COMMONWEALTH of AUSTRALIA
Patents Act 1952

616307

APPLICATION FOR A STANDARD PATENT

I/We

Pharmacia AB

of

S-751 82 Uppsala, Sweden

hereby apply for the grant of a Standard Patent for an invention entitled:

Novel pyridyl- and pyrimidyl derivatives

which is described in the accompanying complete specification.

Details of basic application(s):-

Number	Convention Country	Date
8803429-3	Sweden	28 September 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this TWENTY FIFTH day of SEPTEMBER 1989

To: THE COMMISSIONER OF PATENTS

Keith Gosling

a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

M 012625 250989

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention entitled: "NOVEL PYRIDYL- AND PYRIMIDYL DERIVATIVES"

Insert title of invention

I Eva Thylen
of PHARMACIA AB
S-751 82 UPPSALA
Sweden

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

do solemnly and sincerely declare as follows :-

1. (a) ~~I am the applicant for the patent~~

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

or (b) I am authorized by Pharmacia AB, ~~Sweden~~

the applicant..... for the patent to make this declaration on its behalf.

2. (a) ~~I am the actual inventor of the invention~~

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

or (b)

Knut Gunnar Olsson, Baltzarsgatan 2, S-211 36 Malmö, Sweden
Aina Lisbeth Abramo, Järavallsvägen 30 A, S-237 00 Bjärred, Sweden
Erik Torbjörn Lundstedt, Gökblomstervägen 37, S-240 21 Lödde-köpinge, Sweden
Curt Nordvi, Granholmsgatan 1, S-213 63 Malmö, Sweden

~~is~~ are the actual inventor..... of the invention and the facts upon which the applicant..... ~~is~~ entitled to make the application are as follows :-

State manner in which applicant(s) derive title from inventor(s)

Applicant is the assignee of the invention from the actual inventors by virtue of an assignment dated September 30, 1988.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ were made

in Sweden on the 28th of September, 19..

by PHARMACIA AB, S-751 82 Uppsala, Sweden

in ..... on the .....

by .....

in ..... on the .....

by .....

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~ were the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Helsingborg this 6th day of September, 1989

Signature of declarant(s) (no attestation required)

PHARMACIA AB

Eva Thylén

Eva Thylén, Authorized Signing Officer

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-41737/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 616307

(54) Title
NOVEL PYRIDYL AND PYRIMIDYL DERIVATIVES

International Patent Classification(s)
(51)[4] C07D 213/72 C07D 213/78 C07D 213/82 C07D 401/04
A61K 031/495
(51)[5] C07D 213/74 C07D 213/81

(21) Application No. : 41737/89 (22) Application Date : 25.09.89

(30) Priority Data

(31) Number (32) Date (33) Country
8803429 28.09.88 SE SWEDEN

(43) Publication Date : 05.04.90

(44) Publication Date of Accepted Application : 24.10.91

(71) Applicant(s)
PHARMACIA AB

(72) Inventor(s)
KNUT GUNNAR OLSSON; AINA LISBETH ABRAMO; ERIK TORBJORN LUNDSTEDT; CURT NORDVI

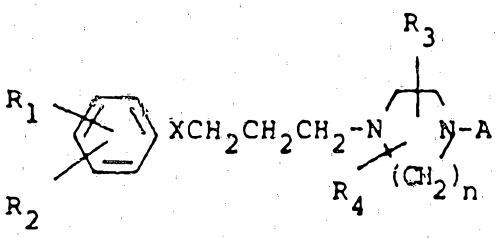
(74) Attorney or Agent
DAVIES & COLLISON , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 24327/88 C07D 239/42
AU 69607/87 C07D 403/12
AU 68588/87 C07D 213/74

(57) Compounds act at 5HT-receptors

CLAIM

1. Novel compounds having the general formula (I)



(I)

wherein R_1 is halogen or hydrogen and R_2 is halogen;

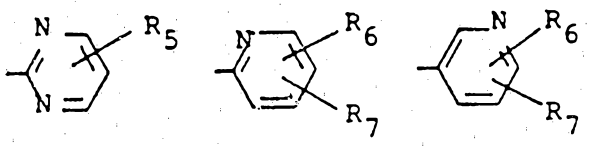
X is either oxygen, sulfur or methylene;

