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

(75) Inventors: **Jeffrey A. Robl**, Newtown, PA (US); **Richard B. Sulsky**, Pennington, NJ (US); **David J. Augeri**, Princeton, NJ (US); **David R. Magnin**, Sumter, SC (US); **Lawrence G. Hamann**, Cambridge, MA (US); **David A. Betebenner**, Lawrenceville, NJ (US)

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

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(51) **Int. Cl.**
C07D 209/02 (2006.01)
A61K 31/403 (2006.01)

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

(58) **Field of Classification Search** 514/412; 548/452
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,325,478	A	6/1967	Hermann et al.
3,906,044	A	9/1975	Aigami et al.
4,254,057	A	3/1981	Day et al.
4,255,334	A	3/1981	Day et al.
4,379,785	A	4/1983	Weyer et al.
5,462,928	A	10/1995	Bachovchin et al.
5,561,146	A	10/1996	Kim et al.
5,939,560	A	8/1999	Jenkins et al.
5,998,463	A	12/1999	Hulin et al.
6,011,155	A	1/2000	Villhauer
6,060,432	A	5/2000	Adams et al.
6,110,949	A	8/2000	Villhauer
6,166,063	A	12/2000	Villhauer
6,297,233	B1	10/2001	Stein et al.
6,555,542	B1	4/2003	O'Connor et al.
6,803,357	B1	10/2004	Bachovchin et al.
6,890,898	B2	5/2005	Bachovchin et al.
7,078,381	B2	7/2006	Bachovchin et al.
7,205,432	B2	4/2007	Berner et al.
7,250,529	B2	7/2007	Williams
2006/0287317	A1	12/2006	Smith et al.

FOREIGN PATENT DOCUMENTS

DE	2449840		4/1975
DE	2521895		4/1976
DE	33 24 263	A1	1/1985
DE	39 26 606	A1	2/1991
EP	0 007 652	A1	2/1980
EP	0 219 782	A2	4/1987
EP	0686642		12/1995
EP	1050540	A2	11/2000
WO	WO 97/15576		5/1997
WO	WO 99/26659		6/1999
WO	WO 99/38501		8/1999
WO	WO 99/47545		9/1999
WO	WO 99/67279		12/1999
WO	WO 00/10549		3/2000
WO	WO 034241	A1	6/2000
WO	WO 00/47207		8/2000
WO	WO 00/53171		9/2000
WO	WO 00/56296		9/2000
WO	WO 00/56297		9/2000
WO	WO 00/69868		11/2000
WO	WO 97/40832		11/2001
WO	WO 02/060894		8/2002

OTHER PUBLICATIONS

Hermann Stetter and Elli Rauscher, Zur Kenntnis der Adamantan-carbonsaure-(1) Chemische Berichte, 1960, vol. 93, No. 5, pp. 1161-1166.

Von R. Hiltmann et al., "2-Acylaminopyridin-Derivate mit morphinagonistischer und antagonisterischer Wirksamkeit, Arzneimittel-Forschung," 1974, vol. 24, No. 4a, pp. 584-600.

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.

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.

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.

Hiltmann, Arzneim.-Forsch. 24 (4) 548-600 1974 Abstract only.*

Lin, J. et al, Proc. Natl. Acad. Sci, USA, vol. 95, pp. 14020-14024, Nov. 1998.

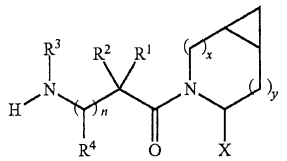
(Continued)

Primary Examiner — Gregg Polansky

(74) *Attorney, Agent, or Firm* — Woodcock Washburn LLP

(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.

41 Claims, No Drawings

OTHER PUBLICATIONS

Augustyns, KJL et al, Eur. J. Med. Chem. 32, 301-309, (1997).
Hughes, T.E. et al, Biochemistry, 28, 11597-11603, 19993.
Yamada, M. et al, Bioorganic & Medicinal Chemistry Letters 8, 1537-1540 (1998).
Tanaka, S. et al, Immunopharmacology 40, 21-26 (1998).
Li, J. et al, Archives of Biochemistry and Biophysics, vol. 323, No. 1, pp. 148-154, Oct. 20, 1995.
Ashworth, D.M. et al, Bioorganic & Medicinal Chemistry Letter, vol. 6, No. 22, pp. 2745-2748, 1996.
Yamada, M. et al, Bioorganic & Medicinal Chemistry Letter 8, 1537-1540 (1998).
Ashworth, D.M. et al, Bioorganic & Medicinal Chemistry Letter, vol. 6, No. 10, pp. 1163-1166, 1996.
Lambeir, A.-M., et al, Biochimica et Biophysica Acts, 1290, pp. 76-82 (1996).
Yoshimoto, T. et al, Agric. Biol. Chem., 55(4), pp. 1135-1136, 1991.
Belyaev, A. et al, J. Med. Chem., 42, 1041-1052, 1999.
Stockel, A. et al, Peptides: Chemistry, Structure and Biology, pp. 709-710, 1996.
Asai, Y. et al, The Journal of Antibiotics, vol. 50, No. 8, pp. 653-657, Aug. 1997.
Demuth, H.-U. et al, FEBS Letters, vol. 320, No. 1, pp. 23-27, Mar. 1993.
Ohnuki, T. et al, Drugs of the Future, 24(6):665-670, 1999.
Demuth, H.-U. et al, Diabetes, 2000, vol. 49, suppl. 1,A102.
Rotherberg, P. et al, Diabetes, 2000, vol. 49, Suppl. 1, A39.
Sagnard, I. et al, Tetrahedron Letters, vol. 36, No. 18, pp. 3149-3152, 1995.
Tverezovsky, V. V. et al., Tetrahedron, vol. 53, No. 43, pp. 14773-14792, 1997.
Hanessian, S. et al, Bioorganic & Medicinal Chem. Letters, vol. 8, No. 16, pp. 2123-2128, Aug. 18, 1998.

