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(54) Title: GABA ENHANCERS IN THE TREATMENT OF DISEASES RELATING TO REDUCED NEUROSTEROID ACTIVITY

(57) Abstract: The invention provides the use of a non-steroid compound which act on the GABA receptor for the treatment of disorders relating to reduced neurosteroid activity. The non-steroid compounds may be GABA agonists, GABA uptake inhibitors or enhancers of GABAergic activity.

GABA enhancers in the treatment of diseases relating to reduced neurosteroid activity.

The invention provides the use of non-steroid compounds which are GABA agonists, GABA uptake inhibitors or enhancers of GABAergic activity in the treatment of disorders relating to reduced neurosteroid activity

Background of the invention

Receptors for the major inhibitory neurotransmitter, gammaamino butyric acid (GABA), are divided into two main classes: $GABA_A$ receptors which are members of the ligand gated ion channel superfamily; and the $GABA_B$ receptors which are G-protein coupled receptors.

$GABA_A$ receptors are formed as a pentameric assembly of different families of receptor subunits. The assembly, which in most receptors includes 2 α subunits, 2 β subunits and a γ or δ subunit, determines the pharmacology of the functional receptor. The binding site for benzodiazepines is located at the interface between the α and γ subunit, whereas the binding site for GABA and other $GABA_A$ agonists is located at the interface between the α and β subunit.
$GABA_A$ receptor assemblies which do exist include, amongst many others, $\alpha_1\beta_2\gamma_2$, $\alpha_1\beta_{2/3}\gamma_2$, $\alpha_3\beta\gamma_{2/3}$, $\alpha_5\beta_3\gamma_{2/2}$, $\alpha_6\beta\gamma_2$ $\alpha_6\beta\delta$, $\alpha_4\beta\delta$ and $\alpha_4\beta_2\gamma_2$. Subtypes containing the α_1 subunit are present in most brain regions and may contribute to the functional action of a number of benzodiazepines.

In a number of clinical conditions, hypoactivity of the inhibitory GABA system has been hypothesised as the underlying mechanism of the pathology in question. These conditions include epilepsy, anxiety, stress, sleep disorders and pain. However, although positive modulators of the $GABA_A$ receptor complex, such as benzodiazepines, in a number of circumstances are very effective, there is a general consensus that unselective benzodiazepines produce so many side effects that compounds substituting for presently used drugs are needed (Costa and Guidotto *Trends Pharmacol. Sci.***1996**, *17*, 192-200).

The α_4 containing receptors exist predominantly in the thalamic area (Sur et al. **1999**). Recent studies (Sassoè-Pognetto et al.. *J Comp Neurol* **2000**, *15*, 420: 481-98 ; Mody, 2000, Presentation at GABA2000 meeting July 23 to July 29.) have indicated that some of these receptors may be located extrasynaptically, making them a potentially very interesting drug target.

There are differences between benzodiazepines and GABA agonists. One is that benzodiazepines are inactive at α_4 and δ containing receptors, whereas $GABA_A$ agonists will act irrespective of the subunit composition (e.g. Ebert et al. *Mol. Pharmacol.***1997**, *52*, 1150-1156). Another, that the benzodiazepines react at a specific site at the GABA complex, thereby causing the GABA receptor to undergo an allosteric change which influences the efficacy of GABA in promoting chloride channel opening. The GABA receptor modulators exhibit considerable side-effects.

In relation to disorders such as anxiety and pre-menstrual dysphoric disorder modulation of the thalamic areas may play a key role. In these areas a high abundance of $\alpha_4\beta_3\delta/\gamma_2$ containing receptors are found, making interaction with these receptors particularly interesting. With the large density of α_4 containing receptors located exstrasynaptically (Sur et al. *Mol. Pharmacol.* **1999**, *56*, 110-115; Sassoè-Pognetto et al. *J Comp Neurol* **2000**, *15*,420: 481-98; Mody, 2000, Presentation at GABA2000 meeting July 23 to July 29) only a relatively low level of activation at the individual extrasynaptic receptors will sum up to a significant inhibition of the neurone, raising the possibility that highly functional selective compounds can be developed for these receptors.