R_3 and R_4 are the same or different and selected from hydrogen and lower alkyl;

n is 2 or 3;

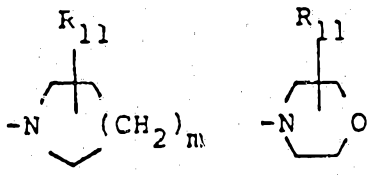
.../2

A is selected from the following pyrimidyl or pyridyl groups:



wherein R_5 is selected from hydrogen, lower alkyl or halogen; R_6 and R_7 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_8$, $CONR_9R_{10}$ or CO-B; wherein R_8 is hydrogen or lower alkyl; R_9 and R_{10} are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



wherein m is 1, 2, 3 or 4.

R_{11} is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof.

616307

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PATENTS ACT 1952

COMPLETE SPECIFICATION

NAME & ADDRESS OF APPLICANT:

Pharmacia AB
S-751 82 Uppsala

Sweden

NAME(S) OF INVENTOR(S):

Knut Gunnar OLSSON
Aina Lisbeth ABRAMO
Erik Torbjorn LUNDSTEDT
Curt NORDVI

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

Novel pyridyl- and pyrimidyl derivatives

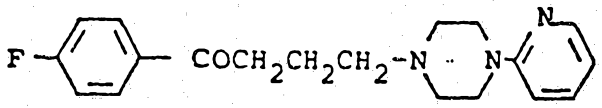
The following statement is a full description of this invention, including the best method of performing it known to me/us:-

Background

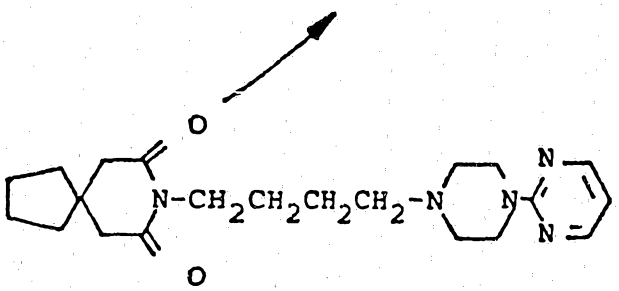
There is an urgent need for efficient drugs in the treatment of mental disorders which are more effective and which have fewer side effects than the drugs in clinical use today. Antipsychotic drugs in current use produce a range of troublesome extrapyramidal movement disorders (e.g. acute dystonic reactions and tardive dyskinesia) and are poor in ameliorating the negative symptoms (e.g. restricted or blunted emotional arousal) of schizophrenia. The main disadvantage of the antidepressants is that they fail to alleviate depression in 30 to 40 % of patients. Anxiolytics are commonly associated with addictive properties.

Prior art

Various pyridyl- and pyrimidyl-piperazine derivatives pharmacologically active in the central nervous system are known in the art. Some representative examples can be mentioned. Azaperone, a neuroleptic drug of the butyrophenone series, is a sedative for pigs. Buspirone is an anxiolytic. The anxiolytic effect is thought to be mediated via effects on the 5HT-receptors.



azaperone

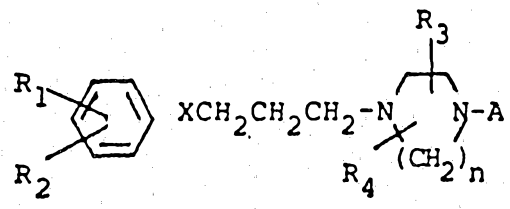


buspirone

Description of the invention

Pyridyl- and pyrimidyl-piperazines substituted in the 4-position of the piperazine ring with a phenyl-butyl or phenoxypropyl group have unexpectedly been found to exhibit pharmacological properties superior to compounds known in the art.

