

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property

Organization
International Bureau

(43) International Publication Date
2 June 2016 (02.06.2016)



(10) International Publication Number
WO 2016/083820 A1

(51) International Patent Classification:

C07D 401/14 (2006.01) *A61K 31/506* (2006.01)
C07D 413/14 (2006.01) *C07D 231/14* (2006.01)
A61K 31/415 (2006.01) *C07D 401/06* (2006.01)
A61K 31/454 (2006.01) *C07D 401/10* (2006.01)
A61K 31/4709 (2006.01) *C07D 403/10* (2006.01)
A61K 31/497 (2006.01) *C07D 409/14* (2006.01)

(21) International Application Number:

PCT/GB2015/053615

(22) International Filing Date:

26 November 2015 (26.11.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1421083.5 27 November 2014 (27.11.2014) GB

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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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, KM, ML, MR, NE, SN, TD, TG).

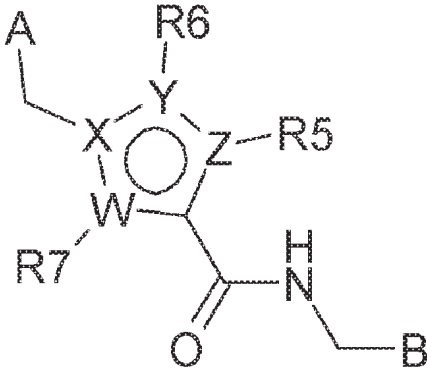
Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

(54) Title: N-((HET)ARYLMETHYL)-HETEROARYL-CARBOXAMIDES COMPOUNDS AS PLASMA KALLIKREIN INHIBITORS,



(I)

(57) Abstract: The present invention provides compounds of formula (I): (I) compositions comprising such compounds; the use of such compounds in therapy (for example in the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated); and methods of treating patients with such compounds; wherein R5, R6, R7, A, B, W, X, Y and Z are as defined herein.

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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 P065120WO	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/GB2015/053615	International filing date (day/month/year) 26.11.2015	Priority date (day/month/year) 27.11.2014	
International Patent Classification (IPC) or national classification and IPC INV. C07D401/14			
Applicant Kalvista Pharmaceuticals Limited			
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 <u>9</u> 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 <u>13</u> 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 3ter 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 conclusion 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 15.09.2016		Date of completion of this report 10.02.2017	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Kirsch, Cécile Telephone No. +49 89 2399-2191	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2015/053615

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

1-101 as originally filed

Claims, Numbers

1-17 filed with the letter of

22-12-2016

- ☐ 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 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/GB2015/053615

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 01.02.2017 (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	<u>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-17</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)
and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: WO 2005/049578

D2: WO 2007/11328

D3: "2-Thiophenecarboxamide", Chemical catalogue: AKos Consulting and Solutions GmbH, 18 December 2008 (2008-12-18), XP055244196

D4: "2-Thiophenecarboxamide, 4-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(4-morpholinyl)", Chemical catalogue AKos Consulting and Solutions GmbH, 22 January 2009 (2009-01-22), XP055244198

D5: "1H-Pyrazole-4-carboxamide, N-[[4-[(2-amino-2-oxoethyl)amino]carbonyl]phenyl]methyl]-3-(4-methylphenyl)-1-[(4-methylphenyl)methyl]-", Chemical catalogue: Ukrorgsyntez Ltd, 3 August 2012 (2012-08-03), XP055244204

D6: DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 August 2009 (2009-08-02), Chemical Catalogue: Ambinter: "1H-Pyrazole-4-carboxamide, N-[[4-(acetylamino)phenyl]methyl]-3-(4-methylphenyl)-1-[(4-methylphenyl)methyl]-", XP055244636, Database accession no. 1171693-25-6

D7: WO 2012/017020

D8: WO 2013/111108

D9: WO 2014/108679

D10: WO 2014/188211 (P-document)

D11: J. TANG ET AL "Expression, Crystallization, and Three-dimensional Structure of the Catalytic Domain of Human Plasma Kallikrein", J. Biol. Chem., 2005, 280(49), p. 41077-41089

The present application deals with N-((het)arylmethyl)-heteroaryl-carboxamides compounds as plasma kallikrein inhibitors, useful for treating e.g. diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, etc.

