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(74) Agents: **JULIAN-ARNOLD, Gianna** et al.; 500 East Pratt Street, Suite 900, Baltimore, Maryland 21201 (US).

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

5 January 2012

(54) Title: METHODS FOR PRODUCING VILOXAZINE SALTS AND NOVEL POLYMORPHS THEREOF

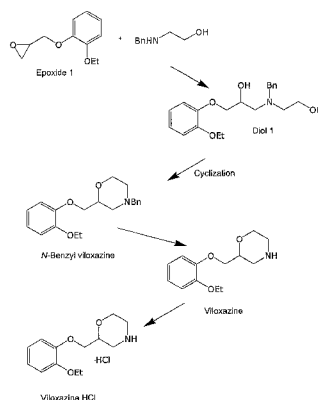


Figure 4

(57) Abstract: Provided here are methods of manufacture of viloxazine and its various salts, as well as viloxazine-related compounds, such as novel intermediate reaction products and polymorphs thereof. In particular, the methods provide a substantially pure API of viloxazine HCl while avoiding undesirable impurities. The methods further provide for separating, identifying, and characterizing novel polymorphs of viloxazine. Further provided are methods for synthesis and identification and characterization of novel intermediates of viloxazine, as well as for some important metabolites and precursors of metabolites of viloxazine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/032013

A. CLASSIFICATION OF SUBJECT MATTER INV. C07C217/54 C07D265/30 C07D265/32 A61K31/5375 A61P25/00 ADD.		
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) C07C C07D		
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 practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 712 890 A (LEE S) 23 January 1973 (1973-01-23) cited in the application examples 1,3 column 7, line 4 - line 5 column 7, line 21 - line 22; compounds RN35609-87-1	1-3,5,9, 10,12, 18,22-31
X	US 3 714 161 A (MALLION K ET AL) 30 January 1973 (1973-01-30) cited in the application examples 5, 8 column 3, line 10 ----- <div style="text-align: center;">-/-</div>	1-4
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"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</p> <p>"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</p> <p>"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.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
25 October 2011	21/11/2011	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Brandstetter, T	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/032013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HOWE R; LEIGH T; RAO B S; TODD A H: "Optical isomers of 2 (2 ethoxyphenoxyethyl)tetrahydro 1,4 oxazine (viloxazine) and related compounds", JOURNAL OF MEDICINAL CHEMISTRY, vol. 19, 1976, pages 1074-1076, XP002640387, DOI: 10.1021/jm00230a021 cited in the application scheme 1</p>	1-4
X	<p>----- WO 2007/030366 A1 (SMITHKLINE BEECHAM CORP [US]; HORNBERGER KEITH [US]; CHEUNG MUI [US];) 15 March 2007 (2007-03-15) steps B and C; page 105 - page 106; example 4</p>	5
X	<p>----- ANDREW G. MYERS ET AL: "A Solid-Supported, Enantioselective Synthesis Suitable for the Rapid Preparation of Large Numbers of Diverse Structural Analogues of (-)-Saframycin A", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 124, no. 44, 1 November 2002 (2002-11-01), pages 12969-12971, XP055008003, ISSN: 0002-7863, DOI: 10.1021/ja027729n supportive information p. S4</p>	5
X	<p>& ANDREW G. MYERS ET AL: "A Solid-Supported, Enantioselective Synthesis Suitable for the Rapid Preparation of Large Numbers of Diverse Structural Analogues of (-)-Saframycin A", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 124, no. 44 1 November 2002 (2002-11-01), pages S1-S24, XP002659951, Retrieved from the Internet: URL:dfpcorec-p/wf/web/citenpl/citenpl.html ?id%3Ddoi%3A10.1021/ja027729n%26rft.genre% 3Darticle%2Cchapter%2Cbookitem%26svc.fullt ext%3Dyes [retrieved on 2011-09-25] synthesis of; page S4, paragraph 4 - paragraph 6</p> <p>----- -/--</p>	5

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/032013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JINBO Y ET AL: "Synthesis and Antibacterial Activity of Thiazolopyrazine-incorporated Tetracyclic Quinolone Antibacterial Agents", JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 17, 1 January 1994 (1994-01-01), pages 2791-2796, XP002991758, AMERICAN CHEMICAL SOCIETY, US ISSN: 0022-2623, DOI: 10.1021/JM00043A018 scheme 1, synthesis of compound 10h; page 2792; compound 10h -----	5-8, 13-17,19
X	FIRESTONE R ET AL: "Selective Delivery of Cytotoxic Compounds to Cells by the LDL Pathway", JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 8, 1 January 1984 (1984-01-01), pages 1037-1043, XP002991759, AMERICAN CHEMICAL SOCIETY, US ISSN: 0022-2623, DOI: 10.1021/JM00374A017 scheme 1; page 1040 page 1041, column 2, paragraph 2 -----	5
X	DATABASE WPI Week 200534 Thomson Scientific, London, GB; AN 2005-326476 XP002660143, "New substituted phenoxy propanol amine derivatives, are tyrosinase inhibitors used in skin external preparations as skin-whitening agents", -& JP 2005 112818 A (KAO CORP) 28 April 2005 (2005-04-28) 1-(4-benzyloxy phenoxy)-3-(2-hydroxyethylamino) propan-2-ol, residue (2) in example -----	9
X	EP 0 092 945 A2 (ICI PLC [GB]) 2 November 1983 (1983-11-02) fourth entry of first table; page 15; compounds RN-73964-26-8 -----	9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 April 2010 (2010-04-02), XP002660039, retrieved from STN Database accession no. 1215605-65-4 abstract ----- -/--	9,11

