EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent: 30.05.2001 Bulletin 2001/22

(21) Application number: 93915840.8

(22) Date of filing: 06.07.1993

(54) NOVEL 4-(3-BENZOFURANYL) PIPERIDINYL AND 4-(3-BENZOTHIENYL) PIPERIDINYL DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

NEUE 4-(3-BENZOFURANYL) PIPERIDINYL UND 4-(3-BENZOTHIENYL) PIPERIDINYL-DERIVATE UND DIESE ENTHALTENDE PHARMAZEUTISCHE ZUSAMMENSTELLUNGEN

NOUVEAUX DERIVES DE 4-(3-BENZOFURANYL) PIPERIDINYLE ET 4-(3-BENZOTHIENYLE) PIPERIDINYLE ET COMPOSITIONS PHARMACEUTIQUES LES CONTENANT

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE LI LU NL PT SE


(43) Date of publication of application: 20.09.1995 Bulletin 1995/38

(73) Proprietor: JANSSEN PHARMACEUTICA N.V. 2340 Beerse (BE)

(72) Inventors:
• VANDENBERK, Jan
  B-2340 Beerse (BE)
• KENNIS, Ludo, Edmond, Josephine
  B-2300 Turnhout (BE)

• VAN HEERTUM, Albertus, Henricus, Maria,
  Theresia
  B-2350 Vosselaar (BE)

(74) Representative: Quaghebeur, Luc et al
  Janssen Pharmaceutica N.V.,
  Patent Department,
  Turnhoutseweg 30
  2340 Beerse (BE)

(56) References cited:
EP-A- 0 037 265
EP-A- 0 453 042
EP-A- 0 070 053

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification.

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention.)
Description

Description of the invention

[0002] The invention is concerned with novel compounds of the formula

\[
\text{(I)},
\]

\[X \text{ is oxygen or sulphur;}
\]
\[R^1 \text{ is hydrogen or halo;}
\]
\[R^2 \text{ is hydrogen, C}_1^{-4}\text{alkyl, phenylmethyl or halophenylmethyl;}
\]
\[\text{Alk is C}_1^{-4}\text{alkanediyl;}
\]
\[-Z-A- \text{ is a bivalent radical selected from the group consisting of } \text{-S-CH}_2\text{-CH}_2\text{-, } \text{-S-CH}_2\text{-CH}_2\text{-CH}_2\text{-, } \text{-S-CH=CH-}, \text{-CH=CH-CH=CH-}, \text{-C(=CHR}_3\text{)-CH}_2\text{-CH}_2\text{-CH}_2\text{-}, \text{-CHR}_4\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-, } \text{-CHR}_4\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-;}
\]
\[\text{wherein in said bivalent radicals one hydrogen may be replaced by C}_1^{-4}\text{alkyl;}
\]
\[R^3 \text{ is phenyl or halophenyl; and}
\]
\[\text{each R}_4\text{ independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl.}
\]
tandedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The term acid addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

R¹ is suitably hydrogen or fluoro;
R² is suitably phenylmethyl or C₁₋₄ alkyl, preferably methyl;
Alk is suitably C₂₋₃ alkanediyl, preferably 1,2-ethanediyl or 1,3-propanediyl;
R³ is suitably phenyl or fluorophenyl, especially 4-fluorophenyl;
R⁴ is suitably hydrogen, hydroxy or halophenylmethyl, especially fluorophenylmethyl.

[0006] Particular compounds are those compounds of formula (I), wherein -Z-A- is a bivalent radical of formula -S-CH₂CH₂-, -S-CH₂CH₂CH₂-, -S-CH≡CH-, -S-CH=CH-CH₃-, -CH=CH-CH=CH₂-, -CH=C(CH₃)-CH=CH-, -CH=CH-O-,
or -CH=C(CH₃)-O-.

[0007] Also particular compounds are those compounds of formula (I), wherein -Z-A- is a bivalent radical of formula -CHR₄-CH₂CH₂-, -CHR₄-CH₂CH₂CH₂-, or -CHR₄-CH₂CH₂CH₂CH₂-, wherein R⁴ is hydrogen, hydroxy or halophenylmethyl, especially fluorophenylmethyl; or-C(=CHR₃)-CH₂CH₂CH₂-, wherein R₃ is phenyl or halophenyl, particularly 4-halophenyl, especially fluorophenyl.

[0008] A first group of particularly interesting compounds are those compounds, wherein Alk is 1,2-ethanediyl or 1,3-propanediyl, R⁴ is hydrogen and X is oxygen or sulfur, preferably oxygen.