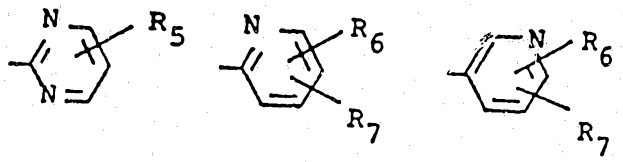
According to the invention there are provided novel compounds having the general formula (I).



(I)

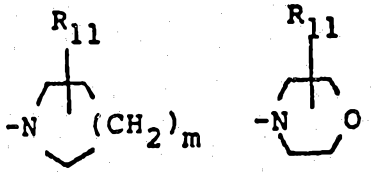
wherein R_1 is halogen or hydrogen and R_2 is halogen;
wherein X is either oxygen, a sulfor or a methylene;
R_3 and R_4 are the same or different and selected from hydrogen and lower alkyl;
n is 2 or 3;

A is selected from the following pyrimidyl or pyridyl groups



wherein R_5 is selected from hydrogen, lower alkyl or halogen; R_6 and R_7 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_8$, $CONR_9R_{10}$ or CO-B; wherein R_8 is hydrogen or lower alkyl; R_9 and R_{10} are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



wherein m is 1, 2, 3 or 4.

R_{11} is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof, and when used in the foregoing definitions the term lower alkyl is meant to include straight and branched, saturated hydrocarbon groups having from 1 to 5 carbon atoms;

the term cycloalkyl is meant to include cyclic hydrocarbon groups having from 3 to 8 carbon atoms;

the term lower alkoxy is meant to include straight or branched, saturated hydrocarbon groups having from 1 to 5 carbon atoms;

the term halogen is meant to include fluoro, chloro and bromo.

It is preferred that R_1 is hydrogen and R_2 is halogen, fluoro is preferred.

As regards R_3 and R_4 hydrogen or methyl are preferred, especially hydrogen.

As regards R_5 hydrogen, alkyl or halogen, especially fluoro, is preferred.

As regards R_6 hydrogen, alkyl, alkoxy, amide, nitro, carboxy, trifluoromethyl, halogen, hydroxy or cyano is preferred.

It is preferred that R_7 is hydrogen, alkyl, alkoxy, nitro, carboxy, halogen, hydroxy, cyano or an amide group.

Compounds wherein A is 2-substituted pyridyl are of special interest, especially those carrying an alkoxy, hydroxy, alkyl, amide, cyano or hydrogen substituent in the 3-position.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with

acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, oxalic, succinic, fumaric, tartaric, citric and pamoic acid.

Conversely, the salt form can be converted into the free base form by treatment with alkali.

The compounds of formula (I) and their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression and anxiety. Stress and anxiety in animals can also be treated. The compounds of the present invention show psychotropic properties. For example, they show affinity for 5-HT_2 and D_2 binding sites in the brain. In behavioural test models the compounds show a limbic profile of action, i.e. they show potent effects in tests for exploratory behaviour, e.g. the staircase test.

Compounds with a combined 5-HT_2/D_2 affinity, e.g. clozapine, have antipsychotic effect with a low degree of extrapyramidal side-effects. Furthermore, compounds with affinity for 5-HT_2 binding sites has been found to affect depressive illness as well as anxiety states.

Effective quantities of any of the foregoing pharmacologically active compounds of formula (I) may be administered to a human being or an animal for therapeutic purposes according to usual routes of administration and in usual forms, such as orally in solutions, emulsions, suspensions, pills, tablets and capsules, in pharmaceutically acceptable carriers and parenterally in the form of sterile solutions. For the parenteral administration of the active substance the carrier of excipient may be a sterile, parenterally acceptable liquid, e.g. water, or a parenterally acceptable oil, e.g. arachidic oil.

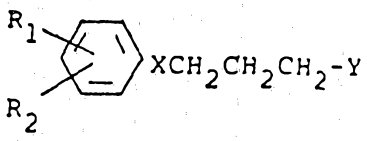
Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in the cases of administration to subjects having a relatively low body weight, unit dosages are usually from 2 milligrams upwards, preferably 10, 25 or 50 milligrams or even higher depending on the condition to be treated and the age and weight of the patients as well as the response to the medication.

