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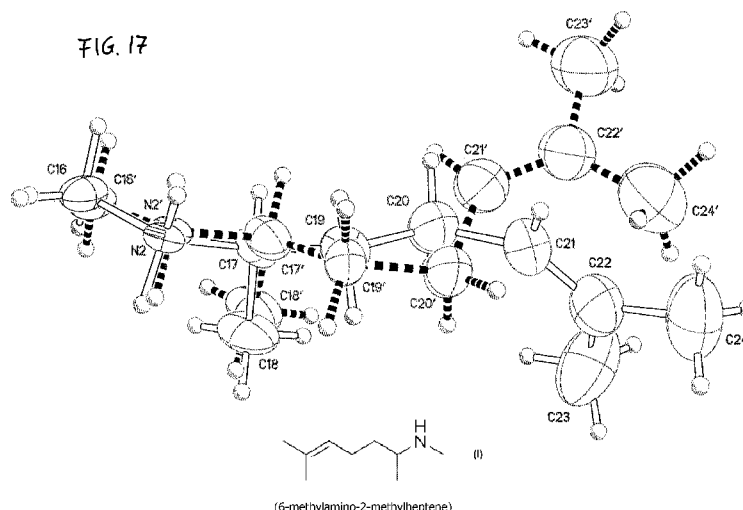
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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.

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[Continued on next page]

(54) Title: ISOMETHEPTENE ISOMER



(57) Abstract: The invention relates to a purified Isometheptene compound comprising the structure according to Formula (I), (Formula (I)) or a hydrochloride, or a pharmaceutically acceptable addition salt thereof. In particular, the disclosure relates to the synthesis, purification and characterization of an Isometheptene isomer mucate crystal 2, wherein the Isometheptene isomer 2 is stereochemically characterized as (R)-enantiomer, respectively. The Isometheptene (R)-enantiomer activity indicates a selective centrally acting selective ligand for Imidazoline subtype 1 (I1) receptor sites; and more specifically, the disclosure provides an antihypertensive composition for treatment of migraine and other neurovascular or neurogenic pain from abdominal distress. (R)-Isometheptene enantiomer or isomer 2 may be an anti-hypertensive agent with lower side effects than the racemate form. Therefore (R)-Isometheptene is believed to be effective against episodic tension-type headaches (ETTH). The (R)-Isometheptene enantiomer or isomer 2 is believed to effectively lower blood pressure, used alone or together with other headache ameliorating drugs. Methods of synthesis and treatment are described. Regarding (R)- Isometheptene crystals data of X-ray crystallography are presented.



Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

— *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))*

Published:

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

(88) Date of publication of the international search report:

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/012142**A. CLASSIFICATION OF SUBJECT MATTER****C07C 211/21(2006.01)i, A61K 31/131(2006.01)i, A61P 29/00(2006.01)i, A61P 37/00(2006.01)i, C07B 55/00(2006.01)i**

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

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
C07C 211/21; A61K 9/48; A61K 31/131; A61P 29/00; A61P 37/00; C07B 55/00Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility modelsElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: isometheptene isomer**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WESLEY G. TAYLOR et al., "Preparation of two metabolites of isometheptene", CAN. J. CHEM., (1979) Vol. 57, pp. 2103-2107 See the abstract; and page 2103, left column, lines 1-5.	1-39,51-54
A		50
X	FOTIOS M. PLAKOGIANNIS et al., "Simultaneous GLC Determination of Acetaminophen, Dichloralantipyrine, and Isometheptene Mucate", J. Pharm. Sci., (1977) Vol. 66(4), pp. 604-605 See the abstract; and page 604, left column, lines 1-8.	1-39,51-54
A		50
X	EMMANOUIL LYRIS et al, "Metabolism of isometheptene in human urine and analysis by gas chromatography-mass spectrometry in doping control", J. Chromatogr. B, (2005) Vol. 827, pp. 199-204 See the abstract; and page 199, left column, lines 2-11.	1-39,51-54
A		50
X	KR 10-2000-0031737 A (SUHEUNG CAPSULE CO., LTD) 05 June 2000 See the abstract	1-39,51-54
A		50

☐ 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

"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

Date of the actual completion of the international search

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Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/012142

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.: 40,41,43-49
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 40,41,43-49 pertain to methods for treatment of the human by therapy, as well as diagnostic method, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☒ Claims Nos.: 42
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:
Claim 42 dependent on claim 30, relates to the method wherein the composition is administered in combination with one or more additional therapeutics, however claim 30 relates to the composition wherein Isometheptene enantiomer comprises therapeutic efficacy. For this reason claim 42 does not clearly define the matter for which protection is sought, thereby resulting in lack of clarity when used to interpret them.
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:

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 an 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.:

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

Information on patent family members

International application No.

PCT/US2014/012142

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 10-2000-0031737 A	05/06/2000	None	