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REISSUE PATENT APPLICATION TRANSMITTAL

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Attorney Docket No.	BMS-2856
First Named Inventor	Jeffrey A. Robl
Original Patent Number	6,395,767
Original Patent Issue Date (Month/Day/Year)	May 28, 2002
Express Mail Label No.	

APPLICATION FOR REISSUE OF: *(Check applicable box)* ☑ Utility Patent ☐ Design Patent ☐ Plant Patent

APPLICATION ELEMENTS (37 CFR 1.173)

1. ☐ Fee Transmittal Form (PTO/SB/56)
2. ☐ Applicant claims small entity status. See 37 CFR 1.27.
3. ☑ Specification and Claims in double column copy of patent format *(amended, if appropriate)*
4. ☑ Drawing(s) *(proposed amendments, if appropriate)*
5. ☑ Reissue Oath/Declaration (original or copy) (37 C.F.R. 1.175) (PTO/SB/51 or 52)
6. ☑ Power of Attorney
7. ☑ Original U.S. Patent currently assigned? ☑ Yes ☐ No
   (If Yes, check applicable box(es))
   - ☑ Written Consent of all Assignees (PTO/SB/53)
   - ☑ 37 CFR 3.73(b) Statement (PTO/SB/96)
8. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
   - ☐ Landscape Table on CD
9. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, items a. – c. are required))*
   - a. ☐ Computer Readable Form (CRF)
   - b. Specification Sequence Listing on:
     - i ☐ CD-ROM (2 copies) or CD-R (2 copies); **or**
     - ii ☐ paper
   - c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

10. ☑ Statement of status and support for all changes to the claims. See 37 CFR 1.173(c).
11. ☐ Foreign Priority Claim (35 U.S.C. 119) *(if applicable)*
12. ☑ Information Disclosure Statement (IDS) PTO/SB/08 or PTO-1449
    - ☑ Copies of citations attached
13. ☐ English Translation of Reissue Oath/Declaration *(if applicable)*
14. ☑ Preliminary Amendment
15. ☐ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
16. ☐ Other:

17. CORRESPONDENCE ADDRESS

☑ The address associated with *Customer Number:* 46339 ***OR*** ☐ *Correspondence address below*

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Signature	/S. Maurice Valla/	Date	December 1, 2011
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US006395767B2

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

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

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

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(*) 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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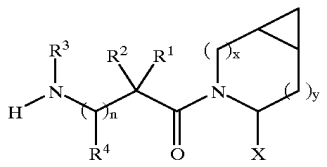
(57) **ABSTRACT**

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

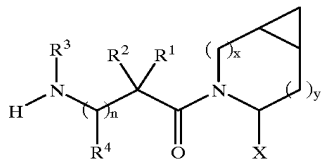
Depeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous 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

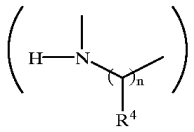
x=0 when y=1);

n is 0 or 1;

X is H or CN (that is cyano);

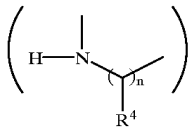
R^1, R^2, R^3 and $R^4$are the same or different and are independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, 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

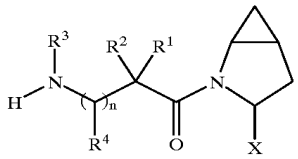


form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

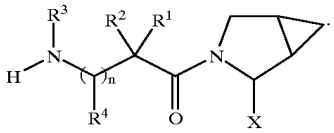
and including pharmaceutically acceptable salts thereof, and prodrug esters thereof, and all stereoisomers thereof.

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.

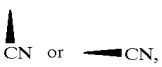
The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than DP4 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-modulating agents (including anti-atherosclerosis agents), and/or one or more infertility agents, 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.

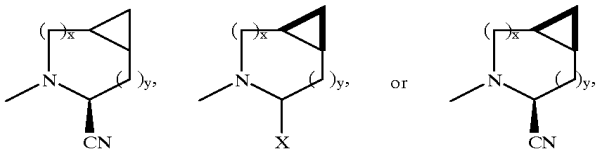
Preferred are compounds of formula I wherein R^3 is H or alkyl, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxytricycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxyalkylcycloalkyl, R^2 is H or alkyl, n is 0, X is CN, x is 0 or 1 and y is 0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

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



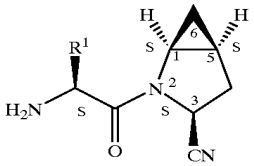
and/or wherein the fused cyclopropyl group is identified as

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



Particularly preferred are the following compounds:

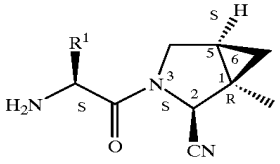
A)



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

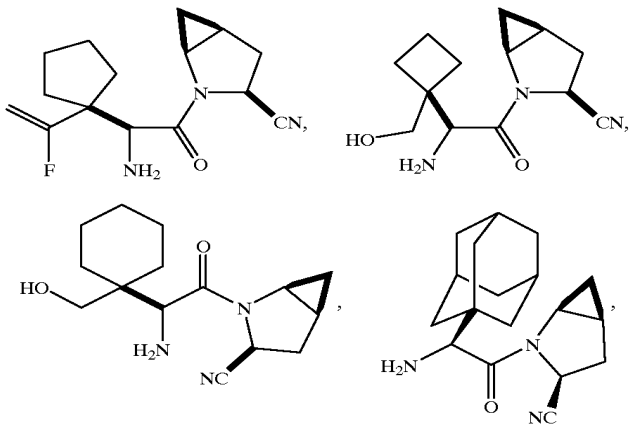
wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl or hydroxytricycloalkyl;

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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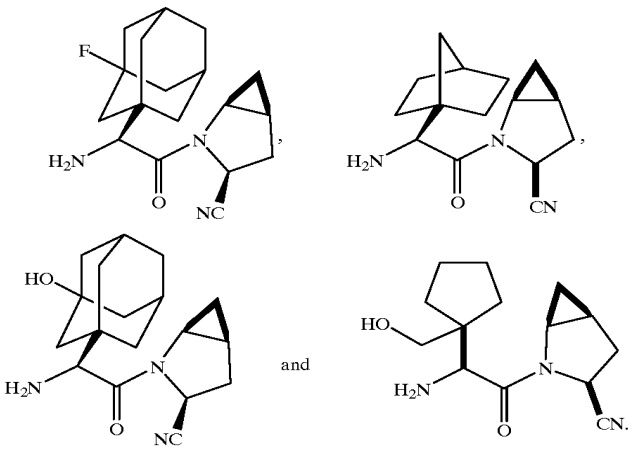


DETAILED DESCRIPTION OF THE INVENTION

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.

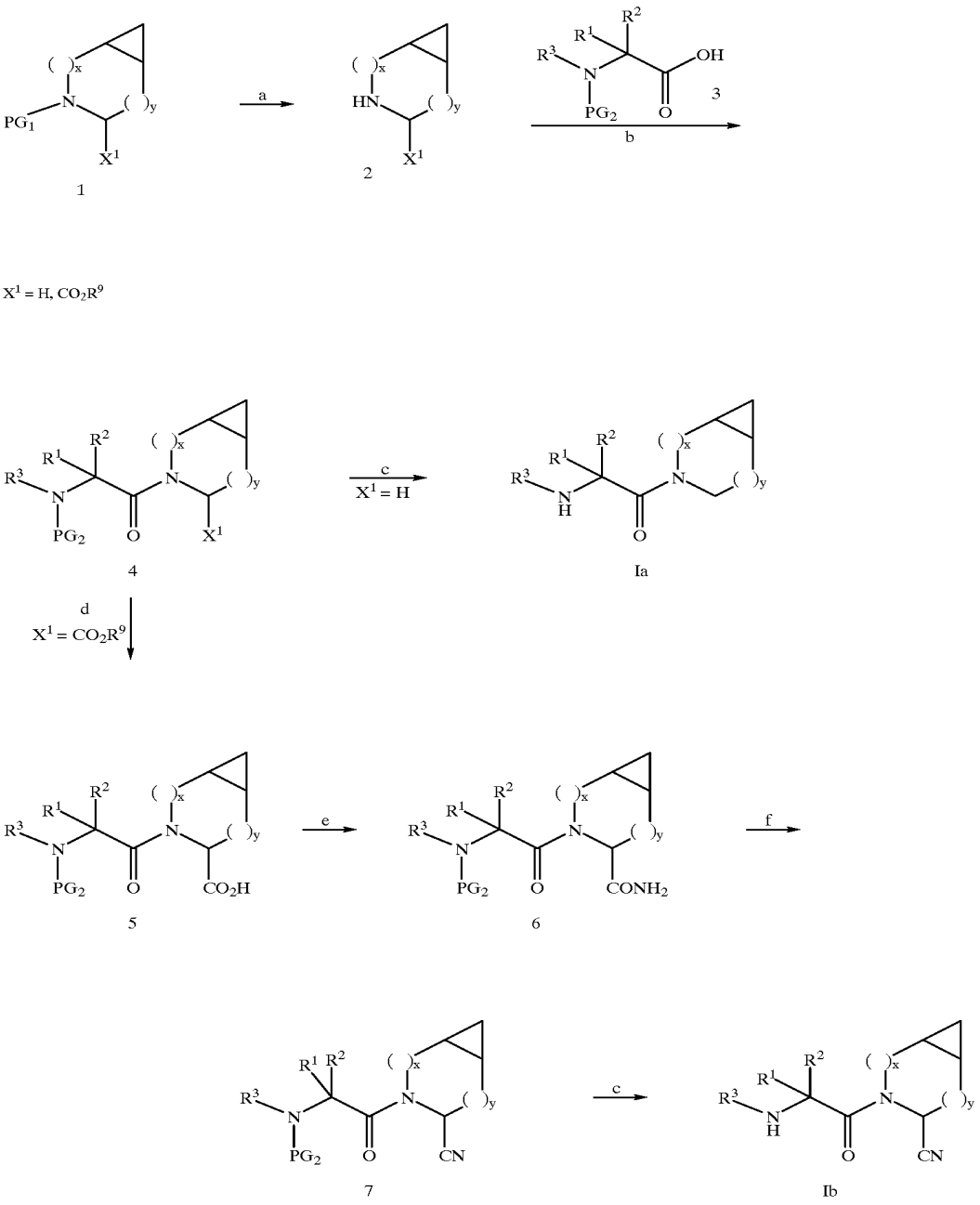
In the case where X^1=CO_2R^9 (where R^9 is alkyl or aralkyl groups such as methyl, ethyl, t-butyl, or benzyl), the ester may be hydrolyzed under a variety of conditions, for example with aqueous NaOH in a suitable solvent such as methanol, THF, or dioxane, to provide the acid 5. Conversion of the acid 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.

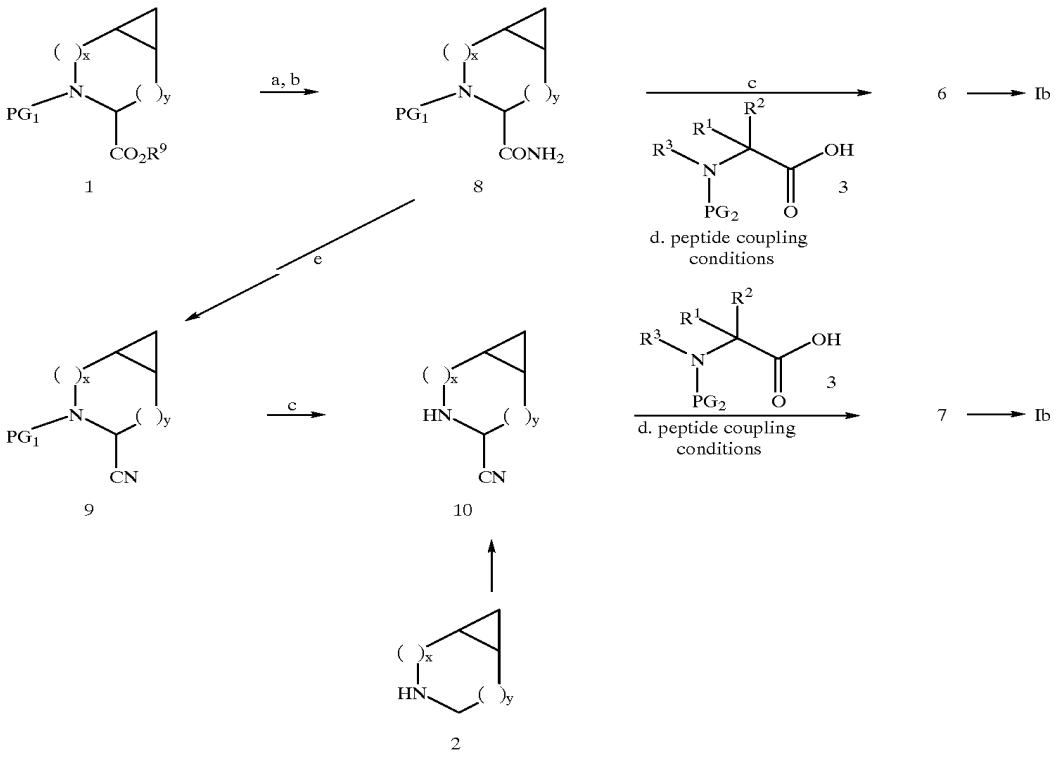
Alternately, the carboxamide group in 8 may be converted to the nitrile as described above to give compound 9. Deprotection of PGI affords 10 which may be subject to standard peptide coupling conditions to afford 7, an intermediate in the synthesis of Ib. Compound 10 may also be generated by oxidation 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



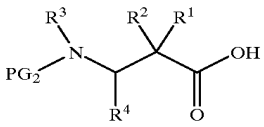
a. PG_1 = Boc, TFA or HCl; PG_1 = Cbz, H_2/Pd/C or TMSI; PG_1 = FMOC, Et_2NH b. EDAC, HOBT, DMF or i-BuOCOCl/TEA or PyBop, NMM c. PG_2 = PG_1, (see conditions for a) d. LiOH or NaOH MeOH or THF/H_2O or dioxane e. i-BuOCOCl/NMM or i-BuOCOCl/TEA or EDAC, then NH_3 in dioxane or Et_2O f. $POCl_3$, pyridine,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

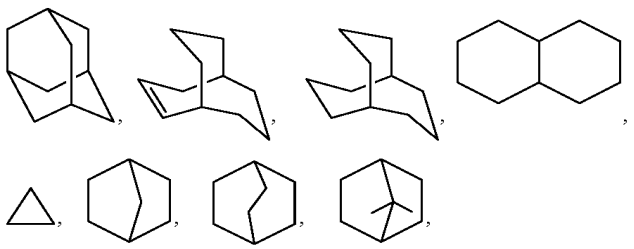
In a like manner, β-amino acids such as



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,

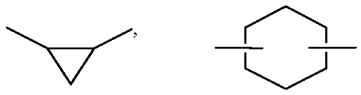


any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl,

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.

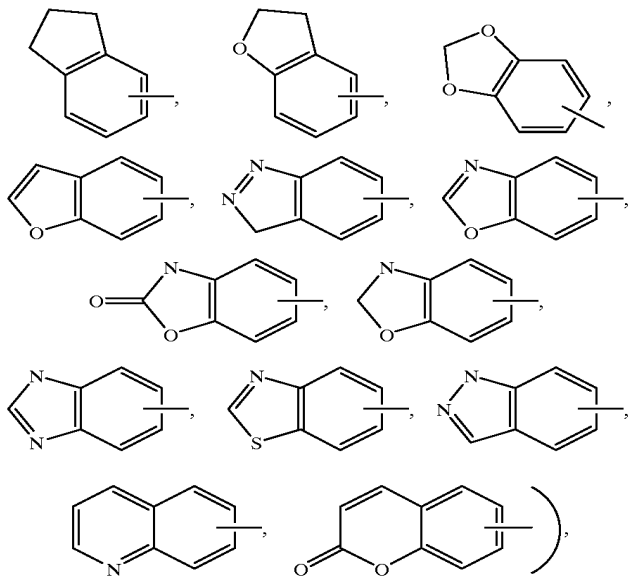
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

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-l-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-l-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

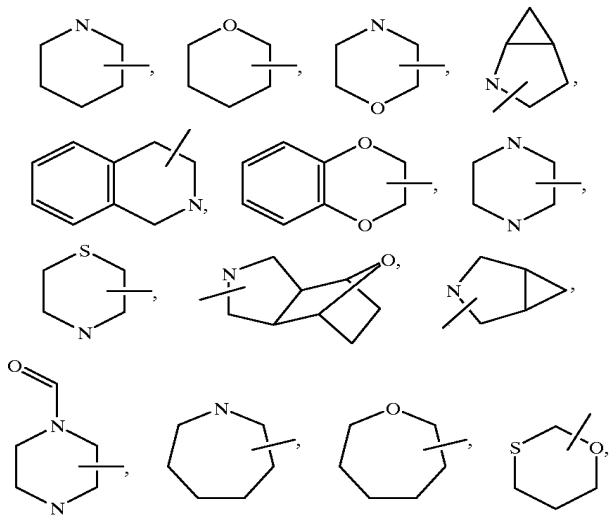
Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

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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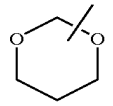
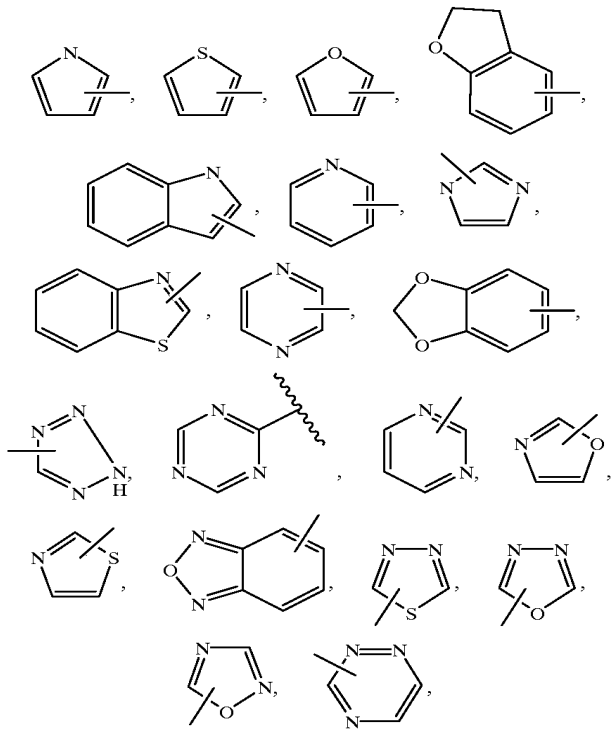


and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

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.

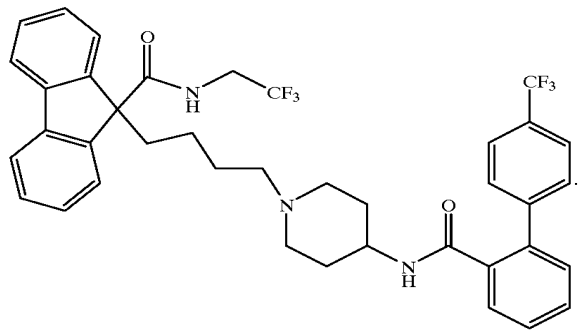
The hypolipidemic agent or lipid-modulating agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase 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

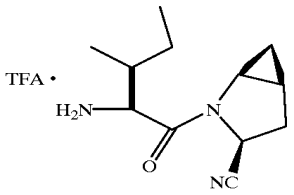
MS or Mass Spec=mass spectrometry

NMR=nuclear magnetic resonance

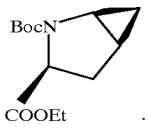
mp=melting point

The following Examples represent preferred embodiments of the invention.

EXAMPLE 1



Step 1

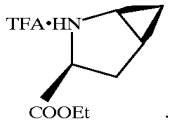


Step 1 title compound was synthesized by following the literature procedure [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128] or with the following modifications. L-pyroglutamic acid ethyl ester was N-protected as 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.

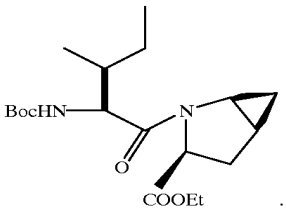
Cyclopropanation of 4,5-dehydro-L-proline ethyl ester: 4,5-Dehydro-L-proline ethyl ester (35.0 g, 0.145 mol) was added to a solution of neat Et_2Zn (35.8 g, 0.209 mol) in 1 liter of 1,2-dichloroethane at −15° C. To this mixture was added a dropwise addition of $ClCH_2I$ (102 g, 0.58 mol) over 1 h and 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



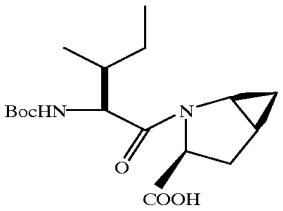
To a stirred solution of Step 1 compound (411 mg, 1.61 mmol) in CH_2Cl_2 (1.5 mL) at rt was added TFA (1.5 mL). The reaction mixture was stirred at rt for 2 h and evaporated. The residue was diluted with CH_2Cl_2 and then evaporated and re-evaporated three times to give the title compound as a colorless 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.

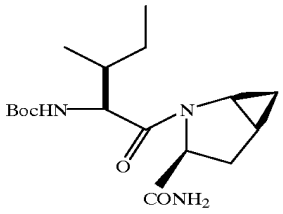
Step 4



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

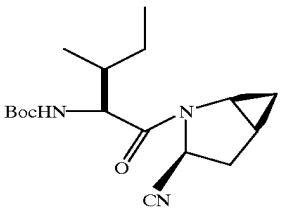
added to the residue and extracted with Et_2O (2×10 mL). The aqueous layer was acidified to ~pH 4 by adding 4% $KHSO_4$ dropwise. The milky solution was extracted with EtOAc (15 mL×3). Combined EtOAc layers were washed with brine, dried over Na_2SO_4 and evaporated to give the title compound as a white solid, 440 mg, 90% yield.

Step 5



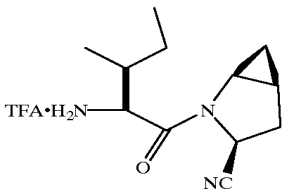
To a stirred solution of Step 4 compound (300 mg, 0.88 mmol) in THF (6 mL) at −15° C. under nitrogen, was added 4-methylmorpholine (0.12 mL, 1.06 mmol) and then isobutyl chloroformate (0.13 mL, 0.97 mmol) over 2 min. White precipitate was formed. The reaction mixture was stirred at −15° C. under nitrogen 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



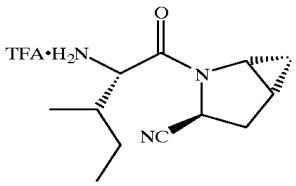
To a stirred solution of Step 5 compound (248 mg, 1.38 mmol) and imidazole (94 mg, 1.38 mmol) in dry pyridine (12 mL) at −35° C. under nitrogen was added $POCl_3$ (0.26 mL, 2.76 mmol) dropwise. The reaction mixture was stirred between −35° C. to −20° C. for 1 h and evaporated. CH_2Cl_2 (10 mL) was added 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

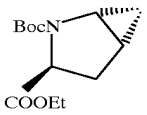


To a stirred solution of Step 6 compound (130 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) at rt was added TFA (2 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a pre-cooled slurry of $NaHCO_3$ (3.8 g) in H_2O (3 mL). The mixture was extracted with CH_2Cl_2 (6 mL×5), 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

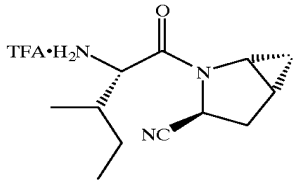


Step 1



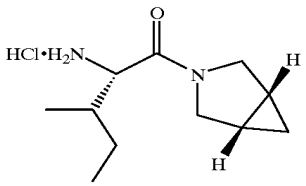
Step 1 title compound was synthesized by following the literature procedure. [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128.]

Step 2

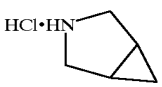


The title compound was prepared from Step 1 compound, employing the same procedure as that described for Example 1, Steps 2–6. LC/MS gave the correct molecular ion $[(M+H)^+=222]$ for the desired compound.

EXAMPLE 3

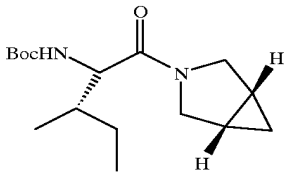


Step 1



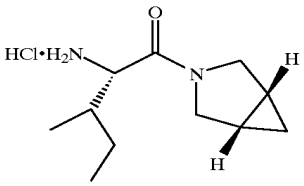
Step 1 title compound was prepared by following the literature procedure. [Willy D. Kollmeyer, U.S. Pat. No. 4,183,857.].

Step 2



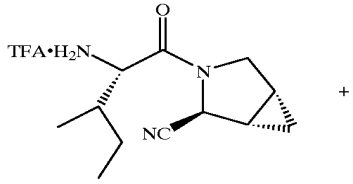
To a stirred solution of (S)-N-tert-butoxycarbonyl-isoleucine (231 mg, 1 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (780 mg, 1.5 mmol) in CH_2Cl_2 (6 mL) under nitrogen at rt was added 4-methylmorpholine (0.33 mL, 3 mmol). After 5 min, Step 1 compound (120 mg, 1 mmol) 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 (2.4×20 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

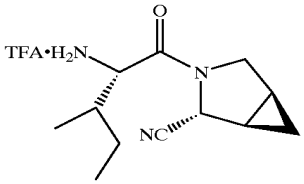


The reaction mixture of Step 2 compound (220 mg, 0.74 mmol) and 4 M HCl in dioxane (1.5 mL, 6 mmol) was stirred at rt for 2 h and evaporated under reduced pressure. Et_2O was added to the residue and a precipitate was formed. Et_2O was decanted and this was done three times. The precipitate was dried 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

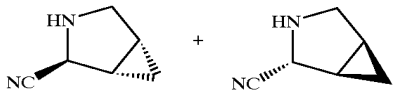


(Example 4)



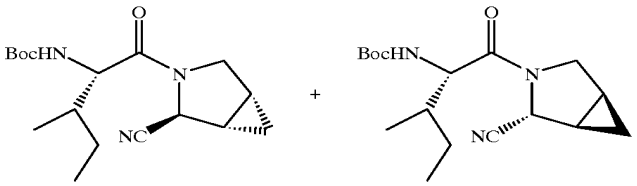
(Example 4A)

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.]

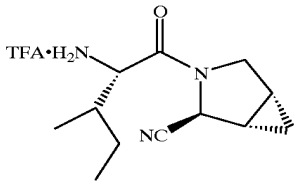
Step 2



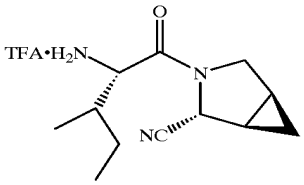
A slurry of (S)-N-tert-butoxycarbonyl-isoleucine (92.5 mg, 0.4 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (77 mg, 0.4 mmol) and HOAT (54.4 mg, 0.4 mmol) in $ClCH_2CH_2Cl$ (0.3 mL) was stirred under nitrogen at rt for 1 h, then Step 1 compound (22 mg, 0.2 mmol) was added, followed by Et_3N (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



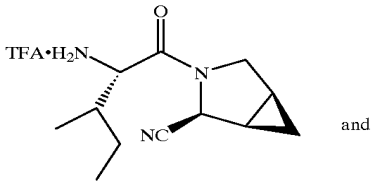
(Example 4)



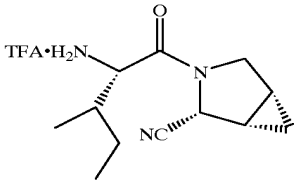
(Example 4A)

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

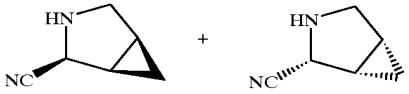


(Example 5)



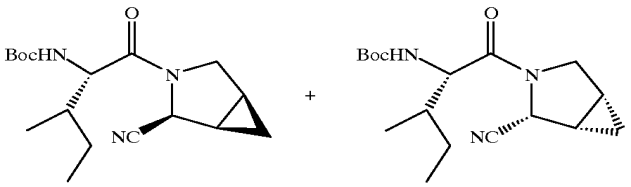
(Example 5A)

Step 1



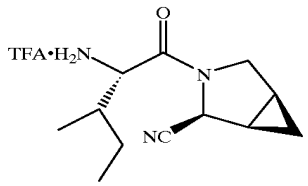
To a solution of Example 4, Step 1 compound (150 mg, 1.39 mmol) in 2-propanol (0.8 mL), was added NaCN (40 mg, 1.0 mmol). The reaction mixture was heated to reflux for 3 h. After cooling to rt, the reaction mixture was evaporated and then slurried in Et_2O (5 mL). After filtration, the filtrate was evaporated 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

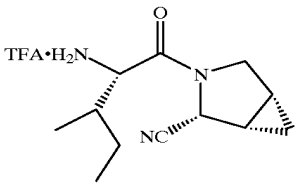


A slurry of (S)-N-tert-butoxycarbonyl-isoleucine (595 mg, 2.57 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (493 mg, 2.57 mmol) and 1-hydroxy-7-azabenzotriazole (350 mg, 2.57 mmol) in $ClCH_2CH_2Cl$ (2 mL) was stirred under nitrogen at rt for 1 h, then Step 1 compound mixture (139 mg, 1.28 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



(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_2C1_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.

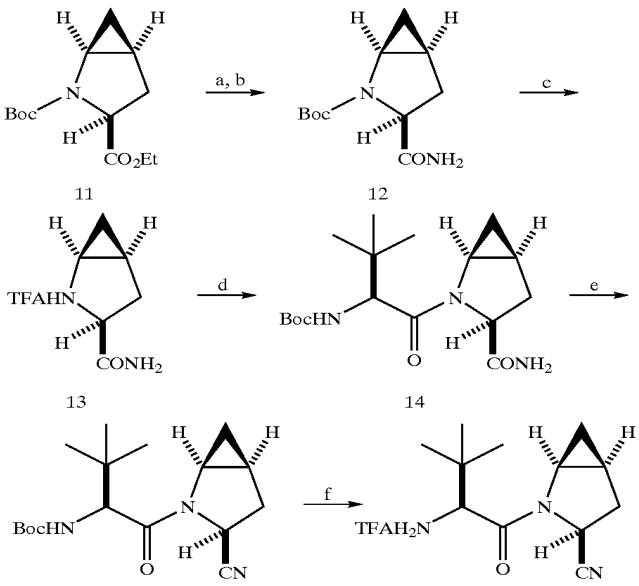
EXAMPLE 6

General Method A: Parallel array synthesis methods for preparation of inhibitors from commercially available amino

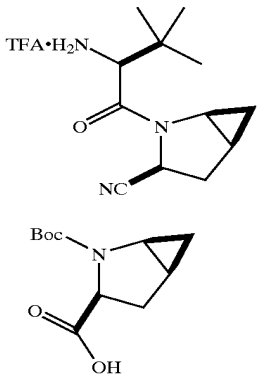
acids. As shown in Scheme 3, the ester 11, described in Example 1 Step 1, was saponified to the acid with LiOH in THF/HO and converted to the amide 12 by treatment with isobutyl chloroformate/NMM followed by ammonia in dioxane. The Boc protecting group was removed under acidic conditions using TFA in 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)



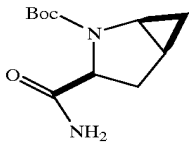
a. LiOH in THF/H_2O or MeOH/H_2O b. i-BuOCOCl/NMM or i-BuOCOCl/TEA at -30 C or EDAC, then NH_3 in dioxane or Et_2O at RT c. TFA, CH_2Cl_2, RT d. Boc-t-butylglycine and PyBop/NMM or EDAC, DMAP, CH_2Cl_2 e. $POCl_3$, pyridine, imidazol, -20 C f. TFA, CH_2Cl_2, RT



Step 1

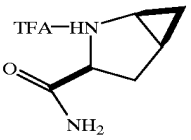
To a stirred solution of Example 1 Step 1 compound (1.40 g, 5.49 mmol) in 40 mL of a 1:1 methanol:water solution at rt was added lithium hydroxide (0.20 g, 8.30 mmol). The reaction mixture was stirred at rt for 18 h and then heated to 50° C. for 2 h. The mixture was diluted with equal volumes of ether 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



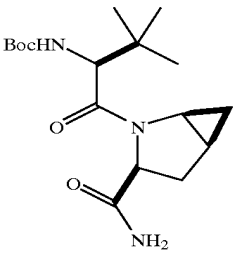
To a stirred solution of Step 1 compound (1.20 g, 5.28 mmol) in THF (20 mL) at −15° C. under nitrogen was added 4-methylmorpholine (0.71 mL, 6.50 mmol) and then isobutyl chloroformate (0.78 mL, 6.00 mmol) over 5 min. The reaction was stirred at −15° C. for 30 min, cooled to −30° C. and treated with a 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.

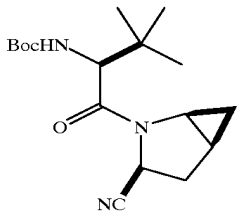
Step 4



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

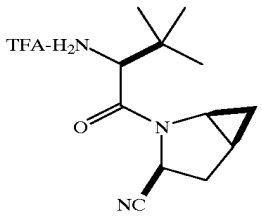
in a 6 mL column) by loading the material on a SCX ion exchange column and successively washing with CH_2Cl_2 (5 mL), 30% methanol in CH_2Cl_2 (5 mL), 50% methanol in CH_2Cl_2 (5 mL) and methanol (10 mL). The product containing fractions were concentrated under reduced pressure to give the desired amide. 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%.

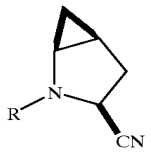
Step 6



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



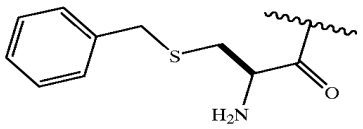
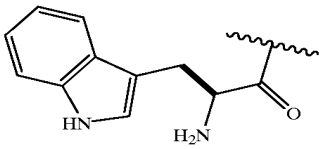
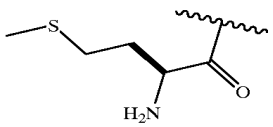
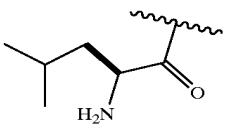
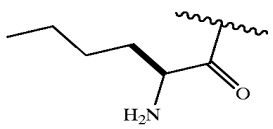
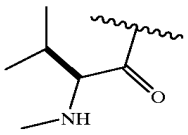
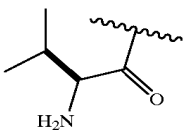
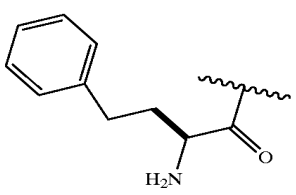
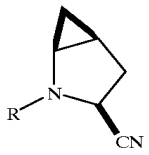
Example	R	[M + H]
7		302
8		295
9		240
10		222
11		222
12		222
13		208
14		270

TABLE 1-continued



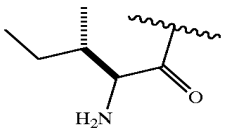
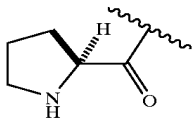
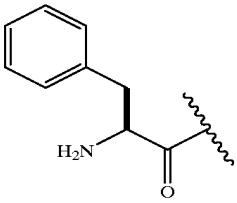
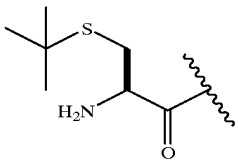
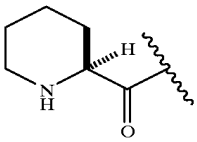
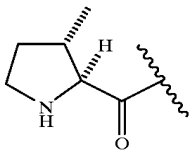
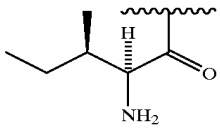
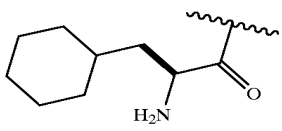
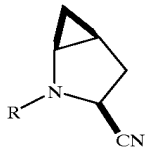
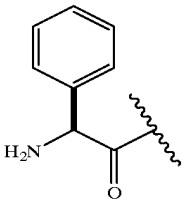
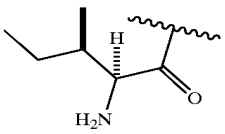
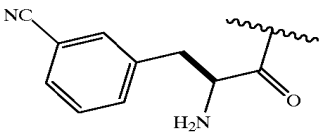
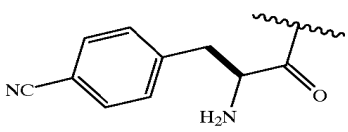
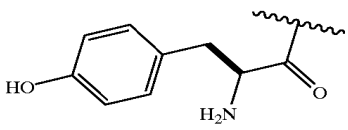
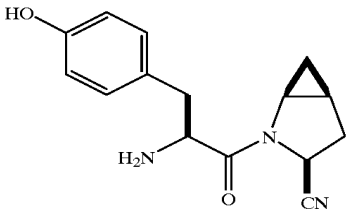
Example	R	[M + H]
15		222
16		206
17		256
18		268
19		220
20		220
21		210
22		262

TABLE 1-continued



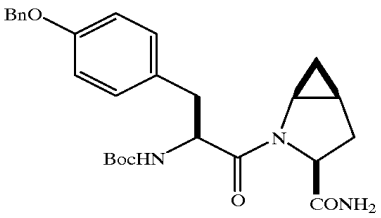
Example	R	[M + H]
23		242
24		210
25		281
26		281
27		272

EXAMPLE 27



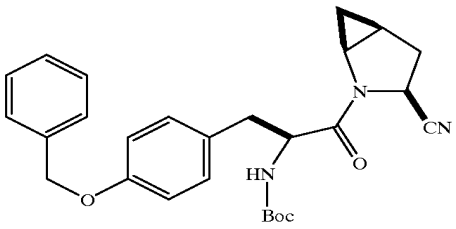
-continued

Step 1



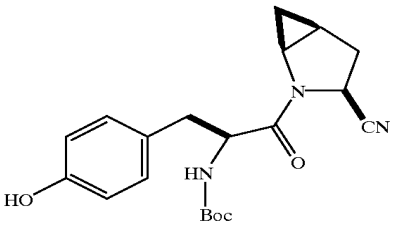
(2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt (53 mg, 0.22 mmol) was coupled to N-Boc-L-Tyrosine-benzyl ether (82 mg, 0.22 mmol) using PyBop (172 mg, 0.33 mmol) and N-methylmorpholine (67 mg, 0.66 mmol) in 4 mL CH_2Cl_2. The reaction stirred for 16 h, was taken up in EtOAc, washed with H_2O, 1N aqueous HCl, brine, then evaporated and purified by silica gel flash chromatography to give the coupled product (FAB MH+480).

Step 2



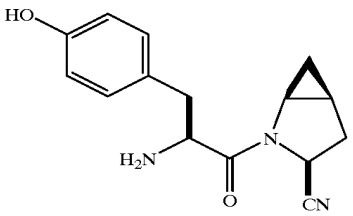
The Step 1 amide was dehydrated to the nitrile using the general method C (which follows Example 29) (FAB MH+462).

Step 3



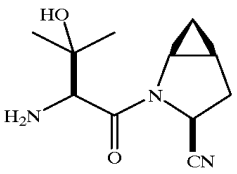
The Step 2 benzyl ether was cleaved by catalytic hydrogenolysis using 10% palladium on carbon and 1 atmosphere hydrogen gas in MeOH at rt for 1.5 h. The reaction was filtered through celite and concentrated to an oil and taken on without further purification (FAB MH+372).

Step 4



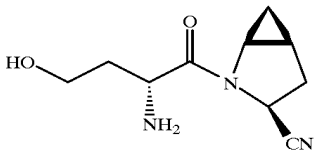
Step 3 N-[N-Boc-L-Tyrosine-]-(2S,4S,5S)-2-cyano-4,5-methano-L-prolylamide was dissolved in CH_2Cl_2 and TFA was added at rt. The reaction stirred for 1 h and was evaporated and purified by preparative HPLC as described in general method B (set out following Example 29) to afford the title compound (FAB MH+272).

EXAMPLE 28

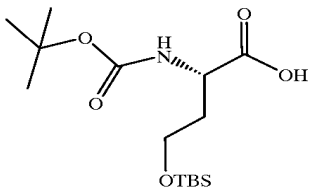


The title compound was prepared by coupling (2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt described in Example 6 Step 3 compound with N-(tert-butyloxy-carbonylhydroxyvaline. After hydroxyl protection with triethylsilyl chloride and dehydration of the amide with $POCl_3$/imidazole in pyridine and deprotection (N-terminal nitrogen and valine hydroxyl) with TFA using general method C (FAB MH+224), the title compound was obtained.

EXAMPLE 29

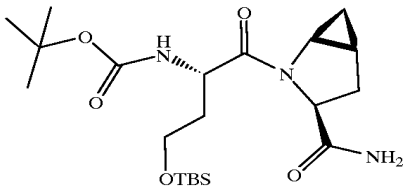


Step 1



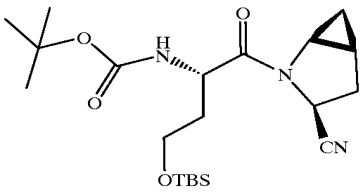
N-Boc-L-homoserine (1.20 g, 5.47 mmol) upon treatment with tert-butyldimethylsilyl chloride (1.67 g, 11.04 mmol) and imidazole (938 mg, 13.8 mmol) in THF (17 mL) was stirred as thick slurry for 48 h under N_2. The solvent was evaporated, and the crude material was dissolved in MeOH (10 mL). The resulting 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_2layer 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



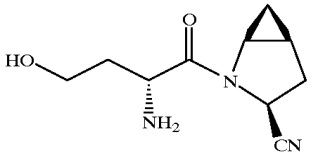
To a stirred solution of Step 1 compound (333 mg, 1.0 mmol) in 6 mL of CH_2Cl_2 was added 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (256 mg, 1.32 mmol). The solution was then stirred at rt for 30 min, followed by addition with Example 6 Step 3 amine TFA salt (160 mg, 0.66 mmol) and 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



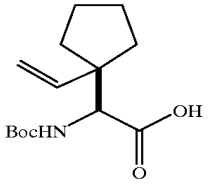
An oven-dried 10-mL round bottomed flask was charged with Step 2 compound (350 mg, 0.79 mmol), imidazole (108 mg, 1.58 mmol), pyridine (3 mL). The flask under argon was cooled to −30° C. Slow addition of $POCl_3$ (0.30 mL, 3.16 mmol) gave after mixing a thick slurry. The slurry was mixed at −30° C. for 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).

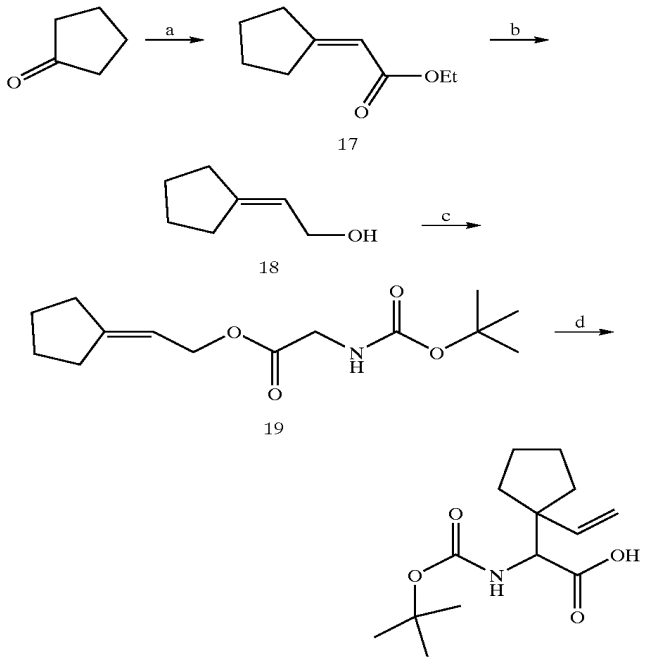
General Method B: Claisen rearrangement sequence to Boc-protected amino acids.



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.