[0009] Another group of particularly interesting compounds are those compounds, wherein -Z-A- is a bivalent radical of formula -S-CH₂CH₂-, -S-CH₂CH₂CH₂-, or -S-CH₂CH₂CH₂CH₂-, or -CH=CH-O-.

[0010] Preferred compounds are:

6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2,5-dimethyl-7H-isoxazolo[2,3-a]pyrimidin-7-one ;
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl]ethyl]-2,9-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[3-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]propyl]-2,9-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-(phenylmethyl)-4H-pyrido[1,2-a]pyrimidin-4-one, the stereochemically isomeric forms and the pharmaceutically acceptable acid addition salts thereof.

[0011] Most preferred compounds are:

3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one
and the pharmaceutically acceptable acid-addition salts thereof.

[0012] The compounds of formula (I) can generally be prepared by N-alkylating an intermediate of formula (II) with an intermediate of formula (III). In formula (III) and the formulae hereinafter, W¹ represents a reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxyc group, e.g. methanesulfonyloxy, 4-methylbenzenesulphonyloxy and the like.

6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
6-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-2,5-dimethyl-7H-isoxazolo[2,3-a]pyrimidin-7-one ;
6-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl(ethyl)]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one ;
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl(ethyl)]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[2-[4-(3-benzo[b]thienyl)-1-piperidinyl(ethyl)]-2,9-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[3-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]propyl]-2,9-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
3-[2-[4-(6-fluoro-3-benzofuranyl)-1-piperidinyl(ethyl)]-2-(phenylmethyl)-4H-pyrido[1,2-a]pyrimidin-4-one, the stereochemically isomeric forms and the pharmaceutically acceptable acid addition salts thereof.

[0013] The reaction of (II) with (III) can conveniently be conducted in a reaction-inert organic solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, dimethylbenzene and the like; a lower alkanol, e.
g. methanol, ethanol, 1-butanol and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; N,N-dimethylformamide, N,N-dimethylacetamide, nitrobenzene, 1-methyl-2-pyridilidinone and the like. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, alkoxide or hydride, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride and the like, or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine and the like, may be useful to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of a iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I), can also be prepared following art-known cyclizing procedures for preparing pyrimidin-4-ones such as, for example, by reacting an amine of formula (IV) with a β-dicarbonyl derivative of formula (V) or by cyclizing a reagent of formula (VI) with an enamine of formula (VII). In formula (V) and in the formulae hereinafter each \( W^2 \) independently represents an appropriate leaving group such as, for example, hydroxy, halo, \( C_{1-4} \)alkyloxy, \( C_{1-4} \)alkylcarbonyloxy, amino, mono- or di(\( C_{1-4} \)alkyl)amino.

Said cyclization reactions may generally be carried out by stirring the reactants, optionally in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydrocarbon, e.g. hexane, cyclohexane or benzene and the like; or pyridine, N,N-dimethylformamide and the like dipolar aprotic solvents. Elevated temperatures may be appropriate to enhance the reaction rate; more in particular it may be advantageous to carry out the reaction at the reflux temperature of the reaction mixture.

Following the same procedure the compounds of formula (I) can also be prepared by cyclizing an intermediate of formula (VII) with a reagent of formula (VIII).

\[ \text{cyclization} \]

\[ \text{reaction} \]
The compounds of formula (I) wherein Z-A is a bivalent radical \(-\text{S-CH}_2\text{-CH}_2\) or \(-\text{S-CH}_2\text{-CH}_2\text{-CH}_2\) and wherein in said bivalent radicals one hydrogen may be replaced by \(\text{C}_{1-4}\) alkyl, said compounds being represented by the formula (I-a), can also be prepared by cyclizing a 2-mercaptopyrimidinone of formula (IX) with a reagent of formula (X), wherein \(n\) is 2 or 3 and wherein one hydrogen may be replaced by \(\text{C}_{1-4}\) alkyl.

The compounds of formula (I) wherein Z-A is a bivalent radical of formula \(-\text{S-CH=CH}\), wherein one hydrogen may be replaced by \(\text{C}_{1-4}\) alkyl, said compounds being represented by the formula (I-b), can be prepared by cyclizing a 2-mercapto-pyrimidinone of formula (IX) with a reagent of formula (XI) wherein one hydrogen atom may be replaced by \(\text{C}_{1-4}\) alkyl.

Said cyclization reactions for preparing the compounds of formulae (I-a) and (I-b) may generally be carried out by stirring the reactants, if desired, in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydrocarbon, e.g. hexane, cyclohexane or benzene and the like; or pyridine, \(\text{N},\text{N}\)-dimethyl-formamide and the like dipolar aprotic solvents. Elevated temperatures may be appropriate to enhance the reaction-rate, more in particular it may be preferred to carry out the reaction at the reflux temperature of the reaction mixture.

