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(54) Title: ISOQUINOLINE-3-CARBOXYLIC ACID AMIDES AND PHARMACEUTICAL USES THEREOF

(57) Abstract: The present invention relates to novel isoquinoline-3-carboxylic acid amides having α7 nicotinic acetylcholine receptor agonistic activity, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

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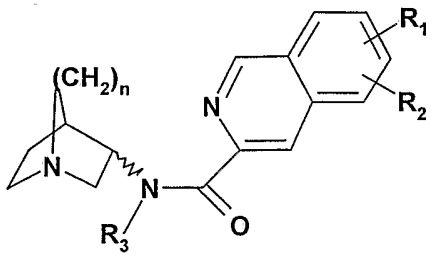
Isoquinoline-3-carboxylic Acid Amides and Pharmaceutical Uses Thereof

The present invention relates to novel isoquinoline-3-carboxylic acid amides having α7 nicotinic acetylcholine receptor agonistic activity, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



I

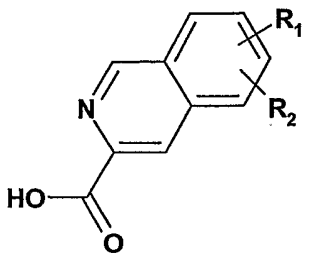
wherein R_1 and R_2, independently, are hydrogen, (C_{1-4})alkyl, halogen, hydroxy, (C_{1-4})alkoxy, di(C_{1-4})alkylamino, (C_{1-4})alkylthio, cyano or trifluoromethyl, R_3 is hydrogen or (C_{1-4})alkyl and n is 1 or 2, in free base or acid addition salt form.

Halogen denotes fluorine, bromine, chlorine or iodine.

Any alkyl, alkoxy or alkylthio groups are branched or straight chain groups. They are preferably methyl, methoxy or methylthio groups. n is preferably 2.

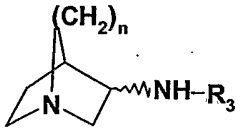
On account of the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.
(S)-1-azabicyclo[2.2.2]oct-2-yl-amino and (S)-1-azabicyclo[2.2.1]hept-2-yl-amino compounds are preferred.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the step or reacting a compound of formula II



II

wherein R_1 and R_2 are as defined above, with a compound of formula III



III

wherein R_3 and n are as defined above, and recovering the resulting compound of formula I in free base or acid addition salt form.

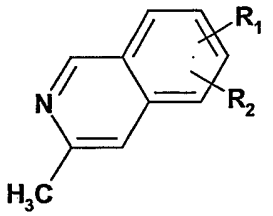
The reaction can be effected according to conventional methods, e.g. as described in the examples.

Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

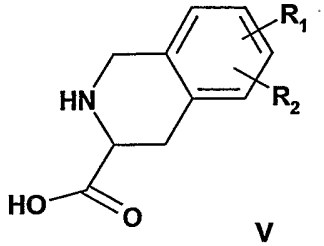
Acid addition salts may be produced from the free bases in known manner, and vice versa.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures. Alternatively, optically pure starting materials can be used.

The starting compounds of formula II may be obtained by conventional methods e.g. by oxidation of compounds of formula IV or V



IV



V

wherein R_1 and R_2 are as defined above, according to conventional methods.

The starting materials of formula III, IV and V are known or may be obtained from known compounds, e.g. as described in the Examples.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (nAChR) agonists.

In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at α7 nAChR is carried out with a rat pituitary cell line stably expressing the α7 nAChR. As a read out, the calcium influx upon stimulation of the receptor is used. In this assay, agents of the invention exhibit pEC_{50} values of about 5 to about 8.

b) To assess the selectivity of the agents of the invention, a similar functional assay is carried out using a human epithelial cell line stably expressing the neuronal α4β2 nAChR subtype. In this assay, agents of the invention display no or little activity at the α4β2 nAChR.

c) To assess the selectivity of the compounds of the invention, similar functional assays as described under a) are carried out with a human epithelial cell line stably expressing the

ganglionic nACHR subtype or a cell line endogenously expressing the muscle type of nicotinic receptors. In these assays, agents of the invention display no or little activity on the ganglionic and muscle type of nicotinic receptor subtypes.