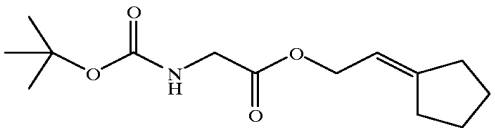
Step 2

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

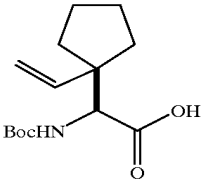
(2-Cyclopentylideneethyl)-N-(tert-Butyloxycarbonyl) glycinate



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

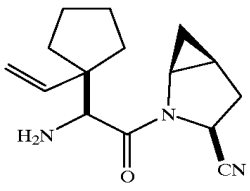
N-(tert-Butyloxycarbonyl)(1'vinylcyclopentyl)-glycine



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

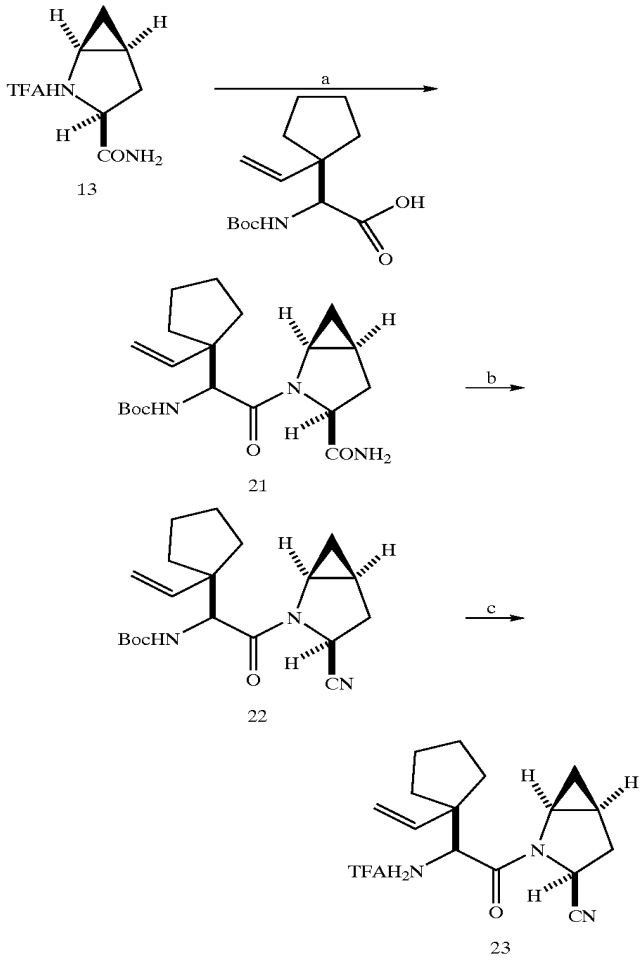
General Method C: Peptide coupling to 4,5-methano-prolinamide, amide dehydration and final deprotection.



The TFA salt of amide 13 was coupled to a variety of racemic quaternary protected amino acids using HOBT/

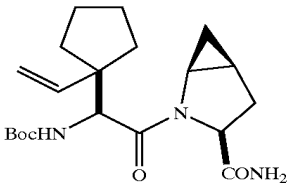
EDC in DMF at rt to give a D/L mixture of diastereomers at the N-terminal amino acid. The desired L diastereomer was chromatographically isolated either as the amide 21 or as the nitrile 22. Nitrile 22 was obtained by treatment of the amide with $POCl_3$/imidazole in pyridine at −20° C. The final target 23 was obtained by deprotection under acidic conditions using TFA in CH_2Cl_2.

Scheme 5
General Method C



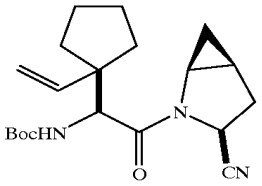
a. EDAC, HOBT, DMF b. $POCl_3$, pyridine, imidazole, -20 C c. TFA, CH_2Cl_2, RT

Step 1



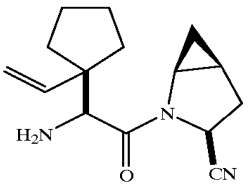
Example 6 Step 3 compound (877 mg, 3.65 mmol) and N-Boc cyclopentylvinylamino acid, described in Step 4 of general method B (1.13 g, 4.20 mmol) were dissolved in 20 mL anhydrous DMF, cooled to 0° C. and to this mixture was added EDAC (1.62 g, 8.4 mmol), HOBT hydrate (2.54 g, 12.6 mmol, and TEA (1.27 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).

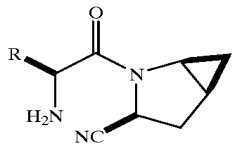
Step 3



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-dimethylcylopentanone, and 4-pyranone, cyclopropaneethylhemiacetal, acetone, and 3-pentanone respectively.

TABLE 2



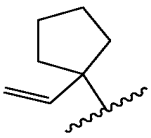
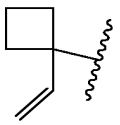
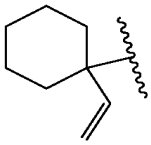
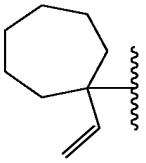
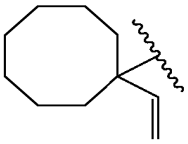
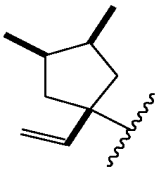
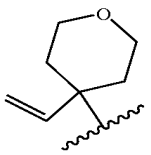
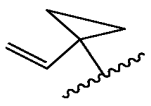
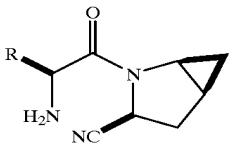
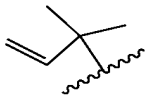
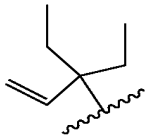
Example	R	MS [M + H]
30		260
31		246
32		274
33		288
34		302
35		288
36		276
37*		232

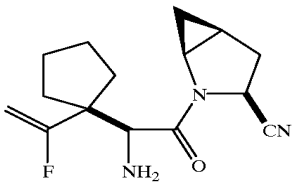
TABLE 2-continued



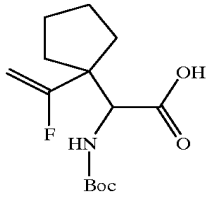
Example	R	MS [M + H]
38		234
39		262

*Step 3 compound was prepared by the method described in Tetrahedron Letters 1986, 1281–1284.

EXAMPLE 40

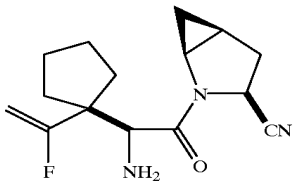


Step 1



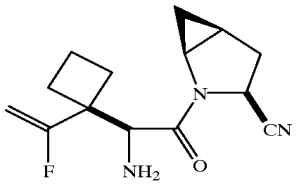
Step 1 compound was prepared employing general method B starting from cyclopentanone and 2-fluoro-triethylphos-phonoacetate instead of triethylphosphonoacetate.

Step 2

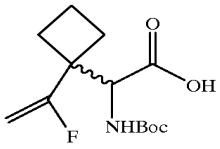


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C [MS (M+H) 278].

EXAMPLE 41

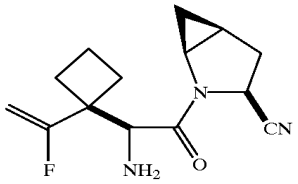


Step 1



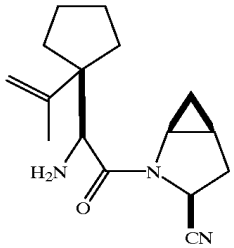
Step 1 compound was prepared employing general method B starting from cyclobutanone and 2-fluoro-triethylphos-phonoacetate instead of triethylphosphonoacetate.

Step 2

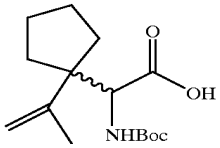


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 264.

EXAMPLE 42

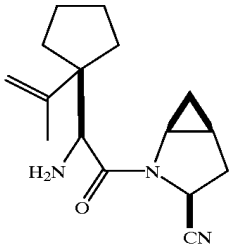


Step 1



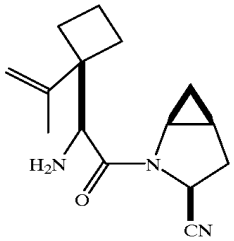
Step 1 compound was prepared employing general method B starting from cyclopentanone and triethylphosphono propionate instead of triethylphosphonoacetate.

Step 2

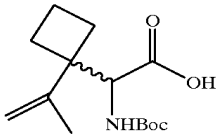


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 274

EXAMPLE 43

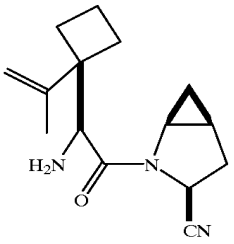


Step 1



Step 1 compound was prepared employing general method B starting from cyclobutanone and triethylphosphono propionate instead of triethylphosphonoacetate.

Step 2

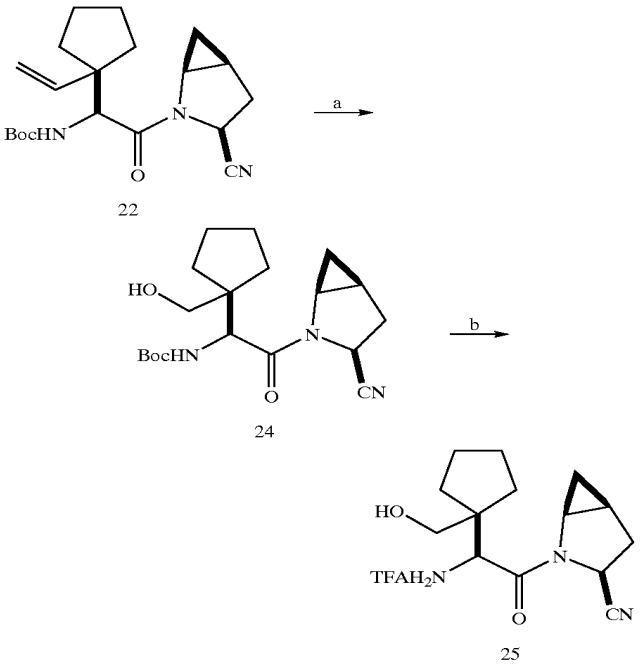


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 260.

EXAMPLE 44

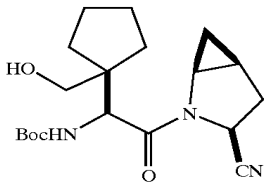
General Method D: Oxidative cleavage of vinyl substituent by ozonolysis. The protected cyclopentylvinyl nitrile 22 was treated with ozone for 6–8 min and subjected to a reductive quench with sodium borohydride to furnish the hydroxymethyl analog 24 directly. This compound was deprotected under acidic 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



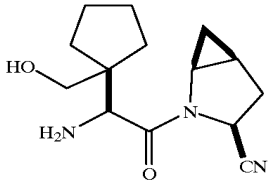
a. O_3, MeOH:CH_2Cl_2, 10:4, -78 C; then $NaBH_4$, -78 C to 0 C, 79%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C.

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

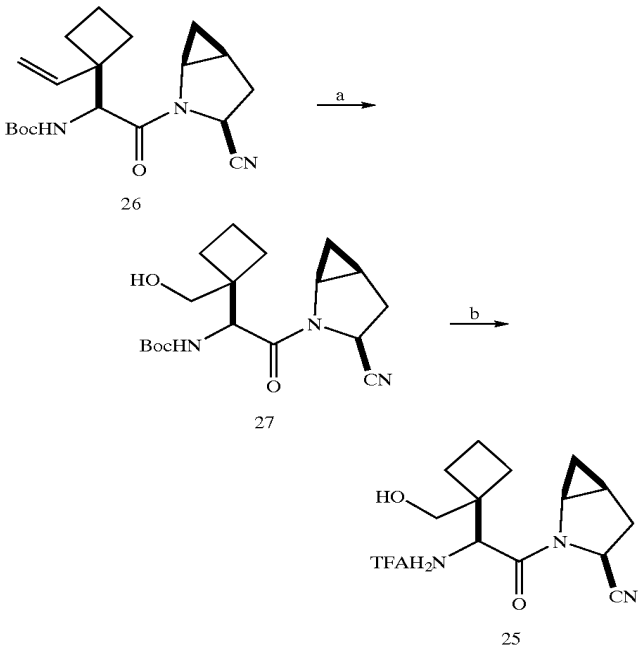


Step 1 compound (900 mg, 2.48 mmol) was dissolved in 60 mL of CH_2Cl_2, cooled to 0° C. and treated with 20 mL of freshly distilled TFA. The reaction was complete in 80 min and the mixture was evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30×100 mm, 18 minute gradient 80% Solv A:Solv 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

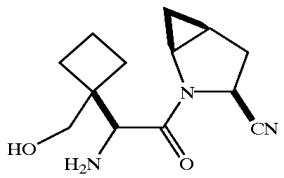
General Method E: Oxidative cleavage of vinyl substituent by osmium tetroxide-sodium periodate followed by sodium borohydride reduction to alcohol. The cyclobutylolefin 26 was treated with osmium tetroxide and sodium periodate in THF:water, 1:1, and the intermediate aldehyde was isolated crude and immediately 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

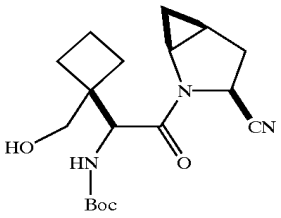


a. OsO_4, THF:H_2O; 1:1; $NaIO_4$; workup, then $NaBH_4$, MeOH, RT. 56%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C to RT.

-continued

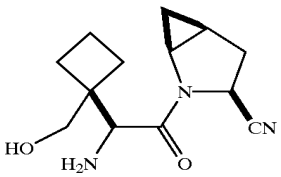


Step 1



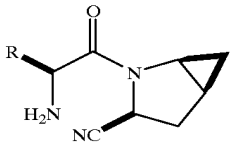
N-Boc protected cyclobutylvinyl compound (Example 31, prepared by general method C) (0.16 g, 0.46 mmol) was dissolved in 10 mL of a 1:1 mixture of THF:water and treated with OSO_4 (12 mg, catalyst) and $NaIO_4$ (0.59 g, 2.76 mmol, 6 equiv). After 2 h, the reaction mixture was diluted with 50 mL of ether 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.

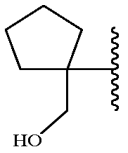
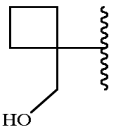
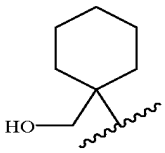
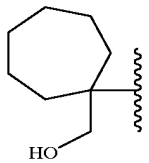
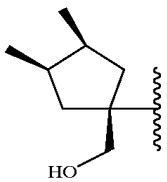
Step 2



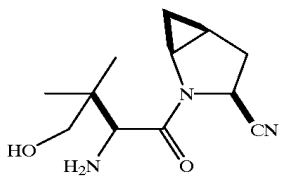
Step 1 compound (90 mg, 0.26 mmol) was dissolved in 3 mL of CH_2Cl_2, cooled to 0° C. and treated with 3 mL of freshly distilled TFA. The reaction was complete in 80 min and evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30×100 mm, 10 minute gradient 100%A to 100% Solvent A=10% MeOH-90%H20O-0.1% 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

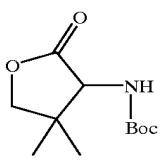


Example	R	Method of Preparation	[M + H]
44		Ozonolysis/ borohydride	264
45		Osmium/periodate/ borohydride	250
46		Ozonolysis/ borohydride	278
47		Osmium/periodate/ borohydride	292
48		Ozonolysis/ borohydride	292

EXAMPLE 49



Step 1

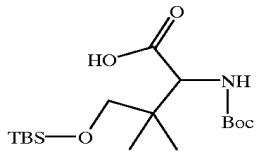


Part A. A 50-mL flask was charged with dihydro-4,4-dimethyl-2,3-furandione (5.0 g, 39.0 mmol), acetic acid (10 mL), sodium acetate (3.82 g, 39.0 mmol) and hydroxylamine hydrochloride (2.71 g, 39.0 mmol). The reaction mixture was stirred for 2 h at rt and concentrated under reduced pressure to remove 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.

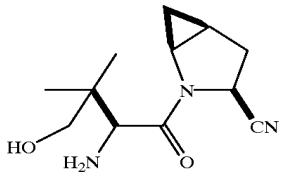
Part C. A 250-mL round bottomed flask was charged with Part B solid and diluted with THF (50 mL) and water (15 mL). The mixture was treated with di-tert-butyldicarbonate (12.7 g, 117 mmol) and sodium bicarbonate (10.0 g, 117 mmol). After 4 h of stirring the mixture was diluted with 50 mL of ether and 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.

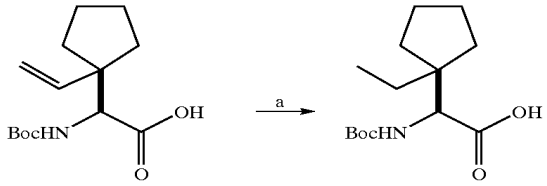
Step 3



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

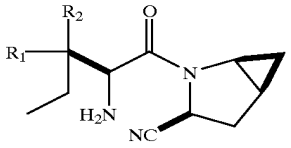
a. 10% Pd/C, 1atm H_2, MeOH, 12h, 100%

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)

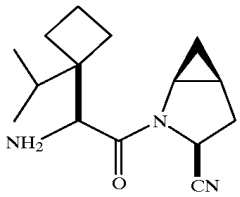
Examples 50–56 were prepared by the peptide coupling of amino acids (where the vinyl substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C.

TABLE 4



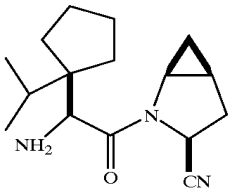
Example	R1, R2	MS [M + H]
50	Cyclopentyl	262
51	cyclobutyl	248
52	cycloheptyl	290
53	4-pyranyl	278
54	methyl, methyl	236
55	ethyl, ethyl	264
56	methyl, ethyl	250

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

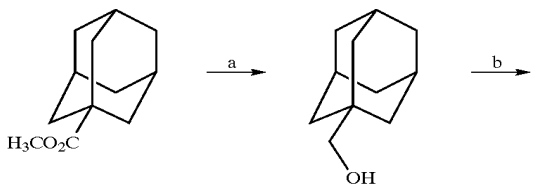


The title compound in Example 58 was prepared by the peptide coupling of the isopropyl cyclopentane amino acid (where the olefin substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C. MS (M+H) 276

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.

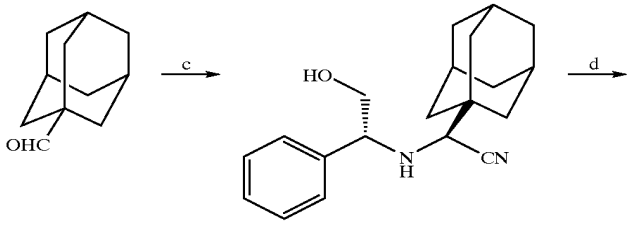
Scheme 9

General Method G, Examples 59–64

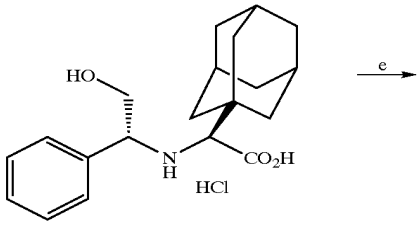


30 31

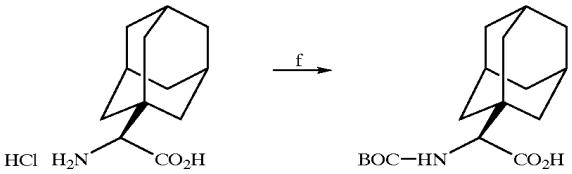
-continued



32 33



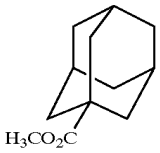
34



35 36

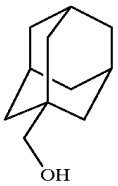
a. LAH, THF, 0 C TO RT, 96% b. ClCOCOCl, DMSO, CH_2Cl_2, -78 C, 98% c. R-(-)-2-Phenylglycinol, $NaHSO_3$, KCN d. 12M HCl, HOAc, 80 C, 16h, 78% e. 20% $Pd(OH)_2$, 50 psi H_2, MeOH:HOAc, 5:1 f. $(Boc)_2O$, K_2CO_3, DMF, 92%, 2 steps

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



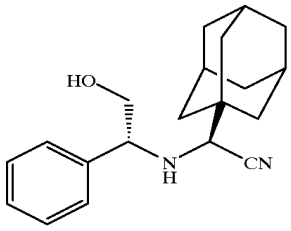
Step 1 compound (10.7 g, 0.055 mmol, 1 equiv) was dissolved in anhydrous THF (150 mL) under argon and was treated with a solution of $LiAlH_4$ (1 M in THF, 69 mL, 69 mmol, 1.25 equiv). After stirring at rt for 1.5 h, the reaction was cooled to 0° C. and quenched sequentially with H_2O (5.1 mL), 15% aq 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

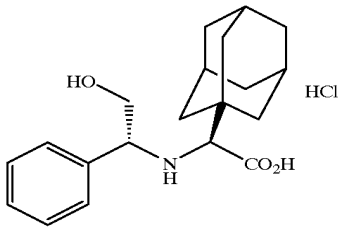
An oven-dried 3-neck flask equipped with 125-mL addition funnel was charged with anhydrous CH_2Cl_2 (150 mL) and anhydrous DMSO (10.3 mL, 0.145 mol, 2.5 equiv) under argon atmosphere and cooled to −78° C. Slow dropwise addition of oxalyl chloride (6.7 mL, 0.0768 mol, 1.32 equiv) followed by stirring 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



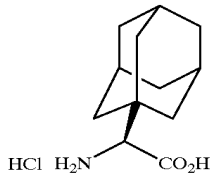
Step 3 compound (9.40 g, 57 mmol, 1 equiv) was suspended in H_2O (145 mL) and cooled to 0° C. The mixture was treated with $NaHSO_3$ (5.95 g, 57 mmol, 1 equiv), KCN (4.0 g, 59 mmol, 1.04 equiv), and a solution of (R)-(−)-phenylglycinol (8.01 g, 57 mmol, 1 equiv) in MeOH (55 mL). The resulting mixture 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



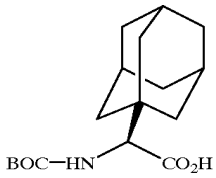
The Step 4 nitrile (5.65 g, 18 mmol) was heated in conc. HCl (120 mL) and HOAc (30 mL) at 80° C. for 18 h, at which time the reaction was cooled in an ice bath. Vacuum filtration of the resulting precipitate afforded the desired product as a white solid (5.21 g, 14 mmol, 78%). MS m/e 330 $(m+H)^+$.

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.

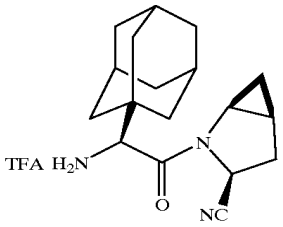
Step 7



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

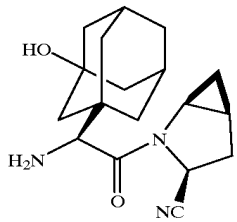
fully acidifying the aqueous to pH 3 with 1N aq HCl. The layers separated and the aqueous extracted with EtOAc (100 mL). The combined EtOAc extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and the filtrate concentrated by rotary evaporation. The residue was purified by SiO_2 flash 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

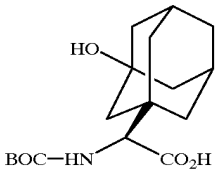


The title compound in Example 59 was prepared by the peptide coupling of the Step 7 compound in general method G followed by dehydration and deprotection as described in general method C.MS m/e 300 $(m+H)^+$.

EXAMPLE 60

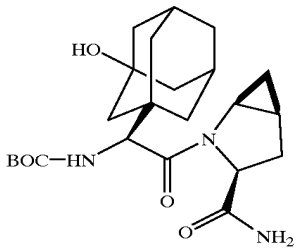


Step 1



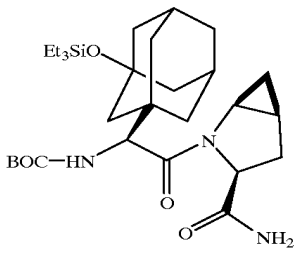
A solution of $KMnO_4$ (337 mg, 2.13 mmol, 1.1 equiv) in 2% aq KOH (6 mL) was heated to 60° C. and Step 7 compound in general method G (600 mg, 1.94 mmol, 1 equiv) was added in portions, and heating increased to 90° C. After 1.5 h, the reaction was cooled to 0° C., EtOAc (50 mL) was added, and the mixture 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



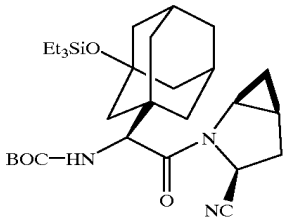
The Step 1 compound (404 mg, 1.24 mmol, 1 equiv) was dissolved in anhydrous DMF (10 mL) under argon and cooled to 0° C. The following were added in order: Example 6 Step 3 salt (328 mg, 1.37 mmol, 1.1 equiv), HOBT (520 mg, 3.85 mmol, 3.1 equiv), EDAC (510 mg, 2.61 mmol, 2.1 equiv), and TEA (0.54 mL, 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



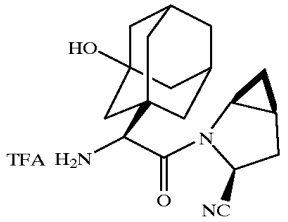
The Step 2 compound (95 mg, 0.22 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) under argon and cooled to −78° C. The mixture was treated with diisopropylethylamine (65 μL, 0.37 mmol, 1.7 equiv), and triethylsilyl triflate (75 μL, 0.33 mmol, 1.5 equiv), and stirred at 0° C. for 1.5 h. The 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



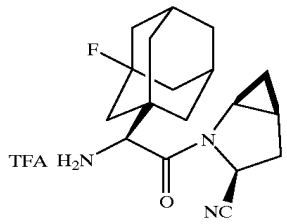
The Step 3 compound (90 mg, 0.16 mmol, 1 equiv) was dissolved in anhydrous pyridine (2 mL) under argon and cooled to −30° C. Treatment with imidazole (24 mg, 0.35 mmol, 2.1 equiv) and phosphorous oxychloride (66 μL, 0.67 mmol, 4.1 equiv), and continued stirring at −30° C. for 45 min gave a thick slurry. 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



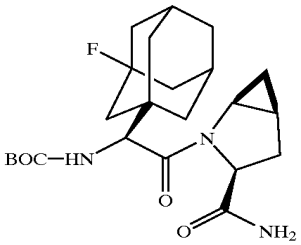
The Step 4 compound (76 mg, 0.14 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0° C. and treated with TFA (1 mL) and H_2O (2 drops) and stirred for 1.5 hr at 0° C. The solvents were removed by rotary evaporation and the residue was chased with toluene (5 mL) and dried under reduced pressure. Trituration with Et_2O afforded the title compound as a white solid (54 mg, 88%): MS m/e 316 $(m+H)^+$.

EXAMPLE 61



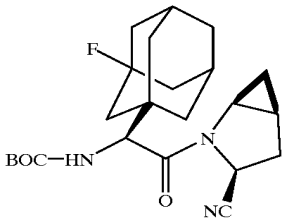
-continued

Step 1



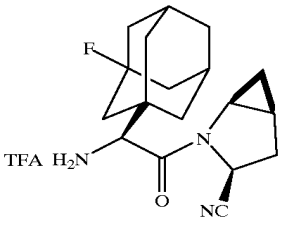
An oven-dried flask purged with argon was charged with anhydrous CH_2Cl_2 (3 mL) and cooled to −78° C. Treatment with diethylaminosulfur trifluoride (DAST, 60 μL, 0.45 mmol, 1.5 equiv), followed by a solution of the Example 60 Step 2 compound (131 mg, 0.30 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL). After 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 $(m+H)^+$.

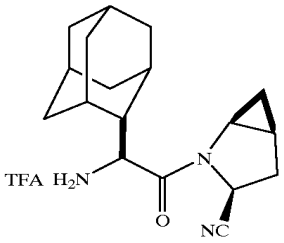
Step 3



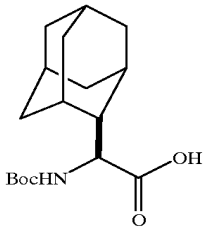
The Step 2 compound (125 mg, 0.30 mmol) was dissolved in TFA/CH_2Cl_2 (1:1 v/v, 2 mL), and stirred at rt. After 30 min, the solvents were removed by rotary evaporation, the

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

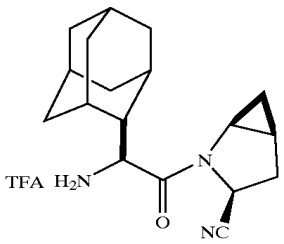


Step 1



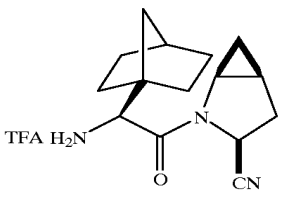
The Step 1 compound was prepared beginning with 2-adamantanal and elaborated to the homochiral Boc-amino acid by an asymmetric Strecker synthesis according to general method G.

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.

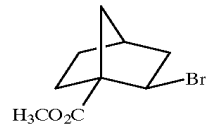
EXAMPLE 63



-continued

Step 1

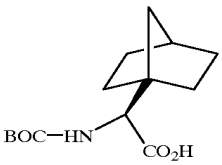
An oven-dried flask equipped with a condenser and drying tube was charged with norbornane-2-carboxylic acid (4.92 g, 35 mmol, 1 equiv) and treated with bromine (2.1 mL, 41 mmol, 1.15 equiv) and phosphorous trichloride (0.153 mL, 1.8 mmol, 0.05 equiv). The mixture was heated at 85° C. for 7 h protected 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 $NaHS0_3$ (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 $(m+H)^+$.

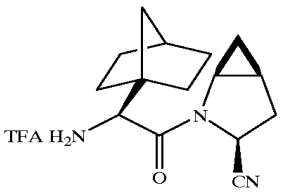
Methyl exo-2-bromonorbornane-1-carboxylate (2.0 g, 8.58 mmol, 1 equiv) was dissolved in anhydrous THF (50 mL) in an oven-dried 3-neck flask equipped with a condenser, and purged with argon. The mixture was treated with AIBN (288 mg, 1.71 mmol, 0.2 equiv) and tributyltin hydride (3.6 mL, 12.87 mmol, 1.5 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



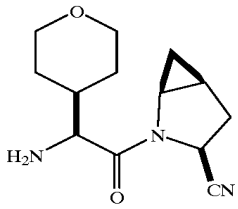
The Step 1 compound was prepared beginning with 1-norbonyl methyl carboxylate and elaborated to the homochiral Boc amino acid by an asymmetric Strecker synthesis according to general method G.

Step 3

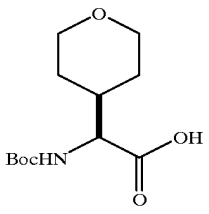


The title compound in Example 63 was prepared by the peptide coupling of the 1-norbonyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 260.

EXAMPLE 64

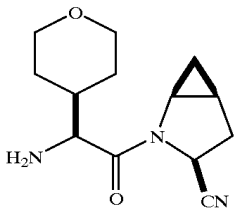


Step 1



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

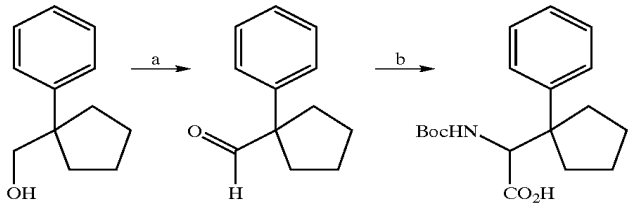


The title compound in Example 64 was prepared by the peptide coupling of the 4-pyranyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 250.

General Method H: Strecker Synthesis of Racemic Amino Acids.

Scheme 10

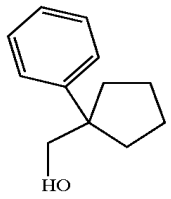
General Method H, Examples 65–66



37 38 39

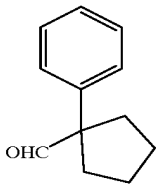
a. celite, PCC, CH_2Cl_2, RT, 91% b. NH_4Cl, NaCN, MeOH; 12M HCl, HOAc; $(Boc)_2O$, TEA, DMF.

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.

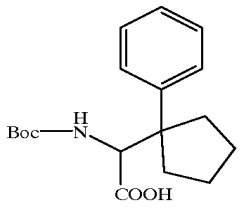
Step 2



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.

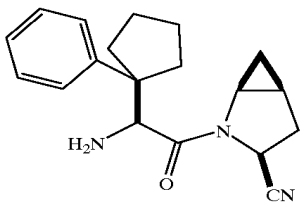
Step 3



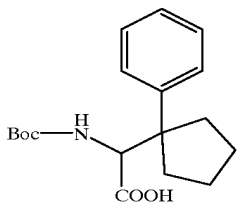
To a 50-mL round-bottomed flask containing Step 2 compound (0.72 g, 4.20 mmol) in 9 mL of water at rt was added NaCN (0.20 g, 4.20 mmol) followed by NH_4Cl (0.20 g, 5.00 mmol). To this reaction mixture was then added methanol (8 mL) and the mixture was allowed to stir overnight. The reaction mixture 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

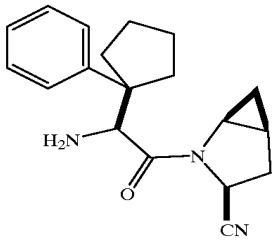


Step 1



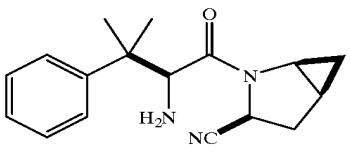
The synthesis of the Step 1 compound was described in general method H for the Strecker synthesis of racemic amino acids.

Step 2

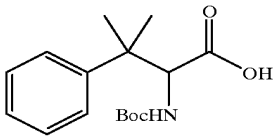


The title compound in Example 65 was prepared by the peptide coupling of the cyclopentylphenyl amino acid described in Step 1 and general method H followed by dehydration and deprotection as described in general method C. MS (M+H) 310.

EXAMPLE 66

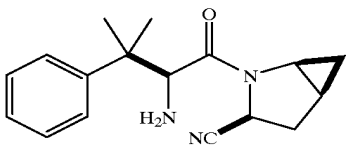


Step 1



Step 1 compound was prepared using racemic Strecker synthesis according to general method H starting from 2,2-dimethyl-phenylacetic acid.

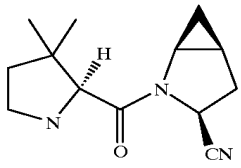
Step 2



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

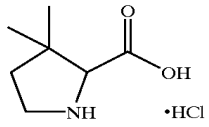
Step 1



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 (2×50 mL),10% sodium hydrogen carbonate (2×50 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).

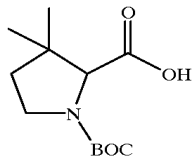
Step 2



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).

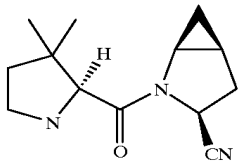
This diester (850 mg) was refluxed in 5 M hydrochloric acid (10 mL)/TFA (1 mL) for 8 h to give, after evaporation, a powdery white solid. Crystallization from methanol/ether gave 3,3-dimethyl-dl-proline hydrochloride (190 mg) as white crystals mp 110–112° C.

Step 3



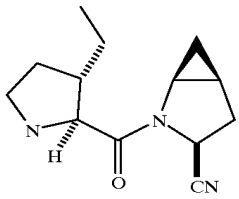
Step 2 compound (173 mg, 0.97 mmol) was dissolved in DMF (3 mL)/water (3 mL). To this clear solution was added triethylamine (0.46 mL, 3.18 mmol) and di-t-butyl dicarbonate (0.23 g, 1.06 mmol), and the reaction mixture was stirred at rt for 5 h. The solution was evaporated and the residue chromatographed 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

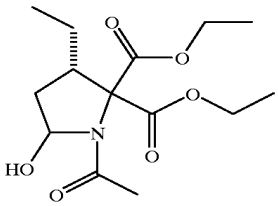


The title compound in Example 67 was prepared by the peptide coupling of the t-butyloxycarbonyl-3,3-dimethyl-dl-proline amino acid described in Step 3 followed by dehydration and deprotection as described in general method C. MS (M+H) 220.

EXAMPLE 68

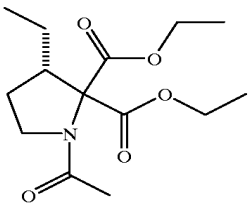


Step 1



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 (2×5 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).

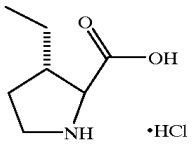
Step 2



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

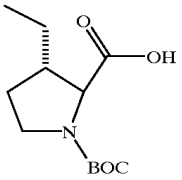
25° C. by means of an ice bath. After stirring for 4 h at rt, the solution was concentrated. The residue was diluted with CH_2Cl_2 (100 mL) , then treated with H_2O (50 mL) and solid Na_2CO_3 with vigorous stirring until the mixture was basic. The organic layer was separated, dried (Na_2SO_4), filtered, 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



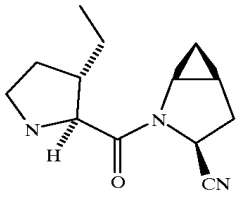
Step 2 compound (3.73 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was then cooled, washed with EtOAc (20 mL), the n concentrated to give an oil which crystallized upon trituration with et her to give the title compound (1.2 g, 70.6%) (LC/Mass, + ion): 144 (M+H).

Step 4



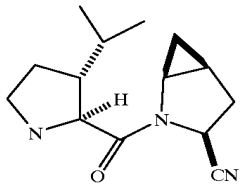
Step 3 compound (692 mg, 3.76 mmol) was dissolved in acetone (12 mL)/ water (12 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-t-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solvents were evaporated and the residue chromatographed 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

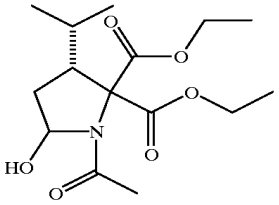


Example 68 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 234).

EXAMPLE 69

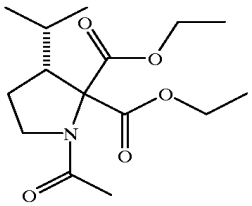


Step 1



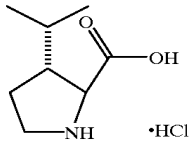
Sodium ethoxide (940 mg, 2.9 mmol; 21% w/w solution in ethanol) in ethanol (2 mL) was added to a stirred solution of diethyl acetamidomalonate (4.31 g, 19.8 mmol) in EtOH (23 mL) at rt under argon. The reaction mixture was cooled to 0° C.; and 4-methyl-2-pentenal (1.77 g, 18.0 mmol)was added dropwise 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



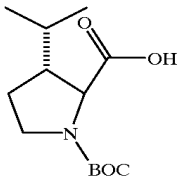
To a solution of Step 1 compound (3.0g, 9.5 mmol) and triethylsilane (2.28 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) under argon was added TFA (7.35 mL, 95.3 mmol) dropwise with stirring while maintaining the internal temperature at 25° C., by means of an ice bath. After stirring for 4 h at rt, the solution 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



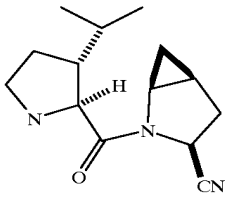
Step 2 compound (3.8 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (20 mL), then concentrated to give an oil which crystallized upon trituration with ether to give the step 3 compound (1.4 g, 76.0%). LC/Mass: + ions, 158 (M+H).

Step 4



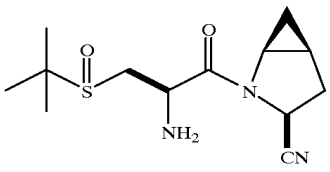
Step 3 compound (728 mg, 3.76 mmol) was dissolved in a 1:1 acetone/water solution (24 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-t-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solution was evaporated and the residue chromatographed 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



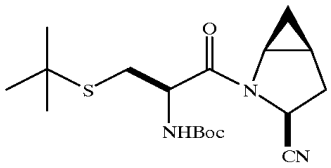
Example 69 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 248).

EXAMPLE 70



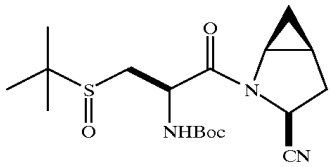
-continued

Step 1



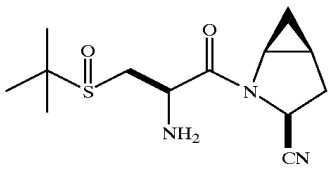
Step 1 compound was prepared by the procedure described in General Method C starting from N-Boc-S-t-butylcysteine.

Step 2



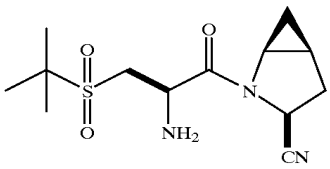
A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with Step 1 compound (78 mg, 0.21 mmol) and chloroform (3 mL). The mixture was cooled to 0° C. and treated with m-chloroperoxybenzoic acid (85 mg, 0.44 mmol) in $CHCl_3$ (2 mL). After 3 h the solution was diluted 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

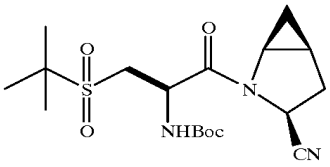


Trifluoroacetic acid (1.5 mL) was added to a cooled (0° C.) solution of Step 2 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was then stirred at 0° C. for 1.5 h, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase 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

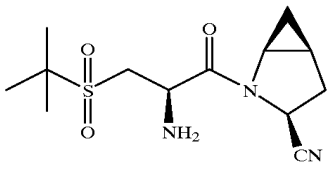


Step 1



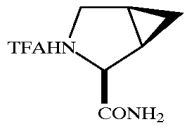
A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with compound from Example 70, Step 1 (78 mg, 0.21 mmol) in chloroform (3 mL). The mixture was cooled to 0° C. and treated with m-chloroperoxybenzoic acid (144 mg, 0.84 mmol) in $CHCl_3$ (2 mL). After 30 min 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



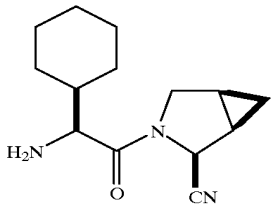
Trifluoroacetic acid (1.5 mL) was added to a cooled (0° C.) and stirred solution of Step 1 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was stirred at 0° C. for 30 min, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse 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



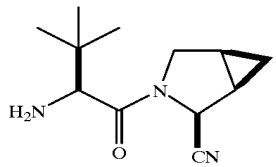
The title compound was prepared following a published procedure (Sasaki et al, Tetrahedron Lett. 1995, 36, 3149, Sasaki et al. Tetrahedron 1994, 50, 7093) used to synthesize (2S,3R,4S)-N-Boc-3,4-methano-L-proline carboxylate. The corresponding amide was prepared by general method A and deprotected with TFA to give the TFA salt also as described in general method A.

EXAMPLE 73



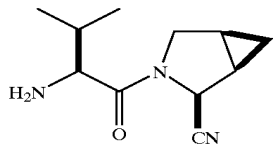
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-cyclohexylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+248).

EXAMPLE 74



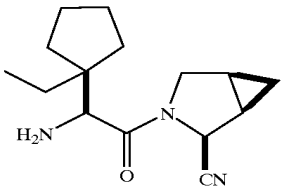
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-tert-butylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+222).

EXAMPLE 75



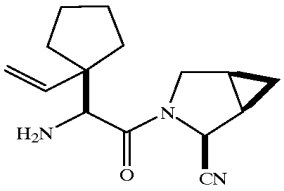
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-valine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+207).

EXAMPLE 76



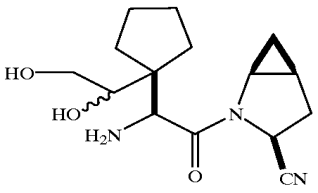
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(tert-butyloxycarbonyl)-(1'ethylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+262).

EXAMPLE 77



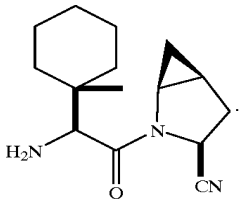
The title compound was prepared by coupling (2S,3R, 4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(tert-butyloxycarbonyl)-(1'vinylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POC1_3$/imidazole and deprotected (N-terminal 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).

