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United States Patent [19]

Villhauer

[11] **Patent Number: 6,110,949**

[45] **Date of Patent: *Aug. 29, 2000**

[54] **N-(SUBSTITUTED GLYCYL)-4-CYANOTHIAZOLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV**

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[73] Assignee: **Novartis AG**, Basel, Switzerland

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/339,503**

[22] Filed: **Jun. 24, 1999**

[51] **Int. Cl.**[7] **C07D 207/00**

[52] **U.S. Cl.** **514/365**; 548/200

[58] **Field of Search** 548/200; 514/365

[56] **References Cited**

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95/11689	5/1995	WIPO .
95/13069	5/1995	WIPO .
95/15309	6/1995	WIPO .
95/29190	11/1995	WIPO .
95/29691	11/1995	WIPO .
95/34538	12/1995	WIPO .
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Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Joseph J. Borovian

[57] **ABSTRACT**

The invention discloses certain N-(substituted glycyl)-4-cyanothiazolidines, pharmaceutical compositions containing said compounds as an active ingredient thereof, and the use of said compounds in inhibiting dipeptidyl peptidase-IV.

38 Claims, No Drawings

N-(SUBSTITUTED GLYCYL)-4-CYANOTHIAZOLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV

FIELD OF THE INVENTION

The present invention relates to the area of dipeptidyl peptidase-IV inhibition and, more particularly, relates to certain N-(substituted glycyl)-4-cyanothiazolidines, pharmaceutical compositions containing said compounds, and the use of said compounds in inhibiting dipeptidyl peptidase-IV.

BACKGROUND OF THE INVENTION

Dipeptidyl peptidase-IV (DPP-IV) is a serine protease which cleaves N-terminal dipeptides from a peptide chain containing, preferably, a proline residue in the penultimate position. Although the biological role of DPP-IV in mammalian systems has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, attachment of cancer cells to the endothelium and the entry of HIV into lymphoid cells.

More recently, it was discovered that DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1). More particularly, DPP-IV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Since the half-life for DPP-IV cleavage is much shorter than the half-life for removal of GLP-1 from circulation, a significant increase in GLP-1 bioactivity (5- to 10-fold) is anticipated from DPP-IV inhibition. Since GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition appears to represent an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM).

Although a number of DPP-IV inhibitors have been described in the literature, all have limitations relating to potency, stability or toxicity. Accordingly, it is clear that a great need exists for novel DPP-IV inhibitors which are useful in treating conditions mediated by DPP-IV inhibition and which do not suffer from the above-mentioned limitations of known DPP-IV inhibitors.

DESCRIPTION OF THE PRIOR ART

WO 95/15309 discloses certain peptide derivatives which are inhibitors of DPP-IV and, therefore, are useful in treating a number of DPP-IV mediated processes.

WO 95/13069 discloses certain cyclic amine compounds which are useful in stimulating the release of natural or endogenous growth hormone.

European Patent 555,824 discloses certain benzimidazolyl compounds which prolong thrombin time and inhibit thrombin and serine-related proteases.

Archives of Biochemistry and Biophysics, Vol. 323, No. 1, pgs. 148–154 (1995) discloses certain aminoacylpyrrolidine-2-nitriles which are useful as DPP-IV inhibitors.

Journal of Neurochemistry, Vol. 66, pgs. 2105–2112 (1996) discloses certain Fmoc-aminoacylpyrrolidine-2-nitriles which are useful in inhibiting prolyl oligopeptidase.

Bulletin of the Chemical Society of Japan, Vol. 50, No. 7, pgs. 1827–1830 (1977) discloses the synthesis of an aminohexapeptide, viz., Z-Val-Val-lmPro-Gly-Phe-Phe-OMe, and its related aminopeptides. In addition, the antimicrobial properties of said compounds were examined.

Bulletin of the Chemical Society of Japan, Vol. 51, No. 3, pgs. 878–883 (1978) discloses the synthesis of two known peptide antibiotics, viz., Bottromycins B_1 and B_2 according to the structures proposed by Nakamura, et al. However, since the resultant compounds were devoid of antimicrobial properties, it was concluded that the structures proposed by Nakamura, et al. were erroneous.