The compounds of formula (I) may also be converted into each other using art-known functional group transformations. For example, compounds of formula (I), wherein \(R^1\) is hydrogen may be converted into compounds of formula (I) wherein \(R^1\) is halo using art-known halogenation techniques.

A number of intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds. The intermediates of formula (III) and their preparations are described in U.S. Patent No. 4,804,663 and in the references cited therein.

The intermediates of formula (II) wherein \(X\) is oxygen, said intermediates being represented by formula (II-a), can be prepared by cyclizing an aldehyde of formula (XII) and deprotecting the intermediate of formula (XIII). In formula (XII) and the formulae hereinunder \(P\) represents a protective group such as for example \(\text{C}_{1-6}\) alkylcarbonyl and \(W^3\) represent a reactive leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo.
Said cyclization may conveniently be conducted by treating the aldehyde of formula (XII) with an appropriate base in an reaction-inert organic solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, dimethylbenzene and the like, an ether, e.g. 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and like; a dipolar aprotic solvent, such as, for example N,N-dimethylformamide, N,N-dimethylacetamide and the like. Appropriate bases are for example alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide, alkoxide, hydride, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride and the like, or an organic base such as a tertiary amine, e.g.

N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine and the like.

The intermediate aldehyde of formula (XII) can be prepared by reacting an epoxide of formula (XIV) with an acid, such as, for example, a mineral acid, e.g. perchloric acid, sulphuric acid and the like; a Lewis acid, e.g. boron trifluoride, magnesium dibromide, aluminium trichloride and the like. Appropriate solvents are water; alkanols, e.g. methanol, ethanol and the like; aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; ethers, e.g. 1,1'-oxybisethane, tetrahydrofuran and like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like. Stirring and elevated temperatures may enhance the rate of the reaction.

The epoxides of formula (XIV) can be obtained by stirring a ketone of formula (XV) with a sulphur ylide, such as dimethyloxosulfonium methylide or dimethylsulfonium methylide in an appropriate solvent, such as, for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 2,2'-oxybispropane and the like; a dipolar aprotic solvent, e.g. dimethylsulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide and the like.

The ketones of formula (XV) can be prepared by a Friedel-Crafts acylation of piperidines of formula (XVI) wherein W4 is a reactive leaving group such as for example hydroxy, halo, C1-4 carbonyloxy and the like, with benzenedederivative of formula (XVII). Said Friedel-Crafts acylation can be performed by stirring the reactants in the presence of an acid in a reaction-inert solvent, such as for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 2,2'-oxybispropane and the like; a dipolar aprotic solvent, e.g. dimethylsulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide and the like.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts have useful pharmacological properties. For example, the compounds of formula (I) possess anti-dopamine activity and show good affinity for several serotonin receptors, especially 5HT1A. Said compounds can also inhibit neuronal serotonin reuptake. Furthermore the compounds of formula (I) antagonize the action of reserpine (cfr. Example 3). Due to their pharmacological
activities, the compounds of formula (I) and their pharmaceutically acceptable acid addition salts can be used in the
5 treatment of psychotic diseases and in the treatment of a variety of complaints in which serotonin is of predominant
importance. The present compounds may block serotonin-induced contractions of bronchial tissues and of blood ves-
sels, arteries as well as veins. Particularly in view of their reserpine-antagonizing activity the compounds of formula (I)
also have useful properties as anti-depressants, anxiolytics, antitremor agents and show activity against obsessive
5 compulsive disorders, such as anorexia, bulimia and addiction, e.g. alcohol abuse.

[0026] The compounds of the present invention therefore may be used as medicines against above-mentioned con-
ditions. Said use as a medicine or method of treatment comprises the systemic administration to patients of an amount
effective to combat the conditions such as depression, anxiety, obsessive compulsive disorders, tremor and the like.

[0027] The subject compounds may be formulated into various pharmaceutical forms for administration purposes.
Said pharmaceutical forms or compositions are deemed novel and consequently constitute another aspect of the
present invention. Also the preparation of said compositions constitutes a further aspect of the present invention. To
prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or
5 acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable
carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration.
These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally,
rectally, percutaneously, or by parenteral injection.

[0028] For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may
be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such
as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders,
5 disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in admin-
istration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharma-
aceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water,
5 at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for
example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and
5 glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending
agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier option-
ally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable addi-
tives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions.
These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.
Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more
suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for
ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers
to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingre-
dient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Ex-
amples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets,
5 wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples there-
of.

