PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P11145PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2015/070504	International filing date *(day/month/year)* 08.09.2015	Priority date *(day/month/year)* 08.09.2014

International Patent Classification (IPC) or national classification and IPC
INV. A61K38/05

Applicant
LANDSTEINER GENMED, S.L.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 16 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*ter* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.08.2016	13.12.2016

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2015/070504

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-56 as originally filed

   Claims, Numbers

   1-28 filed in electronic form on 13-10-2016

   ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-*bis*)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:
   - ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
   - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).

6. ☒ With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
   - ☒ A top-up search was carried out by this Authority on 18.11.2016 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
     - ☐ Additional relevant documents have been discovered during the top-up search.
   - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.

7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* *If item 4 applies, some or all of those sheets may be marked "superseded".*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-28
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Furthermore and with regard to claim 11 it may also be helpful to note that the EPO also no longer accepts "Swiss" type claims in applications having a filing or an earliest priority date after 29.01.2011. Only claims drafted in the general form "*compound/composition for use in*" a wholly therapeutic method can be accepted as being a medical indication claim. Furthermore any dependent claims defining such a medical indication should be drafted in the form "*compound/composition for use according to*" a previous claim (rather than e.g. "*The compound/composition of*" a previous claim).

2 Prior Art: Reference is made to the following documents cited in the International Search Report and the passages identified therein:

D1	US 5 514 694 A (POWERS JAMES C [US] ET AL) 7 May 1996 (1996-05-07)
D2	US 5 610 297 A (POWERS JAMES C [US]) 11 March 1997 (1997-03-11)
D3	WO 00/16767 A1 (CEPHALON INC [US]) 30 March 2000 (2000-03-30)
D4	WO 2005/056519 A1 (SENJU PHARMA CO [JP]; SHIRASAKI YOSHIHISA [JP]; MIYASHITA HIROYUKI [JP]) 23 June 2005 (2005-06-23)
D5	ALICE LEE-DUTRA ET AL: "Cathepsin S inhibitors: 2004 - 2010", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 21, no. 3, 1 March 2011 (2011-03-01), pages 311-337, XP055100095, ISSN: 1354-3776, DOI: 10.1517/13543776.2011.553800

2.1 Documents D1 and D2 disclose dipeptidyl ketoamides of formula (I) and their in vivo uses such as the treatment of ischemia, stroke, restenosis or Alzheimer's disease.

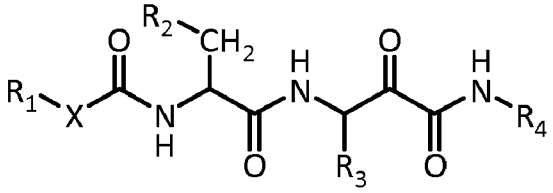
2.2 Documents D3 discloses dipeptidyl ketoamides of formula (I) and their in vivo uses such as the treatment of neurodegeneration, stroke or Alzheimer's.

2.3 Document D4 discloses dipeptidyl ketoamides of formula (I) and their in vivo uses such as the treatment of ischemic disease or Alzheimer's disease.

2.4 Document D5 discloses that Cat S inhibition may have applications as therapy against Alzheimer's disease, atherosclerosis and obesity while suitable inhibitors are alpha-ketoamides.

3 The present application seems to meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-28 seems to be novel (Article 33(2) PCT) and involve an inventive step (Article 33(3) PCT).

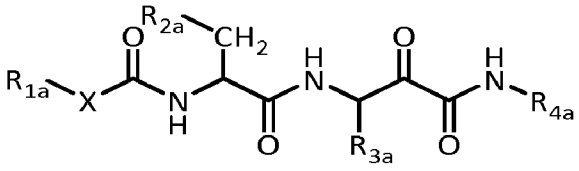
3.1 Claim 1 relates to a compound of formula (I):



(I)

.... for use in the treatment and/or prevention obesity-related conditions selected form the group consisting of obesity, lipid storage disease and hyperlipemia, while claims 11 and 12 relate to the corresponding uses and methods and claim 13 relates to the corresponding non-therapeutic use.

Claim 15 relates to a compound of formula (II):



(II)

...., while claims 26-28 relate to the process for the preparation of a compound of formula (II), to the corresponding pharmaceutical composition and to its use as a medicament, respectively.

3.2 Document D5 which may be regarded as being the prior art closest to the subject-matter of claim 1 differs with respect to the ketoamides used. It is noted that the compounds of document D5 differ in the core structure (mono- or tri-peptidyl instead of di-peptidyl) as well as in the side chains (presence of sulfonyl-group or bicyclic ring instead of alkyl, alkoxy-alkyl or cycloalkyl-alkyl).