In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the agents of the invention induce significant sensory gating at concentrations of about 10 to about 40 μM.

The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia, mania, depression and anxiety, and for the treatment of neurodegenerative disorders such as senile dementia, Alzheimer's disease and other intellectual impairment disorders, such as attention deficit hyperactivity disorders (ADHD), cognitive dysfunctions and memory deficits; Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, furthermore for the treatment of pain, epilepsy and inflammatory disorders such as rheumatoid arthritis and Crohn's disease. The usefulness in inflammatory disorders is based on the finding that α-7 agonists reduce TNF release from macrophages, as reported in Wang et al., Nature,2002:421, 384. The usefulness of α7 nAChR agonists in neurodegeneration is also documented in the literature, e.g. in Wang et al., J. biol. Chem. 275, 5626-5632 (2000).

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 100, preferably from about 0.1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 5 to about 300 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of any condition mentioned above.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from about 1 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Example 1: Isoquinoline-3-carboxylic acid {(S)-1-azabicyclo[2.2.2]oct-2-yl}-amide

529 mg of isoquinoline-3-carboxylic acid hydrate are dissolved in 18 ml of DMF, followed by addition of 508 mg of 1-hydroxy-benzotriazol and 1.81 g of dicyclohexyl-carbodiimide. After stirring for 1 h at r.t., the precipitated dicylohexyl-urea is filtered off and 500 mg of 3(S)-aminoquinuclidine dihydrochloride and 1.3 ml of ethyl-diisopropylamine is added to the filtrate. After stirring for 48 h at room temperature, a second portion of dicylohexyl-urea is filtered off and washed with MeOtBu/DMF (4:1). Wash solution and filtrate are combined and crystallized by standing over night at 5°. The crystalline precipitate is filtered off and washed with MeOtBu/DMF (4:1), followed by MeOtBu to yield the title compound as monohydrochloride.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.75 (1H, t), 1.96 (2H, m), 2.12 (1H, q), 2.24 (1H, d), 3.24 (3H, m), 3.43 (2H, m), 3.65 (1H, t), 4.49 (1H, q), 7.86 (1H, t), 7.92 (1H, t), 8.24 (1H, d), 8.30 (1H, d), 8.61 (1H, s), 9.31 (1H, d), 9.46 (1H, s), 10.59 (1H, br).
MS (ES^+): 282 $(MH)^+$

Example 2: Isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The compound is prepared as monohydrochloride according to Example 1 starting from 3(R)-aminoquinuclidine and isoquinoline-3-carboxylic acid hydrate.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.76 (1H, t), 1.96 (2H, q), 2.12 (1H, q), 2.24 (1H, d), 3.22 (3H, m), 3.45 (2H, m), 3.64 (1H, t), 4.49 (1H, q), 7.88 (1H, t), 7.96 (1H, t), 8.25 (1H, d), 8.33 (1H, d), 8.71 (1H, s), 9.38 (1H, d), 9.49 (1H, s), 10.77 (1H, s).
MS (ES^+): 282 $(MH)^+$

Example 3: 6-Fluoro-isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The compound is prepared according to Example 1 starting from 3(R)-aminoquinuclidine and 6-fluoro-isoquinoline-3-carboxylic acid. Further purification is achieved by chromatography on silica gel eluting with MeOtBu/EtOH/conc. aqu. NH_3 (75/22.5/2.5).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.38 (1H, m), 1.63 (2H, dt), 1.78 (1H, m), 1.93 (1H, q), 2.65-2.80 (4H, m), 2.94 (1H, dt), 3.18 (1H, dt), 4.06 (1H, m), 7.72 (1H, dt), 8.04 (1H, dd), 8.39 (1H, q), 8.57 (1H, s), 8.76 (1H, d), 9.42 (1H, s).
MS (ES^+): 300 $(MH)^+$

The starting material can be prepared as follows:

6-Fluoro-isoquinoline-3-carboxylic acid hydrochloride

2.15 g of 6-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester are dissolved in 120 ml of xylene. 1.6 g of Pd-C (10%) is added and the suspension is refluxed during 8 h. The catalyst is filtered off, washed with MeOH and the filtrate, combined with the wash solution, evaporated to dryness.
1 g of the resulting crude 6-fluoro-isoquinoline-3-carboxylic acid methyl ester is dissolved in 20 ml of MeOH/THF (1:1) and slowly mixed at 5° with a solution of 510 mg of LiOH hydrate in 10 ml of water. The resulting solution is stirred at room temperature overnight and poured into a solution consisting of 50 ml of MeOtBu, 10 ml of water and 7 ml of 2N aqu. HCl. The precipitate is filtered off and washed with MeOtBu.

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 7.77 (1H, dt), 8.04 (1H, dd), 8.38 (1H, dt), 8.66 (1H, s), 9.43 (1H, s).
MS (ES^-): 190 $(M-H)^-$

6-Fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester

2 g of m-fluoro-DL-phenylalanine are suspended in 20 ml of conc. hydrochloric acid and 8 ml of aqu. 37% formaldehyde solution and stirred during 3.5 h at 90° during which a partial solution takes place. Stirring is continued overnight at room temperature and the precipitate filtered off and washed with cold water. Filtrate, combined with the wash solutions are evaporated to dryness, the residue suspended in 50 ml of MeOH saturated with HCl and stirred overnight, during which a clear solution is formed. The solvent is evaporated, the residue dissolved in CH_2Cl_2/MeOH (9:1) and extracted with 2N Na_2CO_3 solution and brine. The organic phases are dried over Na_2SO_4, evaporated and chromatographed on silica gel using MeOtBu. The title compound is obtained as an oil, MS (ES^+): 210 $(MH)^+$.

In addition, 6-fluoro-3-methyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester and 8-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester can be isolated as byproducts.

Example 4: 8-Fluoro-isoquinoline-3-carboxylic acid {(R)-1-azabicyclo[2.2.2]oct-2-yl}-amide

The title compound is prepared according to Example 1 starting from 3(R)-aminoquinuclidine and 8-fluoro-isoquinoline-3-carboxylic acid. Further purification is achieved by chromatography on silica gel eluting with MeOtBu/EtOH/conc. aqu. NH_3 (80/18/2).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 1.38 (1H, m), 1.63 (2H, dt), 1.78 (1H, m), 1.93 (1H, q), 2.64-2.81 (4H, m), 2.93 (1H, dt), 3.17 (1H, dt), 4.07 (1H, m), 7.63 (1H, dt), 7.90 (1H, dd), 8.09 (1H, d), 8.63 (1H, s), 8.79 (1H, d), 9.53 (1H, s).
MS (ES^+): 300 $(MH)^+$

The starting material can be prepared as follows:

8-Fluoro-isoquinoline-3-carboxylic acid hydrochloride
The compound is prepared by oxidation of 8-fluoro-1,2,3,4-tetrahydro-isoquinoline -3-carboxylic acid methyl ester, followed by saponification according to the preparation of 6-fluoro-isoquinoline-3-carboxylic acid (Example 3).

NMR (^{1}H, 400 MHz, δ_H d_6-DMSO) : 7.68 (1H, dd), 7.92 (1H, dd), 8.09 (1H, d), 8.71 (1H, s), 9.57 (1H, s).
MS (ES^-) : 190 $(M-H)^-$

8-Fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester
The compound is obtained as a byproduct during the synthesis of 6-fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester (see Example 3).
MS (EI): 209 (M^+)

Example 5: 8-Fluoro-isoquinoline-3-carboxylic acid {(S)-1-azabicyclo[2.2.2]oct-2-yl}-amide

2-Fluoro-6-iodo-benzaldehyde

Buthyllithium (1.6 M, 60 ml, 0.113 mol) is added to an ice cooled solution of diisopropyl-amine (17.6 ml, 0.124 mol) in THF (200 ml). The solution is stirred at 0°C for 30 minutes and is cooled to -78 °C . 1-Fluoro-3-iodo-benzene (25 g, 0.113 mol) in THF (20 ml) is slowly added to the preformed LDA mixture. The resulting solution is stirred for another hour after which DMF (9.55 ml, 0.124 mol) is added and stirring is continued for another 30 minutes at -78 °C. The reaction is quenched first with acetic acid (20 ml) followed by water (200 ml). The mixture is extracted with ether. The organic layer is washed with a 2N HCl solution , brine, is dried over $MgSO_4$ and evaporated to afford the desired compound (28.3 g).

