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205
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-**SANOFI-AVENTIS**.-Solicitud de Patente de
Invencción en Fase Nacional PCT para "N-
AMINOACETIL-PIRROLIDINA-2-CARBONITRILOS Y
SU USO COMO INHIBIDORES DE DPP-IV".-Clase
C07D 451/04.-Expediente número 04-085.813.-

1. Me refiero a mi memorial de 3 de Febrero de 2005.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **562** de 31 de Marzo de 2006, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Por otro lado, atentamente me permito manifestar a usted que en el extracto de la solicitud arriba nombrada, publicado en la Gaceta de la Propiedad Industrial número **562** de 31 de Marzo de 2006, página 410, el nombre del solicitante aparece publicado en forma equivocada, el nombre correcto del solicitante es **SANOFI-AVENTIS**, como se informó en nuestro memorial de 3 de Febrero de 2005 radico ante ese Despacho.

4. En vista de lo anterior, muy comedidamente solicito a usted que las aclaraciones correspondientes sean incluidas en la Fe de Erratas de la próxima Gaceta de la Propiedad Industrial.

5. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.

6. Anexo me permito presentar:

(a) Recibo número 06-43.085, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa; y

(b) Copia del extracto de la solicitud, tal como fue presentado a ese Despacho con mi memorial de 3 de Febrero de 2005.

7. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

207

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 43,085
FECHA : JUNIO 7 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLORED A Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47518763	07/06/2006	2,479,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-11 EXAMEN DE PATENTIBILID	194,000.00
	TOTAL :	\$ 194,000.00

SON: CIENTO NOVENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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(31) No. DE SOLICITUD: P 0200849

(72) INVENTOR/ES:

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Katalin y VARGA, Márton.

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(33) PAÍS: HU

(74) REPRESENTANTE LEGAL:

ALICIA LLOREDA RICAURTE

(54) TÍTULO:

" N-AMINOACETIL-PIRROLIDINA-2-CARBONITRILOS Y SU USO COMO INHIBIDORES DE DPP-IV "

(57) RESUMEN:

Reivindicación número 1.-

compuestos CARACTERIZADOS PORQUE responden a la fórmula general (I) donde

-R¹ significa una unidad aromática que contiene nitrógeno que consiste en uno o dos anillos aromáticos, preferiblemente anillo(s) piridilo, piridazinilo, pirimidinilo, pirazinilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, oxadiazolilo, quinolinilo, isoquinolinilo, cinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, benzimidazolilo, indazolilo, benzotiazolilo, benzisotiazolilo, benzoxazolilo, o benzisoxazolilo, tetrazolilo, triazinilo; que, en un caso determinado, está(n) mono-o disustituido(s) independientemente uno del otro por uno o dos de los siguientes grupos: grupos alquilo C₁₋₄, grupos alcoxi C₁₋₄, átomo de halógeno, grupo trihalogenometilo, grupo metiltio, grupo nitro, grupo ciano,

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04-085813

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 562 DE

FECHA 31 DE MARZO DE 2006 EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 05 DE JULIO DEL 2006

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 _____

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International Bureau(43) International Publication Date
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PCT

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09/592,336 13 June 2000 (13.06.2000) US(71) Applicant (for all designated States except AT, US): NO-
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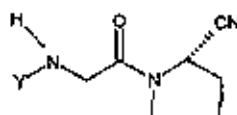
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07960 (US).(74) Agent: BECKER, Konrad; Novartis AG, Corporate In-
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 01/96295 A2

(54) Title: ORGANIC COMPOUNDS

(57) Abstract: The present invention relates to certain N-(substituted glycol)-2-cyanopyrrolidines of formula (I) wherein Y is as de-
fined herein, in free form or in acid addition salt form. Compounds of formula (I) 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.

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.

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "halo" refers to chloro, fluoro, bromo or iodo.

The term "C₁₋₆alkyl" and the "C₁₋₆alkyl" portion of "di-C₁₋₆alkylaminocarbonyl" refers to straight or branched chain hydrocarbon groups having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, more preferably 1 or 2 carbon atoms. Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like.

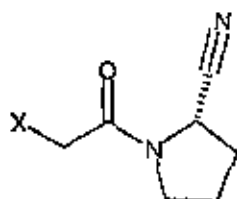
The "C₁₋₆alkyl" portion of "C₁₋₆alkylcarbonyl", in addition to the definition above, also refers to cyclic hydrocarbon groups, e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The C₃₋₆ portion of C₃₋₆cycloalkyl-carbonyl refers to e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

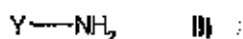
The bond containing the wavy line signifies the point of attachment of the "Y" group to the glycy-2-cyanopyrrolidine moiety.

The N-(substituted glycy)-2-cyanopyrrolidines of the invention may be prepared, e.g., by a process which comprises coupling a reactive (2-cyanopyrrolidine)carbonylmethylene compound with an appropriate substituted amine. More particularly, the compounds of formula I may be prepared by reacting a compound of formula II

- 11 -



where X is a reactive group (preferably a halogen group such as chlorine, bromine or iodine, more preferably chlorine) with a compound of formula III

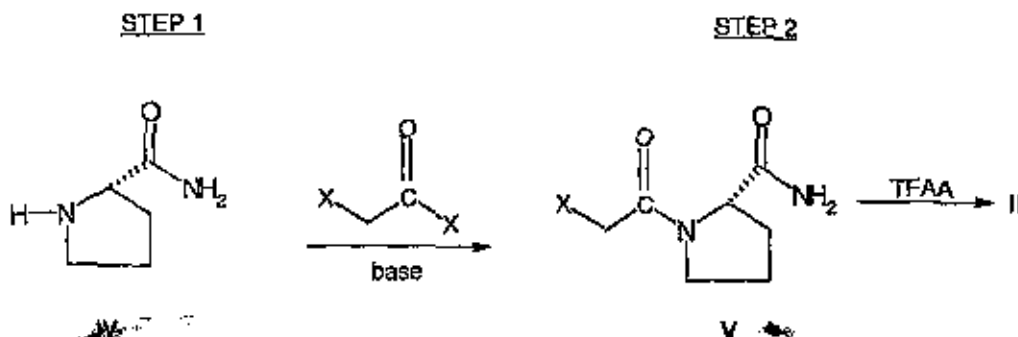


where Y is as defined above, and recovering the resultant compound of formula I in free form or in acid addition salt form.

The coupling may be effected by reacting the compound of formula II with 1 to 3 equivalents, preferably 3 equivalents, of a primary amine compound of formula III. The reaction is conveniently conducted in the presence of an inert, organic solvent, preferably a chlorinated, aliphatic hydrocarbon such as methylene chloride or a cyclic ether such as tetrahydrofuran, at a temperature of from about 0° to about 35°C., preferably from about 0° to about 25°C.

The compounds of the invention may be isolated from the reaction mixture and purified in conventional manner, e.g., by chromatography.

The starting compounds of formula II may be prepared by the following two-step reaction:



acetate) provides the target amine monohydrochloride. The following amines can be prepared in a similar fashion: a) 1-[1-(4-phenyl-2-thiazolyl)-4-piperidinyl]amine from 2-bromoacetophenone, and b) 1-[1-(4-(4-chlorophenyl)-2-thiazolyl)-4-piperidinyl]amine from 2-bromo-4'-chloroacetophenone.

The compounds of formula I having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable acid addition salts. For example, the free base of a compound of formula I can be reacted with hydrochloric acid in gaseous form to form the corresponding mono- and di-hydrochloride salt forms, whereas reacting the free base with methanesulfonic acid forms the corresponding mesylate salt form. All pharmaceutically acceptable acid addition salt forms of the compounds of formula I are intended to be embraced by the scope of this invention.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

As indicated above, all of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are useful in inhibiting DPP-IV. The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may be demonstrated employing the Caco-2 DPP-IV Assay which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression was accomplished as described by Reisher, et al. in an article entitled "Increased expression of intestinal cell line Caco-2" in *Proc. Natl. Acad. Sci.*, Vol. 90, pgs. 5757-5761 (1993). Cell extract is prepared from cells solubilized in 10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u.aprotinin, 0.5% nonidet-P40, pH 8.0, which is centrifuged at 35,000 g for 30 min.

at 4°C. to remove cell debris. The assay is conducted by adding 20 µg solubilized Caco-2 protein, diluted to a final volume of 125 µl in assay buffer (25 mM Tris HCl pH 7.4, 140mM NaCl, 10 mM KCl, 1% bovine serum albumin) to microtiter plate wells. After a 60 min. incubation at room temperature, the reaction is initiated by adding 25 µl of 1 mM substrate (H-Alanine-Proline-pNA; pNA is *p*-nitroaniline). The reaction is carried out at room temperature for 10 minutes after which time a 19 µl volume of 25% glacial acetic acid is added to stop the reaction. Test compounds are typically added as 30 µl additions and the assay buffer volume is reduced to 95 µl. A standard curve of free *p*-nitroaniline is generated using 0-500 µM solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved /min). The endpoint is determined by measuring absorbance at 405 nm in a Molecular Devices UV Max microtiter plate reader.

The potency of the test compounds as DPP-IV inhibitors, expressed as IC₅₀, is calculated from 8-point, dose-response curves using a 4-parameter logistic function.

The following IC₅₀'s were obtained:

Compound	Caco-2 DPP-IV (nM)
Ex. 1	2
Ex. 2A	2
Ex. 2B	5
Ex. 2C	99
Ex. 2D	44
Ex. 2E	27
Ex. 2F	45
Ex. 2G	270
Ex. 2H	79
Ex. 2I	80
Ex. 2J	41
Ex. 2K	58
Ex. 2L	3

Ex. 2M	34
Ex. 2N	5
Ex. 2O	8
Ex. 2P	15
Ex. 2Q	30
Ex. 2R	4
Ex. 2S	3
Ex. 2T	31
Ex. 2U	39
Ex. 2V	9
Ex. 2W	13
Ex. 2X	22
Ex. 2Y	12
Ex. 2Z	86
Ex. 2AA	56
Ex. 2BB	19
Ex. 2CC	29
Ex. 2DD	156
Ex. 2EE	23
Ex. 2FF	15
Ex. 2GG	22
Ex. 2HH	18
+ Ex. 2II	44
+ Ex. 2JJ	94
+ Ex. 2KK	28
+ Ex. 2LL	61
+ Ex. 2MM	22
Ex. 3	124
Ex. 4A	24
Ex. 4B	35
Ex. 4C	83
Ex. 4D	114

Ex. 5	36
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The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described by Kubota, et al. in an article entitled "Involvement of dipeptidylpeptidase IV in an *in vivo* immune response" in Clin. Exp. Immunol., Vol. 89, pgs. 192-197 (1992). Briefly, 5 μ l of plasma are added to 96-well flat-bottom microtiter plates (Falcon), followed by the addition of 5 μ l of 80 mM $MgCl_2$ in incubation buffer (25 mM HEPES, 140 mM NaCl, 1% RIA-grade BSA, pH 7.8). After a 60 min. incubation at room temperature, the reaction is initiated by the addition of 10 μ l of incubation buffer containing 0.1 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-4-methylcoumarin). The plates are covered with aluminum foil (or kept in the dark) and incubated at room temperature for 20 min. After the 20 min. reaction, fluorescence is measured using a CytoFluor 2350 fluorimeter (Excitation 380 nm Emission 460nm; sensitivity setting 4). Test compounds are typically added as 2 μ l additions and the assay buffer volume is reduced to 13 μ l. A fluorescence-concentration curve of free AMC is generated using 0-50 μ M solutions of AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50} , is calculated from 8-point, dose-response curves using a 4 parameter logistic function.

The following IC_{50} 's were obtained:

Compound	human plasma DPP-IV (nM)	rat plasma DPP-IV (nM)
Ex. 1	30	6
Ex. 2A	10	5
Ex. 2B	59	11
Ex. 2C	50	25
Ex. 2D	93	71
Ex. 2E	27	19

Ex. 2F	46	37
Ex. 2G	153	111
Ex. 2H	79	46
Ex. 2I	73	31
Ex. 2J	421	49
Ex. 2K	305	38
Ex. 2L	9	4
Ex. 2M	10	6
Ex. 2N	10	5
Ex. 2O	8	9
Ex. 2P	16	11
Ex. 2Q	38	38
Ex. 2R	23	15
Ex. 2S	4	2
Ex. 2T	26	37
Ex. 2U	27	14
Ex. 2V	28	11
Ex. 2W	19	7
Ex. 2X	47	20
Ex. 2Y	124	37
Ex. 2Z	122	88
Ex. 2AA	33	16
Ex. 2BB	38	13
Ex. 2CC	38	21
Ex. 2DD	66	38
Ex. 2EE	150	46
Ex. 2FF	94	42
Ex. 2GG	20	10
Ex. 2HH	18	10
Ex. 2II	37	12
Ex. 2JJ	45	5
Ex. 2KK		

Ex. 2LL	649	123
Ex. 2MM	71	58
Ex. 3	204	107
Ex. 4A	48	20
Ex. 4B	77	31
Ex. 4C	68	48
Ex. 4D	104	59
Ex. 5	5	4

In view of their ability to inhibit DPP-IV, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are useful in treating conditions mediated by DPP-IV inhibition. Based on the above and findings in the literature, it is expected that the compounds disclosed herein are useful in the treatment of conditions such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation and calcitonin-osteoporosis. In addition, based on the roles of glucagon-like peptides (such as GLP-1 and GLP-2) and their association with DPP-IV inhibition, it is expected that the compounds disclosed herein are useful for example, to produce a sedative or anxiolytic effect, or to attenuate post-surgical catabolic changes and hormonal responses to stress, or to reduce mortality and morbidity after myocardial infarction, or in the treatment of conditions related to the above effects which may be mediated by GLP-1 and/or GLP-2 levels.

