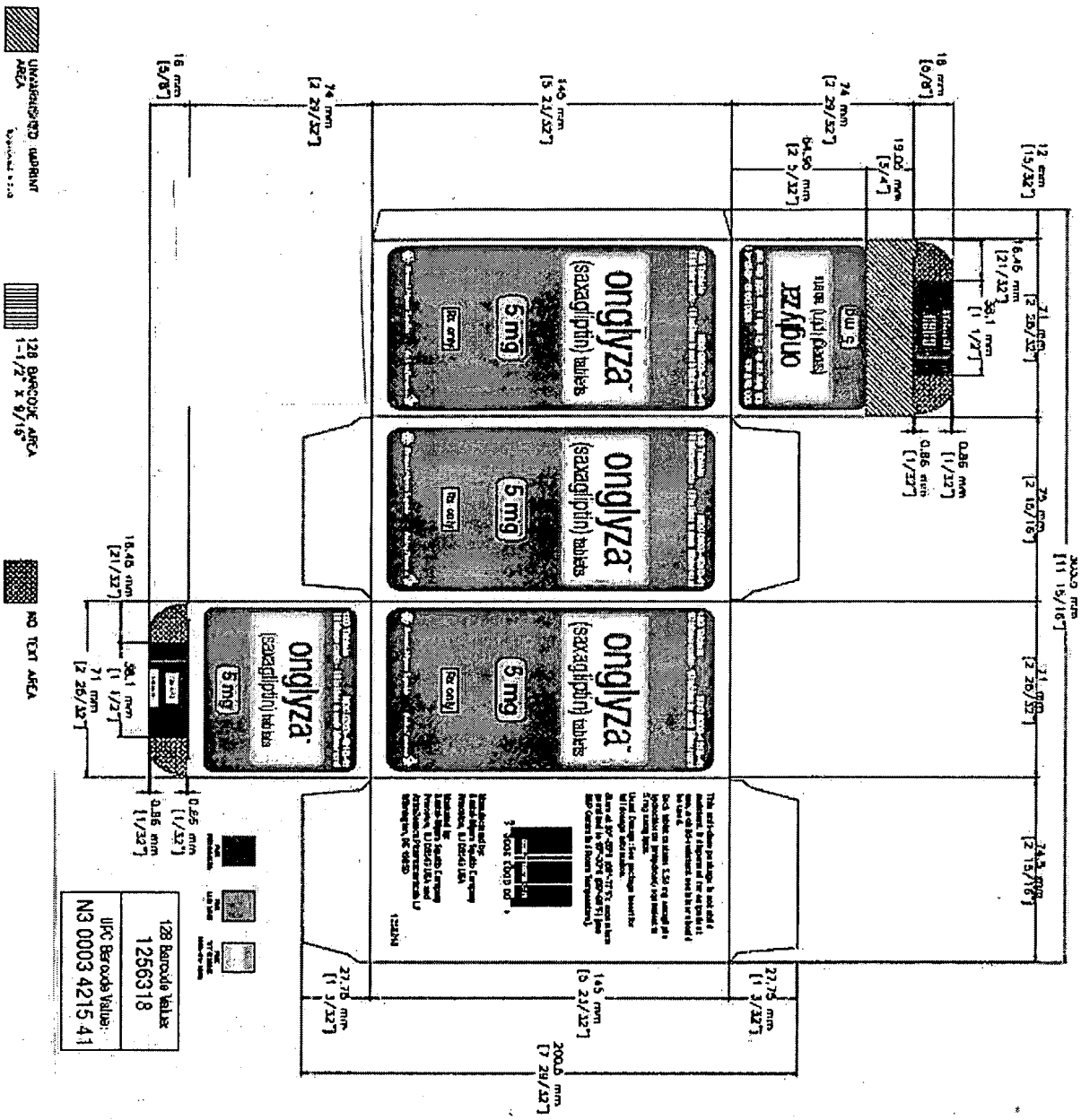

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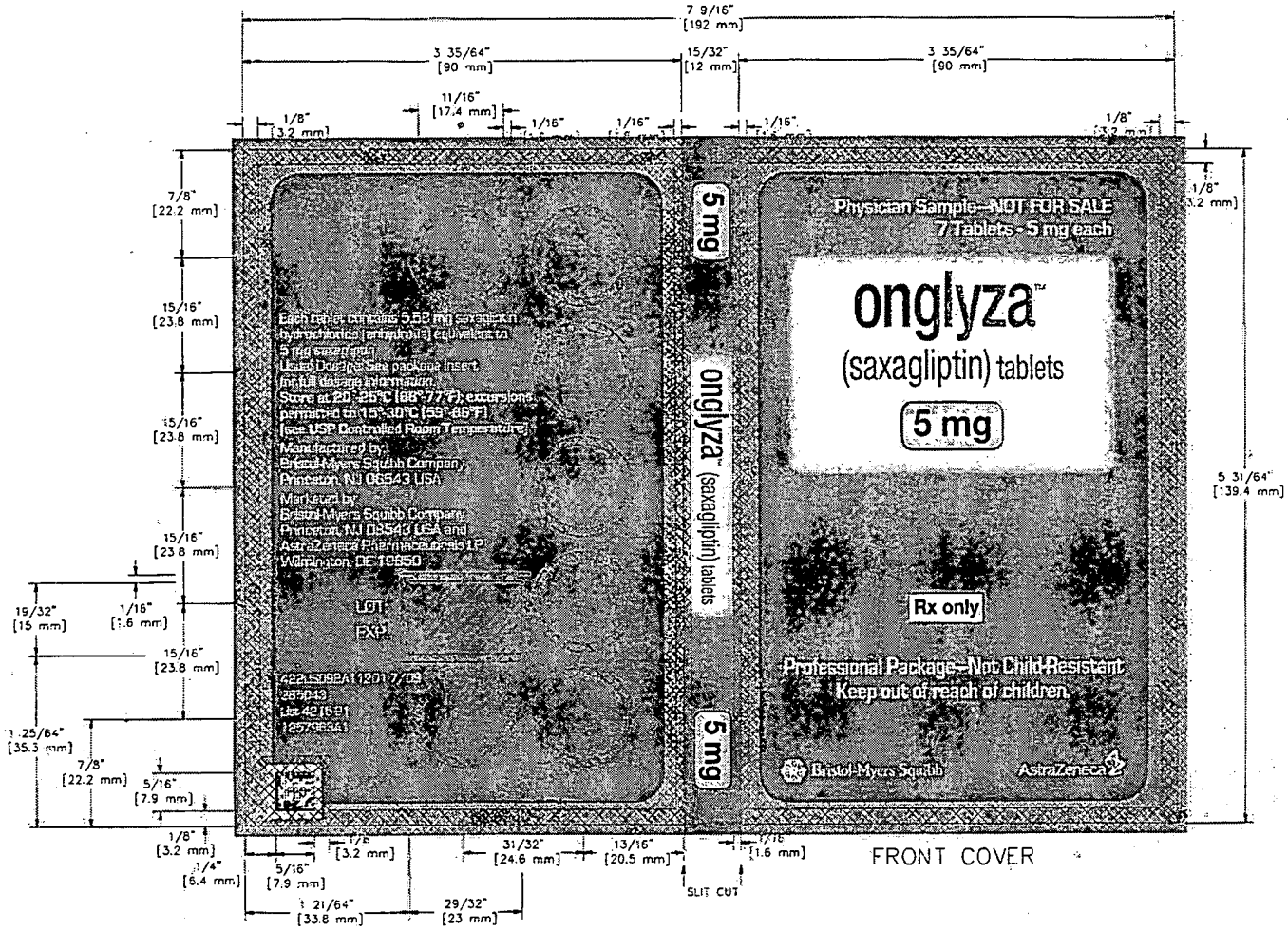

