

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2024/077295

International filing date (day/month/year)
27.09.2024

Priority date (day/month/year)
28.09.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61P9/00 A61P11/00 A61P25/28 A61P29/00 A61P43/00 C07D413/14 C07D417/14 C07D491/052

Applicant
BAYER AKTIENGESELLSCHAFT

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ 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 Rule 43bis.1(a)(i) with regard to novelty, inventive step and 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

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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D-80298 Munich
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Bedel, Christian

Telephone No. -0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ 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 (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	<u>1-16</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-16</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

Re Item V

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

1 Preliminary remark

The subject-matter of claim 16 concerns a method of treatment and is therefore 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 claim 16 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 Reference is made to the following documents:

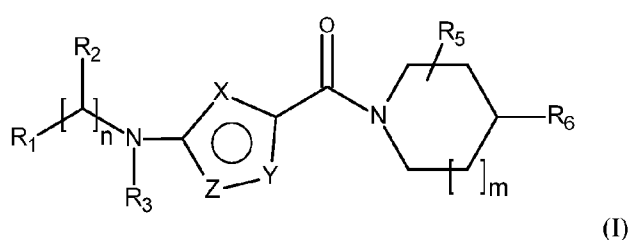
- D1 WO 2006/058905 A1 (DEVGEN NV [BE]; BLOM PETRA [BE] ET AL.) 8 June 2006 (2006-06-08)
- D2 WO 2019/002074 A1 (BAYER AG [DE]; BAYER PHARMA AG [DE]) 3 January 2019 (2019-01-03)
- D3 DATABASE CHEMCATS [Online] 6 April 2023 (2023-04-06), "RN 2974543-03-6", XP093225534, Database accession no. 0300466902
- D4 DATABASE CHEMCATS [Online] 6 April 2023 (2023-04-06), "RN 1358081-36-3", XP093225514, Database accession no. 1502615470
- D5 DATABASE CHEMCATS [Online] 6 April 2023 (2023-04-06), "RN 1954022-51-5", XP093225507, Database accession no. 1846083409
- D6 DATABASE CHEMCATS [Online] 6 April 2023 (2023-04-06), "RN 2974525-71-6", XP093225529, Database accession no. 0867745744
- D7 DATABASE CHEMCATS [Online] 6 April 2023 (2023-04-06), "RN 2394582-60-0", XP093225464, Database accession no. 1709760042
- D8 WO 2021/089683 A1 (BAYER AG [DE]) 14 May 2021 (2021-05-14)

D9 WO 2005/118579 A2 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB] ET AL.) 15 December 2005 (2005-12-15)

D10 WO 2022/048631 A1 (INNOVSTONE THERAPEUTICS LTD [CN]) 10 March 2022 (2022-03-10)

3 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claim 1 is not new.

3.1 Present application concerns in claim 1 a compound of general formula (I):



in which

X is S, N or O;

Y is N, S or O,

where, when X is S, Z is N;

where, when X is O, Z is N;

Y is CR₄, O or NR₄,

where, when X is N and Z is N, Y is O;

where, when X is S, Y is CR₄ or NR₄;

R₁ is 5- to 10-membered heteroaryl, phenyl, (C₄-C₁₀)-heterocycloalkyl or (C₃-C₁₀)-cycloalkyl,

in which 5- to 10-membered heteroaryl may be substituted by 1 to 3 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, halogen;

where (C₁-C₄)-alkyl may be up to trisubstituted by halogen,

where (C₁-C₄)-alkoxy may be up to trisubstituted by halogen,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₃-C₅)-cycloalkyl, (C₁-C₄)-alkoxy, cyano, hydroxy, halogen;

where (C₁-C₄)-alkyl may be up to trisubstituted by halogen,

in which (C₃-C₁₀)-cycloalkyl and (C₄-C₁₀)-heterocycloalkyl may be substituted by 1 to 2 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₃-C₅)-cycloalkyl, (C₁-C₄)-alkoxy, cyano, hydroxy, halogen;

where (C₁-C₄)-alkyl may be up to trisubstituted by halogen,

in which (C₃-C₁₀)-cycloalkyl and (C₄-C₁₀)-heterocycloalkyl may be fused to 5- to 10-membered

heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy and halogen;