More specifically, for example, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, improve early insulin response to an oral glucose challenge and, therefore, are useful in treating non-insulin-dependent diabetes mellitus. The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to improve early insulin response to an oral glucose challenge may be measured in insulin resistant rats according to the following method:

Male Sprague-Dawley rats that had been fed a high fat diet (saturated fat = 57% calories) for 2-3 weeks were fasted for approximately 2 hours on the day of testing, divided into groups of 7-10, and dosed orally with 10 μ mol/kg of test

- o) 1-[4-[[4-(trifluoromethyl)-2-pyrimidinyl]amino]cyclohexyl]amine;
 p) 1-[4-[[3-(trifluoromethyl)-2-pyridinyl]amino]cyclohexyl]amine;
 q) 1-[4-[[4-(4-chlorophenyl)sulfonyl]amino]cyclohexyl]amine;
 r) 1-[4-[[5-(trifluoromethyl)-2-pyridinyl]amino]cyclohexyl]amine;
 s) 1-[4-[[2-chloro-4-pyrimidinyl]amino]cyclohexyl]amine;
 t) 1-[4-[[4-chlorobenzoyl]amino]cyclohexyl]amine;
 u) 1-[4-[[2,2-dimethyl-1-oxopropyl]amino]cyclohexyl]amine;
 v) 1-[4-[[2-benzothiazolyl]amino]cyclohexyl]amine;
 w) 1-[4-[[4-cyanophenyl]amino]cyclohexyl]amine;
 x) 1-[4-[[cyclohexylcarbonyl]amino]cyclohexyl]amine;
 y) 1-[4-[[5-chloro-2-benzothiazolyl]amino]cyclohexyl]amine;
 z) 1-[4-[[[4-(trifluoromethyl)phenyl]sulfonyl]amino]cyclohexyl]amine;
 aa) 1-[4-[[2-thienyl]sulfonyl]amino]cyclohexyl]amine;
 bb) 1-[2-(4-fluorophenyl)-1,1-dimethylethyl]amine (commercially available);
 cc) 1-(1,1-dimethyl-2-phenylethyl)amine (commercially available);
 dd) 1-(4-pentylbicyclo[2.2.2]oct-1-yl)amine (commercially available);
 ee) 1-[4-[4-(trifluoromethyl)phenoxy]cyclohexyl]amine;
 ff) 1-[4-[4-(4-chlorophenoxy)]cyclohexyl]amine;
 gg) 1-[4-[3-(trifluoromethyl)phenoxy]cyclohexyl]amine;
 hh) 1-[4-[3-chlorophenoxy]cyclohexyl]amine;
 ii) 1-[1-[[4-(4-chlorophenyl)amino]carbonyl]-4-piperidinyl]amine;
 jj) 1-[1-[[diisopropylamino]carbonyl]-4-piperidinyl]amine;
 / kk) 1-[1-(4-phenyl-2-thiazolyl)-4-piperidinyl]amine;
 / ll) 1-[1-[4-(4-chlorophenyl)-2-thiazolyl]-4-piperidinyl]amine; and
 / mm) 1-[1-[4-(4-methoxyphenyl)-2-thiazolyl]-4-piperidinyl]amine,

there is obtained the following products as hydrochloride salt or, if (C) in Example 1 is not performed, the free base:

A) 1-[[[2-[[5-cyano-2-pyridinyl]amino]-1,1-dimethylethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, free base as a white solid (melting point = 47°-49°C., ¹³C NMR δ 118.87 ppm (CN));

- W) 1-[[[4-[(4-cyanophenyl)amino]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, dihydrochloride as a white solid (melting point = 185°-167°C, ^{13}C NMR δ 119.29 ppm (CN));
- X) 1-[[[4-[(cyclohexylcarbonyl)amino]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine monohydrochloride as a white solid (melting point = 189°-190°C, ^{13}C NMR δ 119.34 ppm (CN));
- Y) 1-[[[4-[(5-chloro-2-benzothiazolyl)amino]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, dihydrochloride as a white fluffy solid (melting point = 290°-294°C, ^{13}C NMR δ 120.32 ppm (CN));
- Z) 1-[[[4-[[[4-(trifluoromethyl)phenyl]sulfonyl]amino]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a very light yellow solid (melting point = 135°-137°C, ^{13}C NMR δ 119.17 ppm (CN));
- AA) 1-[[[4-[(2-thienyl)sulfonyl]amino]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a white fluffy solid (melting point = 75°-77°C, ^{13}C NMR δ 119.58 ppm (CN));
- BB) 1-[[[2-[(4-fluorophenyl)-1,1-dimethylethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a light fluffy yellow solid (melting point = 198°-200°C, ^{13}C NMR δ 119.28 ppm (CN));
- CC) 1-[[[1,1-dimethyl-2-phenylethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a white solid (melting point = 212°-214°C, ^{13}C NMR δ 118.61 ppm (CN));
- DD) 1-[[[4-(pentylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a fluffy, very light-yellow solid (melting point = 99°-102°C, ^{13}C NMR δ 119.25 ppm (CN));
- EE) 1-[[[4-[4-(trifluoromethyl)phenoxy]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as an off-white solid (decomposed > 260°C, ^{13}C NMR δ 119.29 ppm (CN));
- FF) 1-[[[4-[4-chlorophenoxy]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as an off-white solid (melting point = 232°-235°C, ^{13}C NMR δ 119.61 ppm (CN));
- GG) 1-[[[4-[(3-trifluoromethyl)phenoxy]cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a fluffy, very light-yellow solid (melting point = 120°-122°C, ^{13}C NMR δ 119.23 ppm (CN));

- HH) 1-[[[4-[(3-chlorophenoxy)cyclohexyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a fluffy, light-yellow solid (melting point = 72°-74°C, ^{13}C NMR δ 122.02 ppm (CN));
- II) 1-[[[1-[(4-chlorophenyl)amino]carbonyl]-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a brown solid (melting point = 172°-174°C, ^{13}C NMR δ 119.64 ppm (CN));
- JJ) 1-[[[1-[(diisopropylamino)carbonyl]-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a white solid (melting point = 82°-84°C, ^{13}C NMR δ 118.11 ppm (CN));
- ✓ KK) 1-[[[1-[(4-phenyl-2-thiazolyl)-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as a white solid (melting point = 141°-143°C, ^{13}C NMR δ 119.64 ppm (CN));
- LL) 1-[[[1-[(4-(4-chlorophenyl)-2-thiazolyl)-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as an off-white solid (melting point = 160°-162°C, ^{13}C NMR δ 119.3 ppm (CN)); and
- MM) 1-[[[1-[(4-(4-methoxyphenyl)-2-thiazolyl)-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride as an off-white solid (melting point = 154°-156°C, ^{13}C NMR δ 119.3 ppm (CN)).

EXAMPLE 3

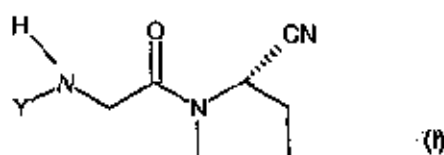
1-[[[1-[(4-Chlorophenyl)sulfonyl]-4-piperidinyl]amino]acetyl]-2-cyano-(S)-pyrrolidine, monohydrochloride

A. Preparation of the title compound as free base

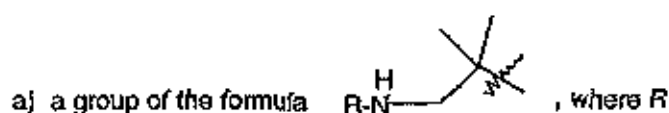
To a 200 ml flask containing 75 ml of CH_2Cl_2 is added 4.0 g (20.0 mmol) of 1-(tert-butoxycarbonylamino)piperidine and 7.4 g (53.3 mmol) of K_2CO_3 and the mixture is cooled in an ice bath. To this cooled mixture is slowly added 2.30 g (13.3 mmol) of the above chloride compound prepared in 1A) dissolved in 30 ml of CH_2Cl_2 . The resultant mixture is stirred at room temperature for 3 days. The K_2CO_3 is then removed via filtration and the filtrate is concentrated via rotovaping. The crude form is then purified on silica gel employing a SIMS/Biotage Flash chromatography system and a 3% solution of methanol in methylene chloride as the eluent to yield the

WHAT IS CLAIMED IS:

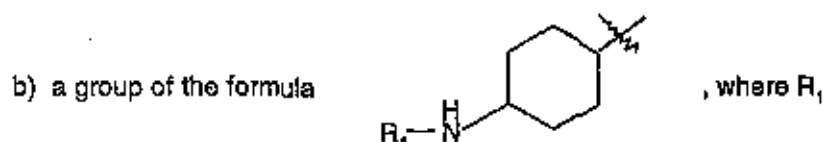
1. A compound of formula I:



where Y is selected from the group consisting of:

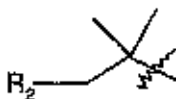


is an unsubstituted pyridine or pyrimidine ring; a pyridine or pyrimidine ring which is mono- or independently di-substituted by halo, trifluoromethyl, cyano, nitro or C_{1-6} alkyl; unsubstituted benzoyl; a benzoyl group which is mono- or di-substituted by halo or C_{1-6} alkyl; C_{1-6} alkylcarbonyl; di- C_{1-6} alkylaminocarbonyl; unsubstituted phenylaminocarbonyl; or a phenylaminocarbonyl group which is mono- or di-substituted on the phenyl ring by halo or C_{1-6} alkyl;

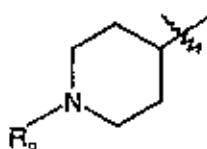


is an unsubstituted pyridine, pyrimidine or phenyl ring; a pyridine, pyrimidine or phenyl ring which is mono- or independently di-substituted by halo, trifluoromethyl, cyano, nitro or C_{1-6} alkyl; an unsubstituted phenylsulfonyl group; a phenylsulfonyl group which is mono- or di-substituted on the phenyl ring by halo, trifluoromethyl, cyano, nitro or C_{1-6} alkyl; unsubstituted benzoyl; a benzoyl group which is mono- or di-substituted by halo or C_{1-6} alkyl; C_{1-6} alkylcarbonyl; thienyl sulfonyl;

unsubstituted benzothiazole; or a benzothiazole group which is substituted on the phenyl ring by halo or C₁₋₆alkyl;

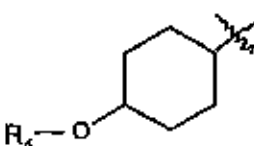
c) a group of the formula , where R₂

is an unsubstituted phenyl ring; or a phenyl ring which is mono- or di-substituted by halo or C₁₋₆alkyl;

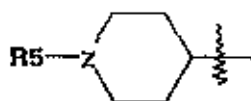
d) a group of the formula , where R₃

is an unsubstituted phenylsulfonyl group; a phenylsulfonyl group which is mono- or di-substituted on the phenyl ring by halo, trifluoromethyl, cyano, nitro or C₁₋₆alkyl; C₁₋₆alkylcarbonyl; di-C₁₋₆alkylaminocarbonyl; unsubstituted benzoyl; a benzoyl group which is mono- or di-substituted by halo or C₁₋₆alkyl; unsubstituted phenylaminocarbonyl; phenylaminocarbonyl which is mono- or di-substituted on the phenyl ring by halo or C₁₋₆alkyl; a phenyl-substituted thiazole ring; or a phenyl-substituted thiazole ring wherein the phenyl ring is mono- or di-substituted by halo or C₁₋₆alkoxy;

e) a (4-pentylbicyclo[2.2.2]oct-1-yl)amine group;

f) a group of the formula , where R₄

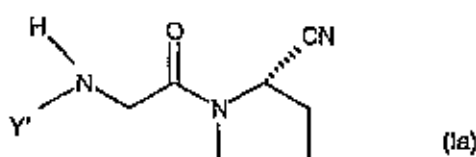
is an unsubstituted phenyl ring; or a phenyl ring which is mono- or di-substituted by halo, trifluoromethyl, cyano, nitro or C₁₋₆alkyl; and



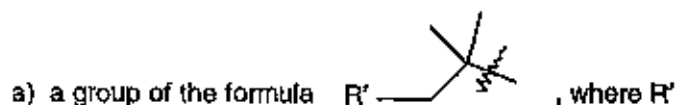
where R₅ is C₃₋₈cycloalkyl-carbonyl, if Z is N; or R₅ is C₃₋₈cycloalkyl-carbonylamino, if Z is CH;

and wherein the bond containing the wavy line signifies the point of attachment of the "Y" group to the glycyl-2-cyanopyrrolidine moiety;
or an acid addition salt thereof.

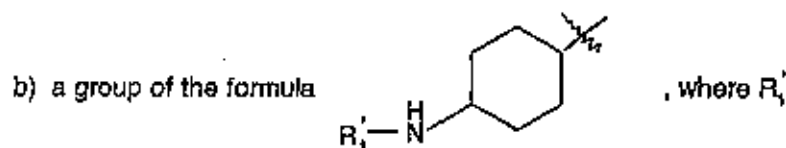
2. A compound according to Claim 1 of formula Ia:



where Y' is selected from the group consisting of:



is an unsubstituted pyridine or pyrimidine ring; a pyridine or pyrimidine ring which is mono- or independently di-substituted by halo, trifluoromethyl or cyano; unsubstituted benzoyl; a benzoyl group which is monosubstituted by halo or C₁₋₆ alkyl; C₁₋₆alkylcarbonyl; di-C₁₋₆alkylaminocarbonyl; unsubstituted phenylaminocarbonyl; or a phenylaminocarbonyl group which is monosubstituted on the phenyl ring by halo or C₁₋₆alkyl;



is an unsubstituted pyridine, pyrimidine or phenyl ring; a pyridine, pyrimidine or phenyl ring which is monosubstituted by halo, trifluoromethyl, cyano, nitro or C₁₋₆alkyl; an unsubstituted phenylsulfonyl group; a phenylsulfonyl group which is monosubstituted on the phenyl ring by halo,



US006011155A

United States Patent [19]
Villhauer

[11] **Patent Number:** **6,011,155**
[45] **Date of Patent:** **Jan. 4, 2000**

- [54] **N-(SUBSTITUTED GLYCYL)-2-CYANOPYRROLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV**
- [75] **Inventor:** Edwin Bernard Villhauer, Morristown, N.J.
- [73] **Assignee:** Novartis AG, Basle, Switzerland
- [21] **Appl. No.:** 08/962,168
- [22] **Filed:** Oct. 31, 1997

Related U.S. Application Data

- [60] Provisional application No. 60/090,570, Nov. 7, 1996.
- [51] **Int. Cl.⁷** C07D 207/34; C07D 207/42; C07D 401/06; C07D 405/10; C07D 409/06
- [52] **U.S. Cl.** 544/333; 544/326; 544/330; 546/208; 546/276.4; 546/279.1; 548/530; 548/540
- [58] **Field of Search** 548/530, 540, 548/517; 546/276.4, 279.1, 208; 544/516, 330, 328, 333

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WO95/11689	5/1995	WIPO	
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WO9534538 12/1995 WIPO.

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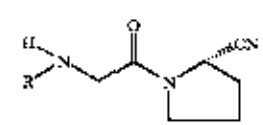
Ashworth et al., Bioorganic and Medicinal Chemistry Letters, vol. 6, No. 22, pp. 2745-2748 (1996).

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Primary Examiner—Floyd D. Higel
Attorney Agent, or Firm—Joseph J. Borovian

[57] **ABSTRACT**

N-(N-substituted glycyI)-2-cyanopyrrolidines of formula I



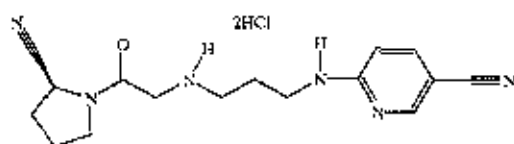
Compounds of formula I inhibit DPP-IV (dipeptidyl-peptidase-IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP-IV and in the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.

11 Claims, No Drawings

31

EXAMPLE 63

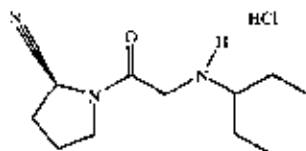
Pyrrolidine, 1-[(3-[(5-cyano-2-pyridinyl)amino]propyl)amino]acetyl-2-cyano-, dihydrochloride



2(3-Aminopropylamino)-5-cyanopyridine (preparation described above) was used as the amine nucleophile. The title compound was a white sticky solid. Melting point=210° C.-212° C. ¹³C NMR(ppm)=119.33.

EXAMPLE 64

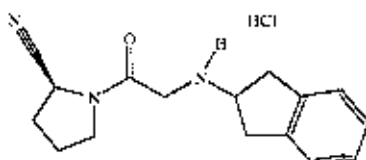
Pyrrolidine, 1-[(1-ethylpropyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



3-Aminopentane (commercially available) was used as the amine nucleophile. The title compound was a white fluffy sticky solid. ¹³C NMR ppm=119.35.

EXAMPLE 65

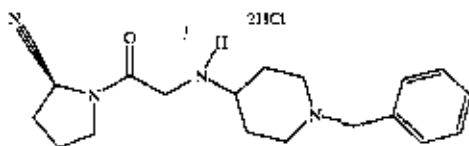
Pyrrolidine, 1-[(2,3-dihydro-1H-inden-2-yl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-Aminoindan (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=182° C.-184° C. ¹³C NMR (ppm)=121.38.

EXAMPLE 66

Pyrrolidine, 1-[(1-phenylmethyl-4-piperidinyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



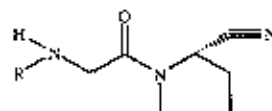
1-Phenyl-4-piperidine (commercially available) was used as the amine nucleophile. The title compound was

32

a white solid. Melting point=280° C.-283° C. decomposed. ¹³C NMR (ppm)=121.39.

