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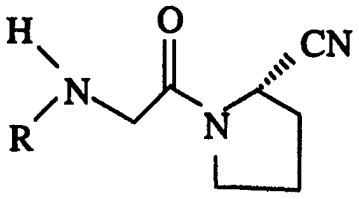
(54) Title: N–SUBSTITUTED 2–CYANOPYRROLIDINES

(57) Abstract

N–(N'–substituted glycyl)–2–cyanopyrrolidines, e.g. the compounds of formula (I) wherein R has various significances, are novel. They inhibit DPP–IV (dipeptidyl–peptidase–IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP–IV and in the treatment of conditions mediated by DPP–IV, such as non–insulin–dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.



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N-SUBSTITUTED 2-CYANOPYRROLIDINES

Field

The present invention relates to N-substituted 2-cyanopyrrolidines. More particularly, it provides novel N-glycyl-2-cyanopyrrolidine derivatives.

Background

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. 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**).

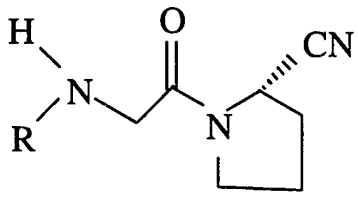
Although a number of DPP-IV inhibitors have been described, all have limitations relating to potency, stability or toxicity. Accordingly, a great need exists for novel DPP-IV inhibitors which are useful in treating conditions mediated by DPP-IV inhibition and which do not suffer from the above-mentioned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

Summary of the invention

The invention provides novel N-(N'-substituted glycyl)-2-cyanopyrrolidines which are effective as DPP-IV inhibitors in treating conditions mediated by DPP-IV. It also concerns corresponding pharmaceutical compositions, a process for their preparation, a method of inhibiting DPP-IV comprising administering to a patient in need of such treatment a therapeutically effective amount thereof, the compounds for use as a pharmaceutical, and their use in a process for the preparation of a medicament for treating a condition mediated by DPP-IV.

Detailed description

The invention concerns N-(N'-substituted glycyl)-2-cyanopyrrolidines, hereinafter briefly named "**the compounds of the invention**"; more particularly, it concerns compounds of formula I:



I

wherein **R** is:

a) **$R_1R_{1a}N(CH_2)_m$-** wherein

R_1 is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

R_{1a} is hydrogen or (C_{1-8})alkyl; and

m is 2 or 3;

b) **(C_{3-12})cycloalkyl** optionally monosubstituted in the 1-position with (C_{1-3})hydroxyalkyl;

c) **$R_2(CH_2)_n$-** wherein either

R_2 is phenyl optionally mono- or independently di- or independently trisubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is (C_{1-8})alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl;

a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; cyclohexene; or adamantyl; and

n is 1 to 3; or

R_2 is phenoxy optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; and

n is 2 or 3;

d) **$(R_3)_2CH(CH_2)_2$-** wherein each R_3 independently is phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

e) **$R_4(CH_2)_p$-** wherein R_4 is 2-oxopyrrolidinyl or (C_{2-4})alkoxy and

p is 2 to 4;

f) **isopropyl** optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

g) **R_5** wherein R_5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl; adamantyl; or (C_{1-8})alkyl optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

in free form or in acid addition salt form.

The compounds of formula I can exist in free form or in acid addition salt form. Salt forms may be recovered from the free form in known manner and vice-versa. Acid addition salts may e.g. 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 the invention may exist in the form of optically active isomers or diastereoisomers and can be separated and recovered by conventional techniques, such as chromatography.

"Alkyl" and "alkoxy" are either straight or branched chain, of which examples of the latter are isopropyl and tert-butyl.

R preferably is a), b) or e) as defined above. R_1 preferably is a pyridinyl or pyrimidinyl moiety optionally substituted as defined above. R_{1a} preferably is hydrogen. R_2 preferably is phenyl optionally substituted as defined above. R_3 preferably is unsubstituted phenyl.

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