The subject-matter of claims 1, 11-13, 15 and 26-28 is therefore novel (Article 33(2) PCT).

3.3 The problem to be solved by the present invention may therefore be regarded as to provide alternative ketoamides for the reduction of fat accumulation.

3.4 It is noted that in the examples it has been shown that a variety of compounds of formula (I) (variation of R1, R2 and R4) inhibit adipogenesis. In view of the different examples and in the absence of a substantiated doubt to the contrary, it is considered credible that the problem is solved over the whole scope of the claims.

3.5 The solution to this problem proposed, namely the provision of the compounds of formula (I) and its subgroup formula (II), is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: Although the compounds of formula (I) are known in the prior art (documents D1-D4) in the absence of any pointer in any of the available documents the skilled person would not have any motivation to modify the structures of document D5 to those of D1 and even less so with a reasonable expectation of success.

3.6 The dependent claims 2-10, 14 and 16-25 also meets the requirements of the PCT with respect to novelty and inventive step.

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By Epoline

CHAPTER II

N/Ref.: **P11145PC00**
Application No.: **PCT/EP2015/070504**
Publication No.: **WO 2016/038040**

Madrid, 13 October 2016

Re.: International application No. PCT/EP2015/070504 for "DIPEPTIDYL KETOAMIDE COMPOUNDS AND THEIR USE FOR THE TREATMENT AND/OR PREVENTION OF FAT ACCUMULATION", in the name of LANDSTEINER GENMED, S.L.
Filing amendments and arguments for IPE *[MR]*

Dear Sirs,

This is in response to the invitation from the IPEA to submit amendments under PCT Rule 60.1(g). Thus, a response to the written opinion under Rule 43bis.1 PCT is included herein. Demand for the preliminary examination of this application was filed on 30 August 2016. It is respectfully submitted that the following amendments to the claims and comments are taken into consideration when carrying out the International Preliminary Examination (IPE).

The administrative fees were paid through Epoline.

AMENDED CLAIMS

Further to the written opinion of the ISA, we enclose herewith an amended set of claims to replace the ones currently held on file.

- New claim 8 has been added. Support for this claim is found in original claim 7 as dependent on claim 5.

- New claim 22 has been added. Support for this claim is found in original claim 20 as dependent on original claim 19.

- New claim 25 has been added. This claim finds basis in Example 61 (page 50) of the application.

A working copy is enclosed for the Examiner's convenience showing the amendments in the new claims as compared to the original claims. Any deletions of subject matter or claims are done without prejudice to their ulterior reintroduction into the present application or their inclusion in a future national/regional phase of the present application.

It is submitted that all the amended claims meet the requirements of Article 19.2 PCT.

COMMENTS TO WRITTEN OPINION

In response to the written opinion, applicant respectfully submits the following comments to be taken into consideration when carrying out the International Preliminary Examination.

Cited prior art

The following documents were cited by the ISA:

- **D1**: US 5,514,694 A
- **D2**: US 5,610,297 A
- **D3**: WO 00/16767 A1
- **D4**: WO 2005/056519 A1
- **D5**: A. Lee-Dutra et al., Expert Opinion on Therapeutic Patents 2011, 21(3), 311-337.

Unity of invention (R. 13 PCT)

In the written opinion of the ISA, the application was considered as allegedly not meeting the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

In the examiner's opinion, the application includes two separate inventions:

- Invention 1 (original claims 1-13): directed to uses of compounds of formula (I), and
- Invention 2 (original claims 14-25): directed to compounds of formula (II).

The examiner considers that the special technical feature in the present case is a common structural feature (the dipeptidyl ketoamide core structure). Since such structure was already known in the prior art, the examiner concludes that there is no special technical feature in the sense of R.13.2 PCT providing a link between all claimed inventions so as to form a single general inventive concept.

The objection is respectfully traversed for the following reasons.

In **W 48/90** and **W 50/90** the board noted that as far as chemical compounds were concerned, unity of invention was no mere question of the respective structural features, but had to be decided taking into account the technical problem to be solved and whether or not the respective compounds contributed to the solution found.