* cited by examiner

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

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

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

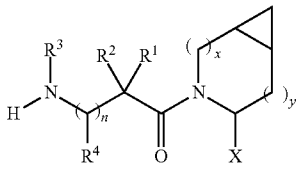
Depeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous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

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);

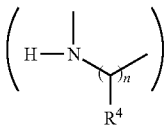
n is 0 or 1;

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;

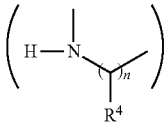
and R^1 and R^3 may optionally be taken together to form —$(CR^5R^6)_m$— where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, 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, alkyl-

loxycarbonyl, 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

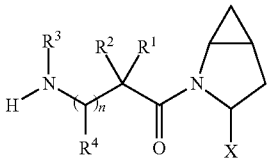


form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

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



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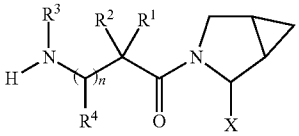


In addition, in accordance with the present invention, a method is provided for treating diabetes, especially Type II diabetes, as well as impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, 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 inflam-

pound 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.

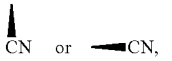
The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than DP4 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-modulating agents (including anti-atherosclerosis agents), and/or one or more infertility agents,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

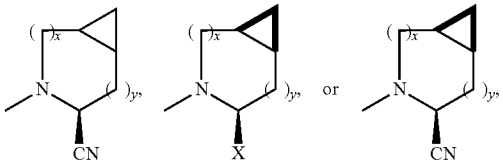
Preferred are compounds of formula I wherein R^3 is H or alkyl, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcyclo alkyl, hydroxyalkyl, hydroxytricyclo alkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxyalkylcycloalkyl, R^2 is H or alkyl, n is 0, X is CN, x is 0 or 1 and y is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

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



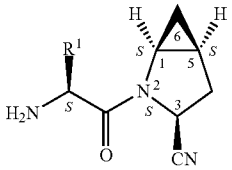
and/or wherein the fused cyclopropyl group is identified as

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



Particularly preferred are the following compounds:

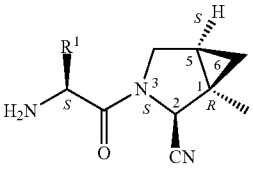
A)



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

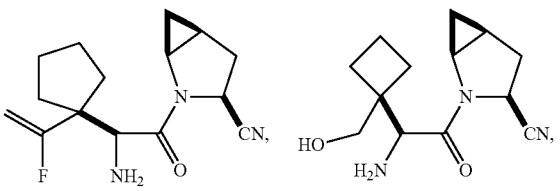
wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl or hydroxytricycloalkyl;

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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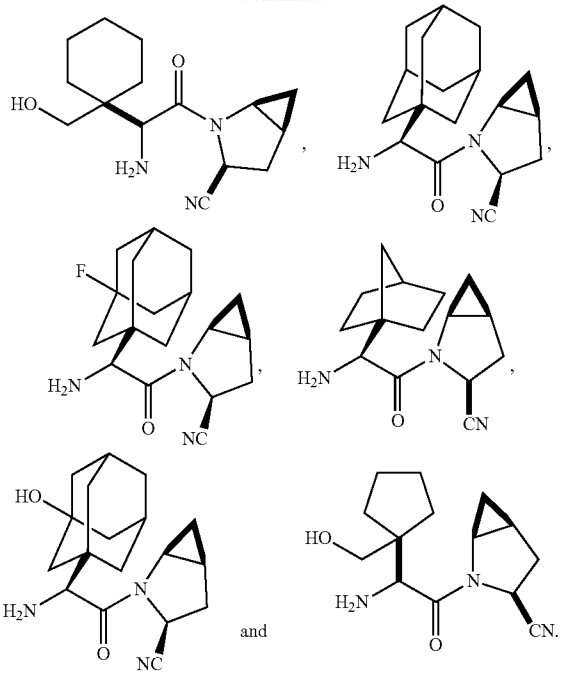

and

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-BuCOCOCl/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-BuOCOCl/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

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