EUROPEAN PATENT SPECIFICATION

Date of publication of patent specification: 02.05.91 Bulletin 91/18
Application number: 86901539.6
Date of filing: 31.01.86
International application number: PCT/SE86/00038
International publication number: WO 86/04584 14.08.86 Gazette 86/18

PIPERAZINECARBOXAMIDES HAVING A PHENOXYALKYL OR THIOPHENOXYALKYL SIDE CHAIN.

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

Priority: 08.02.85 SE 8500573
Date of publication of application: 04.03.87 Bulletin 87/10
Date of grant of the patent: 02.05.91 Bulletin 91/18
Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

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Description

Background of the Invention

Drugs in use today for the treatment of mental disorders most often are associated with serious side effects. Antipsychotic drugs commonly cause disturbing extrapyramidal symptoms, and long term treatment may result in tardive dyskinesia. Antidepressants often exhibit cardiotoxicity, and anxiolytic drugs have addicting properties. As a result of these drawbacks efforts are being made to find new pharmacologically active drugs which have fewer side effects.

The present invention relates to novel piperazine- and homopiperazinecarboxamides bearing a phenoxyalkyl or thiophenoxyalkyl side chain, which exhibit valuable pharmacological properties, and which have a low tendency to cause side effects.

Pharmacologically valuable piperazine-carboxamides are previously known from GB-A-2,037,745. However, the compounds according to the British application differ from the compounds according to the present invention in being substituted in the 4-position with a very lipophilic 4,4-diphenylbutyl group. Furthermore, these previous compounds are very active in pharmacological models which may indicate potentiation of noradrenaline and serotonin (e.g. inhibition of muricide behaviour), which in turn may cause unwanted side effects, e.g. anorexigenic. The compounds of the present invention are considerably less active in these pharmacological models indicating that fewer side effects are to be expected when compounds according to the present invention are used.

Piperazinecarboxamides substituted in the 4-position with a butyrophenone side chain are known from Collect. Czech. Chem. Commun 1975, 40(4), 1218-30 C.A. 83 (1975), 31539u. The butyrophenone side chain is chemically distinctly different from a phenoxyalkyl or thiophenoxyalkyl group. Besides, the authors state that their compounds display CNS-activity only at high doses.


Description of the Invention

According to the invention there are provided novel compounds having the general formula:

![Chemical structure formula]

(wherein \( \text{R}_1 \) is selected from fluoro, chloro or bromo

X is oxygen or sulfur;

m is 2 or 3;

Y is oxygen or sulfur;

Z is selected from:

\(-\text{NR}_2\text{R}_3\)

or

\(-\text{NR}_2\text{R}_3\)

or

\(-\text{NR}_2\text{R}_3\)
wherein $R_2$ and $R_3$ are the same or different and selected from hydrogen, C$_{1-10}$ alkyl, C$_{3-8}$ cycloalkyl, C$_{6-4}$ cycloalkyl C$_{1-10}$ alkyl, hydroxy-C$_{1-10}$ alkyl, C$_{1-10}$ alkoxy C$_{1-10}$ alkyl or C$_{1-10}$ alkanoyloxy C$_{1-10}$ alkyl, phenyl or phenyl-C$_{1-10}$ alkyl, wherein the phenyl groups may be monosubstituted with halogen or CF$_3$;
$n$ is 0, 1, 2 or 3;
$R_4$ and $R_5$ are the same or different and selected from hydrogen, C$_{1-4}$ alkyl, hydroxy, C$_{1-4}$ alkoxy or C$_{1-4}$ alkanoyloxy;
$p$ is 2 or 3;
$R_6$ and $R_7$ are the same or different and selected from hydrogen or C$_{1-4}$ alkyl;
$R_8$ is hydrogen, C$_{1-4}$ alkyl or C$_{1-4}$ alkanoyl,
and the pharmaceutically active salts thereof.

The compounds of formula (I) have basic properties and consequently they may be converted to their therapeutically active acid addition salts by treatment with appropriate acids; e.g. inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric 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.

In the compounds of the general formula (I) it is preferred that $R_4$ is situated in the m- or p-position.

It is preferred that X is oxygen.

It is preferred that $m = 2$.

It is preferred that $Y$ is oxygen.

When $Z$ is NR$_2$R$_3$ those compounds are preferred wherein $R_2$ and $R_3$ together contain less than ten carbon atoms.

Also, as regards the substituents $R_2$ and $R_3$ those compounds are preferred wherein $R_2$ and $R_3$ are selected from hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and hydroxyalkyl, especially alkyl and cycloalkyl.

As regards the substituents $R_4$ and $R_5$ it is preferred that one of them is hydrogen and the other hydrogen or lower alkyl.

As regards the substituents $R_6$ and $R_7$ those compounds are preferred wherein both of them are hydrogen.

When $Z$ is a heterocyclic ring containing two heteroatoms, it is preferred that one of the heteroatoms is oxygen.

Also as regards Z it is preferred that Z does not contain any asymmetric carbon atoms.