R₂ is hydrogen, (C₁-C₄)-alkyl or (C₃-C₅)-cycloalkyl;

in which (C₁-C₄)-alkyl may be up to trisubstituted by halogen,

in which (C₁-C₄)-alkyl may be substituted by cyano or (C₁-C₄)-alkoxy,

in which (C₃-C₅)-cycloalkyl may be up to trisubstituted by halogen,

or

together with the carbon atom to which R₂ is bonded forms a (C₃-C₄)-cycloalkyl ring,

or

R₁ and R₂ together form a (Cs-Cs)-cycloalkyl or (C₅-C₁₀)-heterocycloalkyl ring,

in which (Cs-Cs)-cycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy and halogen;

in which (C₃-C₁₀)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy and halogen;

R₃ is hydrogen, (C₁-C₄)-alkyl,

in which (C₁-C₄)-alkyl may be up to trisubstituted by halogen,

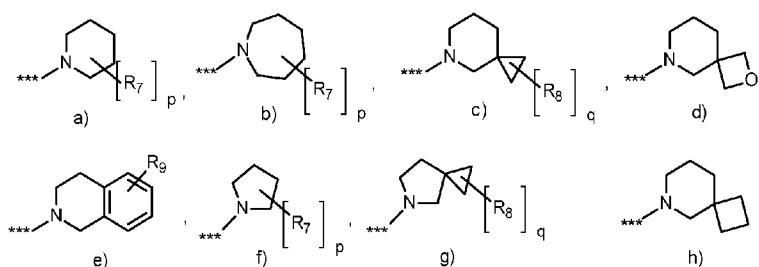
R₄ in CR₄ is hydrogen, (C₁-C₄)-alkyl, (C₃-C₄)-cycloalkyl, phenyl, halogen;

in which (C₁-C₄)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

in NR₄ is absent or is hydrogen, (C₁-C₄)-alkyl, (C₃-C₄)-cycloalkyl, phenyl; in which (C₁-C₄)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

Rs is hydrogen, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, halogen,

R₆ is a group of formula a), b), c), d), e), f) or g)



in which *** marks the attachment to the adjacent piperidine ring,

in which R₇ is hydrogen, (C₁-C₄)-alkyl, (C₃-C₄)-cycloalkyl, (C₁-C₄)-alkoxy, (C₃-C₄)-cycloalkoxy, phenyl,

where (C₁-C₄)-alkyl may be substituted by (C₃-C₄)-cycloalkyl, (C₁-C₄)-alkoxy, (C₃-C₄)-cycloalkoxy and up to trisubstituted by halogen,
where (C₁-C₄)-alkoxy may be substituted by (C₃-C₄)-cycloalkyl and up to trisubstituted by halogen,
where (C₃-C₄)-cycloalkyl may be substituted by monofluoromethyl, difluoromethyl or trifluoromethyl and up to disubstituted by halogen,
where (C₁-C₄)-alkoxy may be substituted by (C₃-C₄)-cycloalkyl and up to trisubstituted by halogen,
where (C₃-C₄)-cycloalkyl may be mono- or disubstituted by halogen,
where (C₃-C₄)-cycloalkoxy may be up to disubstituted by halogen, in which R_S is hydrogen or fluorine,
in which R₉ is hydrogen, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, halogen;
where (C₁-C₄)-alkyl may be substituted by (C₁-C₄)-alkoxy,
n represents 0 or 1,
m represents 0, 1 or 2,
p represents 0, 1 or 2 and
q represents 0, 1 or 2,
and the salts, solvates and solvates of the salts thereof.

- 3.2 D1-D2 disclose a series of compounds that fall within the scope of claim 1 (see details in search report).
- 3.3 D4, D5 and D7 disclose the subject-matter of claims 1-2.
- 3.4 D3 and D6 disclose the subject-matter of claims 1-5.
- 3.5 D1 also concerns a bioactive compounds and more particularly discloses medical applications that overlap with the ones of the present application (see for instance respiratory distress syndrome as well as cardiac and neurodegenerative disorders). Therefore the subject-matter of medical application claims 7-16 is considered to be anticipated by D1.
- 3.6 As regard process claim 6, D1-D2 use the same process (see p.56-61) as detailed in [C] alternative method of said claim 6.
- 4 Inventive step (Art. 33(3)).
- 4.1 Since none of the present claims is novel, no inventive step can be envisaged.
- 4.2 However since the subject-matter of claims 2-5 is anticipated only by single compounds disclosed in CHEMCATS database, without any suggested medical application, the following opinion is given.
- 4.3 Concerning said claims the closest prior art should be D8 which discloses compounds of general formula (I), which are alpha-2C adrenergic receptor antagonists:

