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(54) Title: PYRAZOLOETHER ANALOGS AS MGLU5 NEGATIVE ALLOSTERIC MODULATORS AND METHODS OF MAKING AND USING THE SAME

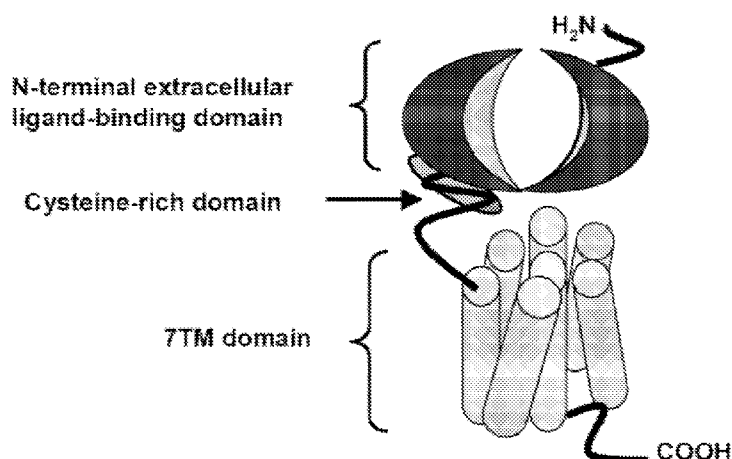


FIG. 1

(57) Abstract: Negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGlu5); synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction using the compounds and compositions.



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- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/32756

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/44, A61K 31/395, A61K 31/415, A61K 31/166 (2023.01)

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CPC - INV. A61K 31/44, A61K 31/395, A61K 31/415, A61K 31/166

ADD. A61K 31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0172248 A1 (Conn et al.), 14 July 2011 (14.07.2011), entire document, especially para[0008], [0010], [0279]; page 20, row 2, last compound listed; page 23, fifth row, first compound listed	1, 3, 6, 10-11, 22-24
Y	US 8,822,497 B2 (Novartis AG), 02 September 2014 (02.09.2014), entire document, especially col 3, ln 49-67; col 4, ln 1-17; col 13, ln 52-53	1, 3, 6, 10-11, 22-24
A	"Pubchem CID 141419641", Create date: 06 December 2019 (06.12.2019), entire document, especially page 2, compound listed	1, 3, 6, 10-11, 22-24
A	WO 2017/045615 A1 (Jikai Biosciences, Inc.), 23 March 2017 (23.03.2017), entire document, especially page 5, para 7; page 6, para 1	1, 3, 6, 10-11, 22-24
A	US 2014/0336377 A1 (Raqualia Pharma Inc.), 13 November 2014 (13.11.2014), entire document, especially para[0029]-[0066], [1487]-[1488]	1, 3, 6, 10-11, 22-24
A	WO 2006/123257 A2 (Gagliardi et al.), 23 November 2006 (23.11.2006), entire document, especially page 4, para 3; page 5-6	1, 3, 6, 10-11, 22-24

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/32756

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

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
---see supplemental box---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3, 6, 10-11, 22-24

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/32756

Box III: lack of unity

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

Group I+: Claims 1-12 and 22-24 are directed to a compound having a structure represented by the following formula as seen in instant claim 1. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound having a structure represented by the following formula as seen in instant claim 1 wherein A is the structure listed in instant claim 1 wherein X1 is NR1 wherein R1 is H, X2 is CH, X3 is CH, and X4 is CH; B is the first structure listed in instant claim 1 wherein X5 is N, X6 is CH, X7 is CH, X8 is CH, and X9 is CH; wherein at least one of X1-X4 is NR1 or N, and wherein at least one of X5-X9 is N. It is believed that claims 1, 3, 6, 10-11, 22-24 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a structure represented by the following formula as seen in instant claim 1 wherein A is the structure listed in instant claim 1 wherein X1 is CH, X2 is NR1 wherein R1 is H, X3 is CH, and X4 is CH; B is the first structure listed in instant claim 1 wherein X5 is N, X6 is CH, X7 is CH, X8 is CH, and X9 is CH; wherein at least one of X1-X4 is NR1 or N, and wherein at least one of X5-X9 is N (i.e., claims 1, 3, 6, 10-11, 22-24).

Group II: Claims 13-21 are directed to a method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with metabotropic glutamate receptor activity in the subject.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Each invention in Group I+ includes the technical feature of a unique compound of the formula listed in instant claim 1, which is not required by any other invention of Group I+.

Group II requires a method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with metabotropic glutamate receptor activity in the subject, which is not required by Group I+.

Common Technical Features:

The inventions of Groups I+ and II share the technical feature of a compound of the formula listed in instant claim 1.

These shared technical features, however, do not provide a contribution over the prior art as being obvious over US 2011/0172248 A1 to Conn et al. (hereinafter 'Conn') in view of a document entitled "Pubchem CID 141419641" (hereinafter 'Pubchem-641'). Conn teaches a compound analogous to a compound having a structure represented by the following formula as seen in instant claim 1 wherein A is a structure analogous to the structure listed in instant claim 1 wherein X1 is CH, X2 is N, X3 is CH, X4 is CH; B is the first structure listed in instant claim 1 wherein X5 is N, X6 is CR1 wherein R1 is CH3, X7 is CH, X8 is CH, X9 is CH; wherein at least one of X1-X4 is NR1 or N, and wherein at least one of X5-X9 is N; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof (see page 20, row 2, last compound listed) but does not teach wherein A is a 5-membered heteroaryl ring. However, Pubchem-641 does teach a compound analogous to a compound having a structure represented by the formula as seen in instant claim 1 wherein A is a heteroaryl ring wherein X1 is CH, X2 is N, X3 is CH, X4 is CH (see page 2, compound listed). Therefore, based on the structural similarities between the two compounds, it would have been obvious to a person of ordinary skill in the art to combine these references and replace the 6-membered heteroaryl ring (i.e., pyridine) of Conn's compound with a pyrrole substitution as taught by Pubchem-641 in order to isolate all possible derivatives of Conn's compounds by routine experimentation.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Groups I+ and II thus lack unity under PCT Rule 13.

Note:

Claim 1 lacks unity. The dotted lines in A and B are not defined. For the purposes of this opinion, it will be interpreted that the dotted lines can be either single bonds or double bonds as long as the ring is aromatic and completes valency based on instant claim 8 and instant para[00122], [00124].

Claim 20 lacks clarity. It is a self-dependent claim. For the purposes of this opinion, it will be interpreted that claim 20 is dependent upon claim 18.