The ovarian hormone progesterone and its metabolites have been demonstrated to have profound effects on brain excitability. The levels of progesterone and its metabolites vary with the phases of the menstrual cycle. It has been documented that progesterone and its metabolites decrease prior to the onset of menses. The monthly recurrence of certain physical symptoms prior to the onset of menses has also been well documented. These symptoms which have been associated with premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) include stress, anxiety, and migraine headaches. Patients suffering from PMS have a monthly recurrence of symptoms that are present in premenses and absent in postmenses. In a similar fashion, a reduction in progesterone has also been temporally correlated with an increase in seizure frequency in female epileptics. A more direct correlation has been

observed with a reduction in progesterone metabolites. In addition, for patients with primarily generalized petit mal epilepsy, the temporal incidences of seizures have been correlated with the incidence of the symptoms of PMS.

A syndrome also related to low progesterone levels is postnatal depression (PND). Immediately after delivery, progesterone levels decrease dramatically leading to the onset of PND. The symptoms of PND range from mild depression to psychosis requiring hospitalization. PND is also associated with severe anxiety and irritability. PND associated depression is amenable to treatment by classical antidepresants and women experiencing PND show an increased incidence of PMS.

Premenstrual dysphoric disorder (PMDD) is thought to be a consequence of the rapid drop in progesterone levels, and especially progesterone metabolites, which act as positive modulators of the GABAergic activity (Gallo and Smith, 1993 *Pharmacol. Biochem. Behav.* **46**, 897-904).

The effect of the neuroactive steroids with direct effect at the $GABA_A$ receptor has been investigated. Although neurosteroids like alfaxalone and 3α–5α-dihydroxyprogesterone are interacting with all types of GABA receptors, data with $\alpha_4\beta_3\delta$ containing receptors indicate that the potency and efficacy at the receptors are higher than at other types of $GABA_A$ receptors. Neurosteroids have been developed for the treatment of PMDD and other indications, however side effects have resulted in discontinuation of most of these compounds. Further, a series of studies have shown that prolonged application of neurosteroids as hypnotics results in compensatory mechanisms which ultimately lead to dependence (Lancel et al. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 1213-1218).

The present invention provides non-steroid compounds interacting directly with the recognition site at the $GABA_A$ receptor as agonists or GABA uptake inhibitors or as enhancers of GABAergic activity, which all have beneficial effects in disease states relating to reduced neurostoroidal activation.

The diseases, including premenstrual syndrome, postnatal depression and post menopausal related dysphoric disorders, are significantly better treated with $GABA_A$ agonists and GABA uptake inhibitors or enchancers of GABAergic activity than with benzodiazepines and neurosteroids which produce tolerance after short term treatment.

The present invention also provides specific non-allosteric GABA agonistic compounds useful for the treatment of the disorders relating to reduced neurosteroid activation. The compounds are known as useful in the treatment of other diseases and disorders.

Detailed description of the invention

The invention provides the use of a non-steroid compound which increases GABA activity in the brain for the manufacture of a medicament for the treatment of disorders resulting from reduced neurosteroidal activation.

Increases in the GABA activity in the brain can be achieved by administering a GABA agonist. GABA agonists are compounds like tolgabide, fengabine, gabapentin, zonisamide, muscimol, baclophen, β-phenyl-GABA, AFAA and homo-beta-proline. Administration of a GABA prodrug like progabide, likewise affects the GABA activity in the brain.

An increase in the GABA activity in the brain could also be achieved by GABA uptake inhibitor such as tiagabine or by GABA transamine inhibitors such as vigabatrin or pivagabine.

The invention provides the use of a non-steroid compound wherein the compound is an enhancer of the GABAergic activity.

In a preferred embodiment of the invention, the compound has an affinity for the GABA complexes containing the α_4 subunit.

In an embodiment of the invention, the non-steroid compound according to the above is a non-allosteric receptor agonist.

The invention provides the use of a non-steroid compound as above, wherein the compound is a GABA uptake inhibitor.

The invention provides the use of a compound as described above, wherein the non-steroid compound is selected from the group comprising THIP (Gaboxadol), cyclopropylGABA, isoguvacine, muscimol, imidazole-4-acetic acid, gabapentin and tiagabine.

The invention also provides the use as described above, wherein the disease or disorder is resulting from fluctuations in the neurosteroid level.

In a preferred embodiment of the invention, the disease or disorder is resulting from a decline in the neurosteroid level.