The unit dose may be from 0.1 to 100 milligrams, preferably from 10 to 50 milligrams. Daily dosages should preferably range from 10 milligrams to 200 milligrams. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

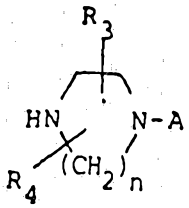
Methods of preparation

The compounds having the general formula (I) may be prepared by conventional methods.

Method 1



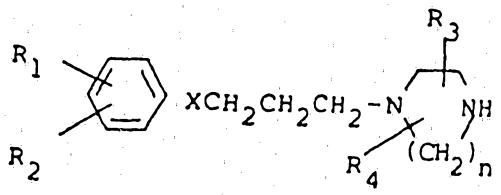
II



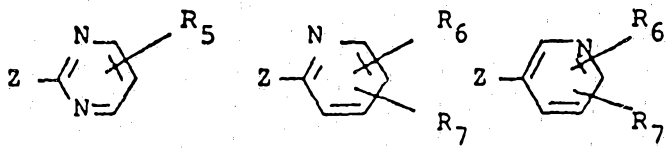
III

A compound of formula (II), wherein R_1, R_2 and X are as previously defined and Y is a suitable leaving group such as halogen and alkyl- or arylsulfonate is reacted with a compound of formula (III) wherein R_3, R_4, A and n are as defined previously. The reactions may be carried out using standard N-alkylating procedures.

Method 2



IV



V VI VII

A compound of formula (IV), wherein R_1, R_2, R_3, R_4, X and n are as previously defined is reacted with a compound of formula (V), (VI) or (VII), wherein R_5, R_6 and R_7 are as previously defined and Z is a leaving group, e.g. halogen.

Examples

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for our intended purposes. These compounds have been designated by a number code, a:b, where a means the number of the example, wherein the preparation of the compound in

question is described, and b refers to the order of the compounds prepared according to that example. Thus, compound 1:2 means the second compound prepared according to Example 1.

The structures of the compound are confirmed by NMR, masspectra and elementary analysis. When melting points are given, these are uncorrected.

Example 1

4-/4-(p-fluorophenyl)butyl/-1-(2-pyridyl)piperazine fumarate

6.0 g (0.0323 mol) of 4(p-fluorophenyl)butylchloride, 5.3 g (0.0323 mol) of pyridylpiperazine, 5.2 g of sodiumcarbonate and 0.1 g of iodide was heated together with 25 ml of xylene at 150°C (temperature of oil bath) for 20 h.

After cooling the reaction mixture to ~ 100°C, 50 ml of toluene was added and the mixture was filtered. 25 ml of ether was added to the filtrate. The organic solution was washed three times with 25 ml of water and finally once with 25 ml of a saturated sodiumchloride solution.

Evaporation of the solvents yielded crude base which was crystallized by cyclohexane. The melting point obtained for the free base is 57-58°C.

The free base was then dissolved in ethanol/ether and the fumarate was precipated with excess of fumaric acid in ethanol.

Recrystallization from ethanol yielded 4.8 g of the title compound (1:1), m.p. 160-161°C.

Example 2

4-/4-(p-fluorophenyl)butyl/-1-/2-(3-carbamylpyridyl)/ piperazine dihydrochloride

5.9 g (0.025 mol) of 1-/4-(p-fluorophenyl)butyl/ piperazine, 3.9 g (0.025 mol) of 2-chloronicotinic acid amide and 3.1 g of sodiumcarbonate was refluxed together with 20 ml of toluene for 20 h.

After cooling a solid mixture was obtained which ws dissolved by ethylacetate and water. The toluene/ ethylacetate phase was separated and then washed with water and sodiumchloride solution and was then dried with sodiumsulfate.

Evaporation of the solvents yielded the crude free base, which was recrystallized from toluene. The free base obtained melted at 135-136°C.

5 g of the free base was dissolved in ethanol and the dihydrochloride was precipated by excess of hydrochloric acid in ethanol. Recrystallization yielded 3.0 g of the titled compound (2:1), m.p. 210-213°C.