It has been stablished by the boards of appeal that determining unity of invention requires as a precondition an analysis of the technical problem or problems underlying the respective group of inventions (**W 11/89**, **W 6/97**, **T 188/04**), i.e. whether or not the subject-matter claimed as the solution to such a problem represents a single general inventive concept (**W 6/91**). In **W 8/94** the board held that a discussion of the problem underlying the claimed subject-matter was required, because only then was it possible to decide whether or not a common special technical feature within the meaning of R. 13.1 and R. 13.2 PCT existed for different embodiments (**W 11/89**, **W 14/89**, **W 59/90**, **W 14/91**, **W 17/91**).

In **W 6/97** the board found that establishing the technical problem underlying a claimed invention or group of inventions in relation to the state of the art should start, as a rule, from what was considered in the description as having been achieved by the claimed invention,

since claims directed to compositions of matter at least were normally silent on the technical effects to be achieved by such compositions. As soon as the search revealed prior art which was clearly more relevant than that already acknowledged in the description of the international application, it was necessary to determine what was to be considered as the particular technical problem in view of both the disclosure of the international application as a whole and the prior art thus revealed (see **W 6/91**). Unity of invention might be assessed only after the technical problem had been determined in such a manner.

Therefore, in order to determine whether Inventions 1 and 2 meet the unity of invention requirements, the technical problem underlying each invention must be assessed. The problem solved by Invention 1 is the provision of compounds of formula (I) useful for the treatment of certain obesity-related conditions. The problem solved by Invention 2 is the provision of compounds of formula (II) useful for the treatment of certain obesity-related conditions. Importantly, Formula (II) is a sub-formula of formula (I), having a dipeptidyl ketoamide core structure.

Therefore, the technical feature provided by both inventions, and thus the single general inventive concept, is not the provision of dipeptidyl ketoamide compounds as alleged by the examiner, but the provision of dipeptidyl ketoamide compounds for the treatment of certain obesity-related conditions. Utility of such compounds of formula (I) for the prevention/treatment of such conditions was not known in the prior art. As a consequence, the application complies with the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

This is clearly supported by **W 29/88**, where the board held that a particular use of a class of compounds on the one hand, and, on the other hand, a claim to certain members of that class of compounds could form a single general inventive concept. The board stressed that the salient point was not the identity of the respective structural scopes, but the question whether **the compounds claimed per se contributed to the solution of the problem underlying the use invention**.

Finally, the examiner's attention is drawn to PCT International Search and Preliminary Examination Guidelines, paragraph 10.24 (page 80), where a claim directed to the use of a family of compounds in a particular application (claim 1) and a claim directed to a compound belonging to the same family (claim 2) are mentioned as a particular situation where the requirements of unity are met provided that the special technical feature provided by claim 1 is the use of the compounds in that particular application and the compound in claim 2 is also useful in that particular application:

> 10.24 *Example 4*
>
> *Claim 1: Use of a family of compounds X as insecticides.*
>
> *Claim 2: Compound X_1 belonging to family X.*
>
> Provided X_1 has the insecticidal activity and the special technical feature in claim 1 is the insecticidal use, unity is present.

In view of the above, it is submitted that the present application complies with the unity of invention requirements.

Clarity (Art. 6 PCT)

In the written opinion of the ISA, claims 3 and 4 were objected to as allegedly lacking clarity. In particular, the examiner considered that it is not clear whether there are any limitations for R_1 in dependent claim 3 and whether there are any limitations for X in dependent claim 4.

We respectfully disagree and submit that claims 3 and 4 are clear under Art. 6 PCT.

Claim 3 refers to a compound of formula (I) according to claim 1 or 2, wherein X is a single bond. Since no further limitations are specified in the claim, it is clear that the remaining groups (including R_1) are as defined in the preceding claims.

In preceding claims 1 and 2, meanings taken by R_1 are defined depending on the value of X. When X is a single bond, then R_1 can only take the meanings d)-h). That is, R_1 is already limited to d)-h) in claims 1 and 2 when X is a single bond.

Since claim 3 requires that X is a single bond and it is dependent on claims 1 and 2, the skilled person would readily understand that R_1 is also limited to meanings d)-h) in that claim. There is no other reasonable interpretation of the scope of protection conferred by claim 3 and so it is clear under Art. 6 PCT.

Claim 4 refers to a compound of formula (I) according to claims 1-3, wherein R_1 can take the meanings d)-h). Since no further limitations are specified in the claim, it is clear that the remaining groups (including X) are as defined in the preceding claims.

In preceding claims 1 and 2, meanings taken by R_1 are defined depending on the value of X. R_1 can only take the meanings d)-h) when X is a single bond or an –NH- group. That is, X is already limited to the group consisting of a single bond and an –NH- group, when R_1 is selected from d)-h).

Since claim 4 requires that R_1 is selected from d)-h) and it is dependent on claims 1 and 2, the skilled person would readily understand that X is necessarily limited in that claim to the group consisting of a single bond and an –NH- group. There is no other possible interpretation of the scope of claim 4 that is consistent with the information provided in the application. Consequently, the scope of protection conferred by claim 4 is clear for the skilled person and so it complies with the clarity requirements under Art. 6 PCT.

Inventive step (Art. 33(3) PCT)

The ISA considered that none of the claims of the application involves an inventive step. According to the examiner, document **D5** discloses that Cat S inhibition may have applications as therapy against obesity, among others, while suitable inhibitors are alpha-ketoamides. Taking this into account, the examiner considers that it would have been obvious for the skilled person to replace the ketoamides in **D5** by those in **D1-D4** to arrive at the claimed invention.

The objection is respectfully traversed for the following reasons.

Documents **D1-D4** disclose dipeptidyl ketoamides covered by formula (I) and their use in some therapeutic applications. None of these documents refer to the utility of this type of

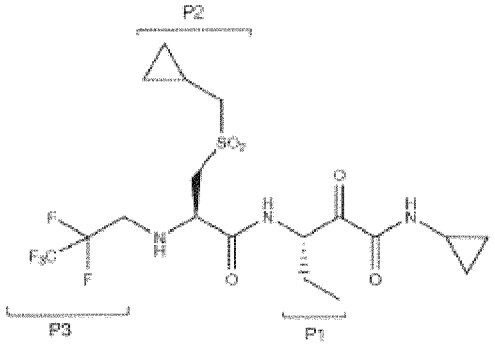
compounds in the prevention and/or treatment of obesity-related conditions as defined in claim 1.

Document **D5** mentions that Cathepsin S (Cat S) may have applications as therapy against neuropathic pain as well as rheumatoid arthritis, multiple sclerosis, asthma and allergy, chronic obstructive pulmonary diseases, emphysema, neuropathic pain, Alzheimer's disease, cancer, atherosclerosis and obesity (page 312, left column, second paragraph). **D5** also discloses inhibition of Cat S by some specific ketoamides. In particular, **D5** teaches that compounds 16-19 inhibit Cat S (pages 316-317; point 2.1.3 and Figure 3).

First, it is important to note that the utility of compounds 16-19 in the treatment or prevention of obesity-related conditions is not disclosed in **D5**.

Additionally, it seems that the examiner has considered **D5** to teach that **any** ketoamide will inhibit Cat S. In our opinion, this clearly goes beyond what **D5** objectively teaches. Once a new idea has been formulated it can often be shown theoretically how it might be arrived at, starting from something known, by a series of apparently easy steps. However, the question is not whether it is possible to show how to arrive at the invention starting from the prior art, but whether it would have been *obvious* to arrive at the invention starting from the prior art.

As mentioned above, document **D5** only refers to the activity of four particular ketoamides (compounds 16-19).



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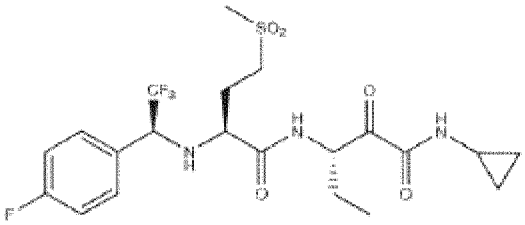

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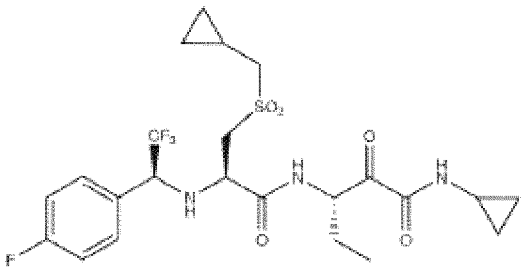
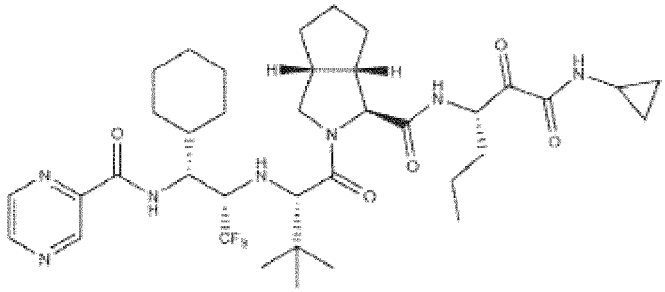


18 (VBY-825)



19

All these compounds present several structural differences with respect to compounds of formula (I) and **D5** does not provide any hint or motivation to make the structural modifications required to arrive at the compounds in the present application.

Compounds 16-18 differ from compounds of formula (I) at least because they have a mono-peptidyl alpha-ketoamide skeleton and a sulphone group (-SO_2-) at the position corresponding to R_2 in formula (I). At least for these structural differences, the skilled person would have not expected that compounds of formula (I) would present the same biological activity as compounds 16-18. This document does not provide any motivation to select the peptidyl ketoamide skeleton in these compounds, to add a second peptidyl group and to further remove the sulphone group, which seems to be essential in those compounds to gain the claimed biological activity. Thus, the skilled person would not find any guidance, among the great number of existing possibilities, to make the specific structural modifications required to arrive at the compounds of formula (I) in the present application.

Compound 19 differs from compounds of formula (I) at least by the presence of an octahydrocyclopenta[c]pyrrole in the peptidyl ketoamide skeleton, and by the presence of a very specific and complex group at the position corresponding to R_1 which is not possible in the compounds of formula (I). Indeed compound 19 is a tripeptidyl compound. At least for these structural differences, the skilled person would have not expected that compounds of formula (I) would present the biological activity shown by compound 19. Again, this document does not provide any motivation, among the great number of existing possibilities, to specifically select the dipeptidyl ketoamide backbone in compound 19 but removing the bicyclic ring in such backbone as well as the third peptidyl unit present in compound 19. Furthermore, the skilled person would have not objectively expected to maintain the biological activity after such modifications.

In view of the structural modifications required to arrive at claimed compounds of formual (I) from any of compounds 16-19 and the lack of motivation in **D5** to make them, the skilled person would have not tried compounds of formula (I) in the prevention or treatment of obesity-related conditions with reasonable expectation of success. There are many different options to modify the structure of compounds 16-19. However, the question is not whether the skilled person *could* have modified the compounds in **D5** in order to arrive at the compounds of the present invention, but whether he *would* have done so because the prior art incited him to do so in the hope of solving the posed problem. Since the skilled person would have not objectively expected from **D5** that di-peptidyl alpha-ketoamide compounds with the substitution pattern defined in claim 1 would be useful in the prevention/treatment of obesity-related conditions, it is submitted that claims 1-14 would not be obvious in view of **D5** in combination with **D1**-**D4**.

Claims 15-28 comply with the inventive step requirement for the same reasons. In view of the structural differences between compounds of formula (II) and compounds 16-19 in **D5**, the skilled person would have not objectively expected that they would present the same biological activity.

Finally, the examiner alleged that it does not seem plausible that all the claimed compounds would solve the problem posed. In other words, this is a question of scope, i.e. how far the particular evidence can support the non-obviousness of other compounds falling within the general formula (I).

Claims are a generalization from the particular examples (Guidelines for Examination, F-IV 6.2). In this regard, the Board held in T 391/91 that "*as there was no reason to doubt that it was possible to generalise the specific teaching of the examples given, it would be unfair to*

the appellant to require a restriction to the claim by incorporating therein of the specific features of the examples". That is, it would be contrary to the principle of granting a fair protection if all obvious modifications, equivalents and variants of the examples were not covered by the claims.

Compounds of present claim 1 differ from the compounds in **D5** in the core dipeptidyl ketoamide core skeleton. We respectfully submit that evidence showing the technical effect (inhibition of adipogenesis) afforded by such core structure would give support to a claim wherein said structure is the distinguishing feature over the prior art.

Biological data included in the application demonstrates that 28 different compounds presenting the basic core structure of formula (I) have the claimed activity. Once such technical effect has been discovered by the inventors, the Examiner will appreciate that several variations on the substituents of the peptides forming the core structure would be expected to present a similar biological activity. Indeed, compounds defined by claim 1 only include a few structural variations on the substitution at some positions.

Additionally, radicals R_2/R_{2a} and R_3/R_{3a} have been generalized to only very close variants or derivatives of the groups for which the claimed activity has been shown. Therefore, it is in principle credible that substantially all the variants covered by the claims possess the same activity as the compounds exemplified in the application.

Otherwise, incorporation into the claims of the particular characteristics of the examples would represent an undue limitation of the scope that would deprive the applicant from a just reward of the disclosure of his invention.