FRONT COVER

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Onglyza Green (Custom Color)

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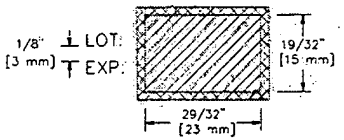

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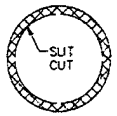

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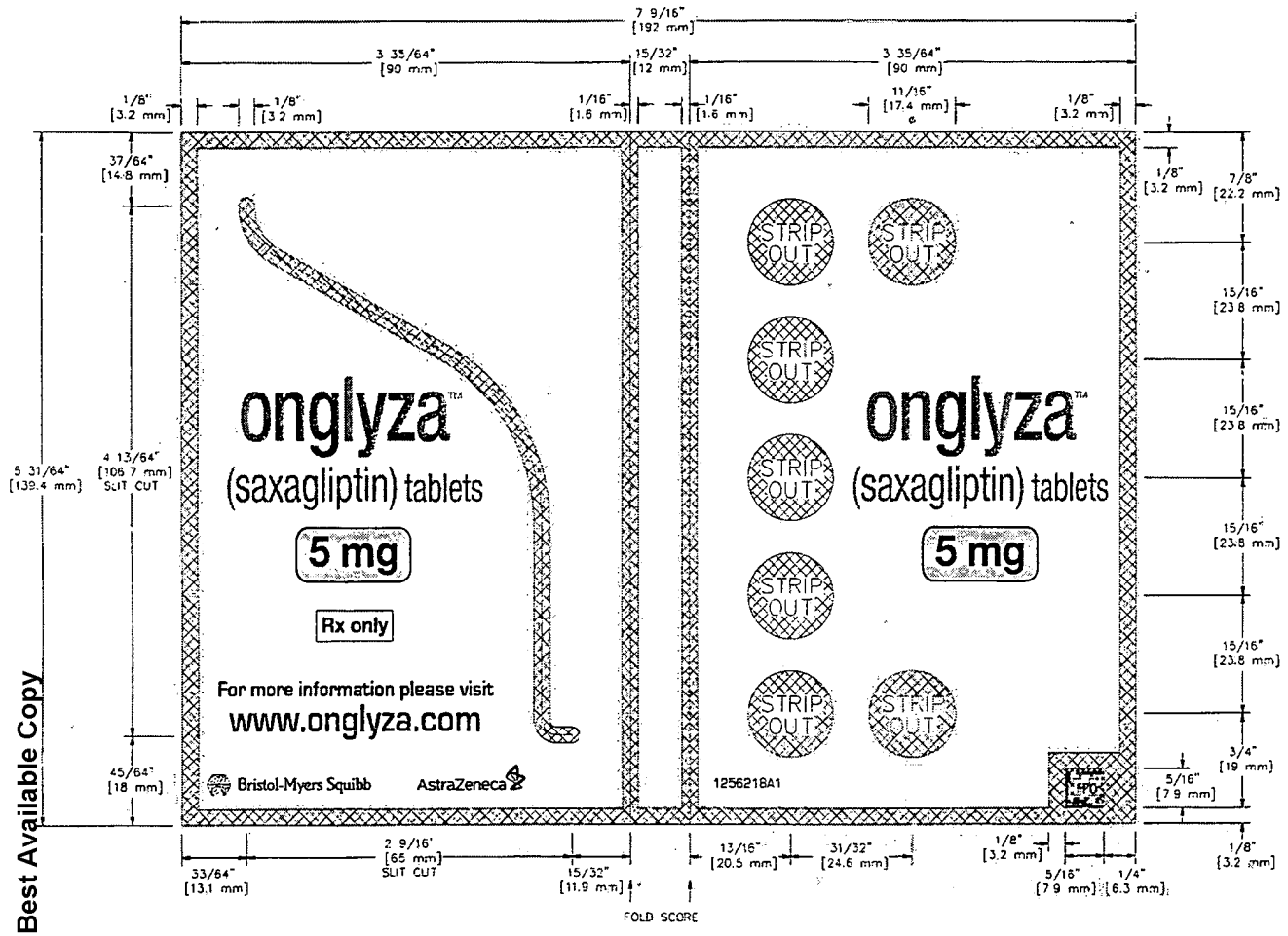

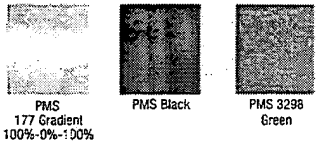

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1256218A1

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/s/

CURTIS J ROSEBRAUGH
07/31/2009

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United States Patent and Trademark Office

9

Maintenance Fee Statement **09/16/2009 03:35 PM EDT**

Patent Number: 6395767

Customer Number: 23914

LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,395,767	$900.00	$0.00	11/04/05	09/788,173	05/28/02	02/16/01	04	NO	LA0050 NP

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E

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 91,
Lines 9-10, should read -- A compound having the structure: --
Line 54, should read -- A compound which is --.