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/032013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 September 2009 (2009-09-13), XP002660048, retrieved from STN Database accession no. 1183212-94-3 abstract	9
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X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 January 2003 (2003-01-22), XP002660051, retrieved from STN Database accession no. 479674-32-3 abstract	9,11
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/032013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& UCH. ZAP. AZERB. UN-T. SER. KHIM. N. , (1), 69-72 FROM: REF. ZH., KHIM. 1980, ABSTR. NO. 3ZH164, 1979, -----	
X	DATABASE PubChem Compound [Online] NCBI; 16 August 2005 (2005-08-16), "AC1MMD0Q - Compound Summary", XP002660054, Database accession no. CID 3236825 CID 3236825;compounds RN-473568-32-0 -----	9,11
X	J. OUHABI ET AL: "Structure du chlorure d'[(éthoxy-2 phénoxy)méthyl]-2 morpholinium: chlorhydrate de viloxazine", ACTA CRYSTALLOGRAPHICA SECTION C CRYSTAL STRUCTURE COMMUNICATIONS, vol. 46, no. 11, 15 November 1990 (1990-11-15), pages 2160-2162, XP055008246, ISSN: 0108-2701, DOI: 10.1107/S0108270190001627 the whole document -----	27-30
A	SERAJUDDIN ET AL: "Salt formation to improve drug solubility", ADVANCED DRUG DELIVERY REVIEWS, vol. 59, no. 7, 24 August 2007 (2007-08-24), pages 603-616, XP022211982, ELSEVIER BV, AMSTERDAM, NL ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2007.05.010 the whole document -----	27-30
A	BYRN S ET AL: "PHARMACEUTICAL SOLIDS: A STRATEGIC APPROACH TO REGULATORY CONSIDERATIONS", PHARMACEUTICAL RESEARCH, vol. 12, no. 7, 1 July 1995 (1995-07-01), pages 945-954, XP000996386, KLUWER ACADEMIC PUBLISHERS, NEW YORK, NY, US ISSN: 0724-8741, DOI: 10.1023/A:1016241927429 the whole document ----- -/--	27-30

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/032013

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLACKBURN T P ET AL: "Effects of viloxazine, its optical isomers and its major metabolites on biogenic amine uptake mechanisms in vitro and in vivo", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 52, no. 3-4, 1 December 1978 (1978-12-01), pages 367-374, XP023840121, ISSN: 0014-2999, DOI: 10.1016/0014-2999(78)90291-1 [retrieved on 1978-12-01] page 370; table 2 -----	31
A	GÉRARD SOULA: "Tris(polyoxaalkyl)amines (Trident), anew class of solid-liquid phase-transfer catalysts", JOURNAL OF ORGANIC CHEMISTRY, vol. 50, no. 20, 4 October 1985 (1985-10-04), pages 3717-3721, XP002105964, AMERICAN CHEMICAL SOCIETY, EASTON.; US ISSN: 0022-3263, DOI: 10.1021/J000220A009 the whole document -----	6,13

INTERNATIONAL SEARCH REPORT

International application No.
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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 additional 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 an 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.:

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/ US2011/ 032013

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4

a composition consisting of viloxazine or a salt thereof

2. claims: 5-8, 12-21

methods for manufacturing 2-substituted morpholines
comprising reaction of a diol derivative

3. claims: 9-11

intermediate diol compounds for the synthesis of
2-substituted morpholines

4. claims: 22-26

methods for manufacturing viloxazine comprising reacting
1-(2-ethoxyphenoxy)-2,3-epoxypropane with 2-aminoethyl
hydrogen sulfate

5. claims: 27-30

compositions comprising viloxazine hydrochloride polymorph A
and/or B

6. claim: 31

compositions comprising a) synthesis intermediates for the
preparation viloxazine or derivatives thereof or b)
viloxazine or derivatives thereof or c) metabolites of
viloxazine or derivatives thereof

7. claim: 32

side-products in the synthesis of viloxazine

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/032013

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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