The following compounds are preferred:
4-[3-(p-fluorophenoxo) propyl]-N-methyl-1-piperazinecarboxamide
4-[3-(p-fluorophenoxo) propyl]-N-ethyl-1-piperazinecarboxamide
4-[3-(p-fluorophenoxo) propyl]-N-cyclopropyl-1-piperazinecarboxamide
4-[3-(m-fluoromethyl-phenoxo) propyl]-N-ethyl-1-piperazinecarboxamide
4-[3-(p-fluorophenoxo) propyl]-N-methyl-1-piperazinethiocarboxamide
4-[3-(p-fluoroisophenoxo) propyl]-N-methyl-1-piperazinecarboxamide
4-[3-(p-fluoroisophenoxo) propyl]-N-ethyl-1-piperazinecarboxamide
4-[3-(p-fluoroisophenoxo) propyl]-N-cyclopropyl-1-piperazinecarboxamide
4-[3-(p-fluoroisophenoxo) propyl]-N-methyl-1-piperazinethiocarboxamide
4-[3-(p-fluoroisophenoxo) propyl]-N,N-dimethyl-1-piperazinecarboxamide
1-morpholinocarbonyl-4-[3-(p-fluoroisophenoxo) propyl]-piperazine

The compounds of formula (I) and their pharmaceutically acceptable salts have valuable pharmacological properties making them useful for treatment of mental disorders such as psychoses, depression and anxiety. For example they may be useful for the prophylaxis and/or treatment of schizophrenia, mania or senile, involitional or organic psychoses as well as depressive psychoses, depression and anxiety.

Psychosomatic disorders caused by anxiety and stress should be alleviated by compounds of formula (I).

The new compounds may also be used in the prophylaxis and treatment of aggressive behaviour, which may be associated with mentally retarded and/or behaviourally disturbed patients and other form of aggression of either known or unknown etiology.
The new compounds may be useful in the treatment of aggressive behaviour in animals, especially in pigs, and also in promoting the development of a natural hierarchy in groups of animals without bursts of aggression and in calming of anxious and stressed animals.

The compounds of formula (I) have a clear limbic profile of action and are thus not likely to cause extrapyramidal side effects. This is evidenced by their ability to inhibitamphetamine induced loomotion in mice, whereas they do not block amphetamine induced stereotypies. Their ability to inhibit isolation induced aggression in male mice is also the result of activity in limbic brain areas. Extrapyramidal side effects are highly undesirable and are commonly seen with antipsychotics in clinical use today.

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.

The compounds of formula (I) may be used in various slow release formulations.

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 25, 50 or 100 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 200 milligrams, preferably from 10 to 50 milligrams. Daily dosages should preferably range from 10 milligrams to 400 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**

\[
\begin{align*}
\text{II} & \quad \text{III} \\
\text{X-CH}_2\text{CH}_2\text{CH}_2\text{M} & \quad \text{HN} \\
& \quad \text{Y} \\
& \quad \text{Z} \\
& \quad \text{(CH}_2\text{)}_m
\end{align*}
\]

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

**Method 2**

\[
\begin{align*}
\text{IV} & \quad \text{R}_2\text{-NCO} \quad \text{(V)} \\
& \quad \text{R}_2\text{-NCS} \quad \text{(VI)} \\
& \quad \text{L-C-Z} \quad \text{(VII)}
\end{align*}
\]

A compound of formula (IV), wherein R, X and m are as defined above, is reacted with an isocyanate of formula (V) or an isothiocyanate of formula (VI) or a carbamoyl derivative of formula (VII), wherein R, Y and Z are as previously defined, and wherein L is a suitable leaving group such as halogen, phenoxy and substituted phenoxy (e.g. p-nitrophenoxy). The reactions may be carried out using standard procedures. The addition of an appropriate base may in some instances facilitate the reaction, and may if acid is formed during the reaction serve to neutralize this.
Method 3

\[
\begin{align*}
\text{VIII} & \quad \text{IX} \\
R_1 & \quad \text{M-CH}_2\text{CH}_2\text{CH}_2-\text{N} \quad \text{N} \\
& \quad \text{CH}_2\text{CH}_2-\text{N} \\
& \quad \text{Y} \\
& \quad \text{Z}
\end{align*}
\]

A compound of formula (VIII) wherein \( R_1 \) and \( X \) are as previously defined is reacted with a compound of formula (IX) wherein \( M, m, Y \) and \( Z \) are as defined previously. The reaction is carried out using standard phenolate or thiophenolate alkylating conditions.

Method 4

\[
\begin{align*}
\text{X} & \quad \\
R_1 & \quad \text{X-CH}_2\text{CH}_2\text{CH}_2-\text{N} \\
& \quad \text{N} \\
& \quad \text{CH}_2\text{CH}_2-\text{N} \\
& \quad \text{Y} \\
& \quad \text{L}
\end{align*}
\]

A compound of formula (X) wherein \( R_1, X, m, Y \) and \( L \) are as defined above is reacted with a compound of formula Z-H wherein \( Z \) is as previously defined. The reaction is carried out using standard procedures. When \( L \) is a poor leaving group and/or when \( Z-H \) is a poor nucleophile it may be advantageous to use a large excess of \( Z-H \) and/or to heat the reaction mixture for a longer period of time.