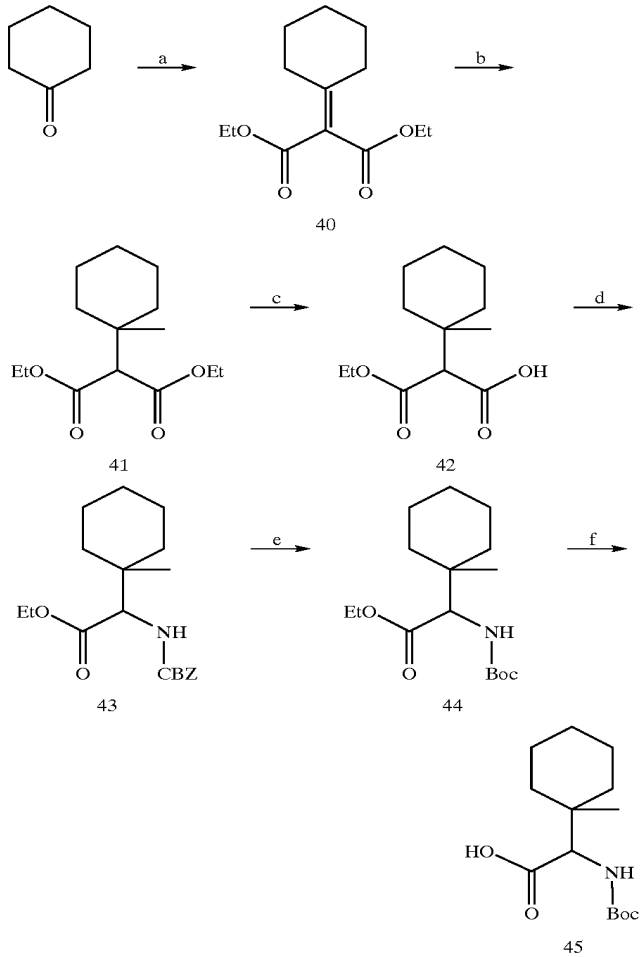
EXAMPLE 79



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.

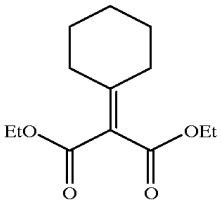
Scheme 11
General Method I



-continued

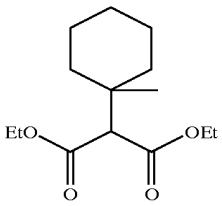
a. THF, CCl_4, $TiCl_4$, diethylmalonate, 0 C; pyridine, THF, 0 to RT 72 h b. MeMgBr, CuI, Et_2O, 0 C c. 1N NaOH, EtOH, RT 6 days d. Ph_2PON_3, TEA, RT to reflux to RT, BnOH e. 10% $Pd(OH)_2/C$, EtOAc; $(Boc)_2O$, K_2CO_3, THF f. IN NaOH, dioxane

Step 1



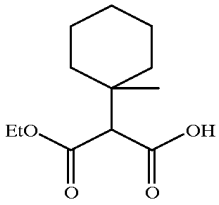
According to literature procedure (Tetrahedron 1973, 29, 435), a mixture of dry tetrahydrofuran (400 mL) and dry carbon tetrachloride (50 mL) was cooled to 0° C. (ice-salt bath) and treated with titanium tetrachloride (22.0 mL, 0.2 mole). The resulting yellow suspension was stirred at 0° C. for 5 min, 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.

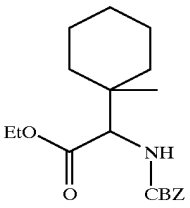
Step 3



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.

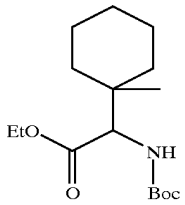
Or alternately: solutions of the diester in a mixture of ethanol, THF, dioxane and water or mixtures thereof may be hydrolyzed with sodium hydroxide.

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



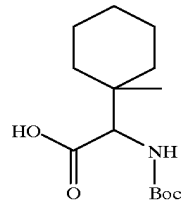
A solution of Step 4 compound (1.15 g, 3.46 mmol) in EtOAc (60 mL) was treated with palladium hydroxide on carbon (298 mg) and hydrogenated at rt for 20 h. The mixture was filtered through a celite pad and then washing the pad well with EtOAc (3×25 mL) then the filtrate was concentrated to give the free 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.

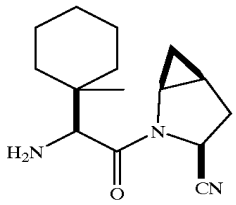
Or alternately: Solutions of the benzylcarbamate in methanol may be subjected to hydrogenolysis in the present of di-t-butyldicarbonate to give the BOC-protected amine in a "one-pot" manner.

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.

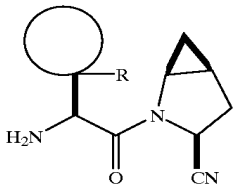
Step 7



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.

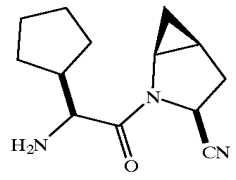
Compounds 90–100 were prepared by General Method I and General Method C starting from cyclohexanone, cyclopentanone and cyclobutanone, and employing methyl-, ethyl-, allyl- and propylmagnesium halides as Grignard reagents.

TABLE 5

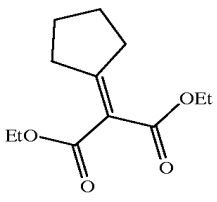


Example #	Cycloalkane	R	NS Data M + H
79	cyclohexane	Methyl	262
80	cyclohexane	Ethyl	276
81	cyclopentane	Methyl	248
82	cyclopentane	Allyl	274
83	cyclopentane	Propyl	276
84	cyclobutane	Methyl	234

EXAMPLE 85



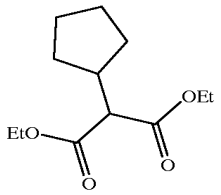
Step 1



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

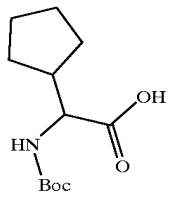
mol) and distilled diethylmalonate (7.6 mL, 0.05 mol) then stirred at 0° C. for 30 min. The reaction mixture was then treated with a solution of dry pyridine (16 mL, 0.20 mol) in dry THF (30 mL), stirred at 0° C. for 1.0 h, then at rt for 20 h. The reaction mixture was quenched with water (50 mL), stirred 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



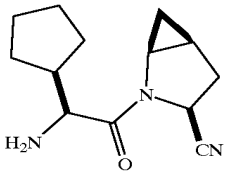
A solution of Step 1 compound (1.00 g 4.42 mmol) in methanol (50 mL) was treated with 10% Pd/C (0.20 g, 10 mol %) and hydrogenated (balloon pressure) at rt for 20 h. The mixture was diluted with methanol and filtered through a pad of celite. The filtrate was concentrated and purified by flash column 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



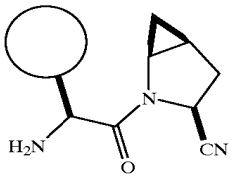
The Step 3 compound was prepared by the process outlined in General Method H, where the ester underwent hydrolysis, Curtius Rearrangement, protecting group exchange, and again final ester hydrolysis.

Step 4



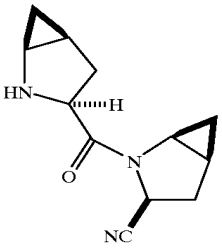
The title compound was prepared from Step 3 compound according to the procedure in General Method C where the amino acid was coupled, the amide was dehydrated, and the protecting group removed to give the title compound. MS (M+H) 234.

Examples 86 and 87 were prepared by the procedures used for Example 85 starting from cyclohexanone and cyclobutanone respectively

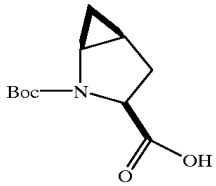


Example #	Cycloalkane	Mass Spec M + H
85	cyclopentyl	234
86	cyclohexyl	248
87	cyclobutyl	220

EXAMPLE 89

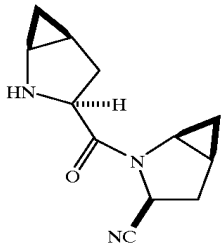


Step 1



Step 1 compound was prepared in Example 6 Step 1.

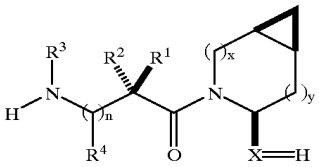
Step 2

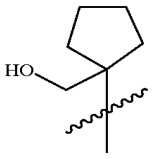
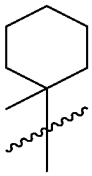
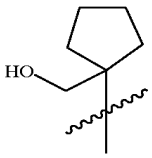
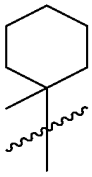


The title compound was prepared from Step 1 compound according to General Method C, where the carboxylic acid underwent a peptide coupling, the amide dehydration and protecting group removal. MS (M+H) 218.

EXAMPLES 90 TO 99

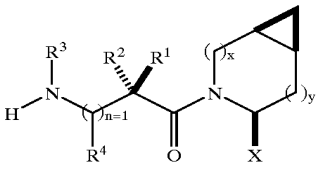
Examples of compounds where X=H include the following compounds which may be prepared employing procedures as described hereinbefore.

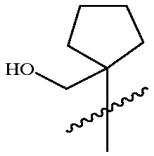
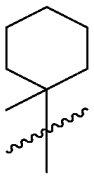
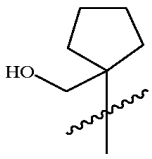
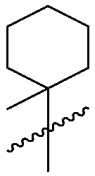


Ex. #	n	x	y	R^1	R^2	R^3	R^4
90	0	0	1	t-Bu	H	H	—
91	0	0	1	adamantyl	H	H	—
92	0	0	1		H	H	—
93	0	0	1		H	Me	—
94	0	1	0	t-Bu	H	H	—
95	0	1	0	adamantyl	H	H	—
96	0	1	0		H	H	—
97	0	1	0		H	Me	—
98	1	0	1	H	H	H	t-Bu
99	1	1	0	Me	H	H	t-Bu

EXAMPLES 100 TO 109

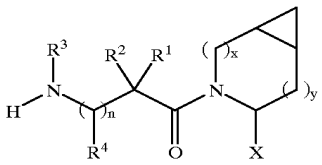
Examples of compounds where n=1 include the following compounds which may be prepared employing procedures as described hereinbefore.



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

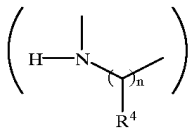
x=0 when y=1; and wherein

n is 0 or 1;

X is H or CN;

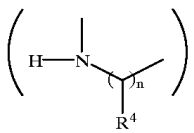
R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, 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



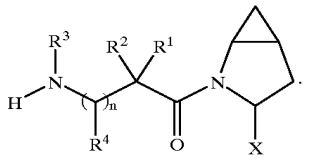
form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

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;

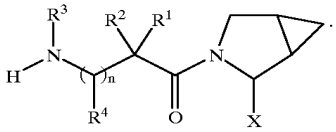
including all stereoisomers thereof;

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

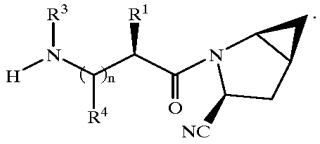
2. The compound as defined in claim **1** having the structure:



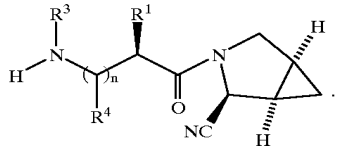
3. The compound as defined in claim **1** having the structure:



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



5. The compound as defined in claim **1** having the structure:



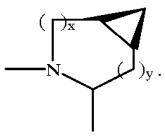
6. The compound as defined in claim **1** wherein:

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

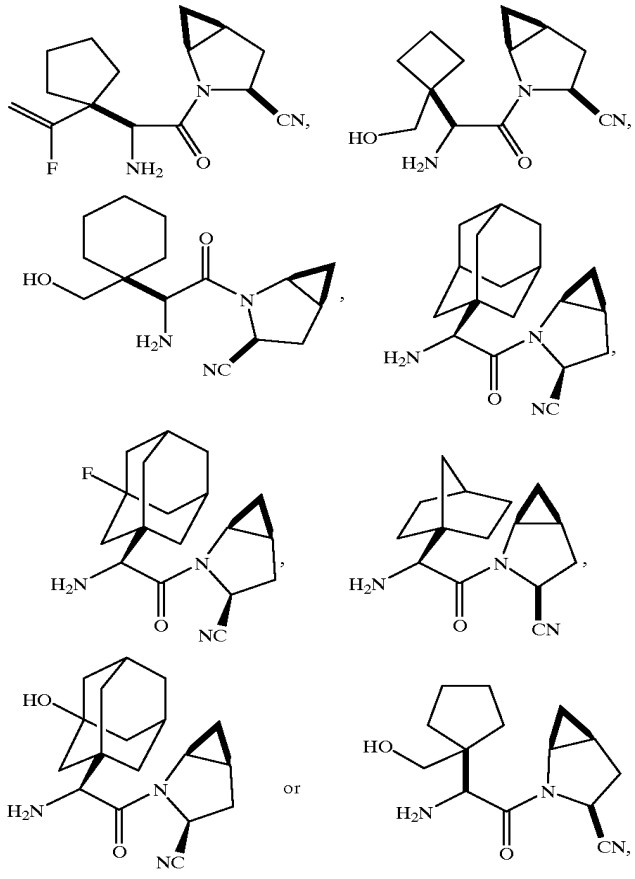
R^2 is H or alkyl, n is 0,

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:

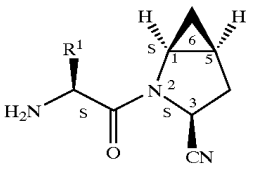


or a pharmaceutically acceptable salt thereof.

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

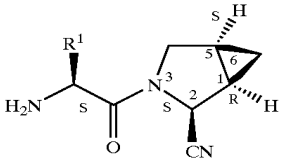


(1S,2(2S),3S,5S)

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, Gl -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

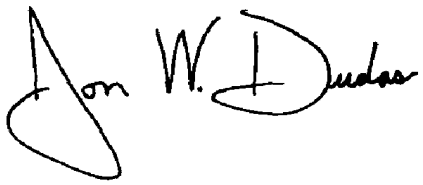
PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

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

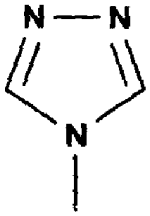
UNITED STATES PATENT AND TRADEMARK OFFICE

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% --.

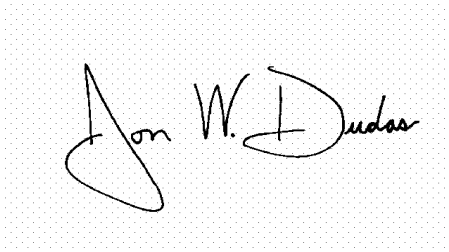
Column 82,
Line 65, change "10EtOAc" to -- 10% EtOAc --.

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

DOCKET NO.: LA0050USNP (BMS-2856) REISSUE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Reissue Application of: **Jeffrey A. Robl, et al.**	**Confirmation No.: Not yet assigned**
U.S. Patent No.: 6,395,767	**Issued: May 28, 2002**
Application No.: Not yet assigned	**Group Art Unit: Not yet assigned**
Filing Date: Herewith	**Examiner: Not Yet Assigned**

For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REISSUE APPLICATION DECLARATION BY ASSIGNEE[1]

1. ☒ Declaration by Assignee:

Bristol-Myers Squibb Company, a Corporation organized under the laws of the State of Delaware, declares that the entire title to letters patent number 6,395,767 for CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD, granted on May 28, 2002 to Jeffrey A. Robl (a citizen of the United States of America), Richard B. Sulsky (a citizen of the United States of America), David J. Augeri (a citizen of the United States of America), David R. Magnin (a citizen of the United States of America), Lawrence G. Hamann (a citizen of the United States of America), and David A. Betebenner (a citizen of the United States of America), is vested in Bristol-Myers Squibb Company, and that Bristol-Myers Squibb Company believes said named inventors to be original, first, and part inventors of the subject matter that is described and claimed in the aforesaid letters patent and in the foregoing specification and for which invention Bristol-Myers Squibb Company solicits a reissue patent.

[1] This declaration is accompanied by Consent of Assignee for Reissue and Assignee's Statement of Ownership Interest.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims as amended by the Preliminary Amendment.

I acknowledge the duty to disclose all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

☒ In compliance with this duty attached herewith is an Information Disclosure Statement in accordance with 37 CFR § 1.97.

PRIORITY CLAIM

I hereby claim priority benefit under 35 U.S.C. § 119 of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed.

☐ No such applications have been filed.

☒ Such applications have been filed as follows:

Country	Application No.	Date Filed	Priority Claimed
United States	60/188,555	March 10, 2000	Yes

STATEMENT OF INOPERATIVENESS OR INVALIDITY OF ORIGINAL PATENT 37 CFR §1.175

I hereby state that I believe one or more claims of the original patent to be partly inoperative or invalid by reason of the patentee claiming more or less than it had a right to claim. Specifically, I believe the patentee failed to include narrower claims to which the patentee was entitled.

All errors being corrected in this reissue application up to the time of filing of this declaration under 35 CFR §1.175(a) arose without any deceptive intentions on the part of the applicants.

The scope of the claims of the original patent is not enlarged by this reissue application.

SURRENDER OF ORIGINAL PATENT 37 CFR §1.178

Pursuant to 37 C.F.R. §1.178(a), this application for reissue constitutes an offer to surrender the patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By assignee or person authorized to sign on behalf of assignee:

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O.Box 4000
Princeton, NJ 08543-4000

Warren K. Volles

Warren K. Volles
Title: Assistant General Counsel
Reg. No. 33,810
Phone: 203-677-6997
Date: Nov 29, 2011

DOCKET NO.: LA0050USNP (BMS-2856) REISSUE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Reissue Application of: **Jeffrey A. Robl, et al.**	**Confirmation No.: Not yet assigned**
U.S. Patent No.: 6,395,767	**Issued: May 28, 2002**
Application No.: Not yet assigned	**Group Art Unit: Not yet assigned**
Filing Date: Herewith	**Examiner: Not Yet Assigned**

For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

CONSENT OF ASSIGNEE FOR REISSUE
and
ASSIGNEE'S STATEMENT OF OWNERSHIP INTEREST IN REISSUE

1. In accordance with 37 CFR 1.172(a), said assignee, having an undivided interest in United States Patent No. **6,395,767**, hereby consents to reissue of said patent for the reasons set forth in the accompanying Reissue Declaration, and establishes ownership of said patent and its rights to take action therein under 37 CFR 3.73(b).

STATEMENT UNDER 37 CFR § 3.73(b)

Bristol-Myers Squibb Company , a Corporation, states that it is:

☒ the assignee of the entire right, title, and interest; or

☐ an assignee of an undivided part interest

in the patent application/patent identified above by virtue of either:

2. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

From: **Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, and David A. Betebenner**

To: **Bristol-Myers Squibb Company.** The document was recorded in the Patent and Trademark Office at Reel **011607**, Frame(s) **0369**.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O.Box 4000
Princeton, NJ 08543-4000

Warren K. Volles
Title: Assistant General Counsel
Reg. No. 33,810
Phone: 203-677-6997
Date: Nov 29, 2011

DOCKET NO.: LA0050USNP (BMS-2856) REISSUE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Reissue Application of: **Jeffrey A. Robl, et al.**	**Confirmation No.: Not yet assigned**
U.S. Patent No.: 6,395,767	**Issued: May 28, 2002**
Application No.: Not yet assigned	**Group Art Unit: Not yet assigned**
Filing Date: Herewith	**Examiner: Not Yet Assigned**

For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

ASSIGNEE POWER OF ATTORNEY, CHANGE OF CORRESPONDENCE ADDRESS AND STATEMENT UNDER 37 C.F.R. § 3.73(b)

The undersigned hereby revokes all previous powers of attorney given in the above-identified patent. The undersigned hereby appoints all the practitioners associated with Customer Number 23377 to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith. Each practitioner associated with Customer Number 23377 is an attorney registered before the United States Patent and Trademark Office.

Send all future correspondence to 23377 at the correspondence address associated with Customer No. 23377.

STATEMENT UNDER 37 CFR § 3.73(b)

Bristol-Myers Squibb Company , a Corporation, states that it is:

☒ the assignee of the entire right, title, and interest; or

☐ an assignee of an undivided part interest

in the patent application/patent identified above by virtue of either:

1. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

   From: **Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, and David A. Betebenner**

   To: **Bristol-Myers Squibb Company.** The document was recorded in the Patent and Trademark Office at Reel **011607**, Frame(s) **0369**.

   ☐ Additional documents in the chain of title are listed on a supplemental sheet.

   ☐ Copies of assignments or other documents in the chain of title are attached.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O.Box 4000
Princeton, NJ 08543-4000

Warren K. Volles
Title: Assistant General Counsel
Reg. No. 33,810
Phone: 203-677-6997
Date: Nov 29 2011

DOCKET NO.: BMS-2856 **REISSUE**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Reissue Application of: **Jeffrey A. Robl, et al.**	**Confirmation No.: Not yet assigned**
U.S. Patent No.: 6,395,767	**Issued: May 28, 2002**
Application No.: Not yet assigned	**Group Art Unit: Not yet assigned**
Filing Date: Herewith	**Examiner: Not Yet Assigned**

For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method

MAIL STOP REISSUE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PRELIMINARY AMENDMENT IN APPLICATION FOR REISSUE PURSUANT TO 37 C.F.R. § 1.173

This is a preliminary amendment filed concurrently with a request for reissue of the above-identified patent. Applicants confirm that no new matter is introduced via this amendment. All amendments have been made relative to the issued patent pursuant to 37 C.F.R. § 1.173(d). The status of claims and support for claim changes are supplied on pages following this amendment. Accordingly, applicants respectfully request entry of this amendment.

REMARKS

This is an application for reissue of U.S. Patent No. 6,395,767 ("the 767 patent"), which issued on May 28, 2002. Bristol-Myers Squibb Company ("the Patent Owner") is the assignee of the entire right of the patent.

Claims 1-22 and 25-40 are pending. Claim 13 is amended. Claims 23 and 24 are canceled without prejudice or disclaimer, and claims 25-40 have been added. All amendments have been made relative to the issued patent pursuant to 47 C.F.R. § 1.173(d). Patent Owner does not believe that any new matter is introduced via this amendment. A listing of support for amendments pursuant to 37 C.F.R. 1.173(d) may be found herein at page 6.

Patent Owner respectfully submits that the claims are in condition for allowance. Favorable consideration and an early notice of allowance are earnestly solicited.

STATUS OF CLAIMS AND SUPPORT FOR CLAIM CHANGES PURSUANT TO 37 C.F.R. § 1.173(d)

Support for the amendment to claim 13 and for new claims 25-40 may be found in U.S. 6,395,767, for example, as more specifically shown as follows:

Claim	**Support in US 6,395,767**
13	Claim 12 and col. 15, lines 17-35
25	Claims 1, 8, 9, 10, and Example 60 at col. 61, line 35-col. 63, line 50
26	Claims 1, 8, 9, 10, and Example 60 at col. 61, line 35-col. 63, line 50
27	Claims 1, 8, 9, 10, 11; col. 22, lines 41-45; and Example 60 at col. 61, line 35-col. 63, line 50
28	Claims 1, 8, 9, 10, 11; col. 22, lines 41-45; and Example 60 at col. 61, line 35-col. 63, line 50
29	Claims 1, 8, 9, 10, 11, 12, 15, col. 15, lines 17-45, col. 22, lines 41-45; and Example 60 at col. 61, line 35-col. 63, line 50
30	Claims 1, 8, 9, 10, 11, 12, 15, col. 15, lines 17-45, col. 22, lines 41-45; and Example 60 at col. 61, line 35-col. 63, line 50
31	Claims 1, 8, 9, 10, 11, 12, 15, col. 15, lines 17-45, col. 22, lines 41-45; and Example 60 at col. 61, line 35-col. 63, line 50
32	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, and Example 60 at col. 61, line 35-col. 63, line 50
33	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, and Example 60 at col. 61, line 35-col. 63, line 50
34	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.

Claim	**Support in US 6,395,767**
35	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.
36	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.
37	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.
38	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.
39	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.
40	Claims 1, 8, 9, 10, 23, 24, col. 3, lines 44-61, col. 15, lines 17-45, and Example 60 at col. 61, line 35-col. 63, line 50.

Date: December 1, 2011

/S. Maurice Valla/

S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Filer:	SAMUEL VALLA/D. McCarty
Attorney Docket Number:	BMS-2856

Filed as Large Entity

Reissue (Utility) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility Reissue Basic	1014	1	380	380
Design and utility Reissue Basic	1114	1	620	620
Design and utility Reissue Basic	1314	1	750	750
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1750**

Electronic Acknowledgement Receipt

EFS ID:	11519175
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	46339
Filer:	SAMUEL VALLA/D. McCarty
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	01-DEC-2011
Filing Date:	
Time Stamp:	11:36:37
Application Type:	Reissue (Utility)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1750
RAM confirmation Number	11383
Deposit Account	233050
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Reissue Application	BMS-2856-Transmittal-Reissue.PDF	249738 ab8f29753aceb9b27445b32bfdcd42849e484a0f	no	2
Warnings:					
Information:					
2	Specification	BMS-2856-US6395767.PDF	365866 771056fc2324064143ba9bcb54c536a856d963a2	no	52
Warnings:					
Information:					
3	Reissue dec filed in accordance with MPEP 1414	BMS-2856-Declaration-by-Assignee.PDF	78609 7ce18f3d67e14974a58caa9aef0856c93177ee91	no	3
Warnings:					
Information:					
4	Consent of Assignee accompanying the declaration	BMS-2856-Consent-of-Assignee.PDF	41867 6dcb7b21e8635635a0af8fb048dc52cabf6a0dd6	no	2
Warnings:					
Information:					
5	Power of Attorney	BMS-2856-Power-of-Attorney-Assignee.PDF	45987 ee9a3d8e409cd73c1e08789984c25102c8097937	no	2
Warnings:					
Information:					
6		BMS-2856-Preliminary-Amendment.PDF	89333 5c35c2fb82a7426ae26dac37cdda33f6f016d25c	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	7

Warnings:

Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32742 d04f52478497a904aa8c1512e9116f7422189d12	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	904142	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
(use as many sheets as necessary)				**Examiner Name**	Not yet assigned
Sheet	1	of	1	**Attorney Docket Number**	BMS-2856

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	7,078,381	07-18-2006	Bachovchin et al.
	2	6,890,898	05-10-2005	Bachovchin et al.
	3	6,803,357	10-12-2004	Bachovchin et al.
	4	6,555,542	04-29-2003	O'Connor et al.
	5	5,561,146	10-01-1996	Kim et al.
	6	6,297,233	10-02-2001	Stein et al.
	7	4,255,334	03-10-1981	Day et al.
	8	6,060,432	05-09-2000	Adams et al.
	9	6,166,063	12-26-2000	Villhauer
	10	7,205,432	04-17-2007	Berner et al.
	11	7,250,529	07-31-2007	Williams
	12	3,325,478	06-13-1967	Hermann et al.
	13	3,906,044	09-16-1975	Aigami et al.
	14	2006/0287317	12-21-2006	Smith et al.

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number - Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T
	15	WO 02/060894	08-08-2002	Bristol-Myers Squibb Co.	
	16	WO 00/47207	08-17-2000	Bristol-Myers Squibb Co.	
	17	WO 97/15576	05-01-1997	E.I. Du Pont de Nemours and Co.	
	18	EP 0686642	12-13-1995	Bristol-Myers Squibb Co.	
	19	DE 2521895	04-08-1976	Pliva Pharmazeutische and Chemische Fabrik	T
	20	DE 2449840	04-24-1975	Kao Soap Corp.	T

Examiner Signature		**Date Considered**	

Substitute for 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
(use as many sheets as necessary)				**Examiner Name**	Not yet assigned
Sheet	2	of	1	**Attorney Docket Number**	BMS-2856

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
	21	Hermann Stetter and Elli Rauscher, Zur Kenntnis der Adamantan-carbonsaure-(1) Chemische Berichte, 1960, vol. 93, no. 5, pp 1161-1166	T
	22	Von R. Hiltmann et al., "2-Acylaminopyridin-Derivate mit morphinagonistischer und antagonisterischer Wirksamkeit, Arzneimittel-Forschung," 1974, vol. 24, no. 4a, pp 584-600	T
	23	Peter Beak et al.," Intramolecular Cyclizations of alpha-Lithioamine Synthetic Equivalents: Convenient Synthesis of 3-, 5-, and 6-Membered Ring Heterocyclic Nitrogen Compounds and Elaborations of 3-Mimbered Ring Systems," J. Org. Chem. vol. 59, no. 2. 1994, pp 276-277.	
	24	David J. Augeri et al., "Discovery and Preclinical Profile of Saxagliptin (BMS-477118): A Highly Potent, Long-Acting, Orally Active Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes," J. Med. Chem. 2005, 48, 5025-5037.	
	25	David R. Magnin et al. "Synthesis of Novel Potent Dipeptidyl Peptidase IV Inhibitors with Enhanced Chemical Stability: Interplay Between the N-Terminal Amino Acid Alkyl Side Chain and the Cyclopropyl Group of α-Aminoacyl-L-cis-4,5-methanoloprolinenitrile-Based Inhibitors," J. Med. Chem. 2004, 47, 2587-2598.	

Examiner Signature		**Date Considered**	

Electronic Acknowledgement Receipt

EFS ID:	11522654
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	46339
Filer:	SAMUEL VALLA/lori roman
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	01-DEC-2011
Filing Date:	
Time Stamp:	15:13:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	BMS-2856_IDS_Transmittal.PDF	104921 0eb7ba8233471acb768cb802030cf48acd194635	no	3

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	BMS-2856_IDS.PDF	134492 492e1d1ff5e23a803f0d6f6eb56a489eadb8e8bc	no	2
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Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO02060894.PDF	19707565 051b3ee4b29f2fdadcf7915f69df4c31165ea9a3	no	246
Warnings:					
Information:					
4	Foreign Reference	WO0047207.PDF	16736001 0275839e6ea6502b5042814738f74840dc70d654	no	284
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Information:					
5	Foreign Reference	WO9715576.PDF	20785931 6afccb2a0ae360b75b8bfe889cf995f33e6fcd58	no	318
Warnings:					
Information:					
6	Foreign Reference	EP0686642.PDF	3538649 beb8872d3bcb6f5927fdd33bbcadf5427fcce2a2	no	87
Warnings:					
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7	Foreign Reference	DE2521895_translation.PDF	415140 6a8755bdee3720059a2cd206f09991739e0e1219	no	7
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10	Non Patent Literature	Stetter_XP002629671.PDF	654476 3621c83ee1e55241f858ec695dcb2255430b4934	no	6

Warnings:					
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13	Non Patent Literature	Beak_Intramolecular_Cyclizations_JOrgChem_1994_276-277.PDF	299041 51cd6919f8089f24d4c4bfa4d2db8d7963d5b636	no	2
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14	Non Patent Literature	Augeri_JMEDCHEM_2005_48_5025-5037.PDF	3277271 e5b72384003d6d85aafee9611537a82d39c3accb	no	13
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15	Non Patent Literature	Magnin_JMEDCHEM_2004_47_2587-2598.PDF	2794590 5c768fe88ec5e5202515e8bd7c0b028ba85f7d8f	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	76968837		

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DOCKET NO.: BMS-2856 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jeffrey A. Robl **Confirmation No.: Not Yet Assigned**

Application No.: Not Yet Assigned **Group Art Unit: Not Yet Assigned**

Filing Date: Herewith **Examiner: Not Yet Assigned**

For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method

Filed Via EFS

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

☒ **IDS Filed Under 37 CFR 1.97(b)**

In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

☐ **IDS filed Under 37 CFR 1.97(c)**

In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.116 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

☐ Certification in Accordance with § 1.97(e) is attached; or

☐ The fee of **$180.00** as set forth in § 1.17(p) is attached.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **$180.00** as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ Copies of reference numbers 1-14 listed on the attached Form PTO-1449 are not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☒ Copies of reference numbers 15-25 listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: December 1, 2011

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

WOODCOCK WASHBURN LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

AMENDMENT

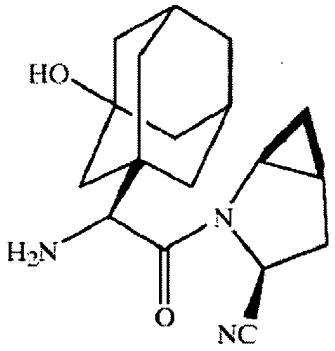
In the claims:

13. (Amended) The pharmaceutical combination as defined in claim 12 comprising said DP4 inhibitor compound and [an] the antidiabetic agent other than a DP4 inhibitor.

23. (Canceled)

24. (Canceled)

25. (New) A compound that is



; or a pharmaceutically acceptable salt thereof.

26. (New) The compound as defined in claim 25, wherein the pharmaceutically acceptable salt is the hydrochloride salt.

27. (New) A pharmaceutical composition comprising the compound of claim 25 and a pharmaceutically acceptable carrier therefor.

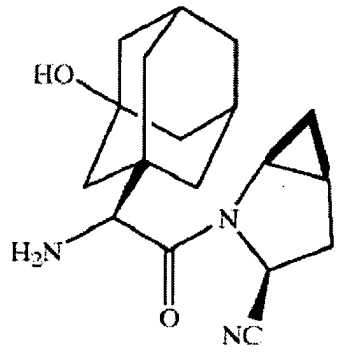
28. (New) A pharmaceutical composition comprising the compound of claim 26 and a pharmaceutically acceptable carrier therefor.

29. (New) The composition of claim 27 or 28 further comprising another antidiabetic agent other than a DP4 inhibitor.

30. (New) The composition of claim 29 wherein the other antidiabetic agent is metformin.

31. (New) The composition of claim 29, wherein the other antidiabetic agent is a SGLT2 inhibitor.

32. (New) A method for treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, impaired glucose homeostasis, or impaired glucose tolerance in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound that is



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

33. (New) The method of claim 32, wherein the pharmaceutically acceptable salt is the hydrochloride salt.

34. (New) The method of claim 32, for treating diabetes.

35. (New) The method of claim 33, for treating diabetes.

36. (New) The method of claim 34, for treating type II diabetes.

37. (New) The method of claim 35, for treating type II diabetes.

38. (New) The method of any one of claims 32, 33, 34, 25, 26, or 37, wherein the pharmaceutical composition further comprises another antidiabetic agent other than a DP4 inhibitor.

39. (New) The method of claim 38, wherein the other antidiabetic agent is metformin.

40. (New) The composition of claim 38, wherein the other antidiabetic agent is a SGLT2 inhibitor.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **$180.00** as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ Copies of reference numbers 1-14 listed on the attached Form PTO-1449 are not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☒ Copies of reference numbers 15-25 listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: December 1, 2011

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

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Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 09788173 **Filing Dt:** 02/16/2001 **Patent #:** 6395767 **Issue Dt:** 05/28/2002

PCT #: NONE **Publication #:** US20020019411 **Pub Dt:** 02/14/2002

Inventors: Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, David A. Betebenner

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

Assignment: 1

Reel/Frame: 011607 / 0369 **Received:** 05/25/2001 **Recorded:** 02/16/2001 **Mailed:** 05/30/2001 **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
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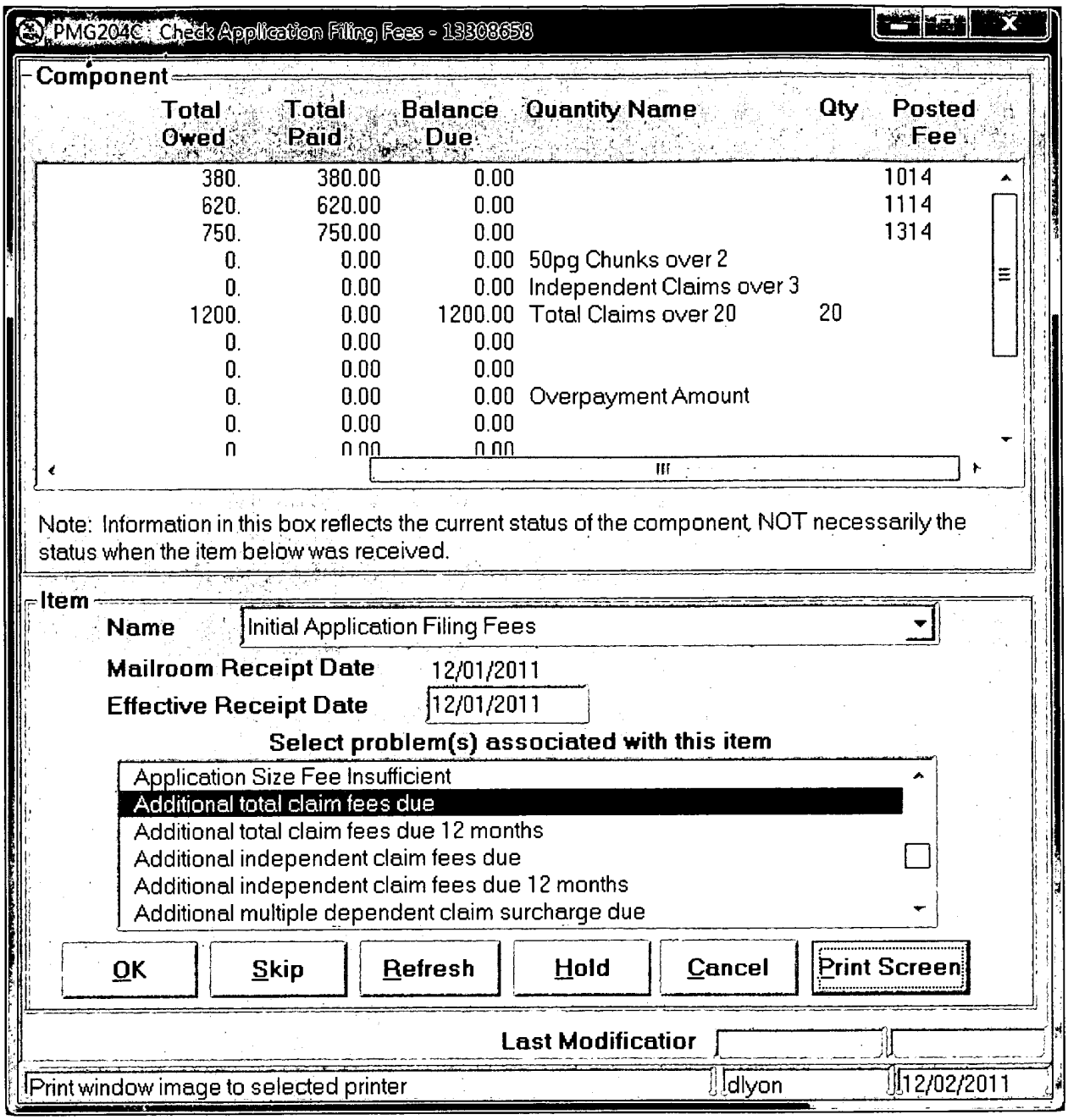
Search Results as of: 12/02/2011 11:44 AM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Total Paid
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Item
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12/02/2011

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Filer:	SAMUEL VALLA/D. McCarty
Attorney Docket Number:	BMS-2856

Filed as Large Entity

Reissue (Utility) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility Reissue Basic	1014	1	380	380
Design and utility Reissue Basic	1114	1	620	620
Design and utility Reissue Basic	1314	1	750	750
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

12/06/2011 GDIRETA1 00000047 233050 13308658
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

FILING RECEIPT

OC00000051337996

Date Mailed: 12/19/2011

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, Residence Not Provided;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

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2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

NOTICE

OC000000051337997

Date Mailed: 12/19/2011

NOTICE OF INFORMAL APPLICATION

This application is considered to be informal since it does not comply with the regulations for the reason(s) indicated below. The period within to correct the informalities noted below and avoid abandonment is set in the accompanying Office action.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

A new oath or declaration, identifying this application number, or, if appropriate, an application data sheet (37 CFR 1.76), is required. The oath or declaration does not comply with 37 CFR 1.63 in that it:

- does not identify the residence (e.g., city and either state or foreign country) of each inventor.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

POA ACCEPTANCE LETTER

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC00000051287127

Date Mailed: 12/19/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/01/2011.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dalyon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

POWER OF ATTORNEY NOTICE

46339
BMS/WOODCOCK WASHBURN
PATENT DEPARTMENT
PO BOX 4000
PRINCETON, NJ 08543-4000

OC00000051287074

Date Mailed: 12/19/2011

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/01/2011.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/dalyon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

DOCKET NO.: BMS-2856 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Jeffrey A. Robl et al.
Confirmation No.: 7781
Application No.: 13/308,658
Group Art Unit: 1629
Filing Date: December 1, 2011
Examiner:
For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV and Method

Office of Initial Patent Examination
Customer Service Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

1. Attached is a copy of the official filing receipt issued by the U.S. Patent and Trademark Office in connection with the above-referenced re-issue application for which issuance of a corrected filing receipt is respectfully requested. The requested changes are noted thereon, as well as listed below.

2. There is an error with respect to the names and residences of the Applicants.

   (a) Please add the residence for applicant Jeffrey A. Robl which is Newtown, PA (US).

   (b) In addition to Jeffrey A. Robl, there are five additional names that should be listed as applicants and are listed in U.S. Patent No. 6,395,767 which is the subject of this re-issue application. Please add the names listed below:

   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)

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: January 3, 2012

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

FILING RECEIPT

OC000000051337996

Date Mailed: 12/19/2011

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, ~~Residence Not Provided;~~ Newtown, PA (US)

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

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)

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Electronic Acknowledgement Receipt

EFS ID:	11748441
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	23377
Filer:	SAMUEL VALLA/Ann Trevisani
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	03-JAN-2012
Filing Date:	01-DEC-2011
Time Stamp:	16:04:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	Request_Corrected_Filing_Receipt.PDF	154027 4ed253dfeacd816928c1007f364a220cce48c52c	no	5

Warnings:	
Information:	

Total Files Size (in bytes):	154027

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

CORRECTED FILING RECEIPT

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC00000051838602

Date Mailed: 01/06/2012

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, Newtown, NJ;
Richard B. Sulsky, West Trenton, NJ;
David J. Augeri, Princeton, NJ;
David R. Magnin, Hamilton, NJ;
Lawrence G. Hamann, Cherry Hill, NJ;
David A. Betebenner, Lawrenceville, NJ;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

DOCKET NO.: BMS-2856 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Jeffrey A. Robl et al.
Confirmation No.: 7781
Application No.: 13/308,658
Group Art Unit: 1629
Filing Date: December 1, 2011
Examiner:
For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV and Method

Office of Initial Patent Examination
Customer Service Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

1. Attached is a copy of the corrected filing receipt issued by the U.S. Patent and Trademark Office on January 6, 2012 in connection with the above-referenced re-issue application for which issuance of a second corrected filing receipt is respectfully requested. The requested change is noted thereon, as well as listed below.

2. There is an error with respect to the residence of applicant Jeffrey A. Robl. Please see below:

   Incorrect Data: Jeffrey A. Robl, Newtown, NJ

   CORRECT DATA: Jeffrey A. Robl, Newtown, PA

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: January 9, 2012

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

CORRECTED FILING RECEIPT

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC000000051838602

Date Mailed: 01/06/2012

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, ~~Newtown, NJ;~~ Newtown, PA
Richard B. Sulsky, West Trenton, NJ;
David J. Augeri, Princeton, NJ;
David R. Magnin, Hamilton, NJ;
Lawrence G. Hamann, Cherry Hill, NJ;
David A. Betebenner, Lawrenceville, NJ;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

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Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Electronic Acknowledgement Receipt

EFS ID:	11789288
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	23377
Filer:	SAMUEL VALLA/Ann Trevisani
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	09-JAN-2012
Filing Date:	01-DEC-2011
Time Stamp:	14:49:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	Request_Corrected_Filing_Receipt.PDF	126803 8ae60b3d75f462f4f2a7a506e82e8a23227b25b7	no	5

Warnings:	
Information:	

Total Files Size (in bytes):	126803

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

CORRECTED FILING RECEIPT

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC000000051975275

Date Mailed: 01/13/2012

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

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

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856	7781

23377 7590 05/08/2012

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
05/08/2012	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	13/308,658	ROBL ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1629	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22 and 25-40* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-22 and 25-40* is/are rejected.

8)☒ Claim(s) *38* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☒ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/01/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-13 and 25-40 are pending.

2. By way of the submission filed on 12/01/2011, Applicants have canceled Claims 23 and 24, amended Claim 13, and added Claims 25-40.

Reissue Applications

3. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 6,395,767 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

4. The reissue oath/declaration filed with this application is defective because it fails to identify at least one specific error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414.

Further, unless such information is supplied on an application data sheet in accordance with § 1.76, the oath or declaration must also identify the mailing address, and the residence if an inventor lives at a location which is different from where the

inventor customarily receives mail, of each inventor. The declaration presented did not give the mailing address and thus is defective.

It is suggested that Applicants use form PTO/SB/52 (Reissue Application Declaration By The Assignee) for preparing a the declaration.

Specification and Claim Objections

5. Changes to the Specification and Claims made Certificate of Correction to the original patent grant (Patent No. 6,395,767) have not been properly incorporated into the reissue patent. The applicant should include any changes, additions, or deletions that were made by a Certificate of Correction to the original patent grant in the reissue application without underlining or bracketing. Because these changes are retroactively a part of the original patent and are made before the reissue application will issue as a patent, they must show up in the printed reissue patent document as part of the original patent, i.e., not in italics or bracketed. See MPEP 1411.

When making the Certificate of Correction changes to the specification it is not called an amendment and the changes should be made without using underlining or brackets. Because the Certificate of Correction changes are retroactively a part of the original patent and are made before the reissue application will issue as a patent, they must show up in the printed reissue patent document as part of the original patent, i.e., not in italics or bracketed.

For example, to incorporate the following certificate of correction change:

Column 82,

Line 65, change “10EtOAc” to -- 10% EtOAc --.

Applicants would submit, for example, the following:

Certificate of Correction

Per the Certificate of Correction, please substitute the following paragraph for the paragraph at column 82, beginning at line 52:

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 (2x3 mL), back-extracting the citric acid wash with ether (40 mL). The combined organic extracts were washed with 5% sodium bicarbonate (2x3 mL), dried (MgSO4), filtered, and concentrated. Flash chromatography on silica gel of the crude product with 10% EtOAc in hexane (1.0 L) gave step 4 compound as a clear thick syrup. Yield: 1.15 g (90%). MS(M+H) 334.

6. Claim 38 is objected to because of the following: The claim recites “The method of any one of claims 32, 33, 34, **25**, **26**, or 37, wherein… [emphasis added]”. The

recitation of “25” and “26” appears to be a typographical error and should be changed to “35” and “36”.

7. Claim 38 is objected to because of the following: The claim recites (at lines 5-6 of the claim) “an agent for preventing inhibiting allograft rejection in transplantation…” It appears that the word “or” should be between the words “preventing” and “inhibiting” (i.e. “preventing or inhibiting”).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7, 11-22, 29-31 and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a compound having the Markush structure recited in the claim “**and** a pharmaceutically acceptable salt thereof…[emphasis added].” It is unclear whether the claim limitations are met by (or would be anticipated by) just a compound reading on the Markush structure (or, alternatively, a salt of the compound), or if the claim limitations are only met by (or would only be anticipated by) having both said compound and a salt of the compound. Thus, it is not possible to ascertain with reasonable precision when the claim is infringed and when it is not.

Claim 12 recites the limitation "a DP4 inhibitor compound as defined in claim 1". Similarly, Claim 22 recites “A pharmaceutical combination comprising a DP4 inhibitor

compound as defined in claim 1…" Claim 1 is drawn to a compound having the recited structure; Claim 1 does not define "a DP4 inhibitor compound". Thus, there is insufficient antecedent basis for this limitation in the claim. Claim 13, which depends from Claim 12, is similarly rejected.

Claim 17 contains parenthetical subject matter that renders the claim indefinite. The claim recites (at line 3 of the claim) "a serotonin (and dopamine) reuptake inhibitor…" It is not clear whether "and dopamine" in parentheses is a limitation or an option.

Claim 29 recites "The composition of claim 27 or 28 further comprising **another** antidiabetic agent other than a DP4 inhibitor [emphasis added]." Claims 27 and 28 (and the claims from which they depend) do not claim an "antidiabetic agent" and thus do not provide proper antecedence for "another antidiabetic agent".

As discussed above, Claim 38 recites "The method of any one of claims 32, 33, 34, **25**, **26**, or 37, wherein… [emphasis added]". The recitation of "25" and "26" appears to be a typographical error and should be changed to "35" and "36"; however, the claim must be examined as presently recited. Claims 25 and 26 are drawn to compounds and not to a method and thus do not provide proper antecedence for Claim 38.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-7 and 11-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claim 1 is drawn to a compound having the Markush structure recited in the claim "…or a prodrug ester thereof…." There is insufficient written basis in the Specification for prodrugs of the compounds recited in the claim.

Regarding the requirement for adequate written description of chemical entities, Applicants' attention is directed to MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Elli Liily*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure…" *Enzo Biochem,*

Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Elli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicants have failed to provide any structural characteristics, chemical formula, name(s) or physical properties of prodrug esters of the claimed compounds, aside from a broad recitation that such are contemplated for use in the invention (see column 3, line 24 of the Specification). The Specification does not provide even a single example of a prodrug ester of any instant compound.

As such, it is not apparent that Applicant was actually in possession of, and intended to use within the context of the present invention, any specific prodrugs of the claimed compounds at the time the present invention was made. The skilled artisan could not "immediately envisage" the claimed compounds based on the description in the disclosure.

Conclusion

12. Claims 1-13 and 25-40 are rejected.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JAMES D ANDERSON/
Primary Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13308658	ROBL ET AL.
	Examiner	Art Unit
	GREGG POLANSKY	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	05/01/2012								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
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	23	-								
	24	-								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	✓								
	34	✓								
	35	✓								
	36	✓								

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✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	05/01/2012								
	37	✓								
	38	✓								
	39	✓								
	40	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13308658	ROBL ET AL.
	Examiner	Art Unit
	GREGG POLANSKY	1629

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST Search: see EAST Search Histroy	5/2/2012	GP
STN Search: see STN Search History	5/2/2012	GP
Litigation Search: see Litigation Search History	5/2/2012	GP
PALM Inventor Search	5/2/2012	GP

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/GREGG POLANSKY/ Examiner.Art Unit 1629	

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
				Examiner Name	Not yet assigned
Sheet	1	of	2	**Attorney Docket Number**	BMS-2856

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	7,078,381	07-18-2006	Bachovchin et al.
	2	6,890,898	05-10-2005	Bachovchin et al.
	3	6,803,357	10-12-2004	Bachovchin et al.
	4	6,555,542	04-29-2003	O'Connor et al.
	5	5,561,146	10-01-1996	Kim et al.
	6	6,297,233	10-02-2001	Stein et al.
	7	4,255,334	03-10-1981	Day et al.
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	12	3,325,478	06-13-1967	Hermann et al.
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Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number - Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T
	15	WO 02/060894	08-08-2002	Bristol-Myers Squibb Co.	
	16	WO 00/47207	08-17-2000	Bristol-Myers Squibb Co.	
	17	WO 97/15576	05-01-1997	E.I. Du Pont de Nemours and Co.	
	18	EP 0686642	12-13-1995	Bristol-Myers Squibb Co.	
	19	DE 2521895	04-08-1976	Pliva Pharmazeutische and Chemische Fabrik	T
	20	DE 2449840	04-24-1975	Kao Soap Corp.	T

Examiner Signature		**Date Considered**	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.P./

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
				Examiner Name	Not yet assigned
Sheet	2	of	2	**Attorney Docket Number**	BMS-2856

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
	21	Hermann Stetter and Elli Rauscher, Zur Kenntnis der Adamantan-carbonsaure-(1) Chemische Berichte, 1960, vol. 93, no. 5, pp 1161-1166	T
	22	Von R. Hiltmann et al., "2-Acylaminopyridin-Derivate mit morphinagonistischer und antagonisterischer Wirksamkeit, Arzneimittel-Forschung," 1974, vol. 24, no. 4a, pp 584-600	T
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Examiner Signature	/Gregg Polansky/	**Date Considered**	04/30/2012

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.P./

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BIB DATA SHEET

CONFIRMATION NO. 7781

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/308,658	12/01/2011	514	1629	BMS-2856

APPLICANTS

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David J. Augeri, Princeton, NJ;
David R. Magnin, Hamilton, NJ;
Lawrence G. Hamann, Cherry Hill, NJ;
David A. Betebenner, Lawrenceville, NJ;

**** CONTINUING DATA ***************************

This application is a REI of 09/788,173 02/16/2001 PAT 6,395,767
which claims benefit of 60/188,555 03/10/2000

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/06/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /GREGG POLANSKY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA		40	3

ADDRESS

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2929 ARCH STREET
PHILADELPHIA, PA 19104-2891
UNITED STATES

TITLE

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

FILING FEE RECEIVED		
2950	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	("6395767").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2012/04/30 15:06
S2	5	onglyza	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:31
S3	1193	saxagliptin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:31
S4	1195	S2 or S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:32
S5	339	BMS-477118	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:39
S6	431	BMS adj "477118"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:39
S7	431	BMS adj2 "477118"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:39
S8	431	S5 or S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:39
S9	0	"361442-05-9"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 16:49

5/1/2012 9:32:30 PM
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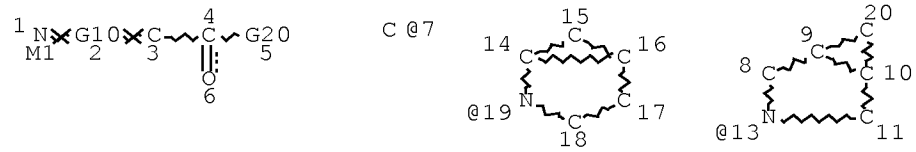


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VAR G20=13/19
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NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  14  13
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE
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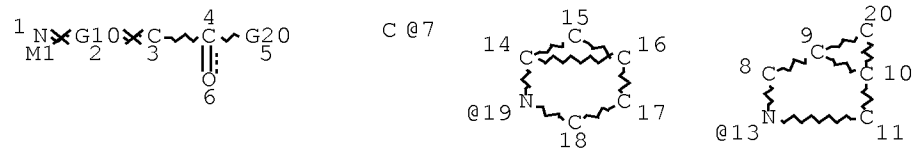


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REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
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NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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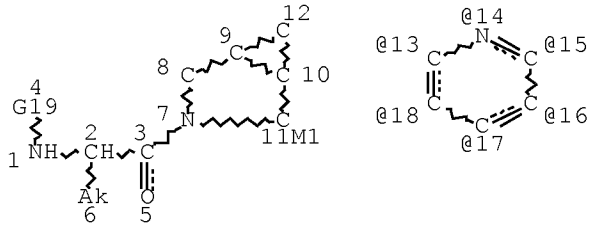

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NODE ATTRIBUTES:
HCOUNT IS M1   AT 11
CONNECT IS E1 RC AT   6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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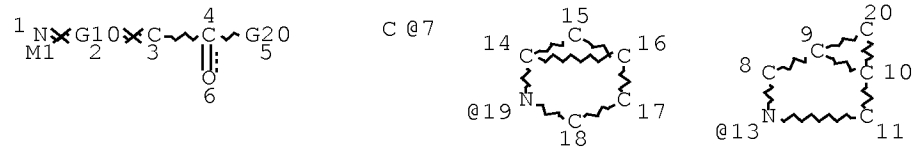

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VAR G20=13/19

NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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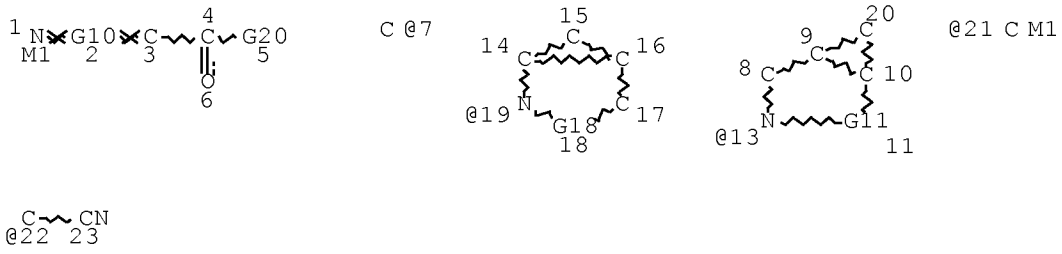
L20 STR



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VAR G11=21/22
VAR G18=21/22
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
HCOUNT IS M1 AT 21
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
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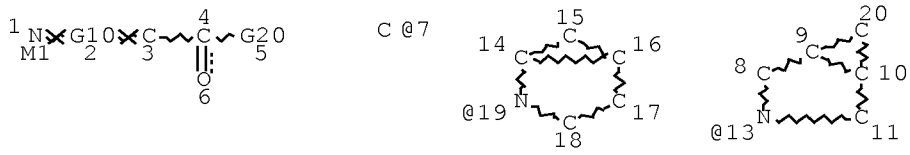

REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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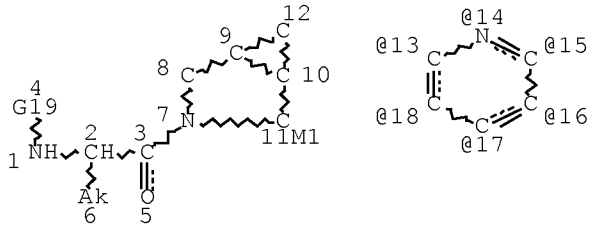
L17 STR



VAR G19=13/14/15/16/17/18
NODE ATTRIBUTES:
HCOUNT IS M1 AT 11
CONNECT IS E1 RC AT 6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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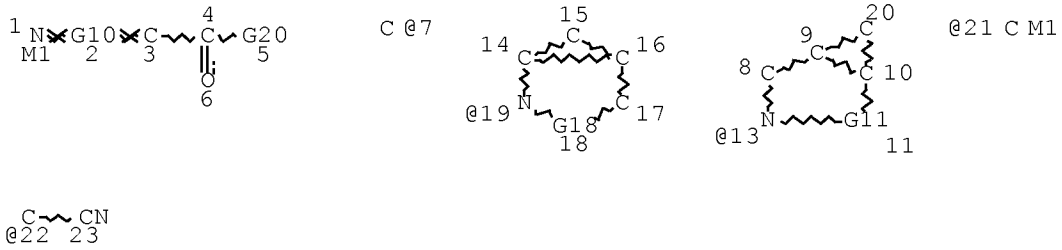
L20 STR



REP G10=(0-1) 7
VAR G11=21/22
VAR G18=21/22
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
HCOUNT IS M1 AT 21
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
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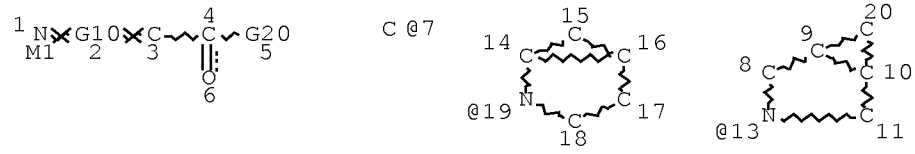
L12 STR



REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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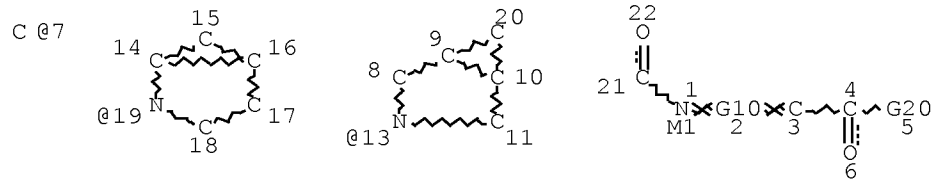
L39   STR



REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1   AT   1
NSPEC   IS RC   AT   1
NSPEC   IS RC   AT   3
NSPEC   IS RC   AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
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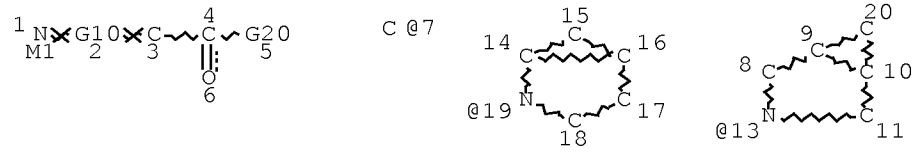

REP G10=(0-1) 7

VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
NSPEC IS RC AT 1
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NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 19

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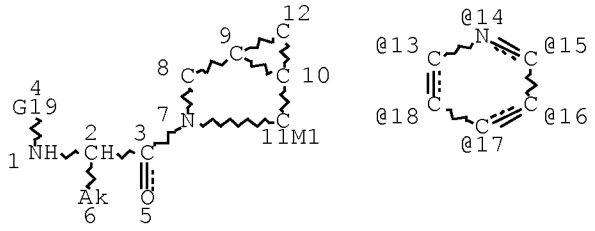

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NODE ATTRIBUTES:
HCOUNT IS M1 AT 11
CONNECT IS E1 RC AT 6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
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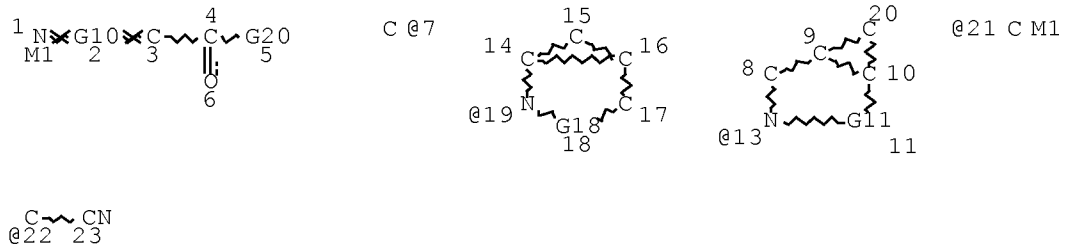

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VAR G18=21/22
VAR G20=13/19
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HCOUNT  IS M1     AT  21
NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
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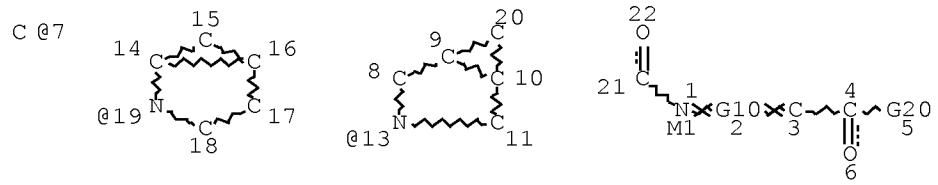


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NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
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=> d que nos l49
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L12              STR
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L30              QUE  SPE=ON  ABB=ON  PLU=ON  BETEBENNER, D?/AU,AUTH,IN
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L44          427 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L42
L45           15 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L44 AND (L24 OR L25
                 OR L26 OR L27 OR L28 OR L29 OR L30)
L46            0 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L1 NOT L45
L47           15 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L45 OR L46)
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L49           87 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L48 AND L32
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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y



L49  ANSWER 1 OF 87  HCAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:307629  HCAPLUS  Full-text
DOCUMENT NUMBER:         156:327731
TITLE:                   DPP-4 inhibitors in the treatment of type 2 diabetes
AUTHOR(S):               Duez, Helene; Cariou, Bertrand; Staels, Bart
CORPORATE SOURCE:        Univ Lille Nord de France, Lille, F-59000, Fr.
SOURCE:                  Biochemical Pharmacology (2012), 83(7), 823-832
                         CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; General Review; (online computer file)
LANGUAGE:                English
ED   Entered STN:  02 Mar 2012
AB    A review.  Although being a primary objective in the management of type 2
      diabetes, optimal glycemic control is difficult to achieve and usually not
      maintained over time.  Type 2 diabetes is a complex pathol., comprising
      altered insulin sensitivity and impaired insulin secretion.  Recent
      advances in the understanding of the physiol. functions of incretins and
      their degrading enzyme dipeptidyl-peptidase (DPP)-4 have led to the
      discovery' of a new class of oral anti-diabetic drugs.  Several DPP-4
      inhibitors (or gliptins) with different chemical structures are now
      available.  These agents inhibit the degradation of the incretins
      glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic
      polypeptide (GIP) and hence potentiate glucose-dependent insulin secretion.
      DPP-4 inhibitors inhibit DPP-4 activity by almost 100% in vitro, maintaining
      a ≥80% inhibition throughout the treatment period in vivo, thus prolonging
      GLP-1 half-life, and significantly reducing HbA1c generally by -0.7 to 0.8%
      as well as fasting and post-prandial glycemia.  They are well-tolerated with
      no weight gain and few adverse effects, and, of particular interest, no
      increase in hypoglycemic episodes.  Although different by their chemical
      structure and pharmacokinetic properties, the DPP4 inhibitors currently
      available have proven similar glucose lowering efficacy.
IT   361442-04-8, Saxagliptin
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (DPP-4 inhibitors in treatment of type 2 diabetes)
RN   361442-04-8  HCAPLUS
CN   2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
     2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
     (1S,3S,5S)-  (CA INDEX NAME)

Absolute stereochemistry.
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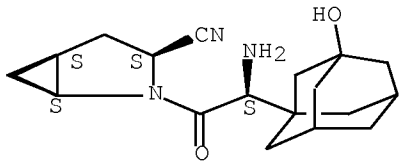
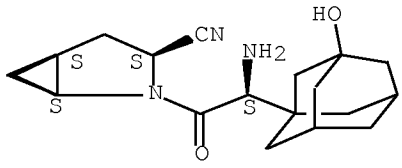


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

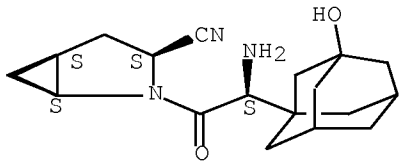
L49 ANSWER 2 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:21882 HCAPLUS Full-text
TITLE: Pharmacological and clinical evaluations of a new drug on treating type 2 diabetes:saxagliptin
AUTHOR(S): Lu, Ju-ming
CORPORATE SOURCE: Department of Endocrionology, Chinese PLA General Hospital, Beijing, 100853, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2011), 20(21), 2039-2043
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 05 Jan 2012
AB This review with 28 refs. summarizes the action mechanisms, pharmacokinetics, clin. studies and adverse reactions of saxagliptin as a therapeutic drug with new action mechanisms for treating type 2 diabetes.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. and clin. evaluations of saxagliptin on treating type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 3 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1662838 HCAPLUS Full-text
TITLE: Medicinal chemistry and applications of incretins and DPP-4 inhibitors in the treatment of Type 2 diabetes mellitus
AUTHOR(S): Lotfy, Mohamed; Singh, Jaipaul; Kalasz, Huba; Tekes, Kornelia; Adeghate, Ernest
CORPORATE SOURCE: Department of Biology, Faculty of Science, UAE University, Al Ain, United Arab Emirates
SOURCE: Open Medicinal Chemistry Journal (2011), 5, 82-92
CODEN: OMCJB6; ISSN: 1874-1045
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 27 Dec 2011
AB Diabetes mellitus (DM) is a major metabolic disorder currently affecting over 200 million people worldwide. Approx. 90% of all diabetic patients suffer from Type 2 diabetes mellitus (T2DM). The world's economy coughs out billions of dollars annually to diagnose, treat and manage patients with diabetes. It has been shown that the naturally occurring gut hormones incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) can preserve the morphol. and function of pancreatic beta cell. In addition, GIP and GLP-1 act on insulin receptors to facilitate insulin-receptor binding, resulting in optimal glucose metabolism This review examines the medicinal chemical and roles of incretins, specifically, GLP-1 and drugs which can mimic its actions and prevent its enzymic degradation The review discussed GLP-1 agonists such as exenatide, liraglutide, taspoglutide and albiglutide. The paper also identified and reviewed a number of inhibitors, which can block dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for the rapid degradation of GLP-1. These DPP-4 inhibitors include sitagliptin, saxagliptin, vildagliptin and many others which are still in the exptl. phase.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(medicinal chemical and applications of incretins and dipeptidyl peptidase
4 inhibitors in the treatment of type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

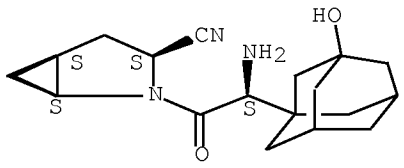
Absolute stereochemistry.



REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 4 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1607699 HCAPLUS Full-text
TITLE: A review of gliptins in 2011
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders, and Division of Clinical Pharmacology, Department of Medicine, University of Liege, CHU Sart Tilman (B35), Liege, B-4000, Belg.
SOURCE: Expert Opinion on Pharmacotherapy (2012), 13(1), 81-99
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Dec 2011
AB Introduction: Dipeptidylpeptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes (T2DM).Areas covered: This paper is an updated review, providing an anal. of both the similarities and the differences between the various compds. known as gliptins, currently used in the clinic (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin). This paper discusses the pharmacokinetic and pharmacodynamic characteristics of gliptins; both the efficacy and safety profiles of gliptins in clin. trials (compared with classical glucose-lowering agents), given as monotherapy or in combination, including in special populations; the positioning of DPP-4 inhibitors in the management of T2DM in recent guidelines; and various unanswered questions and perspectives.Expert opinion: The role of DPP-4 inhibitors in the therapeutic armamentarium of T2DM is evolving, as their potential strengths and weaknesses become better defined. Future critical issues may include the durability of glucose control, resulting from better β-cell protection, pos. effects on cardiovascular outcomes and long-term safety issues.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin may be safe, effective and may show favorable pharmacokinetic and pharmacodynamic characteristics in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 136 THERE ARE 136 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

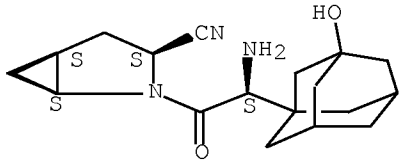
L49 ANSWER 5 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1607697 HCAPLUS Full-text
TITLE: Metformin + saxagliptin for type 2 diabetes
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Department of Medicine, Division of Diabetes, Nutrition and Metabolic Disorders, and Division of Clinical Pharmacology, University of Liege, CHU Sart Tilman (B35), Liege, B-4000, Belg.
SOURCE: Expert Opinion on Pharmacotherapy (2012), 13(1), 139-146
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Dec 2011
AB Introduction: Metformin is considered as the first-line drug therapy for the management of type 2 diabetes. Dipeptidyl peptidase-4 (DPP-4) inhibitors, by promoting insulin secretion and reducing glucagon secretion in a glucose-dependent manner, offer new opportunities for oral therapy after failure of metformin.Areas covered: An updated review of the literature demonstrates that saxagliptin, a DPP-4 inhibitor, and metformin may be administered together, sep. or in fixed-dose combination (FDC), either as saxagliptin added to metformin or as initial combination in drug-naive patients. Both compds. exert complementary pharmacodynamic actions leading to better improvement in blood glucose control (fasting plasma glucose, postprandial glucose, HbA1c) than either compound sep. Adding saxagliptin to metformin monthotherapy results in a consistent, sustained and safe reduction in HbA1c levels. Tolerance is excellent without hypoglycemia or weight gain.Expert opinion: The combination saxaglitpin plus metformin may be used as first-line or second-line therapy in the management of type 2 diabetes, especially as a valuable alternative to the classical metformin-sulfonylurea combination.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(metformin plus saxagliptin exerted complementary pharmacodynamic actions leading to better improvement in fasting plasma glucose, postprandial glucose and glycated Hb in patient with type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 6 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1569695 HCAPLUS Full-text

TITLE: Saxagliptin: a dipeptidyl peptidase-4 inhibitor in the treatment of type 2 diabetes mellitus

AUTHOR(S): Dave, Darshan J.

CORPORATE SOURCE: Department of Pharmacology, P.D.U. Medical College, Rajkot, 360 001, India

SOURCE: Journal of Pharmacology and Pharmacotherapeutics (2011), 2(4), 230-235
CODEN: JPPOGN; ISSN: 0976-500X

PUBLISHER: Medknow Publications and Media Pvt. Ltd.

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

ED Entered STN: 07 Dec 2011

AB Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin deficiency or resistance. Management starts with single oral antidiabetic drug (OAD) but eventually switch over to combination therapy because of progressive β-cell dysfunction. Hypoglycemia, weight gain, and adverse cardiovascular events are major limitations of the available OADs (Sulfonylureas [SUs], thiazolidinediones [TZDs]). Saxagliptin, a reversible, competitive dipeptidyl peptidase-4 inhibitor, is recently approved agent in the treatment of T2DM. It acts by preventing the degradation of glucagon-like peptide-1 and hence increases secretion of insulin and decreases secretion of glucagon. It is a well-tolerated agent with commonly reported adverse events which include upper respiratory tract infection, urinary tract infection, and headache. Hypoglycemia, weight gain, and adverse cardiovascular events are negligible as compared with other OADs. In clin. studies, saxagliptin was found to be effective and well tolerated when used as a monotherapy as well as in combination with metformin,

SUs and TZDs. It is administered in the dose range of 2.5 to 5 mg once a day regardless of meal. Dosage reduction is required in patients having moderate to severe renal impairment as well as with concurrent administration of strong CYP3A4/5 inhibitors. To conclude, saxagliptin because of its novel mechanism of action (preserving beta cell function) and better tolerability profile seems to be a promising agent in the treatment of T2DM, especially in the early stage of the disease, but long-term clin. studies are required to prove its status in the management of T2DM.

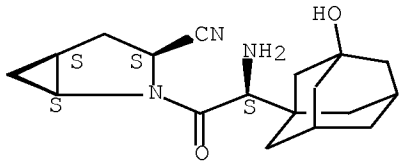
IT INDEXING IN PROGRESS

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dipeptidyl peptidase-4 inhibitor saxagliptin was well tolerated and effective as monotherapy or as combination therapy with oral antidiabetic drugs in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 7 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1506904 HCAPLUS Full-text

TITLE: Tolerability of Dipeptidyl Peptidase-4 Inhibitors: A Review

AUTHOR(S): Richard, Kathleen R.; Shelburne, Jamie S.; Kirk, Julienne K.

CORPORATE SOURCE: Wake Forest School of Medicine, Winston-Salem, NC, USA

SOURCE: Clinical Therapeutics (2011), 33(11), 1609-1629
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

ED Entered STN: 24 Nov 2011

AB Background: Oral glucose-lowering agents are used to treat patients with type 2 diabetes mellitus (T2DM). Most patients require multiple agents to maintain glycemic targets. Dipeptidyl peptidase-4 (DPP-4) inhibitors are administered as monotherapy and in combination therapy for the treatment of T2DM. Objective: The aim of this article was to provide a thorough review of published tolerability data on 5 DPP-4 inhibitors. Methods: PubMed and Web of Science were searched for English-language clin. trials published from

Jan. 2000 to June 2001, using the following key words: dipeptidyl peptidase-4 inhibitor, vildagliptin, alogliptin, sitagliptin, saxagliptin, linagliptin, safety, tolerability, efficacy, effect, AE, and adverse effect. Studies were considered for inclusion if they were randomized, double-blind trials performed in patients ≥18 years of age with T2DM and with a Hb A1c of ≥6.5%; included ≥1 arm that received monotherapy with DPP-4; and reported adverse events (AEs). Studies in patients with a history of type 1 or secondary forms of diabetes, significant diabetic complications or cardiovascular disease within the 6 mo before the start of the study, hepatic disease or abnormalities, and/or renal abnormalities were excluded. Results: A total of 45 clin. trials, 5 pharmacokinetic studies, and 28 meta-analyses or reviews were included. The duration of studies ranged from 7 days to 104 wk. The most commonly reported AEs were nasopharyngitis, upper respiratory infections, all-cause infections, headache, gastrointestinal symptoms, and musculoskeletal pain. Based on the findings from the studies, the DPP-4 inhibitors had minimal impact on weight and were not associated with an increased risk for hypoglycemia relative to placebo. Rates of nasopharyngitis were higher with the DDP-4 inhibitors than with placebo. Pancreatitis was reported at lower rates with the DPP-4 inhibitors compared with other oral antihyperglycemic agents. Cardiovascular events were limited, and postmarketing studies are ongoing. Conclusions: The tolerability of DPP-4 inhibitors is supported by published clin. trials. The rates of weight gain, gastrointestinal AEs, and hypoglycemia were minimal with the DPP-4 inhibitors studied.

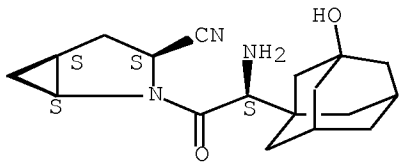
IT INDEXING IN PROGRESS

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tolerability of dipeptidyl peptidase-4 inhibitors)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 8 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1489656 HCAPLUS Full-text

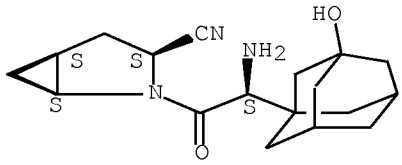
TITLE: Choosing a gliptin

AUTHOR(S): Gupta, Vishal; Kalra, Sanjay

CORPORATE SOURCE: Department of Endocrinology, Jaslok Hospital and

Research Centre, Mumbai, 400026, India
SOURCE: Indian Journal of Endocrinology and Metabolism (2011), 15(4), 298-308
CODEN: IJEMGB; ISSN: 2230-9500
PUBLISHER: Medknow Publications and Media Pvt. Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Nov 2011
AB The treatment of type 2 diabetes mellitus (T2DM) has included the use of metformin and sulfonylurea (SU) as first-line anti-diabetic therapies world over since years. This remains, despite the knowledge that the combination results in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an addnl. pharmacol. agent to maintain the glycosylated Hb (HbA1c) <7.0% (UKPDS). Gliptins represent a novel class of agents that improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. They function by augmenting the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4). Not only are they efficacious but also safe (weight neutral) and do not cause significant hypoglycemia, making it a unique class of drugs. This review focuses on gliptins (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) discussing pharmacokinetics, pharmacodynamics, efficacy and safety.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin was safe and effective in treatment of patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

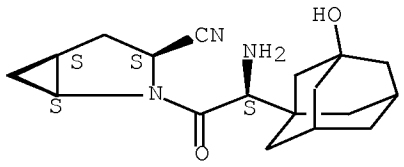


REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 9 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1292912 HCAPLUS Full-text
TITLE: Linagliptin and newer DPP-4 inhibitors: newer uses and newer indications
AUTHOR(S): Kalra, Sanjay; Unnikrishnan, Ambika G.; Agrawal, Navneet; Singh, Anupam K.
CORPORATE SOURCE: Bharti Hospital, Karnal, India

SOURCE: Recent Patents on Endocrine, Metabolic & Immune Drug Discovery (2011), 5(3), 197-202
CODEN: RPEMBB; ISSN: 1872-2148
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Oct 2011
AB The dipeptidyl peptidase-4 (DPP-4) inhibitors linagliptin, sitagliptin, saxagliptin, vildagliptin and alogliptin are being developed and have been approved for the treatment of type-2 diabetes. These agents may be used either as monotherapy for the treatment of type-2 diabetes or in combination with other anti-diabetic drugs. The present review highlights the use of linagliptin and other new (DPP-4) inhibitors in the management of type-2 diabetes. The review also highlights advantages, comparative pharmacokinetic, safety profile and other potential uses including potential newer indications of DPP-4 inhibitors and relevant patents. The other potential uses that are not restricted to diabetes include obesity, cardiovascular disease, neurol. disease, hepatobiliary disease, wound healing, and other inflammatory illnesses.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(uses and new indications of linagliptin and newer DPP-4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

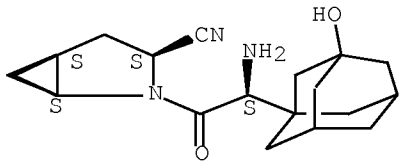


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 10 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1255500 HCAPLUS Full-text
TITLE: Pharmacology of dipeptidyl peptidase-4 inhibitors:similarities and differences
AUTHOR(S): Baetta, Roberta; Corsini, Alberto
CORPORATE SOURCE: Department of Pharmacological Sciences, University of Milan, Milan, Italy
SOURCE: Drugs (2011), 71(11), 1441-1467
CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis Data Information BV
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 04 Oct 2011
AB The dipeptidyl peptidase (DPP)-4 inhibitors, which enhance glucose-dependent insulin secretion from pancreatic β cells by preventing DPP-4-mediated degradation of endogenously released incretin hormones, represent a new therapeutic approach to the management of type 2 diabetes mellitus. The 'first-in-class' DPP-4 inhibitor, sitagliptin, was approved in 2006; it was followed by vildagliptin (available in the EU and many other countries since 2007, although approval in the US is still pending), saxagliptin (in 2009), alogliptin (in 2010, presently only in Japan) and linagliptin, which was approved in the US in May 2011 and is undergoing regulatory review in Japan and the EU. As the number of DPP-4 inhibitors on the market increases, potential differences among the different members of the class become important when deciding which agent is best suited for an individual patient. The aim of this review is to provide a comprehensive and updated comparison of the pharmacodynamic and pharmacokinetic properties of DPP-4 inhibitors, and to pinpoint pharmacol. differences of potential interest for their use in therapy. Despite their common mechanism of action, these agents show significant structural heterogeneity that could translate into different pharmacol. properties. At the pharmacokinetic level, DPP-4 inhibitors have important differences, including half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites and excretion routes. These differences could be relevant, especially in patients with renal or hepatic impairment, and when considering combination therapy. At the pharmacodynamic level, the data available so far indicate a similar glucose-lowering efficacy of DPP-4 inhibitors, either as monotherapy or in combination with other hypoglycemic drugs, a similar weight-neutral effect, and a comparable safety and tolerability profile. Data on nonglycemic parameters are scant at present and do not allow a comparison among DPP-4 inhibitors. Several phase III trials of DPP-4 inhibitors are currently ongoing; these trials, along with post-marketing surveillance data, will hopefully increase our knowledge about the long-term efficacy and safety of DPP-4 inhibitor therapy, the effect on pancreatic cell function and peripheral glucose metabolism, and the effect on cardiovascular outcomes in patients with type 2 diabetes.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. of dipeptidyl peptidase-4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 166 THERE ARE 166 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

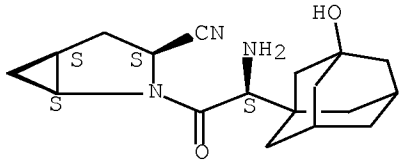
L49 ANSWER 11 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1006450 HCAPLUS Full-text
DOCUMENT NUMBER: 155:398157
TITLE: Patient considerations and clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes
AUTHOR(S): Derosa, Giuseppe; Maffioli, Pamela
CORPORATE SOURCE: Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
SOURCE: Diabetes, Metabolic Syndrome and Obesity (2011), 4, 263-271
CODEN: DMSOAD; ISSN: 1178-7007
URL: http://www.dovepress.com/getfile.php?fileID=10436
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Aug 2011
AB A review. Introduction: Targeting glycated Hb (HbA1c) levels below 7.0% is considered a primary goal of diabetes care, given its importance in obtaining a sustained reduction in microvascular and possibly macrovascular complications. Aim: The aim of this review was to evaluate the clin. utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes. Evidence Review: The combination of saxagliptin/metformin was well tolerated and produced sustained glycemic control for up to 76 wk, with greater improvements in glycemic parameters compared with either drug alone. The saxagliptin/metformin combination also proved its non-inferiority compared with either sulfonylurea/metformin or sitagliptin/metformin combinations. Place in Therapy: Clin. practice recommends lifestyle interventions together with starting metformin at the time that the type 2 diabetes mellitus is diagnosed. Once metformin fails to maintain glycemic control, the addition of DPP-4 inhibitors should be the logical choice because of their effects on HbA1c compared to the addition of a sulfonylurea or glitazone and because of their pos. effects on beta cell function and their neutral effects on body weight Furthermore, DPP-4 inhibitors prevent the risk of hypoglycemia posed by sulfonylureas.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);

THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(patient considerations and clin. utility of fixed dose combination of saxagliptin/metformin in treatment of type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 12 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:938884 HCAPLUS Full-text

DOCUMENT NUMBER: 156:378948

TITLE: Comment on Gerich - DPP-4 inhibitors: What may be the clinical differentiators?

AUTHOR(S): Chen, Roland; Oehman, Peter; Kirby, Mark

CORPORATE SOURCE: Bristol-Myers Squibb, Princeton, NJ, 08543, USA

SOURCE: Diabetes Research and Clinical Practice (2011), 93(1), e3-e4
CODEN: DRCPE9; ISSN: 0168-8227

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

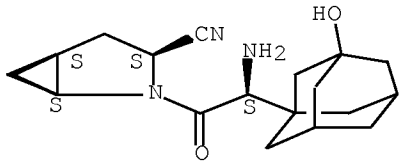
ED Entered STN: 28 Jul 2011

AB A review. A polemic in response to Gerich (Diabetes Res. Clin. Pract. 2010; 90: 131-140), who summarize the emerging use and benefits of DPP-4 inhibitors in the treatments of patients with type 2 diabetes. Chen et al. however, claim that the manuscript contains a number of statements which are either inaccurate or require further clarification. Gerich presents two previous studies with fundamentally different methodologies and concludes, 'in a study that compared saxagliptin with glyburide treatment, no statistically significant difference in the incidence of reported and confirmed hypoglycemic events between the two treatments was found'. Chen et al. believe that this conclusion is inaccurate and inappropriate given that the cited saxagliptin study was not a comparative study vs. glyburide but rather assessed the use of saxagliptin in combination with glyburide, thus all subjects in the study would be exposed to the hypoglycemic effects of glyburide.

IT 361442-04-8, Saxagliptin

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use and benefits of DPP-4 inhibitors in the treatment of patients with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

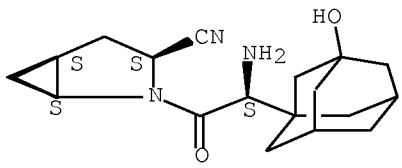


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 13 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:756534 HCAPLUS Full-text
DOCUMENT NUMBER: 156:185905
TITLE: QbD, control strategy and the regulatory experience
AUTHOR(S): Didonato, Gerald C.; Liebowitz, Stephen M.
CORPORATE SOURCE: Bristol-Myers Squibb Company, Princeton, NJ, 08534, USA
SOURCE: Chimica Oggi (2011), 29(2), 34-37
CODEN: CHOGDS; ISSN: 0392-839X
PUBLISHER: Tekno Scienze
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Jun 2011
AB A review. Quality by Design (QbD) is a science and risk-based approach to pharmaceutical development. Products developed under a QbD paradigm create a knowledge base to formulate a holistic control strategy that assures conformance of a drug product to its intended performance profile. Saxagliptin, a new drug for the treatment of Type II diabetes, was developed under QbD principles and submitted for regulatory approval in the US, EU and several other countries. Development experimentation to support the control strategy and its presentation in the applications are discussed.
IT 361442-04-8, Saxagliptin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug developed under quality by design may be useful to formulate holistic control strategy to assure product with its intended performance profile like saxagliptin that presented to regulatory approval for treatment of type II diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,

2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

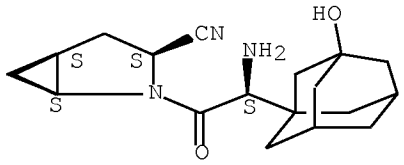
L49 ANSWER 14 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:748467 HCAPLUS Full-text
DOCUMENT NUMBER: 156:167858
TITLE: Clinical Pharmacology of Incretin Therapies for Type 2 Diabetes Mellitus: Implications for Treatment
AUTHOR(S): Neumiller, Joshua J.
CORPORATE SOURCE: College of Pharmacy, Washington State University, Spokane, WA, USA
SOURCE: Clinical Therapeutics (2011), 33(5), 528-576
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 16 Jun 2011
AB A review. Background: Increased understanding of the role of incretin hormones in maintaining glucose homeostasis has enabled the development of pharmacotherapies that target deficient incretin activity in type 2 diabetes mellitus (T2DM). Incretin therapies are premised on 1 of 2 approaches: (1) augmenting the activity of the hormone glucagon-like peptide (GLP)-1 (GLP-1 receptor agonists) and (2) inhibiting the degradation of GLP-1 by dipeptidyl peptidase (DPP)-4 (DPP-4 inhibitors). Objective: This review discusses the pharmacokinetic properties and clin. profiles of the GLP-1 receptor agonists (exenatide twice daily, liraglutide once daily, exenatide once weekly, taspoglutide, and albiglutide) and the DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, and alogliptin) available for use or in late-stage development. Methods: A search of PubMed for literature published between 2000 and mid-2010 was conducted using the names of each agent as key words. Phase III and IV studies were included in the review of efficacy and tolerability. Supplemental searches of abstrs. from major diabetes conferences provided addnl. information on pharmacokinetic properties. Searches of all reference lists were performed to identify addnl. refs. of interest. Results: The PubMed search identified multiple randomized, controlled clin. studies of the GLP-1 receptor agonists and the DPP-4 inhibitors administered as monotherapy or in combination regimens. Redns. from baseline in glycosylated Hb ranged from 0.4% to 1.5% with exenatide 5 to 10 μg/d (7 studies), 0.6% to 1.5% with liraglutide 0.6 to 1.8

mg/d (6 studies), 0.3% to 1.0% with sitagliptin 25 to 200 mg/d (9 studies), 0.5% to 0.9% with saxagliptin 2.5 to 10 mg/d (3 studies), 0.4% to 1.0% with vildagliptin 50 to 100 mg/d (6 studies), and 0.4% to 0.8% with alogliptin 12.5 to 25 mg/d (4 studies). Dosage adjustments and caution in prescribing incretin therapies are recommended in patients with renal disease, with those recommendations varying based on the agent and the degree of dysfunction. Incretin therapies have been associated with few interactions with commonly used antihyperglycemic and cardiovascular therapies. Conclusion: Based on the pharmacokinetic and therapeutic characteristics described in previously published Phase III and IV studies of incretin therapies, these agents may provide an option for the management of T2DM.

