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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

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16 April 2009

(54) Title: NONCARDIOTOXIC PHARMACEUTICAL COMPOUNDS

(57) Abstract: The present invention relates to novel noncardiotoxic compounds and pharmaceutical compositions useful in the treatment of a variety of disorders including the treatment of depression, allergies, psychoses, cancer and gastrointestinal disorders. In particular, the present invention describes pharmaceutical compositions that mitigate life-threatening arrhythmias such as torsade de pointes. *Torsade de pointes* is a particular cardiac problem associated with many therapeutic agents and has been implicated as a possible cause of sudden death, particularly in those individuals with a past history of disturbances of cardiac rhythm, myocardial infarction, congenital repolarization abnormalities and cardiac risk factors such as hyperlipidemia and age. This arrhythmia is a variant of paroxysmal ventricular tachycardia associated with a prolonged QTc interval or prominent U waves on the ECG. *Torsade de pointes* is potentially lethal because it can progress to ventricular fibrillation, life-threatening arrhythmias or precipitate sudden death.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/28137

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07F 9/06(2006.01),9/08(2006.01),9/02(2006.01),9/28(2006.01);A61K 31/41(2006.01),31/435(2006.01)

USPC: 546/21,22;514/359,277;568/8;548/111,112

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. : 546/21,22; 514/359,277; 568/8; 548/111,112

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)
STN, File registry , file caplus. (search done at STIC)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Qiang Xiao et al , 2003, Facile Synthesis of 3beta -cholesterol H-Phosphonates . See compound 4f on page 523.	1
X	Michael Hemenaway et al , 1999, J. Org. Chem. Syntheses of New Phosphorus-Containing Azabicycloalkanes and their Microbial Hydroxylation Using Beauveria Bassiana. See figure I. on page 6312, compounds 7, 10, 13 on page 6314.	1, 56-59,
Y	Y.W. Wu et al , 2004, Synthesis, In Vitro Anticancer Evaluation, and Interference with Cell Cyce progression of N-Phosphoamino Acid Esters of Zidovudine and Stavudine, See 3a-3e , 4a-4e on page 1799	83, 86-89, 93.
X	Mark Gamble et al , 1998, A novel phosphinamide catalyst for the asymmetric reduction of Ketones by Borane , 1998, see compound 2 page 6068.	1
Y	Caplus English Abstract DN 134:28996 Gajda T. et al . See RN # 118132-91-5, 2000.	86-89



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 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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INTERNATIONAL SEARCH REPORT

International application No.
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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y ✓	Basarab Gregory et al 2002, Design of Inhibitors of Scytalone Dehydratase.. See compound 7 page 4145.	1
(Y) ✓	Caplus English Abstract DN 56:45951, Campen M. G. See whole document. See RN 95159-07-2, 1961	1, 3, 5
(Y) ✓	Caplus English Abstract , DN 99:207981 , 1983, Kaszubska J et al , See RN # 87834	1
(A) ✓	Caplus, English Abstract ,ES 2006099, DN 113:40732 , Lopez Molini et al 03 March 1989.	23
(Y) ✓	WO 99/02531 (BRANDS KAREL et al) 21 January 1999 (21.01.1999) , See page 18, 3-5-5; 1-3. , 1-1 on page 12.	1
(Y) ✓	EP 0671389 (Mitsubishi Chemical Corporation) 13.09.1995 , See formula 1 on page 6 .	1
Y	US 5,070,082, (KEITH MURDOCK et al) 03 December 1991 (03.12.1991) , See column 16 reaction scheme.	1, 3-6,9, 38, 41-51,56-71, 73-76, 86-89, 96-98, 100,102-111.
A	WO 2006026395, 3 September 2006, Keyser Donald Jeffrey et al . Date not good.	1, 3-6,9, 38, 41-51,56-71, 73-76, 86-89, 96-98, 100,102-111.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/28137

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.: 2,7,8,10-22, 24-37,39,40,52-55,72,77-82 84-85,90-95 and 99
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 2 and the dependent claims , which are dependent from claim 1 , do not have any antecedent basis for X , in claim 1, Claim only has Y which can only be a CH2. Also there is no antecedent basis for R 25.
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.:

- 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.

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, 13 drawn to compounds wherein n is 0 and R3 is heteroaryl

Group II, claim(s) 1, drawn to compounds wherein n is 0 and R3 is an aryl or an alkyl aryl.

Group III, claim(s) 1, 3-6, 41, 47, 48, drawn to compound wherein n is 1 and R3 is an aryl or an alkylaryl.

Group IV, claim(s) 1 in part drawn to n is 2 and R3 is an aryl or an alkyl aryl.

Group V, claim(s) 1 in part 9, 38, 41-46, 49, 50, 51 and 54, drawn to compounds wherein N is 1 or 2 and R3 is a heteroring.

Group VI, claim(s) 56, 73-76, 86-89, 97, 98, 102 and 103, drawn to compounds wherein R21 is a aryl or an alkyl aryl or an alkylaryloxy.

Group VII, claim(s) 56-108 in part, drawn to compounds wherein R21 is an indole.

Group VIII, claim(s) 56-108 in part, drawn to compounds wherein R21 is a substituted or an unsubstituted phenothiazine.

Group IX, claim(s) 56-108 in part, drawn to compounds wherein R21 is a substituted or an unsubstituted dibenzoxazepine.

Group X, claim(s) 56-108 in part, drawn to compounds wherein R21 is a substituted or unsubstituted dibenzthiazepine.

Group XI, claim(s) 56-108 in part, drawn to compounds wherein R21 is substituted or unsubstituted oxophthalazine.

Group XII, claim(s) 56-108 in part, drawn to compounds wherein R21 is a substituted and unsubstituted quinoline or dihydroquinoline.

Group XIII, claim(s) 56-108 in part, drawn to compounds wherein R21 is substituted or unsubstituted dibenzodiazepine.

Group XIX, claim(s) 56-108 in part, drawn to compounds wherein R21 is a substituted or unsubstituted benzocycloheptapyridine.

Group XX, claim(s) 56-108 drawn to compounds wherein R21 is a substituted or unsubstituted carbazol or tetrahydrocarbazol.

Group XXI, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted dibenzocycloheptene.

Group XXII, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted benzimidazole.

Group XXIII, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted piperazine.

Group XXIV, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or an unsubstituted benzamide.

Group XXV, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or an unsubstituted benzhydrol.

Group XXVI, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or an unsubstituted diazabenzazulene.

Group XXVII, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted oxobenzimidazol.

Group XXVIII, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted pyrolohydroquinoline.

Group XXIX, claim(s) 56-108, drawn to compounds wherein R21 is a substituted or unsubstituted carbamoyl-tetrahydro-carbazol.

Group XXX- XXXXXIX, claim(s) 109-111, drawn to a modified drug and pharmaceutical compositions.

The inventions listed as Groups I-XXX 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:

(f) Markush Practice. The situation involving the so-called Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(ii) In paragraph (f)(i)(B)(1), above, the words significant structural element is shared by all of the alternatives refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art. The structural element may be a single component or a combination of individual components linked together.

The different R1, R2, R3, Y, Z with substituted and unsubstituted groups have so many variables with the heterocyclic and non-hetero groupings, they have different bonding and properties, and have achieved a different status in the art, and is burdensome to search and hence are objected to as being drawn to an improper Markush group on the grounds of lack of a common nucleus. The terms R1, R2, R3, Y and Z, are so broad in scope that a prior art reference anticipating the claims with respect to one member under 35 USC 102(b) would not render obvious the same claims under 35 USC 103a with respect to another member.