Re Item I

Basis of the report

Support for the amendments is to be found in the application as originally filed. The limited definitions for R5 and R6 is based on original claim 7. The definitions of R8 and R9 find basis on page 15, line 5. The definition -COOR10 has been deleted from the list of possible substituents on alkoxy. The compounds of examples 41, 66 and 77 have been introduced in newly filed claim 10.

These amendments fulfil the requirements of Article 34(2)(b) PCT.

Re Item V

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

Claims 14 and 16-17 relate 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. Patentability, in particular novelty and inventive step, of claims 14, 16-17 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

1. Novelty, Article 33(2) PCT

The compounds of D1 are substituted on the phenyl ring with a carboxymethyloxy group. According to pending formula (I), phenyl ring B may be substituted by an alkoxy. However, alkoxy may not carry a carboxy group.

Due to the nature of W (CH) in the present application, the furane and imidazole rings R3 of D2 do not take away the novelty of the claimed subject-matter.

Documents D3 to D6 describes specific compounds. The additional substituent on the 5-membered ring does not correspond to the possible groups R5 and R6 according to the current set of claims.

Documents D7 to D9 deal with N-((het)arylmethyl)-heteroaryl-carboxamides as plasma kallikrein inhibitors. The compounds of D7 and D9 differ from the present claimed subject-matter due to the nature of the substituent on the ring corresponding to B (amino in D7, amino substituted-alkyl in D9). The compounds of D8 are not further substituted on the 5-membered core structure.

Novelty vis-à-vis D1 to D9 is acknowledged.

2. Inventive step, Article 33(3) PCT

2.1. Document D8 may be considered the closest prior art. Document D8 discloses N-((het)arylmethyl)-heteroaryl-carboxamides as plasma kallikrein inhibitors. The compounds of D8 lack the additional substituent on the 5-membered core structure.

2.2. The problem to be solved may be considered as the provision of further N-((het)arylmethyl)-heteroaryl-carboxamide derivatives as plasma kallikrein inhibitors.

In the light of the biological data provided on pages 94-101 of the application, the problem may be considered as solved.

2.3. Document D7 and D9 describe similar compounds with the same biological activity as those of D8. They both disclose compounds wherein the 5-membered core structure is substituted in accordance with the present claimed subject-matter (see e.g. formula (I) and ex. 79 of D7 and formula (I) and ex. 25, 55, 56, 84, 124, 132-133 of D9). Thus, D7 and D9 shows that substitutions at these positions also provide active compounds. It would be obvious to the person skilled in the art, namely when the same result is to be achieved, to apply these features to the compounds according of D8, thereby arriving at the claimed subject-matter.

2.4. In the application it is argued that none of D7 to D9 provide in vivo data so that it is not apparent whether the compounds disclosed therein would prove efficient for the claimed treatment. It is however an established principle that showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application. In bio-medical sciences, studies in vitro wherein a given product is shown to have a biological effect, are normally, and logically, followed by experiments in vivo in an animal model where the effect can be tested in the more complex context of a living organism. One of the purposes of such animal models, from the simplest to the more complex, is indeed to serve as an intermediary step before clinical testing in patients, thus as a sort of barrier between potentially harmful products and human exposure. Thus, the person skilled in the art would not ignore this clear teaching of the art.

2.5. It is also argued that the compounds of the prior art are poorly selective for plasma kallikrein over KLK1. Although the present application provides data showing the selectivity of the claimed compounds for plasma kallikrein with regard to KLK1, there is at present no evidence that this effect does not occur in the compounds known from the prior art. Accordingly, this effect cannot be taken into account for the assessment of inventive step.

2.6. In the present case, the sole difference between the present claimed subject-matter and the closest prior art represented by D8 lies with the presence of an additional substituent on the 5-membered ring. Therefore any surprising effect that may be shown should be based on this specific feature. However, in the light of the teaching of D7 and D9, the skilled person would expect the pharmacological effect to be retained.

