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No. 05-129153-00003-0000

Le: 2020 NUECREACIONE
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Re: **P1.-MERCK & CO., INC.-Solicitud de patente de Invención en Fase Nacional PCT para "SAL DE ACIDO FOSFORICO DE UN INHIBIDOR DE LA DIPEPTIDIL PEPTIDASA-IV".-Clase C07D 487/04.- Expediente número 05-129.153.-**

1. Me refiero a mi memorial de 23 de Enero de 2007.
2. Por medio del presente atentamente ruego a usted, se sirva pronunciarse en relación con el examen de fondo de la solicitud arriba nombrada, ya que desde el 31 de Julio de 2006, esto hace mas de un (1) año que fue publicada la solicitud en la Gaceta 566, y en su debido momento mediante memorial de 23 de Enero de 2007, se solicitó y canceló el examen de patentabilidad sin que hasta el momento haya sido adelantado dicho trámite.
3. Cabe anotar que esta demora en el trámite acarrea grave perjuicio para mi representado.

Señor Superintendente,


ALICIA LLORED A RICAURTE

T.P.53.215

AMCW/fegv



I HEREBY CERTIFY THAT THE ABOVE IS A TRUE AND CORRECT COPY OF THE ORIGINAL DOCUMENTS FILED IN THIS CASE.

PCT

(10) International Publication Number
WO 03/004498 A1

- (51) **International Patent Classification⁷:** C07D 487/04, (74) **Common Representative:** MERCK & CO., INC.; 126
A61K 31/4985, A61P 3/10 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) **International Application Number:** PCT/US02/21349
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60/303,474 6 July 2001 (06.07.2001) US
- (71) **Applicant (for all designated States except US):** MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) **Inventors; and**
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- (81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/00498 A1

- (54) Title:** BETA-AMINO TETRAHYDROIMIDAZO (1, 2-A) PYRAZINES AND TETRAHYDROTRIAZOLO (4, 3-A) PYRAZINES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES
- (57) Abstract:** The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

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In the present invention it is more preferred that R^2 is selected from the group consisting of:

- (1) hydrogen,
- (2) methyl,
- 5 (3) ethyl,
- (4) CF_3 ,
- (5) CH_2CF_3 ,
- (5) CF_2CF_3
- (6) phenyl,
- 10 (7) (4-methoxy)phenyl,
- (8) (4-trifluoromethoxy)phenyl,
- (9) 4-fluorophenyl, and
- (10) 3,4-difluorophenyl.

15 In the present invention it is even more preferred that R^2 is CF_3 or CF_2F_3 .

In the present invention it is preferred that R^3 is F, Br or CF_3 .

20 The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The compounds of the instant invention have one asymmetric center at the beta carbon atom. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will
25 independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

30 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers.

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The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

Formula I shows the structure of the class of compounds without preferred stereochemistry. Formula Ia shows the preferred stereochemistry at the carbon atom that is attached to the amine group of the beta amino acid from which these compounds are prepared.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines

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including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, 5 glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and 10 organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, ~~phosphoric~~, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, 15 sulfuric, fumaric, and tartaric acids. *→ preferred*

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C₁₋₈, as in 20 C₁₋₈-alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that C₁₋₈-alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl. Likewise, C₀, as in C₀-alkyl is defined to identify the presence of a direct covalent bond. A group which is designated as being independently substituted with 25 substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein is intended to include 5- or 6-membered ring systems which are within the following listing: benzimidazolyl, benzodioxanyl, benzofuranyl, benzopyrazolyl, benzothiadiazolyl, benzotriazolyl, benzothiophenyl, benzoxadiazolyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, 30 isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, triazolyl, azetidyl, 1,4-dioxanyl, hexahydroazepinyl, 35 piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl,

Según las reivindicaciones 1-35 se refiere a una sal de ácido fosfórico del compuesto de fórmula (I) o un hidrato farmacéuticamente aceptable de la misma o el monohidrato cristalino del mismo.

El problema planteado en esta solicitud es la necesidad de la sal de ácido fosfórico monohidratada cristalina del compuesto de fórmula (I).

Para solucionar este problema técnico la solicitud en estudio proporciona el procedimiento de obtención del monohidrato cristalino de la sal de ácido fosfórico del compuesto de fórmula (I).

- Clasificación Internacional de Patentes A 61 K 31/4985

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- Las reivindicaciones 8, 11, 14-16 se refieren a las figuras, lo cual no es correcto, ya que no describe de manera correcta la materia que se pretende proteger.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

- El contenido de las reivindicaciones 27-28, que trata de "Un procedimiento para el tratamiento de diabetes...", no es patentable, debido a que se relaciona con métodos de tratamiento aplicados a un ser humano o animal.

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

El contenido de las reivindicaciones 31-32, que trata de "El uso de la sal...", no es patentable, debido a que la legislación vigente únicamente contempla los productos y procedimientos como objeto de patente.

6. 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 24.06.03, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta:

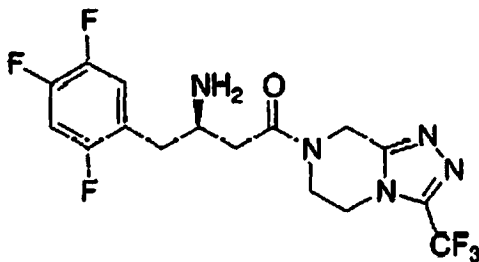
N°	Documento	Título	Fecha de Publicación
D1	WO 03004498	"Beta-amino tetrahidroimidazo (1,2-a) pirazinas y tetrahidrotriazolo (4,3-a) pirazinas como inhibidores de la dipeptidil peptidasa para el	16.01.03

		tratamiento o prevención de diabetes"	100
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7. Análisis de patentabilidad (artículo 14 D486)

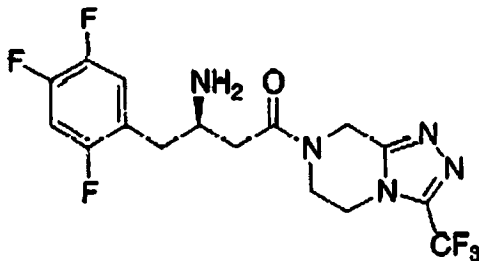
7.1. Novedad (artículo 16 D486)

- La publicación WO 03004498 revela el compuesto específico de



fórmula , así como su sales de ácido fosfórico, enantiómeros e hidratos en forma cristalina

- La presente solicitud se relaciona con el la sal de ácido fosfórico del



compuesto , así como su monohidrato cristalino

Comparando elemento por elemento, D1 ya revela todos los elementos característicos (estructura, sal, enantiómero y monohidrato cristalino) del compuesto que se reivindica y puede afectar la novedad de la presente solicitud.

8. Conclusión:

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

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO 03004498	1-26, 29-30, 33-35	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