[0029] In view of the usefulness of the subject compounds in the treatment of neurotransmitter mediated diseases
it is evident that the present invention provides a method of treating warm-blooded animals suffering from such dis-
edases, said method comprising the systemic administration of a pharmaceutically effective amount of a compound of
formula (I) or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutical carrier. Those
of skill in the treatment of diseases associated with neurotransmitters could easily determine the effective amount. In
general it is contemplated that an effective amount would be from 0.01 mg/kg to 4 mg/kg body weight, preferably from
0.04 mg/kg to 2 mg/kg body weight.

[0030] The exact dosage and frequency of administration depends on the particular compound of formula (I) used,
the particular condition being treated, the severity of the condition being treated, the age, weight and general physical
5 condition of the particular patient as well as other medication the individual may be taking, as is well known to those
skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on
the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds
of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore guidelines only and
are not intended to limit the scope or use of the invention to any extent.

[0031] The following examples are intended to illustrate and not to limit the scope of the present invention in all its
aspects. Unless otherwise stated all parts therein are by weight.
Experimental part

A. Preparation of intermediates

Example 1

[0032]

a) To a stirred mixture of 56 ml of 1,3-difluorobenzene, 130 g of aluminium chloride and 147 ml of dichloromethane, a solution of 95 g of 1-acetyl-4-piperidinecarbonyl chloride in 50 ml of dichloromethane was added dropwise while cooling. Upon completion, stirring was continued for 3 hours at room temperature. The reaction mixture was poured out into a mixture of crushed ice and hydrochloric acid. The product was extracted with dichloromethane. The organic layer was dried, filtered and evaporated, yielding 48 g (36%) of 1-acetyl-4-(2,4-difluorobenzoyl)piperidine as a residue (interm. 1).

b) 31.2 g of a dispersion of sodium hydride in mineral oil (50%) under a nitrogen atmosphere was washed twice with petroleum ether. There were added 230 ml of dimethyl sulfoxide. After stirring for 45 minutes at 70-75°C, the reaction mixture was cooled to a temperature of about 10°C. Then a suspension of 143 g of trimethylsulfoxonium iodide in 100 ml of dimethyl sulfoxide was added. The whole was stirred for 5 minutes and there was added a suspension of 135 g of intermediate (1) in 170 ml of tetrahydrofuran. The temperature was rised to 25-35°C, and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was poured out into crushed ice and the product was extracted with 2,2'-oxybispropane. The extract was stirred with activated charcoal, dried, filtered and evaporated, yielding 96g (68.3%) of 1-acetyl-4-[2-(2,4-difluorophenyl)oxiranyl]piperidine as an oily residue (interm. 2).

c) To a mixture of 96 g of intermediate (2) and 24.2 g of boron trifluoride etherate at room temperature were added 700 ml of benzene. After stirring for 45 minutes at reflux temperature, the reaction mixture was cooled and washed twice with petroleum ether. There were added 230 ml of dimethyl sulfoxide. After stirring for 45 minutes at 70-75°C, the reaction mixture was cooled to a temperature of about 10°C. Then a suspension of 143 g of trimethylsulfoxonium iodide in 100 ml of dimethyl sulfoxide was added. The whole was stirred for 5 minutes and there was added a suspension of 135 g of intermediate (1) in 170 ml of tetrahydrofuran. The temperature was rised to 25-35°C, and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was poured out into crushed ice and the product was extracted with dichloromethane. The extract was stirred with activated charcoal, dried, filtered and evaporated, yielding 80 g (83.6%) of 1-acetyl-(2,4-difluorophenyl)acetone as an oily residue (interm. 3).

d) 2.4 g of a dispersion of sodium hydride in mineral oil (50%) under a nitrogen atmosphere was washed twice with petroleum ether. There were added 60 ml of N,N-dimethylformamide. The whole was stirred at room temperature and a solution of 11.2 g of intermediate (3) in 40 ml of N,N-dimethylformamide was added dropwise. After stirring for 3 hours at 100-105°C, the reaction mixture was evaporated and the residue was washed with water. The product was extracted with dichloromethane. The extract was separated, dried, filtered and evaporated. The residue was stirred in acetonitrile and mixed with activated charcoal. The whole was filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH2Cl2/CH3OH 95/5). The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 9 g (86.1%) of 1-acetyl-(6-fluoro-3-benzofuranyl)piperidine (interm. 4).

e) A mixture of 63 g intermediate (4) in 630 ml of hydrochloric acid 6N was stirred for 3 hours at reflux temperature. After cooling, the reaction mixture was washed with methylbenzene. The mixture was stirred at room temperature and a precipitate was formed. The precipitate was filtered off and washed with some 2-propanone and dried, yielding 34 g (55.4%) of product (fraction 1). The filtrate was evaporated and the residual oil was dissolved in 2-propanone. This solution was stirred at room temperature and a precipitate was formed, yielding 9 g (15%) of product (fraction 2). Total yield: 43g (70.4%) of 4-(6-fluoro-3-benzofuranyl)piperidine hydrochloride; mp. 238.1°C; (interm. 5).

