

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 February 2008 (28.02.2008)

PCT

(10) International Publication Number
WO 2008/024284 A3

(51) International Patent Classification:
A61K 31/4965 (2006.01) A61K 31/497 (2006.01)

(21) International Application Number:
PCT/US2007/018287

(22) International Filing Date: 17 August 2007 (17.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/839,073 21 August 2006 (21.08.2006) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
20 November 2008

(54) Title: SULFONYLATED PIPERAZINES AS CANNABINOID-1 RECEPTOR MODULATORS

(57) Abstract: Novel compounds of the structural formula (I) are antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. The compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, Alzheimer's disease, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, the treatment of obesity or eating disorders, as well as the treatment of asthma, constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and the promotion of wakefulness.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/18287

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: **A61K 31/4965(2006.01),31/497(2006.01)**

USPC: **514/255.01,252.13**
 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)
 U.S. :

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/20820 (Rueger et al.) 12 June 1997 (12.06.2007); p. 63, Example 4 a)	9-10, 12

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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 27 August 2008 (27.08.2008)	Date of mailing of the international search report 24 SEP 2008
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/18287

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.: 1-5
because they relate to subject matter not required to be searched by this Authority, namely:
Please See Continuation Sheet
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:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any 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.: 9-10, 12 (species: compound (1) of claim 9; (ii-a))

- 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.
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Box II Observations where certain claims were found unsearchable I. because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-5 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-5 are indefinite for the following reason(s): the recitation of "use of a compound" does not make clear the subject matter of the claims; use can be interpreted as 1) a compound, 2) a method of preparing a medicament (without the recitation of any method steps), or 3) a method of treating, preventing, or suppressing diseases mediated by the cannabinoid receptor (also without the recitation of any method steps). These alternative possible interpretations of the subject matter render the claims indefinite. Additionally, the claims to a method without providing any steps of the method are non-statutory under 35 USC 101.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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

Group I, claim(s) 1-14, drawn to a compound/composition.

Group II, claim(s) 1-5, drawn to a method of preparing a medicament.

Group III, claim(s) 1-5, drawn to a method for the treatment, prevention or suppression of diseases mediated by the cannabinoid-1 receptor.

Note: the "use" claims (1-5) can be interpreted as product, method of preparing a medicament or as method of treatment, reflected by the placement into multiple groups.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

(i) Elect a single compound of formula (I); specify each substituent to identify a formula or specify a compound as recited in claims 5, or 9-10.

(ii) For the compound/composition group, specify whether the composition:

(ii-a) does not comprise a second compound, different from a compound of claim 6 or 9 (claim 1); or

(ii-a) does comprise a second compound, different from a compound of claim 6 or 9; if elected, specify a single compound specie from claims 13-14 (claims 13-14).

The claims are deemed to correspond to the species listed above in the following manner:

(i) all claims

(ii-a) claims 1-12

(ii-b) all claims

The following claim(s) are generic: all claims are generic for (i); claims 1-12 are generic for (ii).

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The first Group that appears in the claims is Group I; the first specie is a compound of formula (I), where Ar¹ is aryl, R¹ is C₁₋₁₀ alkyl, R² and R³ is H. The first compound within the group is the first compound recited in claims 5, 9 and 10. This compound has been searched since no additional fee was paid.

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

The technical feature linking the claims is a compound with the core structure of formula (I). Rueger et al. (WO 97/20820; 1997) teaches a compound with the core structure of formula (I): 4-(Naphthalene-1-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (p. 63, Example 1 a). Therefore, since the technical feature linking the claims has been taught in the prior art, the technical feature is not "special". Accordingly the inventions are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

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

The technical feature linking the species is a compound with the core structure of formula (I). As pointed out above, Rueger et al. (WO 97/20820; 1997) teaches a compound with the core structure of formula (I): 4-(Naphthalene-1-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (p. 63, Example 1 a). Therefore, since the technical feature linking the species has been taught in the prior art, the technical feature is not "special". Accordingly the inventions are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

STN

compound name search, structure search