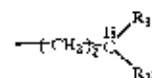
What is claimed is:

1. A compound of formula I:



wherein

R' is a group $-(CH_2)_m-N-R_1$; an unsubstituted (C_{3-12}) -cycloalkyl ring; a (C_{3-12}) -cycloalkyl ring substituted in the 1-position by a hydroxy (C_{1-3}) -alkyl group; a group $-(CH_2)_n-R_2$; a group



a group $(CH_2)_p-R_4$; an isopropyl group; an isopropyl group substituted in the i-position by a hydroxy (C_{1-3}) -alkyl group; or R_5 ;

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

R_2 is an unsubstituted phenyl ring; a phenyl ring mono-, di- or tri-substituted by halo, (C_{1-3}) -alkoxy or a phenyl sulfide (optionally substituted with a (C_{1-3}) -alkoxy); phenoxy; (C_{1-3}) -alkyl; 3,1,1 bicyclic ring system (optionally substituted with 1 or more (C_{1-6}) -alkyl groups); unsubstituted pyridine ring; naphthyl, cyclohexene; or adamantyl;

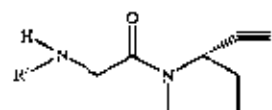
each R_3 , independently, is an unsubstituted phenyl ring; or a phenyl ring mono-substituted by halo or (C_{1-3}) -alkoxy;

R_4 is a 2-oxopyrrolidine group or a (C_{2-12}) -alkoxy group; R_5 is indan; pyrrolidine (unsubstituted or substituted with $-CH_2$ -phenyl); piperidine (unsubstituted or substituted with $-CH_2$ -phenyl); a 2,2,1 bicyclic ring system (unsubstituted or substituted with 1 or more (C_{1-3}) -alkyl groups); adamantyl; a straight or branched chain (C_{1-9}) -alkyl (unsubstituted or substituted by one or more substituents selected from hydroxy, $-CH_2OH$ and phenyl); or a 3,1,1 bicyclic ring system (unsubstituted or substituted with 1 or more (C_{1-6}) -alkyl groups); and m and n independently are integers of 1 to 3;

p is an integer of 2 to 4;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 of formula Ia:



where

R' is a group $-(CH_2)_m-N-R_1$; an unsubstituted (C_{3-7}) -cycloalkyl ring; a (C_{3-7}) -cycloalkyl ring substituted in

236 D₃
227

United States Patent [19]

Danilewicz et al.

[11] 4,001,422

[45] Jan. 4, 1977

[54] 4-AMINOQUINAZOLINE CARDIAC STIMULANTS

[75] Inventors: John C. Danilewicz, Ash; Anthony G. Evans, Sandwich; Allan L. Ham, Broadstairs; Colin Thomson, Sandwich, all of England

[73] Assignee: Pfizer Inc., New York, N.Y.

[22] Filed: July 24, 1975
(Under Rule 47)

[21] Appl. No: 598,723

[30] Foreign Application Priority Data

July 25, 1974 United Kingdom 32805/74
Jan. 6, 1975 United Kingdom 416/75

[52] U.S. Cl. 424/251; 260/256.4 Q

[51] Int. Cl.² A01N 9/22; C07D 239/72

[58] Field of Search 260/256.4 Q; 424/251

[56]

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Primary Examiner—Lewis Gotts

Assistant Examiner—D. R. Phillips

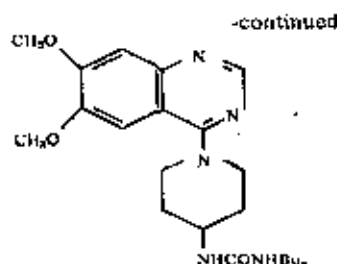
Attorney, Agent, or Firm—Connolly and Hutz

[57]

ABSTRACT

6,7-Dialkoxy-4-aminoquinazoline cardiac stimulants and synthetic methods for the preparation thereof.

24 Claims, No Drawings



The mono maleate salt was prepared by treating an alcoholic solution of the free base with an alcoholic solution of maleic acid. The precipitated salt was recrystallized (from EtOH) m.p. 195°-197° C.

- 5 The following compounds were prepared, using the method of Example I, from the appropriate 4-chloroquinazoline derivative and amine, and were isolated in the form indicated. Both the theoretical and found analyses of the compounds are given, the found 10 analyses being in parenthesis.

TABLE I

Ex.	R ₁	R	Y	Position of Y and R in piperidine nucleus	Salt/Free Base/Hydrate m.p.° C	Analysis % (Found in brackets)		
						C	H	N
2	H	H	-NHCOCH ₃	4-	monohydrochloride monohydrate, 236 - 238° C	53.05 (53.43)	6.55 (6.19)	14.56 (14.92)
3	CH ₃	H	-NHCONH(CH ₂) ₂ CH ₃	4-	monomaleate, 210 - 212° C	58.01 (57.77)	6.82 (6.72)	13.53 (13.26)
4	H	H	-NHCOCH ₃	3-	free base, 172 - 173° C	61.80 (62.10)	6.71 (6.78)	16.96 (16.86)
5	H	H	-CH ₂ COOC ₂ H ₅	4-	monohydrochloride, 192 - 194° C	57.64 (57.13)	6.62 (6.32)	10.61 (10.73)
6	H	H	-NHCONH(CH ₂) ₂ CH ₃	3-	free base, 124 - 126° C	61.99 (62.02)	7.54 (7.68)	18.08 (18.02)
7	CH ₂ CH ₃	H	-NHCONH(CH ₂) ₂ CH ₃	4-	hydrate, 154 - 156° C	62.24 (62.14)	8.07 (7.92)	16.49 (16.34)
8	(CH ₂) ₂ CH	H	-NHCONH(CH ₂) ₂ CH ₃	4-	monohydrochloride monohydrate, 205 - 209° C	57.07 (56.78)	7.91 (7.45)	14.47 (14.38)
9	H	H		4-	free base, 242 - 245° C	65.17 (64.96)	5.72 (5.89)	17.27 (16.92)

EXAMPLE 10

Part A

Preparation of 4-[4-(2-pyridylmethyl amino) piperidino]-6,7-dimethoxyquinazoline.

1-(6,7-Dimethoxyquinazolin-4-yl)piperid-4-one (2.9g) (which may be prepared as in part A of Example 91, hereinafter), and 2-aminomethylpyridine (1.19g) were refluxed together for two hours in benzene (50 ml.) in a flask fitted with a Dean and Stark trap. Ethanol (50 ml.) was added to the cooled solution followed by the slow addition of sodium borohydride (0.76g) with stirring. On completion of the addition stirring as continued for two hours followed by the addition of excess acetic acid. The mixture was poured into water, basified with 5N sodium hydroxide and was extracted with chloroform. Evaporation of the chloroform layer gave a yellow oil which solidified on trituration with ether. Recrystallization from ethyl acetate gave 4-[4-(2-pyridylmethyl-amino)piperidino]-6,7-dimethoxyquinazoline (2 g) m.p. 151°-155° C.

PART B

4-Chloro-6,7-dimethoxyquinazoline (45 g), 4-(3-n-butylureido)piperidine monohydrochloride (80 g) and triethylamine (140 ml) were refluxed in ethanol (450 ml) for 1 1/4 hours. The mixture was then concentrated in vacuo and the resultant solid was stirred in water which was then basified to pH 11 with 5N NaOH solution. The suspension was shaken with chloroform and the organic layer was separated, dried (Na₂CO₃) and evaporated to dryness in vacuo to give a yellow oily solid. Trituration with ether followed by recrystallization from ethanol gave 4-(4-[3-n-butylureido]-piperidino)-6,7-dimethoxyquinazoline (37 g). Small traces of impurities were removed by running a chloroform solution of the product down a glass column packed with "Florisil" and eluting with 10% isopropanol in chloroform. After evaporation, appropriate fractions were bulked and recrystallized from ethanol to give a pure product (21 g), m.p. 204°-5° C.

Anal. Calcd. for: C₂₀H₂₄N₄O₂: C, 62.0; H, 7.5; N, 18.1; Found: C, 62.1; H, 7.6; N, 18.3

United States Patent [19]

Stokbroekx et al.

[11] Patent Number: 5,001,125

[45] Date of Patent: Mar. 19, 1991

[54] ANTI-VIRALLY ACTIVE PYRIDAZINAMINES

[75] Inventors: Raymond A. Stokbroekx, Beerse;
Marcel J. M. Van der Aa, Kasterlee;
Joannes J. M. Willems, Turnhout;
Marcel G. M. Luyckx, Geel, all of
Belgium

[73] Assignee: Janssen Pharmaceutica N.V., Beerse,
Belgium

[21] Appl. No.: 702,772

[22] Filed: Feb. 15, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 593,444, Mar. 26,
1984, abandoned.

[51] Int. Cl.³ C07D 237/06; C07D 237/34

[52] U.S. Cl. 514/252; 544/235;
544/238

[58] Field of Search 514/252; 544/235, 238

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Primary Examiner—Veronica P. Hoke

Attorney, Agent, or Firm—Charles J. Metz

[57] ABSTRACT

Anti-virally active pyridazinamines, compositions containing the same and methods of treating viral diseases in warm-blooded animals.

28 Claims, No Drawings

2-propanone. The salt was filtered off and dried, yielding 0.5 parts (6.6%) of 6-[4-(3-methylphenyl)-1-piperazinyl]-3-pyridazinamine dihydrochloride; mp. 178.3° C. (compound 220).

Example 38

A mixture of 4 parts of 6-chloro-3-(4-ethylphenoxy)-pyridazine and 6 parts of 1-(3-methylphenyl)piperazine was stirred and heated for 3 hours in an oil bath at 110° C. The whole was allowed to stand overnight. Concentrate ammonium hydroxide and trichloromethane were added. The precipitate was filtered off and the filtrate was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 1.7 parts (27%) of 3-(4-ethylphenoxy)-6-[4-(3-methylphenyl)-1-piperazinyl]pyridazine; mp. 106.6° C. (compound 221).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:

3-methyl-6-[4-(3-methylphenyl)-1-piperazinyl]pyridazine; mp. 152.9° C. (compound 222); and
3-[4-(3-methylphenyl)-1-piperazinyl]-6-(methylthio)-pyridazine; mp. 145.0° C. (compound 223).

Example 39

A mixture of 22 parts of ethyl 4-(6-chloro-5-methyl-3-pyridazinyl)-1-piperazinecarboxylate, 28 parts of potassium hydroxide and 160 parts of 1-butanol was stirred overnight at reflux temperature. The reaction mixture was evaporated. Water was added. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. 2,2'-Oxybispropane was added. The product was filtered off and dried, yielding 17 parts (100%) of 3-chloro-4-methyl-6-(1-piperazinyl)-pyridazine (compound 224).

Example 40

A mixture of 6 parts of ethyl [1-(6-chloro-3-pyridazinyl)-4-piperidinyl]carbamate and 60 parts of concentrate hydrochloric acid was stirred and refluxed for 24 hours. The reaction mixture was evaporated. Water was added and the whole was treated with concentrate ammonium hydroxide. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated, yielding 3.8 parts (82%) of 1-(6-chloro-3-pyridazinyl)-4-piperidinamine; mp. 260° C. (dec.) (compound 225).

Example 41

A mixture of 3.6 parts of 3-chloro-6-(1-piperazinyl)-pyridazine monohydrochloride, 5.3 parts of sodium carbonate and 90 parts of N,N-dimethylacetamide was stirred for a while at 60° C. Then there were added 3 parts of (3-bromopropyl)benzene and the whole was stirred overnight at 60° C. The reaction mixture was poured into water. The product was filtered off and converted into the hydrochloride salt in 2-propanol. The salt was filtered off and dried, yielding 3.2 parts (60%) of 3-chloro-6-[4-(3-phenylpropyl)-1-piperazinyl]-pyridazine monohydrochloride; mp. 207.3° C. (compound 226). In a similar manner there were also prepared:

3-chloro-4-methyl-6-[4-(3-phenylpropyl)-1-piperazinyl]pyridazine monohydrochloride 1-

butanol(1:1), monohydrate; mp. 187.2° C. (compound 227);

3-methoxy-6-[4-(3-phenylpropyl)-1-piperazinyl]pyridazine; mp. 78.4° C. (compound 228);

5 3-[4-(3-phenylpropyl)-1-piperazinyl]pyridazine dihydrochloride, monohydrate; mp. 209.0° C. (compound 229); and

1-acetyl-4-(6-chloro-3-pyridazinyl)piperazine; mp. 153.6° C. (compound 230).

Example 42

A mixture of 3 parts of 3-chloro-6-(1-piperazinyl)-pyridazine, 2 parts of benzeneacetylaldehyde, 1 part of a solution of thiophene in methanol 4% and 200 parts of methanol was hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 1.5 parts (33%) of 3-chloro-6-[4-(2-phenylethyl)-1-piperazinyl]pyridazine; mp. 140.0° C. (compound 231).

In a similar manner there were also prepared:

25 3-(4-butyl-1-piperazinyl)-6-chloropyridazine (E)-2-butenedioate(1:1); mp. 188.2° C. (compound 232);

3-chloro-6-(4-cyclohexyl-1-piperazinyl)pyridazine; mp. 187.2° C. (compound 233); and

1-(6-chloro-3-pyridazinyl)-N-(phenylmethyl)-4-piperidinamine; mp. 93.8° C. (compound 234).

Example 43

A mixture of 4 parts of 1-(6-chloro-3-pyridazinyl)-4-(3-methoxyphenyl)-4-piperidinol, 80 parts of ethanol and 50 parts of a hydrochloric acid solution 6 N was stirred for 6 hours at reflux temperature. The reaction mixture was evaporated. Water was added and the whole was treated with concentrate ammonium hydroxide. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 2.5 parts (64%) of 3-chloro-6-[3,6-dihydro-4-(3-methoxyphenyl)-1(2H)-pyridinyl]pyridazine; mp. 126.4° C. (compound 235).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:

3-chloro-6-[4-(3-chlorophenyl)-3,6-dihydro-1(2H)-pyridinyl]pyridazine; mp. 133.9° C. (compound 236);

3-chloro-6-[3,4-dihydro-5-phenyl-1(2H)-pyridinyl]pyridazine; mp. 146.0° C. (compound 237);

3-chloro-6-[3,4-dihydro-5-(3-methylphenyl)-1(2H)-pyridinyl]pyridazine; mp. 160.0° C. (compound 238);

3-chloro-6-[4-(3-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]pyridazine; mp. 124.7° C. (compound 239);

3-chloro-6-[4-(2,3-dimethylphenyl)-3,6-dihydro-1(2H)-pyridinyl]pyridazine; mp. 144.2° C. (compound 240);

60 3-chloro-6-[4-(3-chlorophenyl)-3,6-dihydro-5-methyl-1(2H)-pyridinyl]pyridazine; mp. 88.5° C. (compound 241);

3-chloro-6-[3,4-dihydro-5-[3-(trifluoromethyl)phenyl]-1(2H)-pyridinyl]pyridazine; mp. 163.2° C. (compound 242);

3-chloro-6-[3,6-dihydro-5-[3-(trifluoromethyl)phenyl]-1(2H)-pyridinyl]pyridazine; mp. 112.5° C. (compound 243);


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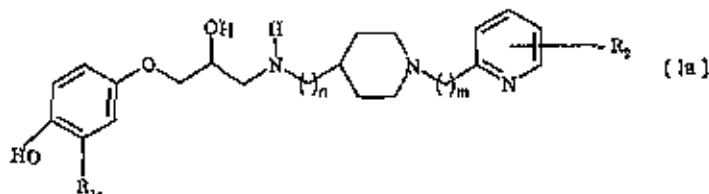
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(54) Title: PHENOXYLPROPANOLAMINES, METHOD FOR THE PRODUCTION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

(54) Titre: PHENOXYLPROPANOLAMINES, PROCÉDÉ POUR LEUR PRÉPARATION ET COMPOSITIONS PHARMACEUTIQUES LES CONTENANT

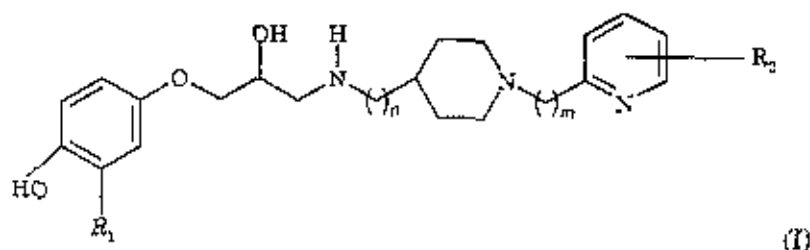


(57) Abstract

The invention relates to compounds of formula (1a), wherein R_1 represents hydrogen, an $-S(O)_2-(C_1-C_4)Alk$ group, a $-CO(C_1-C_4)Alk$ group, an $-NH(SO_2-(C_1-C_4)Alk)$ group, an $NHCO(C_1-C_4)Alk$ group, a 2-furyl group or a halogen; R_2 represents hydrogen or a $(C_1-C_4)Alk$ group, a $(C_1-C_4)oxalkylate$ group, a halogen, $-COOH$, $-COO(C_1-C_4)Alk$, $-CN$, $-CONR_3R_4$, $-NO_2$, $-SO_2NH_2$, $-NH(SO_2(C_1-C_4)Alk)$; m and n independently represent 0, 1 or 2; R_3 and R_4 represent independently hydrogen or a $(C_1-C_4)Alk$ group; Z is 1 or 2. The invention also relates to the salts or solvates, pharmaceutical compositions containing said compounds, a method for the preparation thereof and to synthesis intermediates.