It is noted that both D7 and D9 requires the presence of an amino group that may have some quantitative influence on the level of inhibition. D8, which is the closest prior art, does not require such structural feature so that the skilled person would not regard this structural element as necessary to obtain the plasma kallikrein effect. Documents D7 and D9 are only relevant with regard to D8 in as far as they teach that the presence of substituents on the 5-membered ring does not lead to inactive compounds.

For these reasons, it is considered that on the basis of D8 interpreted in the light of either D7 and D9, the skilled person would have considered the addition of substituents on the 5-membered ring and would have expected the claimed activity to be retained.

The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT with respect to inventive step because these features are already known from the cited prior art, see e.g. D9 which reveals CF3 as a possible substituent with good activity (compounds 83, 117-120, 125-126, or 129-130).

The subject-matter of claims 1 to 17 does not fulfil the requirements of Article 33(3) PCT.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (<i>valid claim</i>) (day/month/year)
WO2014/188211	27/11/2014	23/05/2014	23/05/2013 14/08/2013

Document D10 has been published on the priority date of the present application. According to Rule 64.3 PCT, this document may not be taken into account for the assessment of novelty and inventive step during the international phase. The attention of the applicant is however drawn to the fact that this document may prove relevant in the examination process during regional phase. A preliminary opinion as to novelty is provided for information.

The definition of B according to D10 differs from the claimed subject-matter because either the bicyclic ring comprises at least one nitrogen atom (i.e. not benzofurane/benzothiophene) or it is aromatic (i.e. not benzomorpholine).

It is noted that the priority would seem to be only partially valid. The definition of B encompasses benzomorpholine which finds no support in the priority document. Also, the definition of W (CH) in combination with the broad definitions of X, Y and Z does not directly derive from the priority document. Should the priority be found invalid, document D10 would be relevant for the assessment of both novelty and inventive step.

Re Item VIII

Certain observations on the international application

Clarity, Article 6 PCT

1. The term "isomers" employed in claim 1 includes all the chemical compounds having same molecular formula but different structural formulas, and it is unclear which compounds are covered by such a definition in structural terms. Support within the meaning of Article 6 PCT is to be found, however, only for the compounds of structural formula (I). Other constitutional isomers are not supported by the description. Consequently the claimed subject-matter does not fulfil the requirements of Article 6 PCT.

2. Claims 13 to 17, which subject matter is by reference to a mechanism of action (modulation of plasma kallikrein) cannot be considered:

i) as industrially applicable as the modulation of plasma kallikrein cannot be considered in itself as a therapeutic application. The discovery, that a substance modulates plasma kallikrein, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art, and

ii) as clear, since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition e.g. any condition susceptible of being improved or prevented by the modulation of plasma kallikrein, and accordingly within the scope of the claim.

3. The subject-matter described on page 6, line 33- page 7, line 2 and page 32, lines 13-16 (N-oxides, prodrugs) does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

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Electronically submitted

Your Ref
Our Ref P065120WO:GMP
Date 22nd December 2016

Dear Sirs,

**Re: International Patent Application No. PCT/GB2015/053615
KALVISTA PHARMACEUTICALS LIMITED**

I refer to the written opinion issued by the IPEA dated 24th October 2016. Further examination of this application is to be based upon the enclosed amendments to the claims made pursuant to Article 34 PCT. A copy of the amendments showing tracked changes relative to the claims filed on 15th September 2016 is also enclosed for the IPEA's reference.

The applicant's comments on the objections raised in the written opinion dated 24th October 2016 are as follows:

Amendments

The COOR10 substituent has been deleted from the list of optional alkoxy substituents in claim 1. This amendment does not add matter beyond the scope of the application as filed because it is a deletion from a single list of substituents.

Any subject matter excluded by this amendment is not abandoned.

Novelty

In D1, the left hand side of the general formula (I) comprises a substituted alkoxy group (-O(CR¹R²)COOH) attached to a phenyl group. This substituent does not fall within the scope of amended claim 1. The definition of an alkoxy group in amended claim 1 is as follows:

“alkoxy is a linear O-linked hydrocarbon of between 1 and 6 carbon atoms (C₁-C₆) or a branched O-linked hydrocarbon of between 3 and 6 carbon atoms (C₃-C₆); alkoxy may optionally be substituted with 1 or 2 substituents independently selected from OH, CN, CF₃, CONR10R11, fluoro and NR10R11”

The COOH substituent on the alkoxy group in general formula (I) of D1 does not fall within the scope of any of the optional alkoxy substituents listed in claim 1, as shown above. Since the definition of the alkoxy substituent in amended claim 1 does not permit the alkoxy group to be substituted by COOH, amended claim 1 is novel over D1.

The enclosed claims are therefore novel over the cited prior art.

Inventive Step

The IPEA is of the opinion that D11 identifies many positions as relevant for the kallikrein inhibitory activity. The IPEA also considers that D11 particularly insists on the capacity of inhibitors to displace water.

The applicant respectfully disagrees with the IPEA that the Asp¹⁸⁹ residue in plasma kallikrein is not an important residue for binding in plasma kallikrein. D11 does focus on the interaction with Asp¹⁸⁹ as being important in the binding of plasma kallikrein inhibitors. For example, Asp¹⁸⁹ is specifically mentioned in the initial discussion of the S1 binding site (which the plasma kallikrein inhibitors of the present invention occupy) in the paragraph bridging pages 41082 and 41083. Furthermore, Asp¹⁸⁹ is identified as important in the S1 binding site in the passage bridging 41085 and 41086 (emphasis added):

“At the bottom of the S1 site of plasma kallikrein lies negatively charged Asp¹⁸⁹, which forms hydrogen-bonded salt bridges with positively charged Arg or Lys residues that are the P1 residues of protein or peptide substrates for this protease. This interaction with Asp¹⁸⁹ constitutes the structural basis for the selectivity of plasma kallikrein for Arg or Lys at the S1 site (Fig. 5) (52). The role of Asp¹⁸⁹ in recognition at the S1 site of plasma kallikrein is apparent in the structure of the benzamidine complex, in which Asp¹⁸⁹ makes hydrogen-bonded salt bridges with the amidine group (Fig. 5), as in other trypsin-like serine proteases (52). Other hydrogen bonds to benzamidine involve the carbonyl group of Gly²¹⁹ and a water molecule.”

It is accepted that D11 also teaches that Gly²¹⁹ and a water molecule are involved in binding, but D11 undoubtedly focuses on the interaction with Asp¹⁸⁹ as the primary interaction in the S1 site.

Indeed, the Asp¹⁸⁹ residue (D189) is the only residue in the S1 binding site specifically shown in Figure 3(a) of D11. The strong interaction of a basic plasma kallikrein inhibitor with Asp¹⁸⁹ is also shown by the presence of two binding interactions with Asp¹⁸⁹ in Figures 5, 6, and 8 of D11. It is therefore clear from D11 that the interaction with the Asp¹⁸⁹ residue is important for inhibitors of plasma kallikrein that bind at the S1 site.

The IPEA also suggested that D11 referred only to amidine and guanidine moieties, but not to an amino group (like the compounds of D7 and D9). The skilled person would have understood the compounds of D7 and D9 to bind to plasma kallikrein in a similar way to the basic amidines and guanidines of D11 because the compounds of D7 and D9 are also basic. The aminopyridine compounds of D7 are comparatively basic because the lone pair of electrons of the amino group is conjugated to the nitrogen in the pyridine. The benzylamines of D9 are also basic. The passage at the start of page 41086 specifies that the Asp¹⁸⁹ makes hydrogen-bonded salt bridges with the amidino group. The skilled person would expect other basic groups (such as an amine or aminopyridine) to be able to form a salt bridge with the Asp¹⁸⁹ group, and so would understand the teachings of D11 to also apply to the compounds of D7 and D9.

This is confirmed in Figure 1 of the enclosed document which shows a crystal structure of Example 3 of D9 bound to plasma kallikrein. In Figure 1 of the enclosed document, Example 3 of D9 is overlaid with the crystal structure of the similar benzamidine (specifically the “benzamidine” referred to in D11) bound to plasma kallikrein. As can be seen, the amino group of the benzylamine also exhibits a binding interaction with the Asp¹⁸⁹ residue (as expected based on the teachings in D11). Furthermore, the position of the rest of the molecule is completely conserved in both the benzylamine and benzamidine. The skilled person would also have expected the basic aminopyridine group to exhibit a similar binding interaction to the Asp¹⁸⁹ residue.

Unlike the vast majority of known plasma kallikrein inhibitors, including those of D7 and D9, the compounds of the present invention do not rely on a basic group interaction with Asp¹⁸⁹ for their activity. Accordingly, the compounds of the present invention will bind to plasma kallikrein in a manner that is quite different from the binding exhibited by the compounds of D7 and D9.

This different binding mode is clearly illustrated in Figures 2-5 of the attached document. The black structure in each of Figures 2-5 is a crystal structure of Example 3 of D9 bound to plasma kallikrein. The residues Asp¹⁸⁹ and Tyr²²⁸ are shown in white. Overlaid in grey in each of Figures 2-5 is a crystal structure of four different compounds from the present application (Examples 41, 66, 77 and 53) bound to plasma kallikrein. Figures 6 and 7 have been included to highlight the difference in the interaction with the P1 pocket of plasma kallikrein between Example 3 of D9 and the compounds of the invention (wherein Example 77 has been used to illustrate this).

As can be seen from Figures 2-5, the phenyl ring (which is not basic) of the compounds of the present invention does not bind to the Asp¹⁸⁹ residue and so is oriented differently to the benzylamine in Example 3 of D9. In the Examples shown, the methoxy group on the phenyl substituent interacts with a different residue, Tyr²²⁸. As a result of this different binding mode, the amide is oriented differently in the compounds of the present application compared to Example 3 of D9. Furthermore, the 5-membered core is significantly spatially displaced in the compounds of the present application compared to Example 3 of D9. This means the R5 and R6 substituents in the compounds of the present invention interact with a different part of plasma kallikrein compared to the compounds of D9. Thus, the enclosed crystal structures provide further evidence that the SAR of the compounds of D8 and the present invention would be expected to be different to that of the basic compounds of D7 and D9.

Taking D8 as the closest prior art, the difference between the compounds of the present invention and those of D8 is that the compounds of the present invention bear at least one substituent

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selected from CH_2OCH_3 , cycloalkyl, CN, -NR₈R₉, -NR₈COR₉ and CF_3 on the ring containing W, X, Y and Z. The technical effect of this difference is that the compounds of the present invention are also plasma kallikrein inhibitors. The technical problem is therefore to provide further compounds that are plasma kallikrein inhibitors. Evidence that the technical problem is solved is provided by the data present in the application as filed.

The compounds of the present invention are not obvious in light of D8 because there is no suggestion in D8 that ring B (which is equivalent to the ring containing W, X, Y and Z in the compounds of the present invention) could be substituted and plasma kallikrein activity retained. On the contrary, D8 does not allow ring B to be substituted. More specifically, there are no substituents (either optional or non-optional) on ring B in formula I of D8, substitution is not mentioned in the definition of B on page 6, first complete paragraph and the preferred ring B groups are (non-substituted) pyrazole or triazole. Thus, D8 actually teaches away from any substitution on ring B.

The examiner has suggested that D7 or D9 would have motivated the skilled person to substitute ring B of D8 in order to solve the technical problem. However, this would not have been the case because, as explained above, the compounds of D7 and D9 bind to plasma kallikrein in a manner that is quite different from the binding exhibited by a number of the compounds of D8 and all of the compounds of the present invention. It does not make technical sense to apply structure-activity-relationship information from compounds that rely on a basic group interaction with Asp¹⁸⁹ when binding to plasma kallikrein to compounds that do not rely on this interaction when binding to the same target. This is clearly illustrated in the enclosed data showing the different binding modes of the compounds of the present invention, and those of D9. Accordingly, the skilled person would not have applied the teaching of D7 and D9 to D8 with an expectation of solving the above technical problem.