CONCLUDING REMARKS

It is therefore submitted that the application claims subject-matter which is new and involves an inventive step and hence, it is requested that a positive International Preliminary Examination Report is issued. In case the IPEA intends to depart from this request, a written opinion under R. 66.2 PCT is respectfully requested.

Yours faithfully,

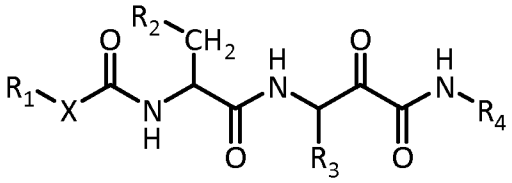
Carbonell

Enric Carbonell Vallès
European Patent Attorney
ABG Patentes, S.L.

Encl.: - Amended claims (working copy and clean copy).

CLAIMS

1. A compound of formula (I):



(I)

wherein

X is selected from the group consisting of a single bond, an oxygen atom and a -NH- group;

when X is O, R_1 is selected from the group consisting of a) C_{1-8}-alkyl, optionally substituted by one C_{1-8} alkoxy group, b) C_{6-10}-aryl-C_{1-4}alkyl and c) C_{5-10}heteroaryl-C_{1-4}alkyl wherein the C_{5-10}heteroaryl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur,

when X is a single bond or a –NH- group, R_1 is selected from the group consisting of d) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl; C_{1-6} linear or branched alkoxy and halogen atoms; e) naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; f) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest is saturated or unsaturated and comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g) C_{1-6} linear or branched alkyl, optionally substituted by one C_{1-8} alkoxy group and h) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

R_2 is selected from the group consisting of i) C_{1-8}-alkyl optionally substituted with 1, 2 or 3 fluor atoms, j) C_{1-8}-alkoxy-O-C_{1-8}-alkyl and k) C_{3-6}cycloalkyl-C_{0-2}alkyl wherein the cycloalkyl ring is optionally substituted with 1, 2 or 3 fluor atoms;

R_3 is selected from the group consisting of l) C_{1-8}-alkyl and m) benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms;

R_4 is selected from the group consisting of n) C_{1-8}-alkyl, o) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by C_{1-4}-alkyl and p) C_{1-8}-alkoxy; and

R_5 and R_6 are independently selected from the group consisting of hydrogen atoms and C_{1-6} linear or branched alkyl groups;

or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of an obesity-related condition selected from the group consisting of obesity, lipid storage disease and hyperlipemia.

2. A compound of formula (I) for use according to claim 1 wherein:

X is selected from the group consisting of a single bond, an oxygen atom and a -NH- group,

when X is O, R_1 is selected from the group consisting of a) C_{1-8}-alkyl, b) C_{6-10}-aryl-C_{1-4}alkyl and c) C_{5-10}heteroaryl-C_{1-4}alkyl wherein the C_{5-10}heteroaryl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur,

when X is an single bond or a –NH- group, R_1 is selected from the group consisting of d) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl; C_{1-6} linear or branched alkoxy and halogen atoms; e) naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; f) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest is saturated or unsaturated and comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g) C_{1-6} linear or branched alkyl and h) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

R_2 is selected from the group consisting of i) C_{1-8}-alkyl, j) C_{1-8}-alkoxy-O-C_{1-8}-alkyl and k) C_{3-6}cycloalkyl-C_{0-2}alkyl;

R_3 is selected from the group consisting of l) C_{1-8}-alkyl and m) benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms;

R_4 is selected from the group consisting of n) C_{1-8}-alkyl and o) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by C_{1-4}-alkyl; and

R_5 and R_6 are independently selected from the group consisting of hydrogen atoms and C_{1-6} linear or branched alkyl groups;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I) for use according to any one of the preceding claims, wherein X is a single bond.

4. A compound of formula (I) for use according to any one of the preceding claims, wherein R_1 is selected from the group consisting of d) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; and f) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest is saturated or unsaturated and comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms.

5. A compound of formula (I) for use according to any one of the preceding claims, wherein R_2 is selected from the group consisting of linear or branched C_{2-5}-alkyl and C_{3-5} cycloalkyl.

6. A compound of formula (I) for use according to claim 5, wherein R_2 is selected from the group consisting of isopropyl, propyl and cyclopropyl, preferably isopropyl.

7. A compound of formula (I) for use according to any one of the preceding claims, wherein R_3 is benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms.

8. A compound of formula (I) for use according to any one of the preceding claims, wherein R_3 is benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms; and R_2 is selected from the group consisting of isopropyl, propyl and cyclopropyl, preferably isopropyl.