2-(2-Fluoro-6-iodo-phenyl)-[1,3]dioxane

2-Fluoro-6-iodo-benzaldehyde (3.0 g, 12 mmol), 1,3-propanediol (1.3 ml, 18 mmol), and para-toluenesulfonic acid (342 mg, 1.8 mmol) is heated at reflux in toluene (60 ml) using a Dean-Stark apparatus for 2 hours. The organic layer is washed with brine and dried over $MgSO_4$ and evaporated to afford the desired compound (3.65 g).

2-Acetylamino-3-(2-[1,3]dioxan-2-yl-3-fluoro-phenyl)-acrylic acid methyl ester

A DMF (10 ml) solution of 2-(2-fluoro-6-iodo-phenyl)-[1,3]dioxane (1.85 g, 6 mmol), 2-acetylamino-acrylic acid methyl ester (906 mg, 6.33 mmol), sodium bicarbonate (1.26 g, 15 mmol), tetrabutyl ammonium chloride (1.35 g, 4.86 mmol) and palladium (II) acetate (52 mg, 0.23 mmol) is heated at 90°C for 18 hours. The reaction mixture is poured onto water and the aqueous phase is extracted with ethylacetate. The organic layer is washed with brine and dried over $MgSO_4$ and evaporated. The crude product is purified by chromatography (CH_2Cl_2 / MeOH, 95/5) to afford the desired compound (240 mg). MS (ES^+): m/e = 346.3 (MNa^+)

8-Fluoro-isoquinoline-3-carboxylic acid methyl ester

2-Acetylamino-3-(2-[1,3]dioxan-2-yl-3-fluoro-phenyl)-acrylic acid methyl ester (10.6 g, 32.8 mmol) and pyridinium para-toluene sulfonate (2.06 g, 8.2 mmol) are heated to reflux for 20 hours in an acetone / water (120 ml / 15 ml) mixture. The solvents are removed by

evaporation and the aqueous residue is extracted with ethylacetate. The organic layer is washed with brine and dried over $MgSO_4$ and evaporated. The crude product is recrystallised from ethylacetate / ether to afford 5.1 g of the desired compound. MS (ES^+): m/e = 206.2 (MH^+)

8-Fluoro-isoquinoline-3-carboxylic

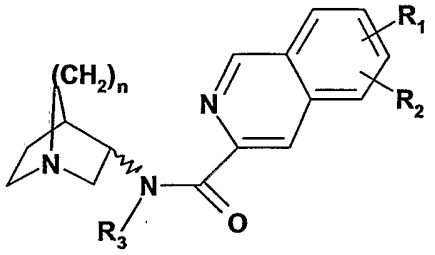
Lithium hydroxide (525 mg, 21.93 mmol) is added to a solution of 8-Fluoro-isoquinoline-3-carboxylic acid methyl ester (1.5 g, 7.31 mmol) in methanol (63 ml) and water (7 ml). The solution is stirred at room temperature for 18 hours. The solvent mixture is removed by evaporation and the residue is redissolved in a methanol / water mixture. The resulting solution is acidified to pH1 using a concentrated HCl solution. The methanol is removed and the crystals are gathered by filtration and dried to afford 1.05 g of the desired compound.