The intermediate X may be prepared by standard procedures according to:

Method 5

\[
\begin{align*}
\text{IV} + \text{L-C-L'} & \quad \rightarrow \quad \text{X} \\
& \quad \text{XI}
\end{align*}
\]

A compound of formula IV is reacted with a compound of formula XI wherein \( L \) and \( Y \) are as previously defined, and \( L' \) is a suitable leaving group such as halogen, phenoxy and substituted phenoxy (e.g. \( p \)-nitrophenoxy). Most commonly at least one of \( L \) and \( L' \) is halogen. The reaction is preferably performed in an inert solvent, and an appropriate base may be added to take care of the acid formed during the reaction.

The intermediate IV may be prepared by conventional methods according to:

Method 6

\[
\begin{align*}
\text{II} & \quad \\
R_1 & \quad \text{X-CH}_2\text{CH}_2\text{CH}_2-\text{M} \\
& \quad \text{HN} \\
& \quad \text{NH} \\
& \quad \text{CH}_2\text{CH}_2-\text{m} \\
& \quad \text{IV}
\end{align*}
\]

A compound of formula II is reacted with an excess of amine, using standard N-alkylating conditions.

Examples

The following examples are intended to illustrate the scope of the invention; 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 compounds are confirmed by NMR, mass spectra and elementary analysis. When melting points are given, these are uncorrected.

Example 1

3.6 g (0.015 mole) of 1-[3-(p-fluoroophenoxo) propyl]-piperazine was dissolved in 20 ml of toluen and cooled in an ice bath. 0.9 g (0.015 mole) of methylisocyanate dissolved in 35 ml of toluene was added dropwise during 15 minutes. The reaction mixture was allowed to reach room temperature and the solvent was subsequently removed by evaporation. The residue was recrystallized from toluene/ligroin to yield 4.2 g of 4-[3-(p-fluorophenoxy) propyl]-N-methyl-1-piperazinecarboxamide (1 : 1), M.p. 122-123°C.

The corresponding hydrochloride (1 : 2) was prepared by dissolving 4.0 g of the base in ether/abs. ethanol and adding and excess of HCl in ethanol. The hydrochloride which precipitated was recrystallized from abs. ethanol. Yield 3.6 g, m.p. 222-224°C.

Using essentially the same procedure the following compounds are prepared (isolated as the free bases or as the corresponding salts) from the corresponding starting materials.

1 : 3 4-[3-(p-fluoroophenoxy) propyl]-N-ethyl-1-piperazinecarboxamide hydrochloride, m.p. 211-212°C
1 : 4 4-[3-(p-fluoroophenoxy) propyl]-N-cyclopropyl-1-piperazinecarboxamide hydrochloride, m.p. 217-218°C
1 : 5 4-[3-(p-fluoroophenoxy) propyl]-N-(1-methylethyl)-1-piperazinecarboxamide
1 : 6 4-[3-(p-fluoroophenoxy) propyl]-N-hexyl-1-piperazinecarboxamide
1 : 7 4-[3-(p-fluoroophenoxy) propyl]-N-cyclohexyl-1-piperazinecarboxamide
1 : 8 4-[3-(p-fluoroophenoxy) propyl]-N-(2-propenyl)-1-piperazinecarboxamide
1 : 9 4-[3-(p-chloroophenoxy) propyl]-N-ethyl-1-piperazinecarboxamide
1 : 10 4-[3-(m-trifluoromethyl-phenoxy) propyl]-N-ethyl-1-piperazinecarboxamide hydrochloride, m.p. 196-198°C
1 : 11 4-(3-phenoxypyropyl)-N-ethyl-1-piperazinecarboxamide
1 : 12 4-[3-(p-fluoroophenoxy) propyl]-N-methyl-1-piperazinethiocarboxamide hydrochloride, m.p. 182-183°C
1 : 13 4-[3-(p-fluorothiophenoxo) propyl]-N-ethyl-1-piperazinecarboxamide hydrochloride, m.p. 195-197°C
1 : 14 4-[3-(p-fluorothiophenoxo) propyl]-N-cyclopropyl-1-piperazinecarboxamide
1 : 15 4-[3-(p-fluorothiophenoxo) propyl]-N-methyl-1-piperazinethiocarboxamide
1 : 16 4-[3-(p-fluoroophenoxy) propyl]-2,5-trans-dimethyl-N-ethyl-1-piperazinecarboxamide
1 : 17 4-[3-(p-fluoroophenoxy) propyl]-2,5-trans-dimethyl-N-cyclopropyl-1-piperazinecarboxamide
1 : 18 4-[3-phenoxypyropyl]-2,5-trans-dimethyl-N-(1-methylthyl)-1-piperazinecarboxamide hydrochloride, m.p. 185-186°C
1 : 19 4-[3-(p-fluoroophenoxy) propyl]-N-ethyl-1-(1,4-diazacycloheptane-1,4-carboxamide)
1 : 20 4-[3-(p-fluoroophenoxy) propyl]-N-cyclohexyl-1-(1,4-diazacycloheptane-1,4-carboxamide) hydrochloride, m.p. 221-224°C (dec.)
1 : 21 4-[3-(p-fluorothiophenoxo) propyl]-N-ethyl-1-(1,4-diazacycloheptane-1,4-carboxamide)
1 : 22 4-[3-(p-fluoroophenoxy) propyl]-N-phenyl-1-piperazinecarboxamide hydrochloride, m.p. 202-203°C
1 : 23 4-[3-(p-fluoroophenoxy) propyl]-N-p-chlorophenyl-1-piperazinecarboxamide
1 : 24 4-[3-(p-fluoroophenoxy) propyl]-N-phenylmethyl-1-piperazinecarboxamide

