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(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**(75) Inventors: **Jeffrey A. Robl**, Newtown, PA (US);  
**Richard B. Sulsky**, West Trenton, NJ  
(US); **David J. Augeri**, Princeton, NJ  
(US); **David R. Magnin**, Hamilton, NJ  
(US); **Lawrence G. Hamann**, Cherry  
Hill, NJ (US); **David A. Betebenner**,  
Lawrenceville, NJ (US)(73) Assignee: **Bristol-Myers Squibb Company**,  
Princeton, NJ (US)(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.(21) Appl. No.: **09/788,173**(22) Filed: **Feb. 16, 2001****Related U.S. Application Data**(60) Provisional application No. 60/188,555, filed on Mar. 10,  
2000.(51) **Int. Cl.<sup>7</sup>** ..... **C07D 209/07**; A61K 31/403(52) **U.S. Cl.** ..... **514/412**; 548/452(58) **Field of Search** ..... 548/452; 514/412(56) **References Cited****U.S. PATENT DOCUMENTS**

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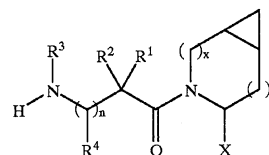
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*Primary Examiner*—Robert Gerstl(74) *Attorney, Agent, or Firm*—Burton Rodney(57) **ABSTRACT**Dipeptidyl peptidase IV (DP 4) inhibiting compounds are  
provided having the formula

where

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

x=1 when y=0 and x=0 when y=1);

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

and wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> 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 combi-  
nation of such DP 4 inhibitor and one or more of another  
antidiabetic agent such as metformin, glyburide, troglita-  
zone, 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**

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**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**

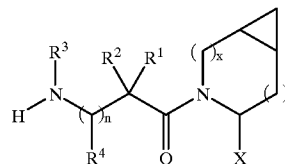
Dipeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous 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 ( $t_{1/2} \approx 1.5$  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

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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);

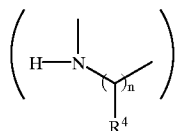
n is 0 or 1;

X is H or CN (that is cyano);

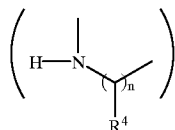
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and are independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, 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, alkoxy carbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroaryl amino, aryl amino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxy carbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxy carbonylamino, alkylsulfonyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

and R<sup>1</sup> and R<sup>3</sup> may optionally be taken together to form  $-(CR^5R^6)_m-$  where m is 2 to 6, and R<sup>5</sup> and R<sup>6</sup> 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, alkoxy carbonylamino, aryloxy carbonylamino, alkoxy carbonyl, aryloxy carbonyl, or alkylaminocarbonylamino, or R<sup>1</sup> and R<sup>4</sup> may optionally be taken together to form  $-(CR^7R^8)_p-$  where p is 2 to 6, and R<sup>7</sup> and R<sup>8</sup> 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, alkoxy carbonylamino, aryloxy carbonylamino, alkoxy carbonyl, aryloxy carbonyl, or alkylaminocarbonylamino, or optionally R<sup>1</sup> and R<sup>3</sup> together with

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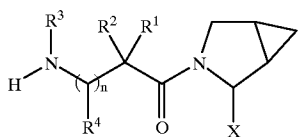
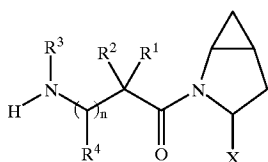


form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO<sub>2</sub>; or optionally R<sup>1</sup> and R<sup>3</sup> together with



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



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 erythematosus 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

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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.