Signed and Sealed this

Twenty-seventh Day of July, 2004

Jon W. Dudas

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

LA0050

UNITED STATES PATENT AND TRADEMARK OFFICE US-NP

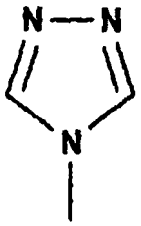
CERTIFICATE OF CORRECTION

Rodney

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,
Line 6, change "PGI" to -- PG_1 --.

Column 14,
Line 50, insert --  --.

Line 56, between "refers" and "cycloheteroakyl", insert -- to --.
Line 57, between "a" and "atom", insert -- C --.

Column 15,
Line 54, change "γ" to -- β --.

Column 20,
Line 59, "2,1" should be -- 2,3 --.

Column 29,
Line 23, change "w" to -- % --.

Column 30,
Line 2, after "$(M+H)^+$" and before "197", insert -- = --.

Column 32,
Line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Column 33,
Line 3, change "HO" to read -- H_2O --.
Line 7, change "CH2cl2" to read -- CH_2Cl_2 --.
Line 11, after "METHOD", insert -- A --.

Column 34,
Line 62, delete "15".

Column 41,
Line 43, after "was", delete "a".
Line 44, after "over", delete "a".

LA0050

UNITED STATES PATENT AND TRADEMARK OFFICE US-NP Rdnc

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 43,
Line 36, delete "E".
Line 55, change "48.61" to -- 8.61 --.

Column 44,
Line 39, change "200" to -- 300 --.

Column 46,
Line 58, change "ter" to -- water --.
Line 58, after "20" and before "Detection", insert -- mL/min. --.
Line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Column 52,
Line 64, change "25" to -- 28 --.

Column 53,
Line 31, change "OSO_4" to -- OsO4 --.
Line 65, after "100%" and before "Solvent A", insert -- B, --.
Line 66, after "vent B =" and before "MeOH", insert -- 90% --.

Column 62,
Line 67, change "549" to -- 540 --.

Column 66,
Line 24, change "$CH2Cl_2$" to read -- CH_2Cl_2 --.

Column 69,
Line 21, change "9" to -- 8 --.
Line 30, change "Hbl" to -- HCl --.

Column 70,
Line 56, move "Step 1" to line 65.

Column 72,
Line 36, change "50°" to -- 5° --.
Line 65, change "2.2(" to -- 2.28 --.
Line 65, change "30mL2" to -- 30 mL --.

Column 73,
Line 25, change "the n" to -- then --.
Line 26, change "et her" to -- ether --.

LA0050

US-NP
Rodney

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 74,
Line 32, change "50°" to -- 5° --.

Column 79,
Line 61, change "100" to -- 10% --.

Column 82,
Line 65, change "10EtOAc" to -- 10% EtOAc --.

Column 84,
Line 34, change "NS" to -- MS --.

Column 92,
Line 42, change "APR" to -- AR --.

Signed and Sealed this

Twenty-ninth Day of November, 2005

JON W. DUDAS
Director of the United States Patent and Trademark Office

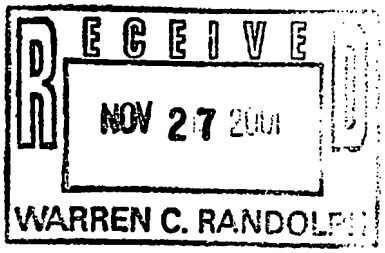
F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,634



Bristol-Myers Squibb
Attention: Warren Randolph
Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 63,634

Sponsor: Bristol-Myers Squibb

Name of Drug: BMS-477118 for Oral Administration

Date of Submission: November 8, 2001

Date of Receipt: November 8, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before December 8, 2001, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-6381.

Sincerely,

{See appended electronic signature page}

James T. Cross
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Cross
11/16/01 04:21:56 PM

(b)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-350

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

Dear Dr. Smith:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ONGLYZA (saxagliptin) Tablet 2.5 mg, 5mg

Date of Application: June 30, 2008

Date of Receipt: June 30, 2008

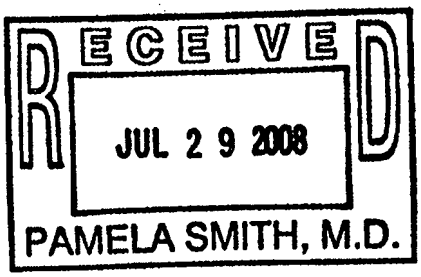
Our Reference Number: NDA 22-350

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266



If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rachel E Hartford
7/21/2008 09:22:25 AM

