

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No . 03-028249

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **544**

DE FECHA 30 DE **SEPTIEMBRE DE 2004** EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL 29 DE **DICIEMBRE DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO__ _X _ _

Bogotá D.C, AGOSTO DE 2007



US006110949A

United States Patent [19]
Villhauer**[11] Patent Number: 6,110,949**
[45] Date of Patent: *Aug. 29, 2000

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

95/15309 6/1995 WIPO .
95/29190 11/1995 WIPO .
95/29691 11/1995 WIPO .
95/34538 12/1995 WIPO .
98/19998 5/1998 WIPO .
99/38501 8/1999 WIPO .

[75] **Inventor: Edwin Bernard Villhauer, Morristown, N.J.**

[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**

U.S. PATENT DOCUMENTS

5,939,560 8/1999 Jenkins 548/535

FOREIGN PATENT DOCUMENTS

555 824 8/1993 European Pat. Off. .
1581 09 12/1982 Germany .
296 075 11/1991 Germany .
90/12005 10/1990 WIPO .
91/16339 10/1991 WIPO .
93/08259 4/1993 WIPO .
95/11689 5/1995 WIPO .
95/13069 5/1995 WIPO .

OTHER PUBLICATIONS

Archives of Biochemistry and Biophysics, vol. 323, No. 1, pp. 148-154 (1995).

Journal of Neurochemistry, vol. 66, pp. 2105-2112 (1996).

Bulletin of the Chemical Society of Japan, vol. 50, No. 7, pp. 1827-1830 (1977).

Bulletin of the Chemical Society of Japan, vol. 51, No. 3, pp. 878-883 (1978).

Derwent Abstract 95: 302548.

Derwent Abstract 84: 177689.

Derwent Abstract 96: 116353.

Biochimica et Biophysica, vol. 1293, pp. 147-153.

Bioorganic and Medicinal Chemistry Letters, vol. 6, No. 10, pp. 1163-1166 (1996).

J. Med. Chem., vol. 39, pp. 2087-2094 (1996).

Diabetes, vol. 44, pp. 1126-1131 (Sep. '96).

Bioorganic and Medicinal Chemistry Letters, vol. 6, No. 22, pp. 2745-2748 (1996).

Eur. J. Med. Chem., vol. 32, pp. 301-309 (1997).

Biochemistry, vol. 38, pp. 11597-11603 (1999).

Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Joseph J. Borovian

[57] **ABSTRACT**

The invention discloses certain N-(substituted glycyI)-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

3

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-cyanothiazolidines which are inhibitors of DPP-IV.

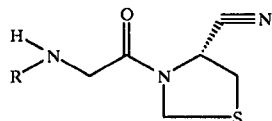
Eur J. Med. Chem., Vol. 32, pgs. 301-309 (1997) discloses certain homologues and 3-substituted analogues of pyrrolidides and thiazolidides which inhibit DPP-IV.

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 glycy)-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 glycy)-4-cyanothiazolidine. 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 glycy)-4-cyanothiazolidine.

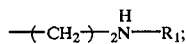
DETAILED DESCRIPTION OF THE INVENTION

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

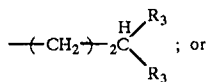


wherein

R is C₁₋₁₂alkyl; a group



an unsubstituted (C₃₋₇)cycloalkyl ring; a group
 $-(CH_2)_2-R_2$; a group



a group $-(CH_2)_3-R_4$;

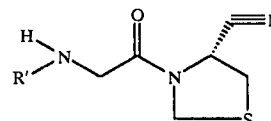
R₁ is an unsubstituted pyridine ring; a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; an unsubstituted pyrimidine ring; or a pyrimidine ring monosubstituted by halo, trifluoromethyl, cyano or nitro;

R₂ is an unsubstituted phenyl ring; or a phenyl ring mono-, di- or tri-substituted by halo or (C₁₋₃)alkoxy; each R₃, independently, is an unsubstituted phenyl ring; or a phenyl ring monosubstituted by halo or (C₁₋₃)alkoxy; and

