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(54) **PYRROLIDINE COMPOUNDS AND METHODS FOR SELECTIVE INHIBITION OF DIPEPTIDYL PEPTIDASE-IV**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to pyrrolidinylaminoacetyl pyrrolidine boronic acid compounds that display selective, potent dipeptidyl peptidase IV inhibitory activity. These compounds are useful for the treatment of disorders that can be regulated or normalized via inhibition of DPP-IV including those characterized by impaired glycemic control such as Diabetes Mellitus and related conditions. The compounds can be administered alone or with another medicament that displays pharmacological activity for treatment of these and other diseases.

27 Claims, No Drawings

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PYRROLIDINE COMPOUNDS AND METHODS FOR SELECTIVE INHIBITION OF DIPEPTIDYL PEPTIDASE-IV

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 10/514,575, filed on Oct. 27, 2005, which is a national stage application of PCT/US04/037820, which claims priority to U.S. provisional application No. 60/519,566, filed on Nov. 12, 2003; U.S. provisional application No. 60/557,011, filed on Mar. 25, 2004; and U.S. provisional application No. 60/592,972, filed on Jul. 30, 2004. This application is also a continuation-in-part of U.S. application Ser. No. 60/676,808, filed on May 2, 2005. These applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a pyrrolidinylaminoacetyl pyrrolidine boronic acid compound and its use as a selective inhibitor of post-proline/alanine cleaving amino-dipeptidases, particularly dipeptidyl peptidase-IV (DPP-IV). The invention also relates to methodology for employing a pyrrolidine compound, alone or with another medicament, to treat a DPP-IV-related disease, including but not limited to disorders characterized by impaired glycemic control, especially Diabetes Mellitus and related conditions. Thus, the invention has applications in the medicinal, chemical, pharmacological, and medical fields.

BACKGROUND OF THE INVENTION

Dipeptidyl peptidase-IV (DPP-IV) is a serine protease that belongs to a group of post-proline/alanine cleaving amino-dipeptidases. DPP-IV catalyzes the release of an N-terminal dipeptide of any configuration from proteins, and preferably, the dipeptide contains an N-terminal penultimate proline or alanine.

The physiological role of DPP-IV has not been established fully. It is believed to play an important role in regulatory peptide metabolism, which, among other things, controls various physiological functions including but not limited to glycemic control and insulin sensitivity. In particular, DPP-IV has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones, glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which are inactivated by removal of their two N-terminal amino acids.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of insulinotropic hormones including, GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, consequent improved glucose tolerance. Therefore, such inhibitors have been proposed for the treatment of patients with impaired glycemic control such as Diabetes Mellitus and related conditions.

This proposal has significant difficulties, however. Additional dipeptide cleaving amino-dipeptidases have also been discovered, including DPP-VII, DPP-VIII, DPP-IX, and fibroblast activation protein (FAP), which can have substrate and inhibitor specificity similar to DPP-IV. The precise physiological role of each of these dipeptide cleaving enzymes is not well defined. But, their propensity to cleave N-terminus dipeptides from proteins in general indicates that these amino-dipeptidases are involved in many physiological cycles. Thus, the difficulty concerning inhibitors of DPP-IV is that they can also affect the other members of the enzyme group. The evidence indicates that, for example, other inhibitors of DPP-IV, which also inhibit the other amino-dipeptidases such as DPP-VIII, will cause toxic effects in animals.

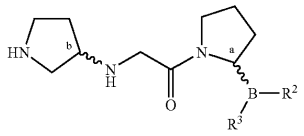
Accordingly, a need exists for compounds that are useful for inhibiting DPP-IV without an adverse event profile that precludes chronic administration.

SUMMARY OF THE INVENTION

The present invention is directed to a selective DPP-IV inhibitor and methods of use that are effective in treating conditions that may be regulated or normalized by inhibition of DPP-IV. More particularly, the invention is directed to a pyrrolidinylaminoacetyl pyrrolidine boronic acid compound. This pyrrolidinylaminoacetyl pyrrolidine boronic acid compound is useful at effective doses for treatment of malconditions associated with DPP-IV activity and is a selective inhibitor of DPP-IV.

A pyrrolidinylaminoacetyl boronic acid compound of the invention (hereinafter the pyrrolidine compound of the invention) has a structure represented in part by Formula I.

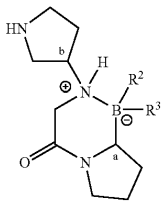
(I)



The substituents and bond designations of formula I include R^2 and R^3, which, independently or together, are —OH, —O^-M^+ wherein M^+ is a cation, a hydroxyl bearing a boronic acid protecting group, or a group capable of being hydrolyzed to a hydroxyl group in an aqueous solution at physiological pH or in biological fluids; and the wavy lines at asymmetric carbons C^a and C^b, which independently indicate for each asymmetric carbon an R configuration, an S configuration, or a mixture of both configurations such that all stereoisomers and all stereomeric mixtures are included. Also included within the scope of the invention are a cyclic isomer thereof, any pharmaceutically acceptable salt thereof, any prodrug thereof, and any solvate thereof.

A pyrrolidine compound of the invention may exist in either of two forms, the linear form represented by formula I above and the cyclic isomer form represented by formula V below.