The compounds of the present invention are therefore neither obvious over D8 alone or over D8 in combination with D7 or D9.

The IPEA suggested that the position of the substituent is not of relevance as it may be either at R5 or R6. The IPEA considered this to show that the substituent does not play any relevant role in the biological activity of the claimed compounds. It is submitted that the IPEA is using hindsight analysis in arriving at this conclusion because data from the application as filed have been used to compare the activities of compounds with substituents in the R5 or R6 position. As discussed above, the skilled person would not have applied the teaching of D7 and D9 to D8, and so would not have been motivated to add the R5 and R6 groups.

The applicant requests that further international preliminary examination be based upon the comments presented herein and the enclosed amended claims. The applicant requests that the IPEA issued a further written opinion after reviewing the above comments and amended claims.

If the IPEA does not agree with the above arguments and intends to issue an unfavourable IPRP, a further opportunity to submit arguments or amendments is requested (Rule 66.4(b) PCT) and a telephone discussion with the IPEA under Article 34(2)(a) and Rule 66.6 PCT is requested.

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Yours faithfully,

// ELECTRONICALLY SIGNED AND SUBMITTED //

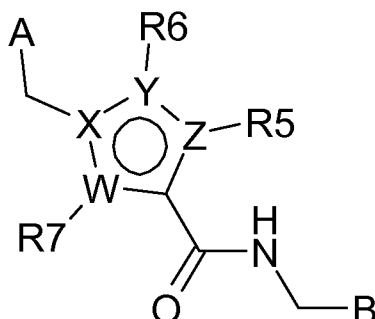
PHILLIPS, Gillian Margaret

Carpmaels & Ransford LLP Professional Association No. 182

Encl. Amended claims (clean and tracked)
 Crystal structure data

CLAIMS

1. A compound of formula (I),



Formula (I)

5

wherein

B is phenyl substituted with 1 to 4 substituents selected from alkyl^b, alkoxy, OH, halo, CN, heteroaryl, COOR₈, NHCOR₈, CONR₈R₉, OCF₃, and CF₃;

- 10 or B is selected from benzothiophenyl, benzofuranyl, benzomorpholinyl and a 5 or 6 membered heterocyclic ring containing one or two heteroatoms selected from N, O and S; wherein said 5 or 6 membered heterocyclic ring may be aromatic or non-aromatic; and wherein said benzothiophenyl, said benzofuranyl, said benzomorpholinyl or said 5 or 6 membered heterocyclic ring is substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, OH, oxo, halo, CN, heteroaryl, COOR₈, NHCOR₈, CONR₈R₉, OCF₃ and CF₃;
- 15

W is C and X, Y and Z are independently selected from C, N, O and S, such that the ring containing W, X, Y and Z is a five membered aromatic heterocycle;

- 20 R₅ and R₆ are independently absent or independently selected from H, CH₂OCH₃, cycloalkyl, CN, -NR₈R₉, -NR₈COR₉ and CF₃; wherein at least one of R₅ and R₆ is present and is not H; R₇ is H;

- A is selected from aryl and heteroaryl; wherein aryl is substituted with 1, 2 or 3 substituents
- 25 independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, heteroaryl, -(CH₂)₀₋₃-O-heteroaryl, aryl^b, -O-aryl^b, -(CH₂)₁₋₃-aryl^b, -(CH₂)₁₋₃-heteroaryl, -COOR₁₀, -CONR₁₀R₁₁, -(CH₂)₀₋₃-NR₁₀R₁₁, OCF₃ and CF₃; and heteroaryl is substituted with 1, 2 or 3

substituents independently selected from alkyl, alkoxy, OH, OCF₃, halo, CN, aryl, -(CH₂)₁₋₃-aryl, -(CH₂)₀₋₃-NR10R11, heteroaryl^b, -COOR10, -CONR10R11 and CF₃;