Example 2

[0033] A mixture of 3.8 g of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 3.8 g of intermediate (5), 10 g of sodium carbonate and a few crystals of potassium iodide in 180 ml of 4-methyl-2-pentanone was stirred overnight at reflux temperature. After cooling, the reaction mixture was poured out into water. The separated organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel (eluens: CH2Cl2/CH3OH 95/5). The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 3.8 g (62.5%) of 3-[2-(4-fluoro-3-benzofuranyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 159.8°C; (comp. 1).

[0034] In this manner were prepared:
<table>
<thead>
<tr>
<th>Co. No.</th>
<th>-Z-A-</th>
<th>R²</th>
<th>n</th>
<th>X</th>
<th>R¹</th>
<th>mp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-\text{CH}=\text{CH}-\text{CH}=\text{CH}-)</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>159.8°C</td>
</tr>
<tr>
<td>2</td>
<td>(-\text{(CH₂)₄}-)</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>164.7°C</td>
</tr>
<tr>
<td>3</td>
<td>(-\text{S-(CH₂)₂}-)</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>192.5°C</td>
</tr>
<tr>
<td>4</td>
<td>(-\text{S-CH=CH}-)</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>161.1°C</td>
</tr>
<tr>
<td>5</td>
<td>(-\text{CH=C(CH₃)-O-})</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>150.8°C</td>
</tr>
<tr>
<td>6</td>
<td>(-\text{S-CH=CH}-)</td>
<td>CH₃</td>
<td>2</td>
<td>S</td>
<td>H</td>
<td>135.8°C</td>
</tr>
<tr>
<td>7</td>
<td>(-\text{(CH₂)₄}-)</td>
<td>CH₃</td>
<td>2</td>
<td>S</td>
<td>H</td>
<td>122.8°C</td>
</tr>
<tr>
<td>8</td>
<td>(-\text{C(CH₃)=CH-CH=CH}-)</td>
<td>CH₃</td>
<td>2</td>
<td>S</td>
<td>H</td>
<td>161.3°C</td>
</tr>
<tr>
<td>9</td>
<td>(-\text{S-CH=C(CH₃)-})</td>
<td>CH₃</td>
<td>3</td>
<td>O</td>
<td>6-F</td>
<td>216.9°C</td>
</tr>
<tr>
<td>10</td>
<td>(-\text{S-(CH₂)₃}-)</td>
<td>CH₃</td>
<td>3</td>
<td>O</td>
<td>6-F</td>
<td>198.9°C</td>
</tr>
<tr>
<td>11</td>
<td>(-\text{S-(CH₂)₂}-)</td>
<td>CH₃</td>
<td>3</td>
<td>O</td>
<td>6-F</td>
<td>204.1°C</td>
</tr>
<tr>
<td>12</td>
<td>(-\text{C(=CH-C₆H₅)-(CH₂)₃}-)</td>
<td>CH₃</td>
<td>2</td>
<td>O</td>
<td>6-F</td>
<td>135.9°C</td>
</tr>
<tr>
<td>13</td>
<td>(-\text{S-CH=CH}-)</td>
<td>CH₃</td>
<td>3</td>
<td>O</td>
<td>6-F</td>
<td>186.9°C</td>
</tr>
<tr>
<td>14</td>
<td>(-\text{C(CH₃)=CH-CH=CH}-)</td>
<td>CH₃</td>
<td>3</td>
<td>O</td>
<td>6-F</td>
<td>104.7°C</td>
</tr>
</tbody>
</table>
C. Pharmacological example

Example 3: Reserpine Tremor Test

Female Wistar rats weighing 200-220 g were used. These test animals were food deprived for 24 hours. Said rats were pretreated orally (po) or subcutaneously (sc) with a test compound at 90 minutes before testing. This pre-treatment was followed by an intravenous injection of 2 mg/kg reserpine at 60 minutes before testing. Two control groups of 20 rats each were included in the experiment. The first control group consisted of rats that were only treated with a saline solution and the second control group consisted of animals which only received a saline reserpine solution.

At the start of the test, the rats were individually placed in specially designed test cages and tremor activity was measured continuously during a 15-min test session.