WO 90/12005 discloses certain amino acid compounds which inhibit prolylendopeptidase activity and, therefore, are useful in treating dementia or amnesia.

Derivent Abstract 95: 302548 discloses certain N-(aryl (alkyl)carbonyl) substituted heterocyclic compounds which are cholinesterase activators with enhanced peripheral selectivity useful in treating conditions due to the lowering of cholinesterase activity.

Derivent Abstract 84: 177689 discloses certain 1-acyl-pyrrolidine-2-carbonitrile compounds which are useful as intermediates for proline compounds exhibiting angiotensin converting enzyme (ACE) inhibiting activity.

Derivent Abstract 96: 116353 discloses certain 3-amino-2-mercapto-propyl-proline compounds which are Ras farnesyl-transferase inhibitors useful in treating various carcinomas or myeloid leukemias.

WO 95/34538 discloses certain pyrrolidides, phosphonates, azetidines, peptides and azaprolines which inhibit DPP-IV and, therefore, are useful in treating conditions mediated by DPP-IV inhibition.

WO 95/29190 discloses certain compounds characterized by a plurality of KPR-type repeat patterns carried by a peptide matrix enabling their multiple presentation to, and having an affinity for, the enzyme DPP-IV, which compounds exhibit the ability to inhibit the entry of HIV into cells.

WO 91/16339 discloses certain tetrapeptide boronic acids which are DPP-IV inhibitors useful in treating autoimmune diseases and conditions mediated by IL-2 suppression.

WO 93/08259 discloses certain polypeptide boronic acids which are DPP-IV inhibitors useful in treating autoimmune diseases and conditions mediated by IL-2 suppression.

WO 95/11689 discloses certain tetrapeptide boronic acids which are DPP-IV inhibitors useful in blocking the entry of HIV into cells.

East German Patent 158109 discloses certain N-protected peptidyl-hydroxamic acids and nitrobenzoyloxamides which are useful as, inter alia, DPP-IV inhibitors.

WO 95/29691 discloses, inter alia, certain dipeptide proline phosphonates which are DPP-IV inhibitors useful in the treatment of immune system disorders.

East German Patent 296075 discloses certain amino acid amides which inhibit DPP-IV.

Biochimica et Biophysica Acta, Vol. 1293, pgs. 147–153 discloses the preparation of certain di- and tri-peptide p-nitroanilides to study the influence of side chain modifications on their DPP-IV and PEP-catalyzed hydrolysis.

Bioorganic and Medicinal Chemistry Letters, Vol. 6, No. 10, pgs. 1163–1166 (1996) discloses certain 2-cyanopyrrolidines which are inhibitors of DPP-IV.

J. Med. Chem., Vol. 39, pgs. 2087–2094 (1996) discloses certain prolineboronic acid-containing dipeptides which are inhibitors of DPP-IV.

Diabetes, Vol. 44, pgs. 1126–1131 (September 1996) is directed to a study which demonstrates that GLP-I amide is

rapidly degraded when administered by subcutaneous or intravenous routes to diabetic and non-diabetic subjects.

Bioorganic and Medicinal Chemistry Letters, Vol. 6, No. 22, pgs. 2745–2748 (1996) discloses certain 4-cyanothiazolidides which are inhibitors of DPP-IV.

Eur J. Med. Chem., Vol. 32, pgs. 301–309 (1997) discloses certain homologues and 3-substituted analogues of pyrrolidides and thiazolidides which inhibit DPP-IV.

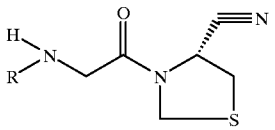
SUMMARY OF THE INVENTION

The present invention provides new DPP-IV inhibitors which are effective in treating conditions mediated by DPP-IV inhibition. More particularly, the present invention relates to certain N-(substituted glycyl)-4-cyanothiazolidines which inhibit DPP-IV. In addition, the present invention provides pharmaceutical compositions useful in inhibiting DPP-IV comprising a therapeutically effective amount of a certain N-(substituted glycyl)-4-cyano-thiazolidine. Moreover, the present invention provides a method of inhibiting DPP-IV comprising administering to a mammal in need of such treatment a therapeutically effective amount of a certain N-(substituted glycyl)-4-cyanothiazolidine.