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glucagon-like peptide-1 receptor agonist and DPP-4 inhibitors sitagliptin, saxagliptin, vildagliptin and alogliptin administered as monotherapy or in combination regimens may be helpful in treatment of patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

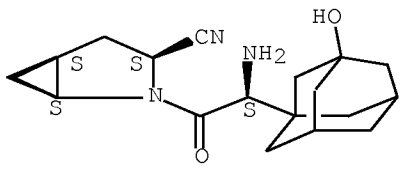


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 167 THERE ARE 167 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 15 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:736727 HCAPLUS Full-text
DOCUMENT NUMBER: 156:113716
TITLE: DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors
AUTHOR(S): Dicker, Dror
CORPORATE SOURCE: Internal Medicine D and Obesity Clinic, Hasharon Hospital, Rabin Medical Center, Tel Aviv University, Tel Aviv-Jaffa, Israel
SOURCE: Diabetes Care (2011), 34(Suppl. 2), S276-S278
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

ED Entered STN: 14 Jun 2011
AB A review on the dipeptidyl peptidase 4 inhibitors namely, sitagliptin, saxagliptin, and vildagliptin as treatment for diabetes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(impact of DPP-4 inhibitors on glycemic control and cardiovascular risk factors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 16 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:556777 HCAPLUS Full-text
DOCUMENT NUMBER: 156:46211
TITLE: Potential effects of DPP-4 inhibitors on cardiovascular disease
AUTHOR(S): Fonseca, Vivian A.
CORPORATE SOURCE: Italy
SOURCE: Hot Topics in Cardiometabolic Disorders (2010), (2), 17-21
CODEN: HTCDBS; ISSN: 2037-9080
URL: http://www.hottopicsin.com/dwl/potential effects of dpp-4_inhibitors_on_cardiovascular_disease_13501cdf35b854e3632b.pdf

PUBLISHER: FBCommunication srl.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 05 May 2011
AB A review. Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors) are a relatively new class of drugs used for the treatment of diabetes. They exert their effect by inhibiting the breakdown of endogenous glucagon-like peptides (GLP-1 and 2) and glucose-dependent insulinotropic peptide (GIP), resulting in an increase in glucose mediated insulin secretion and a suppression of glucagon secretion. Three DPP-4 inhibitors are currently on

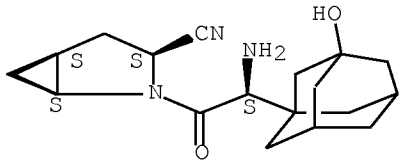
the market: sitagliptin, saxagliptin and vildagliptin. Of these, only sitagliptin and saxagliptin are currently available in the United States, whereas all three are available in Europe. Several other DPP-4 inhibitors are currently in the development stage. Because of the known increased incidence of cardiovascular disease in diabetes, regulatory authorities such as the Food and Drug Administration (FDA) are requiring long-term cardiovascular safety in the development of new diabetes medications while maintaining the current efficacy guidelines with regard to glucose control. Since GLP-1 is known to have many effects beyond glucose lowering, including cardiovascular protective effects, there is interest in determining whether DPP-4 inhibitors will also have similar effects. DPP-4 inhibitors have been shown to improve glucose control without weight gain, hypoglycemia or an increase in blood pressure, and some have even exhibited a significant decrease in the risk of major cardiovascular events. They are consequently considered to be a promising drug class that may meet the demands for both efficacy in the treatment of diabetes, as well as a safe cardiovascular profile. Although many short-term studies have been encouraging, long-term clin. trials are needed to determine whether DPP-4 inhibitors are clearly safe in terms of cardiovascular risk, and whether they may even exert a potential cardiovascular benefit.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitor saxagliptin may be useful to improve glucose control without weight gain, hypoglycemia and to reduce risk of cardiovascular event in diabetes patient with cardiovascular disease)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

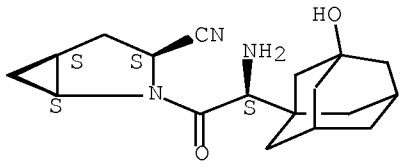


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 17 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:438689 HCAPLUS Full-text
DOCUMENT NUMBER: 155:291988
TITLE: Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycemic control
AUTHOR(S): Anagnostis, P.; Athyros, V. G.; Adamidou, F.; Panagiotou, A.; Kita, M.; Karagiannis, A.;

Mikhailidis, D. P.
CORPORATE SOURCE: Endocrinology Clinic, Hippokration Hospital, Thessaloniki, Greece
SOURCE: Diabetes, Obesity and Metabolism (2011), 13(4), 302-312
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Apr 2011
AB A review. Type 2 diabetes mellitus is a well-established risk factor for cardiovascular disease (CVD). New therapeutic approaches have been developed recently based on the incretin phenomenon, such as the degradation-resistant incretin mimetic exenatide and the glucagon-like peptide-1 (GLP-1) analog liraglutide, as well as the dipeptidyl dipeptidase (DPP)-4 inhibitors, such as sitagliptin, vildagliptin, saxagliptin, which increase the circulating bioactive GLP-1. GLP-1 exerts its glucose-regulatory action via stimulation of insulin secretion and glucagon suppression by a glucose-dependent way, as well as by weight loss via inhibition of gastric emptying and reduction of appetite and food intake. These actions are mediated through GLP-1 receptors (GLP-1Rs), although GLP-1R-independent pathways have been reported. Except for the pancreatic islets, GLP-1Rs are also present in several other tissues including central and peripheral nervous systems, gastrointestinal tract, heart and vasculature, suggesting a pleiotropic activity of GLP-1. Indeed, accumulating data from both animal and human studies suggest a beneficial effect of GLP-1 and its metabolites on myocardium, endothelium and vasculature, as well as potential anti-inflammatory and antiatherogenic actions. Growing lines of evidence have also confirmed these actions for exenatide and to a lesser extent for liraglutide and DPP-4 inhibitors compared with placebo or standard diabetes therapies. This suggests a potential cardioprotective effect beyond glucose control and weight loss. Whether these agents actually decrease CVD outcomes remains to be confirmed by large randomized placebo-controlled trials. This review discusses the role of GLP-1 on the cardiovascular system and addresses the impact of GLP-1-based therapies on CVD outcomes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dipeptidyl dipeptidase-4 inhibitor such as saxagliptin increased circulating bioactive GLP-1 which exerted its glucose-regulatory action via stimulation of insulin secretion and glucagon suppression in patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

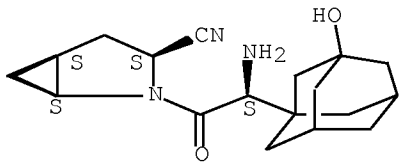


OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 18 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:350190 HCAPLUS Full-text
DOCUMENT NUMBER: 155:647621
TITLE: New drug therapy for Type 2 diabetes mellitus: DPP-IV inhibitors
AUTHOR(S): Kulkarni, Vivek S.; Senthil Kumar, G. P.; Lele, Manish D.; Gaikwad, Dinanath T.; Patil, Manoj D.; Gavitre, Bhaskar B.; Bobe, Kisan R.
CORPORATE SOURCE: Indira Institute of Pharmacy, Devrukh, 415804, India
SOURCE: International Journal of Pharmaceutical Sciences Review and Research (2011), 6(2), 147-151
CODEN: IJPSRR; ISSN: 0976-044X
URL: http://globalresearchonline.net/journalcontents/volume6issue2/Article-027.pdf

PUBLISHER: Global Research Online
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Mar 2011
AB A review. Drugs inhibiting the enzyme Dipeptidyl peptidase-IV are under development in preclin. and clin. studies. These drugs have potential to treat the Type 2 diabetes mellitus. DPP-IV enzyme inhibits rapidly the incretin hormones Glucagon like peptide-1 which is released after food administration to increase insulin level. DPP-IV inhibitor drugs are orally bioactive and after administration stabilize endogenous GLp-1 level and induce insulin secretion in glucose dependent manner. Drug sitagliptin is approved by US FDA. And other drugs like vidagliptin, saxagliptin are under development and late stages of clin. trials. So, DPP-IV inhibitors drugs are good choice for treatment of T2DM with very less side effects.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-IV inhibitors as a new drug therapy for type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

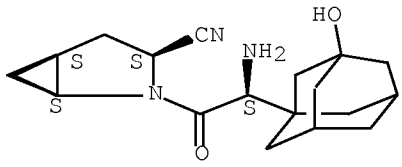
Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 19 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:218071 HCAPLUS Full-text
DOCUMENT NUMBER: 155:398027
TITLE: Dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes: safety, tolerability, and efficacy
AUTHOR(S): Cox, Mary Elizabeth; Rowell, Jennifer; Corsino, Leonor; Green, Jennifer B.
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition, Duke University Medical Center, Durham, NC, USA
SOURCE: Drug, Healthcare and Patient Safety (2010), 2, 7-19
CODEN: DHPSBA; ISSN: 1179-1365
URL: http://www.dovepress.com/getfile.php?fileID=5719
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Feb 2011
AB A review. Although glycemic control is an important and effective way to prevent and minimize the worsening of diabetes-related complications, type 2 diabetes is a progressive disease which often proves difficult to manage. Most affected patients will eventually require therapy with multiple medications in order to reach appropriate glycemic targets. The dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a relatively new class of oral medications for the treatment of type 2 diabetes, which has become widely incorporated into clin. practice. This review summarizes the available data on the efficacy, safety, and tolerability of these medications.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety, tolerability, and efficacy of dipeptidyl peptidase-4 inhibitors in management of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

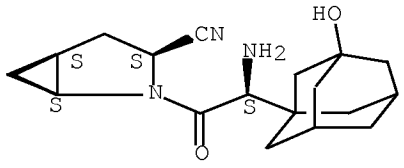
L49 ANSWER 20 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:145057 HCAPLUS Full-text
DOCUMENT NUMBER: 155:397940
TITLE: Saxagliptin: a selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus
AUTHOR(S): Shubrook, Jay; Colucci, Randall; Guo, Aili; Schwartz, Frank
CORPORATE SOURCE: Department of Family Medicine, Ohio University College of Osteopathic Medicine (OU-COM), Athens, OH, 45701, USA
SOURCE: Clinical Medicine Insights: Endocrinology and Diabetes (2011), 4, 1-12
CODEN: CMIEBP; ISSN: 1179-5514
URL:
http://www.la-press.com/redirect_file.php?fileId=3311&filename=2433-

CMED-Saxagliptin:-A-Selective-DPP-4-Inhibitor-for-the-Treatment-of-Type-2-D.pdf&fileType=pdf

PUBLISHER: Libertas Academica
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 04 Feb 2011
AB A review. The prevalence of type 2 diabetes mellitus is high and growing rapidly. Suboptimal glycemic control provides opportunities for new treatment options to improve the morbidity and mortality of this progressive disease. Saxagliptin, a selective DPP-4 inhibitor, increases endogenous incretin levels and incretin activity. In controlled clin. trials saxagliptin reduces both fasting and postprandial glucose and works in monotherapy and in combination with metformin, TZDs and sulfonylureas. Saxagliptin has a very favorable side effect profile and may have other beneficial non-glycemic effects. The authors review the current available evidence for the safety, efficacy and saxagliptin's place in therapy for type 2 diabetes mellitus. As understanding of the incretin hormones (GLP-1, GIP) expand we may see addnl. important non-glycemic effects that may affect the chronic management of type 2 diabetes mellitus.
IT 361442-04-8, Saxagliptin

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin as a selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

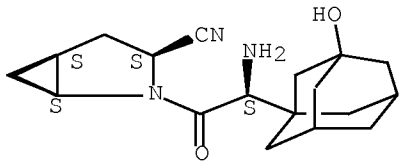
Absolute stereochemistry.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 21 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:136698 HCAPLUS Full-text
DOCUMENT NUMBER: 154:350909
TITLE: Synthetic approaches to the 2009 new drugs
AUTHOR(S): Liu, Kevin K.-C.; Sakya, Subas M.; O'Donnell, Christopher J.; Flick, Andrew C.; Li, Jin
CORPORATE SOURCE: Pfizer Inc., La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry (2011), 19(3), 1136-1154
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 02 Feb 2011
AB A review. New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biol. target. These new chemical entities (NCEs) provide insights into mol. recognition and also serve as leads for designing future new drugs. This review covers the syntheses of 21 NCEs marketed in 2009.
IT 361442-04-8P, Onglyza
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthetic approaches to the 2009 new drugs)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

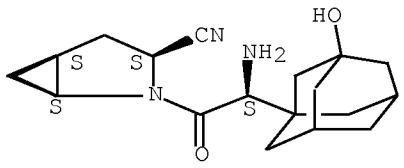
Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 22 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:57251 HCAPLUS Full-text
DOCUMENT NUMBER: 155:290017
TITLE: Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review
AUTHOR(S): Deacon, C. F.
CORPORATE SOURCE: Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Copenhagen N, Den.
SOURCE: Diabetes, Obesity and Metabolism (2011), 13(1), 7-18
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Jan 2011
AB A review. The dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antihyperglycemic agents which were developed for the treatment of type 2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme. Although they differ in terms of their chemical, they are all small mols. which are orally available. There are some differences between them in terms of their absorption, distribution, metabolism and elimination, as well as in their potency and duration of action, but their efficacy, both in terms of inhibiting plasma DPP-4 activity and as antidiabetic agents, appears to be similar. They improve glycemic control, reducing both fasting and postprandial glucose levels to lower HbA1c levels, without weight gain and with an apparently benign adverse event profile. At present, there seems to be little to distinguish between the different inhibitors in terms of their efficacy as antidiabetic agents and their safety. Long-term accumulated clin. experience will reveal whether compound-related characteristics lead to any clin. relevant differences.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 23 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1631727 HCAPLUS Full-text
DOCUMENT NUMBER: 154:124214
TITLE: The role for saxagliptin within the management of type 2 Diabetes mellitus: an update from the 2010 European Association for the Study of Diabetes (EASD) 46th annual meeting and the American Diabetes Association (ADA) 70th scientific session
AUTHOR(S): Aschner, Pablo J.
CORPORATE SOURCE: Javeriana University, Bogota, Colombia
SOURCE: Diabetology & Metabolic Syndrome (2010), 2, 69
CODEN: DMSIBU; ISSN: 1758-5996
URL: http://www.dmsjournal.com/content/pdf/1758-5996-2-69.pdf

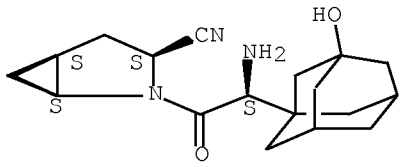
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 31 Dec 2010
AB A review. Saxagliptin is a potent, selective DPP4 inhibitor. Highlights from abstrs. presented at the 2010 meetings of the European Association for the Study of Diabetes and the American Diabetes Association include studies and analyses that shed light on the promising role for saxagliptin within the management of type 2 diabetes mellitus. Data show that saxagliptin combination therapy improves HbA1c levels compared with placebo, particularly in patients with high HbA1c at baseline, long duration of disease, low baseline creatinine clearance, and low homeostasis model assessment 2 β-cell function at baseline. These efficacy benefits are achieved without any increase in hypoglycemia or other adverse events. The study results also show that the saxagliptin plus metformin combination is a good candidate for initial therapy in drug-naive patients treated for as long as 72 wk. Survey data presented confirm that hypoglycemia (and fear of hypoglycemia) is a barrier to patients' acceptance of diabetes treatment, limiting its efficacy. Therefore, therapies such as saxagliptin that have a low risk of hypoglycemia may be more acceptable to patients in helping them to achieve glycemic control and to optimize their quality of life. In

patients with renal impairment, for whom metformin is contraindicated, saxagliptin monotherapy is a promising option for antidiabetic management as, when given at a reduced dose, it is well-tolerated with a safety profile similar to that of placebo.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin was safe and effective in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 24 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1447898 HCAPLUS Full-text
DOCUMENT NUMBER: 155:200105
TITLE: Clinical overview of saxagliptin for Type 2 diabetes management
AUTHOR(S): Rosenstock, Julio
CORPORATE SOURCE: Dallas Diabetes and Endocrine Center, Dallas, TX, 75230, USA
SOURCE: Expert Review of Endocrinology & Metabolism (2010), 5(6), 809-823
CODEN: EREMBI; ISSN: 1744-6651
PUBLISHER: Expert Reviews Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 22 Nov 2010
AB A review. Saxagliptin (Onglyza, Bristol-Myers Squibb, NJ, USA and AstraZeneca, DE, USA) is a potent, orally active, once-daily dipeptidyl peptidase-4 inhibitor that is indicated as an adjunct to diet and exercise alone, or in combination with metformin, a thiazolidinedione or a sulfonylurea to improve glycemic control in adults with Type 2 diabetes mellitus. By inhibiting dipeptidyl peptidase-4, saxagliptin increases concns. of the intact forms of the incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, prolonging their effects.

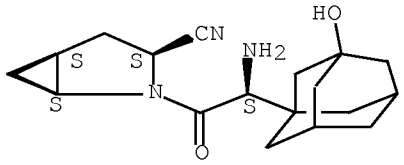
Saxagliptin also improves β-cell function, increases postprandial insulin secretion and reduces postprandial glucagon secretion. Saxagliptin is generally well tolerated with weight-neutral effects and a low incidence of hypoglycemia. Multicenter randomized trials have shown that saxagliptin as monotherapy, as initial therapy with metformin or as add-on therapy with metformin, a sulfonylurea or a thiazolidinedione leads to significant decreases in glycated Hb levels, fasting and postprandial plasma glucose levels and higher percentages of patients attaining target glycated Hb of less than 7% compared with controls.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. overview of saxagliptin for type 2 diabetes management)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 25 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1440105 HCAPLUS Full-text

DOCUMENT NUMBER: 153:595329

TITLE: Saxagliptin (Onglyza): new inhibitor of the dipeptidylpeptidase-4 for the oral treatment of type 2 diabetes

AUTHOR(S): Scheen, A. J.

CORPORATE SOURCE: Service de Diabetologie, Nutrition et Maladies metaboliques et Unite de Pharmacologie clinique, CHU Liege, Universite de Liege, Belg.

SOURCE: Revue Medicale de Liege (2010), 65(9), 527-532
CODEN: RMLIAC; ISSN: 0370-629X

PUBLISHER: Revue Medicale de Liege

DOCUMENT TYPE: Journal; General Review

LANGUAGE: French

ED Entered STN: 21 Nov 2010

AB A review. Saxagliptin (Onglyza) is a specific and reversible inhibitor of dipeptidylpeptidase-4 (DPP-4), which inhibits the activity of the enzyme for at least 24 h after one single oral administration. It increases the

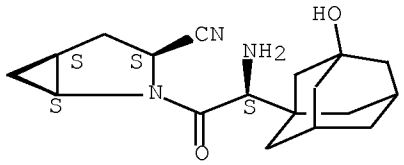
circulating levels of incretin hormones (GLP-1, GIP), which contributes to amplify the insulin secretory response to meals and to reduce postprandial hyperglycemia and, subsequently, fasting glycemia. Saxagliptin, 5 mg once daily, has been shown to be effective in patients with type 2 diabetes treated with diet alone, metformin, sulfonylurea or glitazone, with a favorable tolerance profile. Reduction in glycated Hb (HbA1c) averaged 0.6-0.8 %, without increasing the risk of hypoglycemia or promoting weight gain. The only indication of saxagliptin that is currently reimbursed in Belgium is the treatment of patients not controlled with metformin, the oral antidiabetic agent that is recommended as first line therapy in the management of type 2 diabetes.

IT 361442-04-8, Saxagliptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Onglyza; Saxagliptin as new DPP-4 inhibitor for oral treatment of type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 26 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1361201 HCAPLUS Full-text

DOCUMENT NUMBER: 155:173558

TITLE: Saxagliptin: a review

AUTHOR(S): Evans, Marc

CORPORATE SOURCE: UK

SOURCE: British Journal of Diabetes & Vascular Disease (2010), 10(1), 14-20
CODEN: BJDVAI; ISSN: 1474-6514

PUBLISHER: Sage Publications Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 02 Nov 2010

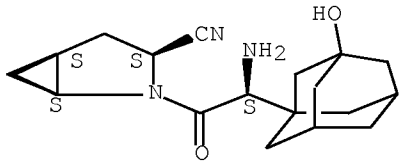
AB A review. Modulation of the effects of incretin hormones provides a novel mechanism of action for some of the newer therapies for patients with type 2 diabetes. The selective, reversible dipeptidyl peptidase-4 inhibitor saxagliptin has demonstrated robust improvements in glycemic control, as

monotherapy or as add-on therapy to metformin, sulfonylureas and thiazolidine-diones, without significant change in body weight and while exhibiting a low risk of hypoglycemia.

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin alone or in combination with metformin, sulfonylurea and thiazolidinedione showed improvement in glycemic control and no change in body weight in patient with type 2 diabetes)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 27 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1327711 HCAPLUS Full-text
DOCUMENT NUMBER: 155:82260
TITLE: Liraglutide: effects beyond glycemic control in diabetes treatment
AUTHOR(S): McGill, J. B.
CORPORATE SOURCE: Division of Endocrinology, Metabolism and Lipid Research, Washington University in St. Louis, St. Louis, MO, 63110, USA
SOURCE: International Journal of Clinical Practice, Supplement (2010), 64(Suppl. 167), 28-34
CODEN: ICPSFY; ISSN: 1368-504X
URL: http://onlinelibrary.wiley.com/doi/10.1111/j.1742-1241.2010.02495.x/pdf

PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 26 Oct 2010
AB A review. To review the non-glycemic effects of liraglutide, including potential improvements in body weight, systolic blood pressure (SBP) and pancreatic beta-cell function. Liraglutide induced weight loss of around 2-3 kg compared with weight increases of 1-2 kg with active comparators such as insulin glargine, rosiglitazone and glimepiride. Exenatide demonstrated

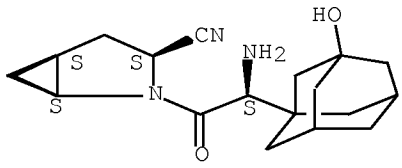
similar weight benefits to liraglutide, but the dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin, saxagliptin and vildagliptin, were weight neutral. Liraglutide was associated with decreases in SBP of 2-7 mmHg, whereas exenatide, vildagliptin and sitagliptin demonstrated SBP redns. of around 2-3 mmHg. Measures of pancreatic beta-cell function were improved with liraglutide vs. placebo, rosiglitazone and exenatide. However, DPP-4 inhibitors appear to have less effect on beta-cell function than glucagon-like peptide-1 (GLP-1) receptor agonists. In addition to glycemic control, liraglutide and the other incretin-based therapies offer addnl. non-glycemic benefits to varying degrees. The ability of GLP-1 receptor agonists to provide modest, but clin. relevant improvements in body weight and SBP, and to potentially benefit beta-cell function make them an exciting therapeutic option for individuals with diabetes. In contrast, DPP-4 inhibitors are weight neutral and may have lesser benefits on beta-cell function.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin did not affect body weight in patient with diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 28 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1318024 HCAPLUS Full-text

DOCUMENT NUMBER: 155:82235

TITLE: Saxagliptin: a new dipeptidyl peptidase 4 inhibitor for type 2 diabetes

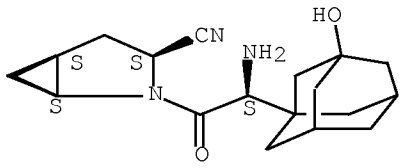
AUTHOR(S): Borja-Hart, Nancy L.; Whalen, Karen L.

CORPORATE SOURCE: Department of Pharmacy Practice, College of Pharmacy, Nova Southeastern University, Ft. Lauderdale, FL, USA

SOURCE: Annals of Pharmacotherapy (2010), 44(6), 1046-1053
CODEN: APHRER; ISSN: 1542-6270
URL: http://www.theannals.com/cgi/content/abstract/44/6/1046

PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 24 Oct 2010
AB OBJECTIVE: To review the pharmacol., pharmacokinetics, efficacy, and safety of saxagliptin, a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. DATA SOURCES: Searches of PubMed (1966-March 2010) and International Pharmacy Abstrs. (1970-March 2010) were conducted using the key words saxagliptin, Onglyza, and BMS-477118. A review of bibliogs. of retrieved articles was also performed to identify addnl. refs. STUDY SELECTION AND DATA Extraction: All identified studies published in English and involving efficacy and safety of saxagliptin in the treatment of type 2 diabetes were reviewed. DATA SYNTHESIS: Saxagliptin is a competitive inhibitor of DPP-4 that slows the degradation of incretin hormones, thereby stimulating insulin secretion, reducing postprandial glucagon, and decreasing glucose levels. Saxagliptin is well absorbed after oral administration and demonstrates a pharmacokinetic profile that is compatible with once-daily dosing. Clin. trials with saxagliptin monotherapy for the treatment of type 2 diabetes showed a reduction in Hb A1c (A1C) of 0.43-0.9%. Saxagliptin has demonstrated similar redns. in A1C when used as add-on therapy with metformin, sulfonylureas, and thiazolidinediones. The combination of saxagliptin and metformin for initial therapy in treatment-naive patients was associated with greater improvements in A1C than either agent alone. In general, saxagliptin therapy is well tolerated. The most common adverse effects occurring in clin. trials were headache, nasopharyngitis, upper respiratory tract infections, and urinary tract infections. CONCLUSIONS: Saxagliptin is effective as monotherapy or add-on therapy for the management of type 2 diabetes. Because saxagliptin has a higher cost and reduces A1C and other surrogate markers of glucose control to a lesser extent than other well-validated therapies, such as metformin, saxagliptin should be reserved for patients who fail or are intolerant of conventional treatments for type 2 diabetes.
IT 361442-04-8, Onglyza
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(onglyza alone or in combination with metformin, sulfonylureas and thiazolidinediones showed favorable pharmacokinetic profile and was safe, effective in treatment of patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

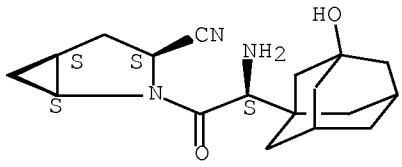
Absolute stereochemistry.



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 29 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1268539 HCAPLUS Full-text
DOCUMENT NUMBER: 155:111600
TITLE: DPP-4 inhibitors: What may be the clinical differentiators?
AUTHOR(S): Gerich, John
CORPORATE SOURCE: Clinical Research Center, University of Rochester School of Medicine, Rochester, NY, 14642, USA
SOURCE: Diabetes Research and Clinical Practice (2010), 90(2), 131-140
CODEN: DRCPE9; ISSN: 0168-8227
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Oct 2010
AB A review. Attenuation of the prandial incretin effect, mediated by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), contributes to hyperglycemia in type 2 diabetes mellitus (T2DM). Since the launch of sitagliptin in 2006, a compelling body of evidence has accumulated showing that dipeptidyl peptidase-4 (DPP-4) inhibitors, which augment endogenous GLP-1 and GIP levels, represent an important advance in the management of T2DM. Currently, three DPP-4 inhibitors - sitagliptin, vildagliptin and saxagliptin - have been approved in various countries worldwide. Several other DPP-4 inhibitors, including linagliptin and alogliptin, are currently in clin. development. As understanding of, and experience with, the growing number of DPP-4 inhibitors broadens, increasing evidence suggests that the class may offer advantages over other antidiabetic drugs in particular patient populations. The expanding evidence base also suggests that certain differences between DPP-4 inhibitors may prove to be clin. significant. This therapeutic diversity should help clinicians tailor treatment to the individual patient, thereby increasing the proportion that safely attain target HbA1c levels, and reducing morbidity and mortality. This review offers an overview of DPP-4 inhibitors in T2DM and suggests some characteristics that may provide clin. relevant differentiators within this class.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. differentiators of dipeptidyl peptidase 4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

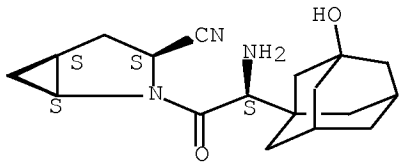
L49 ANSWER 30 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1258350 HCAPLUS Full-text
DOCUMENT NUMBER: 155:58546
TITLE: Saxagliptin: a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus
AUTHOR(S): Neumiller, Joshua J.; Campbell, R. Keith
CORPORATE SOURCE: Department of Pharmacotherapy, College of Pharmacy, Washington State University, Spokane, USA
SOURCE: American Journal of Health-System Pharmacy (2010), 67(18), 1515-1525
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Oct 2010
AB A review. Purpose. The pharmacol., pharmacokinetics, efficacy, safety, and dosage and administration of saxagliptin are reviewed. Summary. Saxagliptin is a selective, reversible inhibitor of dipeptidyl peptidase-4 (DPP-4) approved for the treatment of type 2 diabetes mellitus in adults. By inhibiting DPP-4, saxagliptin reduces the degradation of endogenous incretin hormones, resulting in increased glucose-dependent insulin release and decreased glucagon secretion from the pancreas. Saxagliptin is rapidly absorbed after oral administration, and its pharmacokinetic profile allows for once-daily oral administration. Clin. trials of saxagliptin as monotherapy and as combination therapy with other oral antidiabetic medications including metformin, glyburide, pioglitazone, and rosiglitazone have demonstrated clin. benefits in various glycemic endpoints, including glycosylated Hb (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels over 24 to 102 wk of therapy. Due to its glucose-dependent mechanism of action, saxagliptin as mono-therapy or in combination with metformin results in a low risk for hypoglycemia in patients with type 2 diabetes. Saxagliptin was generally well tolerated in clin. trials, with headache, upper-respiratory-tract infection, and urinary tract infection being the most common adverse events. Saxagliptin has demonstrated a low risk for drug-drug interactions. For patients with moderate or severe renal impairment or end-stage renal disease or patients taking a strong inhibitor of cytochrome P 450 isoenzyme 3A4 or 3A5, the recommended dosage is 2.5 mg once daily. Conclusion. Saxagliptin, a DPP-4 inhibitor approved for the treatment of type 2 diabetes, demonstrated safety

and efficacy in lowering HbA1c, FPG, and PPG levels as both monotherapy and in combination with other oral antidiabetic medications.

IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin either alone or in combination with metformin, glyburide, pioglitazone and rosiglitazone was safe and effective in treatment of adult patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l49 ibib ed abs hitstr 31-60
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L49 ANSWER 31 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1245202 HCAPLUS Full-text
DOCUMENT NUMBER: 154:400831
TITLE: SLCO1B1 polymorphism and oral antidiabetic drugs
AUTHOR(S): Kalliokoski, Annikka; Neuvonen, Pertti J.; Niemi, Mikko
CORPORATE SOURCE: Research Department, Social Insurance Institution, Helsinki, Finland
SOURCE: Basic & Clinical Pharmacology & Toxicology (2010), 107(4), 775-781
CODEN: BCPTBO; ISSN: 1742-7835
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 06 Oct 2010

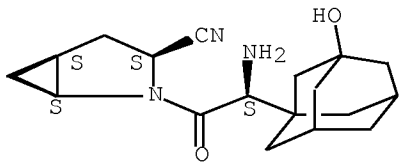
AB A review. Organic anion-transporting polypeptide 1B1 (OATP1B1; gene: SLCO1B1) is an influx transporter expressed on the sinusoidal membrane of human hepatocytes, where it mediates the uptake of its substrates from blood into liver. In vitro, the SLCO1B1 c.521T > C (p.Val174Ala) single-nucleotide polymorphism (SNP) has been associated with reduced and the c.388A > G (p.Asn130Asp) SNP with both enhanced and reduced transport activity of OATP1B1. In vivo in humans, the c.521C allele (present in SLCO1B1*5 and *15 haplotypes) is associated with decreased hepatic uptake and increased plasma concns. of several OATP1B1 substrates. The SLCO1B1*1B (c.388G-c.521T) haplotype is associated with enhanced hepatic uptake and decreased plasma concns. of some OATP1B1 substrates. The SLCO1B1 c.521CC genotype has been associated with an about 60-190% increased, and the SLCO1B*1B/*1B genotype with an about 30% decreased area under the plasma concentration-time curve of repaglinide. Moreover, SLCO1B1 polymorphism can affect the extent of interaction between OATP1B1 inhibitors and repaglinide. Accordingly, SLCO1B1 genotyping may help in choosing the optimal starting dose of repaglinide. In Chinese individuals, the SLCO1B1 c.521C allele has been associated with increased plasma concns. of nateglinide, but the association could not be replicated in Caucasians. SLCO1B1 genotype has had no effect on the pharmacokinetics of rosiglitazone, pioglitazone or their metabolites. The hepatic uptake of metformin is mediated by organic cation transporters 1 and 3, and the liver is not important for the elimination or action of the dipeptidylpeptidase 4 inhibitors sitagliptin, vildagliptin and saxagliptin. Therefore, SLCO1B1 polymorphism unlikely affects the response to these antidiabetics. Possible effects of SLCO1B1 polymorphism on sulfonylureas remain to be investigated.

IT 361442-04-8, Saxagliptin
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(liver was not important for elimination or action of oral saxagliptin in patient with diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

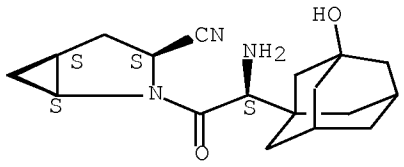
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 32 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1237315 HCAPLUS Full-text

DOCUMENT NUMBER: 153:471412
TITLE: Saxagliptin for type 2 diabetes
AUTHOR(S): Chacra, Antonio R.
CORPORATE SOURCE: Diabetes Center, Federal University of Sao Paulo, Brazil
SOURCE: Diabetes, Metabolic Syndrome and Obesity (2010), 3, 325-335
CODEN: DMSOAD; ISSN: 1178-7007
URL: http://www.dovepress.com/getfile.php?fileID=7746
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 05 Oct 2010
AB A review. Saxagliptin (Onglyza) is a potent, selective, once-daily dipeptidyl peptidase-4 (DPP-4) inhibitor indicated for improving glycemic control in patients with type 2 diabetes (T2D). By blocking DPP-4, saxagliptin increases and prolongs the effects of incretins, a group of peptide hormones released by intestinal cells after meals, which stimulate glucose-dependent insulin secretion to lower blood glucose. In controlled clin. trials, saxagliptin administered as monotherapy or in combination with metformin, glyburide, or a thiazolidinedione improved glycemic control in a clin. significant manner, reflected by significant decreases in glycated Hb (monotherapy, -0.5%; add-on to metformin, thiazolidinedione, or sulfonylurea, -0.6% to 0.9%; initial combination with metformin, -2.5%), fasting plasma glucose, and postprandial glucose compared with controls. Addnl., saxagliptin improved β-cell function, reflected as increases in homeostasis model assessment (HOMA)-2β. Saxagliptin was generally well tolerated; it did not increase hypoglycemia compared with controls, and was weight neutral. A meta-anal. of Phase II and III trials showed that saxagliptin did not increase the risk of major cardiovascular events. Professional organizations have updated their guidelines for T2D to include a DPP-4 inhibitor as an early treatment option - either as initial therapy in combination with metformin, or as add-on therapy for patients whose glycemia is inadequately controlled by a single oral antidiabetic drug.
IT 361442-04-8, Onglyza
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Onglyza inhibited dipeptidyl peptidase-4 with increased, prolonged effect of incretin secreted by intestinal cell that stimulated glucose-dependent insulin secretion which decreased blood glucose in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 33 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1209603 HCAPLUS Full-text
DOCUMENT NUMBER: 155:260
TITLE: Dipeptidylpeptitase-4 inhibitors (gliptins)
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Division of Clinical Pharmaccology and Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liege, Liege, Belg.
SOURCE: Clinical Pharmacokinetics (2010), 49(9), 573-588
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Wolters Kluwer Health
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 28 Sep 2010
AB A review. Patients with type 2 diabetes mellitus (T2DM) are generally treated with many pharmacol. compds. and are exposed to a high risk of drug-drug interactions. Indeed, blood glucose control usually requires a combination of various glucose-lowering agents, and the recommended global approach to reduce overall cardiovascular risk generally implies administration of several protective compds., including HMG-CoA reductase inhibitors (statins), antihypertensive compds. and antiplatelet agents. New compds. have been developed to improve glucose-induced β-cell secretion and glucose control, without inducing hypoglycemia or weight gain, in patients with T2DM. Dipeptidylpeptidase-4 (DPP-4) inhibitors are novel oral glucose-lowering agents, which may be used as monotherapy or in combination with other antidiabetic compds., metformin, thiazolidinediones or even sulfonylureas. Sitagliptin, vildagliptin and saxagliptin are already on the market, either as single agents or in fixed-dose combined formulations with metformin. Other compds., such as alogliptin and linagliptin, are in a late phase of development. This review summarizes the available data on drug-drug interactions reported in the literature for these five DDP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin. Possible pharmacokinetic interferences have been investigated between each of these compds. and various pharmacol. agents, which were selected because there are other glucose-lowering agents (metformin, glibenclamide [glyburide], pioglitazone/rosiglitazone) that may be prescribed in combination with DPP-4 inhibitors, other drugs that are currently used in patients with T2DM (statins, antihypertensive agents),

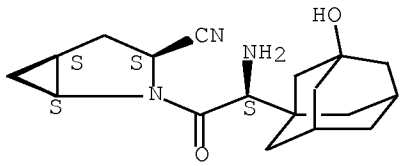
compds. that are known to interfere with the cytochrome P 450 (CYP) system (ketoconazole, diltiazem, rifampicin [rifampin]) or with P-glycoprotein transport (ciclosporin), or agents with a narrow therapeutic safety window (warfarin, digoxin). Generally speaking, almost no drug-drug interactions or only minor drug-drug interactions have been reported between DPP-4 inhibitors and any of these drugs. The gliptins do not significantly modify the pharmacokinetic profile and exposure of the other tested drugs, and the other drugs do not significantly alter the pharmacokinetic profile of the gliptins or exposure to these. The only exception concerns saxagliptin, which is metabolized to an active metabolite by CYP3A4/5. Therefore, exposure to saxagliptin and its primary metabolite may be significantly modified when saxagliptin is coadministered with specific strong inhibitors (ketoconazole, diltiazem) or inducers (rifampicin) of CYP3A4/5 isoforms. The absence of significant drug-drug interactions could be explained by the favorable pharmacokinetic characteristics of DPP-4 inhibitors, which are not inducers or inhibitors of CYP isoforms and are not bound to plasma proteins to a great extent. Therefore, according to these pharmacokinetic findings, which were generally obtained in healthy young male subjects, no dosage adjustment is recommended when gliptins are combined with other pharmacol. agents in patients with T2DM, with the exception of a reduction in the daily dosage of saxagliptin when this drug is used in association with a strong inhibitor of CYP3A4/A5. It is worth noting, however, that a reduction in the dose of sulfonylureas is usually recommended when a DPP-4 inhibitor is added, because of a pharmacodynamic interaction (rather than a pharmacokinetic interaction) between the sulfonylurea and the DPP-4 inhibitor, which may result in a higher risk of hypoglycemia. Otherwise, any gliptin may be combined with metformin or a thiazolidinedione (pioglitazone, rosiglitazone), leading to a significant improvement in glycemic control without an increased risk of hypoglycemia or any other adverse event in patients with T2DM. Finally, the absence of drug-drug interactions in clin. trials in healthy subjects requires further evidence from large-scale studies, including typical subjects with T2DM - in particular, multimorbid and geriatric patients receiving polypharmacy.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin showed minor drug-drug interaction with statins, cyclosporine, antihypertensive agent and glucose-lowering agents but did not modify their pharmacokinetic profile in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

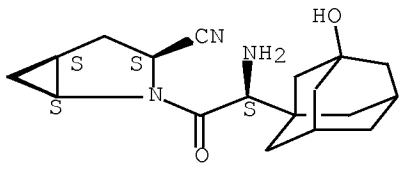
Absolute stereochemistry.



OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 34 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1208417 HCAPLUS Full-text
DOCUMENT NUMBER: 153:397494
TITLE: Saxagliptin, a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. [Erratum to document cited in CA151:023607]
AUTHOR(S): Gallwitz, Baptist
CORPORATE SOURCE: Department of Medicine IV, Eberhard-Karls-University, Tuebingen, 72076, Germany
SOURCE: IDrugs (2009), 12(5), 200
CODEN: IDRUFN; ISSN: 2040-3410
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 28 Sep 2010
AB A review. On page 909, in the left column, in paragraph 4, in lines 6 and 8, "higher" and "lower", were incorrectly given, and should read: "lower" and "higher", resp.; and in line 9, "healthy volunteers than patients.", was incorrectly given, and should read: "healthy volunteers than in patients.".
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase IV inhibitor saxagliptin was safe and effective in improving glucose tolerance and increasing insulin level in animal and patient with type 2 diabetes mellitus (Erratum))
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

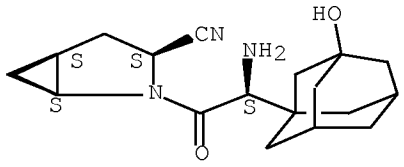
Absolute stereochemistry.



L49 ANSWER 35 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1105677 HCAPLUS Full-text

DOCUMENT NUMBER: 154:556461
TITLE: Saxagliptin: a new dipeptidyl peptidase-IV inhibitor for the treatment of type 2 diabetes
AUTHOR(S): Tan, Ling; Xia, Lu-feng; Sun, Chun-hua
CORPORATE SOURCE: Department of Pharmacy, Beijing Hospital, The Ministry of Health, Beijing, 100730, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2010), 19(13), 1099-1102
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 05 Sep 2010
AB A review. Saxagliptin, a potent and selective reversible inhibitor of dipeptidyl peptidase-IV, has been approved for the treatment of type 2 diabetes in adults. Saxagliptin reduces the degradation of the incretin hormone glucagon-like peptide-1, thereby enhancing its actions, and is associated with improved beta-cell function and suppression of glucagon secretion. Clin. trials have shown that saxagliptin improves glycemic control in monotherapy and provides addnl. efficacy when used in combination with other oral antidiabetic agents (metformin, sulfonylurea and thiazolidinedione). There is a low risk of hypoglycemia. Saxagliptin is reported to be well tolerated with adverse drug reactions profile similar to placebo.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin: dipeptidyl peptidase-IV inhibitor for treatment of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

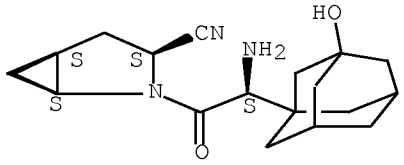
Absolute stereochemistry.



L49 ANSWER 36 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1098157 HCAPLUS Full-text
DOCUMENT NUMBER: 154:50343
TITLE: New drug saxagliptin for treating type 2 diabetes mellitus
AUTHOR(S): Liu, Ping; Zhou, Jing; Yang, Xiaojun; Li, Jin; Cheng, Liyu
CORPORATE SOURCE: Journal of China Pharmacy, Chongqing, 400042, Peop.