Example 2

70 g (0.03 mol) of 1-[3-(p-fluoroophenoxy) propyl]-piperazine was dissolved in 45 ml of conc. acetic acid. 3.2 g (0.04 mol) KOCN was dissolved in 20 ml of H2O and added to the reaction mixture which subsequently was stirred 20 h at RT.

After cooling to 0°C the reaction mixture was made basic by addition of 5N NaOH. The product separated slowly by crystallization and was filtered off. It was dissolved in CH2Cl2 and the solution was washed with H2O, dried with Na2SO4 and the solvents evaporated. The residual oil crystallized and was recrystallized from toluene/ligroin to yield 5.9 g of 4-[3-(p-fluoroophenoxy) propyl]-1-piperazin ecarboxamide (2 : 1), m.p. 98-100°C.

The corresponding hydrochloride was prepared by dissolving 5.5 g of the base in SO ml of a mixture of
abs. ethanol/ether. Addition of an excess of HCl in ethanol and additional ether precipitated the hydrochloride. After recrystallization from isopropanol 4.7 g of the hydrochloride (2:2) was obtained, m.p. 209-210°C.

Using essentially the same procedure (heating of the reaction mixture is required) the following compound is prepared from the corresponding starting materials:

2:3 4-[3-(p-fluorophenoxy)propyl]-1-piperazinethiocarboxamide

Example 3

12.5 g (0.031 mol) of p-nitrophenyl-4-[3-(p-fluorophenoxy)propyl]-1-piperazine carboxylate was stirred in a mixture of 20 ml of dimethylamine and 20 ml of THF at 0°C for 3 days. The reaction mixture was partitioned between ether and H₂O. The ether phase was washed twice with a Na₂CO₃ solution and twice with NaCl-solution. The mixture was dried with Na₂SO₄. After filtration excess of HCl in ethanol was added to precipitate the hydrochloride. After filtration and recrystallization from ethyl acetate/ethanol was obtained 5.5 g of 4-[3-(p-fluorophenoxy) propyl]-N,N-dimethyl-1-piperazinethiocarboxamide, hydrochloride (3:1), m.p. 185-187°C.

Using essentially the same procedure (sometimes omitting the cosolvent THF and heating in the case of more reactive amines) the following compounds were prepared (isolated as the free bases or as the corresponding salts) from the corresponding starting materials.

Example 4

25 g (0.105 mol) of 1-[3-(p-fluorophenoxy)propyl]-piperazine was dissolved in 300 ml of toluene, 20 ml of triethylamine was added and the mixture was cooled to 0°C. 21.2 g (0.105 mol) of p-nitrophenyl-chloroformate in 300 ml of toluene was added dropwise. The reaction mixture was stirred at RT for 3 h. The triethylamine hydrochloride was filtered off and the solvents were evaporated. The residue was dissolved in methanol and the product was allowed to crystallize overnight. The product was filtered off to yield 25 g of p-nitrophenyl-4-[3-(p-fluorophenoxy)propyl]-1-piperazine-carboxylate (4:1), m.p. 101-102°C.

Example 5

82 g (0.43 mol) of 1-chloro-3-(p-fluorophenoxy)-propane and 262 g of piperazine were dissolved in 700 ml of isopropanol and refluxed for 16 h. The reaction mixture was allowed to reach RT and piperazine which had precipitated was filtered off. The solvents were evaporated and the residue was dissolved in CH₂Cl₂. After washing with sat. NaCl-solution and drying with Na₂SO₄ the CH₂Cl₂ was evaporated and the residue distilled to yield 75 g of 1-[3-(p-fluorophenoxy)propyl]-piperazine (5:1), b.p. 104-106°C (0.05 mm Hg).

Example 6

This example illustrates the potency of compounds of formula (I) and their pharmaceutically active acid addition salt for treatment of mental disorders.

Test: Isolation induced aggressive behaviour test

Male mice subjected to prolonged isolation develop aggressive behaviour against each other when paired (Yen, C.Y. et al., Arch. Int. Pharmacodyn. 123, 179, (1959); Valzelli, L., Adv. Pharmacol. 5, 79 (1967). All clinically used neuroleptics and antidepressants studied in this test inhibit this aggressive behaviour although their activity may differ. Also anxiolytic drugs, e.g. diazepam, are active on this kind of aggressive behaviour. The
clinical correlation of this test indicates tranquilizing and anxiolytic activities as well as antiaggressive properties as such (Duncan, R.L. et al., J Med. Chem. 13, 1 (1970)).

