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PTO/SB/16 (6-95)

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c)

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Docket Number LA50(PSP)		Type a plus sign(+) inside this box →		+
INVENTOR(S)/APPLICANT(S)				
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY & STATE OR FOREIGN COUNTRY)	
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TITLE OF THE INVENTION (280 CHARACTERS MAX)				
CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD				
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ENCLOSED APPLICATION PARTS (check all that apply)				
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<input type="checkbox"/> Drawing(s)	<input type="checkbox"/> Number of Sheets	<input type="checkbox"/> Other(specify)		
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METHOD OF PAYMENT				
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03/10/00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No.

Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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SIGNATURE John M. Kilcoyne DATE March 10, 2000

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Additional inventors are being named on separately numbered sheets attached hereto.

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

Field of the Invention

5 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,
10 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.

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Background of the Invention

Depeptidyl peptidase IV (DP-4) is a membrane bound
non-clasical serine aminodipeptidase which is located in
a variety of tissues (intestine, liver, lung, kidney) as
20 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,
25 GLP-2, VIP) in vitro.

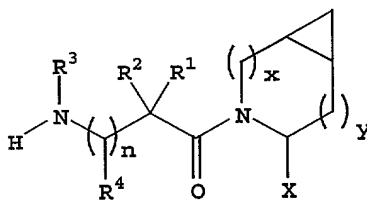
GLP-1(7-36) is a 29 amino-acid peptide derived by
post-translational processing of proglucagon in the small
intestine. GLP-1(7-36) has multiple actions in vivo
including the stimulation of insulin secretion,
30 inhibition of glucagon secretion, the promotion of
satiety, and the slowing of gastric emptying. 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
35 this claim, exogenous administration of GLP-1(7-36)
(continous 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 $y = 1$);

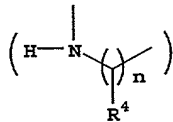
n is 0 or 1;

X is H or CN (that is cyano);

R^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, 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, heteroaryl-amino, aryl-amino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkyl-amino, dialkyl-amino, thiol, alkylthio, 5 alkylcarbonyl, acyl, alkoxy-carbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, 10 alkoxy-carbonylamino, alkylsulfonyl, aminosulfonyl, alkylsulfanyl, sulfonamido or sulfonyl;

and R¹ and R³ may optionally be taken together to form -(CR⁵R⁶)_m- where m is 2 to 6, and R⁵ and R⁶ are the same or different and are independently selected from 15 hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxy-carbonylamino, 20 aryloxy-carbonylamino, alkoxy-carbonyl, aryloxy-carbonyl, or alkylaminocarbonylamino, or R¹ and R⁴ may optionally be taken together to form -(CR⁷R⁸)_p- where p is 3 to 6, and R⁷ and R⁸ are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, 25 alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxy-carbonylamino, aryloxy-carbonylamino, alkoxy-carbonyl, aryloxy-carbonyl, or 30 alkylaminocarbonylamino, or optionally R¹ and R³ together



with $\left(\begin{array}{c} | \\ \text{H}-\text{N} \\ | \\ \text{R}^4 \end{array} \right)_n$ form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO₂;

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