IND 63,634 / NDA 22-350

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
08-NOV-2001	SN0000	INITIAL APPLICATION	SUBMISSION	INITIAL IND DPP4 FOR TYPE 2 DIABETES.
16-NOV-2001		CORRESPONDENCE		FDA LETTER RE: ACKNOWLDEGE RECEIPT OF IND FOR BMS-477118 FOR ORAL ADMINISTRATION. THE IND WAS ASSIGNED NUMBER 63,634.
20-NOV-2001	SN0001	OTHER	SUBMISSION	OTHER: RESPONSE TO FDA REQUEST. DR. COLERANGLE'S TWO QUESTIONS RE: DEGRADANT BMS-537679 AND CMAX VALUES.
21-NOV-2001		CORRESPONDENCE	TELEPHONE	TEL CONTACT RE: OPHTHALMOSCOPIC RESULTS. DR. COLERANGLE CALLED TO REQ. THE OPHTHALMOSCOPIC DATA. HE WAS INFORMED THAT THE DATA WAS SUBMITTED IN THE APPENDIX OF THE RPTS. FILED IN THE IND. HE WAS ALSO INFORMED THAT THE TISSUE SPECIMENS FOR HISTOPATHOLOGY IN THE DOG STUDY WERE TAKEN FROM ANIMALS AT ALL DOSES.
07-DEC-2001		CORRESPONDENCE	TELEPHONE	TEL. CONTACT TO CONFIRM THAT AGENCY DOES NOT INTEND TO PUT BMS-477118 ON CLINICAL HOLD FOLLOWING 30-DAY REVIEW OF IND.
10-DEC-2001	SN0002	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-001, TO INCREASE TOTAL BLOOD VOLUME COLLECTED IN STUDY TO 737 ML PER SUBJECT FOR USE IN ADD'L ANALYSES, AND REVISES SHIPPING INSTRUCTIONS FOR GLP-1 SAMPLES.
17-DEC-2001		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING COMMENTS AND RECOMMENDATIONS FOLLOWING REVIEW OF SUBMISSION DATED 08-NOV-01, SERIAL #0000.
01-FEB-2002	SN0003	OTHER	SUBMISSION	OTHER:CHANGE IN CORRESPONDENT TO J. GENNARO. IND63,634
20-FEB-2002	SN0004	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC. CV181-002
04-MAR-2002	SN0005	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, BMS-477118.
13-MAR-2002	SN0006	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-002. AMEND. 2 (14-FEB-2002), ADMIN. LTR. 1 & 2(14-FEB-02 & 27-FEB-02). AMEND. TO MODIFY HBA1C.
27-MAR-2002	SN0007	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-002, AMEND. 3.
11-APR-2002		CORRESPONDENCE	LETTER	FDA LTR. RE: SN0004, DATED 20-FEB-02, AND INFORMATION RE: THE CLINICAL TRIALS DATA BANK.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
07-JUN-2002	SN0008	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	IND SAFETY RPT.: INITIAL WRITTEN RPT. PRELIMINARY FINDING RE: A DOSE OF 1SN000 UG/ML BMS-477118. A POSITIVE (MINIMAL) RESPONSE NOTED IN THE ABSENCE OF RAT-MICROSOMAL S9 MIX.
09-AUG-2002	SN0009	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	IND SAFETY RPT.: INITIAL RPT. OF DECREASED OSSIFICATION IN FETAL RAT PELVIS, AT MID AND HIGH DOSES, 930002160.
12-NOV-2002	SN0010	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, PROVIDING AMENDMENT AND A REVISED PROTOCOL FOR CV181-001, 930002843, 930000873.
18-NOV-2002	SN0011	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, FINAL TOX STUDY RPTS., 930002039, 930002987, 930002017, 930002469.
18-DEC-2002	SN0012	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PROVIDING PRECLINICAL RPTS., 930003146, 930001339, 930003036, 930003089.
24-JAN-2003	SN0013	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930003282, 930003281.
31-JAN-2003	SN0014	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, 2.5 MG POTENCY CAPSULE, UPDATED HPLC METHODS AND UPDATED DRUG SUBSTANCE STABILITY DATA. Minor API process change, new 2.5 mg capsules, updated API stability, and new HPLC assay method.
21-FEB-2003	SN0015	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930003433.
26-MAR-2003	SN0016	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROT., CHANGE IN PROT., NEW INVESTIGATOR, INFO. AMEND: CMC, INFO. AMEND: CLINICAL, CV181008.
01-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: LAB VALUES AVAILABILITY FOR CV181-002.
03-APR-2003		CORRESPONDENCE	EMAIL	FDA EMAIL PROVIDING SAMPLE FORMAT FOR HISTOPATHOLOGY DATA.
03-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR TOX. RPTS.
04-APR-2003	SN0017	OTHER	SUBMISSION	RESPONSE TO FDA REQUEST FOR INFORMATION PER 01-APR-03 CONTACT, LAB VALUES FOR CV181-002.
08-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR PK DATA, SINGLE/MULTIPLE ASCENDING DOSE STUDIES.
09-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING DATA PER FDA REQUEST 08-APR-03, DATA FROM STUDIES CV181-001, 002.
14-APR-2003	SN0018	ANNUAL REPORT	SUBMISSION	IND ANNUAL RPT. FOR PERIOD 01-DEC-01 TO 30- NOV-02.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
16-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR CLARIFICATION ON NATURE OF BMS-537679.
18-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 16-APR-03, TEL. REQUEST PROVIDING CLARIFICATION OF BMS-537679.
18-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 18-APR-03, TEL. REQUEST PROVIDING CLARIFICATION OF DOSING FOR STUDY DN02015.
18-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST ON CONTROL GROUPS IN EMBRYO-FETAL TOX. STUDIES.
18-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST ON DOSING SCHEDULE IN EMBRYO-FETAL STUDY, DN02015
21-APR-2003	SN0019	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-008, Amendment 02 to Protocol CV181008 VD.
23-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 18-APR-03, HISTORICAL CONTROL DATA FOR EMBRYO-FETAL STUDIES.