(57) Abrégé

L'invention concerne des composés de formule (1a) dans laquelle R_1 représente l'hydrogène, un groupe $-S(O)_2-(C_1-C_4)Alk$, un groupe $-CO(C_1-C_4)Alk$, un groupe $-NH(SO_2-(C_1-C_4)Alk)$, un groupe $NHCO(C_1-C_4)Alk$, un groupe 2-furyle ou un halogène; R_2 représente l'hydrogène ou un groupe $(C_1-C_4)Alk$, un groupe $(C_1-C_4)oxalkyle$, un halogène, $-COOH$, $-COO(C_1-C_4)Alk$, $-CN$, $-CONR_3R_4$, $-NO_2$, $-SO_2NH_2$, $-NH(SO_2(C_1-C_4)Alk)$; m et n représentent indépendamment 0, 1 ou 2; R_3 et R_4 représentent indépendamment l'hydrogène ou un groupe $(C_1-C_4)Alk$; Z est 1 ou 2; et leurs sels ou solvates, les compositions pharmaceutiques les contenant, un procédé pour leur préparation, et des intermédiaires de synthèse.



où

R_1 représente l'hydrogène, un groupe $-S(O)_2-(C_1-C_4)Alk$, un groupe $-CO(C_1-C_4)Alk$ ou un groupe $-NHSO_2-(C_1-C_4)Alk$;

- 5 R_2 représente l'hydrogène ou un groupe $(C_1-C_4)Alk$, un groupe $(C_1-C_4)alcoyle$, un halogène, $-COOH$, $-COO(C_1-C_4)Alk$, $-CONR_3R_4$, $-SO_2NH_2$, $-NHSO_2(C_1-C_4)Alk$;

m et n indépendamment 0, 1 ou 2;

R_3 et R_4 représentent indépendamment l'hydrogène ou un groupe $(C_1-C_4)Alk$;

- 10 Z est 1 ou 2;

et leurs sels ou solvates.

Dans la présente description le terme " $(C_1-C_4)Alk$ " désigne un radical monovalent d'un hydrocarbure en C_1-C_4 saturé à chaîne droite ou ramifiée.

- 15 Les sels des composés de formule (I) et (Ia) selon la présente invention comprennent aussi bien les sels d'addition avec des acides minéraux ou organiques pharmaceutiquement acceptables tels que le chlorhydrate, le bromohydrate, le sulfate, l'hydrogénosulfate, le dihydrogénophosphate, le citrate, le maléate, le tartrate, le fumarate, le gluconate, le méthanesulfonate, le 2-naphtalènesulfonate, etc., que les sels d'addition qui permettent une séparation ou une cristallisation convenable des composés
- 20 de formule (I) ou (Ia) tels que le picrate, l'oxalate ou les sels d'addition avec des acides optiquement actifs, par exemple les acides camphorsulfoniques et les acides mandéliques ou mandéliques substitués.

- De plus, lorsque les composés de formule (I) et (Ia) possèdent un groupe carboxy libre les sels comprennent aussi les sels avec des bases minérales, de préférence celles
- 25 avec des métaux alcalins tels que le sodium ou le potassium, ou avec des bases organiques.

- Les stéréoisomères optiquement purs, ainsi que les mélanges d'isomères des composés de formule (I) et (Ia), dus aux carbones asymétriques ou au groupe sulfinyle dans la signification de R_{1a} ou R_1 , dans une proportion quelconque, sont partie de la
- 30 présente invention.

Des composés préférés de la présente invention comprennent les composés de formule (I) ou (Ia) où le groupe R_2 est dans la position 5 de la pyridine.

D'autres composés préférés comprennent les composés de formule (I) ou (Ia) où le groupe R_2 est dans la position 6 de la pyridine.

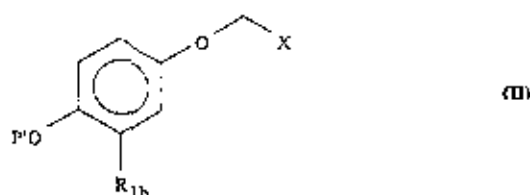
D'autres composés préférés sont ceux où le groupe $(C_1-C_4)Alk$ est un groupe méthyle ou éthyle.

5 D'autres composés préférés sont ceux où R_2 est choisi parmi $-COOH$, $-COO(C_1-C_4)Alk$, $-CN$, $-NO_2$, $-CONR_3R_4$, $-NHSO_2-(C_1-C_4)Alk$.

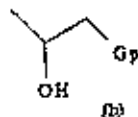
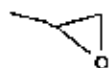
D'autres composés préférés sont ceux où R_2 est un halogène notamment le chlore.

D'autres composés préférés encore sont ceux où n et m sont zéro.

10 Les composés de formule (I) ou (Ia) peuvent être préparés en traitant un composé de formule (II) :

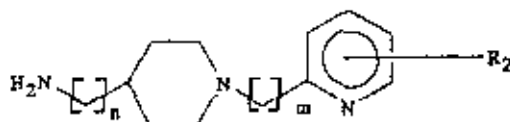


dans laquelle R_{1b} est R_{1a} ou R_1 tels qu'indiqués ci-dessus, P' est un groupe protecteur et X est un groupe de formule (a) ou (b)



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où Gp est un groupe partant tel que le tosylate, le mésylate ou un halogène, avec une amine de formule (III)

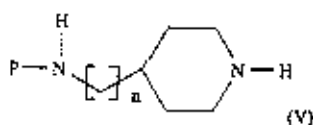


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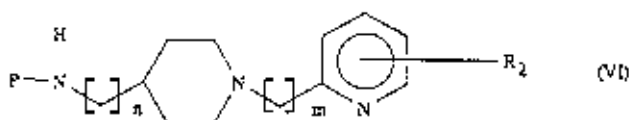
20 où n , m et R_2 sont tels que définis ci-dessus, en clivant le groupe P' selon les méthodes usuelles et éventuellement transformant le composé de formule (I) ou (Ia) ainsi obtenu en un de ses sels.

25 Plus particulièrement, la réaction entre les composés de formule (II) et (III) est réalisée dans un solvant organique, tel qu'un alcool inférieur comme le méthanol, l'éthanol et l'isopropanol; le diméthylsulfoxyde; un éther linéaire ou cyclique; un amide comme le diméthylformamide ou le diméthylacétamide; en utilisant des quantités au moins équimoléculaires des réactifs, éventuellement en faible excès d'amine.

La température de la réaction est comprise entre la température ambiante et la température de reflux du solvant choisi.



où n est tel que défini ci-dessus et P représente un groupe protecteur, dans un solvant organique en présence d'une base, suivie par clivage du groupe P des composés de formule (VI) ainsi obtenus.



5

Comme solvant de réaction, on peut bien utiliser par exemple le diméthylformamide, la pyridine, le diméthylsulfoxyde, un éther linéaire ou cyclique ou un solvant chloruré tel que le dichlorométhane.

Comme base on peut utiliser par exemple un hydroxyde alcalin, un carbonate alcalin tel que le carbonate de potassium ou une amine tertiaire telle que la triéthylamine.

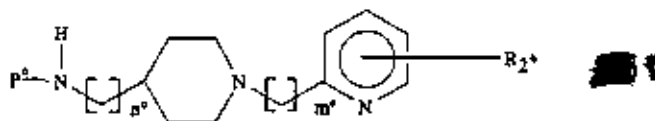
La réaction de condensation ci-dessus est complétée en quelques heures, normalement en 2-12 heures.

La température de réaction est comprise entre la température ambiante et la température de reflux du solvant choisi.

Comme groupes protecteurs P , on peut utiliser les groupes protecteurs usuels par exemple tels que par exemple le *tert*-butoxycarbonyl, l'acétyle, le carbobenzyloxy.

Le clivage de ces groupes protecteurs est effectué selon les méthodes habituelles décrites le groupe protecteur choisi; dans le cas du *tert*-butoxycarbonyl par exemple, le clivage est normalement effectué par hydrolyse acide.

Certaines des amines intermédiaires de formule (III) et (VI), regroupées dans la formule (VII) ci-dessous



25 où

P° est l'hydrogène ou un groupe protecteur;

n° et m° sont 0, 1 ou 2;

R_2° est un $(C_1-C_4)Alk$; $(C_1-C_4)alcoxy$, $-COOH$, $-COO(C_1-C_4)Alk$, $-CN$, $-$

NO_2 , $-CONR_3^\circ R_4^\circ$, $-SO_2NH_2$, $-NHSO_2(C_1-C_4)Alk$;

30 R_3° et R_4° sont l'hydrogène ou un groupe $(C_1-C_4)Alk$;

En opérant comme décrit dans l'exemple 2 mais en utilisant le produit de l'exemple 3 au lieu du produit de l'exemple 1, on obtient le composé du titre. P.f. 148-150°C.

EXEMPLE 5

5 **4-tert-butoxycarbonylamino-1-(5-nitropyrid-2-yl)-pipéridine.**

En opérant comme décrit dans l'exemple 1 mais en utilisant la 2-chloro-5-nitropyridine au lieu du 6-chloronicotinamide, on obtient le composé du titre. P.f. 220°C.

EXEMPLE 6

10 **4-amino-1-(5-nitropyrid-2-yl)-pipéridine.**

En opérant comme décrit dans l'exemple 2 mais en utilisant le produit de l'exemple 5 au lieu du produit de l'exemple 1, on obtient le chlorhydrate composé du titre. P.f. 266-270°C.

On libère la base à l'aide d'une solution de H_2O/NH_4OH et extraction à l'acétate d'éthyle. On obtient le composé du titre. P.f. 115-117°C.

EXEMPLE 7

15 **4-tert-butoxycarbonylamino-1-(5-cyanopyrid-2-yl)-pipéridine.**

En opérant comme décrit dans l'exemple 1 mais en utilisant la 2-chloro-5-cyanopyridine au lieu du 6-chloronicotinamide, on obtient le composé du titre. P.f. 192-194°C.

EXEMPLE 8

20 **4-amino-1-(5-cyanopyrid-2-yl)-pipéridine.**

En opérant comme décrit dans l'exemple 2 mais en utilisant le produit de l'exemple 7 au lieu du produit de l'exemple 1, et en traitant le sel chlorhydrate ainsi obtenu avec une solution aqueuse de NH_4OH , on obtient le composé du titre. P.f. 68-72°C.

EXEMPLE 9

25 **9a/ 3-[1-(5-aminocarbonylpyrid-2-yl)-4-pipéridinylamino]-1-(4-benzyloxyphénoxy)-2-propanol.**

30 On mélange 1,2 g (0,0054 mole) du produit de l'exemple 2 (base), 1,4 g (0,0054 mole) de 4-benzyloxy-1-(2,3-époxypropoxy)benzène dans 50 ml de diméthylsulfoxyde et on chauffe à 70°C pendant 18 heures. On verse dans de l'eau, on extrait à l'acétate d'éthyle, on sèche, on filtre et on évapore le solvant sous pression réduite. On obtient le composé du titre. P.f. 160-162°C.

35 **9b/ 3-[1-(5-aminocarbonylpyrid-2-yl)-4-pipéridinylamino]-1-(4-hydroxyphénoxy)-2-propanol.**

On hydrogène 0,77 g du composé de l'étape précédente à 40 °C à la pression ambiante dans 30 ml de THF et 30 ml d'éthanol en présence de 0,1 g de Pd/C à 10%

EXEMPLE 21

3-[(1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylméthyl)amino]-1-(4-hydroxyphénoxy)-2-propanol (chlorhydrate).

- En opérant comme décrit dans l'exemple 9 mais en utilisant le produit de l'exemple 20 (base) au lieu du produit de l'exemple 1, on obtient le composé du titre base. On prépare le chlorhydrate à l'aide d'une solution d'acide chlorhydrique en isopropanol. On obtient le composé du titre. P.f. 195°C déca.

EXEMPLE 22

4-tert-butylloxycarbonylamino-1-(pyrid-2-yl)-piperidine.

- En opérant comme décrit dans l'exemple 1 mais en utilisant le 2-bromo-pyridine au lieu du p-ter ester éthylique de l'acide 6-chlorométhylamine on obtient le composé du titre. P.f. : 118-120°C.

EXEMPLE 23

4-amino-1-(pyrid-2-yl)-piperidine et son chlorhydrate.

- En opérant comme décrit dans l'exemple 2 mais en utilisant le produit issu de l'exemple 22 on obtient le composé du titre. P.f. : 227-230°C.

EXEMPLE 24

3-[1-(pyrid-2-yl)-4-pipéridinylamino]-1-(4-hydroxy-phénoxy)-2-propanol et son dichlorhydrate hydraté.

- En opérant comme décrit dans l'exemple 9 mais en utilisant le produit de l'exemple 23 base au lieu du produit de l'exemple 2 et de l'éthanol absolu au lieu du diméthylsulfoxyde on obtient le composé du titre base. On prépare le chlorhydrate à l'aide d'une solution d'acide chlorhydrique en isopropanol. On obtient le composé du titre. P.f. : 137-139.

EXEMPLE 25

(2S)-3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-(4-hydroxy-phénoxy)-2-propanol.

25a) (2S)-3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-(4-benzoyloxy-phénoxy)-2-propanol.

- On mélange 0,81 g (0,0033 mole) du produit de l'exemple 4 avec 0,83 g (0,0033 mole) de (2S)-4-benzoyloxy-1-(2,3-époxypropoxy)benzène dans 90 ml de toluène et on chauffe au reflux pendant 20 heures. On évapore le solvant et on ajoute de l'éthanol éthylique. On filtre et on purifie le brut de réaction par chromatographie en éluant par un mélange chlorure de méthylène/méthanol = 95/5.

- On obtient le composé du titre. P.f. : 105-107°C; $[\alpha]_D^{25} = -5,12^\circ$ (C = 1% en CHCl_3).

25b) (2S)-3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-(4-hydroxy-phénoxy)-2-propanol.

Le produit issu de l'étape précédente est soumis à une hydrogénation selon la procédure décrite dans l'exemple 9b. Le brut de réaction est purifié par flash-chromatographie en éluant par un mélange chlorure de méthylène/méthanol = 95/5. On obtient le composé du titre. P.f. 135-137°C; $[\alpha]_D^{25} = 5,64^\circ$ (C=1% en CH_3OH).

EXEMPLE 26

16a) 3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-[(4-benzoyloxy-3-méthylsulfinyl)-phénoxy]-2-propanol.

- On mélange 0,75 g (0,0024 mole) de 4-benzoyloxy-3-méthylsulfinyl-1-(2,3-époxypropoxy)benzène (préparé selon le procédé décrit dans l'US 4,396,629) avec 0,646 g (0,0026 mole) du produit de l'exemple 4 base dans l'éthanol absolu. On chauffe au reflux pendant 4 heures, on sèche et on purifie le brut de réaction par chromatographie en éluant avec des mélanges de CH_2Cl_2 , CH_3OH , NH_4OH dans des proportions variables entre 95:5:0,2 et 90:10:1. On obtient le produit de réaction. P.f. : 113-130°C.