R8 and R9 are independently selected from H and methyl, ethyl, n-propyl and isopropyl;

5

alkyl is a linear saturated hydrocarbon having up to 10 carbon atoms (C₁-C₁₀) or a branched saturated hydrocarbon of between 3 and 10 carbon atoms (C₃-C₁₀); alkyl may optionally be substituted with 1 or 2 substituents independently selected from (C₁-C₆)alkoxy, OH, CN, CF₃, COOR10, CONR10R11, fluoro and NR10R11;

10

alkyl^b is a linear saturated hydrocarbon having up to 6 carbon atoms or a branched saturated hydrocarbon of between 3 and 6 carbon atoms (C₃₋₆); alkyl^b may optionally be substituted with 1 or 2 substituents independently selected from (C₁-C₆)alkoxy, OH, CN, CF₃, COOR10, CONR10R11 and fluoro;

15

cycloalkyl is a monocyclic saturated hydrocarbon of between 3 and 6 carbon atoms;

alkoxy is a linear O-linked hydrocarbon of between 1 and 6 carbon atoms (C₁-C₆) or a branched O-linked hydrocarbon of between 3 and 6 carbon atoms (C₃-C₆); alkoxy may optionally be substituted with 1 or 2 substituents independently selected from OH, CN, CF₃, CONR10R11, fluoro and NR10R11;

20

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, heteroaryl, -(CH₂)₀₋₃-O-heteroaryl, aryl^b, -O-aryl^b, -(CH₂)₁₋₃-aryl^b, -(CH₂)₁₋₃-heteroaryl, -COOR10, -CONR10R11, -(CH₂)₀₋₃-NR10R11, OCF₃ and CF₃;

25

aryl^b is phenyl, biphenyl or naphthyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, -COOR10, -CONR10R11, CF₃ and NR10R11;

30

heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2, 3 or 4 ring members independently selected from N, NR8, S and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl,

alkoxy, OH, OCF₃, halo, CN, aryl, -(CH₂)₁₋₃-aryl, -(CH₂)₀₋₃-NR_{10R11}, heteroaryl^b, -COOR₁₀, -CONR_{10R11} and CF₃;

heteroaryl^b is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where
 5 possible, 1, 2 or 3 ring members independently selected from N, NR₈, S and O; wherein heteroaryl^b may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, aryl, -(CH₂)₁₋₃-aryl, -COOR₁₀, -CONR_{10R11}, CF₃ and NR_{10R11};

R₁₀ and R₁₁ are independently selected from H, alkyl, aryl^b and heteroaryl^b or R₁₀ and R₁₁
 10 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocyclic ring, optionally containing an additional heteroatom selected from N, S and O, which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, halo and CF₃;

15 and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1, wherein B is selected from phenyl substituted with 1
 20 to 4 substituents selected from alkyl^b, alkoxy, OH, halo, CN, heteroaryl, COOR₈, NHCOR₈, CONR_{8R9}, OCF₃, and CF₃; or B is selected from benzothiophenyl, benzofuranyl, and a 5 or 6 membered heterocyclic ring containing one or two heteroatoms selected from N, O and S; wherein said 5 or 6 membered heterocyclic ring may be aromatic or non-aromatic; and wherein said benzothiophenyl, said benzofuranyl or said 5 or 6 membered heterocyclic ring is
 25 substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, OH, oxo, halo, CN, heteroaryl, COOR₈, NHCOR₈, CONR_{8R9}, OCF₃ and CF₃; wherein alkyl^b, alkoxy, R₈ and R₉ are as defined in claim 1.

3. A compound according to claim 1 or claim 2, wherein B is selected from phenyl,
 30 thiophenyl, benzothiophenyl and pyridyl, each substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, halo, CN, COOR₈, CONR_{8R9}, OCF₃ and CF₃; wherein alkyl^b, alkoxy, R₈ and R₉ are as defined in claim 1.