Using essentially the same procedure the following compounds are prepared (isolated and purified by Flashchromatography as the pure base or as the corresponding salts) from the corresponding starting material.

2:2 4-/3-(p-fluorophenoxy)propyl/-1-/6-chloro-2-pyridyl/ piperazine hydrochloride, m.p. 185-186°C

2:3 4-/3-(p-fluorophenoxy)propyl/-1-/2-pyrimidyl/ piperazine hydrochloride hemihydrate, m.p. 208-210°C

2:4 4-/3-(p-fluorophenoxy)propyl/-1-/2-pyridyl/ piperazine dihydrochloride, m.p. 233-235°C

2:5 4-/3-(p-fluorophenoxy)propyl/-1-/3-carbamyl-2--pyridyl/piperazine dihydrochloride, m.p. 240-242°C

2:6 4-/4-(p-fluorophenyl)butyl/-1-/2-pyrimidyl/ piperazine hydrochloride, m.p. 197-198°C

2:7 4-/4-(p-fluorophenyl)butyl/-1-/2-pyridyl/ piperazine fumarate, m.p. 160-161°C

2:8 4-/3-(p-fluorophenoxy)propyl/-1-/3-nitro-2-pyridyl/ piperazine hydrochloride, m.p. 182-183°C

2:9 4-/4-(p-fluorophenyl)butyl/-1-/6-chloro-2-pyridyl/ piperazine hydrochloride, m.p. 150-151°C

2:10 4-/3-(p-fluorophenoxy)propyl/-1-/6-methoxy-2-pyridyl/ piperazine fumarate, m.p. 185-186°C

2:11 4-/3-(p-fluorophenoxy)propyl/-1-/3-carbamyl-2-pyridyl/ -/1,4-diazacycloheptane/ oxalate, m.p. 148-150°C (base m.p. 140-141°C)

2:12 4-/4-(p-fluorophenyl)butyl/-1-/3-ethoxy-2-pyridyl/ piperazine dihydrochloride, hemiisopropanol hemihydrate, m.p. 168-169°C

2:13 4-/3-(p-fluorophenoxy)propyl/-1-(3-carbamyl-2-pyridyl) 2,5-transdimethylpiperazine 1,5 fumarate, m.p. 172-173°C (base m.p. 115-116°C)

2:14 4-/4-(p-fluorophenyl)butyl/-1-/6-methyl-2-pyridyl/ piperazine fumarate, m.p. 172-173°C

2:15 4-/3-(3,4-difluorophenoxy)propyl/-1-/6-methyl-2--pyridyl/piperazine dihydrochloride, d. 230°C

2:16 4-/3-(3,4-difluorophenoxy)propyl/-1-/3-(N-methylcarbamyl)-2-pyridyl/piperazine 1,5 hydrochloride, m.p. 211-213°C

2:17 4-/3-(p-fluorophenoxy)propyl/-1-/3-hydroxy-2--pyridyl/piperazine dihydrochloride, m.p. 240°C (base m.p. 105°C)

2:18 4-/3-(p-fluorophenoxy)propyl/-1-/3-trifluoromethyl--6-chloro-2-pyridyl/piperazine hydrochloride, m.p. 190°C

2:19 4-/3-(p-fluoro~~thiophenoxy~~phenylthio)propyl/-1-/3-carbamyl-2--pyridyl/piperazine dihydrochloride, m.p. 205°C

2:20 4-/3-(p-fluoro~~thiophenoxyl~~phenylthio)propyl/-1-/2-pyridyl/piperazine dihydrochloride, m.p. 150°C

2:21 4-/3-(p-fluorophenoxyl)propyl/-1-/5-morpholinocarbonyl-2-pyridyl/piperazine

2:22 4-/4-(p-fluorophenyl)butyl/-1-/3-piperidinocarbonyl--2-pyridyl/piperazine

AUSTRALIAN PATENT OFFICE

Example 3

Affinity to 5-HT_2 receptors

The binding assay is carried out essentially as described by Leysen et al. (Mol. Pharmacol. 21, 301-14, 1982) using ^{3}H-ketanserine as ligand.