These test cages consisted of a plexiglass chamber. The floor of the test cage consisted of a plexiglass plate which was centered underneath the cage. The cage did not support onto this floor plate. The floor plate rested at its four corners on a rubber point of support. Two pieces of piezo-film were tied up next to each other underneath the middle of the floor plate. Said piezo-films were connected to an amplifier. The test cage was situated in a sound and light attenuating out box, being constantly illuminated and air-ventilated. The piezo-electric response, produced by deformation of the cage floor was amplified by an individual amplifier for each piezo-film separately. The sum of these signals was observed by a noise detection system which prevented further transmission if the signal was below the selected noise level of 100 mVolt. The tremor count in these experiments represented the appearance of 10 successive electrical signals that, after having been amplified and filtered, all exceeded a trigger level of 100 mVolt and differed no more than 400 mVolt from each other. The average activity of the control group that only received a saline solution was about 34 and the tremor activity of the reserpine treated control group was about 152 counts. On this basis, a compound was deemed active at a certain dose if the tremor activity is below 35 counts and deemed inactive when the tremor activity was above said count level. The activity of compounds are shown in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Co No</th>
<th>route</th>
<th>dose (mg/kg)</th>
<th>rats showing a tremor activity below 35 counts</th>
<th>rats tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>sc</td>
<td>2.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>sc</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>sc</td>
<td>2.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>sc</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>po</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

D. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 4: ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol
Example 5: ORAL SOLUTION

[0038] 9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 41 of boiling purified water. In 31 of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 6: CAPSULES

[0039] 20 Grams of the A.I., 6 grams sodium lauryl sulfate, 56 grams starch, 56 grams lactose, 0.8 grams colloidal silicon dioxide, and 1.2 grams magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, comprising each 20 mg of the active ingredient.

Example 7: FILM-COATED TABLETS

Preparation of tablet core

[0040] A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10,000 tablets, each containing 10 mg of the active ingredient.

Coating

[0041] To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 8: INJECTABLE SOLUTION

[0042] 1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Example 9: SUPPOSITORIES

[0043] 3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and triglycerides q.s. ad 300 grams were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Example 10: INJECTABLE SOLUTION

[0044] 60 Grams of A.I. and 12 grams of benzylalcohol were mixed well and sesame oil was added q.s. ad 1 l, giving
a solution comprising 60 mg/ml of A.I. The solution was sterilized and filled in sterile containers.

Claims

1. A compound having the formula

\[
\begin{align*}
\text{X} & \text{ is oxygen or sulphur;} \\
\text{R}^1 & \text{ is hydrogen or halo;} \\
\text{R}^2 & \text{ is hydrogen, C}_{1-4}\text{alkyl, phenylmethyl or halophenylmethyl;} \\
\text{Alk} & \text{ is C}_{1-4}\text{alkanediyl;} \\
\cdot\text{Z}\cdot\text{A} & \text{ is a bivalent radical selected from the group consisting of } \cdot\text{S}-\text{CH}_2-\text{CH}_2-, \\
& \cdot\text{S}-\text{CH}_2-\text{CH}_2-\text{CH}_2-, \cdot\text{CH}=\text{CH}-, \cdot\text{CH}=\text{CH}-\text{CH}=\text{CH}-, \\
& \cdot\text{C}=(\text{CHR}^3)-\text{CH}_2-\text{CH}_2-\text{CH}_2-, \cdot\text{CH}=\text{CH}-\text{O}-, \cdot\text{CHR}^4-\text{CH}_2-
\end{align*}
\]

wherein in said bivalent radicals one hydrogen may be replaced by C$_{1-4}$alkyl; 
R$^3$ is phenyl or halophenyl; and each R$^4$ independently represents hydrogen, hydroxy, phenylmethyl or halophenylmethyl.

2. A compound according to claim 1, wherein R$^1$ is hydrogen or fluoro, R$^2$ is C$_{1-4}$alkyl or phenylmethyl, R$^3$ is phenyl or 4-fluorophenyl, R$^4$ is hydrogen, phenylmethyl or 4-fluoromethylphenyl and Alk represents C$_{2-3}$alkanediyl.

3. A compound according to claim 1 or 2, wherein X is oxygen, Alk is 1,2-ethanediyl or 1,3-propanediyl and R$^4$ is hydrogen.

4. A compound according to claim 1 or 2, wherein X is sulfur, Alk is 1,2-ethanediyl or 1,3-propanediyl and R$^4$ is hydrogen.

5. A compound according to claim 1 or 2, wherein Z·A· is a bivalent radical of formula -S-CH$_2$-CH$_2$-, -S-CH=CH-, -S-CH$_2$-CH$_2$-CH$_2$-, -CH=CH-CH=CH-, -C(=CHR$_3$)-CH$_2$-CH$_2$-CH$_2$-, -CH=CH-O-, -CHR$_4$-CH$_2$-

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient a therapeutically effective amount of a compound as claimed in any of claims 1 to 6.

