



(51) International Patent Classification:

A01N 43/42 (2006.01) C07D 295/00 (2006.01)
A61K 31/47 (2006.01)

(21) International Application Number:

PCT/IB2011/053443

(22) International Filing Date:

3 August 2011 (03.08.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2207/MUM/2010 3 August 2010 (03.08.2010) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

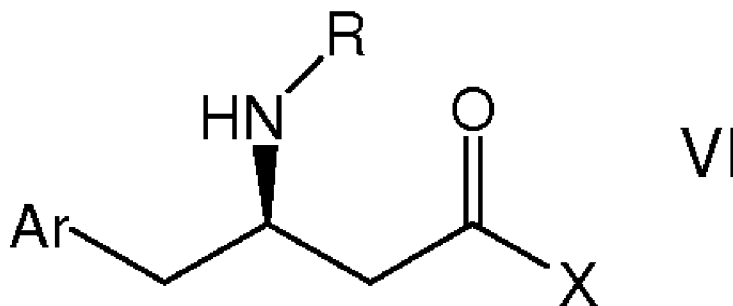
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

[Continued on next page]

(54) Title: NOVEL COMPOUNDS AS DPP-IV INHIBITORS AND PROCESS FOR PREPARATION THEREOF



(57) Abstract: The present invention relates to process for preparation of novel compounds which are acting as inhibitors of dipeptidyl peptidase-IV enzyme and is depicted by the structural formula as given below: Formula VI. Which are useful in the treatment or prevention of diseases in which the dipeptidylpeptidase-IV enzyme is involved, such as diabetes and particularly type-2 diabetes.

WO 2012/017391 A3



Published:

(88) Date of publication of the international search report:

— *with international search report (Art. 21(3))*

26 May 2016

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 11/53443

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/42; A61K 31/47; C07D 295/00 (2012.01) USPC - 514/307 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC - 514/307 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 548/540; 514/423; 514/318; 546/145 (see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: DP-IV inhibitors, peptides, amino acids, glycine, proline, enantiomers, 2,4,5-trifluoro-benzyl, 3-trifluoromethyl, triazolo[4,3-a]pyrazin-7-yl, pyrrolidinyl, administration, mammals, Cadila, dipeptidyl peptidase IV, crystal structure, drug design, binding pocket, ligand, docking, computer modeling. I		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/029422 A1 (KHAMAR et al.) 18 March 2010 (18.03.2010) pg 2 - pg 5; pg 7; pg 13, see Formula 10	1-2
Y	WO 2005/119526 A1 (QIU) 15 December 2005 (15.12.2005) pg 14, ln 14 - pg 15, ln 41; pg 18, ln 28 - pg 19, ln 11; pg 19, ln 21-28; pg 20, ln 14-18; pg 22, ln 14-29	1-2
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 09 February 2012 (09.02.2012)		Date of mailing of the international search report 27 FEB 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 11/53443

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Group I: claims 1-2, restricted to compound 1a of Claim 2.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 11/53443

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: claims 1-2, drawn to a novel DPP-IV inhibitors of formula VI, $\text{Ar-CH}_2\text{-CH(NH-R)-CH}_2\text{-C(O)-X}$; wherein, Ar is phenyl or substituted phenyl having 1 to 5 halogen atoms in the phenyl ring, preferably 2, 4, 5-trifluorophenyl; R is aa1 or aa1-aa2 or aa1-aa2-aa3 or aa1-aa2-aa3-aa4, wherein aa1, aa2, aa3 and aa4 are amino acids selected independently and is linked through a peptide bond; wherein the amino acid (aa1/aa2/aa3/aa4) is selected from any of the following: 2-Amino-propionic acid; Amino-acetic acid; 2-Amino-4-methyl-pentanoic acid; 2-Amino-3-methyl-butyric acid; Pyrrolidine-2-carboxylic acid; 2-Amino-3-methyl-pentanoic acid; 2-Amino-3-(4-benzyloxy-phenyl)-propionic acid; 2-Amino-3-(4-benzyloxy-phenyl)-propionic acid; 2-Amino-3-phenyl-propionic acid; 2-Amino-3-(1H-imidazol-4-yl)-propionic acid; X is defined as any of the substructure X1 to X5, wherein substructures X1 to X5 are structurally depicted. The first invention is restricted to compound 1a of Claim 2. Should an additional fee(s) be paid, Applicant is invited to elect an additional compound(s) to be searched. The exact claims searched will depend on Applicant's election.

Group II+: claims 3-11A, 11B and 12, drawn to a process for the preparation of DPP-IV inhibitors of formula VI, $\text{Ar-CH}_2\text{-CH(NH-R)-CH}_2\text{-C(O)-X}$; using sequence of reactions as depicted in scheme 1 comprises:

- a. Deprotection followed by esterification of N-protected beta-amino acid (formula I) to give chiral beta amino acid derivatives (formula II);
- b. reaction of chiral beta amino acid derivatives (formula II) with carboxyl terminal N'-protected peptide compounds to give beta-amino N-acetyl peptide compounds (formula III);
- c. reaction of beta-amino N-protected compound (formula III) with saponifying agent to provide beta-amino N-acylated-4-(2, 4, 5-trifluorophenyl)-3-amino butyric acid (formula IV);
- d. condensation of beta-amino N-acylated-4-(2, 4, 5-trifluorophenyl)-3-amino butyric acid (formula IV) with any of the compound (a) to (e) to give corresponding amides of beta-amino N-acylated-N'-protected peptide compounds (formula V);
- e. deprotection of amides of beta-amino N-acylated-N'-protected peptide compounds (formula V) to give 4-aryl-3-N-peptide substituted amino acid derivatives (formula VI). The first invention is restricted to the compound of the formula of Claim 9 comprising R1. Should an additional fee(s) be paid, Applicant is invited to elect an additional compound(s) to be searched. The exact claims searched will depend on Applicant's election.

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I+ do not include the inventive concept of a process for the preparation of DPP-IV inhibitors of formula VI, as required by Group II+.

The inventions of Groups I+ and II+ share the technical feature of a novel DPP-IV inhibitors of formula VI, $\text{Ar-CH}_2\text{-CH(NH-R)-CH}_2\text{-C(O)-X}$. However, this shared technical feature does not represent a contribution over prior art as being anticipated by WO 2010/029422 A1 to Khamar et al. (hereinafter 'Khamar'). Khamar discloses Claim 1, a novel DPP-IV inhibitors of formula VI, $\text{Ar-CH}_2\text{-CH(NH-R)-CH}_2\text{-C(O)-X}$; wherein, Ar is 2,4,5-trifluorophenyl; R is aa1-aa2, wherein aa1 and aa2 are amino acids selected independently and is linked through a peptide bond; wherein the amino acid (aa1/aa2) is selected from: 2-Amino-propionic acid; 2-Amino-4-methyl-pentanoic acid; X is defined as the substructure X1 (pg 12, para 3, Formula 8). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Groups I+ and II+ is the specific compounds/formulae recited therein. The inventions do not share a special technical feature, because Khamar discloses a compound of Formula VI (pg 12, para 3, Formula 8). Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

The applicant has elected NOT to pay for the additional invention, so only claim group I: claims 1-2, restricted to compound 1a of Claim 2, on the 206 should be searched.

Continuation of Section 4:

Claims 14-20 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

NOTE: Claims having numerical identifier of 11 are renumbered; the first Claim 11 is renumbered as 11A and the second Claim 11 is renumbered as 11B. Claim 13 is absent.