Table 1

Compound	K_i (nM)
2:9	7
2:10	11
2:19	7

The compounds listed in Table 1 are not given for purpose of limiting the invention thereto but only to exemplify the useful pharmacological activities of compounds within the scope of formula (I).

Example 4

The following formulations are representative for all of the pharmacologically active compounds of this invention. Example of a suitable capsule formulation:

	Per capsule, mg
Active ingredient, as salt	10
Lactose	250
Starch	120
Magnesium stearate	5
Total	385

In case of higher amounts of acive ingredients, the amount of lactose used may be reduced.

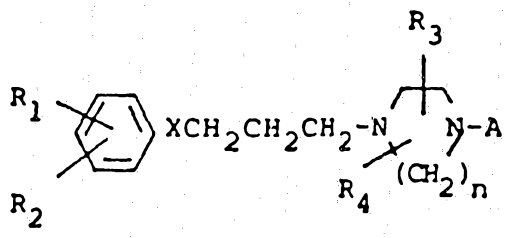
Example of a suitable tablet formulation:

	Per tablet, mg
Active ingredient, as salt	10
Potato starch	90
Colloidal Silica	10
Talc	20
Magnesium stearate	2
5% aqueous solution of gelatin	25
Total	157

Solutions for parenteral applications by injection can be prepared in a aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5% to about 5% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS.

1. Novel compounds having the general formula (I)



(I)

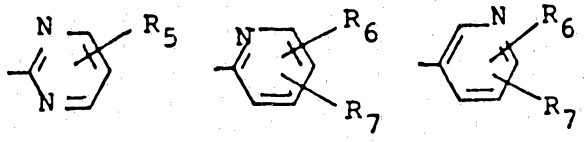
wherein R_1 is halogen or hydrogen and R_2 is halogen;

X is either oxygen, sulfur or methylene;

R_3 and R_4 are the same or different and selected from hydrogen and lower alkyl;

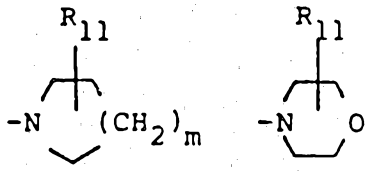
n is 2 or 3;

A is selected from the following pyrimidyl or pyridyl groups:



wherein R_5 is selected from hydrogen, lower alkyl or halogen; R_6 and R_7 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_8$, $CONR_9R_{10}$ or CO-B; wherein R_8 is hydrogen or lower alkyl; R_9 and R_{10} are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



wherein m is 1, 2, 3 or 4.

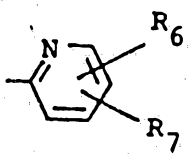
R_{11} is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof.

2. Compounds according to claim 1 wherein R_1 is hydrogen and R_2 is halogen, preferably fluoro.

3. Compounds according to claim 1 ~~and~~ or 2 wherein n=2.

4. Compounds according to claim 1 or 2, wherein R_3 and R_4 are hydrogen or methyl, preferably hydrogen.

5. Compounds according to claim 1, 2 or 3, wherein A is



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6. Compounds according to claim 4, wherein R_6 is hydrogen, alkyl, trifluoromethyl, alkoxy, amide, hydroxy, carboxy, nitro or cyano and R_7 is hydrogen, alkyl, alkoxy, hydroxy, nitro, halogen, carboxy, cyano or an amide group.

7. Compounds according to any one of claims 1 to 6 wherein X is oxygen or methylene.

8. Compounds according to claim 5, wherein R_6 is hydrogen, alkyl, or trifluoromethyl and R_7 is alkoxy, hydrogen, hydroxy, carboxy, nitro, halogen, cyano or an amide group and R_7 is situated in the 3-position.

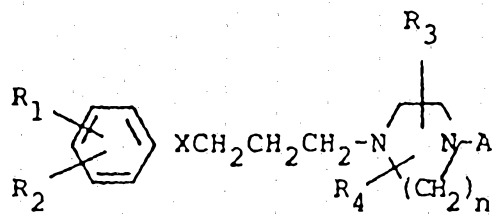
9. Compounds according to any one of claims 1 to 8 wherein X is oxygen.