In one specific embodiment of the invention, the disease or disorder is resulting from recurrent periodical decline in the neurosteroid level.

In another specific embodiment of the invention, the disease or disorder is resulting from extraordinary decline in the neurosteroid level.

In a further specific embodiment of the invention, the disease or disorder is resulting from age-related decline in the neurosteroid level.

In a preferred embodiment of the invention, the neurosteroid is progesterone.

In a more preferred embodiment of the invention, the neurosteroid is a metabolite of progesterone.

In a preferred embodiment of the invention, the disease or disorder is premenstrual disorder, postnatal depression or postmenupausal related dysphoric disorder.

The invention also provides the use as above wherein the medicament is for administration as a unit dose.

In a preferred embodiment of the invention, the unit dose is containing the active ingredient in an amount from about 10 μg/kg to 10mg/kg body weight, preferably 25

μg/day/kg to 1.0 mg/day/kg, most preferably 0.1 mg/day/kg to 1.0 mg/day/kg body weight.

In a more preferred embodiment, the unit dose is containing the active ingredient in an amount from 0.1 mg/day/kg to 1.0 mg/day/kg body weight.

In an embodiment of the invention, the neurosteroid activation is caused by hormones.

In a preferred embodiment, this is progesterone. In another preferred embodiment of the invention, it is the metabolites of progesterone.

According to the invention, the compounds mentioned above may be used as the base of the compound or as a pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt.

According to the invention, the compounds mentioned above or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in an

amount from about 10 μg/kg to 10mg/kg body weight, preferably 25 μg/day/kg to 1.0 mg/day/kg.

The effect of the compounds is tested in a pseudo pregnancy model wherein the progesterone level are fluctuating and especially the effect on the rapid decline is measured as described for example in Gallo et. al. *Pharmacol. Biochem. Behav.* **1993**, *46*, 897-904

Results

Rodent Model of PMS

The described model is a hormone withdrawal model of PMS in the rat, based on the prevailing hypothesis that dysphoric mood is predominantly associated with declining hormone levels (i.e., "hormone withdrawal") in women with PMS. Previous work (Nature 392: 926-930, 1998; J. Neurosci. 18: 5275-5284, 1998) has demonstrated that following a three week period of hormone exposure, withdrawal from elevated levels of the reproductive steroid progesterone 24 hrs after removal of a sc progesterone-filled implant produces a state of increased anxiety and lowered seizure threshold in female rats.

Further evidence that the α4 subunit is increased was provided by electrophysiology data demonstrating a striking insensitivity of hippocampal cells to the GABA-potentiating effect of a benzodiazepine (BDZ) lorazepam. (BDZ insensitivity is characteristic of α4-containing GABA receptors.)

Detailed description of the Experiments:

Animals

Female mice (Charles River) were housed in pairs under a 14 hour light and 10 hour dark cycle with food and water ad libitum. All animals were tested during the light portion of the circadian cycle. In female mice, estrous cycle stage was determined by microscopic examination of the vaginal lavage, as described previously (Smith, 1987) and by measures of vaginal impedance (Bartlewski, 1999 ; Bartos, 1977 ; Koto, 1987 ;

Koto, 1987) throughout one entire cycle prior to testing. Only females in diestrous were used as subjects.

Drugs and Hormone Administration

Progesterone (P) was administered rather than 3α,5α-THP because it is known that elevated circulating levels of P, such as found during the estrous (or menstrual) cycle or after stress, (Persengiev, 1991; Barbaccia, 1996; Barbaccia, 1997; Korneyev, 1993; Wilson, 1997; Elman, 1997; Vallee, 2000; Purdy, 1991; Korneyev, 1993) are readily converted to 3a,5a-THP in the brain and result in 3a-5a THP levels sufficient to potentiate GABAergic inhibition (Schmidt, 1994 ; Smith, 1987 ; Seiki, 1975 ; Bitran, 1995; Karavolas, 1976; Vallee, 2000) and modulate GABAA-R subunit expression [Weiland, 1995].

Progesterone implants were made from silicone tubing (Nalgene Co, 1/16"i.d x 1/ 8" o.d.) was cut to size depending on the body weight of the animal (10 mm tubing per 100 g), filled with crystalline progesterone and sealed with silastic medical adhesive (Dow Corning). The sealed capsules were incubated overnight in a solution containing 1% gelatine and 0.9% saline in a water bath (37 °C) with gentle shaking overnight. Sham implants are empty sealed tubes of the same dimensions. Rats were then anesthestized with 2% halothane (2-bromo-2-chloro-1,1,1-trifluroethane) in oxygen and the capsules implanted subcutaneously in the abdomen. Removal of the implants also occurred under the same regime of halothane anesthesia, and implanted s.c. under anesthesia in the abdominal area of the rat (Smith, 1998; Moran, 1998) for 21 days. This method has been shown to result in CNS levels of 3a,5a-THP in the high physiological range (6-12 ng/gm hippocampal tissue) in association with increased circulating levels of P (40-50 ng/ml plasma, approximately 130-160 nM) (Smith, 1998).

Control animals were implanted exactly the same way with empty (sham) silicone capsules. Animals were either sacrificed or tested 24 hrs after removal of the implant (P withdrawal).

On the day of testing, animals were injected with either THIP (1.25 mg/kg) or saline and tested 40 minutes after the injection.

Behavioral Testing

Mice were tested on the plus maze, elevated 50 cm above the floor, in a room with low, indirect incandescent lighting and low noise levels. The plus maze consists of 2 enclosed arms (50 x 10 x 40 cm) and 2 open arms (50 x 10 cm) and is explained in detail in (Pellow, 1985). The open arms had a small rail outside the first half of the open arm as described in (Fernandes, 1996).

The floor of all four arms was marked with grid lines every 25 cm. On the day of testing, each mouse was placed in the testing room for 30-40 minutes prior to testing in order to acclimatise to the situations. At the time of testing, each animal was tested for 10 minutes after exiting a start box in the centre platform of the plus maze. To be considered as an entry into any arm, the mouse must pass the line of the open platform with all four paws. The duration (in seconds) of time spent in the open arm was recorded from the time of entry into the open arm. Decreased time spent in the open arm generally indicates higher levels of anxiety (Pellow, 1985). Other behavioural measures recorded included the duration of time spent (in seconds) beyond the rail. The amount of time that subjects spend in the open portion of the plus maze in the absence of rails is considered to be more sensitive to anxiolytic agents (i.e. agents that would increase the amount of time spent in the open arm) than the amount of time spent in the open arms with rails (Fernandes, 1996). In order to measure general locomotor activity, the number of total grid crosses was counted. Lastly, the duration of time (in sec) spent grooming was also scored.

The experimenter was blind to all conditions, and animals were tested in a randomised block design.

Statistical analysis

Data from the plus maze were analysed in a 2-way ANOVA (implant condition x injection condition) followed by a post-hoc ANOVA and post hoc t-test. As illustrated in table 1, PWD mice spend significantly less time in the open arm than the control animals.

Table 1:

Means Table for Time Open Arm
Effect: Sex/Cond
Row exclusion: stvw PWD +M F/M D

	Count	Mean	Std. Dev.	Std. Err.
(F) C	14	79.629	59.231	15.830
(F) PWD	13	20.968	24.292	6.737
(F) C THIP (1.25)	3	38.377	48.816	28.184
(F) PWD THIP (1.25)	3	157.023	36.838	21.268

Furthermore, THIP at a dose of 1,25 mg/kg completely reversed the PWD effect. Similar results were obtained when the number of crossings (Table 2)

Table 2:

Means Table for Grid Cross
Effect: Sex/Cond
Row exclusion: stvw PWD +M F/M D

	Count	Mean	Std. Dev.	Std. Err.
(F) C	14	43.643	18.270	4.883
(F) PWD	13	33.308	18.531	5.140
(F) C THIP (1.25)	3	52.000	18.028	10.408
(F) PWD THIP (1.25)	3	83.333	16.166	9.333

The time spend outside the rail was determined (Table 3).

Table 3:

Means Table for Time Outside Rail
Effect: Sex/Cond
Row exclusion: stvw PWD +M F/M D

	Count	Mean	Std. Dev.	Std. Err.
(F) C	14	6.795	7.041	1.882
(F) PWD	13	2.077	4.699	1.303
(F) C THIP (1.25)	3	10.060	17.424	10.060
(F) PWD THIP (1.25)	3	29.503	6.699	3.868

As seen from the results of the animal models THIP was able to counteract the PWD completely.