This type of aggression is interesting because it is known that this kind of emotional behaviour might be located in limbic structures in the brain (MacLean, P.D., Psychosom. Med. 11, 335 (1949)).

Every week male NMRI mice, weighing 20-22 g, were isolated in Makroten cages for three weeks with diet and water ad libitum. A piece of cardboard was placed between the cages to prevent visual contact.

To test aggressiveness the mice were paired in a neutral area, a beaker (14 cm high and diameter 14 cm). A pair is considered aggressive if both the animals show clear signs of fighting within 5 minutes. This fighting is characterized by biting and vocalization. As soon as fighting is seen, the mice are separated and brought to their home cage (every second mouse is marked). If only one of two mice exhibit aggressive behaviour the aggressive one is paired with another to make a well matched, aggressive pair. Animals showing no aggression are discarded.

The frequency of paired mice exhibiting fighting varies from 50-100 per cent depending on the time of the year. The test substance is administered s.c. (0.2-0.4 ml/20 g). The mice are paired 0.5 hour after the injection for trials of 5 minutes' duration.

The ED50-value (mg/kg) reported is the dose inhibiting aggressive behaviour among 50 per cent of the pairs 0.5 hour after drug administration.

Table

Isolation induced aggressive behaviour test

<table>
<thead>
<tr>
<th>Compound</th>
<th>ED50 mg/kg s.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:3</td>
<td>5</td>
</tr>
<tr>
<td>Thioridazine a)</td>
<td>5</td>
</tr>
<tr>
<td>Diazepam b)</td>
<td>6.7</td>
</tr>
</tbody>
</table>

a) Merck Index, 10th Ed., 9202
b) = = = = 2967

Example 7

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

Per capsule, mg

<table>
<thead>
<tr>
<th>Active ingredient, as salt</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>250</td>
</tr>
<tr>
<td>Starch</td>
<td>120</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>385</td>
</tr>
</tbody>
</table>

In case of higher amounts of active ingredient, the amount of lactose used may be reduced.

Example of a suitable tablet formulation:
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 an aqueous solution of 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 pharmaceutical preparations may also contain therapeutically useful substances other than the pharmacologically active compounds of formula (I).

Claims

1. Compounds having the general formula:

\[
\begin{align*}
R_1 & \quad X-(CH_2)_3-N-C\quad Y \\
& \quad (CH_2)_m \\
& \quad Z \\
\end{align*}
\]

wherein R₁ is selected from fluoro, chloro or bromo
X is oxygen or sulfur;
m is 2 or 3;
Y is oxygen or sulfur;
Z is selected from:

\[-NR_2R_3\]

or

\[
\begin{align*}
R_6 & \quad -N-(CH_2)_n \\
R_5 & \quad -N-(CH_2)_p \\
\end{align*}
\]

\[
\begin{align*}
R_7 & \quad -N-(CH_2)_p \\
R_8 & \quad N-R_8 \\
\end{align*}
\]

wherein R₃ and R₆ are the same or different and selected from hydrogen, C₁-10 alkyl, C₃-8 cycloalkyl, C₃-8 cycloalkyl C₁-10 alkyl, hydroxy-C₁-10 alkyl, C₁-10 alkoxy C₁-10 alkyl or C₁-10 alkoxy C₁-10 alkyl, phenyl or phenyl-C₁-10 alkyl, wherein the phenyl groups may be monosubstituted with halogen or CF₃;
n is 0, 1, 2 or 3;
R₄ and R₅ are the same or different and selected from hydrogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy or C₁₋₄ alkanoyloxy;

p is 2 or 3;

R₆ and R₇ are the same or different and selected from hydrogen or C₁₋₄ alkyl;

R₆ is hydrogen, C₁₋₄ alkyl or C₁₋₄ alkanoyl,

and the pharmaceutically active salts thereof.

2. A compound according to claim 1 characterized in that Z is selected from the group consisting of

- \( \text{NR}_2\text{R}_3 \)

or

- \( \text{N} \)

or

- \( \text{O} \)

R₂ and R₃ are selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and hydroxy-alkyl as defined in claim 1;

one of R₄ and R₅ is hydrogen and the other is hydrogen or C₁₋₄ alkyl;

and that R₆ and R₇ are hydrogen.

3. A compound according to any of the claims 1-2 characterized in that m = 2.

4. A compound according to any of the claims 1-3 characterized in that X and Y are oxygen.

5. A compound according to claim 1-5 characterized in that R₄ is F.

6. A compound according to claim 1 selected from the following group:

- 4-[3-(p-fluorophenoxo) propyl]-N-methyl-1-piperazinetricarboxamide
- 4-[3-(p-fluorophenoxo) propyl]-N-ethyl-1-piperazinetricarboxamide
- 4-[3-(p-fluorophenoxo) propyl]-N-cyclopropyl-1-piperazinetricarboxamide
- 4-[3-(p-fluorophenoxo) propyl]-N-methyl-1-piperazinethiocarboxamide
- 4-[3-(p-fluorophenylmercapto) propyl]-N-methyl-1-piperazinetricarboxamide
- 4-[3-(p-fluorophenylmercapto) propyl]-N-ethyl-1-piperazinetricarboxamide
- 4-[3-(p-fluorophenoxo) propyl]-NN-dimethyl-1-piperazinetricarboxamide
- 1-morpholinocarbonyl-4-[3-(p-fluorophenoxo) propyl]-piperazine

