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(54) Title: THE COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND A 5-HT_{2C} ANTAGONIST, INVERSE AGONIST OR PARTIAL AGONIST

(57) Abstract: The present invention relates to the use of compounds and compositions of compounds having serotonin reuptake inhibiting activity and 5-HT_{2C} antagonistic, partial agonistic or inverse agonistic activity for the for the treatment of depression and other affective disorders. The combined serotonin reuptake inhibiting effect and the 5-HT_{2C} antagonistic, partial agonistic or inverse agonistic effect may reside within the same chemical compound or in two different chemical compounds.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00671

A. CLASSIFICATION OF SUBJECT MATTER IPC7:

A61K 31/517, A61K 31/519, A61K 31/55, A61K 31/135, A61K 31/137, A61K 31/15, A61K 31/343
A61K 31/4525, A61K 31/496, A61K 31/451, A61K 31/55, C12Q 1/00, G01N 33/50, G01N 33/00

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)

IPC7: A61K, C12Q, G01N

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0813873 A1 (AKZO NOBEL N.V.), 29 December 1997 (29.12.97) --	1-4,6-12, 14-24,26
X	Pharmacopsychiat, Volume 25, 1992, L.Lauritzen et al, "Combined Treatment with Imipramine and Mianserin" page 182 - page 186 --	1-4,6-12, 14-24,26
X	Journal of Clinical Psychopharmacology, Volume 19, No 2, 1999, Michael Maes et al, "Pindolol and Mianserin Augment the Antidepressant Activity of Fluoxetine in Hospitalized Major Depressed Patients, Including Those with Treatment Resistance." --	1-4,6-12, 14-24,26

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

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 4 April 2001	Date of mailing of the international search report 29 -06- 2001
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00671

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Exp. Opin. Invest. Drugs, Volume 4, No 10, 1995, Paul J Goodnick et al, "New antidepressant agents: Recent pharmacological developments leading to improved efficacy" page 935 - page 943 --	4-5,7-9, 12-13,15-17, 20-24,26
X	Cellular and Molecular Neurobiology, Volume 19, No 4, 1999, Connie Sánchez et al, "Comparison of the Effects of Antidepressants and Their Metabolites on Reuptake of Biogenic Amines and on Receptor Binding." --	4-5,7-9, 12-13,15-17, 20-24,26
P,X	European Neuropsychopharmacology, Volume 10, 2000, Agnés Besson, "Effects of the co-administration of mirtazapine and paroxetine on serotonergic neurotransmission in the rat brain." page 177 - page 188 --	1-4,6-12, 14-24,26
P,X	EP 0966976 A2 (ELI LILLY AND COMPANY), 29 December 1999 (29.12.99) --	1-4,6-12, 14-24,26
A	GB 2303303 A (AMERICAN HOME PRODUCTS CORPORATION), 19 February 1997 (19.02.97), page 2, line 21 - page 5, line 17 --	25-26
A	US 5786157 A (WEINSHANK ET AL), 28 July 1998 (28.07.98), column 10, line 47 - column 11, line 21 --	25-26
A	DE 19900673 A1 (BASF AG), 13 July 2000 (13.07.00), page 3, line 23 - line 34; page 5, line 14 - line 63 --	25-26
A	US 5958429 A (WONG), 28 Sept 1999 (28.09.99), column 8, line 9 - line 34 -- -----	25-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00671

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: **1-24, 26**
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:
see next sheet*

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next 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 fee, this Authority did not invite payment of any additional fee.
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.
 No protest accompanied the payment of additional search fees.

*

Present application (claims 1-24) relates to compounds defined by reference to a desirable characteristic or property, namely a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist and a serotonin reuptake inhibitor. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely mainly those parts relating to the compounds named in claims 11 and 19 and 10 and 18 respectively.

The formulations "disorder responsive to SRI" and "affective disorders", are so broad and unclear that a complete search is impossible to perform. Therefore the search has been focused on the disorders named in the claims 3 and 4.

Present claim 26 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently no search apart from that performed in claims 1-24 has been performed.

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According to Article 34(3)(a-c) and Rule 13.2, an international application shall relate to one invention only, or to a group of inventions, linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution, which each of the inventions makes over the prior art.

The problem the claimed invention intends to solve is to find an improved treatment of depression, anxiety disorders etc. This problem is solved by combining a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist with a serotonin reuptake inhibitor, claims 1-24. This combination is considered to be the special technical feature of the invention. Such combinations are however previously known through for example EP 0813873 A1. Apart from the use of a combination of a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist and a serotonin reuptake inhibitor and a pharmaceutical composition of such compounds, a method for identifying compounds useful for the treatment of depression, anxiety disorders etc is claimed (claims 25-26). The only feature, which this method has in common with the invention of claims 1-24, is that the compounds identified by the method should be 5-HT_{2c} receptor antagonists, partial agonists or inverse agonists and serotonin reuptake inhibitors. This combination is as mentioned above previously known and the method has no technical feature, apart from the prior art, in common with the invention of claims 1-24. The application is therefore considered to lack unity. The International Searching Authority finds that the application comprises two independent inventions:

Invention 1: The use of a compound, which is a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist and a serotonin reuptake inhibitor or a combination of compound, which is a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist and a compound which is a serotonin reuptake inhibitor for the treatment of depression, anxiety disorders etc. A pharmaceutical composition comprising a 5-HT_{2c} receptor antagonist, partial agonist or inverse agonist and a serotonin reuptake inhibitor. Claims 1-24.

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INTERNATIONAL SEARCH REPORT

International application No.
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Invention 2: A method for identifying compounds useful for the treatment of depression, anxiety disorders etc. Compounds identified by this method. Claims 25-26.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/05/01

International application No.
PCT/DK 00/00671

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0813873 A1	29/12/97	AU 727851 B	04/01/01
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		SG 60073 A	22/02/99
		TR 9700522 A	00/00/00
		US 5977099 A	02/11/99
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