DETAILED DESCRIPTION OF THE INVENTION

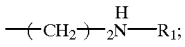
The essence of the instant invention is the discovery that certain N-(substituted glycyl)-4-cyanothiazolidines are useful in inhibiting DPP-IV. In one embodiment, the present invention provides compounds of formula I:

I

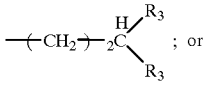


wherein

R is C_{1-12}alkyl; a group



an unsubstituted (C_{3-7})cycloalkyl ring; a group $—(—CH_2—)—_2R_2$; a group



; or

a group $—(—CH_2—)—_3R_4$;

R_1 is an unsubstituted pyridine ring; a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; an unsubstituted pyrimidine ring; or a pyrimidine ring monosubstituted by halo, trifluoromethyl, cyano or nitro;

R_2 is an unsubstituted phenyl ring; or a phenyl ring mono-, di- or tri-substituted by halo or (C_{1-3})alkoxy;

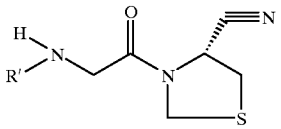
each R_3, independently, is an unsubstituted phenyl ring; or a phenyl ring monosubstituted by halo or (C_{1-3})alkoxy; and

R_4 is a 2-oxopyrrolidine group or a (C_{2-4})alkoxy group;

or a pharmaceutically acceptable acid addition salt thereof.

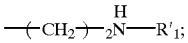
Preferred compounds are those of formula Ia:

Ia



where

R' is C_{1-10}alkyl; a group



an unsubstituted (C_{3-7})cycloalkyl ring; or a group $—(—CH_2—)—_3R_4'$;

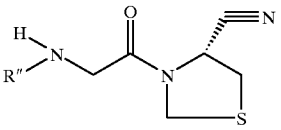
R_1' is an unsubstituted pyridine ring; or a pyridine ring mono- or di- substituted by halo, trifluoromethyl, cyano or nitro; and

R_4' is a (C_{2-4})alkoxy group;

or a pharmaceutically acceptable acid addition salt thereof.

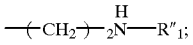
More preferred compounds are those of formula Ib:

Ib



where

R" is C_{1-8}alkyl; a group



an unsubstituted (C_{4-6})—cycloalkyl ring; or a group $—(—CH_2—)—_3R_4'$;

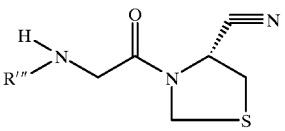
$R_1"$ is a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; and

R_4' is as defined above;

or a pharmaceutically acceptable acid addition salt thereof.

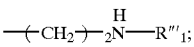
Even more preferred compounds are those of formula Ic:

Ic



where

R'" is C_{1-6}alkyl; a group



an unsubstituted (C_{4-6})—cycloalkyl ring; or a group $—(—CH_2—)—_3R_4'$;

R'" is a pyridine ring monosubstitued by halo, trifluoromethyl, cyano or nitro; and

R_4' is as defined above;

or a pharmaceutically acceptable acid addition salt thereof.

In another embodiment, the instant invention provides pharmaceutical compositions useful in inhibiting DPP-IV comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof, preferably a compound of formula Ia above, or a pharmaceutically acceptable acid addition salt thereof, more preferably a compound of formula Ib above, or a pharmaceutically acceptable acid addition salt thereof, and even more preferably a compound of formula Ic above, or a pharmaceutically acceptable acid addition salt thereof.

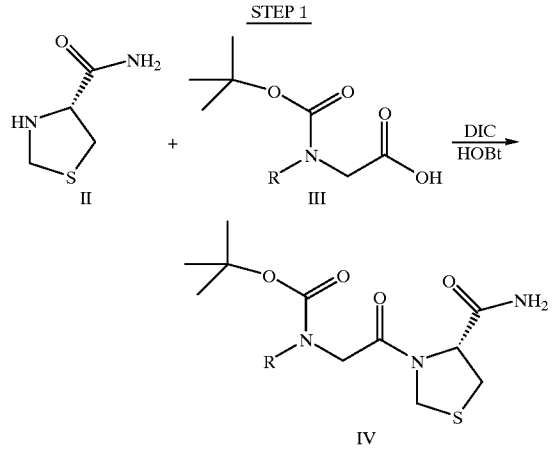
In still another embodiment, the instant invention provides a method of inhibiting DPP-IV comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof, preferably a compound of formula Ia above, or a pharmaceutically acceptable acid addition salt thereof, more preferably a compound of formula Ib above, or a pharmaceutically acceptable acid addition salt thereof, and even more preferably a compound of formula Ic above, or a pharmaceutically acceptable acid addition salt thereof.