Rep. China
SOURCE: Zhongguo Yaofang (2010), 21(1), 80-82
CODEN: ZYHAA4; ISSN: 1001-0408
PUBLISHER: Zhongguo Yaofang Zazhishe
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 02 Sep 2010
AB A review with 11 refs., is given on new drug saxagliptin for treating type 2 diabetes mellitus. Saxagliptin is a new antidiabetic drug for treating type 2 diabetes mellitus, which has been approved by FDA.
IT 361442-04-8, Saxagliptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new drug saxagliptin for treating type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 37 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1075988 HCAPLUS Full-text
DOCUMENT NUMBER: 154:502905
TITLE: Pharmacokinetics of dipeptidylpeptidase-4 inhibitors
AUTHOR(S): Scheen, A. J.
CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders and Division of Clinical Pharmacology, Department of Medicine, CHU Sart Tilman, University of Liege, Liege, Belg.
SOURCE: Diabetes, Obesity and Metabolism (2010), 12(8), 648-658
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 30 Aug 2010
AB A review. Type 2 diabetes (T2DM) is a complex disease combining defects in insulin secretion and insulin action. New compds. have been developed for improving glucose-induced insulin secretion and glucose control, without inducing hypoglycemia or weight gain. Dipeptidylpeptidase-4 (DPP-4) inhibitors are new oral glucose-lowering agents, so-called incretin enhancers, which may be used as monotherapy or in combination with other antidiabetic compds. Sitagliptin, vildaglipin and saxagliptin are already

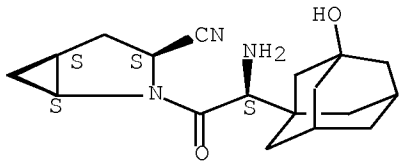
on the market in many countries, either as single agents or in fixed-dose combined formulations with metformin. Other DPP-4 inhibitors, such as alogliptin and linagliptin, are currently in late phase of development. The present paper summarizes and compares the main pharmacokinetics (PK) properties, i.e., absorption, distribution, metabolism and elimination, of these five DPP-4 inhibitors. Available data were obtained in clin. trials performed in healthy young male subjects, patients with T2DM, and patients with either renal insufficiency or hepatic impairment. PK characteristics were generally similar in young healthy subjects and in middle-aged overweight patients with diabetes. All together gliptins have a good oral bioavailability which is not significantly influenced by food intake. PK/pharmacodynamics characteristics, i.e., sufficiently prolonged half-life and sustained DPP-4 enzyme inactivation, generally allow one single oral administration per day for the management of T2DM; the only exception is vildagliptin for which a twice-daily administration is recommended because of a shorter half-life. DPP-4 inhibitors are in general not substrates for cytochrome P 450 (except saxagliptin that is metabolized via CYP 3A4/A5) and do not act as inducers or inhibitors of this system. Several metabolites have been documented but most of them are inactive; however, the main metabolite of saxagliptin also exerts a significant DPP-4 inhibition and is half as potent as the parent compound Renal excretion is the most important elimination pathway, except for linagliptin whose metabolism in the liver appears to be predominant. PK properties of gliptins, combined with their good safety profile, explain why no dose adjustment is necessary in elderly patients or in patients with mild to moderate hepatic impairment. As far as patients with renal impairment are concerned, significant increases in drug exposure for sitagliptin and saxagliptin have been reported so that appropriate redns. in daily dosages are recommended according to estimated glomerular filtration rate. The PK characteristics of DPP-4 inhibitors suggest that these compds. are not exposed to a high risk of drug-drug interactions. However, the daily dose of saxagliptin should be reduced when coadministered with potent CYP 3A4 inhibitors. In conclusion, besides their pharmacodynamic properties leading to effective glucose-lowering effect without inducing hypoglycemia or weight gain, DPP-4 inhibitors show favorable PK properties, which contribute to a good efficacy/safety ratio for the management of T2DM in clin. practice.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of dipeptidylpeptidase-4 inhibitors)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

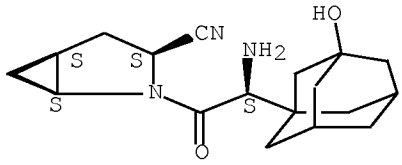


OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 38 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1054512 HCAPLUS Full-text
DOCUMENT NUMBER: 153:349696
TITLE: Saxagliptin: the evidence for its place in the treatment of type 2 diabetes mellitus
AUTHOR(S): Kulasa, Kristen; Edelman, Steven
CORPORATE SOURCE: Division of Endocrinology and Metabolism, VA San Diego Healthcare System, University of California, USA
SOURCE: Core Evidence (2010), 5, 23-37
CODEN: CEOVAF; ISSN: 1555-1741
URL: http://www.dovepress.com/getfile.php?fileID=7383
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 24 Aug 2010
AB A review. The worldwide prevalence of type 2 diabetes mellitus (T2DM) is high, and the chronically poor metabolic control that can result from T2DM is associated with a high risk for microvascular and macrovascular complications. Because of the progressive pathophysiol. of T2DM, oral antidiabetic agents often fail to provide sustained glycemic control, indicating the need for new therapies. Saxagliptin is an oral dipeptidyl peptidase-4 inhibitor, recently approved for the treatment of T2DM. Evidence review: Saxagliptin significantly improves glycemic control vs placebo, as demonstrated by decreasing glycated Hb, fasting plasma glucose, and postprandial plasma glucose levels when used as monotherapy; in initial combination with metformin; and as add-on therapy with metformin, sulfonylurea (SU), or thiazolidinedione (TZD). Saxagliptin also significantly improves β-cell function, is weight neutral, has a low risk for hypoglycemia, and has been shown to have cardiovascular safety. Place in therapy: The clin. profile for saxagliptin indicates that it is useful as an adjunct to diet and exercise as first-line monotherapy and in combination with metformin; or as add-on treatment for patients who cannot achieve glycemic control with a combination of diet and lifestyle changes and metformin, SU, or TZD.
IT 361442-04-8, Onglyza
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. evidence on saxagliptin for the treatment of type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

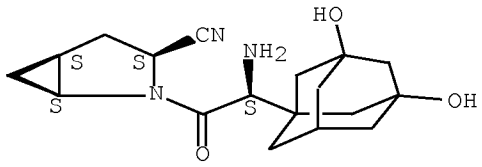


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 39 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:970748 HCAPLUS Full-text
DOCUMENT NUMBER: 154:275051
TITLE: Saxagliptin: a new drug for the treatment of type 2 diabetes
AUTHOR(S): Thareja, Suresh; Aggarwal, Saurabh; Malla, Priyanka; Haksar, Diksha; Bhardwaj, Tilak Raj; Kumar, Manoj
CORPORATE SOURCE: University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160 014, India
SOURCE: Mini-Reviews in Medicinal Chemistry (2010), 10(8), 759-765
CODEN: MMCIAE; ISSN: 1389-5575
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 05 Aug 2010
AB A review. Saxagliptin (BMS-477118), a recently FDA approved drug for the management of T2DM, has been developed by Bristol-Myers Squibb and AstraZeneca under the trade name Onglyza. Saxagliptin is a nitrile-containing selective, potent, reversible and durable DPP IV inhibitor developed as an alternative second-line to Metformin in place of a sulfonylurea. Saxagliptin increases and prolongs the action of incretin hormones by inhibiting the DPP IV enzyme that inactivates incretins usually within minutes. Saxagliptin is well absorbed and has low plasma protein binding and displays slow-binding properties to DPP IV. Saxagliptin is metabolized in vivo to form an active metabolite (BMS-510849), which is twofold less potent than the parent mol. The X-ray crystallog. revealed that Saxagliptin is covalently bound to the DPP IV active site. In drug-naive patients with T2DM and inadequate glycemic control, once-daily Saxagliptin monotherapy for 24 wks demonstrated clin. meaningful with no weight gain and was generally well tolerated.
IT 841302-24-7

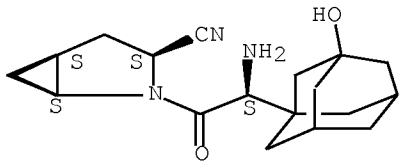
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BMS 510849; Onglyza was metabolized to form active metabolite
BMS-510849 in drug-native patient with type 2 diabetes)
RN 841302-24-7 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3,5-dihydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 361442-04-8, Onglyza
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(Onglyza was well tolerated and effective for treatment of drug-native
patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 40 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:889550 HCAPLUS Full-text
DOCUMENT NUMBER: 154:100629
TITLE: Saxagliptin: new theraphy for type 2 diabetes
AUTHOR(S): Logan, Jill K.; Escano, Alisa K.
CORPORATE SOURCE: Department of Pharmacy, Inova Fairfax Hospital, Falls

Church, VA, USA
SOURCE: Journal of Pharmacy Technology (2010), 26(3), 123-128
CODEN: JPTEEB; ISSN: 8755-1225
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 19 Jul 2010

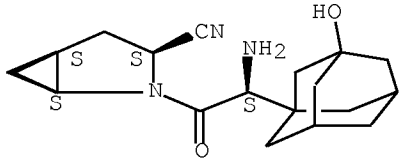
AB A review. Objective: To evaluate the efficacy of saxagliptin for the treatment of hyperglycemia associated with type 2 diabetes. Data Sources: A MEDLINE/PubMed search was conducted of all available date ranges from 1990 through Oct. 2009 for literature in the English language, using the search terms saxagliptin, type 2 diabetes mellitus, incretin hormones, and dipeptidyl peptidase-4 inhibitors. The manufacturer of saxagliptin (Onglyza) was contacted for clin. trial information. Study Selection: Five prospective, randomized controlled trials were reviewed. Studies were included in this review if they had examined saxagliptin and its effects on hyperglycemia. Trials examined included those on saxagliptin monotherapy and those on saxagliptin in combination with metformin, with a sulfonylurea, and with a thiazolidinedione. Data from the MEDLINE/PubMed search, as well as clin. trial data obtained from the manufacturer, were used in this review. Data Synthesis: Saxagliptin demonstrated statistically significant decreases of 0.43-0.54% in Hb A1c (A1C) in the monotherapy treatment group. The A1C-lowering effects were the greatest, with a decrease of 2.5% in patients concomitantly administered metformin and saxagliptin as initial therapy. In addition to its effects on A1C, saxagliptin proved to be weight neutral and had minimal risks of hypoglycemia, with hypoglycemia seen only in the saxagliptin in combination with a sulfonylurea group. Conclusions: Saxagliptin is an effective treatment for hyperglycemia associated with type 2 diabetes. It is currently a third-line option in the American Diabetes Association treatment algorithm for type 2 diabetes and, based on the trials reviewed here, this is an acceptable place in therapy. Saxagliptin is a good option for patients with diabetes who are at high risk of hypoglycemia.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin may be effective in treatment of patient with hyperglycemia associated to type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

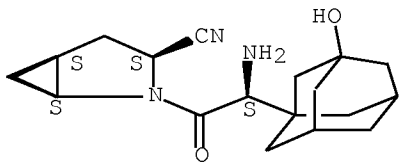
Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 41 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:860078 HCAPLUS Full-text
DOCUMENT NUMBER: 154:426493
TITLE: Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects
AUTHOR(S): Drab, Scott R.
CORPORATE SOURCE: University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA
SOURCE: Pharmacotherapy (2010), 30(6), 609-624
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Jul 2010
AB A review. Incretin-based therapies encompass two new classes of antidiabetic drugs: glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, and exenatide long-acting release), which are structurally related to GLP-1, and the dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin and saxagliptin), which limit the breakdown of endogenous GLP-1. To evaluate the safety and effectiveness of incretin-based therapies for the treatment of type 2 diabetes mellitus and the role of these therapies in clin. practice, a MEDLINE search (Jan. 1985-Nov. 2009) was conducted. Relevant refs. from the publications identified were also reviewed. Of 28 studies identified, 22 were randomized controlled trials. Data show that these therapies affect insulin secretion in a glucose-dependent manner, achieving clin. meaningful redns. in Hb A1c levels, with very low rates of hypoglycemia. In addition, redns. in body weight have been observed with GLP-1 receptor agonists, which also exert a pronounced effect on systolic blood pressure. Various human and animal studies show that GLP-1 improves β-cell function and increases β-cell proliferation in vitro, which may slow disease progression. Thus, incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin may be safe and effective in treatment of patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

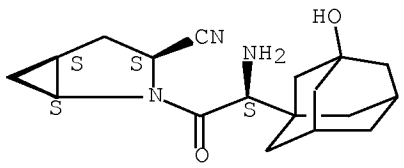


OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 42 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:757641 HCAPLUS Full-text
DOCUMENT NUMBER: 154:54885
TITLE: Diabesity: therapeutic options
AUTHOR(S): Colagiuri, S.
CORPORATE SOURCE: Boden Institute of Obesity, Nutrition and Exercise, University of Sydney, Sydney, NSW, Australia
SOURCE: Diabetes, Obesity and Metabolism (2010), 12(6), 463-473
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 18 Jun 2010
AB A review. A pathogenic relationship exists between type 2 diabetes and obesity. Over the last decade, the escalation in diabetes cases has paralleled the rapid increase in obesity rates, constituting a global health crisis. Environmental risk factors attributed to the global increase in obesity include the consumption of high-calorie, high-fat foods and inadequate phys. activity. Obese individuals may also have a genetic predisposition for obesity. Both diabetes and obesity confer an elevated risk of developing a range of complications and comorbidities, including cardiovascular disease, hypertension and stroke, which can complicate disease management. This review examines the etiol. of the linkages between diabetes and obesity and the range of available therapies. Recent clin. evidence substantiating the efficacy and safety of incretin-based antidiabetic therapies is analyzed, in addition to data on antiobesity therapeutic strategies, such as antiobesity agents, behavior modification and bariatric surgery. Glucose control is often accompanied by weight-neutral or modest weight reduction effects with DPP-4 inhibitor treatment (sitagliptin, vildagliptin, saxagliptin) and weight loss with GLP-1 receptor agonist therapy (exenatide, liraglutide). Studies of antiobesity agents including orlistat, sibutramine and rimonabant have shown attrition rates of 30-40%, and the long-term effects of these agents remain unknown. Bariatric surgical procedures commonly performed are laparoscopic adjustable banding of the stomach and the Roux-en-Y gastric bypass, and have produced type 2 diabetes remission rates of up to 73%. Therapeutic strategies that integrate glycemic control and weight loss will assume greater importance as the prevalence of diabetes and obesity increase.
IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic options for diabesity)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,

2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 144 THERE ARE 144 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 43 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:702461 HCAPLUS Full-text
DOCUMENT NUMBER: 153:609405
TITLE: Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus
AUTHOR(S): Neumiller, Joshua J.; Wood, Lindy; Campbell, R. Keith
CORPORATE SOURCE: Department of Pharmacotherapy and Elder Services, Washington State University, Spokane, WA, USA
SOURCE: Pharmacotherapy (2010), 30(5), 463-484
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Jun 2010
AB A review. Type 2 diabetes mellitus traditionally has been characterized by insulin resistance and β-cell dysfunction, leading to hyperglycemia and eventual micro- and macrovascular complications. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of drugs available for the management of type 2 diabetes. In order to provide a comprehensive evaluation and comparison of the pharmacol., pharmacokinetics, efficacy, and safety of the DPP-4 inhibitors-sitagliptin, vildagliptin, saxagliptin, and alogliptin-in the treatment of type 2 diabetes, we conducted a MEDLINE search (1966-July 2009) for pertinent English-language articles. Abstrs. of the annual meetings of the American Diabetes Association and European Association for the Study of Diabetes from 2005-2009 were also searched. As a drug class, the DPP-4 inhibitors have become widely accepted in clin. practice because of their low risk of hypoglycemia, favorable adverse-effect profile, and once-daily dosing. They are weight neutral (do not cause weight gain or loss) and appear to decrease β-cell apoptosis and increase β-cell survival. Because clin. studies directly comparing agents from this class have not, to our knowledge, been conducted, making comparisons in terms of efficacy and safety will become difficult for clinicians as more agents

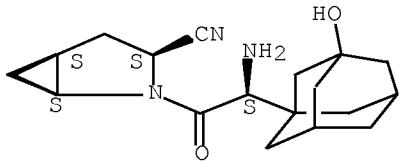
become available. Based on information from preclin., clin., and postmarketing data, there does not appear to be a compelling advantage of one DPP-4 inhibitor over another in terms of efficacy, safety, or ease of clin. use. Although theor. advantages exist for agents with a higher specificity for DPP-4 inhibition vs. inhibition of other isoenzymes associated with toxicity, comparative studies and/or increased clin. experience with this class of drug will determine the clin. advantages, if any, of one agent over another.

IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 143 THERE ARE 143 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 44 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:661501 HCAPLUS Full-text
DOCUMENT NUMBER: 153:163056
TITLE: Role of saxagliptin as monotherapy or adjunct therapy in the treatment of type 2 diabetes
AUTHOR(S): Sharma, Morali D.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, USA
SOURCE: Therapeutics and Clinical Risk Management (2010), 6, 233-237
CODEN: TCRMA6; ISSN: 1178-203X
URL: http://www.dovepress.com/getfile.php?fileID=6268
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 30 May 2010
AB A review. Type 2 diabetes is associated with decreased incretin hormone response to an oral glucose load, and a progressive decline in postprandial

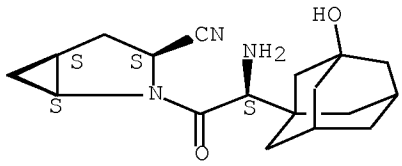
glucagon-like peptide-1 (GLP-1) secretion. Incretin-based therapies offer a new option for treatment of type 2 diabetes. Saxagliptin, a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor specifically designed for extended inhibition of the DPP-4 enzyme, causes increased endogenous GLP-1 concentration In a phase 3 clin. trials program of 24 wk duration, saxagliptin was studied in 6 multicenter, multinational, randomized, controlled studies and in combination with 3 of the most commonly administered oral antidiabetic drugs: metformin, glyburide and a thiozolidinedione (TZD). Saxagliptin provided significant redns. in Hb HbA1c when given with metformin, glyburide, a TZD, or as monotherapy. Saxagliptin also reduced fasting plasma glucose and 2-h post-prandial glucose in each of these studies, and was weight and lipid neutral. Saxagliptin was well tolerated and had a low risk of hypoglycemia when used as monotherapy.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin reduced dipeptidyl peptidase-4 enzyme, increased glucagon-like peptide-1 concentration while alone or in combination with metformin, glyburide or thiazolidinedione reduced glycated Hb in patient with type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 45 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:658952 HCAPLUS Full-text

DOCUMENT NUMBER: 153:521115

TITLE: Appraisal of saxagliptin as treatment of type 2 diabetes

AUTHOR(S): Mikhail, Nasser; Cope, Dennis

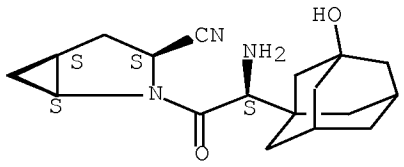
CORPORATE SOURCE: Endocrinology Division, Olive View-UCLA Medical Center, UCLA School of Medicine, USA

SOURCE: Current Drug Therapy (2010), 5(2), 111-117
CODEN: CDTUBV; ISSN: 1574-8855

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 28 May 2010
AB A review. The antidiabetic effect of the dipeptidyl peptidase 4 (DPP-4) inhibitor saxagliptin depends on the prolongation of action of the 2 incretin hormones: glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) by preventing their rapid degradation by the enzyme DPP-4. The use of saxagliptin (5 mg/d) is associated with mean reduction in glycosylated Hb (HbA1c) levels ranging from 0.5% to 0.9% compared with baseline and 0.6 to 0.8% compared with placebo after 24 wk of therapy. The main advantages of saxagliptin are the low risk of hypoglycemia, the neutral effect on body weight, the simplicity of use, and reassuring short-term safety profile. However, its mild-to-moderate efficacy, the lack of long-term safety and efficacy data, and relatively high cost represent its major limitations. Overall, saxagliptin may be a useful second agent for patients with type 2 diabetes who are not optimally controlled on metformin. This drug can also be used as monotherapy in patients with mild hyperglycemia who cannot tolerate metformin or a sulfonylurea (SU).
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin may be useful in treatment of patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

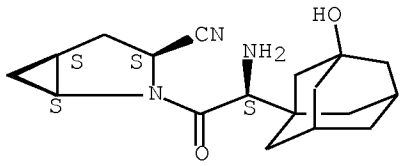
L49 ANSWER 46 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:639040 HCAPLUS Full-text
DOCUMENT NUMBER: 153:494
TITLE: New treatments in the management of type 2 diabetes: a critical appraisal of saxagliptin
AUTHOR(S): Gallwitz, Baptist
CORPORATE SOURCE: Dept. Medicine IV, Tuebingen University, Tuebingen, 72076, Germany
SOURCE: Diabetes, Metabolic Syndrome and Obesity (2010), 3,

117-124
CODEN: DMSOAD; ISSN: 1178-7007
URL: http://www.dovepress.com/getfile.php?fileID=6261
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 25 May 2010

AB A review. Saxagliptin is a novel dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) for the treatment of type 2 diabetes, with a duration profile for once daily dosing. It is highly selective for DPP-4 in comparison to other enzymes of the dipeptidyl peptidase family. DPP-4 inhibitors elevate plasma concns. of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). This effect results in a glucose-dependent stimulation of insulin secretion and an inhibition of glucagon secretion without an intrinsic risk for hypoglycemia. In comparison to sulfonylureas and thiazolidinediones that promote weight gain, DPP-4 inhibitors are weight neutral. Saxagliptin has been approved by the FDA for the US and by the EMEA for Europe in 2009. Clin. trials showed a dose-dependent inhibition of DPP-4 by saxagliptin in doses ranging from 2.5 to 100 mg daily without serious side effects. Type 2 diabetic patients receiving 5 mg to 10 mg saxagliptin once daily had a significant lowering of HbA1c and glycemic parameters along with good tolerability and safety. Saxagliptin has demonstrated a good efficacy for glycemic parameters in various patient populations either in monotherapy or in combination with metformin and other oral antidiabetic drugs as well as a favorable cardiovascular profile. With its high selectivity for DPP-4 and its clin. and cardiovascular profile, saxagliptin is an attractive novel DPP-4 inhibitor.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(management of type 2 diabetes using saxagliptin)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

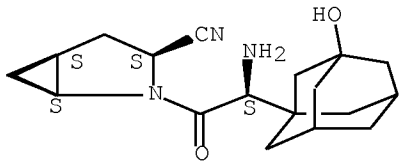


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 47 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:551452 HCAPLUS Full-text
DOCUMENT NUMBER: 154:291821
TITLE: Green process chemistry in the pharmaceutical industry
AUTHOR(S): Cue, Berkeley W.; Zhang, Ji
CORPORATE SOURCE: BWC Pharma Consulting, LLC, Ledyard, CT, USA
SOURCE: Green Chemistry Letters and Reviews (2009), 2(4), 193-211
CODEN: GCLRAI; ISSN: 1751-8253
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 04 May 2010
AB A review. Key factors for deriving environmentally sustainable processes in the synthesis of pharmaceutical intermediates and products are discussed. The selection and use of solvents is emphasized as regards methods to minimize environmental impact. Case studies of successful process development to attain improved green processes are included.
IT 361442-04-8P, Saxagliptin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(green process chemical in pharmaceutical industry)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

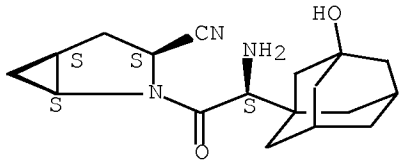


OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 48 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:139419 HCAPLUS Full-text
DOCUMENT NUMBER: 152:278405
TITLE: Medicinal Chemistry of Incretin Mimetics and DPP-4 Inhibitors
AUTHOR(S): Zettl, Heiko; Schubert-Zsilavecz, Manfred; Steinhilber, Dieter
CORPORATE SOURCE: Institute of Pharmaceutical Chemistry, Goethe-University Frankfurt, Frankfurt/Main, 60438, Germany
SOURCE: ChemMedChem (2010), 5(2), 179-185

CODEN: CHEMGX; ISSN: 1860-7179
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 03 Feb 2010
AB A review.
IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal chemical of incretin mimetics and DPP-4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 49 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:31736 HCAPLUS Full-text
DOCUMENT NUMBER: 152:110650
TITLE: Saxagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. [Erratum to document cited in CA151:394956]
AUTHOR(S): Tahrani, Abd A.; Piya, Milan K.; Barnett, Anthony H.
CORPORATE SOURCE: Undergraduate Center, Birkingham Heartlands Hospital, Birmingham, B9 5SS, UK
SOURCE: Advances in Therapy (2009), 26(7), 736
CODEN: ADTHE7; ISSN: 0741-238X
PUBLISHER: Springer Healthcare Communications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 11 Jan 2010
AB A review. On page 252, in the right column, in paragraph 1, in line 4, "Saxaglipton demonstrates greater...compared with DPP-8/9).44", was incorrectly given, and should read: "Saxagliptin demonstrates greater selectivity for DPP-4 than for either the DPP-8 or DPP-9 enzymes (400- and 75-fold, respectively).46. The active metabolite of saxagliptin (BMS-510849) is two-fold less potent than the parent. Selectivity of sitagliptin and vildagliptin for DPP-4 is >2600 and 32-250-fold greater,

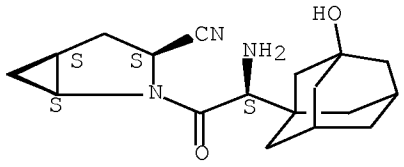
respectively, compared with DPP-8/9.44. Both saxagliptin and BMS-510849 are also highly selective for inhibition of DPP-4 compared with a large panel of other proteases tested (>4000-fold).".

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new dipeptidylpeptidase-4 inhibitor, saxagliptin for treatment of type 2 diabetes mellitus (Erratum))

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L49 ANSWER 50 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1607315 HCAPLUS Full-text

DOCUMENT NUMBER: 152:445498

TITLE: The intersection of safety and adherence: new incretin-based therapies in patients with type 2 diabetes mellitus

AUTHOR(S): Zarowitz, Barbara J.; Conner, Christopher

CORPORATE SOURCE: Omnicare, Inc., Livonia, MI, USA

SOURCE: Pharmacotherapy (2009), 29(12, Pt. 2), 55S-67S
CODEN: PHPYDQ; ISSN: 0277-0008

PUBLISHER: Pharmacotherapy Publications

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 28 Dec 2009

AB A review. One of the challenges facing health care providers in the treatment of patients with type 2 diabetes mellitus is maintaining the balance between achieving Hb A1c targets while simultaneously minimizing adverse events-most notably hypoglycemia and weight gain-that may neg. affect adherence to therapy and thus treatment outcomes. Incretin-based treatments, such as glucagon-like peptide-1 (GLP-1)-receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, are the newest class of therapies for the management of patients with type 2 diabetes. Data from clin. trials in which liraglutide, exenatide, saxagliptin, or sitagliptin were employed as monotherapy or added to ongoing antidiabetic treatment indicate that the incretin-based therapies have very low risk for the development of hypoglycemia and either decrease body weight (GLP-1-receptor agonists) or

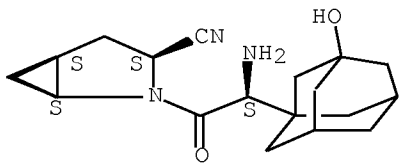
are weight neutral (DPP-4 inhibitors). Decreased risk for hypoglycemia and weight gain may improve adherence. Avoiding weight gain, which is commonly associated with older oral antidiabetic agents and some insulins, also has the potential to decrease the risk for cardiovascular disease. Future pharmacoeconomic studies may demonstrate translation of these benefits into good cost-effectiveness for these therapies.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adherence to saxagliptin may be improved by its decreasing risk for hypoglycemia and weight gain in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 51 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1480821 HCAPLUS Full-text

DOCUMENT NUMBER: 153:27713

TITLE: Exploration of the DPP-4 inhibitors with a focus on saxagliptin

AUTHOR(S): Shubrook, Jay H.; Colucci, Randall A.; Schwartz, Frank L.

CORPORATE SOURCE: Ohio University College of Osteopathic Medicine (OU-COM), Family Medicine, Athens, OH, 45701, USA

SOURCE: Expert Opinion on Pharmacotherapy (2009), 10(17), 2927-2934
CODEN: EOPHF7; ISSN: 1465-6566

PUBLISHER: Informa Healthcare

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 30 Nov 2009

AB A review. Background: Type 2 diabetes (T2DM) has become a worldwide epidemic. Despite a vast array of new compds. to treat T2DM, recommended treatment goals are consistently not achieved in this country thus suggesting a need to increase treatment options. Objective: To review the role of DPP-4 inhibitors in treatment of T2DM with an emphasis on saxagliptin. Methods:

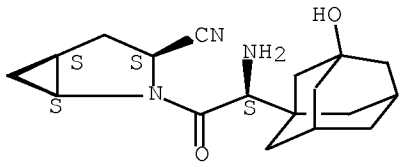
The authors discuss the role of this new class of medications in treatment of T2DM, review the current available studies and the unique characteristics of saxagliptin. Results and conclusions: Saxagliptin, a DPP-4 inhibitor, is one of an important new class of compds., which seems to be particularly safe and effective especially in early treatment of T2DM.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exploration of DPP-4 inhibitors with a focus on saxagliptin)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 52 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1438680 HCAPLUS Full-text

DOCUMENT NUMBER: 153:131

TITLE: Saxagliptin

AUTHOR(S): Dhillon, Sohita; Weber, Juliane

CORPORATE SOURCE: Adis, a Wolters Kluwer Business, Auckland, N. Z.

SOURCE: Drugs (2009), 69(15), 2103-2114
CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis Data Information BV

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 20 Nov 2009

AB A review. Saxagliptin and its active metabolite M2 are dipeptidyl peptidase-4 inhibitors that improve glycemic control by preventing the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. This increases GLP-1 levels, stimulates insulin secretion and reduces postprandial glucagon and glucose levels. In well designed, 24-wk trials in treatment-naive patients with type 2 diabetes mellitus, monotherapy with oral saxagliptin 2.5 or 5 mg once daily significantly improved glycemic control, as measured by mean glycosylated Hb (HbA1c) levels, relative to placebo. In large, well designed, 24-wk trials, combination therapy with saxagliptin 5 mg once daily plus metformin significantly improved HbA1c levels relative to single-agent

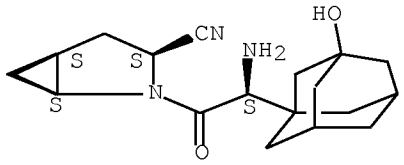
saxagliptin or metformin in treatment-naive patients; in treatment-experienced patients with inadequate glycemic control, the addition of saxagliptin 2.5 or 5 mg once daily to metformin, glyburide or a thiazolidinedione, significantly improved HbA1c levels relative to continued use of existing monotherapy. Saxagliptin as monotherapy or in combination with other oral antihyperglycemics was generally well tolerated, with most adverse events being of mild to moderate severity. In clin. trials, the incidence of hypoglycemic events in patients receiving saxagliptin was generally similar to that in patients receiving placebo or other oral antihyperglycemic agents. Saxagliptin therapy was not associated with an increased risk of cardiovascular events according to pooled data from eight clin. trials. Saxagliptin generally had a weight-neutral effect.

IT 361442-04-8, Onglyza
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. properties, clin. efficacy and tolerability of saxagliptin in patients with type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 53 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1214747 HCAPLUS Full-text

DOCUMENT NUMBER: 152:562715

TITLE: Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition

AUTHOR(S): Kirby, Mark; Yu, Denise M. T.; O'Connor, Steven; Gorrell, Mark D.

CORPORATE SOURCE: Bristol-Myers Squibb, Princeton, NJ, 08540, USA

SOURCE: Clinical Science (2010), 118(1/2), 31-41
CODEN: CSCIAE; ISSN: 0143-5221

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 05 Oct 2009

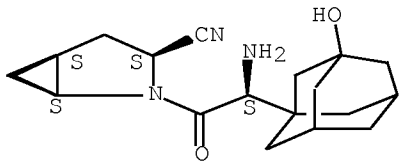
AB A review. DPP-4 (dipeptidyl peptidase-4) degrades the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide), decreasing their stimulatory effects on β-cell insulin secretion. In patients with Type 2 diabetes, meal-related GLP-1 secretion is reduced. DPP-4 inhibitors (alogliptin, saxagliptin, sitagliptin and vildagliptin) correct the GLP-1 deficiency by blocking this degradation, prolonging the incretin effect and enhancing glucose homoeostasis. DPP-4 is a member of a family of ubiquitous atypical serine proteases with many physiol. functions beyond incretin degradation, including effects on the endocrine and immune systems. The role of DPP-4 on the immune system relates to its extra-enzymic activities. The intracytosolic enzymes DPP-8 and DPP-9 are recently discovered DPP-4 family members. Although specific functions of DPP-8 and DPP-9 are unclear, a potential for adverse effects associated with DPP-8 and DPP-9 inhibition by non-selective DPP inhibitors has been posed based on a single adverse preclin. study. However, the preponderance of data suggests that such DPP-8 and DPP-9 enzyme inhibition is probably without clin. consequence. This review examines the structure and function of the DPP-4 family, associated DPP-4 inhibitor selectivity and the implications of DPP-4 inhibition in the treatment of Type 2 diabetes.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor selectivity in the clin. application of dipeptidyl peptidase-4 inhibition)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 54 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1143086 HCAPLUS Full-text

DOCUMENT NUMBER: 152:254010

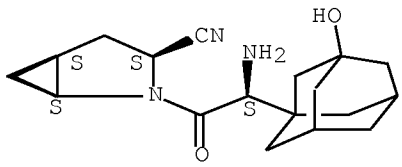
TITLE: Pharmacotherapy of hyperglycemia

AUTHOR(S): Kulasa, Kristen M.; Henry, Robert R.

CORPORATE SOURCE: Veterans' Affairs San Diego Healthcare System, Department of Medicine, University of California, San Diego, CA, 92161, USA

SOURCE: Expert Opinion on Pharmacotherapy (2009), 10(15), 2415-2432
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 18 Sep 2009
AB A review. Type 2 diabetes mellitus (T2DM) is a chronic, progressive disorder that affects more than 230 million people worldwide and is expected to affect 366 million by 2030. Both the prevalence of T2DM and the cost of its long term complications has driven the focus and emphasis on treatments aimed at reducing hyperglycemia and controlling hypertension and dyslipidemia. In the last 5 years new glucose lowering drugs acting on novel pathways have been developed, licensed and launched. These drugs include the glucagon-like peptide (GLP-1) agonists, exenatide, and dipeptidyl peptidase (DPP-IV) inhibitors such as sitagliptin and saxagliptin. This review describes current approaches to T2DM treatment, focusing on newer agents which tend to be associated with less hypoglycemia and possible weight loss, and addresses the potential roles of novel oral pharmacol. agents in the late-stages of development that might provide new options for the management of this disease.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new agents of oral dipeptidyl peptidase-IV inhibitors such as saxagliptin may be effective in controlling hyperglycemia in patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

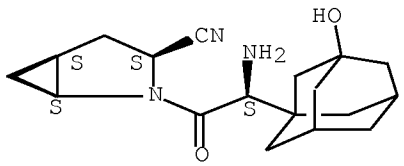


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 55 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1120506 HCAPLUS Full-text
DOCUMENT NUMBER: 152:445281
TITLE: Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin -

diabetes control and potential adverse events
AUTHOR(S): Ahren, Bo
CORPORATE SOURCE: Department of Clinical Sciences, Lund University, Lund, Swed.
SOURCE: Best Practice & Research, Clinical Endocrinology & Metabolism (2009), 23(4), 487-498
CODEN: BPRCE9
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 14 Sep 2009
AB A review. Inhibition of dipeptidyl peptidase-4 (DPP-4) is a novel oral treatment for type 2 diabetes. DPP-4 inhibition increases insulin secretion and reduces glucagon secretion by preventing the inactivation of glucagon-like peptide-1 (GLP-1), thereby lowering glucose levels. Several DPP-4 inhibitors are in clin. development; more studies exist for sitagliptin and vildagliptin. They improve metabolic control in type 2 diabetes in monotherapy and also in combination with metformin, sulfonylurea and thiazolidinediones. HbA1c is reduced by approx. 0.6-1.1% in studies up to 52 wk. Similar, although more limited, results were obtained for saxagliptin. DPP-4 inhibitors are safe and tolerable with no increased risk of adverse events compared to placebo and have a low risk of hypoglycemia. DPP-4 inhibitors are body weight-neutral. The DPP-4 inhibitors are recommended for use in the early stage of type 2 diabetes, in combination with metformin in subjects with inadequate glycemic control. DPP-4 inhibition may also be used in combination with sulfonylurea and thiazolidinediones and potentially also in combination with insulin. The durability and long-term safety of DPP-4 inhibitiors remain to be established.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel oral treatment inhibiting DPP-4 using sitagliptin, vildagliptin or saxagliptin increased insulin, reduced glucagon secretion preventing inactivation of GLP-1 lowering glucose level may be useful in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

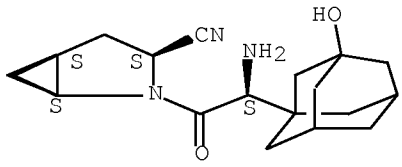


OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS

RECORD (23 CITINGS)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 56 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:700928 HCAPLUS Full-text
DOCUMENT NUMBER: 151:484518
TITLE: Saxagliptin: a new dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes
AUTHOR(S): Deacon, Carolyn F.; Holst, Jens J.
CORPORATE SOURCE: Department of Biomedical Sciences, Panum Institute, Copenhagen N, DK-2200, Den.
SOURCE: Advances in Therapy (2009), 26(5), 488-499
CODEN: ADTHE7; ISSN: 0741-238X
PUBLISHER: Springer Healthcare Communications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 10 Jun 2009
AB A review. Saxagliptin is a potent and selective reversible inhibitor of dipeptidyl peptidase-4, which is being developed for the treatment of type 2 diabetes. It is absorbed rapidly after oral administration and has a pharmacokinetic profile compatible with once daily dosing. Saxagliptin is metabolized in vivo to form an active metabolite, and both parent drug and metabolite are excreted primarily via the kidneys. Saxagliptin reduces the degradation of the incretin hormone glucagon-like peptide-1, thereby enhancing its actions, and is associated with improved β-cell function and suppression of glucagon secretion. Clin. trials of up to 24 wk duration have shown that saxagliptin improves glycemic control in monotherapy and provides addnl. efficacy when used in combination with other oral antidiabetic agents (metformin, sulfonylurea, thiazolidinedione). Both fasting and postprandial glucose concns. are reduce leading to clin. meaningful redns. in glycated Hb, and due to the glucosedependency of its mechanism of action, there is a low risk of hypoglycemia. Saxagliptin is reported to be well tolerated with a side-effect profile similar to placebo. It has a neutral effect on body weight and dose adjustment because of age, gender, or hepatic impairment is not necessary. Saxagliptin is being co-developed by Bristol-Myers-Squibb (New York, NY, USA) and AstraZeneca (Cheshire, UK), and is currently undergoing regulatory review.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin, a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetic patient)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

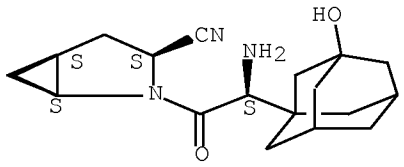


OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 57 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:444622 HCAPLUS Full-text
DOCUMENT NUMBER: 151:394956
TITLE: Saxagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus
AUTHOR(S): Tahrani, Abd A.; Piya, Milan K.; Barnett, Anthony H.
CORPORATE SOURCE: Undergraduate Center, Birmingham Heartlands Hospital, Birmingham, B9 5SS, UK
SOURCE: Advances in Therapy (2009), 26(3), 249-262
CODEN: ADTHE7; ISSN: 0741-238X
PUBLISHER: Springer Healthcare Communications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 14 Apr 2009
AB A review. Type 2 diabetes mellitus (T2DM) is a global epidemic with increasing impact on individuals and health-care providers. Available treatments (such as metformin, sulfonylureas, glitazones, and insulin) have proven unsatisfactory in producing a long-lasting impact on glycemic control. In addition, most of these treatments have undesirable side effects such as weight gain and hypoglycemia. As a result, exploring new treatment targets and new therapies is mandatory in order to treat this condition. The incretin pathway, in particular glucagon-like peptide (GLP-1), plays an important pathol. role in the development of T2DM, and treatments targeting the incretin system have recently become available. These can mainly be divided into two broad categories; GLP-1 agonists/analogs (exenatide, liraglutide), and dipeptidyl peptidase-4 (DPP-4; the enzyme responsible for rapid inactivation of incretins) inhibitors (sitagliptin, vildagliptin). Saxagliptin is a novel DPP-4 inhibitor that has recently completed phase 3 studies. Saxagliptin is a potent and specific inhibitor of DPP-4 (in comparison with other dipeptidyl peptidase enzymes) that is given once daily. Current data suggest that saxagliptin as monotherapy or in combination with metformin, glyburide, or a glitazone results in significant redns. in fasting and postprandial plasma glucose and Hb A1c (HbA1c). Saxagliptin is well tolerated and does not increase hypoglycemia compared with the placebo, and is probably weight neutral. Saxagliptin will be a new effective drug in the currently available variety of antidiabetic medications for patients with T2DM.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(new dipeptidylpeptidase-4 inhibitor, saxagliptin for treatment of type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 58 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:264030 HCAPLUS Full-text
DOCUMENT NUMBER: 150:343958
TITLE: Medicinal chemistry approaches to the inhibition of dipeptidyl peptidase-4 for the treatment of type 2 diabetes
AUTHOR(S): Havale, Shrikanth H.; Pal, Manojit
CORPORATE SOURCE: New Drug Discovery, Anrich Industrial Estate, Matrix Laboratories Limited, Andhra Pradesh, Bollaram, Jinnaram Mandal, Medak District, 502 325, India
SOURCE: Bioorganic & Medicinal Chemistry (2009), 17(5), 1783-1802
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 05 Mar 2009
AB A review. Emerging as an epidemic of the 21st century type 2 diabetes has become a major health problem throughout the globe. The number of deaths attributable to diabetes reflects the insufficient glycemic control achieved with the treatments used in recent past. DPP-4 inhibitors have been investigated as a new therapy with novel mechanisms of action and improved tolerability. DPP-4, a protease that specifically cleaves dipeptides from proteins and oligopeptides after a penultimate N-terminal proline or alanine, is involved in the degradation of a number of neuropeptides, peptide hormones and cytokines, including the incretins GLP-1 and GIP. As soon as released from the gut in response to food intake, GLP-1 and GIP exert a potent glucose-dependent insulinotropic action, thereby playing a key role in the maintenance of post-meal glycemic control. Consequently, inhibiting DPP-4

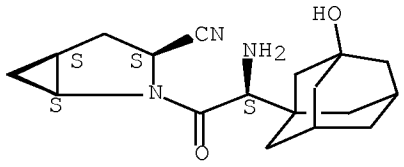
prolongs the action of GLP-1 and GIP, which in turn improves glucose homeostasis with a low risk of hypoglycemia and potential for disease modification. Indeed, clin. trials involving diabetic patients have shown improved glucose control by administering DPP-4 inhibitors, thus demonstrating the benefit of this promising new class of antidiabetics. Intense research activities in this area have resulted in the launch of sitagliptin and vildagliptin (in Europe only) and the advancement of a few others into preregistration/phase 3, for example, saxagliptin, alogliptin and ABT-279. Achieving desired selectivity for DPP-4 over other related peptidases such as DPP-8 and DPP-9 (inhibition of which was linked to toxicity in animal studies) and long-acting potential for maximal efficacy (particularly in more severe diabetic patients) were the major challenges. Whether these goals are achieved with the present series of inhibitors in the advanced stages of clin. development is yet to be confirmed. Nevertheless, treatment of this metabolic disorder especially in the early stages of the disease via DPP-4 inhibition has been recognized as a validated principle and a large number of inhibitors are presently in various stage of pre-clin./clin. development. Sitagliptin is a new weapon in the arsenal of oral antihyperglycemic agents. This review will focus on the journey of drug discovery of DPP-4 inhibitors for oral delivery covering a brief scientific background and medicinal chemical approaches along with the status of advanced clin. candidates.

IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal chemical approaches to inhibition of dipeptidyl peptidase-4 for
treatment of type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (52 CITINGS)

REFERENCE COUNT: 139 THERE ARE 139 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

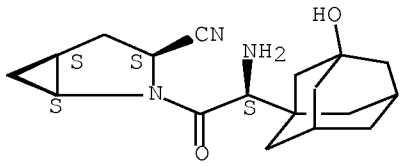
L49 ANSWER 59 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:105647 HCAPLUS Full-text

DOCUMENT NUMBER: 151:23607

TITLE: Saxagliptin, a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes
AUTHOR(S): Gallwitz, Baptist
CORPORATE SOURCE: Department of Medicine IV, Eberhard-Karls-University, Tuebingen, 72076, Germany
SOURCE: IDrugs (2008), 11(12), 906-917
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Thomson Reuters
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 28 Jan 2009
AB A review. Saxagliptin, a dipeptidyl peptidase-IV (DPP-IV) inhibitor, is currently under development by Bristol-Myers Squibb Co, AstraZeneca plc and Otsuka Pharmaceutical Co Ltd for the treatment of type 2 diabetes. The compound has high selectivity for DPP-IV compared with other dipeptidyl peptidases and a duration profile designed for once-daily dosing. DPP-IV inhibitors act by increasing levels of glucagon-like peptide-1, which stimulates insulin secretion. In animal studies, saxagliptin improved glucose clearance and raised insulin levels in rodents. Clin. trials have demonstrated a dose-dependent inhibition of DPP-IV by saxagliptin without serious side effects. Results have demonstrated that treatment with saxagliptin lowers blood glucose levels, with good tolerability and safety. The specific advantages of saxagliptin over other DPP-IV inhibitors may lie in its long-lived, effective and highly specific inhibition of DPP-IV, making once-daily treatment feasible, effective and safe.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase IV inhibitor saxagliptin was safe and effective in improving glucose tolerance and increasing insulin level in animal and patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

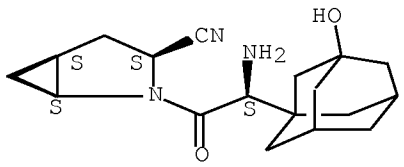


OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 60 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:5612 HCAPLUS Full-text
DOCUMENT NUMBER: 150:486747
TITLE: Progress in the investigation of GLP-1 receptor agonists and DPP-IV inhibitors
AUTHOR(S): Zhou, Yinghong; Huang, Wenlong; Zhang, Huibin; Chi, Yushi
CORPORATE SOURCE: Center of Drug Discovery, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SOURCE: Zhongguo Yaoke Daxue Xuebao (2008), 39(5), 385-391
CODEN: ZHYXE9; ISSN: 1000-5048
PUBLISHER: Zhongguo Yaoke Daxue
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 02 Jan 2009
AB A review with 28 refs. The research advances of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase IV (DPP-IV) inhibitors are reviewed in this paper, and the pharmacol. mechanism of GLP-1 in blood glucose regulation is also presented. GLP-1 receptor agonists (such as Exendin-4, Exenatide LAR, Liraglutide, CJC-1131, a nonpeptidic GLP-1 receptor agonist) and DPP-IV inhibitors (such as Sitagliptin, Vildagliptin, Saxagliptin, and Alogliptin) are also introduced in detail in order to provide refs. for the research and development of medicines for the treatment of type 2 diabetes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(progress in the investigation of GLP-1 receptor agonists and DPP-IV inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

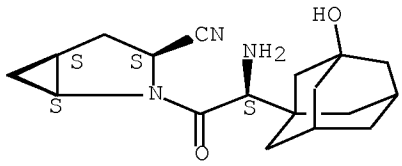


=> d l49 ibib ed abs hitstr 61-87
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L49 ANSWER 61 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1499742 HCAPLUS Full-text

DOCUMENT NUMBER: 150:113564
TITLE: Medicinal chemistry approaches to the inhibition of dipeptidyl peptidase IV
AUTHOR(S): Gwaltney, Stephen L., II
CORPORATE SOURCE: Takeda San Diego, San Diego, CA, 92121, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2008), 8(17), 1545-1552
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Dec 2008
AB A review. Inhibitors of dipeptidyl peptidase IV (DPP-4) have emerged as an important new class of therapeutic agents for type two diabetes. Various medicinal chemical approaches have been applied to this area and have resulted in the identification of numerous late-stage development compds. The discoveries of several of the most advanced DPP-4 inhibitors are reviewed.
IT 361442-04-8, Saxagliptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal chemical approaches to inhibition of dipeptidyl peptidase IV)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

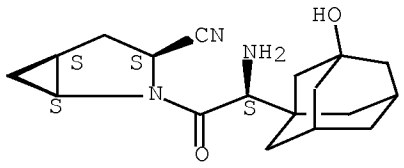


OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 62 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1444868 HCAPLUS Full-text
DOCUMENT NUMBER: 150:554568
TITLE: Emerging dipeptidyl peptidase-4 inhibitors for the treatment of diabetes
AUTHOR(S): Ahren, Bo
CORPORATE SOURCE: Department of Clinical Sciences, Division of Medicine, Lund University, Lund, SE-221 84, Swed.
SOURCE: Expert Opinion on Emerging Drugs (2008), 13(4), 593-607
CODEN: EOEDA3; ISSN: 1472-8214

PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 03 Dec 2008
AB A review. Inhibition of dipeptidyl peptidase-4 (DPP-4) prevents the inactivation of glucagon-like peptide-1 (GLP-1). This increases circulating levels of active GLP-1, stimulates insulin secretion and inhibits glucagon secretion, resulting in lowering of glucose levels and improvement of glycemic control in patients with type 2 diabetes. Several DPP-4 inhibitors are emerging for therapeutic use. Most experience exists for sitagliptin, vildagliptin, saxagliptin and alogliptin. They all improve metabolic control in type 2 diabetes in monotherapy and in combination therapy with metformin, sulfonylurea and thiazolidinediones. Vildagliptin and alogliptin have also been shown to improve glycemic control when added to insulin therapy, and sitagliptin improves glycemic control in triple therapy with metformin plus thiazolidinedione. DPP-4 inhibition also shows a favorable safety profile, high tolerability, only a minimal risk of hypoglycemia, and body-weight neutrality. The main clin. indication for DPP-4 inhibitors will be in the early stage of type 2 diabetes, in combination with metformin or other treatments in subjects with inadequate glycemic control on these treatments alone. The durability and long-term safety of DPP-4 inhibition, as well as clin. positioning in relation to GLP-1 mimetics, remain now to be established.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DPP-4 inhibitor saxagliptin alone or in combination with metformin, sulfonylurea and thiazolidinedione improved metabolic control in patient with diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

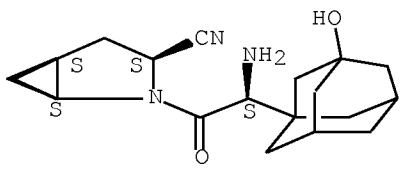


OS.CITING REF COUNT: 37 THERE ARE 37 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)
REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 63 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1351436 HCAPLUS Full-text

DOCUMENT NUMBER: 150:365165
TITLE: Saxagliptin: dipeptidyl peptidase IV inhibitor antidiabetic agent
AUTHOR(S): Cole, P.; Serradell, N.; Bolos, J.; Castaner, R.
CORPORATE SOURCE: Prous Science, Barcelona, 08025, Spain
SOURCE: Drugs of the Future (2008), 33(7), 577-586
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 11 Nov 2008
AB A review. Targeting glucagon-like peptide 1 (GLP-1) is an attractive strategy for the treatment of type 2 diabetes, as this incretin hormone enhances postprandial insulin secretion in a manner dependent on glycemia. Evidence also indicates that GLP-1 reduces glucagon secretion, induces satiety, delays gastric emptying and enhances β-cell function through stimulation of neogenesis and inhibition of apoptosis. One means of utilizing this target is by inhibiting its degradation, which is mediated by dipeptidyl peptidase IV (DPP IV). Saxagliptin is a DPP IV inhibitor that has displayed promising preclin. characteristics, such as dose-dependent clearance of glucose in animal models of diabetes. Data from clin. trials show significantly improved glycosylated Hb (HbA1c) and fasting serum glucose in diabetes patients with saxagliptin alone and in combination with metformin, and the agent was well tolerated. Results from phase III studies are expected to soon provide a comprehensive view of saxagliptin's role in the expanding effort to improve the lives of diabetic patients. Just recently, Bristol-Myers Squibb and AstraZeneca submitted an NDA with the FDA and validation of an MAA to the EMEA for the use of saxagliptin in the treatment of type 2 diabetes.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin showed dose-dependent clearance of glucose in animal model of diabetes and it alone or in combination with metformin improved glycosylated Hb, fasting serum glucose level in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

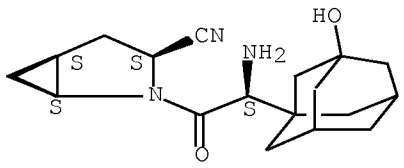


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD

(4 CITINGS)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 64 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:616542 HCAPLUS Full-text
DOCUMENT NUMBER: 149:69240
TITLE: DPP-IV inhibitors: a review of sitagliptin, vildagliptin, alogliptin, and saxagliptin
AUTHOR(S): Miller, Shannon A.; St. Onge, Erin L.; Taylor, James R.
CORPORATE SOURCE: University of Florida, USA
SOURCE: Formulary (2008), 43(4), 122-124, 131-134
CODEN: FORMF9; ISSN: 1082-801X
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 23 May 2008
AB A review. Dipeptidyl peptidase IV (DPP-IV) inhibitors, including sitagliptin, vildagliptin, alogliptin, and saxagliptin, represent a novel approach in the management of type 2 diabetes. DPP-IV inhibitors reduce the rapid degradation of glucagon-like peptide-1 (GLP-1), an incretin hormone that stimulates insulin secretion, slows gastric emptying, decreases glucagon secretion, and improves beta-cell function. These agents significantly reduce Hb A1c (HbA1c) and fasting plasma glucose when they are used as monotherapy or in combination with traditional antidiabetic agents. DPP-IV inhibitors are generally well tolerated and have a weight-neutral effect. These agents may also reduce or reverse the progressive decline in beta-cell function that occurs in type 2 diabetes. Addnl. long-term safety and efficacy data are needed; however, current studies have suggested that these agents may offer several potential advantages over existing therapies.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and efficacy of dipeptidyl peptidase IV inhibitors in management of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

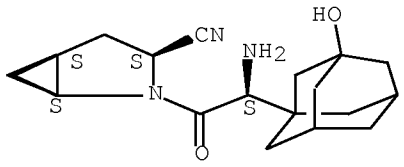


OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD

(6 CITINGS)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 65 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:1287430 HCAPLUS Full-text
DOCUMENT NUMBER: 148:134734
TITLE: Dipeptidyl peptidase 4 (DPP-4) inhibitors and their role in type 2 diabetes management
AUTHOR(S): Crepaldi, G.; Carruba, M.; Comaschi, M.; Del Prato, S.; Frajese, G.; Paolisso, G.
CORPORATE SOURCE: Department of Medical and Surgical Sciences, University of Padua, Padua, Italy
SOURCE: Journal of Endocrinological Investigation (2007), 30(7), 610-614
CODEN: JEIND7; ISSN: 0391-4097
PUBLISHER: Editrice Kurtis
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 13 Nov 2007
AB A review. Dipeptidyl peptidase 4 (DPP-4) inhibitors are a new pharmacol. class of drugs for treating Type 2 diabetes. They improve the capacity of the organism to control glycemia by increasing the levels of active incretins. Their mechanism of action is thus radically different from those of other anti-diabetic drugs currently available. DDP-4 inhibitors use a physiol. mechanism to control hyperglycemia, by stimulating the secretion of insulin from β-cells, decreasing the secretion of glucagon from pancreatic α-cells, and at the same time reducing the production of glucose by the liver. DDP-4 inhibitors have shown significant efficacy in maintaining reduced levels of glycosylated Hb for up to 1 yr. In vitro and animal studies have shown that they can inhibit apoptosis of β-cells and favor their regeneration and differentiation. The oral DPP-4 inhibitors vildagliptin, sitagliptin, and saxagliptin are efficacious both alone and in association with other oral anti-diabetic agents and may be administered in a single daily dose. Lastly, they have substantial advantages with respect to other anti-diabetic drugs, since they involve a low risk of hypoglycemia and do not affect body weight
IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral dipeptidyl peptidase 4 inhibitor like saxagliptin alone or with other oral antidiabetic agents were effective, showed low risk of hypoglycemia and no effect on body weight in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

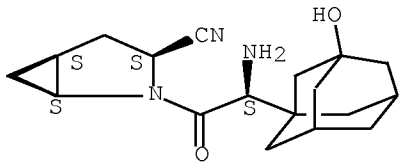


OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 66 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:936967 HCAPLUS Full-text
DOCUMENT NUMBER: 147:356144
TITLE: Dipeptidyl peptidase IV inhibitors and the incretin system in type 2 diabetes mellitus
AUTHOR(S): Langley, Alissa K.; Suffoletta, Terri J.; Jennings, Heath R.
CORPORATE SOURCE: Department of Pharmacy Services, Saint Joseph HealthCare, Lexington, KY, USA
SOURCE: Pharmacotherapy (2007), 27(8), 1163-1180
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 23 Aug 2007
AB A review. As understanding of type 2 diabetes mellitus pathophysiol. expands, treatments continue to evolve and new pharmacol. targets emerge. Patients with type 2 diabetes exhibit deficiencies of the incretin system; thus, methods for increasing insulinotropic hormones have become a popular target for therapy. A new class of oral antidiabetics has emerged-the dipeptidyl peptidase IV (DPP-IV) inhibitors. Unlike conventional oral antidiabetic agents, these agents promote glucose homeostasis through inhibition of DPP-IV, the enzyme responsible for degradation of two key glucoregulatory hormones: glucagon-like peptide-1 (GLP-1), which extends the action of insulin while also suppressing the release of glucagon, and glucose-dependent insulinotropic peptide (GIP). Other proposed mechanisms of action of GLP-1 and thus DPP-IV inhibitors include satiety, increased β-cell production, and inhibition of apoptosis of β cells. Clin. studies have evaluated the potential for DPP-IV inhibition to reduce glucagon levels, delay gastric emptying, and stimulate insulin release. The DPP-IV inhibitors appear to have excellent therapeutic potential in the management of type 2 diabetes as monotherapy or in combination with existing agents, such as metformin. Their pharmacokinetic and pharmacodynamic profiles support once-daily dosing, with sustainable redns. in glycosylated Hb levels and relatively few adverse effects. Their distinctive mechanism of action and adverse-event profiles may offer advantages over existing therapies, including low risk for hypoglycemia and possible augmentation of pancreatic β-cell regeneration.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin promote glucose homeostasis by increasing deficient glucagon-like peptide-1 and glucose-dependent insulinotropic peptide hormone in patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

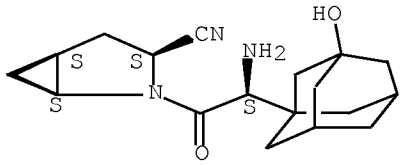


OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 67 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:632837 HCAPLUS Full-text
DOCUMENT NUMBER: 147:249712
TITLE: New and emerging drugs in type 2 diabetes
AUTHOR(S): Park, Ie Byung
CORPORATE SOURCE: Dep. of Endocrinology, Gil Medical Center, Gachon Univ. of Science and Medicine, Incheon, S. Korea
SOURCE: Korean Journal of Medicine (2007), 72(5), 446-450
CODEN: KJMOA5; ISSN: 1738-9364
PUBLISHER: Korean Association of Internal Medicine
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Korean
ED Entered STN: 13 Jun 2007
AB A review. Recent advances in understanding insulin secretion, action and signaling have led to the development of new pharmacol. agents. Several new emerging drugs and drug classes for the management of diabetes are under development, including the incretin mimetic agents (exenatide, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 analogs), the amylin analog pramlintide, the cannabinoid-1 receptor antagonist rimonabant, the mixed peroxisome proliferator-activated receptor agonists muraglitazar and the inhaled insulin preparation Exubera. New drugs and technol. advances being made available will help achieve the goals of treating patients with diabetes to all the appropriate metabolic targets. Longer term studies will help providers weigh the benefits, adverse effects, cost, and unknown long-term risks of these medications.

IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new and emerging drugs for type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L49 ANSWER 68 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:553811 HCAPLUS Full-text
DOCUMENT NUMBER: 146:474635
TITLE: 11 years of cyanopyrrolidines as DPP-IV inhibitors
AUTHOR(S): Peters, Jens-Uwe
CORPORATE SOURCE: Discovery Chemistry, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2007), 7(6), 579-595
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 23 May 2007
AB A review. Cyanopyrrolidines (cyanopyrrolidides, pyrrolidine-2-nitriles, prolinenitriles) as inhibitors of the serine protease dipeptidyl peptidase IV (DPP-IV, DP IV, CD26, EC 3.4.14.5) were first reported in 1995. The interest in this compound class grew immensely when DPP-IV was discovered as a target for the treatment of type 2 diabetes. The research on cyanopyrrolidines cumulated in the discoveries of vildagliptin (LAF237, NVP-LAF237) and saxagliptin (BMS-477118). These compds. entered Phase III clin. trials in 2004 and 2005, resp., and an application for market approval has been filed for vildagliptin in 2006. Today cyanopyrrolidines are, as judged by the nos. of patent applications, the most prominent of several series of DPP-IV inhibitors, and have the potential to become valuable medicines for type 2 diabetes in the near future. This review summarizes some historical aspects of the discovery of cyanopyrrolidine DPP-IV inhibitors, and then focuses mainly on structure-activity-relationships, the evolution of different subseries, the possibilities to improve on the chemical instability that is associated with this compound class, and on the

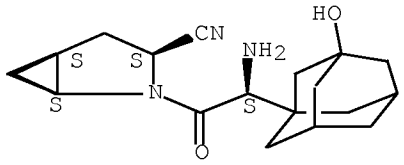
discoveries of vildagliptin and saxagliptin. Within this context, the properties of individual compds. and results from biol. studies are discussed. The rationale of DPP-IV inhibition, clin. data, and the relevance of selectivity over related proteases are extensively reviewed in other contributions to this issue of Curr. Top. Med. Chemical, and are therefore only very briefly touched.

IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(11 years of cyanopyrrolidines as DPP-IV inhibitors)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)

REFERENCE COUNT: 171 THERE ARE 171 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 69 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2007:151062 HCAPLUS Full-text

DOCUMENT NUMBER: 146:229614

TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus

INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; Mc Cormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Wong, Jesse K.; Nair, Latha G.

PATENT ASSIGNEE(S): Schering Corporation Corvas International, Ltd., USA; Dendreon Corporation

SOURCE: U.S. Pat. Appl. Publ., 418 pp., Cont.-in-part of U.S. Ser. No. 908,955.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070032433	A1	20070208	US 2002-52386	20020118 <--
US 7244721	B2	20070717		
US 20030216325	A1	20031120	US 2001-908955	20010719 <--
US 20040254117	A9	20041216		
US 7012066	B2	20060314		
MY 143322	A	20110415	MY 2006-4737	20010719 <--
CN 102206247	A	20111005	CN 2011-10065191	20010719 <--
CN 102372764	A	20120314	CN 2011-10228711	20010719 <--
CA 2473032	A1	20030731	CA 2003-2473032	20030116
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BR 2003006931	A	20050419	BR 2003-6931	20030116
CN 1633446	A	20050629	CN 2003-805933	20030116
JP 2005524628	T	20050818	JP 2003-562142	20030116
JP 4563033	B2	20101013		
MY 140710	A	20100115	MY 2003-137	20030116
NZ 571073	A	20100430	NZ 2003-571073	20030116
AT 469914	T	20100615	AT 2003-731956	20030116
CN 101792483	A	20100804	CN 2010-10143451	20030116
PT 1481000	E	20100819	PT 2003-731956	20030116
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RU 2404189	C2	20101120	RU 2004-125279	20030116
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KR 1020355	B1	20110308	KR 2004-7011022	20030116
NO 2004002792	A	20041015	NO 2004-2792	20040702
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IN 229230	A1	20090320		
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JP 2009051860	A	20090312	JP 2008-275159	20081027 <--
AU 2009210423	A1	20090917	AU 2009-210423	20090821

PRIORITY APPLN. INFO.:

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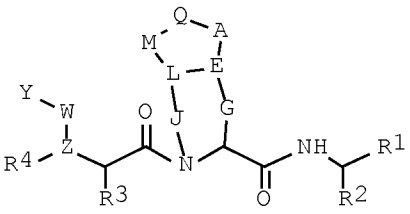
CN 2001-813111	A3	20010719
JP 2002-514149	A3	20010719
MY 2001-3436	A3	20010719
PH 2001-1200101848	A3	20010719
US 2002-52386	A	20020118
AU 2003-216064	A3	20030116
CN 2003-805933	A3	20030116
WO 2003-US1430	W	20030116

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 146:229614; MARPAT 146:229614
ED Entered STN: 09 Feb 2007
GI



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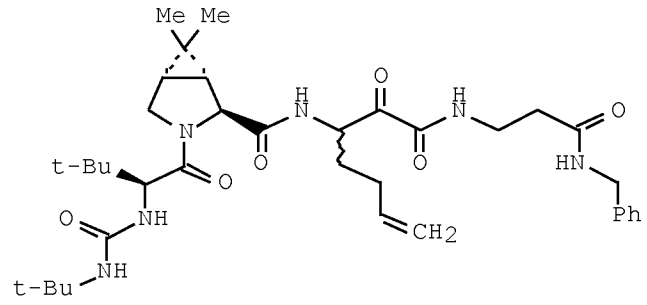


II

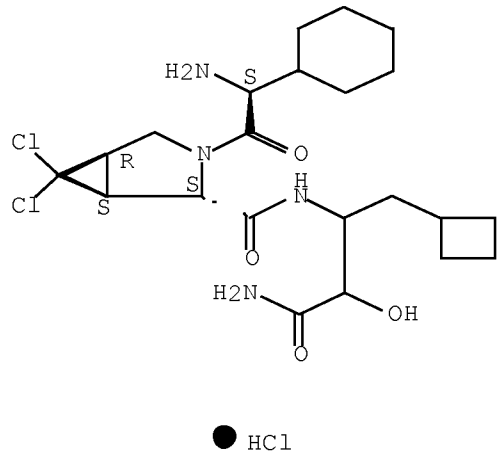
AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is a bond, O, alkylidene, NR, S, SO2, etc.; E is CH and derivs., N, or a double bond; G is alkylidene; p = 0-6; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with

provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. The invention also discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II was prepared and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

IT 1070163-68-6
RL: PRPH (Prophetic)
(Preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)
RN 1070163-68-6 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

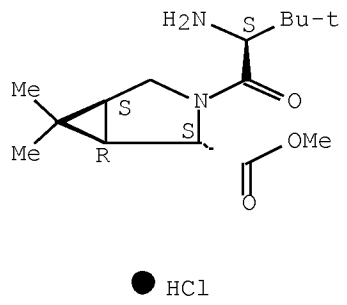
N-[3-amino-1-(cyclobutylmethyl)-2-hydroxy-3-oxopropyl]-3-[(2S)-2-amino-2-cyclohexylacetyl]-6,6-dichloro-, hydrochloride (1:1), (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



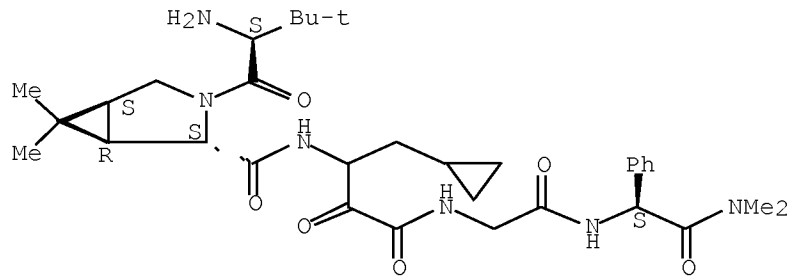
IT 847644-96-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of)
RN 847644-96-6 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxylic acid, 3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, methyl ester, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



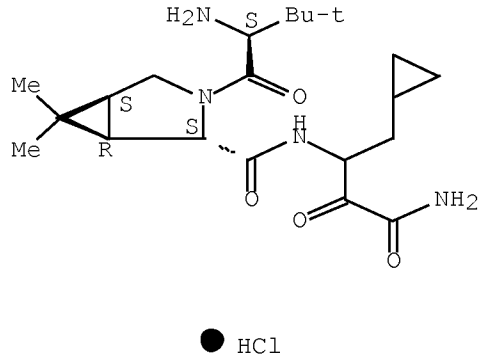
IT 394735-46-7P 394735-49-0P 569678-63-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)
RN 394735-46-7 HCAPLUS
CN Glycinamide, 3-methyl-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-β-amino-α-oxocyclopropanebutanoylglycyl-N,N-dimethyl-2-phenyl-, monohydrochloride, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 394735-49-0 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[3-amino-1-(cyclopropylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

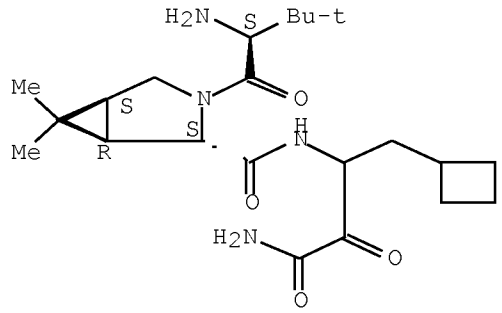
Absolute stereochemistry.



● HCl

RN 569678-63-3 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



● HCl

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 70 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2006:1320516 HCAPLUS Full-text
DOCUMENT NUMBER: 146:114024
TITLE: DPP-4 inhibitors and their potential role in the management of type 2 diabetes
AUTHOR(S): Barnett, A.

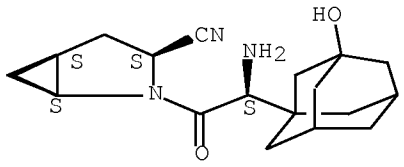
CORPORATE SOURCE: Department of Medicine, University of Birmingham and Heart of England National Health Service Foundation Trust(Teaching), Birmingham, UK
SOURCE: International Journal of Clinical Practice (2006), 60(11), 1454-1470
CODEN: IJCPF9; ISSN: 1368-5031
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 18 Dec 2006

AB A review. The dipeptidyl peptidase 4 (DPP-4) inhibitors enhance the body's own ability to control blood glucose by increasing the active levels of incretin hormones in the body. Their mechanism of action is distinct from any existing class of oral glucose-lowering agents. They control elevated blood glucose by triggering pancreatic insulin secretion, suppressing pancreatic glucagon secretion, and signalling the liver to reduce glucose production The leading DPP-4 inhibitors have shown clin. significant HbA1c redns. up to 1 yr of treatment and offer many potential advantages over existing diabetes therapies including a low risk of hypoglycemia, no effect on body weight, and the potential, based on animal and in vitro studies, for the regeneration and differentiation of pancreatic β-cells. They are efficacious as monotherapy and also in combination with commonly prescribed antidiabetic agents and are suitable for once-daily oral dosing. Consequently, many DPP-4 inhibitors such as vildagliptin (Galvus; LAF-237), sitagliptin (Januvia; MK-0431), and saxagliptin (BMS-477118) have advanced into late-stage human clin. trials. Search strategy and selection criteria This review was built on a systematic MEDLINE search for publications on the subject with the key words: DPP-4 inhibitor; vildagliptin (LAF-237); sitagliptin (MK-0431); saxagliptin (BMS-477118); and type 2 diabetes; up to August 2006. Meeting abstrs. were also searched, as much of the data currently only exists in abstract form. Take home message for clinician The DPP-4 inhibitors appear to have great potential for the treatment of type 2 diabetes, but time will tell if this will be realized. While they do not lower glucose to a greater extent than existing therapies, they offer many potential advantages, including the ability to achieve sustainable redns. in HbA1c with a well-tolerated agent that has a low risk of hypoglycemia and no weight gain, and which can be administered as a once-daily oral dose.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase 4 inhibitor saxagliptin might have role in management of type 2 diabetes in human)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 81 THERE ARE 81 CAPLUS RECORDS THAT CITE THIS RECORD (81 CITINGS)
REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

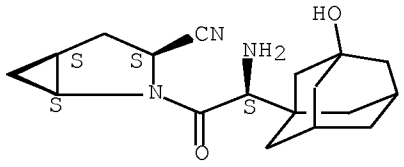
L49 ANSWER 71 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2006:82491 HCAPLUS Full-text
DOCUMENT NUMBER: 145:1093
TITLE: Glucagon-like peptide-1-based therapies for the treatment of type 2 diabetes mellitus
AUTHOR(S): Gallwitz, Baptist
CORPORATE SOURCE: Department of Medicine, Eberhard-Karls-University, Tuebingen, Germany
SOURCE: Treatments in Endocrinology (2005), 4(6), 361-370
CODEN: TERNAN; ISSN: 1175-6349
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 30 Jan 2006
AB A review. The 'incretin effect' describes the phenomenon of an enhanced insulin response following oral ingestion of glucose compared with that after i.v. administration of glucose, leading to identical postprandial plasma glucose excursions. It accounts for up to 60% of the postprandial insulin secretion, but is diminished in patients with type 2 diabetes mellitus. Gastrointestinal hormones that promote the incretin effect are called incretins. Glucagon-like peptide-1 (GLP-1) is an important incretin. Under hyperglycemic conditions in humans, it stimulates insulin secretion and normalizes blood glucose levels. GLP-1 does not stimulate insulin secretion at normal glucose levels; therefore, it does not cause hypoglycemia. Furthermore, it inhibits glucagon secretion and delays gastric emptying. In vitro and animal data have demonstrated that GLP-1 increases β-cell mass by stimulating islet cell neogenesis and by inhibiting the apoptosis of islet cells. The improvement of β-cell function due to GLP-1 can be indirectly observed from the increased insulin secretory capacity of humans receiving such treatment. GLP-1 may represent an attractive therapeutic method for patients with type 2 diabetes because of its multiple effects, including the simulation of satiety in the CNS by acting as a transmitter or by crossing the blood brain barrier. Native GLP-1 is degraded rapidly upon i.v. or s.c. administration and is therefore not feasible for routine therapy. Long-acting GLP-1 analogs (e.g. liraglutide) and exendin-4 (exenatide) that are resistant to degradation, called 'incretin mimetics', are being investigated in clin. trials. Dipeptidyl peptidase-IV inhibitors

(e.g. vildagliptin, sitagliptin, and saxagliptin) that inhibit the enzyme responsible for incretin degradation are also being studied.

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-IV inhibitor saxagliptin that inhibit enzyme responsible for incretin degradation may prove useful therapeutic option for treatment of type 2 diabetes mellitus in patient)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 72 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2003:912843 HCAPLUS Full-text
DOCUMENT NUMBER: 139:381756
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; Mccormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua
PATENT ASSIGNEE(S): Schering Corporation, USA; Dendreon Corporation
SOURCE: U.S. Pat. Appl. Publ., 629 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PT 1385870	E	20100607	PT 2001-954764	20010719 <--
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			PH 2001-1200101848 A3	20010719
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			US 2002-52386 A3	20020118
			US 2005-241656 A1	20050930

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 139:381756
ED Entered STN: 21 Nov 2003
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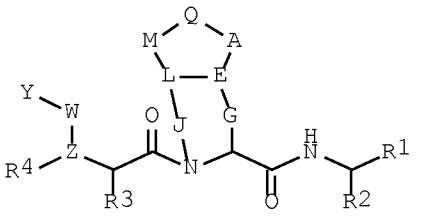

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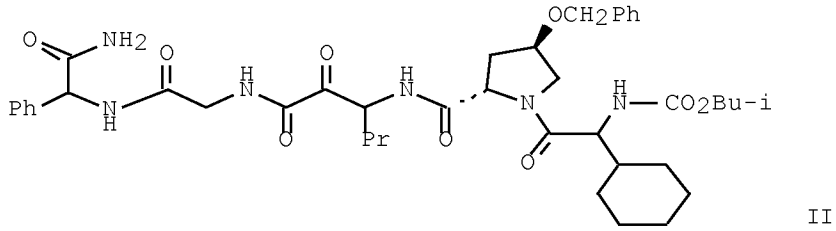


II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II was prepared by the solid-phase method and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

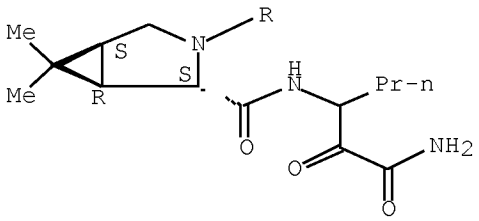
IT 394723-80-9P 394724-40-4P 394724-94-8P
394725-08-7P 394725-09-8P 394725-10-1P
395649-30-6P 395649-34-0P 395649-35-1P
395649-36-2P
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)

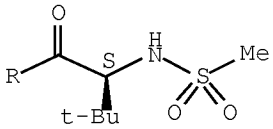
RN 394723-80-9 HCAPLUS

CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-3,3-dimethyl-2-

[(methylsulfonyl)amino]-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

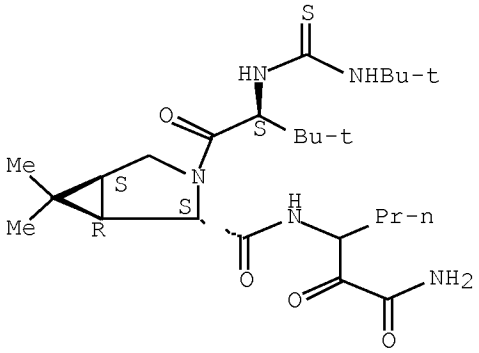
Absolute stereochemistry.





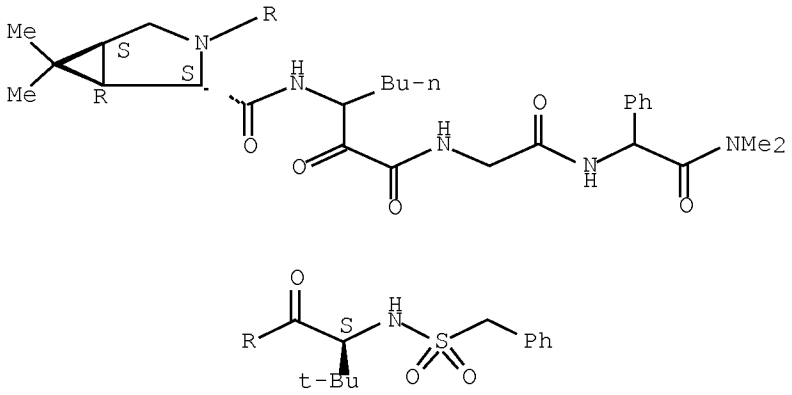
RN 394724-40-4 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]thioxomethyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



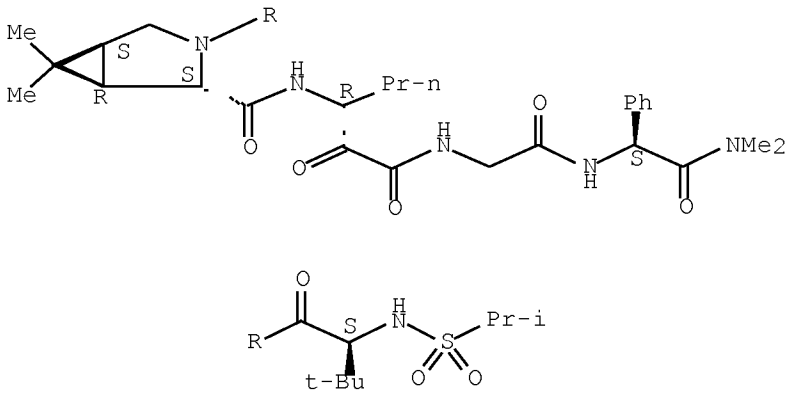
RN 394724-94-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(phenylmethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxoheptanoylglycyl-N,N-dimethyl-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



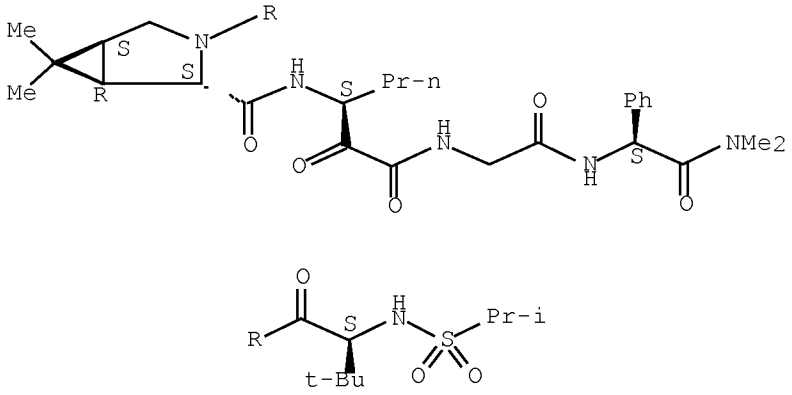
RN 394725-08-7 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3R)-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



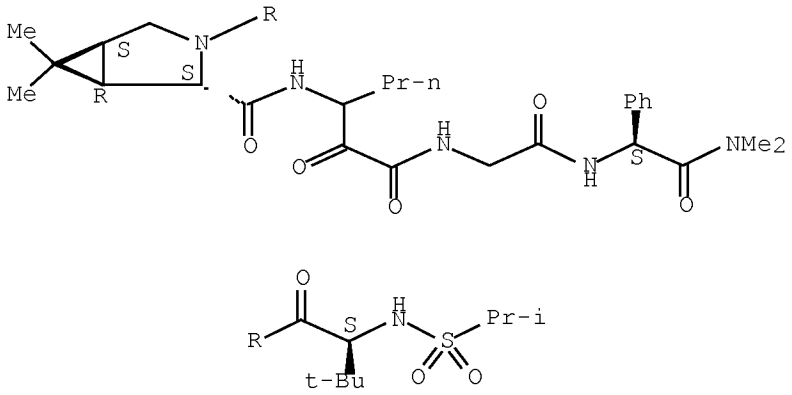
RN 394725-09-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3S)-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



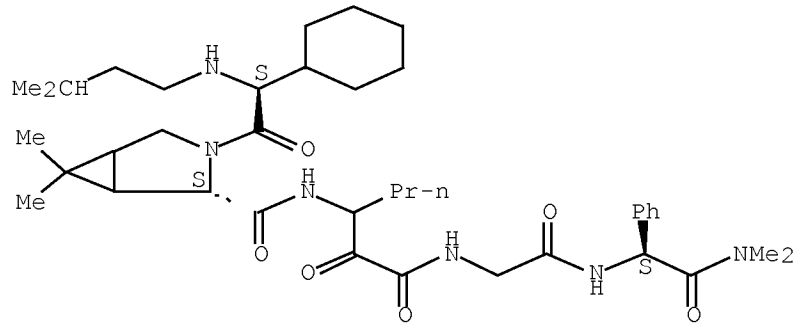
RN 394725-10-1 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



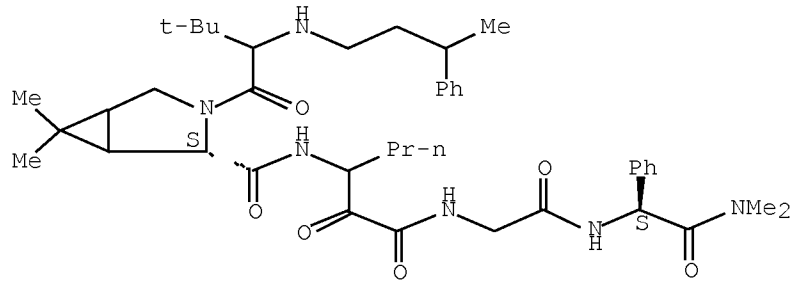
RN 395649-30-6 HCAPLUS
CN Glycinamide, (2S)-2-cyclohexyl-N-(3-methylbutyl)glycyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



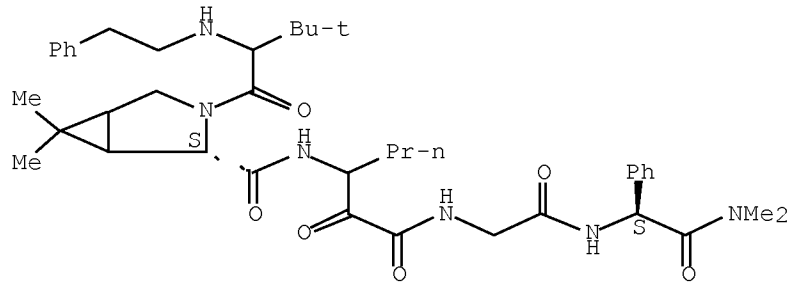
RN 395649-34-0 HCAPLUS
CN Glycinamide, 3-methyl-N-(3-phenylbutyl)valyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



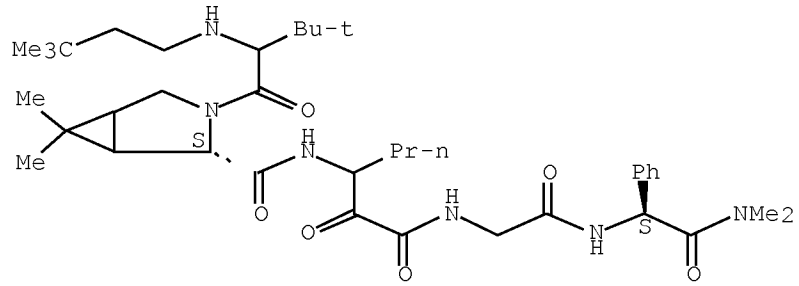
RN 395649-35-1 HCAPLUS
CN Glycinamide, 3-methyl-N-(2-phenylethyl)valyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



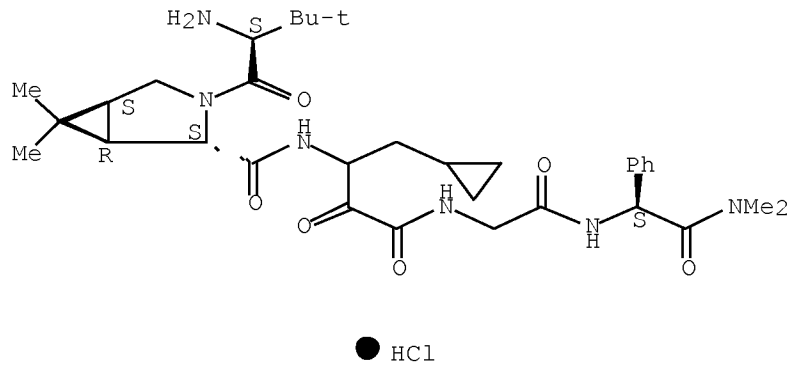
RN 395649-36-2 HCAPLUS
CN Glycinamide, N-(3,3-dimethylbutyl)-3-methylvalyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 394735-46-7P 394735-49-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus)
RN 394735-46-7 HCAPLUS
CN Glycinamide, 3-methyl-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-β-amino-α-oxocyclopropanebutanoylglycyl-N,N-dimethyl-2-phenyl-, monohydrochloride, (2S)- (CA INDEX NAME)

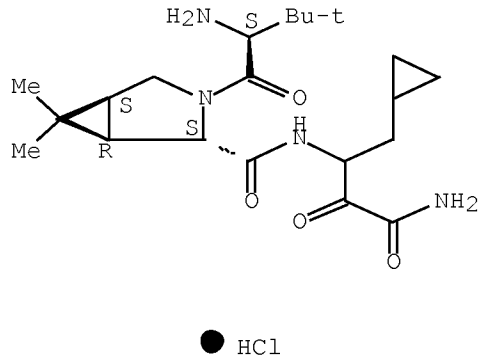
Absolute stereochemistry.



● HCl

RN 394735-49-0 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[3-amino-1-(cyclopropylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



● HCl

OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 73 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2003:591204 HCAPLUS Full-text
DOCUMENT NUMBER: 139:149928
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhn, Viyyoor M.; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; McCormick,

Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, George F.; Arasappan, Ashok; Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Wong, Jesse K.; Nair, Latha G.

PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.; Dendreon Corp.