R₄ is a 2-oxopyrrolidine group or a (C₂₋₄)alkoxy group;

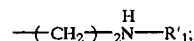
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or a pharmaceutically acceptable acid addition salt thereof. Preferred compounds are those of formula Ia:



where

R' is C₁₋₁₀alkyl; a group

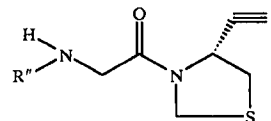


an unsubstituted (C₃₋₇)cycloalkyl ring; or a group
 $-(CH_2)_3-R'_1$;

R'₁ is an unsubstituted pyridine ring; or a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; and

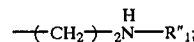
R'₄ is a (C₂₋₄)alkoxy group;

or a pharmaceutically acceptable acid addition salt thereof. More preferred compounds are those of formula Ib:



where

R'' is C₁₋₈alkyl; a group

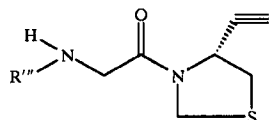


an unsubstituted (C₄₋₆)cycloalkyl ring; or a group
 $-(CH_2)_3-R''_1$;

R''₁ is a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; and

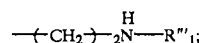
R''₄ is as defined above;

or a pharmaceutically acceptable acid addition salt thereof. Even more preferred compounds are those of formula Ic:



where

R''' is C₁₋₆alkyl; a group

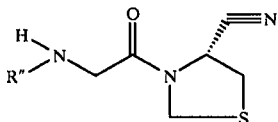


an unsubstituted (C₄₋₆)cycloalkyl ring; or a group
 $-(CH_2)_3-R'''_1$;

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

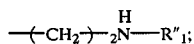
17

R_4' is a (C_{2-4}) alkoxy group;
or a pharmaceutically acceptable acid addition salt thereof.
3. A compound according to claim 2 of formula 1b:



where

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

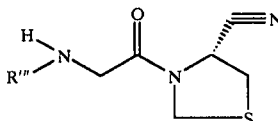


an unsubstituted (C_{4-6}) -cycoalkyl ring; or a group
 $-(CH_2)_3-R_4'$;

R_4' is a pyridine ring mono- or di-substituted by halo,
trifluoromethyl
cyano or nitro; and

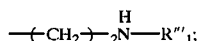
R_4' is as defined in claim 2;
or a pharmaceutically acceptable acid addition salt thereof.

4. A compound according to claim 3 of formula 1c:



where

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



an unsubstituted (C_{4-6}) -cycloalkyl ring; or a group
 $-(CH_2)_3-R_4'$;

R_4' is a pyridine ring monosubstituted by halo,
trifluoromethyl, cyano or nitro; and

R_4' is as defined above;

or a pharmaceutically acceptable acid addition salt thereof.

5. A compound according to claim 4 which is
3-[(cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine, or a
pharmaceutically acceptable acid addition salt thereof.

6. A compound according to claim 5 which is
3-[(cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine
monohydrochloride.

7. A compound according to claim 4 which is 3-[(3-
isopropoxypropyl)amino]acetyl-4-cyano-(R)-thiazolidine,
or a pharmaceutically acceptable acid addition salt thereof.

8. A compound according to claim 7 which is 3-[(3-
isopropoxypropyl)amino]acetyl-4-cyano-(R)-thiazolidine
monohydrochloride.

9. A compound according to claim 4 which is 3-[(isopropyl)
amino]acetyl-4-cyano-(R)-thiazolidine, or a
pharmaceutically acceptable acid addition salt thereof.

10. A compound according to claim 9 which is
3-[(isopropyl)amino]acetyl-4-cyano-(R)-thiazolidine mono-
hydrochloride.

11. A pharmaceutical composition comprising a pharma-
ceutically acceptable carrier or diluent and a therapeutically

18

effective amount of a compound according to claim 1, or a
pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition comprising a pharma-
ceutically acceptable carrier or diluent and a therapeutically
effective amount of a compound according to claim 2, or a
pharmaceutically acceptable acid addition salt thereof.