9. A compound of formula (I) for use according to any one of the preceding claims, wherein R_4 is selected from the group consisting of C_{2-5} linear or branched alkyl and C_{3-5} cycloalkyl both optionally substituted by C_{1-4}-alkyl.

10. A compound of formula (I) for use according to claim 9, wherein R_4 is selected from the group consisting of ethyl, tert-butyl and cyclopropyl.

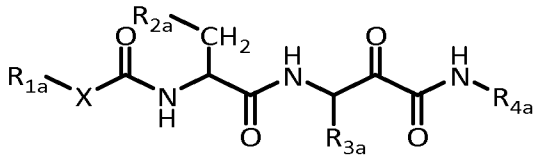
11. Use of a compound of formula (I) as defined in any one of the preceding claims or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of an obesity-related condition selected from the group consisting of obesity, lipid storage disease and hyperlipemia.

12. A method of treatment and/or prevention of an obesity-related condition selected from the group consisting of obesity, lipid storage disease and hyperlipemia in a subject in need thereof, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof.

13. Non-therapeutic use of a compound of formula (I) as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof to reduce fat accumulation in a subject which does not suffer from obesity.

14. Use according to claim 13 wherein reduction of fat accumulation is directed to improve the body appearance of said subject.

15. A compound of formula (II)



(II)

wherein

X is selected from the group consisting of a single bond, an oxygen atom and a -NH- group;

when X is O, R_{1a} is selected from the group consisting of a1) C_{1-8}-alkyl, optionally substituted by one C_{1-8} alkoxy group, b1) C_{6-10}-aryl-C_{1-4}alkyl and c1) C_{5-10}heteroaryl-C_{1-4}alkyl wherein the C_{5-10}heteroaryl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur,

when X is a single bond, R_{1a} is selected from the group consisting of d1) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; e1) naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; f1) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g1) C_{1-6} linear or branched alkyl, optionally substituted by one C_{1-8} alkoxy group and h1) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

when X is a –NH- group, R_{1a} is selected from the group consisting of d2) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; e2) naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; f2) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and

is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g2) C_{1-6} linear or branched alkyl, optionally substituted by one C_{1-8} alkoxy group and h2) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

R_{2a} is selected from the group consisting of i1) C_{1-8}-alkyl optionally substituted with 1, 2 or 3 fluor atoms, j1) C_{1-8}-alkoxy-C_{1-8}-alkyl and k1) C_{3-6}cycloalkyl-C_{0-2}alkyl wherein the cycloalkyl ring is optionally substituted with 1, 2 or 3 fluor atoms with the proviso that when X is O then R_{2a} is not an isopropyl group;

R_{3a} is selected from the group consisting of l1) C_{1-8}-alkyl and m1) benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms with the proviso that when X is a single bond and R_{1a} is a C_{5-10}heterocyclyl-C_{0-2}alkyl group, R_{3a} is not an ethyl group;

R_{4a} is selected from the group consisting of n1) C_{1-8}-alkyl, o1) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by C_{1-4}-alkyl and p1) C_{1-8}-alkoxy; and

R_5 and R_6 are independently selected from the group consisting of hydrogen atoms and C_{1-6} linear or branched alkyl groups;

or a pharmaceutically acceptable salt thereof.

16. A compound of formula (II) according to claim 15 wherein:

X is selected from the group consisting of a single bond, an oxygen atom and a -NH- group,

when X is O, R_{1a} is selected from the group consisting of a1) C_{1-8}-alkyl, b1) C_{6-10}-aryl-C_{1-4}alkyl and c1) C_{5-10}heteroaryl-C_{1-4}alkyl wherein the C_{5-10}heteroaryl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur,

when X is an single bond, R_{1a} is selected from the group consisting of d1) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, $NR_{5a}R_{6a}$, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; e1) naphthyl optionally substituted by 1 to 3

substituents selected from the group consisting of OH, $NR_{5a}R_{6a}$, CN, CF_3, C_{1-6} linear or branched alkyl, C_{1-6} linear or branched alkoxy and halogen atoms; f1) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g1) C_{1-6} linear or branched alkyl and h1) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, $NR_{5a}R_{6a}$, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

when X is a –NH- group, R_{1a} is selected from the group consisting of d2) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; e2) naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, $NR_{5a}R_{6a}$, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; f2) C_{5-10}heterocyclyl-C_{0-2}alkyl wherein the heterocyclyl rest comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, $NR_{5a}R_{6a}$, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms; g2) C_{1-6} linear or branched alkyl and h2) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NH_2, CN, CF_3, C_{1-6} linear or branched alkyl and halogen atoms;