7. A method for the preparation of a compound according to claim 1 by

a) reacting a compound II

wherein X and R₁ are as defined in claim 1 and M is a leaving group, with a compound

- \( \text{HN} \)

\( \text{N} \)

\( \text{Y} \)

\( \text{Z} \)

(\( \text{CH}_2 \))ₘ

III

wherein Y, Z and m are as previously defined in claim 1

b) reacting a compound IV

wherein X, CH₂, CH₂, Z and \( \text{NH} \) (\( \text{CH}_2 \))ₘ

IV
wherein R₁, X and m are as defined in claim 1, with an isocyanate, R₂-NCO (V), wherein R₂ is as defined claim 1, or an isothiocyanate, R₂-NCS, (VI), wherein R₂ is as previously defined, or a carbamoyl derivative, L-CY-Z (VII), wherein Y and Z are as previously defined and L is a leaving group, c) reacting a compound VIII

\[
\text{VIII}
\]

wherein R₁ and X are as previously defined, with a compound

\[
\text{IX}
\]

wherein M, m, Y and Z are as previously defined, or
d) reacting a compound

\[
\text{X}
\]

wherein Rₙ, m, X, Y and L are as previously defined with a compound Z-H, wherein Z is as previously defined.

8. Method according to claim 7 characterized in that Z is selected from the group consisting of

\[
-\text{NR}_2\text{R}_3
\]

\[
-\text{N}(\text{CH}_2)_n
\]

\[
-\text{N}(\text{CH}_2)_p
\]

wherein R₂ and R₃ are selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and hydroxyalkyl as defined in claim 1 of R₄ and R₅ is hydrogen and the other is hydrogen or C₁₋₄ alkyl; and that R₆ and R₇ are hydrogen.

9. Method according to claim 7 characterized in that the compound prepared is selected from the following group:
4-[3-(p-fluorophenoxy) propyl]-N-methyl-1-piperazincarboxamide
4-[3-(p-fluorophenoxy) propyl]-N-ethyl-1-piperazincarboxamide
4-[3-(p-fluorophenoxy) propyl]-N-cyclopropyl-1-piperazincarboxamide
4-[3-(p-fluorophenoxy) propyl]-N-methyl-1-piperazinethiocarboxamide
4-[3-(p-fluorophenylmercapto) propyl]-N-methyl-1-piperazincarboxamide
4-[3-(p-fluorophenylmercapto) propyl]-N-ethyl-1-piperazincarboxamide
4-[3-(p-fluorophenoxy) propyl]-NN-dimethyl-1-piperazincarboxamide
1-morpholinocarboxy-4-[3-(p-fluorophenoxy) propyl]-piperazine

10. Pharmaceutical compositions containing as an active ingredient one or more of the compounds according to claim 1, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.
Ansprüche

1. Verbindungen der allgemeinen Formel

\[
\begin{array}{c}
\text{R}_{1} \quad \text{X} - (\text{CH}_2)_{3} - \text{N} - \text{C} - \text{Y} \\
(\text{CH}_2)_{n} \\
\end{array}
\]

wobei \( \text{R}_1 \) ausgewählt ist aus Fluor, Chlor oder Brom, 
\( \text{X} \) Sauerstoff oder Schwefel ist; 
m gleich 2 oder 3 ist; 
\( \text{Y} \) Sauerstoff oder Schwefel ist; 
\( \text{Z} \) ausgewählt ist aus:

\[-\text{NR}_2\text{R}_3\]

oder

\[
\begin{array}{c}
\text{R}_6 \\
\text{R}_5 \\
\end{array}
\]

wobei \( \text{R}_6 \) und \( \text{R}_5 \) gleich oder verschieden sind und ausgewählt sind aus \( \text{C}_{1-10}-\text{Alkyl} \), \( \text{C}_{3-8}-\text{Cycloalkyl} \), \( \text{C}_{3-8}-\text{Cycloalkyl-C}_{1-10}-\text{Alkyl} \), \( \text{Hydroxy-C}_{1-10}-\text{Alkyl} \), \( \text{C}_{1-10}-\text{Alkoxy-C}_{1-10}-\text{Alkyl} \) oder \( \text{C}_{1-10}-\text{Alkanoyloxy-C}_{1-10}-\text{Alkyl} \), Phenyl oder Phenyl-\( \text{C}_{1-10}-\text{Alkyl} \), wobei die Phenylgruppen monosubstituiert sein können mit Halogen oder CF₃; 
n gleich 0, 1, 2 oder 3 ist;
\( \text{R}_6 \) und \( \text{R}_5 \) gleich oder verschieden sind und ausgewählt sind aus Wasserstoff, \( \text{C}_{1-4}-\text{Alkyl} \), \( \text{Hydroxy-C}_{1-4}-\text{Alkoxy} \) oder \( \text{C}_{1-4}-\text{Alkanoyloxy} \);
p gleich 2 oder 3 ist; 
\( \text{R}_6 \) und \( \text{R}_5 \) gleich oder verschieden sind und ausgewählt sind aus Wasserstoff oder \( \text{C}_{1-4}-\text{Alkyl} \); 
\( \text{R}_6 \) Wasserstoff, \( \text{C}_{1-4}-\text{Alkyl} \) oder \( \text{C}_{1-4}-\text{Alkanoyl} \) und die pharmazeutisch wirksamen Salze derselben ist.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß \( \text{Z} \) ausgewählt ist aus der Gruppe bestehend aus