13. A pharmaceutical composition comprising a pharma-
ceutically acceptable carrier or diluent and a therapeutically
effective amount of a compound according to claim 3, or a
pharmaceutically acceptable acid addition salt thereof.

14. A pharmaceutical composition comprising a pharma-
ceutically acceptable carrier or diluent and a therapeutically
effective amount of a compound according to claim 4, or a
pharmaceutically acceptable acid addition salt thereof.

15. A pharmaceutical composition according to claim 14
comprising a therapeutically effective amount of
3-[(cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine, or a
pharmaceutically acceptable acid addition salt thereof.

16. A pharmaceutical composition according to claim 14
comprising a therapeutically effective amount of 3-[(3-
isopropoxypropyl)amino]acetyl-4-cyano-(R)-thiazolidine,
or a pharmaceutically acceptable acid addition salt thereof.

17. A pharmaceutical composition according to claim 14
comprising a therapeutically effective amount of
3-[(isopropyl)amino]acetyl-4-cyano-(R)-thiazolidine, or a
pharmaceutically acceptable acid addition salt thereof.

18. A method of inhibiting dipeptidyl peptidase-IV
comprising administering to a mammal in need of such treatment
a therapeutically effective amount of a compound according
to claim 1, or a pharmaceutically acceptable acid addition
salt thereof.

19. A method of inhibiting dipeptidyl peptidase-IV
comprising administering to a mammal in need of such treatment
a therapeutically effective amount of a compound according
to claim 2, or a pharmaceutically acceptable acid addition
salt thereof.

20. A method of inhibiting dipeptidyl peptidase-IV
comprising administering to a mammal in need of such treatment
a therapeutically effective amount of a compound according
to claim 3, or a pharmaceutically acceptable acid addition
salt thereof.

21. A method of inhibiting dipeptidyl peptidase-IV
comprising administering to a mammal in need of such treatment
a therapeutically effective amount of a compound according
to claim 4, or a pharmaceutically acceptable acid addition
salt thereof.

22. A method according to claim 21 comprising admin-
istering a therapeutically effective amount of
3-[(cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine, or a
pharmaceutically acceptable acid addition salt thereof.

23. A method according to claim 21 comprising admin-
istering a therapeutically effective amount of 3-[(3-
isopropoxypropyl)amino]acetyl-4-cyano-(R)-thiazolidine,
or a pharmaceutically acceptable acid addition salt thereof.

24. A method according to claim 21 comprising admin-
istering a therapeutically effective amount of 3-[(isopropyl)
amino]acetyl-4-cyano-(R)-thiazolidine, or a pharmaceuti-
cally acceptable acid addition salt thereof.

25. A method of treating conditions mediated by dipep-
tidyl peptidase-IV inhibition comprising administering to a
mammal in need of such treatment a therapeutically effec-
tive amount of a compound according to claim 1, or a
pharmaceutically acceptable acid addition salt thereof.

26. A method of treating conditions mediated by dipep-
tidyl peptidase-IV inhibition comprising administering to a
mammal in need of such treatment a therapeutically effec-
tive amount of a compound according to claim 2, or a
pharmaceutically acceptable acid addition salt thereof.

PCT

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International Bureau



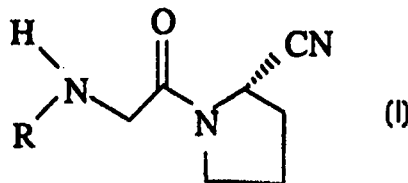
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 207/00, 401/00, C07K 5/00	A2	(11) International Publication Number: WO 98/19998 (43) International Publication Date: 14 May 1998 (14.05.98)
(21) International Application Number: PCT/EP97/06125 (22) International Filing Date: 5 November 1997 (05.11.97) (30) Priority Data: 08/746,295 7 November 1996 (07.11.96) US (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (72) Inventor; and (75) Inventor/Applicant (for US only): VILLHAUER, Edwin, Bernard [US/US]; 20 Dorothy Drive, Morristown, NJ 07960 (US). (74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: N-SUBSTITUTED 2-CYANOPYRROLIDINES

(57) Abstract

N-(N'-substituted glycy)-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.