SOURCE: PCT Int. Appl., 633 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062265	A2	20030731	WO 2003-US1430	20030116
WO 2003062265	A3	20040916		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
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IN 2004CN01564	A	20060224	IN 2004-CN1564	20040715
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PRIORITY APPLN. INFO.:

US 2002-52386	A	20020118
US 2000-220108P	P	20000721
US 2001-908955	A2	20010719
WO 2003-US1430	W	20030116

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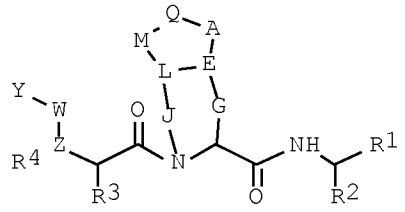
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 139:149928
ED Entered STN: 01 Aug 2003
GI



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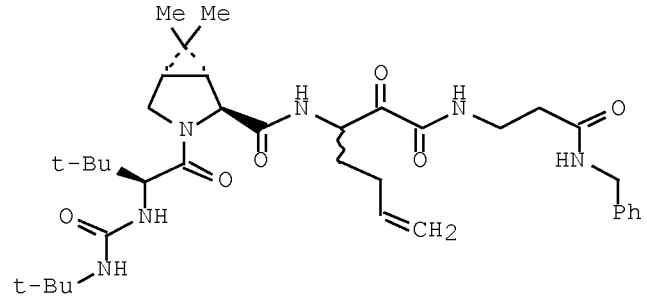


II

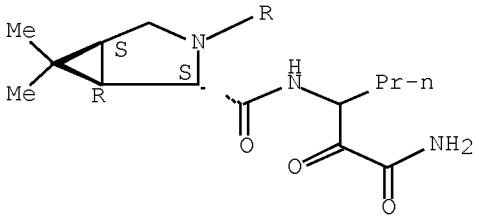
AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II was prepared and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

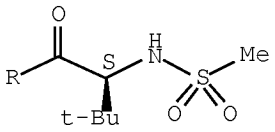
IT 394723-80-9P 394724-40-4P 394724-94-8P
394725-08-7P 394725-09-8P 394725-10-1P
394726-65-9P 394726-95-5P 394727-13-0P
394727-14-1P 394727-15-2P 394727-18-5P
394727-36-7P 394727-38-9P 395649-30-6P

395649-34-0P 395649-35-1P 395649-36-2P
395652-00-3P
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)

RN 394723-80-9 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-3,3-dimethyl-2-[(methylsulfonyl)amino]-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

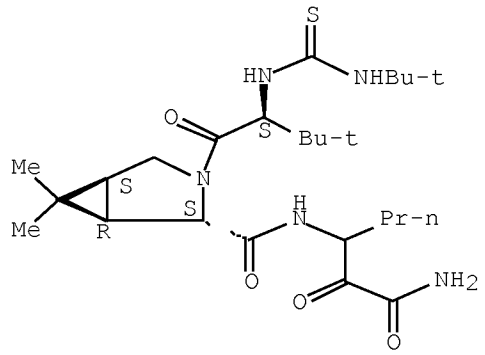
Absolute stereochemistry.





RN 394724-40-4 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]thioxomethyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

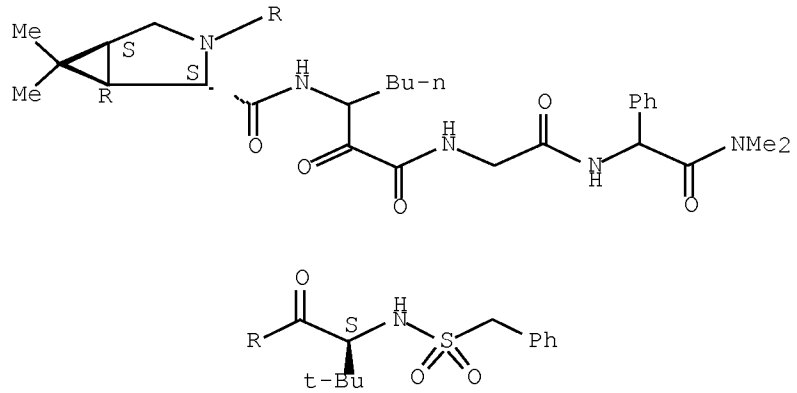
Absolute stereochemistry.



RN 394724-94-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(phenylmethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-

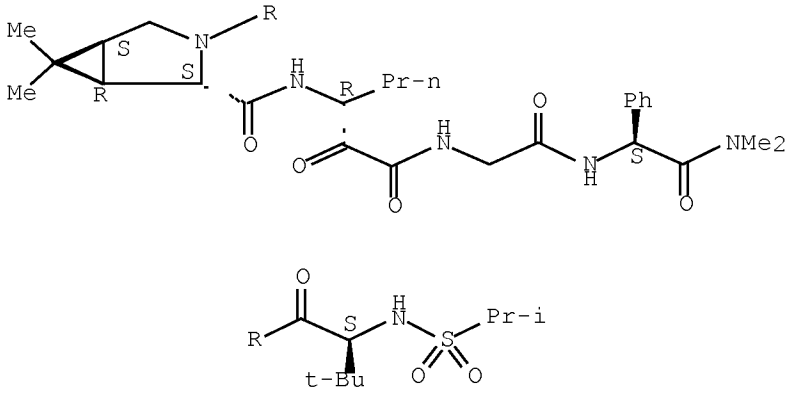
dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxoheptanoylglycyl-
N,N-dimethyl-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



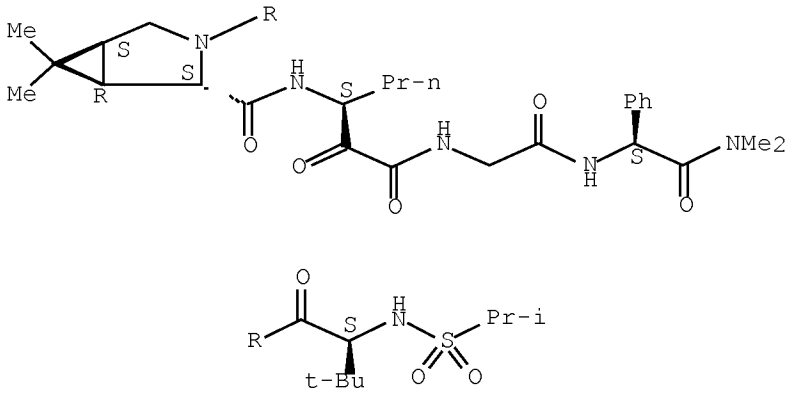
RN 394725-08-7 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-
dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3R)-3-amino-2-
oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 394725-09-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3S)-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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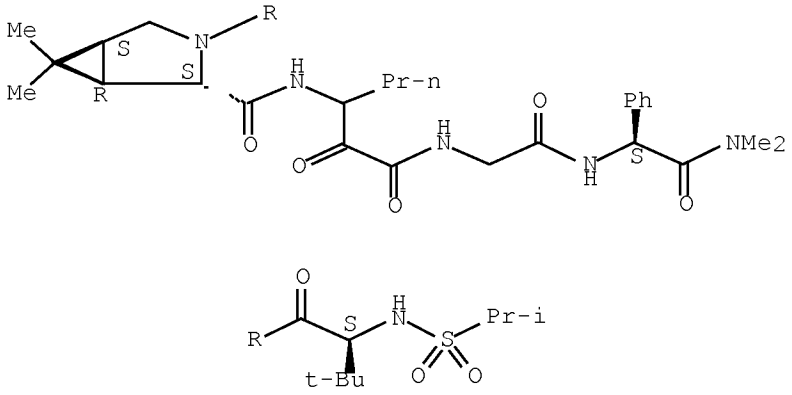
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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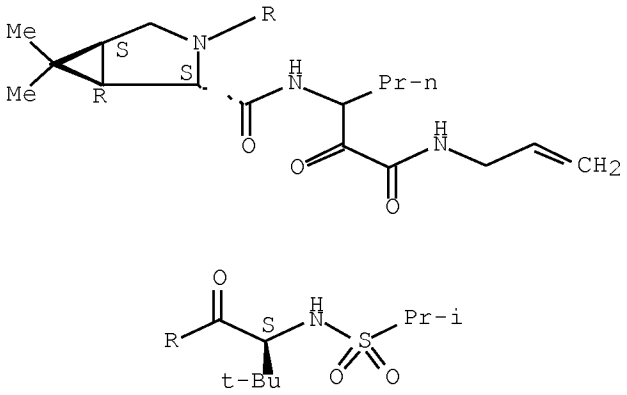
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, 3-[(2S)-3,3-dimethyl-2-[[(1-methylethyl)sulfonyl]amino]-1-oxobutyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]butyl]-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



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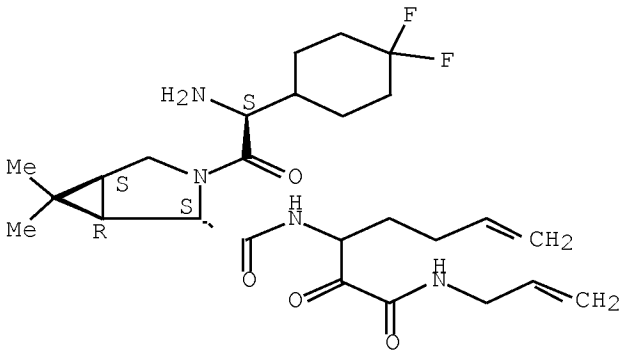
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

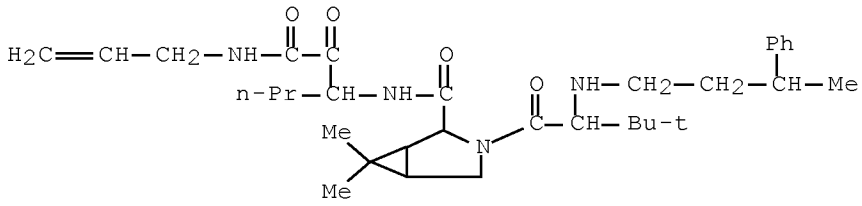
3-[(2S)-2-amino-2-(4,4-difluorocyclohexyl)acetyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]-4-penten-1-yl]-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



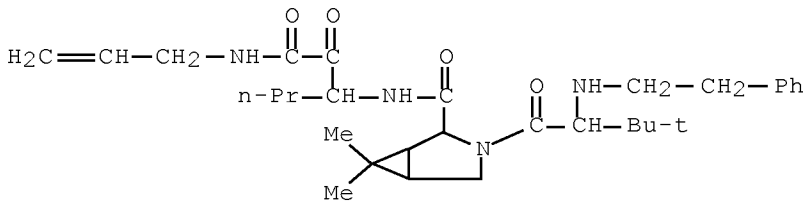
RN 394727-13-0 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

3-[3,3-dimethyl-1-oxo-2-[(3-phenylbutyl)amino]butyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]butyl]- (CA INDEX NAME)



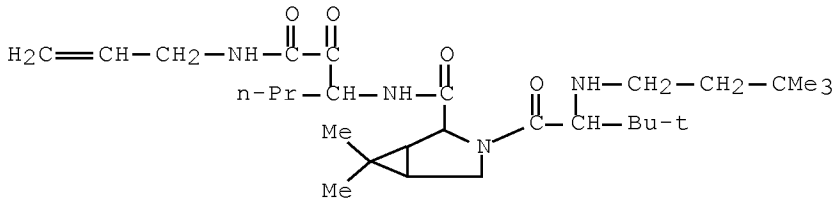
RN 394727-14-1 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

3-[3,3-dimethyl-1-oxo-2-[(2-phenylethyl)amino]butyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]butyl]- (CA INDEX NAME)



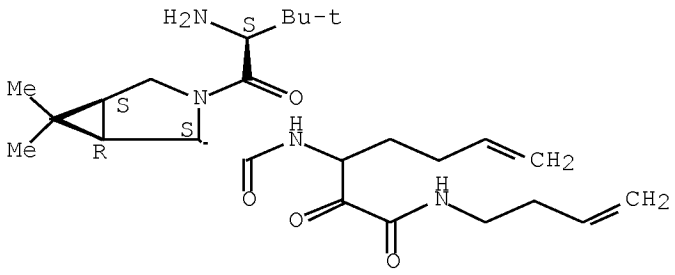
RN 394727-15-2 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

3-[2-[(3,3-dimethylbutyl)amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]butyl]- (CA INDEX NAME)

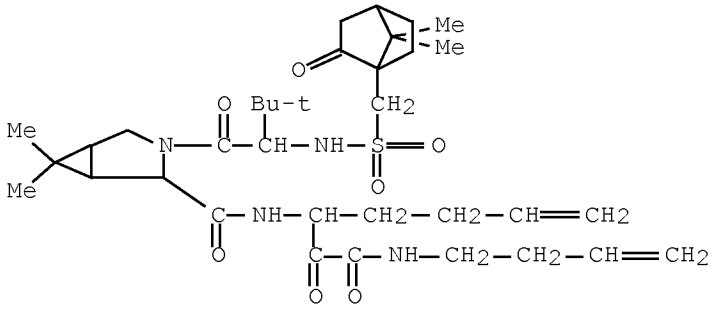


RN 394727-18-5 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-N-[1-[2-(3-buten-1-ylamino)-2-oxoacetyl]-4-penten-1-yl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

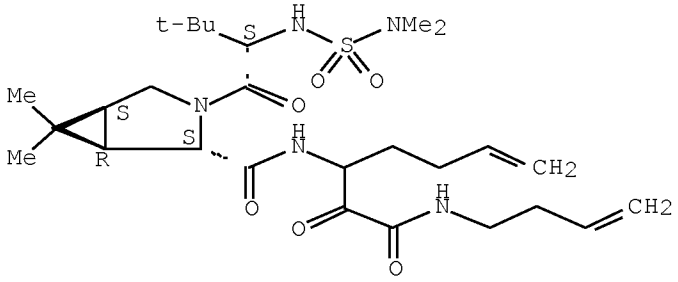


RN 394727-36-7 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[1-[2-(3-buten-1-ylamino)-2-oxoacetyl]-4-penten-1-yl]-3-[(2S)-2-[[[[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl]sulfonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)



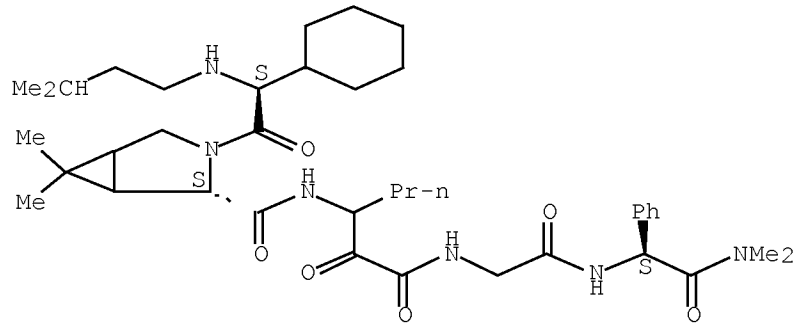
RN 394727-38-9 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-[2-(3-buten-1-ylamino)-2-oxoacetyl]-4-penten-1-yl]-3-[(2S)-2-[[(dimethylamino)sulfonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



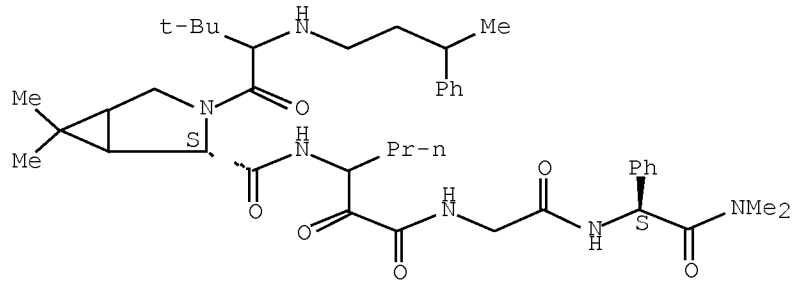
RN 395649-30-6 HCAPLUS
CN Glycinamide, (2S)-2-cyclohexyl-N-(3-methylbutyl)glycyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



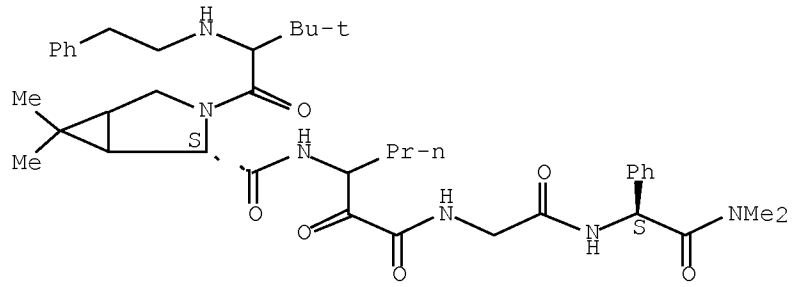
RN 395649-34-0 HCAPLUS
CN Glycinamide, 3-methyl-N-(3-phenylbutyl)valyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



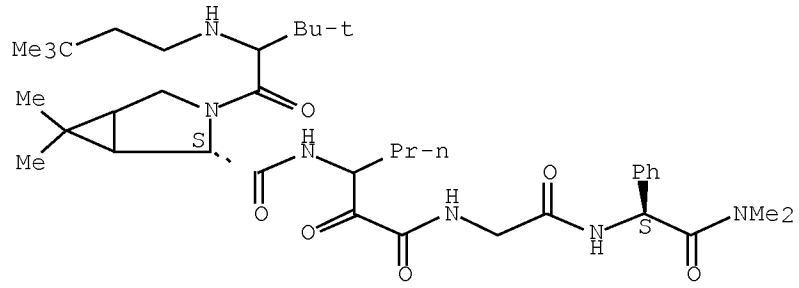
RN 395649-35-1 HCAPLUS
CN Glycinamide, 3-methyl-N-(2-phenylethyl)valyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395649-36-2 HCAPLUS
CN Glycinamide, N-(3,3-dimethylbutyl)-3-methylvalyl-(2S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

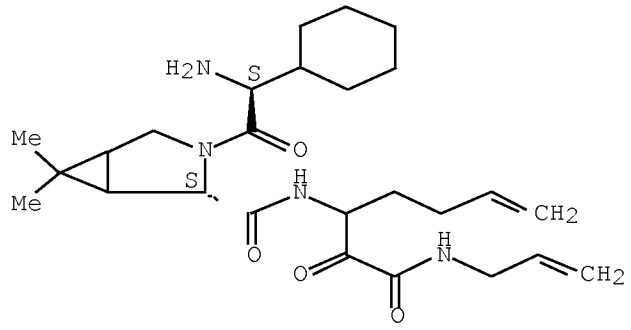
Absolute stereochemistry.



RN 395652-00-3 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

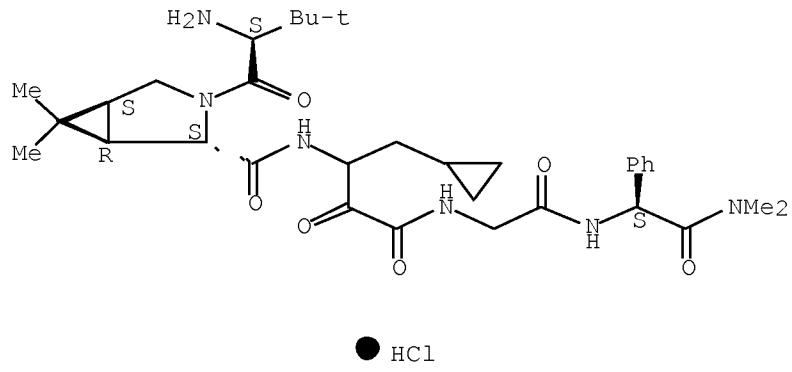
3-[(2S)-2-amino-2-cyclohexylacetyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]-4-penten-1-yl]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



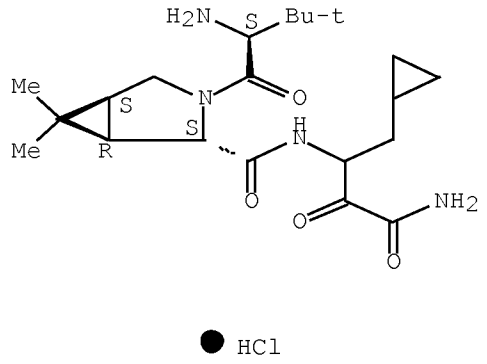
IT 394735-46-7P 394735-49-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)
RN 394735-46-7 HCAPLUS
CN Glycinamide, 3-methyl-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-β-amino-α-oxocyclopropanebutanoylglycyl-N,N-dimethyl-2-phenyl-, monohydrochloride, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



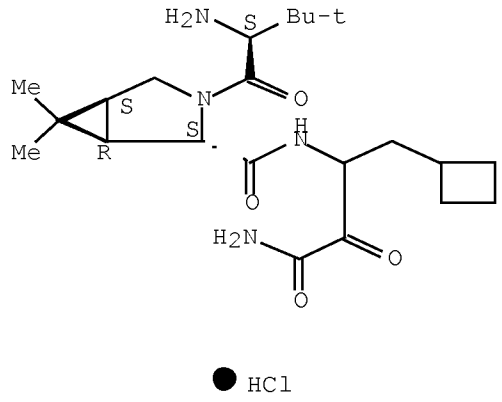
RN 394735-49-0 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[3-amino-1-(cyclopropylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 569678-63-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus)
RN 569678-63-3 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-amino-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, hydrochloride (1:1), (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

L49 ANSWER 74 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

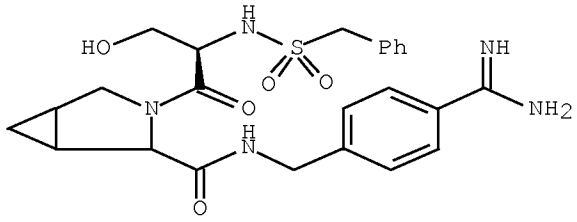
ACCESSION NUMBER: 2002:241339 HCAPLUS Full-text
DOCUMENT NUMBER: 136:263478
TITLE: Preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation
INVENTOR(S): Semple, Joseph Edward; Weinhouse, Michael I.; Levy, Odile Esther; Madison, Edwin L.; Tamiz, Amir P.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 65 pp., Cont.-in-part of U.S. Ser. No. 637,483.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020037857	A1	20020328	US 2000-733645	20001207 <--
US 6586405	B2	20030701		
AT 360028	T	20070515	AT 2000-126874	20001207 <--
ES 2285989	T3	20071201	ES 2000-126874	20001207 <--
AT 517910	T	20110815	AT 2007-6986	20001207 <--
CA 2387002	A1	20020221	CA 2001-2387002	20010810 <--
WO 2002014349	A2	20020221	WO 2001-US25337	20010810 <--
WO 2002014349	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001083347	A	20020225	AU 2001-83347	20010810 <--
AU 785260	B2	20061207		
JP 2004506648	T	20040304	JP 2002-519486	20010810 <--
NZ 518195	A	20050429	NZ 2001-518195	20010810 <--
NZ 538572	A	20060929	NZ 2001-538572	20010810 <--
NZ 547626	A	20071026	NZ 2001-547626	20010810 <--
IL 149042	A	20110131	IL 2001-149042	20010810 <--
ZA 2002002825	A	20030710	ZA 2002-2825	20020410 <--
KR 879673	B1	20090121	KR 2002-7004637	20020411 <--
AU 2006235835	A1	20061130	AU 2006-235835	20061103 <--
AU 2006235835	B2	20090625		

PRIORITY APPLN. INFO.:

US 2000-637483	A2	20000811 <--
EP 2000-126874	A	20001207 <--
US 2000-733645	A	20001207 <--
AU 2001-83347	A3	20010810
NZ 2001-518195	A1	20010810
NZ 2001-538572	A3	20010810
WO 2001-US25337	W	20010810

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 136:263478
ED Entered STN: 28 Mar 2002
GI

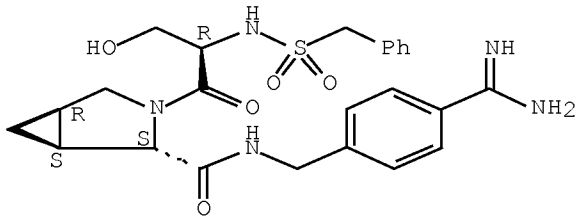


AB Peptides R1-X-NHCHR2CONR3CHR4CONHCHR7-E [X = SO2, NR'SO2 (R' = H, alkyl, aryl, aralkyl), CO, O2C, NHCO, P(O)R' (R' ≠ H), or a direct link; R1 = (un)substituted alkyl, cycloalkyl, heterocyclyl, aryl, etc.; R2 = Me, Et, CH2CH2OH or carboxylate ester derivative, etc.; R3 = H, Me; R4 is in the S configuration and is H, CH2SMe, CH2OH, CH2CN, alkyl, CH2C.tplbond.CH, CH2CH:CH2 or CH:CH2; or R3 and R4 together are in the S configuration and form a prolyl, pipecolyl, azetidine-2-carbonyl, 3- or 4-hydroxyprolyl, 3,4-methanoprolyl or 3,4-dehydroprolyl group; R7 = H or alkyl; E is an amidino- or guanidinoalkyl, -heterocyclyl or -Ph group] were prepared which have activity as non-covalent inhibitors of urokinase and activity in reducing or inhibiting blood vessel formation. These compds. are useful in vitro for monitoring plasminogen activator levels and in vivo in treatment of conditions which are ameliorated by inhibition of or decreased activity of urokinase and in treating pathol. conditions where blood vessel formation is related to a pathol. condition. Biol. test data for fifty peptides, e.g., BuSO2-D-Ser-L-Ala-NHCH2C6H4C(:NH)NH2-p, show that compds. of the invention have a high degree of specificity for the inhibition of urokinase compared to other serine proteases.

IT 400720-16-3P 400729-25-1P 400729-26-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation)

RN 400720-16-3 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

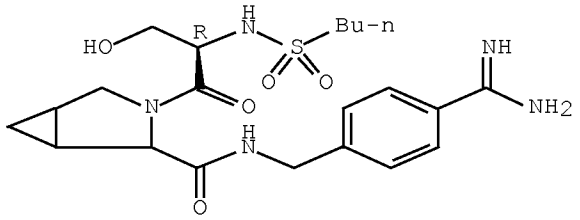
Absolute stereochemistry.



RN 400729-25-1 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

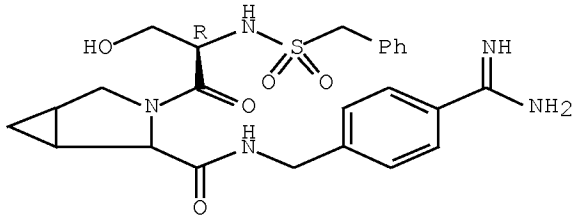
N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-2-[(butylsulfonyl)amino]-3-hydroxy-1-oxopropyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 400729-26-2 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]- (CA INDEX NAME)

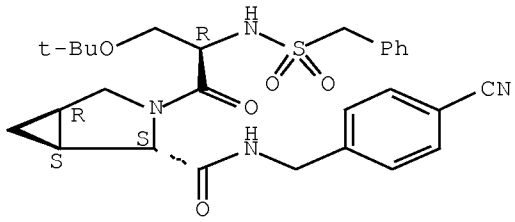
Absolute stereochemistry.



IT 400720-09-4P 400720-14-1P 400720-15-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation)

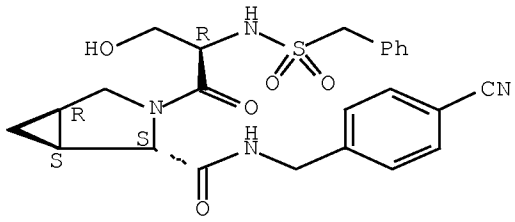
RN 400720-09-4 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[(4-cyanophenyl)methyl]-3-[(2R)-3-(1,1-dimethylethoxy)-1-oxo-2-
[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 400720-14-1 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[(4-cyanophenyl)methyl]-3-[(2R)-3-hydroxy-1-oxo-2-
[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

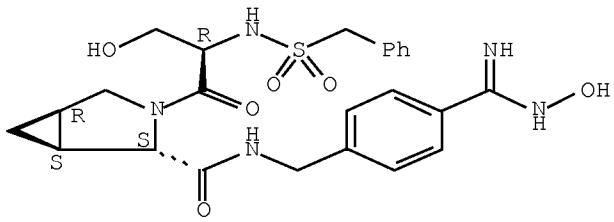
Absolute stereochemistry.



RN 400720-15-2 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

N-[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-
[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L49 ANSWER 75 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2002:142737 HCAPLUS Full-text
DOCUMENT NUMBER: 136:200480
TITLE: Preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation
INVENTOR(S): Levy, Odile Esther; Madison, Edwin L.; Semple, Joseph Edward; Tamiz, Amir P.; Weinhouse, Michael I.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014349	A2	20020221	WO 2001-US25337	20010810 <--
WO 2002014349	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1182207	A2	20020227	EP 2000-126874	20001207 <--
EP 1182207	A3	20020904		
EP 1182207	B1	20070418		
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US 20020037857	A1	20020328	US 2000-733645	20001207 <--
US 6586405	B2	20030701		
EP 1808440	A1	20070718	EP 2007-6986	20001207 <--
EP 1808440	B1	20110727		
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AU 2001083347	A	20020225	AU 2001-83347	20010810 <--
AU 785260	B2	20061207		
JP 2004506648	T	20040304	JP 2002-519486	20010810 <--
NZ 518195	A	20050429	NZ 2001-518195	20010810 <--
IL 149042	A	20110131	IL 2001-149042	20010810 <--
KR 879673	B1	20090121	KR 2002-7004637	20020411 <--
AU 2006235835	A1	20061130	AU 2006-235835	20061103 <--
AU 2006235835	B2	20090625		

PRIORITY APPLN. INFO.: US 2000-637483 A 20000811 <--

EP 2000-126874 A 20001207
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US 2000-733645 A 20001207
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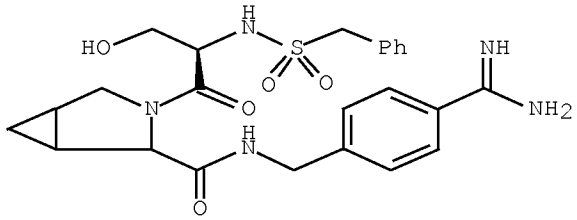
AU 2001-83347 A3 20010810
WO 2001-US25337 W 20010810
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 136:200480
ED Entered STN: 22 Feb 2002
GI



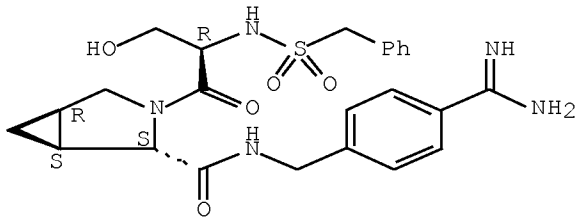
AB Peptides R1-X-NHCHR2CONR3CR4aR4bCONHCHR7-E [X = SO2, NR'SO2 (R' = H, alkyl, aryl, aralkyl), CO, O2C, NHCO, P(O)R' (R' ≠ H), or a direct link; R1 = (un)substituted alkyl, cycloalkyl, heterocyclyl, aryl, etc.; R2 = Me, Et, CH2CH2OH or carboxylate ester derivative, etc.; R3 = H, Me or forms a cyclic group with R4a or R4b; R4a is in the S configuration and is H, CH2SMe, CH2OH, CH2CN, alkyl, CH2C.tplbond.CH, CH2CH:CH2 or CH:CH2 and R4b is H; R4a, R4b = alkyl; R4a and R4b together are (CH2)k (k is 5 or 6) to give a spirocycloalkyl group; R3 and R4a together form a prolyl, pipecolyl, azetidine-2-carbonyl, 3- or 4-hydroxyprolyl, 4-aminoprolyl, 4-(aminomethyl)prolyl, 3,4-methanoprolyl or 3,4-dehydroprolyl group and R4b is H; R7 = H or alkyl; E is an amino-, amidino-, or guanidinoalkyl, -heterocyclyl or -Ph group] were prepared which have activity as non-covalent inhibitors of urokinase and activity in reducing or inhibiting blood vessel formation. These compds. are useful in vitro for monitoring plasminogen activator levels and in vivo in treatment of conditions which are ameliorated by inhibition of or decreased activity of urokinase and in treating pathol. conditions wherein blood vessel formation is related to a pathol. condition. Biol. test data for sixty-six peptides, e.g., BuSO2-D-Ser-L-Ala-NHCH2C6H4C(:NH)NH2-p, show that compds. of the invention have a high degree of specificity for the inhibition of urokinase compared to other serine proteases.

IT 400720-16-3P 400729-25-1P 400729-26-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation)

RN 400720-16-3 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-

[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



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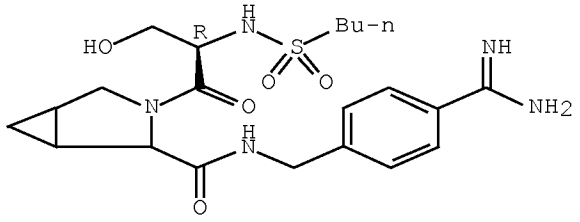
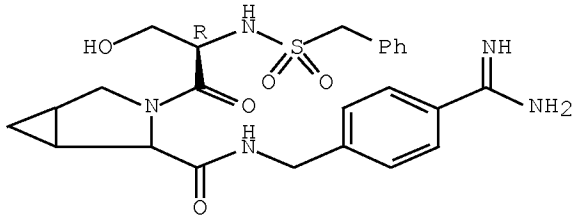
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-2-[(butylsulfonyl)amino]-3-hydroxy-1-oxopropyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 400729-26-2 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[[4-(aminoiminomethyl)phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]- (CA INDEX NAME)

Absolute stereochemistry.

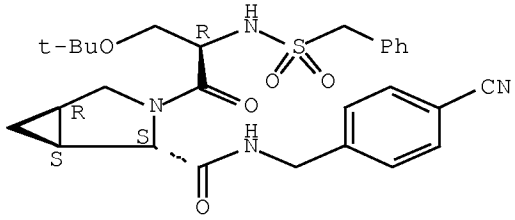


IT 400720-09-4P 400720-14-1P 400720-15-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as non-covalent inhibitors of urokinase and blood vessel formation)

RN 400720-09-4 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[(4-cyanophenyl)methyl]-3-[(2R)-3-(1,1-dimethylethoxy)-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



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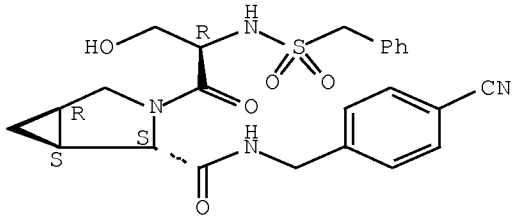
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[(4-cyanophenyl)methyl]-3-[(2R)-3-hydroxy-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

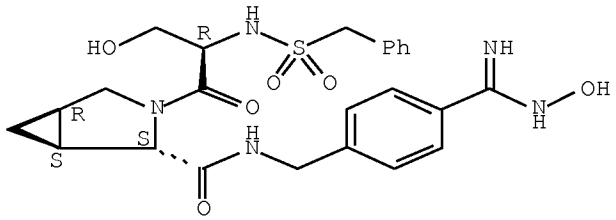
Absolute stereochemistry.



RN 400720-15-2 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,

N-[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]-3-[(2R)-3-hydroxy-1-oxo-2-[[(phenylmethyl)sulfonyl]amino]propyl]-, (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 76 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2002:90062 HCAPLUS Full-text
DOCUMENT NUMBER: 136:167698
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal N.; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 536 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008244	A2	20020131	WO 2001-US22678	20010719 <--
WO 2002008244	A3	20030619		
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     EP 1385870           B1    20100317
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PRIORITY APPLN. INFO.:                      US 2000-220108P     P  20000721 <--
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OTHER SOURCE(S):         MARPAT 136:167698
ED   Entered STN:  01 Feb 2002
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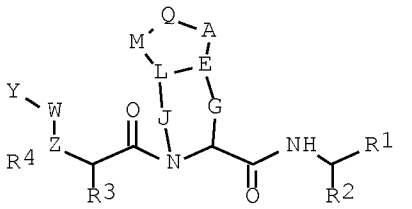

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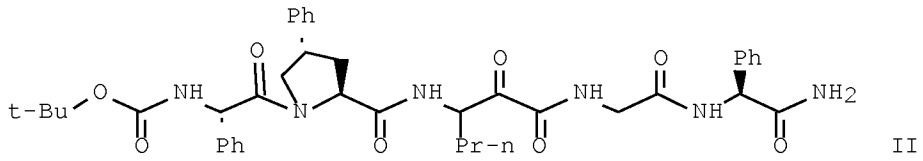


II

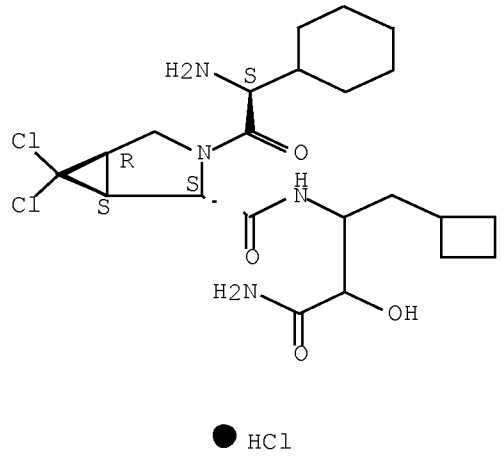
AB Peptides I were prepared wherein Y is alkyl, alkyl-aryl, heteroaryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy,, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino; R1 is acyl, borate; Z is selected from O, N, CH or CR; W, Q, G, J, L, M independently maybe present or absent; W is C=O, C=S, C(=N-CN), or SO; Q is CH, N, P, alkylidene, O, amine,S, or SO; A is O, CH, alkylidene, amine, S, SO or bond; E is CH, N, alkylidene, or double bond; G is alkylidene; J is alkylidene, SO, NH, NR, O; L is CH, alkylidene, O, S or NR; M is O, NR,S, SO, alkylidene; p is 0 to 6; and R-R4 are independently selected from the group consisting of H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus peptide II was prepared and tested as antiviral agent and NS3-serine protease inhibitors of hepatitis C virus with Ki ranges in category A = 1-100 nM; category B = 101-1,000 nM; category C > 1000 nM. Also disclosed is the use of I for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

IT 1070163-68-6
RL: PRPH (Prophetic)
(Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 1070163-68-6 HCAPLUS

CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide,
N-[3-amino-1-(cyclobutylmethyl)-2-hydroxy-3-oxopropyl]-3-[(2S)-2-amino-2-cyclohexylacetyl]-6,6-dichloro-, hydrochloride (1:1), (1S,2S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



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394727-14-1P 394727-15-2P 394727-18-5P
394727-36-7P 394727-38-9P 395649-30-6P
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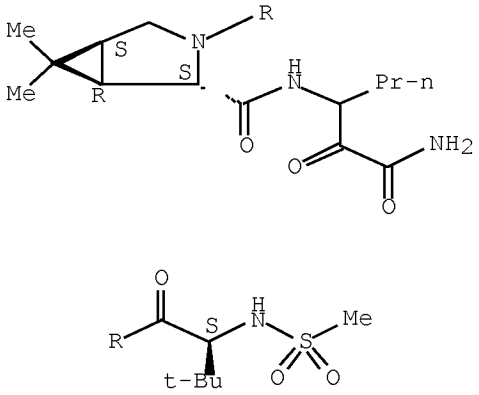
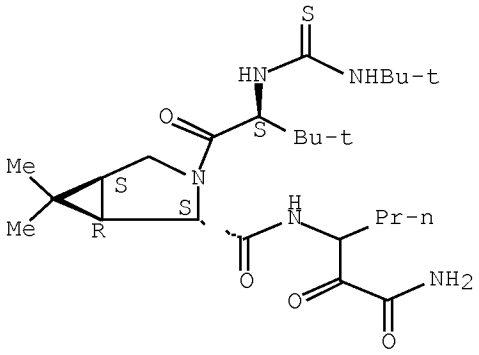
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as NS3-serine protease inhibitors of hepatitis C
virus)
RN 394723-80-9 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-3,3-dimethyl-2-[(methylsulfonyl)amino]-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



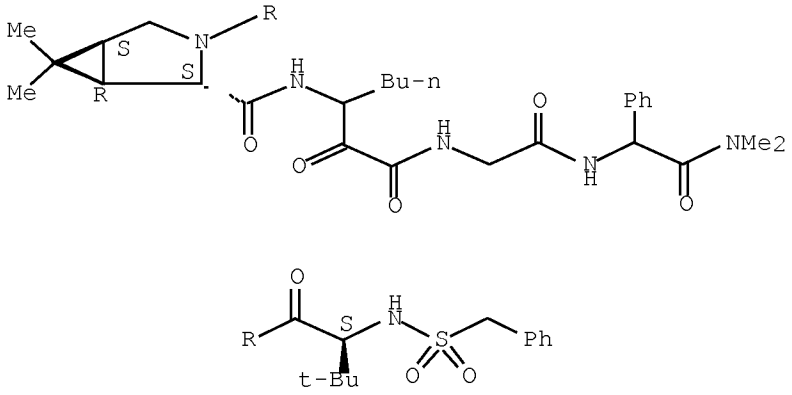
RN 394724-40-4 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[1-(2-amino-2-oxoacetyl)butyl]-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]thioxomethyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 394724-94-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(phenylmethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxoheptanoylglycyl-N,N-dimethyl-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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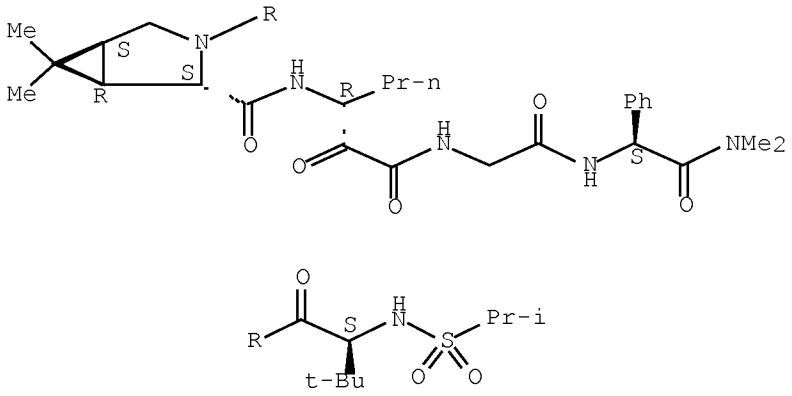
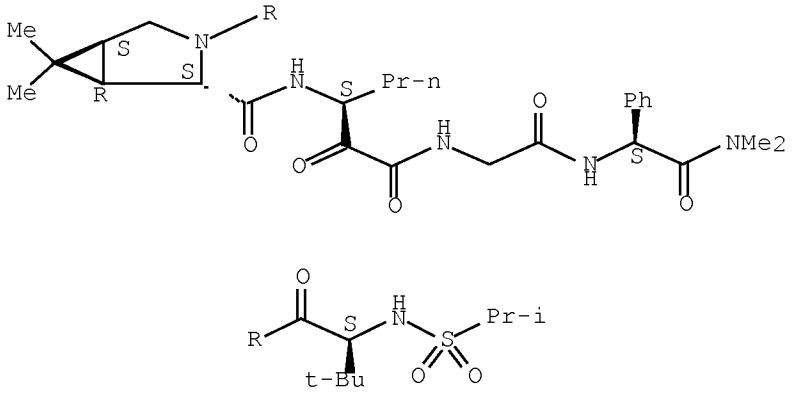
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3R)-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



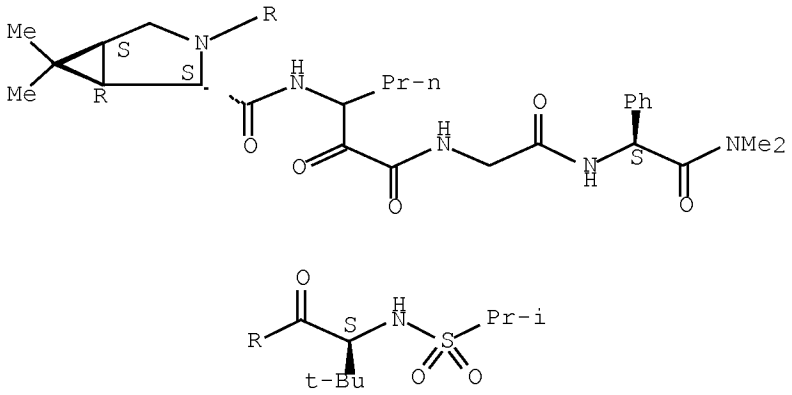
RN 394725-09-8 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-(3S)-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 394725-10-1 HCAPLUS
CN Glycinamide, 3-methyl-N-[(1-methylethyl)sulfonyl]-L-valyl-(1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl-3-amino-2-oxohexanoylglycyl-N,N-dimethyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 394726-65-9 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexane-2-carboxamide, 3-[(2S)-3,3-dimethyl-2-[[(1-methylethyl)sulfonyl]amino]-1-oxobutyl]-6,6-dimethyl-N-[1-[2-oxo-2-(2-propen-1-ylamino)acetyl]butyl]-, (1R,2S,5S)- (CA INDEX NAME)

Absolute stereochemistry.