\[-\text{NR}_2\text{R}_3\]

oder

\[
\begin{array}{c}
\text{R}_6 \\
\text{R}_5 \\
\end{array}
\]

wobei \( \text{R}_6 \) und \( \text{R}_5 \) ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Cycloalkyl-\( \text{Alkyl} \) und Hydroxalkyl gemäß der in Anspruch 1 gegebenen Definition; von \( \text{R}_6 \) und \( \text{R}_5 \) das eine Wasserstoff ist und das andere Wasserstoff oder \( \text{C}_{1-4}-\text{Alkyl} \); und daß \( \text{R}_6 \) und \( \text{R}_5 \) Wasserstoff sind.

3. Verbindung nach einem der Ansprüche 1 bis 2, dadurch gekennzeichnet, daß \( m \) gleich 2 ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß \( \text{X} \) und \( \text{Y} \) Sauerstoff sind.

5. Verbindung nach Anspruch 1 bis 5, dadurch gekennzeichnet, daß \( \text{R}_1 \) Fluor ist.

6. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Gruppe:

4-[3-(\text{p-Fluorphenoxy}) propyl]-N-methyl-1-piperazincarboxamid

4-[3-(\text{p-Fluorphenoxy}) propyl]-N-ethyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-N-cyclopropyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-N-methyl-1-piperazinthiocarboxamid
4-[3-(p-Fluorphenylmercapto) propyl]-N-methyl-1-piperazincarboxamid
4-[3-(p-Fluorphenylmercapto) propyl]-N-methyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-NN-dimethyl-1-piperazincarboxamid
1-Morpholinocarbonyl-4-[3-(p-fluorphenoxy) propyl]-piperazin.
7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, gekennzeichnet durch
a) Umsetzen einer Verbindung II

wobei X und R₁ der in Anspruch 1 gegebenen Definition entsprechen und M eine Endgruppe ist, mit einer Verbindung

wobei Y, Z und m der zuvor in Anspruch 1 gegebenen Definition entsprechen,
b) Umsetzen einer Verbindung IV

wobei R₁, X und m der in Anspruch 1 gegebenen Definition entsprechen, mit einem Isocyanat, R₂-NCO, (V), wobei R₂ der in Anspruch 1 gegebenen Definition entspricht, oder einem Isothiocyanat, R₂-NCS, (VI), wobei R₂ der zuvor gegebenen Definition entspricht, oder einem Carbamoyl-Derivat, L-CY-Z (VII), wobei Y und Z der oben gegebenen Definition entsprechen und L eine Endgruppe ist,
c) Umsetzen einer Verbindung VIII

wobei R₁ und X der zuvor gegebenen Definition entsprechen, mit einer Verbindung

wobei M, m, Y und Z der zuvor gegebenen Definition entsprechen, oder
d) Umsetzen einer Verbindung
wobei $R$, $m$, $X$, $Y$ und $L$ der zuvor gegebenen Definition entsprechen, mit einer Verbindung $Z$-$H$, wobei $Z$ der zuvor gegebenen Definition entspricht.

8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß $Z$ ausgewählt ist aus der Gruppe bestehend aus

$$-\text{NR}_2\text{R}_3$$ oder

oder

wobei $R$, $R_3$ und $R_4$ ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Alkyl, Cycloalkyl, Cycloalkyl-Alkyl und Hydroxyalkyl gemäß der in Anspruch 1 gegebenen Definition von $R_4$ und $R_6$ das eine Wasserstoff ist und das andere Wasserstoff oder $\text{C}_{1-4}$-Alkyl; und daß $R_4$ und $R_6$ Wasserstoff sind.

9. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß die hergestellte Verbindung ausgewählt ist aus der folgenden Gruppe:

4-[3-(p-Fluorphenoxy) propyl]-N-methyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-N-ethyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-N-cyclopropyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-N-methyl-1-piperazinthiocarboxamid
4-[3-(p-Fluorphenylmercapto) propyl]-N-methyl-1-piperazincarboxamid
4-[3-(p-Fluorphenylmercapto) propyl]-N-ethyl-1-piperazincarboxamid
4-[3-(p-Fluorphenoxy) propyl]-NN-dimethyl-1-piperazincarboxamid
1-Morpholinincarbonyl-4-[3-(p-Fluorphenoxy) propyl]-piperazin.