8. A process of preparing a composition as claimed in claim 7 characterized in that a therapeutically active amount of a compound as claimed in any of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.

9. A compound as claimed in any of claims 1 to 6 for use as a medicine.

10. A process for preparing an compound as claimed in claim 1, characterized by N-alkylating an intermediate of formula (II) with an intermediate of formula (III), wherein W$^1$ represents a reactive leaving group,
and, if desired, converting a compound of formula (I) into a therapeutically active non-toxic acid addition salt, or conversely, converting an acid addition salt into a free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

**Patentansprüche**

1. Verbindung der Formel

\[
\text{(III)} + \text{(II)} \rightarrow \text{(I)}
\]

ein pharmazeutisch unbedenkliches Säureadditionssalz davon oder eine stereochemisch isomere Form davon, wobei

- \( X \) für Sauerstoff oder Schwefel steht;
- \( R^1 \) für Wasserstoff oder Halogen steht;
- \( R^2 \) für Wasserstoff, \( C_{1-4}-\text{Alkyl}, \text{Phenylmethyl} \) oder Halogenphenylmethyl steht;
- \( \text{Alk} \) für \( C_{1-4}-\text{Alkandiyl} \) steht;
- \(-Z-A-\) für einen zweiwertigen Rest aus der Gruppe bestehend aus \(-\text{S-CH}_2-\text{CH}_2-, -\text{S-CH}_2-\text{CH}_2-\text{CH}_2-, -\text{S-CH=CH-}, -\text{CH=CH-CH=CH-}, -\text{C(=CHR}_3)-\text{CH}_2-\text{CH}_2-\text{CH}_2-, -\text{CH=CH-CH}=\text{CH}_2-\text{CH}_2-\text{CH}_2-, -\text{CH=CH-CH}=\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-, \)
- in den zweiwertigen Resten ein Wasserstoffatom durch \( C_{1-4}-\text{Alkyl} \) ersetzt sein kann;
- \( R^3 \) für Phenyl oder Halogenphenyl steht; und
- \( R^4 \) jeweils unabhängig voneinander für Wasserstoff, Hydroxy, Phenylmethyl oder Halogenphenylmethyl steht.

2. Verbindung nach Anspruch 1, in der \( R^1 \) für Wasserstoff oder Fluor, \( R^2 \) für \( C_{1-4}-\text{Alkyl} \) oder Phenylmethyl, \( R^3 \) für Phenyl oder 4-Fluorphenyl, \( R^4 \) für Wasserstoff, Phenylmethyl oder 4-Fluormethylphenyl und \( \text{Alk} \) für \( C_{2-3}-\text{Alkandiyl} \) steht.

3. Verbindung nach Anspruch 1 oder 2, in der \( X \) für Sauerstoff, \( \text{Alk} \) für \( 1,2-\text{Ethandiyl} \) oder \( 1,3-\text{Propandiyl} \) und \( R^4 \) für Wasserstoff steht.

4. Verbindung nach Anspruch 1 oder 2, in der \( X \) für Schwefel, \( \text{Alk} \) für \( 1,2-\text{Ethandiyl} \) oder \( 1,3-\text{Propandiyl} \) und \( R^4 \) für Wasserstoff steht.

5. Verbindung nach Anspruch 1 oder 2, in der \(-Z-A-\) für einen zweiwertigen Rest der Formel \(-\text{S-CH}_2-\text{CH}_2-, -\text{S-CH=CH-}, -\text{S-CH}_2-\text{CH}_2-\text{CH}_2-, -\text{CH=CH-CH}=\text{CH}_2-, -\text{CH=CH-CH}=\text{CH}_2-, -\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-, -\text{CH}=\text{C(CH}_3)_2-\text{O-} \) steht.

6. Verbindung nach Anspruch 1, bei der es sich um \( 3-[2-[4-(6-\text{Fluor-3-benzofuranyl})-1-\text{piperidinyl}[\text{ethyl}]-2-\text{methyl-} \)
EP 0 672 043 B1

4H-pyrido-[1,2-a]pyrimidin-4-on, 6-[2-[4-(6-Fluor-3-benzofuranyl)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo-[3,2-a]
pyrimidin-5-on oder ein pharmazeutisch unbedenkliches Säureadditionssalz davon handelt.

7. Pharmazeutische Zusammensetzung, enthaltend einen pharmazeutisch unbedenklichen Träger und als Wirkstoff
eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6.

8. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 7, dadurch gekennzeichnet, daß man eine
therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6 innig mit einem pharmazeutisch
unbedenklichen Träger mischt.

9. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als Arzneimittel.

10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß man ein Zwischen-
produkt der Formel (II) mit einem Zwischenprodukt der Formel (III), worin W¹ für eine reaktive Abgangsgruppe
steht, N-alkyliert

und gegebenenfalls eine Verbindung der Formel (I) in ein therapeutisch wirksames, nicht toxisches Säureadditionssalz
oder umgekehrt ein Säureadditionssalz mit Alkali in die freie Base überführt und/oder stereochemisch
isomere Formen davon herstellt.

Revendications

1. Composé de formule

sel d’addition à un acide pharmaceutiquement acceptable de celui-ci et forme stéréochimiquement isomère de
celui-ci, dans laquelle

X est un oxygène ou un soufre ;
R¹ est un hydrogène ou un halogéno ;
R² est un hydrogène, un alky en C₁-₄, un phénylméthyle ou un halogénophénylméthyle ;
Alk est un C₁-₄-alcandiyile ;
-Z-A- est un radical bivalent choisi parmi le groupe constitué de -S-CH₂-CH₂-, -S-CH₂-CH₂-CH₂-, -S-CH=CH-, -CH=CH-CH=CH-, -S-CH₂-CH₂-CH₂-, -S-CH=CH-CH₂-, -CH=CH-O-, -CH=CH-CH₂-, -CH=CH-CH₂-CH₂-, -CH=CH-CH₂-CH₂-CH₂-, -CH=CH-CH₂-CH₂-CH₂-CH₂- ;

où dans lesdits radicaux bivalents, un hydrogène peut être remplacé par un alky en C₁-₄ ;
R³ est un phényle ou un halogénophényle ; et
dans chaque R⁴ représente indépendamment un hydrogène, un hydroxy, un phénylméthyle ou un halogénophé-
nylméthyle.

14
2. Composé selon la revendication 1, dans lequel R\(^1\) est un hydrogène ou un fluoro, R\(^2\) est un alkyle en C\(_{1-4}\) ou un phénylméthyle, R\(^3\) est un phényle ou un 4-fluorophényle, R\(^4\) est un hydrogène, un phénylméthyle ou un 4-fluorométhylphényle et Alk représente un C\(_{2-3}\)-alcanediyle.

3. Composé selon la revendication 1 ou 2, dans lequel X est un oxygène, Alk est 1,2-éthanediyile ou 1,3-propanediyle et R\(^4\) est un hydrogène.

4. Composé selon la revendication 1 ou 2, dans lequel X est un soufre, Alk est 1,2-éthanediyile ou 1,3-propanediyle et R\(^4\) est un hydrogène.

5. Composé selon la revendication 1 ou 2, dans lequel -Z-A- est un radical bivalent de formule -S-CH\(_2\)-CH\(_2\)-, -S-CH=CH-, -S-CH\(_2\)-CH\(_2\)-CH\(_2\)-, CH=CH-CH=CH-, -CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_2\)- ou -CH=CH(CH\(_3\))-O-.

6. Composé selon la revendication 1, dans lequel le composé est la 3-[2-[4-(6-fluoro-3-benzofuranyl)-1-pipéridinyl]éthyl] 2-méthyl-4\(H\)-pyrido[1,2-a]pyrimidin-4-one, la 6-[2-[4-(6-fluoro-3-benzofuranyl)-1-pipéridinyl]éthyl]-7-méthyl-5\(H\)-thiazolo[3,2-a]pyrimidine-5-one ou un sel d'addition à un acide pharmaceutiquement acceptable de celles-ci.

7. Composition pharmaceutique comprenant un support pharmaceutiquement acceptable et, en tant qu'ingrédient actif, une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 6.

8. Procédé de préparation d'une composition selon la revendication 7, caractérisé en ce qu'une quantité thérapeutiquement active d'un composé selon l'une quelconque des revendications 1 à 6 est mélangée intimement avec un support pharmaceutiquement acceptable.

9. Composé selon l'une quelconque des revendications 1 à 6 destiné à être utilisé en tant que médicament.

10. Procédé de préparation d'un composé selon la revendication 1, caractérisé par la N-alkylation d'un intermédiaire de formule (II) avec un intermédiaire de formule (III), dans laquelle W\(^1\) représente un groupe partant réactif, et, si on le souhaite, la transformation d'un composé de formule (I) en sel d'addition à un acide thérapeutiquement actif et non toxique, ou inversement, la transformation d'un sel d'addition à un acide en une forme basique libre avec un alcali ; et/ou la préparation de formes stéréochimiquement isomères de celui-ci.