28-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO FDA, HISTORICAL CONTROL DATA ON RATS-PARIETALS AND SUPRAOCCIPITALS.
06-MAY-2003	SN0020	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, RESCUE MEDICATION IN UPCOMING CLINICAL STUDIES, BMS-477118-08. IND amendment adding modified Metformin.
21-MAY-2003	SN0021	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEN: PHARM/TOX, 930003282, Six-Month Oral Toxicity Study in Rats.
03-JUN-2003	SN0022	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATORS, CV181-008
25-JUN-2003	SN0023	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATORS, CV181-008.
07-JUL-2003		CORRESPONDENCE	LETTER	FDA LTR. W/ COMMENTS AND REQUEST RE: PRECLINICAL PHARMACOLOGY REVIEW OF IND.
17-JUL-2003	SN0024	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
29-JUL-2003	SN0025	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PRECLINICAL REPORTS, 930000835, 930000844.
31-JUL-2003	SN0026	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-008.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
06-AUG-2003	SN0027	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-010.
11-AUG-2003	SN0028	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, NOTIFICATION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, BMS NOTIFCATION OF SUBMISSION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT.
13-AUG-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: RESPONSE TO AUG. 11 NOTIFICATION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT.
18-AUG-2003	SN0029	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930004458
26-AUG-2003	SN0030	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
15-SEP-2003	SN0031	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
30-SEP-2003	SN0032	OTHER	SUBMISSION	OTHER: REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, CARCINOGENICITY STUDIES, INFO. AMDN: PHARM/TOX.
30-SEP-2003	SN0033	OTHER	SUBMISSION	OTHER: REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, CARCINOGENICITY STUDIES, INFO. AMEND: PHARM/TOX.
06-OCT-2003		CORRESPONDENCE	LETTER	FDA LTR. ACKNOWLEDGING RECEIP OF SUBMISSION DATED 30-SEP-03, SN032, SPECIAL CARC. PROTCOL ASSESSMENT.
07-OCT-2003	SN0034	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
09-OCT-2003	SN0035	OTHER	SUBMISSION	CHANGE IN BMS CORRESPONDENT TO PAMELA SMITH, M.D.
09-OCT-2003	SN0036	GENERAL CORRESPONDENCE	SUBMISSION	GENERAL CORRESPONDENCE PROVIDING CORRECT FDA FORM 1571 FOR SN# 0034.
14-OCT-2003		CORRESPONDENCE	LETTER	FDA LTR. RE: FDA IN REVIEW OF SPECIAL CARC. PROTOCOL ASSESSMENT DATED 30-SEP-03, SN# 033.
15-OCT-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: PHARM/TOX REVIEWER (J. COLERANGEL) DPP4 INHIBITOR, W/ QUESTION RE: MAX. HUMAN DAILY DOSE IN IND 63, 634.
15-OCT-2003		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONT. REP. (15 & 29-OCT) RE: PHARM/TOX REVIEWER ASKED IF MAX. HUMAN DOSE HAD BEEN CHANGED FROM 40 MG TO 200 MG. CONFIRMED AS CORRECT.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
29-OCT-2003		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONT. REP. (15 & 29-OCT) RE: PHARM/TOX REVIEWER ASKED IF MAX. HUMAN DOSE HAD BEEN CHANGED FROM 40 MG TO 200 MG. CONFIRMED AS CORRECT.
30-OCT-2003	SN0037	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181- 008, 930003574, Protocol CV181008 VD.
30-OCT-2003	SN0038	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, 930004940, Administrative Letter 01 to Protocol CV181010 VD.
31-OCT-2003	SN0039	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
10-NOV-2003		CORRESPONDENCE	FAX	FDA FAX RE: RESPONSE TO CARCINOGENICITY SPECIAL PROTOCOL ASSESSMENT REQUEST.
17-NOV-2003	SN0040	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: 4 NEW INVESTS; AND 4 CHANGE OF INVEST. INFO.
02-DEC-2003	SN0041	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: 3 NEW INVESTS; AND 4 CHANGE OF INVEST. INFO.
12-DEC-2003	SN0042	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROT. RE: AMEND. 4 FOR CV181008 ADDING 100 MG DOSE ARM AND AN ADD'L PLACEBO ARM.
18-DEC-2003	SN0043	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: THREE-MONTH ORAL RANGE-FINDING TOXICITY STUDY IN RATS, FULLY AUDITED FINAL REPORT.
23-DEC-2003	SN0044	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: NEW INVEST.
08-JAN-2004	SN0045	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: TWO-WEEK ORAL TOXICOKINETICS STUDY IN RATS; AND QUALIFYING REVERSE-MUTATION STUDY IN SALMONELLA TYPHIMURIUM AND ESCHERICHIA COLI.
16-JAN-2004	SN0046	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: TWO WEEK ORAL TOXICOKINETICS STUDY IN MICE, FULLY AUDITED FINAL REPORT.
29-JAN-2004	SN0047	OTHER	SUBMISSION	RESPONSE TO FDA CAC REVIEW FOR MOUSE AND RAT CARCINOGENICITY STUDY DOSE SELECTION.
03-FEB-2004		CORRESPONDENCE	TELEPHONE	TEL. CONT. REP. RE: IN RESPONSE TO CAC REVIEW BMS WILL BE SUBMITTING A RESPONSE AGREEING TO USE ALL RECOMMENDED DOSES IN MOUSE AND RAT CARCINOGENICITY STUDIES. BMS WILL BE ADDING AN ADD'L DOSE FOR BOTH MALE AND FEMALES IN RAT STUDY TO ENSURE ACHIEVEMENT OF MAXIMAL TOLERATED DOSE (MTD).