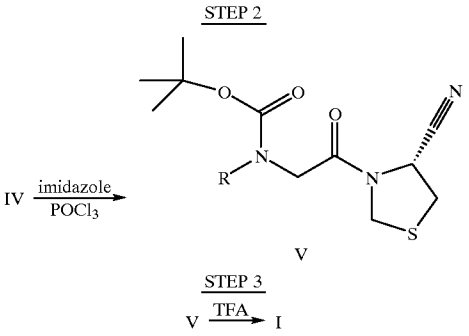
In a further embodiment, the instant invention provides a method of treating conditions mediated by DPP-IV inhibition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof, preferably a compound of formula Ia above, or a pharmaceutically acceptable acid addition salt thereof, more preferably a compound of formula Ib above, or a pharmaceutically acceptable acid addition salt thereof, and even more preferably a compound of formula Ic above, or a pharmaceutically acceptable acid addition salt thereof.

In the above definitions, it should be noted that the "alkyl" and "alkoxy" significances are either straight or branched chain, of which examples of the latter are isopropyl and t-butyl.

The acid addition salts of the compounds of formula I may be those of pharmaceutically acceptable organic or inorganic acids. Although the preferred acid addition salts are the hydrochlorides, salts of methanesulfonic, sulfuric, phosphoric, citric, lactic and acetic acid may also be utilized.

The compounds of formula I may be prepared by the following three-step reaction:





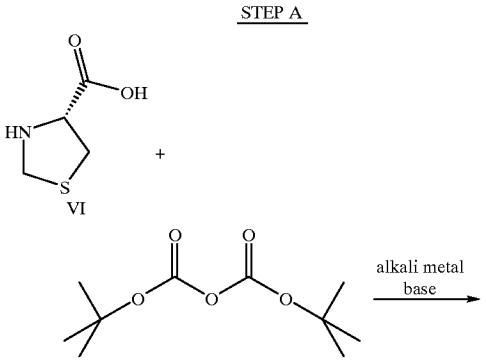
where R is as defined above.

As to the individual steps, Step 1 involves the coupling of an N-t-boc protected N-substituted glycine compound of formula III with a slight molar excess of the amide compound of formula II employing 1,3-diisopropylcarbodiimide as the coupling agent and 1-hydrobenzotriazole hydrate as the activator therefor to obtain a t-boc protected amide compound of formula IV. The coupling reaction is conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of from 10° to 35° C. for a period of between 8 and 36 hours.

The second step concerns the dehydration of the compound prepared in Step 1, i.e., a t-boc protected amide of formula IV, with between 2.5 and 3 equivalents of phosphoryl chloride to obtain a t-boc protected nitrile compound of formula V. The dehydration is conducted in the presence of a mixture of pyridine and imidazole, at a temperature of from −20° to −45° C. for a period of between 30 minutes and 2.5 hours.

The third step involves the deprotection of the compound prepared in the second step, i.e., a t-boc protected nitrile compound of formula V, employing trifluoroacetic acid as the deprotecting agent to obtain an N-substituted glycyl-4-cyanothiazolidine compound of formula I. The deprotection is carried out in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of from 10° to 35° C. for a period of between 2 and 6 hours.