4. A compound according to any one of claims 1 to 3, wherein B is selected from phenyl and pyridyl, each substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, CF₃ and halo; wherein alkyl^b and alkoxy are as defined in claim 1.
5. A compound according to any one of claims 1 to 4, wherein W is C and X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five membered aromatic heterocycle.
6. A compound according to any one of claims 1 to 5, wherein W is C, X is N and Y and Z are selected from C and N.
7. A compound according to any one of claims 1 to 6, wherein A is phenyl substituted with -(CH₂)₁₋₃-heteroaryl or -(CH₂)₁₋₃-NR₁₀R₁₁ and, optionally, 1 or 2 additional substituents independently selected from alkyl, halo and CF₃; wherein alkyl, heteroaryl, R₁₀ and R₁₁ are as defined in claim 1.
8. A compound according to any one of claims 1 to 6, wherein A is pyridyl substituted with heteroaryl^b or -NR₁₀R₁₁ and, optionally, 1 or 2 additional substituents independently selected from alkyl, halo and CF₃; wherein alkyl, heteroaryl^b, R₁₀ and R₁₁ are as defined in claim 1.
9. A compound according to claim 1, selected from:
- 3-Amino-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 2-fluoro-3-methoxy-benzylamide;
- N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
- N-[(2-fluoro-5-methoxyphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
- N-[(2-fluoro-6-(trifluoromethyl)phenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
- N-[(4-chloro-2,6-difluorophenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
- N-[(3-chloro-2-fluoro-6-(trifluoromethyl)phenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(2-fluoro-4-methylphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
 N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(5-chloro-1-benzothiophen-3-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-6-(trifluoromethyl)phenyl)methyl]-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;
 3-cyclopropyl-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-3,6-dimethoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-(dimethylamino)-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-5-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-4-methylphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2,6-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-(difluoromethyl)phenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-(difluoromethyl)-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-amino-N-[(2-fluoro-6-(trifluoromethyl)phenyl)methyl]-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-acetamido-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(3-chloro-2,6-difluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(5-chloro-2-cyanophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxypyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;

N-[(6-cyano-2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[5-methoxy-2-(trifluoromethyl)phenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[2-(difluoromethyl)-6-fluorophenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[2-(difluoromethyl)-5-methoxyphenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[2-(difluoromethyl)-6-fluoro-3-methoxyphenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-carbamoyl-6-fluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-carbamoyl-5-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[3-(difluoromethoxy)-2-fluorophenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[[2-(difluoromethoxy)-6-fluorophenyl]methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2,5-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2-fluoro-6-methylphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(6-chloro-2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-amino-N-[(2-fluoro-3-hydroxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(3-ethyl-2-fluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-(methoxymethyl)-N-[(3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2,6-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(4-methyl-2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2,6-difluoro-3-methoxyphenyl)methyl]-1-({4-[(5-fluoro-2-oxopyridin-1-yl)methyl]phenyl)methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}-2-(trifluoromethyl)imidazole-4-carboxamide;
 3-amino-N-[(7-chloro-4-methyl-2,3-dihydro-1,4-benzoxazin-2-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 3-amino-N-[(7-chloro-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide

and pharmaceutically acceptable salts and solvates thereof.

10. A compound according to claim 1, selected from:

N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(2,6-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;
 N-[(6-cyano-2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl)methyl}pyrazole-4-carboxamide;

10 and pharmaceutically acceptable salts and solvates thereof.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier, diluent or excipient.

15 12. A compound as claimed in any one of claims 1 to 10 for use in medicine.

13. The use of a compound as claimed in any one of claims 1 to 10 in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

20

14. A method of treatment of a disease or condition in which plasma kallikrein activity is implicated comprising administration to a subject in need thereof a therapeutically effective amount of a compound as claimed in any one of claims 1 to 10.

25 15. A compound as claimed in any one of claims 1 to 10 for use in a method of treatment of a disease or condition in which plasma kallikrein activity is implicated.

16. The use of claim 13, the method of claim 14 or a compound for use as claimed in claim 15 wherein, the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy,
- 5 neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.
17. The use of claim 13, the method of claim 14 or a compound for use as claimed in claim
- 10 15, wherein the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.