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
11-FEB-2004	SN0048	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	INIT SAFETY REP. RE: GASTROENTERITIS, REP NO. 12491080
12-FEB-2004	SN0049	ANNUAL REPORT	SUBMISSION	ANNUAL REPORT FOR PERIOD 01-DEC-02 TO 30-NOV-03.
25-FEB-2004	SN0050	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: REVERSE-MUTATION STUDY IN SALMONELLA TYPHIMURIUM AND ESCHERICHIA COLI, 930004892 V.1.O
27-FEB-2004	SN0051	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROT. RE: AMENDS. 1 & 2 OF CV181010; AND AMEN
18-MAR-2004	SN0052	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT, OTHER: CHANGE IN INVESTIGATOR INFORMATION, PROTOCOL CV181-008
19-MAY-2004	SN0053	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, CHANGE IN PROTOCOL, CV181-003.
15-JUN-2004	SN0054	INFO AMENDMENT - CMC	SUBMISSION	To provide information on drug substance in free base monohydrate form and on film-coated tablets (5 and 40 mg)
28-JUN-2004	SN0055	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND.: CMC
16-JUL-2004	SN0056	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND.: CMC
06-AUG-2004	SN0057	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: REVISED PROTOCOL FOR CV181005
25-AUG-2004	SN0058	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND. CMC, To provide information on C14-labeled drug substance and drug product to support the ADME study (CV181-004)
26-AUG-2004	SN0059	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MTG.
13-SEP-2004	SN0060	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MTG. RE: TYPE B MTG. TO REVIEW RESULTS OF CLINICAL TRIALS AND RELEVANT PRECLINICAL STUDIES SUPPORTING PROPOSED PHASE 3.
14-SEP-2004	SN0061	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND. CMC RE: CV181-022.
14-SEP-2004	SN0062	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: ORAL STUDY OF FERTILITY AND EARLY EMBRYONIC DEVELOPMENT IN RATS, 930007579 V.1.O; AND TWELVE-MONTH ORAL TOXICITY STUDY IN DOGS, 930008126 V.1.O
22-SEP-2004		CORRESPONDENCE	LETTER	FDA LTR. RE: TYPE B END OF PHASE 2 MTG SET FOR 19-NOV-04.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
23-SEP-2004	SN0063	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROTOCOL, RE: CV181-022. AMEND. 02
21-OCT-2004		CORRESPONDENCE	FAX	BMS FAX PROVIDING COPY OF IND SAFETY RPT.: NON-CLINICAL EXPEDITED. ADDENDUM TO INV. BROCHURE FOR BMS-477118.
21-OCT-2004		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACTS (OCT. 21 & 22)RE: CANCELLATION OF EOP2 MTG.
21-OCT-2004	SN0064	OTHER	SUBMISSION	IND SAFETY RPT.: NON-CLINICAL EXPEDITED. ADDENDUM TO INV. BROCHURE FOR BMS-477118.
22-OCT-2004		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACTS (OCT. 21 & 22)RE: CANCELLATION OF EOP2 MTG.
20-DEC-2004	SN0066	OTHER	SUBMISSION	OTHER: REQUEST FOR MEETING.
29-DEC-2004		CORRESPONDENCE	LETTER	FDA LTR. RE: NO NEED FOR REQUESTED MTG. PER BMS LTR. DATED 20-DEC-04.
14-JAN-2005	SN0067	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, CONVERSION OF BMS-477118, AND INITIATION OF 104-WK. ORAL GAVAGE CARC. STUDY IN RATS.
07-FEB-2005	SN0068	ANNUAL REPORT	SUBMISSION	Annual Report FOR 01-DEC-03 TO 30-NOV-04, INCLUDING Quality Section.
22-FEB-2005	SN0069	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, 930009626, Placeo-Controlled, Ascending Single-Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of BMS-477118 in Healthy Subjects.
02-MAR-2005	SN0070	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, RESULTS FROM CNS TOXICITY/ HISTOPATHOLOGY STUDY IN RATS.
21-APR-2005	SN0071	INFO AMENDMENT - CMC	SUBMISSION	IND amendment - To provide drug products information to support Phase III clinical studies
28-APR-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT INFORMING FDA THAT UPDATE ON RAT CNS FINDINGS TO BE SUBMITTED SOON.
11-MAY-2005	SN0072	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PROVIDING 1-YEAR INTERIM ANALYSIS OF THE CHRONIC INVESTIGATIONAL CNS TOXICITY STUDY IN RATS.
11-MAY-2005	SN0073	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MEETING.
13-MAY-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT TO CONFIRM AGENCY RECEIPT OF SUBMISSIONS; CNS TOX. SAFETY UPDATE AND REQUEST FOR EOP2 MEETING.
17-MAY-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT STATING THAT CNS TOX. UPDATE REVIEWED BY FDA, AND EOP2 MTG. TO BE SCHEDULED FOR 27-JUL-05.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
19-MAY-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING DETAILS FOR EOP2 MTG. SCHEDULED FOR 27-JUL-05.
01-JUN-2005	SN0074	OTHER	SUBMISSION	OTHER: UPDATED INVESTIGATOR BROCHURE.
16-JUN-2005	SN0075	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND: CMC, CV181-011.
20-JUN-2005	SN0076	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND:PHARM/TOX.
23-JUN-2005	SN0077	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND: CMC.
27-JUN-2005	SN0078	OTHER	SUBMISSION	EOP2 BRIEFING BOOK
27-JUN-2005		OTHER	SUBMISSION	OTHER: RESPONSE TO REQUEST FOR INFORMATION, PROVIDING DESK COPY OF PROTOCOL CV181-011.
08-JUL-2005	SN0079	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, FINAL STUDY RPT. 930011138.
15-JUL-2005	SN0080	INFO AMENDMENT - CMC	SUBMISSION	To request CMC end of Phase 2 meeting
19-JUL-2005		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING ADD'L ANALYSIS OF NON-CLINICAL EXPOSURE FOR SAXAGLIPTIIN.
19-JUL-2005	SN0081	RESPONSE TO REQUEST	SUBMISSION	RESPONSE TO REQUEST FOR ADDITIONAL INFO RE:NONCLINICAL SAXAGLIPTIN EXPOSURE.
20-JUL-2005	SN0082	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMEND:NEW INVESTIGATOR/CHANGE IN INVESTIGATOR
22-JUL-2005	SN0083	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO.AMEND.:CLINICAL CV181-008
26-JUL-2005		CORRESPONDENCE	FAX	FAX CORRESPONDENCE RE:IND 63,634 DRAFT VERSION OF PRE-MEETING RESPONSES FOR END OF PHASE 2 MEETING
01-AUG-2005	SN0084	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO.AMEND.:PHARMACOLOGY/TOXICOLOGY
22-AUG-2005	SN0085	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, CM EOP2 MTG.-BACKGROUND INFO. To provide the briefing package for the CMC end of Phase 2 meeting
23-AUG-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING OFFICIAL MINUTES FROM EOP2 MTG. ON 27-JUL-05.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
24-AUG-2005	SN0086	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014.
24-AUG-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING COMMENTS AND RECOMMENDATIONS FOR SUBMISSION DATED 16-JUN-05, SN 075, CV181-011.
25-AUG-2005	SN0087	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-018.
29-AUG-2005		CORRESPONDENCE	FAX	FDA FAX PROVIDING CMC WITH LTR. COPY PREVIOUSLY SENT RE: EOP2 MTG.
30-AUG-2005	SN0088	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, CV181-008.
08-SEP-2005	SN0089	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014.
09-SEP-2005	SN0091	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-028
09-SEP-2005	SN0090	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-026.
22-SEP-2005	SN0092	OTHER	SUBMISSION	OTHER: REQUEST FOR FDA REVIEW AND COMMENT, RE: CARCINOGENICITY STUDY IN MICE.
27-SEP-2005		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA re: a F/U to the BMS-477118 mouse carcinogenicity study phone discussion on Sep 27, 2005 b/w Dr.El-Hage(US FDA) & Greg Cosma and Joseph Lamendola(both from BMS)
27-SEP-2005	SN0093	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-018, (AMEND. 3 & REVISED PROT. 2).
05-OCT-2005	SN0094	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014, 018, 026.
10-OCT-2005	SN0095	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND. Pharm/Tox. Providing, Tocicology info.Re: Mouse carcinogencity.
13-OCT-2005		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACT (OCT. 13, 18) RE: BMS SUBMISSION OF EXPEDITED NONCLINICAL SAFETY RPT. AND TELECONF. TO BE SCH.TO DISSCUSS FINDINGS IN 1 MTH. MONKEY STUDY.
13-OCT-2005	SN0096	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	RE: IND SAFETY REPORT: NON- CLINICAL EXPEDITED RE: INVESTIGATOR BROCHURE TO BMS