- 26b) 3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-[(4-hydroxy-3-méthylsulfinyl)-phénoxy]-2-propanol et son dichlorhydrate dihydraté

- On chauffe le produit de l'étape précédente pendant 7 heures à 55°C dans 70 ml de CF_3COOH . On évapore partiellement le solvant, on ajoute de l'acétate d'éthyle et du toluène et on évapore encore le solvant. On ajoute de l'eau saturée en Na_2CO_3 et on extrait à l'acétate d'éthyle. Le brut de réaction est séché et purifié par flash-chromatographie en éluant par un mélange de CH_2Cl_2 , CH_3OH , NH_4OH dans des proportions variables entre 92:8:0,8 et 90:10:1. On obtient le composé du titre comme base libre (P.f. : 95-100°C). On dissout le produit dans l'acétone et on ajoute une solution de HCl en isopropanol, on filtre et on lave à l'acétone. On obtient le produit du titre. P.f. : 173-175°C.

EXEMPLE 27

4-tert-butylloxycarbonylamino-1-(5-méthylpyrid-2-yl)-piperidine.

- On chauffe à 130°C pendant une nuit 2,03 g (0,0101 mole) du produit de la préparation 1 avec 3,5 g (0,0203 mole) de 2-bromo-5-méthylpyridine et 1,5 ml de triéthylamine dans 50 ml de diméthylsulfoxyde. On verse dans l'eau, on extrait le brut de réaction qui est purifié par flash-chromatographie (cyclohexane/éthylacétate = 1/3). P.f. : 121-123°C.

EXEMPLE 28

4-amino-1-(5-méthylpyrid-2-yl)-piperidine et son dichlorhydrate hydraté.

- On chauffe au reflux pendant 4 heures une solution contenant le produit de l'exemple 27 dans 18 ml de éthyle acétate et 18 ml de HCl en éthyle acétate (environ 3N). On filtre et on lave à l'acétone. On cristallise en isopropanol et on obtient le composé du titre. P.f. : 281-283°C.

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EXEMPLE 49

3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-[3-bromo-4-

hydroxypiphenoxyl-2-propenyl

On fait réagir le produit de l'exemple 48 avec le produit de l'exemple 4 (base),

selon le procédé décrit dans l'exemple 9a. Le produit issu de cette réaction est traité avec

du CF_3COOH à 55°C pendant 4 heures. Le brut de réaction est purifié par

chromatographie ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ = 93/7). On cristallise le produit dans de

l'isopropanol. P.C. : 123-126 °C.

EXEMPLE 50

4-benzoyloxy-3-[(N-tert-butoxycarbonyl-N-méthylsulfonamido)-1-(2,3-

phenoxypropoxy)-benzène,

On chauffe au reflux pendant 24 heures une solution contenant 1 g (0,0025

moles) de 4-phénylphényloxy-3-[(N-tert-butoxycarbonyl-N-méthylsulfonamido)-1-

phenoxypropoxy)-benzène et 1,1 g (0,008 mole) de K_2CO_3 . On filtre, on évapore le solvant et on

purifie le brut de réaction par chromatographie en échant par un mélange

cyclohexane/diéthyl acétate = 7/3.

EXEMPLE 51

5[1a]-3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-[4-benzoyloxy-3-

méthylsulfonamido)-phenoxy]-2-propenyl

On fait réagir sous agitation pendant 48 heures à température ambiante 0,77 g

(0,00172 mole) du produit de l'exemple 50, 0,86 g (0,0035 mole) du produit de l'exemple

4 (base et 0,2 g de LiClO_4 dans 50 ml de acetonitrile. On chauffe à 40 °C pendant 9

heures et on arrête la réaction. On évapore le solvant et on ajoute 50 ml de CH_2Cl_2 et une

solution 3N de HCl en éthy acétate (20 ml). On chauffe pendant 4 heures à 40 °C pour

évaporer le solvant. On lave à l'acétate et on extrait à l'acétate diéthylique. On évapore le

solvant et on purifie le brut de réaction par flash chromatographie en échant par un

mélange $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ = 9/1. On obtient le produit du titre. P.C. : 112-114 °C

5[1b]-3-[1-(5-éthoxycarbonylpyrid-2-yl)-4-pipéridinylamino]-1-[4-hydroxy-3-

méthylsulfonamido)-phenoxy]-2-propenyl

On hydrolyse le produit de l'exemple 51a selon le procédé décrit dans l'exemple

9b, en opérant à une pression variable entre la pression ambiante et 50 psi. Le brut de

réaction est purifié par flash-chromatographie ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ = 9/1). On obtient le

produit du titre. P.C. : 77-80 °C.

On chauffe au reflux pendant 24 heures 6,7 g (0,035 mole) de 2-bromo-5-

chloropyridine 4,97 g (0,035 mole) de 4-acétylmino-pipéridine et 4,83 g (0,035 mole)

EXEMPLE 52

On chauffe au reflux pendant 5 heures 5,5 g (0,022 moles) du produit de

l'exemple 52 dans 50 ml d'alcool amylique. On évapore le solvant, on ajoute de l'eau et un

extrait au CH_2Cl_2 . On obtient le produit du titre. P.C. : 196-198 °C.

EXEMPLE 53

On obtient le produit du titre. P.C. : 295 °C déc.

3-[1-(5-chloropyrid-2-yl)-4-pipéridinylamino]-1-(4-hydroxy-3-benzoyloxy)-2-propenyl

On opère comme décrit dans l'exemple 12 mais en utilisant le produit de

l'exemple 53 (base) au lieu du produit de l'exemple 6. Après le traitement avec

CF_3COOH on évapore, on ajoute de l'éthyle acétate et on lave à l'eau d'une solution de

NaH_2PO_4 jusqu'à pH 5. On évapore le solvant et on purifie le brut de réaction par flash-

chromatographie en échant par un mélange $\text{CH}_2\text{Cl}_2/\text{méthanol}$ = 9/1. On obtient le

produit du titre. P.C. : 148-150 °C.

EXEMPLE 55

2-chloro-6-éthoxycarbonylpyridine

On chauffe au reflux pendant 8 heures 14,1 g (0,0895 mole) de 2-chloro-6-

éthoxycarbonylpyridine dans 135 ml d'une solution de HCl en éthanol. On évapore le

solvant, on ajoute de l'acétate diéthylique et on lave à l'eau d'une solution de bicarbonate.

On évapore encore le solvant et on purifie le brut de réaction par flash-chromatographie

(cyclohexane/acétate diéthylique = 7/3). On obtient le produit du titre.

EXEMPLE 56

4-tert-butoxycarbonylpyrid-2-yl)-4-pipéridine

On chauffe à 80 °C pendant 24 heures une solution contenant 1,17 g (0,0063

mole) du produit de l'exemple 55, 1,27 g (0,0063 mole) du produit de la préparation 1,

0,9 ml de triéthylamine et du NaI dans 34,2 ml de diméthylformamide. On verse dans

l'eau, on extrait à l'acétate diéthylique et on évapore le solvant. Le brut de réaction est

purifié par flash-chromatographie en échant par un mélange cyclohexane/acétate diéthylique

EXEMPLE 57

4-amino-1-(6-éthoxycarbonylpyrid-2-yl)-4-pipéridine et son chlorohydrate

On chauffe au reflux pendant 8 heures 0,99 g (0,0025 mole) du produit de

l'exemple 56 dans 6 ml d'acétate diéthylique et 6 ml d'une solution de HCl en acétate

diéthylique. On filtre, on lave à l'acétate, on ajoute de l'acétate et on extrait à l'acétate

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N-(SUBSTITUTED GLYCYL)-2-
CYANOPYRROLIDINES,
PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM AND THEIR USE IN
INHIBITING DIPEPTIDYL PEPTIDASE-IV

This application claims the benefit of Provisional Application number 60,030,570 filed on Nov. 7, 1996.

FIELD OF THE INVENTION

The present invention relates to the area of dipeptidyl peptidase-IV (DPP-IV) inhibition. 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.

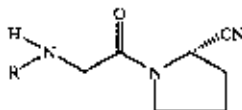
More recently, it was discovered that DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1). More particularly, DPP-IV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Since the half-life 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).

SUMMARY OF THE INVENTION

The present invention provides new DPP-IV inhibitors which are effective in treating conditions mediated by DPP-IV. More particularly, the present invention relates to certain N-(substituted glycyll)-2-cyanopyrrolidines which inhibit DPP-IV. In addition, the present invention provides pharmaceutical compositions useful in inhibiting DPP-IV comprising a therapeutically effective amount of a N-(substituted glycyll)-2-cyanopyrrolidine disclosed herein. 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 N-(substituted glycyll)-2-cyanopyrrolidine.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel N-(substituted glycyll)-2-cyanopyrrolidines of formula I:



wherein R is:

a) $R_1R_2N(CH_2)_m$ wherein

R₁ is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with (C₁₋₄) alkyl, (C₁₋₄)alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen;

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R₂ is hydrogen or (C₁₋₄)alkyl; and m is 2 or 3;

b) (C₂₋₁₂)cycloalkyl optionally monosubstituted in the 1-position with (C₁₋₃)hydroxyalkyl;

c) R₂(CH₂)_n wherein either

R₂ is phenyl optionally mono- or independently di- or independently trisubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is (C₁₋₄)alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C₁₋₄)alkyl; a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen; cyclohexene; or adamantyl; and

n is 1 to 3; or

R₂ is phenoxy optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen; and

n is 2 or 3;

d) (R₃)₂CH(CH₂)₂ wherein each R₃ independently is phenyl optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen;

e) R₄(CH₂)_p wherein R₄ is 2-oxopyrrolidinyl or (C₂₋₄)alkoxy and p is 2 to 4;

f) isopropyl optionally monosubstituted in 1-position with (C₁₋₃)hydroxyalkyl;

g) R₄ wherein R₄ is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with (C₁₋₄)alkyl, (C₁₋₄)alkoxy or halogen; or a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C₁₋₄)alkyl; adamantyl; or (C₁₋₄)alkyl optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with (C₁₋₄)alkyl, (C₁₋₄)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 c) as defined above. R₁ preferably is a pyridinyl or pyrimidinyl moiety optionally substituted as defined above. R₂ preferably is hydrogen. R₃ preferably is phenyl optionally substituted as defined above. R₄ preferably is alkoxy as defined above. R₄ preferably is optionally substituted alkyl as defined above. m preferably is 2. n preferably is 1 or 2, especially 2. p preferably is 2 or 3, especially 3.

Pyridinyl preferably is pyridin-2-yl; it preferably is unsubstituted or monosubstituted, preferably in 5-position. Pyrimidinyl preferably is pyrimidin-2-yl. It preferably is unsubstituted or monosubstituted, preferably in 4-position. Preferred as substituents for pyridinyl and pyrimidinyl are halogen, cyano and nitro, especially chlorine.

When it is substituted, phenyl preferably is monosubstituted; it preferably is substituted with halogen, preferably

chlorine, or methoxy. It preferably is substituted in 2-, 4- and/or 5-position, especially in 4-position.

(C₃₋₇)cycloalkyl preferably is cyclopentyl or cyclohexyl. When it is substituted, it preferably is substituted with hydroxymethyl. (C₁₋₄)alkoxy preferably is of 1 or 2 carbon atoms, it especially is methoxy. (C₂₋₆)alkoxy preferably is of 3 carbon atoms, it especially is isopropoxy. Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially chlorine. (C₁₋₆)alkyl preferably is of 1 to 6, preferably 1 to 4 or 3 to 5, especially of 2 or 3 carbon atoms, or methyl. (C₁₋₄) alkyl preferably is methyl or ethyl, especially methyl. (C₁₋₃)hydroxyalkyl preferably is hydroxymethyl.

A [3.1.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[3.1.1]hept-2-yl optionally disubstituted in 6-position with methyl, or bicyclo[3.1.1]hept-3-yl optionally trisubstituted with one methyl in 2-position and two methyl groups in 6-position. A [2.2.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[2.2.1]hept-2-yl.

Naphthyl preferably is 1-naphthyl. Cyclohexene preferably is cyclohex-1-en-1-yl. Adamantyl preferably is 1- or 2-adamantyl.

A pyrrolidinyl or piperidinyl moiety optionally substituted as defined above preferably is pyrrolidin-3-yl or piperidin-4-yl. When it is substituted it preferably is N-substituted.

A preferred group of compounds of the invention is the compounds of formula I wherein R is R' (compounds Ia), whereby R' is:

R₁"NH(CH₂)₂- wherein R₁" is pyridinyl optionally mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro; or unsubstituted pyrimidinyl;

(C₃₋₇)cycloalkyl optionally monosubstituted in 1-position with (C₁₋₃)hydroxyalkyl;

R₄'(CH₂)₂- wherein R₄' is (C₂₋₆)alkoxy; or

R₅, wherein R₅ is as defined above;

in free form or in acid addition salt form.

More preferred compounds of the invention are those compounds of formula I wherein R is R" (compounds Ib), whereby R" is:

R₁"NH(CH₂)₂- wherein R₁" is pyridinyl mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;

(C₂₋₆)cycloalkyl monosubstituted in 1-position with (C₁₋₃)hydroxyalkyl;

R₂'(CH₂)₂- wherein R₂' is as defined above; or

R₅' wherein R₅' is a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C₁₋₃)alkyl; or adamantyl;

in free form or in acid addition salt form.

Even more preferred compounds of the invention are the compounds of formula I wherein R is R'" (compounds Ic), whereby R'" is:

R₁"NH(CH₂)₂- wherein R₁" is as defined above;

(C₁₋₆)cycloalkyl monosubstituted in 1-position with hydroxymethyl;

R₄'(CH₂)₂- wherein R₄' is as defined above; or

R₅" wherein R₅" is adamantyl;

in free form or in acid addition salt form.

A further group of compounds of the invention is compounds Ip, wherein R is R^p, which is:

a) R₁"NH(CH₂)₂- wherein R₁" is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;

b) (C₃₋₇)cycloalkyl optionally monosubstituted in 1-position with (C₁₋₃)hydroxyalkyl;

c) R₂"(CH₂)₂- wherein R₂" is phenyl optionally mono- or independently di- or independently trisubstituted with halogen or (C₁₋₃)alkoxy;

d) (R₃")₂C=H(CH₂)₂- wherein each R₃" independently is phenyl optionally monosubstituted with halogen or (C₁₋₃)alkoxy;

e) R₄(CH₂)₂- wherein R₄ is as defined above; or

f) isopropyl optionally monosubstituted in 1-position with (C₁₋₃)hydroxyalkyl;

in free form or in pharmaceutically acceptable acid addition salt form.

A further group of compounds of the invention is compounds Is, wherein R is R^s, which is:

a) R₁"R_{1a}"(CH₂)_{ms}- wherein R₁" is pyridinyl optionally mono- or independently disubstituted with chlorine, trifluoromethyl, cyano or nitro; pyrimidinyl optionally monosubstituted with chlorine or trifluoromethyl; or phenyl; R_{1a}" is hydrogen or methyl; and ms is 2 or 3;

b) (C₃₋₇)cycloalkyl optionally monosubstituted in 1-position with hydroxymethyl;

c) R₂"(CH₂)_{ms}- wherein either R₂" is phenyl optionally mono- or independently di- or independently trisubstituted with halogen, alkoxy of 1 or 2 carbon atoms or phenyllithio monosubstituted in the phenyl ring with hydroxymethyl; (C₁₋₆)alkyl; 6,6-dimethylbicyclo[3.1.1]hept-2-yl; pyridinyl; naphthyl; cyclohexene; or adamantyl; and ms is 1 to 3; or

R₂" is phenoxy; and ms is 2;

d) (3,3-diphenyl)propyl;

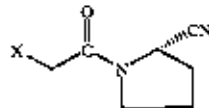
e) R₄'(CH₂)_{ps}, wherein R₄' is 2-oxopyrrolidin-1-yl or isopropoxy and ps is 2 or 3;

f) isopropyl optionally monosubstituted in 1-position with hydroxymethyl;

g) R₅" wherein R₅" is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally N-substituted with benzyl; bicyclo[2.2.1]hept-2-yl; 2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl; adamantyl; or (C₁₋₆)alkyl optionally mono- or independently disubstituted with hydroxy, hydroxymethyl or phenyl;

in free form or in acid addition salt form.