Revendications

1. Composés de formule générale :

$$\text{X}-(\text{CH}_2)_3-\text{N}$$

dans laquelle $R_1$ est choisi parmi fluoro, chloro et bromo

$X$ est l’oxygène ou le soufre,

$m$ est égal à 2 ou 3,

$Y$ est l’oxygène ou le soufre,

$Z$ est choisi parmi :

$$-\text{NR}_2\text{R}_3$$

ou
dans lesquels R₆ et R₇ sont identiques ou différents et sont choisis parmi l’hydrogène, un alkyle en C₁₋₁₀, un cycloalkyle en C₂₋₆, un cycloalkyle en C₃₋₅-alkyle en C₁₋₁₀, un hydroxyalkyle en C₁₋₁₀, un alcoxy en C₁₋₁₀-alkyle en C₁₋₁₀ ou un alcanoxy en C₁₋₁₀-alkyle en C₁₋₁₀, un phényle ou un phénylalkyle en C₁₋₁₀, les groupes phényle pouvant être monosubstitués par un halogène ou CF₃,
n est égal à 0, 1, 2 ou 3,
R₄ et R₅ sont identiques ou différents et sont choisis parmi l’hydrogène, un alkyle en C₁₋₄, un hydroxy, un alcoxy en C₁₋₄ ou un alcanoxy en C₁₋₄,
p est égal à 2 ou 3,
R₆ et R₇ sont identiques ou différents et sont choisis parmi l’hydrogène ou un alkyle en C₁₋₄,
R₈ est l’hydrogène, un alkyle en C₁₋₄ ou un alcanoyle en C₁₋₄,
et leurs sels actifs du point de vue pharmaceutique.

2. Composé selon la revendication 1, caractérisé en ce que Z est choisi dans le groupe formé par –NR₃R₅ ou

30
dans lesquels R₅ et R₆ sont choisis dans le groupe formé par l’hydrogène, un alkyle, un cycloalkyle, un cycloalkyle et un hydroxyalkyle tels que définis dans la revendication 1,
l’un parmi R₄ et R₅ est l’hydrogène et l’autre est l’hydrogène ou un alkyle en C₁₋₄,
et en ce que R₆ et R₇ sont l’hydrogène.

3. Composé selon l’une quelconque des revendications 1 et 2, caractérisé en ce que m = 2.

4. Composé selon l’une quelconque des revendications 1 à 3, caractérisé en ce que X et Y sont l’oxygène.

5. Composé selon l’une quelconque des revendications 1 à 4, caractérisé en ce que R₁ est F.

6. Composé selon la revendication 1 choisi dans le groupe suivant :

7. Procédé de préparation d’un composé selon la revendication 1, caractérisé par

a) la réaction d’un composé de formule II

55
dans laquelle X et R₁ sont tels que définis dans la revendication 1, et dans laquelle M est un groupe partant,
avec un composé de formule (III)
dans laquelle Y, Z et m sont tels que définis précédemment dans la revendication 1
b) la réaction d'un composé de formule (IV)

dans laquelle R₁, X et m sont tels que définis dans la revendication 1, avec un isocyanate, R₂-NCO, (V),
dans lequel R₂ est tel que défini dans la revendication 1, ou un isothiocyanate, R₂-NCS, (VI), dans lequel
R₂ est tel que défini précédemment, ou un dérivé de carbamoyle, L-CY-Z, (VII), dans lequel Y et Z sont
tels que définis précédemment et L est un groupe partant,
c) la réaction d'un composé de formule (VIII)

dans laquelle R₁ et X sont tels que définis précédemment, avec un composé de formule (IX)

dans laquelle M, m, Y et Z sont tels que définis précédemment, ou
d) la réaction d'un composé de formule (X)

dans laquelle R₁, m, X, Y et L sont tels que définis précédemment avec un composé de formule Z-H dans
laquelle Z est tel que défini précédemment.
8. Procédé selon la revendication 7, caractérisé en ce que Z est choisi dans le groupe formé par –NR₃R₅.

dans lesquels R₂ et R₅ sont choisis dans le groupe formé par l’hydrogène, un alkyle, un cycloalkyle, un cycloal-
kyle-alkyle et un hydroxyalkyle tels que définis dans la revendication 1,
l'un parmi R₄ et R₅ est l'hydrogène et l'autre est l'hydrogène ou un alkyle en C₁₋₄,
et en ce que R₆ et R₇ sont l'hydrogène.

9. Procédé selon la revendication 7, caractérisé en ce que le composé préparé est choisi dans le groupe suivant :
4-[3-(p-fluorophénoxy) propyl]-N-méthyl-1-pipérazine-carboxamide
4-[3-(p-fluorophénoxy) propyl]-N-éthyl-1-pipérazine-carboxamide
4-[3-(p-fluorophénoxy) propyl]-N-cyclopropyl-1-pipérazine-carboxamide
4-[3-(p-fluorophénoxy) propyl]-N-méthyl-1-pipérazine-thiocarboxamide

10. Compositions pharmaceutiques contenant comme ingrédient actif un ou plusieurs des composés selon la revendication 1, de préférence avec un véhicule acceptable du point de vue pharmaceutique et, si on le souhaite, d'autres agents actifs du point de vue pharmacologique.