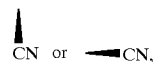
The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than DP4 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-modulating agents (including anti-atherosclerosis agents), and/or one or more infertility agents, 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<sup>3</sup> is H or alkyl, R<sup>1</sup> is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxytricycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxyalkylcycloalkyl, R<sup>2</sup> 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

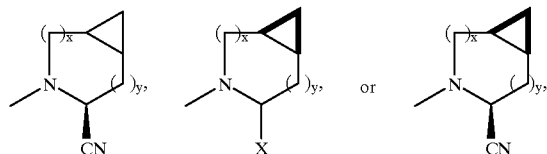


and/or wherein the fused cyclopropyl group is identified as



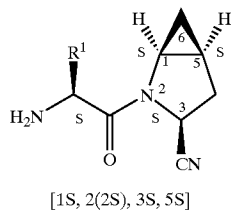
Thus, preferred compounds of formula I of the invention will include the moiety:

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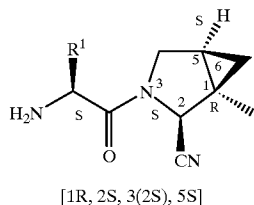
Particularly preferred are the following compounds:

A)

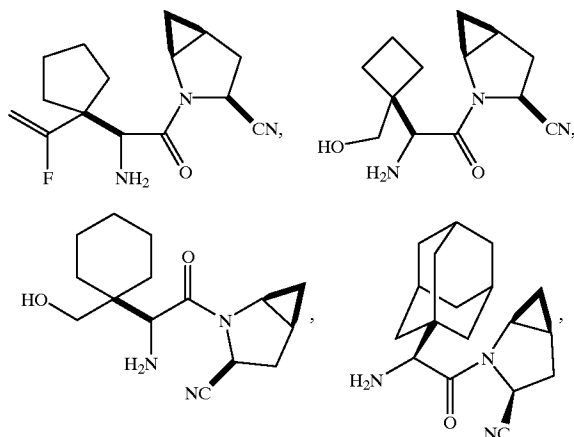


wherein R<sup>1</sup> is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl or hydroxytricycloalkyl;

B)

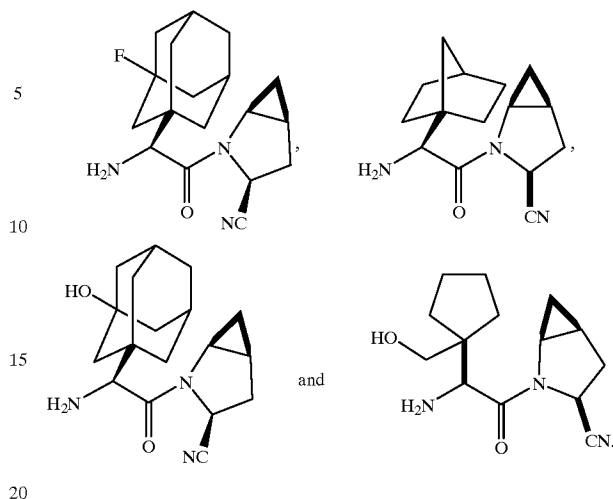


wherein R<sup>1</sup> is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl or hydroxyalkylcycloalkyl as well as the following:



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-continued



### DETAILED DESCRIPTION OF THE INVENTION

25 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<sub>1</sub> is a common amine protecting group such as Boc, Cbz, or Fmoc and X<sup>1</sup> is H or CO<sub>2</sub>R<sup>9</sup> 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<sub>1</sub> group by conventional methods (e.g. (1) TFA or HCl when PG<sub>1</sub> is Boc, or (2) H<sub>2</sub>/Pd/C, TMSI when PG<sub>1</sub> is Cbz, or (3) Et<sub>2</sub>NH when PG<sub>1</sub> is (Fmoc) affords the free amine 2. Amine 2 may be coupled to various protected amino acids such as 3 (where PG<sub>2</sub> can be any of the PG<sub>1</sub> 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<sub>2</sub> provides compound 1a of the invention where X=H.

50 In the case where X<sup>1</sup>=CO<sub>2</sub>R<sup>9</sup> (where R<sup>9</sup> 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*-BuCOCOC1/TEA or EDAC) followed by treatment with NH<sub>3</sub> 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<sub>3</sub>/pyridine/imidazole or cyanuric chloride/DMF or trifluoroacetic anhydride, THF, pyridine) to give 7. Finally, removal of the PG<sub>2</sub> protecting group similar to above provides compound of the invention Ib.