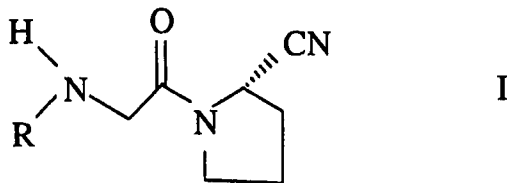


Summary of the invention

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

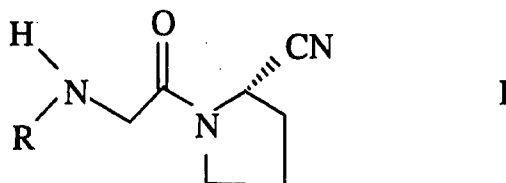
b) (C_{3-12}) cycloalkyl optionally monosubstituted in the 1-position with (C_{1-3}) hydroxyalkyl;

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;

Claims:

1. An N-(N'-substituted glycy)-2-cyanopyrrolidine.
2. A compound of formula I:



wherein **R** is:

- a) $R_1 R_{1a} N(CH_2)_m$ - 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

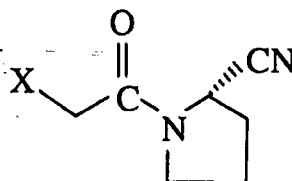
n is 2 or 3;

- 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;

reacting a compound of formula II



II

wherein X is a reactive group,

with a compound of formula III



III

wherein R is as defined in claim 2,

and recovering the resultant compound in free form or in acid addition salt form.

7. A pharmaceutical composition comprising a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form, together with at least one pharmaceutically acceptable carrier or diluent.

8. A compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

9. Use of a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form in the preparation of a medicament for inhibiting DPP-IV or treating conditions mediated by DPP-IV.

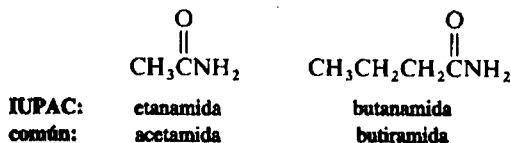
10. A method of inhibiting DPP-IV, or of treating a condition mediated by DPP-IV, which comprises administering a therapeutically effective amount of a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form to a patient in need of such treatment.

SECCIÓN 13.9.

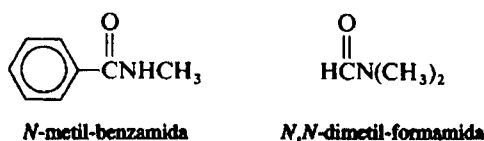
Amidas

A. Nomenclatura de las amidas

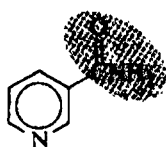
Una amida es un compuesto que tiene un nitrógeno trivalente, unido a un grupo carbonilo. Las amidas se nombran, eliminando la palabra ácido y cambiando la terminación -oico o (-ico) del ácido carboxílico por -amida.



Las amidas con sustituyentes alquílicos sobre el nitrógeno llevan sus nombres precedidos de *N*-alquilo, en donde *N* se refiere al átomo de nitrógeno.

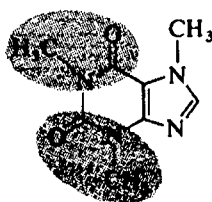


A continuación se dan algunas amidas interesantes; los grupos amida están señalados con un círculo.



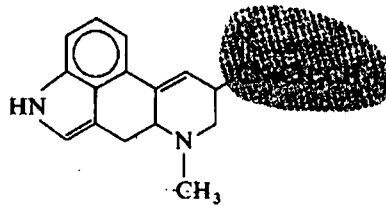
nicotinamida o
niacinamida

una vitamina B



cafeína

una lactama o
amida cíclica



dielil-amida del ácido lisérgico
(LSD)

B. Preparación de las amidas

Las amidas se sintetizan a partir de derivados de ácidos carboxílicos y amoníaco o la amina apropiada. Estas reacciones se han explicado previamente en este capítulo.