10. Compounds according to claim 6, wherein R_6 is hydrogen and R_7 is hydrogen, cyano, nitro, alkoxy, alkyl, hydroxy or an amide substituent.

11. Compounds according to claim 7 wherein R_7 is an amide, hydroxy, hydrogen, methyl, cyano or methoxy substituent.

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12. A method of preparing compounds having the general formula (I)

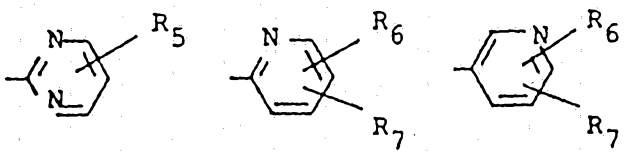


(I)

wherein R_1 is hydrogen or halogen and R_2 is halogen; R_3 and R_4 are the same or different and selected from hydrogen and lower alkyl;

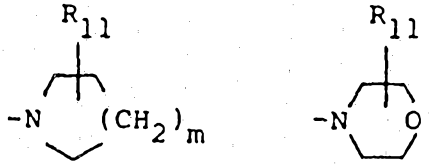
n is 2 or 3;

A is selected from the following pyrimidyl or pyridyl groups:



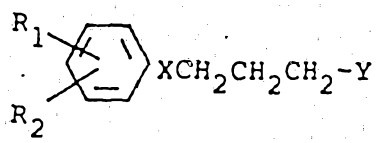
wherein R_5 is selected from hydrogen, lower alkyl or halogen; R_6 and R_7 are the same or different and selected from hydrogen, halogen, lower alkyl, electron donor groups such as lower alkoxy or hydroxy, electron acceptor groups such as cyano, nitro, trifluoromethyl, $COOR_8$, $CONR_9R_{10}$ or CO-B; wherein R_8 is hydrogen or lower alkyl; R_9 and R_{10} are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



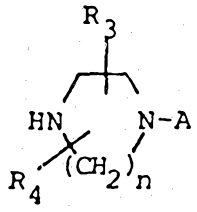
wherein m is 1, 2, 3 or 4.

R_{11} is selected from hydrogen or lower alkyl, and the pharmacologically active salts thereof, wherein a compound having the general formula (II)



II

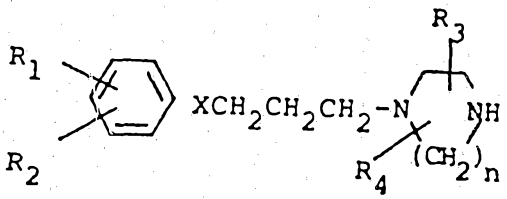
wherein R_1 and R_2 are as defined above and Y is a leaving group, is reacted with a compound having the general formula (III)



III

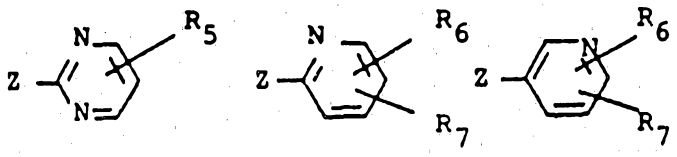
wherein R_3, R_4, n and A are as defined above

or wherein a compound having the general formula (IV)



IV

wherein R_1, R_2, R_3, R_4 and n are as previously defined, is reacted with a compound having the formula (V), (VI) or (VII):



V VI VII

R_5, R_6 and R_7 are as previously defined and Z is a leaving group.

13. Pharmaceutical compositions containing as an active ingredient one or more of the compounds having the general formula (I) according to claim 1, optionally together with a pharmaceutically acceptable carrier and other pharmacologically active agents.

14. A method of treating a living body suffering from a mental disorder, which comprises the step of administering to said living body a compound having the general formula (I) according to claim 1.

15. Compounds of formula (I), method for their preparation or pharmaceutical compositions containing them, substantially as hereinbefore described with reference to the examples.

DATED this 8th day of August, 1991
Pharmacia AB
By Its Patent Attorneys
DAVIES & COLLISON

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