65 In a different sequence (Scheme 2), compound 1 where X<sup>1</sup> is CO<sub>2</sub>R<sup>9</sup> may be saponified to the acid and subsequently

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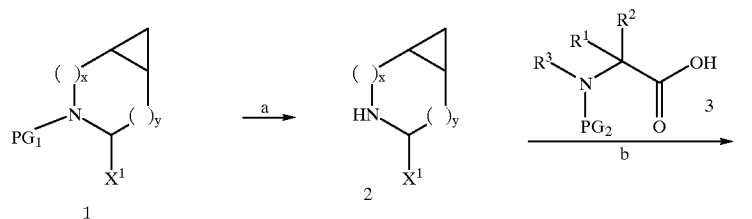
amidated as described above to give amide 8. Removal of the PG<sub>1</sub> group followed by peptide coupling to 3 affords compound 6, an intermediate in the synthesis of Ib.

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 inter-

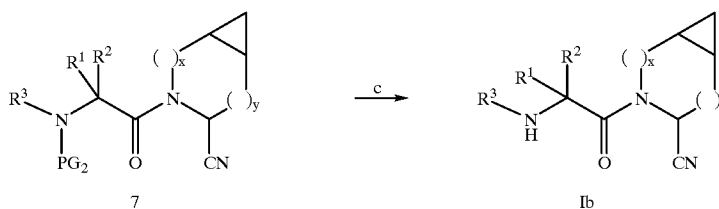
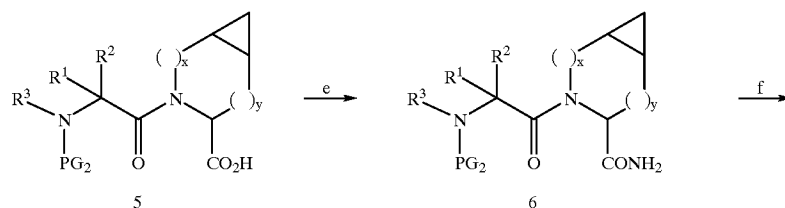
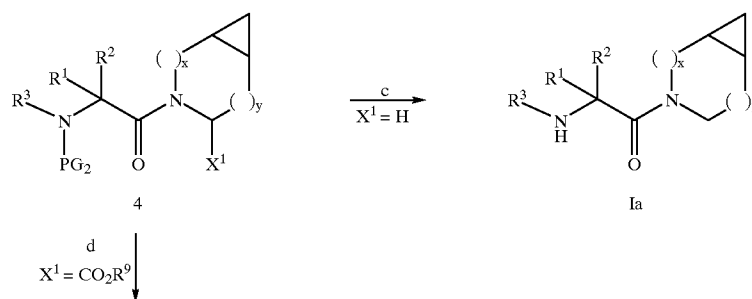
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mediate in the synthesis of Ib. Compound 10 may also be generated by oxidation of the amine 2 (e.g. NCS) followed by hydrolysis and subsequent cyanide treatment. Compound 10 may be obtained as a mixture of stereoisomers or a single isomer/diastereomer which may be epimerized (employing conventional procedures) to afford a mixture of stereoisomers.

Scheme 1



X<sup>1</sup> = H, CO<sub>2</sub>R<sup>9</sup>



a. PG<sub>1</sub> = Boc, TFA or HCl; PG<sub>1</sub> = Cbz, H<sub>2</sub>/Pd/C or TMSI; PG<sub>1</sub> = FMOC, Et<sub>2</sub>NH b. EDAC, HOBT, DMF or i-BuOCOCl/TEA or PyBop, NMM c. PG<sub>2</sub> = PG<sub>1</sub>, (see conditions for a) d. LiOH or NaOH MeOH or THF/H<sub>2</sub>O or dioxane e. i-BuOCOCl/NMM or i-BuOCOCl/TEA or EDAC, then NH<sub>3</sub> in dioxane or Et<sub>2</sub>O f. POCl<sub>3</sub>, pyridine, imidazole or cyanuric chloride, DMF or TFAA, THF, pyridine.

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