The compounds of the invention may be prepared by a process which comprises coupling a reactive (2-cyanopyrrolidino)carbonylmethylene compound with an appropriate substituted amine; more particularly, for the preparation of the compounds of formula I it comprises reacting a compound of formula II



wherein X is a reactive group, with a compound of formula III

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

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X preferably is a halogen such as bromine, chlorine or iodine.

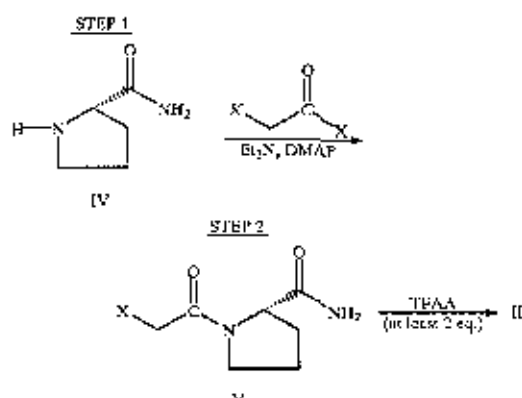
The process of the invention may be effected in conventional manner.

The compound of formula II is preferably reacted with at least 3 equivalents of a primary amine of formula III. The reaction is conveniently conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran. The temperature preferably is of from about 0° to about 35° C., preferably between about 0° and about 25° C.

The compounds of the invention may be isolated from the reaction mixture and purified in conventional manner, e.g. by chromatography.

The starting materials may also be prepared in conventional manner.

The compounds of formula II may e.g. be prepared by the following two-step reaction scheme:



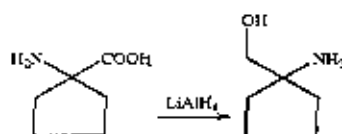
Step 1 involves the reaction of the pyrrolidine of formula IV with a slight molar excess of a haloacetylhalide such as bromoacetyl bromide or chloroacetyl chloride and triethylamine and a catalytic amount of dimethylaminopyridine (DMAP). The reaction conveniently is conducted in the presence of an inert, organic solvent, preferably a chlorinated, aliphatic hydrocarbon such as methylene chloride, at a temperature of from about 0° to about 25° C., preferably at a temperature between about 0° and about 15° C.

Step 2 concerns the dehydration of the compound of formula V, prepared in Step 1, with at least 2 equivalents of trifluoroacetic anhydride (TEAA). The dehydration preferably is conducted in the presence of an inert, organic solvent such as tetrahydrofuran or a chlorinated, aliphatic hydrocarbon such as methylene chloride, at a temperature of from about 0° to about 25° C., preferably at a temperature between about 0° and about 15° C.

Insofar as its preparation is not particularly described herein, a compound used as starting material is known or may be prepared from known compounds in known manner or analogously to known methods or analogously to methods described in the Examples.

For example, the primary amine compounds of formula III are known and may be prepared by procedures documented in the literature. More particularly, a) 1-hydroxymethylcyclopentylamine can be prepared by the reduction of 1-amino-1-cyclopentane carboxylic acid with lithium aluminum hydride as set forth below:

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The reduction is conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at the reflux temperature of the solvent for a period of between 14 and 24 hours. (b) 2-[(5-chloropyridin-2-yl)amino]ethylamine can be prepared by refluxing a mixture of 2,5-dichloropyridine with ethylenediamine in an oil bath for a period of between 6 and 12 hours. (c) Similarly, 2-[(5-trifluoromethylpyridin-2-yl)amino]ethylamine can be prepared by refluxing a mixture of 2-chloro-5-trifluoromethyl pyridine with ethylenediamine in an oil bath for a period of between 6 and 12 hours. (d) 2-[(5-cyanopyridin-2-yl)amino]ethylamine can be prepared by stirring a mixture of 2-chloropyridine-5-carbonitrile and ethylenediamine at a temperature between 20° and 30° C., for a period of between 4 and 6 hours. (e) 2-[(pyrimidin-2-yl)amino]ethylamine can be prepared by adding ethylenediamine to ice-bath cooled 2-chloropyrimidine and allowing the mixture to react at a temperature between 20° and 30° C., for a period of between 12 and 20 hours. (f) 1-amino-1-cyclohexanemethanol can be prepared by the reduction of 1-amino-1-cyclohexane carboxylic acid with lithium aluminum hydride. The reduction is conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran, at the reflux temperature of the solvent for a period of between 14 and 24 hours. (g) 2-(3-aminopropylamino)-5-cyanopyridine can be prepared by refluxing a mixture of 2,5-dichloropyridine with 1,3 propyl diamine in an oil bath for a period of between 6 and 12 hours. Alternatively, the above examples (a) through (g) may be carried out at room temperature.

The instant invention also includes 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, 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, 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.

As indicated above, all of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are useful in inhibiting DPP-IV. The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may be demonstrated employing the Caco-2 DPP-IV Assay which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression was accomplished as described by Reisher, et al. in an article entitled "Increased expression of . . . intestinal

cell line Caco-2" in Proc. Natl. Acad. Sci., Vol. 90, pgs. 5757-5761 (1993). Cell extract is prepared from cells solubilized in 10 mM Tris-HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% nonidet-P40, pH 8.0, which is centrifuged at 35,000 g for 30 min. at 4° C. to remove cell debris. The assay is conducted by adding 20 μ g solubilized Caco-2 protein, diluted to a final volume of 125 μ l in assay buffer (25 mM Tris-HCl pH 7.4, 140 mM NaCl, 10 mM KCl, 1% bovine serum albumin) to microtiter plate wells. The reaction is initiated by adding 25 μ l of 1 mM substrate (H-Alanine-Proline-pNA; pNA is p-nitroaniline). The reaction is run at room temperature for 10 minutes after which time a 19 μ l volume of 25% glacial acetic acid is added to stop the reaction. Test compounds are typically added as 30 μ l additions and the assay buffer volume is reduced to 95 μ l. A standard curve of free p-nitroaniline is generated using 0-500 μ M solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The endpoint is determined by measuring absorbance at 405 nm in a Molecular Devices UV Max microtiter plate reader. The potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50} , is calculated from 8-point, dose-response curves using a 4-parameter logistic function.

The following IC_{50} s were obtained:

Compound	Caco-2 DPP-IV (nM)
Ex. 1	36
Ex. 2	176
Ex. 3	22
Ex. 4	140
Ex. 5	26
Ex. 6	50
Ex. 7A	165
Ex. 8	6
Ex. 7B	175
Ex. 9A	997
Ex. 7C	290
Ex. 9C	295
Ex. 10	54
Ex. 11	213
Ex. 7D	382
Ex. 7E	388
Ex. 12	279
Ex. 13	227
Ex. 14	210
Ex. 15	150
Ex. 16	130
Ex. 18	100
Ex. 19	120
Ex. 20	90
Ex. 21	300
Ex. 22	150
Ex. 23	50
Ex. 24	70
Ex. 25	140
Ex. 26	170
Ex. 27	210
Ex. 28	50
Ex. 29	130
Ex. 30	650
Ex. 31	500
Ex. 32	150
Ex. 34	37
Ex. 35	130
Ex. 36	160
Ex. 37	220
Ex. 38	50
Ex. 39	380
Ex. 40	240
Ex. 41	140

-continued

Compound	Caco-2 DPP-IV (nM)
Ex. 42	240
Ex. 43	850
Ex. 44	25
Ex. 45	700
Ex. 46	150
Ex. 47	10
Ex. 48	35
Ex. 49	12
Ex. 50	13
Ex. 51	250
Ex. 52	20
Ex. 53	860
Ex. 54	240
Ex. 55	270
Ex. 56	350
Ex. 57	470
Ex. 58	50
Ex. 59	390
Ex. 60	600
Ex. 61	310
Ex. 62	270
Ex. 63	46
Ex. 64	220
Ex. 65	80
Ex. 66	60

The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described by Kubota, et al. in an article entitled "Involvement of dipeptidylpeptidase IV in an in vivo immune response" in Clin. Exp. Immunol., Vol. 89, pgs. 192-197 (1992). Briefly, five μ l of plasma are added to 96-well flat-bottom microtiter plates (Falcon), followed by the addition of 5 μ l of 80 mM $MgCl_2$ in incubation buffer (25 mM HEPES, 140 mM NaCl, 1% RIA-grade BSA, pH 7.8). After a 5 min. incubation at room temperature, the reaction is initiated by the addition of 10 μ l of incubation buffer containing 0.1 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-4-methylcoumarin). The plates are covered with aluminum foil (or kept in the dark) and incubated at room temperature for 20 min. After the 20 min. reaction, fluorescence is measured using a CytoFluor 2350 fluorimeter (Excitation 380 nm Emission 460 nm; sensitivity setting 4). Test compounds are typically added as 2 μ l additions and the assay buffer volume is reduced to 13 μ l. A fluorescence-concentration curve of free AMC is generated using 0-50 μ M solutions of AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50} , is calculated from 8-point, dose-response curves using a 4 parameter logistic function.

The following IC_{50} s were obtained:

Compound	human plasma DPP-IV (nM)	rat plasma DPP-IV (nM)
Ex. 1	27	22
Ex. 2	7	6
Ex. 4	40	23
Ex. 5	37	18
Ex. 6	22	32
Ex. 8	12	11
Ex. 10	51	19
Ex. 12	95	38

continued

Compound	human plasma DPP-IV (nM)	rat plasma DPP-IV (nM)
Ex. 14	95	24
Ex. 15	70	40
Ex. 16	170	85
Ex. 17	250	120
Ex. 18	160	75
Ex. 19	180	55
Ex. 20	180	150
Ex. 21	210	110
Ex. 22	170	60
Ex. 23	40	40
Ex. 24	32	19
Ex. 25	110	140
Ex. 26	240	75
Ex. 27	150	165
Ex. 28	160	60
Ex. 29	28	9
Ex. 30	90	90
Ex. 31	60	100
Ex. 32	160	130
Ex. 33	277	141
Ex. 34	277	141
Ex. 35	1090	340
Ex. 36	170	80
Ex. 37	160	150
Ex. 38	65	23
Ex. 39	120	200
Ex. 40	340	370
Ex. 41	100	50
Ex. 42	140	180
Ex. 43	340	120
Ex. 44	10	60
Ex. 45	2130	390
Ex. 46	280	90
Ex. 47	11	5
Ex. 48	60	30
Ex. 49	8	1
Ex. 50	60	40
Ex. 51	180	150
Ex. 52	20	16
Ex. 53	490	400
Ex. 54	90	60
Ex. 55	140	90
Ex. 56	140	100
Ex. 57	420	150
Ex. 58	20	100
Ex. 59	280	150
Ex. 60	250	110
Ex. 61	280	80
Ex. 62	190	100
Ex. 63	50	30
Ex. 64	150	60
Ex. 65	90	40
Ex. 66	130	40

In view of their ability to inhibit DPP-IV, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are useful in treating conditions mediated by DPP-IV inhibition. Based on the above and findings in the literature, it is expected that the compounds disclosed herein are useful in the treatment of conditions such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, and calcitonin-osteoporosis. More specifically, for example, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, improve early insulin response to an oral glucose challenge and, therefore, are useful in treating non-insulin-dependent diabetes mellitus. The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to improve early insulin response to an oral glucose challenge may be measured in insulin resistant rats according to the following method:

Male Sprague-Dawley rats that had been fed a high fat diet (saturated fat=57% calories) for 2-3 weeks were fasted

for approximately 2 hours on the day of testing, divided into groups of 8-10, and dosed orally with 10 μ mol/kg of the test compounds in CMC. An oral glucose bolus of 1g/kg was administered 30 minutes after the test compound directly into the stomach of the test animals. Blood samples, obtained at various timepoints from chronic jugular vein catheters were analyzed for plasma glucose and immunoreactive insulin (IRI) concentrations, and plasma DPP-IV activity. Plasma insulin levels were assayed by a double antibody radioimmunoassay (RIA) method using a specific anti-rat insulin antibody from Linco Research (St. Louis, Mo.). The RIA has a lower limit of detection of 0.5 μ U/ml with intra- and inter-assay variations of less than 5%. Data are expressed as % increase of the mean of the control animals. Upon oral administration, each of the compounds tested amplified the early insulin response which led to an improvement in glucose tolerance in the insulin resistant test animals. The following results were obtained:

Compound	Increase of Insulin Response at 10 μ mol/kg
Ex. 1	61%
Ex. 3	66%
Ex. 5	108%
Ex. 8	142%
Ex. 12	59%

The precise dosage of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to be employed for treating conditions mediated by DPP-IV inhibition depends upon several factors, including the host, the nature and the severity of the condition being treated, the mode of administration and the particular compound employed. However, in general, conditions mediated by DPP-IV inhibition are effectively treated when a compound of formula I, or a corresponding pharmaceutically acceptable acid addition salt, is administered enterally, e.g., orally, or parenterally, e.g., intravenously, preferably orally, at a daily dosage of 0.002-5, preferably 0.02-2.5 mg/kg body weight or, for most larger primates, a daily dosage of 0.1-250, preferably 1-100 mg. A typical oral dosage unit is 0.01-0.75 mg/kg, one to three times a day.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating conditions mediated by DPP-IV inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

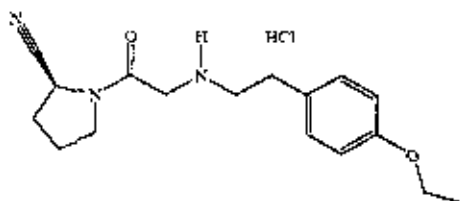
The compounds of formula I (including those of each of the subscopes thereof and each of the examples) may be administered in enantiomerically pure form (e.g., ee $\geq$ 98%,

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Using the procedures described in the above examples, and/or with minor modifications thereto as noted below, the following additional compounds were prepared:

EXAMPLE 16

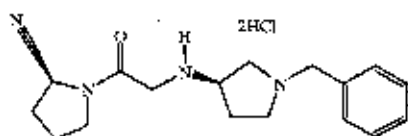
Pyrrolidine, 1-[[2-(4-ethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



4-Ethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=182°-184° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 17

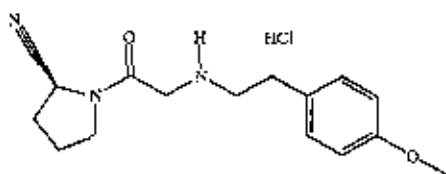
Pyrrolidine, 1-[(1-phenylmethyl-3-pyrrolidinyl)amino]acetyl-2-cyano-, (S)-(R)-, dihydrochloride



(3R)-(-)-1-Benzyl-3-aminopyrrolidine (commercially available) was used as the amine nucleophile. The title compound was an off white solid. Melting point=175° C.-177° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 18

Pyrrolidine, 1-[[2-(4-methoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride

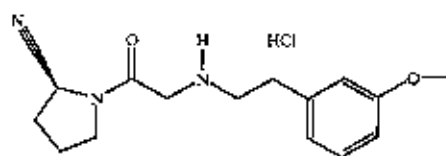


4-Methoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=185° C.-187° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 19

Pyrrolidine, 1-[[2-(3-methoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride

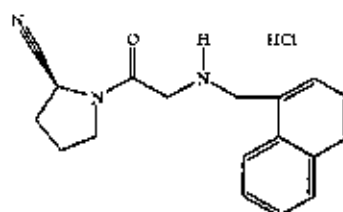
18



3-Methoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=172° C.-174° C. ¹³C NMR (ppm)=119.25.

EXAMPLE 20

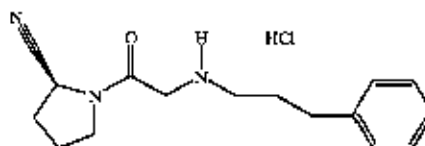
Pyrrolidine, 1-[[[(1-naphthalenyl)methyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



1-Naphthalenemethylamine (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=130° C.-135° C. ¹³C NMR (ppm)=119.29.