R_{2a} is selected from the group consisting of i1) C_{1-8}-alkyl, j1) C_{1-8}-alkoxy-C_{1-8}-alkyl and k1) C_{3-6}cycloalkyl-C_{0-2}alkyl with the proviso that when X is O then R_{2a} is not an isopropyl group,

R_{3a} is selected from the group consisting of l1) C_{1-8}-alkyl and m1) benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms with the proviso that when X is a single bond and R_1a is a C_{5-10}heterocyclyl-C_{0-2}alkyl group, R_{3a} is not an ethyl group;

R_{4a} is selected from the group consisting of n1) C_{1-8}-alkyl and o1) C_{3-6}cycloalkyl-C_{0-2}alkyl optionally substituted by C_{1-4}-alkyl; and

R_{5a} and R_{6a} are independently selected from the group consisting of hydrogen atoms and C_{1-6} linear or branched alkyl groups;

or a pharmaceutically acceptable salt thereof.

17. A compound of formula (II) according to anyone of claims 15 to 16 wherein either (i) X is selected from the group consisting of O and NH and R_{1a} is selected from the group consisting of a1) C_{1-6}-alkyl or ii) X is a single bond and the R_{1a} group is selected from the group consisting of d1) phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of CN, CF_3, C_{1-3} linear or branched alkyl; and halogen atoms and f1) C_{5-10}heterocyclyl wherein the heterocyclyl rest is heteroaromatic and comprises 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur and is optionally substituted by 1 to 3 substituents selected from the group consisting of OH, NR_5R_6, CN, CF_3, C_{1-6} linear or branched alkyl and halogen.

18. A compound of formula (II) according to claim 17 wherein X is a single bond.

19. A compound of formula (II) according to anyone of claims 15 to 18 wherein the R_{2a} group is selected from the group consisting of C_{2-5} linear or branched alkyl and C_{3-5} cycloalkyl with the proviso that when X is O then R_{2a} is not an isopropyl group.

20. A compound of formula (II) according to anyone of claims 15 to 19 wherein the R_{2a} group is selected from the group consisting of isopropyl, propyl and cyclopropyl, preferably isopropyl, with the proviso that when X is O then R_{2a} is not an isopropyl group.

21. A compound of formula (II) according to anyone of claims 15 to 20 wherein the R_{3a} group is benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms.

22. A compound formula (II) according to anyone of claims 15 to 21 wherein the R_{3a} group is benzyl optionally substituted by 1 to 3 substituents selected from the group consisting of C_{1-4}-alkyl, MeO, CN and halogen atoms; and wherein the R_{2a} group is selected from the group consisting of isopropyl, propyl and cyclopropyl, preferably isopropyl, with the proviso that when X is O then R_{2a} is not an isopropyl group.

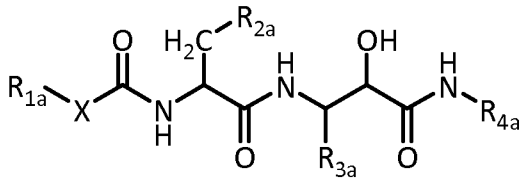
23. A compound of formula (II) according to anyone of claims 15 to 22 wherein the R_{4a} group is selected from the group consisting of C_{2-5} linear or branched alkyl and C_{3-5} cycloalkyl both optionally substituted by C_{1-4}-alkyl.

24. A compound of formula (II) according to claim 23 wherein the R_{4a} group is selected from the group consisting of selected from the group consisting of ethyl, tert-butyl and cyclopropyl.

25. A compound according to claim 14, having the following formula:

- N-[(1S)-1-(1-benzyl-2-methoxycarbamoyl-2-oxo-ethylcarbamoyl)-3-methyl-butyl]-3-methoxy-benzamide.

26. A process for the preparation of a compound of formula (II) as defined in anyone of claims 15 to 25, which comprises the reaction of a compound of formula (IV) with Dess-Martin periodinane



(IV)

wherein X, R_{1a}, R_{2a}, R_{3a} and R_{4a} are as defined in any one of claims 14 to 22.

27. A pharmaceutical composition comprising a compound of formula (II) as defined in anyone of claims 15 to 25 and a pharmaceutically acceptable excipient.

28. A compound of formula (II) as defined in anyone of claims 15 to 25 for use as a medicament.