Claims

1. The use of a non-steroid compound which increases GABA activity in the brain for the manufacture of a medicament for the treatment of disorders resulting from reduced neurosteroidal activation.

2. The use of a non-steroid compound according to claim 1, wherein the compound is a non-allosteric GABA agonist.

3. The use of a non-steroid compound according to the claims 1 and 2, wherein the compound has an affinity for the GABA complexes containing the α_4 subunit

4. The use of a non-steroid compound according to claim 1, wherein the compound is a GABA uptake inhibitor.

5. The use of a non-steroid compound according to claim 1, wherein the compound is an enhancer of the GABAergic activity.

6. The use according to any of the above claims characterised in that the non-steroid compound is selected from the group comprising THIP (Gaboxadol), cyclopropylGABA, isoguvacine, muscimol, imidazole-4-acetic acid, gabapentin and tiagabine.

7. The use according to claim 1, wherein the disease or disorder is resulting from fluctuations in the neurosteroid level.

8. The use according to claim 7, wherein the disease or disorder is resulting from decline in the neurosteroid level.

9. The use according to claims 7 or 8, wherein the disease or disorder is resulting from recurrent periodical decline in the neurosteroid level.

10. The use according to claims 7-9, wherein the disease or disorder is resulting from extraordinary decline in the neurosteroid level.

11. The use according to claims 7-10, wherein the disease or disorder is resulting from age-related decline in the neurosteroid level.

12. The use according to claims 7-11,wherein the neurosteroid is progesterone.

13. The use according to claims 7-11, wherein the neurosteroid is a metabolite of progesterone.

14. The use according to any of the above claims wherein the disease or disorder is premenstrual disorder, postnatal depression or postmenupausal related dysphoric disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00773

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/197, A61K 31/195, A61K 31/4172, A61K 31/42, A61K 31/437, A61K 31/4535, A61P 5/24, A61P 25/24

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, A61P

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)

WPI DATA, EPO-INTERNAL, CHEM.ABS, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9838988 A1 (AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO A.C.R.A.F. S.P.A), 11 Sept 1998 (11.09.98) --	6,14
X	US 5776959 A (COVEY ET AL), 7 July 1998 (07.07.98) --	6,14
X	WO 9305786 A1 (COCENSYS, INC.), 1 April 1993 (01.04.93) --	6,14
A	WO 0005196 A1 (AKZO NOBEL N.V.), 3 February 2000 (03.02.00) --	6,14

[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
22 March 2002	25 -03- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Viveca Norén/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00773

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9616076 A1 (COCENSYS, INC.), 30 May 1996 (30.05.96)	6,14
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A	US 5292906 A (COVEY ET AL), 8 March 1994 (08.03.94)	6,14
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A	WO 9937645 A1 (MERCK SHARP & DOHME LIMITED), 29 July 1999 (29.07.99)	6,14
	--	
P,X	WO 0142190 A1 (WARNER-LAMBERT COMPANY), 14 June 2001 (14.06.01)	6,14
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Int application No.
PCT/DK01/00773

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.: 1-5, 7-13
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:

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 claims 1-5 and 7-14 relate to compounds defined by reference to a desirable characteristic or property, namely their ability to increase GABA activity, being a GABA agonist or a GABA uptake inhibitor or being able to enhance GABAergic activity. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very 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 lack clarity (Article 6 PCT). An attempt is made to define the compounds 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.

Further the diseases treated by said compounds are defined by the underlying mechanism namely a reduced neurosteroidal activation. The medical condition for which a substance can be useful should be described as well defined diseases or medical conditions. Hence claims 1-13 also lack clarity (Article 6 PCT) with regard to the disorders to be treated.

Consequently, the search has been carried out for those parts of the claims, which appear to be clear, supported and disclosed, namely those parts relating to the compounds named in the description page 4, lines 12-20 and page 5, lines 1-4, which are used in the treatment of the disorders of claim 14. This means that the claims searched are claim 6 in combination with claim 14.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/DK 01/00773

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9838988 A1	11/09/98	AU 7031798 A	22/09/98
		IL 131355 D	00/00/00
		IT 1290003 B	19/10/98
		IT MI970456 A	03/09/98
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		EP 0603312 A	29/06/94
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