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14-OCT-2005	SN0097	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND. PHARM/TOX. PROVIDING FINAL STUDY REPORTS.
18-OCT-2005		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACT (OCT. 13, 18) RE: BMS SUBMISSION OF EXPEDITED NONCLINICAL SAFETY RPT. AND TELECONF. TO BE SCH.TO DISSCUSS FINDINGS IN 1 MTH. MONKEY STUDY.
20-OCT-2005	SN0098	OTHER	SUBMISSION	Other: Response to FDA Review and Comment RE: ANCOVA Model
25-OCT-2005	SN0099	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Prot. Amend. New Investigator, CV181-011,014.
01-NOV-2005		CORRESPONDENCE	EMAIL	FDA E-MAIL RE:FDA LTR. RE: DIVISION RECOMMENDS CONDUCTING A 3 MTH. ORAL TOXICITY RELATING TO (DPP-4).
01-NOV-2005		CORRESPONDENCE	LETTER	FDA LTR. RE: DIVISION RECOMMENDS CONDUCTING A 3 MTH. ORAL TOXICITY RELATING TO (DPP-4).
04-NOV-2005	SN0100	OTHER	SUBMISSION	NOTICE OF SITE CLOSURE FOR CV181-014-101
07-NOV-2005	SN0101	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT., AMEND. NEW PROT. NEW INVESTIGATOR, INFO. AMEND.:CMC, CV181-032
16-NOV-2005	SN0102	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Prot. Amend.: New Investigator For CV181-011,014
30-NOV-2005	SN0103	INFO AMENDMENT - CMC	SUBMISSION	Info. Amend: CMC, Information amendment to support BA studies for the 10 mg tablets. The 1 mg tablets formulation will be included in the amendment
01-DEC-2005	SN0104	OTHER	SUBMISSION	Other - Addendum #1 to IB version 3 dated 11-May-2005
01-DEC-2005	SN0105	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-033; Information Amendment - CMC for the clinical supplies to be used in the conduct of Protocol CV181-033
07-DEC-2005	SN0106	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amendment - Change in protocol for CV181-011
12-DEC-2005	SN0107	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment - New Investigator for CV181-011, CV181-014; Other - Change in Investigator Information for CV181-011 & CV181-014
14-DEC-2005	SN0108	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-013; Info. Amendment - CMC
14-DEC-2005	SN0109	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amendment - Change in Protocol for CV181-014