(V)



The cyclic isomer form and the linear form are in thermodynamic equilibrium when in solution. The equilibrium

shifts depending upon pH. Thus, the predominance of one form over the other in solution depends upon the pH so that at acidic pH, the linear isomer predominates while at basic pH, the cyclic isomer predominates. The linear and cyclic isomers are also stable such that either form may be isolated as a solid. The isolated cyclic isomer can function as a prodrug.

The invention also is directed to a pharmaceutical composition containing a pyrrolidine compound of the invention and a pharmaceutical carrier. The pharmaceutical composition may be formulated to be dosed by any administrative route including but not limited to parenteral injection, oral, buccal, rectal and the like.

The invention is as well directed to a method of treatment of a malcondition that can be regulated or normalized via inhibition of DPP-IV. The method involves administration of an effective amount of a pyrrolidine compound of the invention, such as would be present in a pharmaceutical composition of the invention, to mammals, especially humans, to affect a malcondition that can be regulated or normalized via inhibition of DPP-IV. Preferably, an effective amount of a pyrrolidine compound of the invention exhibits lower toxicity than do non-selective inhibitors of DPP-IV, particularly in comparison to boronic acid inhibitors of DPP-IV that also display inhibition of other DPP enzymes and FAP. Therefore, the invention is directed to methods for selectively inhibiting DPP-IV including administering to a patient in need of such treatment a therapeutically effective amount of a pyrrolidine compound of the invention.

The invention further is directed to a pharmaceutical combination of a pyrrolidine compound of the invention and one or more other medicaments that are useful for treatment of a malcondition that can be regulated or normalized via inhibition of DPP-IV. Such malconditions are associated with impairments in glycemic control especially Diabetes Mellitus and related conditions. A pharmaceutical combination may be formulated according to the invention as a pharmaceutical composition.

The invention is also directed to a process for preparing a pyrrolidine compound of the invention, a method for preparing a pharmaceutical composition of the invention, and the use of a pyrrolidine compound of the invention in a method for the preparation of a medicament for treating a malcondition that can be regulated or normalized via inhibition of DPP-IV.

DEFINITIONS

The term "absolute configuration" in connection with an asymmetric carbon is determined by considering the tetrahedral shape of the asymmetric carbon bonds, assigning a priority of 1 through 4 to each of the groups bound to the asymmetric carbon with the group having the highest atomic number having the first priority. If the tetrahedron is viewed from a side remote from group 4, an R absolute configuration is assigned when groups 1-3 are in a clockwise arrangement and an S absolute configuration is assigned when groups 1-3 are in a counterclockwise arrangement.

The term "asymmetric carbon" means a carbon atom covalently bound to four different groups.

The term "beta cell degeneration" is intended to mean loss of beta cell function, beta cell dysfunction, and death of beta cells, such as necrosis or apoptosis of beta cells.

The term "Diabetes Mellitus and related conditions" refers to Type 1 diabetes, Type 2 diabetes, gestational diabetes, MODY, impaired glucose tolerance, impaired fasting glucose, hyperglycemia, impaired glucose metabolism, insulin resistance, obesity, diabetic complications, and the like.

The term "diabetic complications" refers to conditions, diseases and maladies associated with diabetes including retinopathies, neuropathies, nephropathies, cardiomyopathies, dermopathies, arthrosclerosis, coronary artery disease and other known complications of diabetes.

The term "diastereomer" means one member of a group of two or more stereoisomers having at least two asymmetric carbons such that these stereoisomers are not mirror images of each other.

The terms "DPP-VII, DPP-VIII, DPP-IX and FAP" mean respectively amino dipeptidyl peptidase VII, VIII, IX and fibroblast activation protein. The DPP enzymes cleave dipeptide moieties at the N-terminus of their protein or oligopeptide substrates. In particular, the term "DPP-IV" denotes dipeptidyl peptidase IV (EC 3.4.14.5; DPP-IV), also known as "CD-26." DPP-IV preferentially cleaves a dipeptide from the N terminus of a polypeptide chain containing a proline or alanine residue in the penultimate position.

The term "enantiomer" means one member of a pair of stereoisomers having the same molecular structure and at least one asymmetric carbon such that the stereoisomers of the pair are the mirror images of each other. If the enantiomer contains two or more asymmetric carbons, the enantiomeric pair will have opposing asymmetry at each asymmetric carbon.

The term "group that can be hydrolyzed to a hydroxyl" as used herein refers to an ester group formed from the combination of an aliphatic or aromatic alcohol or diol and a boronic acid.

The term "inhibitor" (and its corresponding verb and gerund) means a compound that will reversibly, irreversibly or temporarily interact with an enzyme so as to reduce, modify, slow down or block its enzymatic activity upon its normal substrate. The interaction may occur within or at the enzymatic site or at an allosteric site associated with the enzyme.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in T.W. Greene, P. G. Wuts, "Protective Groups In Organic Synthesis, 3rd Ed." (John Wiley & Sons, New York (1999)), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, chloracetyl, 2-bromoacetyl, trifluoroacetyl, trichloracetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, αα-dimethyl-3,5-dimethoxvbenzyloxvcarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichioroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl,

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