EXAMPLE 21

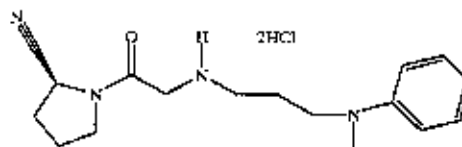
Pyrrolidine, 1-[(3-phenylpropyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



3-Phenyl-1-propylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white fluffy solid. ¹³C NMR (ppm)=119.26.

EXAMPLE 22

Pyrrolidine, 1-[[3-[(phenyl)(methyl)amino]propyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride



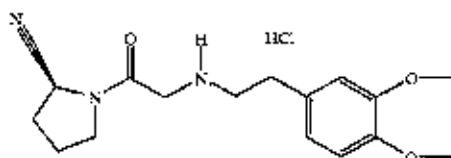
N-(3-Aminopropyl)-N-methylaniline (commercially available) was used as the amine nucleophile. The title

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compound was a white solid. Melting point=96° C.-98° C. (foams). ¹³C NMR (ppm)=121.6.

EXAMPLE 23

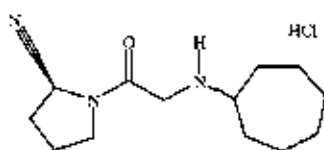
Pyrrolidine, 1-[2-[(3,4-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



3,4-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=170° C.-172° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 24

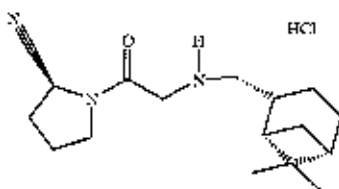
Pyrrolidine, 1-(cycloheptylamino)acetyl-2-cyano-, (S)-, monohydrochloride



Cycloheptylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=68° C.-70° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 25

Pyrrolidine, 1-[[[(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]amino]acetyl-2-cyano-[1S[1α,2α(S*),5α]]-(S)-, monohydrochloride

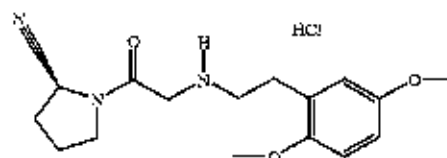


(-)-Cis-myrtanamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=275° C.-279° C., decomposed. ¹³C NMR (ppm)=119.17

20

EXAMPLE 26

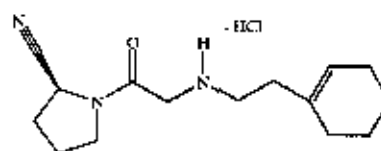
Pyrrolidine, 1-[[2-(2,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2,5-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffly solid. Melting point=65° C.-67° C. ¹³C NMR (ppm)=119.25.

EXAMPLE 27

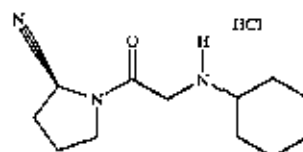
Pyrrolidine, 1-[[2-(1-cyclohexen-1-yl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-(1-Cyclohexenyl) ethylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white fluffly solid. Melting point=162° C.-164° C. ¹³C NMR (ppm)=119.27.

EXAMPLE 28

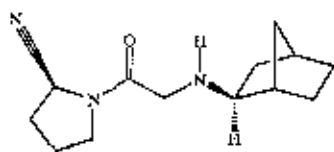
Pyrrolidine, 1-(cyclohexylamino)acetyl-2-cyano-, (S)-, monohydrochloride



Cyclohexylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffly solid. Melting point=182° C.-184° C. ¹³C NMR (ppm)=119.28.

Pyrrolidine, 1-[(bicyclo[2.2.1]hept-2-yl)amino]acetyl-2-cyano-[1S[1α,2α(S*),5α]]-(S)-, monohydrochloride

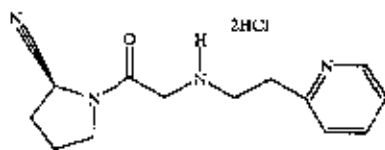
21



(±)-Exo-2-aminonorbornane (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=98° C.-100° C. ¹³C NMR (ppm)=118.36.

EXAMPLE 30

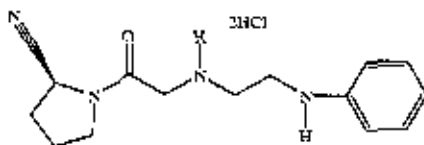
Pyrrolidine, 1-[[2-(2-pyridinyl)ethyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride



2-(2-Aminoethyl) pyridine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=95° C.-97° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 31

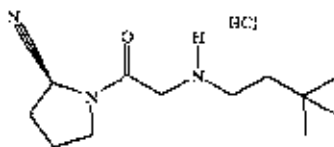
Pyrrolidine, 1-[[2-(2-phenylamino)ethyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride



N-phenylethylenediamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=124° C.-126° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 32

Pyrrolidine, 1-[(3,3-dimethylbutyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride

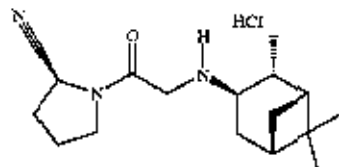


3,3-Dimethylbutylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=164° C.-166° C. ¹³C NMR (ppm)=121.5.

22

EXAMPLE 33

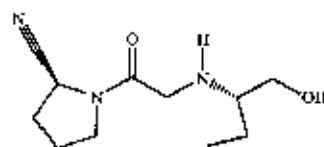
Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-, (S)-[1S [1α,2β,3α(S*),5α]]-monohydrochloride



(1R,2R,3R,5S)-(-)-Isopinocampheylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=82° C.-84° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 34

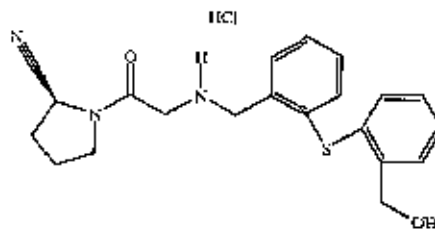
Pyrrolidine, 1-[(1-hydroxymethyl)propyl]amino]acetyl-2-cyano-, (S,S)-



(S)-(+)-2-Amino-1-butanol (commercially available) was used as the amine nucleophile. The title compound was an off-white solid. Melting point=80° C.-82° C. ¹³C NMR (ppm)=118.2.

EXAMPLE 35

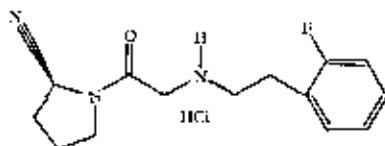
Pyrrolidine, 1-[[[2-[(2-hydroxymethyl)phenyl]thio]phenylmethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-(2-(Aminomethyl) phenylthio) benzyl alcohol (commercially available) was used as the amine nucleophile. The title compound was a yellow solid. Melting point=65° C.-67° C. ¹³C NMR (ppm)=121.4.

25
EXAMPLE 42

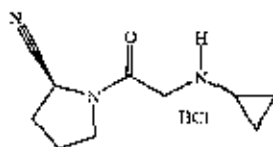
Pyrrolidine, 1-[[2-(2-fluorophenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-Fluorophenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=160° C.-162° C. ¹³C NMR (ppm)=121.70.

EXAMPLE 43

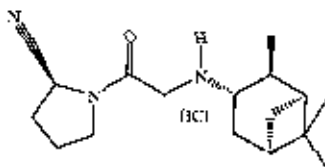
Pyrrolidine, 1-(cyclopropylamino)acetyl-2-cyano-, (S)-, monohydrochloride



Cyclopropylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white solid. Melting point=170° C.-172° C. ¹³C NMR (ppm)=121.62.

~~EXAMPLE 44~~

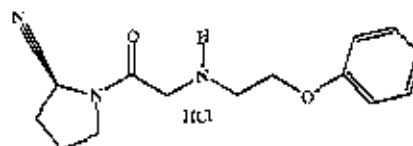
Pyrrolidine, 1-[(2,5,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-, [1S[1α,2α,3β(S*),5α]]-, monohydrochloride



(1S,2S,3S,5R)-(+)-Isopinocampheylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=84° C.-86° C. ¹³C NMR (ppm)=121.8.

26
EXAMPLE 45

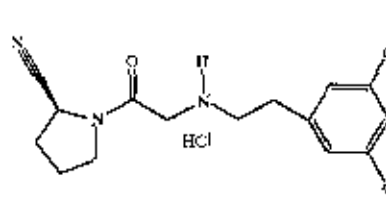
Pyrrolidine, 1-[[2-(2-phenoxyethyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-Phenoxyethylamine (commercially available) was used as the amine nucleophile. The title compound was a sticky golden solid. ¹³C NMR (ppm)=121.7.

EXAMPLE 46

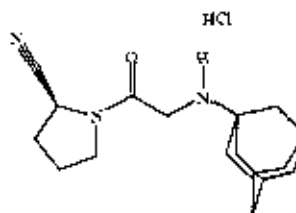
Pyrrolidine, 1-[2-[(3,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



3,5-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=74° C.-76° C. ¹³C NMR (ppm)=121.66.

EXAMPLE 47

Pyrrolidine, 1-[(1-adamantyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



1-Adamantanamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=240° C.-242° C. ¹³C NMR (ppm)=121.80.

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Trámite: 011 PCT-PATENT 379 FASE NAC 011 PRESENTAC
Dependencia: 0000 DIVISION DE MARCAS CREATIVAS

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I.



Capítulo II.

2

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IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual _____

Número _____

3

REPRESENTANTE O APODERADO

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C.C.



NIT



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Otro



Cual _____

Número 17.159.681 TP 10.784

4

INVENTOR(ES) (72)

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Nacionalidad o Domicilio: Estados Unidos de América.

5

PCT (86)

Solicitud Internacional No. PCT/US02/20471

Fecha: 26/06/02

Publicación Internacional No. WO 03/002531 A2

Fecha: 09/01/03

6

Título (54) "FLUOROPIRROLIDINAS COMO INHIBIDORES DE DIPEPTIDIL PEPTIDASA"

7

Clasificación Internacional (51) C07D 207/16 A61K31/40

8

Prioridad

SI



NO



(33) País de Origen

(32) Fecha

(31) Número de Solicitud

US

27/06/2001

60/301,333

US

26/04/2002

60/376,015

248
12
245

seguido por hidrato de hidróxido de litio (103.6 g, 2.46 moles) a temperatura ambiente. La solución resultante se agitó durante 23 horas (nota: a través de TLC, la reacción apareció realizada después de 5 horas) en ese tiempo, el volumen de dioxano se removió al vacío. El material residual se disolvió en H₂O adicional y después se agregó carbón. Después de agitar durante 15 minutos, la solución se filtró a través de un lecho de Celite. El filtrado se hizo sólido agregando NaCl hasta que no se disolvió más. Después se enfrió en un baño de agua de hielo y se acidificó con HCl concentrado a un pH de 3, mientras mantenía la temperatura de solución entre 5-10°C. El producto comenzó a precipitarse a un pH de 4 y después llegando a un pH de 3 el sólido canela se recogió a través de filtración al vacío. Después de bombear bajo alto vacío durante la noche, el sólido se disolvió en 1.5 litros de CH₃CN y se secó sobre MgSO₄. La remoción del solvente al vacío y el secado bajo alto vacío produjeron 92.7 g (0.40 moles, rendimiento del 81%) del compuesto como un sólido canela.

¹H NMR (d₆-DMSO) 400 MHz δ 12.5 (s(br), 1H), 5.22 (d(br), 1H, J=54 Hz), 4.25 (m, 1H), 3.60-3.43 (m, 2H), 2.45 (m, 1H), 2.20 (m, 1H), 1.33 (m, 9H) ppm.

E. (2S, 4S)-2-(aminocarbonil)-4-fluoro-1-pirrolidincarboxilato de ~~ter~~butilo

A un matraz de 2 litros, de 3 cuellos equipado con un agitador impulsado por aire se le agregó el compuesto D (92.7 g, 0.40 moles),

249
13
BT

residual se purificó a través de cromatografía de columna ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (15:1)) produciendo 560 mg (2.45 mmoles, rendimiento del 56%) de un compuesto B como un sólido blanco.

^1H NMR (d_6 -DMSO) 400 MHz δ 7.58 (s(br), 1H), 7.15 (s(br), 1H, rotámero), 7.09 (s(br), 1H, rotámero), 4.51 (d, 1H, $J=9.7$ Hz, rotámero), 4.46 (d, 1H, $J=8.8$ Hz, rotámero), 3.76-3.64 (m, 2H), 3.02 (m, 1H), 2.28 (m, 1H), 1.39 (s, 3H, rotámero), 1.37 (s, 6H, rotámero) ppm.

10 C. (2S)-2-(~~amino-3,4-dihidro-2H-pirrolidin-2-yl~~)-4,4-difluoro-1-pirrolidincarboxilato de ter-butilo

A una solución de 10 ml de CH_2Cl_2 conteniendo el compuesto B (423 mg, 1.85 mmoles) enfriada a -70°C se agregó DAST (889 mg, 5.50 mmoles). La solución resultante se agitó a -70°C durante 30 minutos y después a temperatura ambiente durante 2 horas. La reacción se extinguió con NaHCO_3 y los productos orgánicos se extrajeron con CH_2Cl_2 . Después de secar sobre MgSO_4 , el sólido amarillo residual se purificó a través de cromatografía de columna ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (15:1)) produciendo 211 mg (0.84 mmoles, 46% de rendimiento) del compuesto C.

^1H NMR (d_4 -MeOH) 400 MHz δ 4.38 (m, 1H), 3.84-3.75 (m, 2H), 2.76 (m, 1H), 2.41 (m, 1H), 1.44 (s(br), 9H) ppm.

D. (2S)-2-ciano-4,4-difluoro-1-pirrolidincarboxilato de ter-butilo

25 A una solución de 20 ml de piridina conteniendo el compuesto

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	04-85813
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	098.4
	Folios	048

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	<u>PCT/HU03/00017</u>		
Fecha de Presentación Interna.	<u>04-03-2003</u>		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

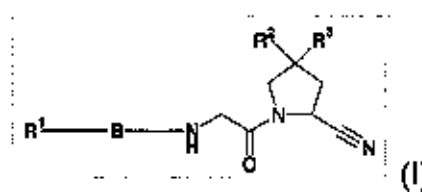
- | | | |
|------|--------------------------|---|
| 1.1. | <u>Descripción:</u> | Folios <u>93-147 y 161-163</u> como se radicó inicialmente. |
| 1.2. | <u>Reivindicaciones:</u> | Folios <u>148-160</u> como se radicó inicialmente. |
| | | Folio <u>250-256</u> como se radicó el 11-08-2006. |
| 1.3. | <u>Prioridad:</u> | Folio <u>1</u> HU, P0200849, 06-03-2002 |

2. Objeto de la invención

Título de la solicitud: N-AMINOACETIL-PIRROLIDINA-2-CARBONITRILOS Y SU USO COMO INHIBIDORES DE DPP-IV (folio 1).

El objeto de la presente solicitud de patente de invención consiste en:

Reivindicaciones 1-18: compuestos de formula general (I) y sus sales isómeros, tautómeros, solvatos e hidratos.

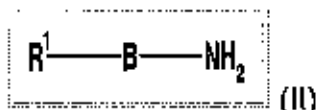


Reivindicación 19: una formulación farmacéutica que comprende un compuesto de formula general (I).

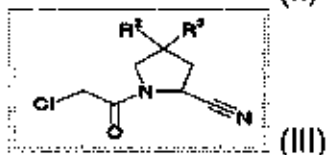
Reivindicación 20: un proceso para la preparación de compuestos de formula general (I).

Reivindicaciones 21-22: el uso de un compuesto de formula general I.

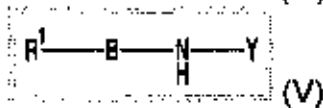
Reivindicación 23: compuestos de formula general (II).



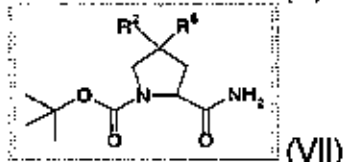
Reivindicación 24: compuestos de formula general (III).



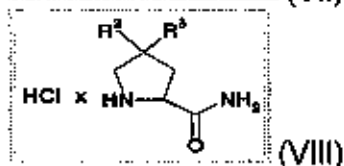
Reivindicación 25: compuestos de formula general (V).