8-Fluoro-isoquinoline-3-carboxylic acid {(S)-1-azabicyclo[2.2.2]oct-2-yl}-amide

Dicyclohexyl-carbodiimide (7.69 g, 30 mmol) is added to a solution of 8-fluoro-isoquinoline-3-carboxylic acid (5.1 g, 22.4 mmol) , ethyl-diisopropyl-amine (4.6 ml, 26.88 mmol) and hydroxybenztriazole (5.36 g, 33.6 mmol) in DMF (150 ml). The mixture is stirred for 2 hours at room temperature. (S)-(1-Aza-bicyclo[2.2.2]oct-3-yl)amine (4.46 g, 49.28 mmol) and ethyl-diisopropyl-amine (8.7 ml, 49.28 mmol) are added and the solution is stirred for another 18 hours at room temperature. The solvent is removed by evaporation and the residue is dissolved in methylenedichloride and washed with a saturated K_2CO_3 solution and brine. The organic layer is dried over $MgSO_4$ and evaporated. The crude product is purified by chromatography (CH_2Cl_2 / MeOH/ NH_4OH, 92.5/7.5/0.75) to afford the desired compound (2.35 g). The product is recrystallized from ethanolic HCl to give 2 g. of the hydrochloric salt. MS (ES^+): m/e = 300 (MH^+)

Claims:

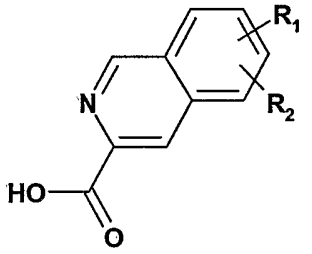
1. A compound of formula I



I

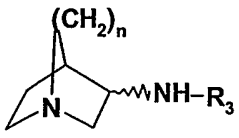
wherein R_1 and R_2, independently, are hydrogen, (C_{1-4})alkyl, halogen, hydroxy, (C_{1-4})alkoxy, di(C_{1-4})alkylamino, (C_{1-4})alkylthio, cyano or trifluoromethyl, R_3 is hydrogen or (C_{1-4})alkyl and n is 1 or 2, in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

wherein R_1 and R_2 are as defined in claim 1, with a compound of formula III



III

wherein R_3 and n are as defined in claim 1, and recovering the resulting compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic and neurodegenerative disorders.

5. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of psychotic and neurodegenerative disorders.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic and neurodegenerative disorders.

8. A method for the treatment of psychotic and neurodegenerative disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/08 A61K31/4725 A61P25/28

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)
IPC 7 C07D A61K A61P

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, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/085901 A (GROPPI VINCENT E JR ; MYERS JASON K (US); UPJOHN CO (US); JACOBSEN E J) 31 October 2002 (2002-10-31) Page 1, paragraph 1; page 12, paragraphs 2 and 3; page 14, paragraphs 3 and 4; claims; examples 1a, 2a, 2b.	1-8
Y	WO 03/037896 A (CORBETT JEFFREY W ; GROPPI VINCENT E JR (US); JACOBSEN ERIC JON (US);) 8 May 2003 (2003-05-08) Abstract; page 1, paragraph 1; page 16, paragraph 2, to page 17, paragraph 2; claims; examples.	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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
27 July 2004	03/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weisbrod, T

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/022856 A (CORBETT JEFFREY W ; GROPPI VINCENT E JR (US); RAUCKHORST MARK R (US);) 20 March 2003 (2003-03-20) Abstract; page 1, paragraph 1; page 71, paragraph 2, to page 72, paragraph 3; claims; page 119, example 9.	1-8
P,X	WO 03/072578 A (GROPPI JR VINCENT E ; JACOBSEN ERIC JON (US); MYERS JASON K (US); UPJO) 4 September 2003 (2003-09-04) Abstract; page 40, paragraph 3; page 42, paragraph 4, to page 44, paragrph 1; claims; examples 13; 14.	1-8
E	WO 2004/052461 A (JACOBSEN ERIC JON ; MYERS JASON KENNETH (US); PIOTROWSKI DAVID WALTER) 24 June 2004 (2004-06-24) Abstract; claims 1, 3, 4 (in claim 4, entries 3 and 9).	1-8
E	WO 2004/052348 A (CORBETT JEFFREY WAYNE ; UPJOHN CO (US); GROPPI VINCENT EDWARD JR (US)) 24 June 2004 (2004-06-24) Absract; claims 1, 3 (in claim 3, entries 3 and 9).	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/005042

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

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 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 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/005042

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