The amide compound of formula II may be prepared in accordance with the following four-step reaction scheme:



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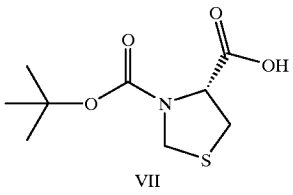
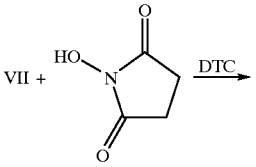
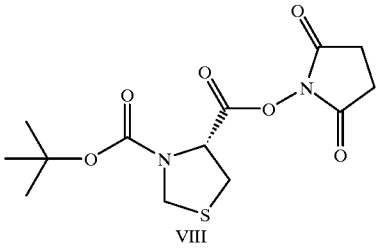


VII

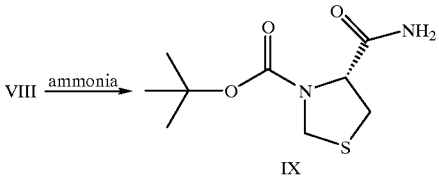
STEP B





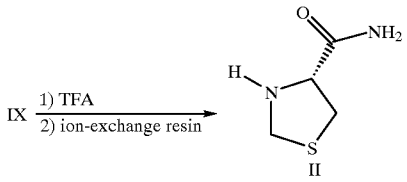
VIII

STEP C



IX

STEP D



II

With regard to the individual steps, Step A involves the amino protection of the carboxylic acid compound of formula VI employing di-t-butyl dicarbonate as the activating agent to obtain the t-boc protected carboxylic acid compound of formula VII. The reaction is conducted in the presence of an alkali metal base, preferably an alkali metal hydroxide such as sodium hydroxide, and an aqueous mixture comprising a cyclic either, e.g., a mixture of water and dioxane. The reaction is conducted at a temperature of from 10° to 35° C. for a period of between 1 and 4 hours.

Step B concerns the coupling of the compound prepared in Step A, i.e., the t-boc protected carboxylic acid of formula VII, with a slight molar excess of N-hydroxysuccinimide employing 1,3-diisopropylcarbodiimide as the coupling agent to obtain a mixture of the t-boc protected anhydride compound of formula VIII and 1,3-diisopropylurea. The coupling reaction is conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of from 10° to 35° C. for a period of between 1 and 4 hours.

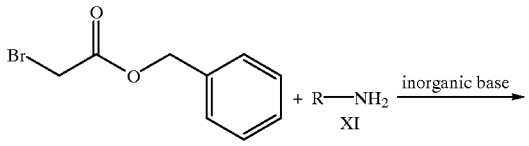
Step C relates to the amidation of the compound prepared in Step B, i.e., the t-boc protected anhydride of formula VIII, employing ammonia to obtain a mixture of the t-boc protected amide compound of formula IX and 1,3-diisopropylurea. The amidation is conducted in the presence of an inert, organic solvent, preferably an aliphatic halogenated hydrocarbon such as methylene chloride, at a temperature of from 10° to 35° C. for a period of between 2 and 6 hours.

The first part of Step D involves the acidic decarboxylation of the compound prepared in Step C, i.e., the t-boc protected amide compound of formula IX, employing trifluoroacetic acid to obtain a mixture of the trifluoroacetic acid salt of the desired amide compound of formula II and 1,3-diisopropylurea. The acidic decarboxylation is conducted at a temperature of from 10° to 35° C. for a period of between 1 and 4 hours.

The second part of Step D involves subjecting the mixture obtained in the first part to an ion-exchange resin, preferably Amberlite IRA 400(OH), to obtain the amide compound of formula II. The ion-exchange is conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of from 10° to 35° C. for a period of between 15 and 45 minutes.

The N-t-boc protected N-substituted glycine compounds of formula III may be prepared by the following three-step reaction:

STEP 1A



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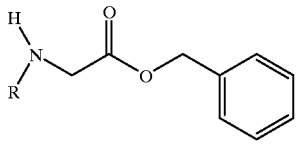
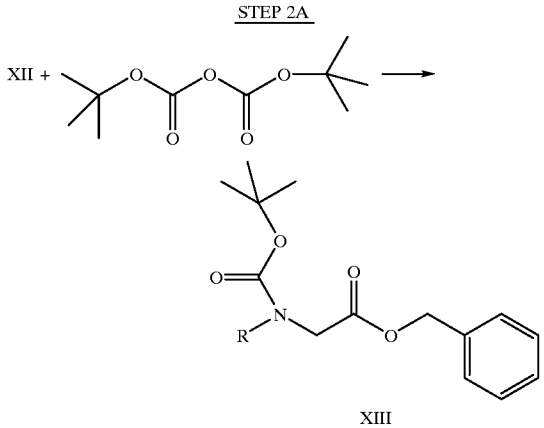


XII

STEP 2A



XIII

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