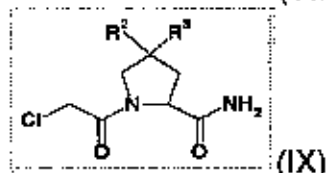
Reivindicación 26: compuestos de formula general (VII).



Reivindicación 27: compuestos de formula general (VIII).



Reivindicación 28: compuestos de formula general (IX).



Reivindicación 29: el uso de un compuesto de formula (II), (III), (V), (VII), (VIII) y (IX).

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de obtener nuevos compuestos de N-sustituido-1-aminoacetil-2-ciano-pirrolidinas inhibidores de la enzima DPP-IV, útiles en el tratamiento de diabetes mellitus no insulino dependiente, obesidad e hiperlipidemia entre otras condiciones.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de formula general (I), un proceso para su preparación, una composición farmacéutica que contiene uno de estos compuestos de formula (I), y compuestos intermediarios de formulas (II), (III), (V), (VII), (VIII) y (IX).

La presente invención se cataloga en A61K31/40, A61K31/4439, A61K31/445, A61K31/454, A61K31/4545, C07D207/00, C07D207/16, A61P3/04, A61P3/10, de acuerdo con la Clasificación Internacional de Patentes (IPC).

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

De la descripción se concentraron las siguientes abreviaciones:

Falta de claridad en la estructura química del compuesto 26 (folio 131, pág. 38), puesto que se encuentra borroso.

De acuerdo con las anteriores observaciones se concluye que en la descripción existe falta de claridad de la información de acuerdo con los requisitos del artículo 28 Decisión 486.

3.2. Reivindicaciones (artículo 30 D 486)

De la revisión del capítulo reivindicatorio se tienen las siguientes consideraciones:

Existe falta de claridad en el capítulo reivindicatorio al señalar compuestos de diversas formulas sin dar la estructura de las mismas en la correspondiente reivindicación, es necesario que la estructura de cada compuesto se incluya en la reivindicación respectiva.

Bajo las reivindicaciones 1-18, la materia objeto de protección se define mediante un compuesto de formula (I) con sustituyentes R^1 , R^2 , R^3 y B. Pero, se encuentra que existe falta de concisión, puesto que:

- R^1 puede ser seleccionado de una larga y variada lista de sustituyentes que van desde grupos heteroaromáticos con N de 5 y 6 miembros con uno a tres heteroátomos, grupos heteroaromáticos con N bicíclicos condensados con uno a tres heteroátomos, grupos heteroaromáticos de 5 miembros conteniendo O ó S, fenilo, bencilo, p-toluenosulfonilo, alquilcarbonilo, fenilcarbonilo, feniletilcarbonilo, feniletenilcarbonilo, piridincarbonilo, pirrolidincarbonilo, piperidincarbonilo, piperazincarbonilo, algunos de estos sustituyentes nuevamente sustituidos.

Sin embargo, de esta gran variedad de opciones en R^1 , en los ejemplos de compuestos sólo se observa que R^1 es piridilo, piridazinilo, pirimidinilo, pirazinilo, imidazolilo, tiazolilo, quinolinilo, isoquinolinilo, quinoxalinilo, benzotiazolilo, tetrazolilo, triazinilo, bencilo y feniletenilcarbonilo.

En consecuencia, es necesario que el solicitante concrete la materia reivindicada bajo la formula I, acorde con los ejemplos presentados y con los compuestos que indudablemente puedan ser sustentados mediante datos de resultados de su actividad como inhibidores de la enzima DPP-IV, de manera que la materia objeto de protección sea concisa, tenga un alcance plenamente definido y esté totalmente sustentada por los resultados de actividad biológica.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, concisión y sustento de acuerdo con las exigencias del artículo 30 de la Decisión 486.

4. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

De acuerdo con los artículos anteriores las reivindicaciones 21-22 y 29, relacionadas con el uso de un compuesto, no se consideran objeto de protección puesto que el uso no es un producto o un procedimiento tecnológico. Por lo que se recomienda al solicitante eliminarlas del alcance de la invención.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 29-03-2002, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

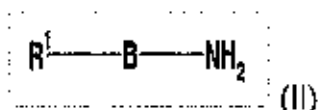
N°	Documento	Título	Fecha de publicación
D1	WO 0196295	Organic compounds	20-12-2001
D2	US 6011155	N-(substituted glycol)-2-cyanopyrrolidines, pharmaceutical compositions containing them and their use in inhibiting dipeptidyl peptidase-IV.	04-06-2000
D3	US 4001422	4-aminoquinazoline cardiac stimulants	04-01-1977
D4	US 5001125	Anty-virally active pyrazinamines	19-03-1991
D5	WO 9965895	Phenoxypropanolamines, method for the production thereof and pharmaceutical compositions containing the same.	23-12-1999
D6	CO 03111632	Fluoropirrolidinas como inhibidores de peptidil peptidasa	22-12-2003 (presentación)

Anterioridad D1 en folios 210-224, D2 en folios 225-235, D3 en folios 236-237, D4 en folios 238-239, D5 en folios 240-246 y D6 en folios 247-249.

6. Análisis de patentabilidad (artículo 14 D486)

7.1 Novedad (artículo 16 D486)

- La presente solicitud de patente busca protección en la reivindicación 23, para un compuesto de formula general (II), Con sustituyentes R^1 y B según capítulo reivindicatorio.

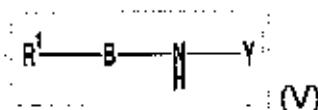


Mediante comparación del objeto de la presente solicitud elemento por elemento con el estado de la técnica, esta oficina encuentra que:

D1	compuesto intermediario tipo amina: kk) 1-[1-(4-fenil-tiazolil)-4-piperidinil]amina, usado también para la síntesis de compuestos inhibidores de DPP-IV derivados de N-(glicil sustituidos)-2-cianopirrolidinas (folios 210 y 219).
D2	Compuestos intermediarios de formula III: NH_2R ej. 17. 1-benzyl-3-aminopyrrolidine (folio 231) ej. 66. 4-amino-1-benzilpiperidin-4-ilo (folio 235) Usados de igual forma para la síntesis de compuestos inhibidores de DPP-IV derivados de N-(glicil sustituidos)-2-cianopirrolidinas.
D4	Compuesto 1-(6-cloro-3-piridazinil)-4-piperidinamina (ej. 40, folio 239 col. 47).
D5	Compuestos intermediarios tipo amina de formula (III):  n: 0 m: 0 R ₃ : H, alquilo C ₁₋₄ , alcoxi C ₁₋₄ , halógeno, CN, NO ₂

Compuestos reclamados bajo la formula (II) de la presente solicitud, ya se encuentran divulgados tal como se expone por D1, D2, D4 y D5, por lo que no pueden considerarse nuevos.

- La presente solicitud de patente busca protección en la reivindicación 25, para un compuesto de formula general (V), con sustituyentes R^1 , B y Y según capítulo reivindicatorio.

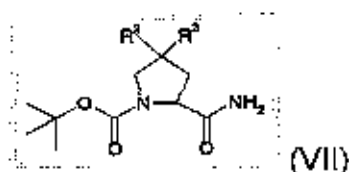


Mediante comparación del objeto de esta solicitud elemento por elemento con el estado de la técnica, esta oficina halla que:

D3	Compuestos de la siguiente formula: Ej. 2 R^1: H R: H Y: -NHCOCH₃ Y y R en posición 4 del núcleo de piperidina Ej. 4 R^1: H R: H Y: -NHCOCH₃ Y y R en posición 3 del núcleo de piperidina (folio 237)
D5	Compuestos intermediarios de formula (VII): (VII) n^o: 0 m^o: 0 R^2: H, alquilo C₁₋₄, alcoxi C₁₋₄, halógeno, CN, NO₂. P^o: tertbutoxicarbonilo o acetilo como grupos protectores para aminas. Ej. 5,7,22,27,52 (folios 243-246)

Compuestos reclamados bajo la formula (V) de la presente solicitud, ya se encuentran divulgados tal como se expone por D3 y D5, por lo que no pueden considerarse nuevos.

- La presente solicitud de patente busca protección en la reivindicación 26, para un compuesto de formula general (VII), Con sustituyentes R^1 y R^3 según capítulo reivindicatorio.



Mediante comparación del objeto de la presente solicitud elemento por elemento con el estado de la técnica, esta oficina encuentra que:

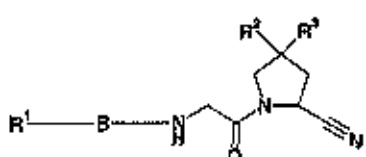
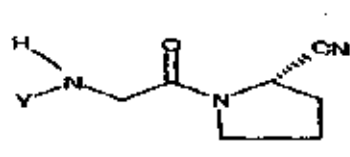
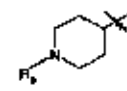
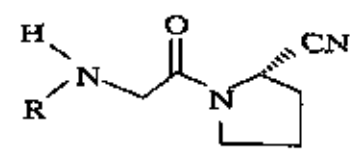
D6	Compuestos intermediarios: (2S, 4S)-2-(aminocarbonil)-4-fluoro-1-pirrolidincarboxilato de terbutilo (compuestos 1E, folio 248). (2S)-2-(aminocarbonil)-4,4-difluoro-1-pirrolidincarboxilato de terbutilo (compuestos 2C, folio 249).
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Los compuestos solicitados bajo la formula (VII) ya son divulgados por D6 y por tanto no son nuevos.

6.1 Nivel inventivo (artículo 18 D486)

La presente solicitud de patente busca protección en las reivindicaciones 1- 20 y 23- 28 para compuestos de formula general (I), para una composición farmacéutica que contiene uno de éstos, para un proceso de preparar los compuestos de formula (I) y para compuestos intermediarios de formulas (II), (III), (V), (VII), (VIII) y (IX).

Compuestos de formula (I)

SOLICITUD	D1	D2
compuestos de formula general (I)  Con sustituyentes R¹, R², R³ y B según capítulo reivindicatorio.	Un compuestos de formula (I)  Donde Y puede ser un grupo de formula:  R₃: - fenilsulfonilo sustituido en el anillo por alquilo C₁₋₆, - Alquil(C₁₋₆)carbonilo, - benzoilo, - tiazol sustituido con fenilo. (Folios 222-223).	Un compuesto de formula I  Donde R puede ser: - pirrolidinilo o piperidinilo opcionalmente sustituido con bencilo - un grupo bicíclico (Folio 226)

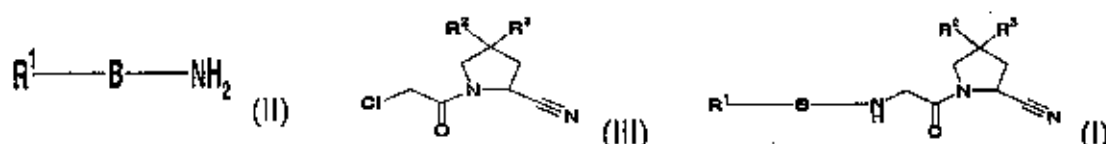
El documento D1 revela compuestos N-(glicil sustituida)-2-cianopirrolidinas de formula I con sustituyente Y como se enseña arriba en el cuadro comparativo, divulgados como compuestos inhibidores de la enzima DPP-IV, usados para el tratamiento de diabetes mellitus no insulino dependiente, artritis y osteoporosis entre otras condiciones (folios 210, 222-223). Adicionalmente, D1 aporta datos de IC₅₀ para compuestos de formula (I) como inhibidores de DPP-IV, que dejan ver que la gran mayoría tienen IC₅₀ < 100nM (tablas de folios 214-218).

El documento D2 igualmente enseña compuestos N-(glicil sustituida)-2-cianopirrolidinas de formula I con sustituyente R como se muestra en el cuadro comparativo, señalados como inhibidores de de la enzima DPP-IV, usados para el tratamiento de diabetes mellitus no insulino dependiente, artritis y osteoporosis entre otras condiciones (folio 226). D2 también aporta datos de IC₅₀ para compuestos de formula I como inhibidores de DPP-IV, que permiten ver que existen compuestos con IC₅₀ < 100nM (tablas de folios 229-230).

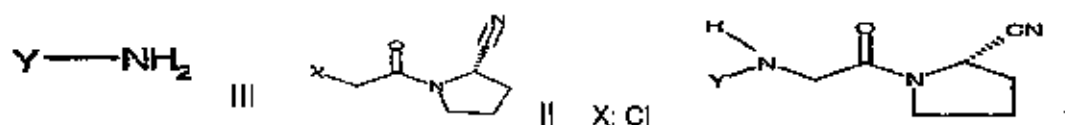
La diferencia tanto con D1 como con D2, es que en los compuestos de la presente solicitud existen 1 o dos F en la posición 4 de la pirrolidina, lo que al parecer no concede un efecto inesperado, puesto que tanto los compuestos de D1 como de D2 también poseen una actividad inhibitoria de DPP-IV con un IC₅₀ < 100nM, como se asegura para los compuestos de la solicitud (folio 113).

Teniendo en cuenta que el problema planteado está relacionado con la necesidad de obtener nuevos compuestos de N-sustituido-1-aminoacetil-2-ciano-pirrolidinas, como inhibidores de la enzima DPP-IV, útiles en el tratamiento de diabetes mellitus no insulino dependiente, obesidad e hiperlipidemia entre otras condiciones; y que al adicionar uno o dos F en la posición 4 de la pirrolidina a los compuestos de D1 o D2, la actividad biológica sigue siendo la misma ($IC_{50} < 100nM$), parece que el problema se resolvió sin involucrar una actividad inventiva y en ausencia de datos que permitan reconocer una mejora técnica o ventaja inesperada en relación con los compuestos del arte previo, no se considera que la solicitud tenga nivel inventivo.

- Proceso para preparar los compuestos de formula (I) (reivindicación 20), que comprende hacer reaccionar un compuestos de formula (II) con un compuesto de formula (III).



El documento D1 divulga un proceso de preparación de un compuestos de formula (I) mediante la reacción de un compuesto de formula II con uno de formula III (folios 211-212).



Por lo que el proceso reivindicado no se considera que tenga nivel inventivo.

- Intermediarios de formula (III), (VIII) y (IX) (reivindicaciones 24, 27 y 28)

SOLICITUD	D1
 (III)	 II X: Cl
 (VIII)	 IV
 (IX)	 V X:Cl

Dado que D1 divulga intermediarios de formula II, IV y V (folio 212) en donde la única diferencia con los intermediarios (III), (VIII) y (IX) de la solicitud respectivamente, es que no tienen los sustituyentes R² (F o H) y R³ (F) en la posición 4 de la pirrolidina, no se considera que tales intermediarios solicitados tengan nivel inventivo.

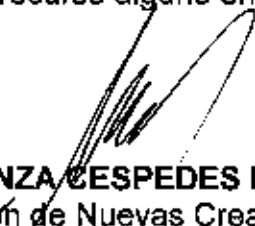
7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 0196295	23 1-20, 23-28	Novedad Nivel inventivo
D2	US 6011155	23 1-20, 23-28	Novedad Nivel inventivo
D3	US 4001422	25	Novedad
D4	US 5001125	23	Novedad
D5	WO 9965895	23 y 25	Novedad
D6	CO 03111632	26	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
 Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
 01 AGO. 2008

CONCEPTO TECNICO
 No. 1621

EXAMINADOR TECNICO
 Código No. 202079

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	04-85813
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	09815
	Folios	001

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- Augustyns KJL Lambeir AM Borloo M De Meester I Vedemikova I Vanhoof G Hendriks D Scharpe S Haemers A; **Pyrrolidides: synthesis and structure-activity relationship as inhibitors of dipeptidyl peptidase IV**; EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, - ISSN 0223-5234, Vol. 32, Nr. 4, Page(s): 301 – 309; 1997-01-01; XP004086653.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud W/O equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

En cumplimiento del artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del plazo que no exceda los tres meses contados a partir de la fecha de notificación de la presente comunicación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 01 AGO. 2008

CONCEPTO TÉCNICO
No. 1621

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