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14-DEC-2005		CORRESPONDENCE	LETTER	FDA ltr. providing comments & recommendations upon completion of review of submission dated 07-Nov-2005 (Serial# 101).
16-DEC-2005	SN0110	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-020; Info. Amendment CMC.
16-DEC-2005	SN0111	OTHER	SUBMISSION	Other - Transfer of Obligations to a CRO (ICON Clinical Research,Inc.) for CV181-013
19-DEC-2005	SN0112	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-036; Info. Amendment - CMC
22-DEC-2005	SN0113	OTHER	SUBMISSION	Other - Request for FDA review & comment, on the draft protocol synopsis of Protocol CV181-039 and its acceptability to support an indication for first line combination therapy w/ Saxagliptin & Metformin as well as ques. re: CV181-039
23-DEC-2005	SN0114	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Info. Amendment - Pharm/Tox. as a follow-up to the phone discussion that took place b/w Jeri El Hage from US FDA and Greg Cosma & Joseph Lamendola, both from BMS re: BMS-477118 mouse carcinogenecity study.
28-DEC-2005		CORRESPONDENCE	LETTER	Telephone contact w/ FDA re: completing arrangements for the Nov 2 teleconference.
29-DEC-2005		CORRESPONDENCE	LETTER	Telephone contact w/ FDA re: our proposed statistical aproach for the pivotal Phase 3 studies to include subgroup analysis by region
12-JAN-2006	SN0115	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment - New Investigator for CV181-011 & CV181-014, Other - Change in Investigator Information for CV181-011
13-JAN-2006	SN0116	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharmacology/Toxicology, One Month Subcutaneous Investigative Toxicity Study in Rats
17-JAN-2006	SN0117	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharmacology/ Toxicology Re: 104 Week Oral Rat Carcinogenicity Study.
19-JAN-2006		CORRESPONDENCE	LETTER	FDA ltr. re: completion of review of amendment dated 14-Dec-2005 (serial 108). FDA provided comments & recommendations.
25-JAN-2006		CORRESPONDENCE	EMAIL	Email sent to FDA re: Saxagliptin initial combination questions. Per FDA request, the ques re: review of study design for Protocol 039, was provided in MS Word format.
27-JAN-2006	SN0118	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-019 & CV181-027 & Info amendment CMC re: CV181-019 & CV181-027
30-JAN-2006		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA re: the control group in the rat carcinogenicity study.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
30-JAN-2006		CORRESPONDENCE	LETTER	FDA ltr. re: completion of review of the Amendment dated 22-Dec-2005. FDA provided comments to BMS' questions
31-JAN-2006		CORRESPONDENCE	EMAIL	FDA email w/comments re: the Protocol synopsis (CV181-039), submitted by BMS on 22-Dec-2005
01-FEB-2006		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA to clarify BMS' interest on Dr.Misbin's (Clinical Reviewer) comments on Protocol 013 (TZD study), as well as BMS' decision to accept Dr. El-Hage's suggestion re: control group in the rat carcinogenicity study.
02-FEB-2006		RESPONSE TO REQUEST	SUBMISSION	Other - Response to Request for Info. re: a desk copy of Study DN03009, three-month Oral range finding toxicity study in rats
03-FEB-2006	SN0119	ANNUAL REPORT	SUBMISSION	IND annual report for the period 01-Dec-2004 to 30-Nov-2005
03-FEB-2006		CORRESPONDENCE	FAX	BMS Fax Re: Saxagliptin: 1 to 3-Month Monkey Toxicity Study.
13-FEB-2006		CORRESPONDENCE	EMAIL	FDA Email re: IND 63,634, Draft Statement for ESR (Saxagliptin).
14-FEB-2006	SN0120	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT: NEW INVESTIGATOR OTHER: CHANGE IN INVESTIGATOR INFORMATION
15-FEB-2006	SN0121	OTHER	SUBMISSION	RE IND SAFETY REPORT: NON-CLINICAL EXPEDITED
24-FEB-2006	SN0122	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFORMATION AMENDMENT: PHARMACOLOGY/TOXICOLOGY
03-MAR-2006		CORRESPONDENCE	EMAIL	FDA Email re: Draft Informed Consent. The Agency reviewed proposed revised language for the informed consent.
07-MAR-2006	SN0123	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROTOCOL AMENDMENT: NEW PROTOCOL, NWE INVESTIGATOR INFORMATION AMENDMENT: CHEMISTRY, MANUFACTURING, AND CONTROL. CV181037
13-MAR-2006	SN0124	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT: NEW INVESTIGATOR OTHER: CHANGE IN INVESTIGATOR INFORMATION. CV181-013
17-MAR-2006	SN0125	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amend: Change in Protocol. Amendment #03 and Revised Protocol 01 and 02 to Protocol CV181-019 and CV181-032.
23-MAR-2006	SN0126	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharm/Toxic: BMS-477118
23-MAR-2006	SN0127	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amend: New Protocol, New Investigator Info Amend: CMC: Primary Obj. of Protocol CV181-040 is to compare after 24 weeks of oral adm. of double-blind treatment.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
23-MAR-2006	SN0128	OTHER	SUBMISSION	Other: Revised Informed Consent Form: BMS-477118 and email communication approving text for ICFs.
30-MAR-2006	SN0129	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment: New Investigator:Protocol CV181-013.
12-APR-2006		CORRESPONDENCE	LETTER	FDA Ltr. Re: Saxagliptin (BMS-477118) Capsules and Amendment dated 01/12-05 (serial #105) New Protocol CV181033: Pharmacokinetic Drug Interaction Study with Saxagliptin and Simvastatin in Healthy Subjects," completed review with comments and recommendations.
20-APR-2006	SN0130	OTHER	SUBMISSION	Other - Request for Meeting via teleconference to discuss our plans to monitor events of special interest in the saxagliptin program
24-APR-2006	SN0131	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Invesitgator Info Amend: CMC and Control Other: Transfer of Obligations to Contract Research Organization. Re: CV181038
24-APR-2006	SN0132	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Invesitgator Info Amend: CMC and Control Other: Transfer of Obligations to Contract Research Organization. Re: CV181039
26-APR-2006		CORRESPONDENCE	TELEPHONE	FDA Telephone Contact re: Off-target binding activities (other DPP enzymes) of Saxagliptin.
27-APR-2006	SN0133	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amend: Change in Protocol re: Protocol CV181027 study has been discontinued due to protocol deviation.
28-APR-2006	SN0134	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amend: New Investigator: Other: Change in Investigator Information re: Protocols CV181013 & CV181040.
28-APR-2006		CORRESPONDENCE	LETTER	FDA Ltr. re: The Request for a Teleconference mtg to discuss Saxagliptin prog have been denied, FDA provided written reponses to questions included in meeting request.
11-MAY-2006	SN0135	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protcol, New Investigator Information Amendment: CMC re: Protocol CV181035
17-MAY-2006	SN0136	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Investigator Information Amendment1: CMC re: Protocol CV181052
17-MAY-2006		CORRESPONDENCE	LETTER	FDA orginal Ltr re: FDA respond to BMS question regarding BMS Amendment dated 20-Apr-06, Serial #130 requesting a teleconference to discuss plans to implement additional monitor to collect info on saxagliptin prg. FDA denied mtg with written response to questions included in meeting request.