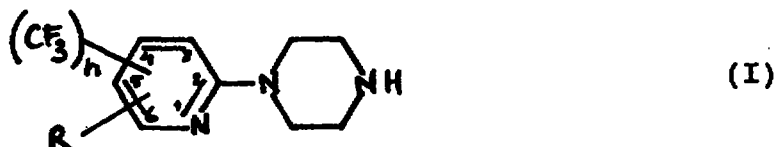


Description

The present invention relates to a pharmaceutical composition containing 1-[mono- or bis-(trifluoromethyl)2-pyridinyl]piperazines which is useful as a medicament, to new chemical compounds, and to the use of compounds for the preparation of a medicament which act on the central nervous system, in particular as antidepressants, and against obsessive compulsive disorders, anxiety disorders, among which generalized anxiety, panic attacks and agoraphobia, obesity, aggression and alcohol addiction.

Such compounds correspond, more precisely, to the following general formula



in which $n=1$ or 2 , for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring and the substituent R denotes either hydrogen or a halogen substituent, such as chlorine, at position(s) of the pyridinyl ring not occupied by CF_3 .

The invention also relates to pharmaceutical compositions containing pharmaceutically acceptable addition salts of the said compounds. These salts are usually obtained by combining the free base (I) with inorganic or organic acids such as hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation.

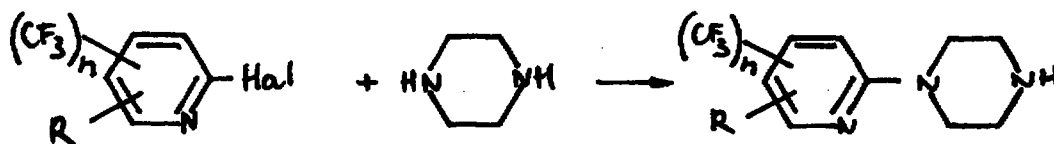
In the prior art, several pyridinylpiperazines containing one or two substituents on the pyridine ring are already known. There may be mentioned, for example, the publication by Walfred S. Saari which appeared in J. Med. Chem. 26 (12), 1696-1701, (1983). 1-(4-trifluoromethyl-2-pyridinyl)piperazine and 1-(5-trifluoromethyl-2-pyridinyl)piperazine, described in EP 282,390 and EP 220,873 respectively, are known chemical intermediates, albeit without any pharmaceutical utility.

The subject of the invention is a pharmaceutical composition containing pyridinylpiperazines necessarily containing one or two trifluoromethyl substituents at the 4- and/or 5-positions of the pyridinyl ring which is useful as a medicament with activity for the treatment of disorders of the central nervous system. Such medicaments preferably contain 1-(4-trifluoromethyl-2-pyridinyl)piperazine or 1-(5-trifluoromethyl-2-pyridinyl)-piperazine.

The compounds of formula I in which the trifluoromethyl substituent is at the 4-position, at the 5-position, or at 4- and 5-positions of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF_3 , and their pharmaceutically acceptable salts, with the proviso that R denotes a halogen when only one trifluoromethyl substituent is present, are new.

The compounds with formula I possess specific antidepressant activity, resulting especially from their 5HT_{1B} type serotonergic agonist properties, and are prepared according to known processes for similar compounds.

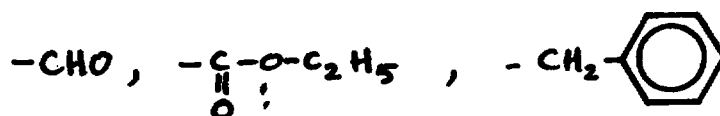
According to one embodiment, an excess of piperazine is reacted with a suitably substituted 2-halopyridine in an organic solvent, heating to reflux of the solvent. Acetonitrile can be taken, for example, as a suitable solvent. This process corresponds to the following scheme:



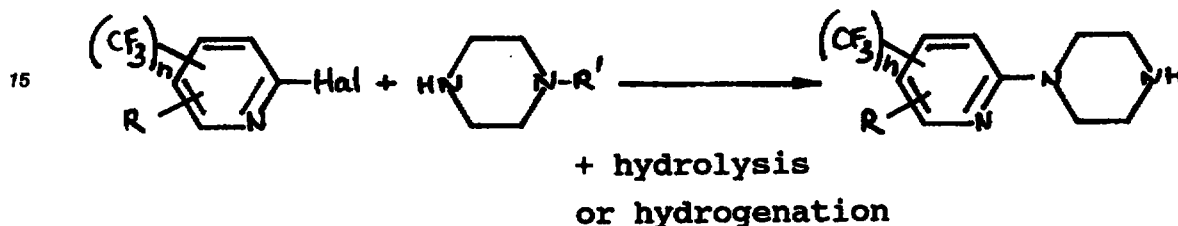
Hal denotes a halogen such as chlorine.

According to another embodiment, a suitably substituted 2-halopyridine is reacted in an organic solvent in the presence of a base with a piperazine in which one of the $>\text{NH}$ groups is protected by a group R' , and the protective group is then removed in the usual manner such as by hydrolysis or hydrogenation. By using an alcohol such as butanol as the organic solvent, the base may be a carbonate or a tertiary amine

such as triethylamine. As a protective group R', the following will be used, for example:



This process corresponds to the following scheme:



Hal denotes a halogen such as chlorine.

The compounds of the invention and the processes for producing them are described in the examples below, without this constituting a limitation to the different embodiments.

EXAMPLE 1 :

1-(3-chloro-5-trifluoromethyl-2-pyridinyl)piperazine

A solution of 10.8 g (0.05 mol) of 2,3-dichloro-5-trifluoromethylpyridine and 12.9 g (0.15 mol) of anhydrous piperazine in 100 ml of acetonitrile was introduced into a reactor, and the mixture was then heated under reflux for 2 hours. After the mixture was cooled, the precipitate was filtered off and washed with acetonitrile and the filtrate was then evaporated. The residue was then taken up with chloroform and washed with water. After the organic phase was dried and the solvent then evaporated off, the residue was distilled and the product of the title was obtained in the form of a base having a boiling point B.p. _{0.06} of 101 °C.

To obtain the hydrochloride, the base obtained was treated with an ethanol/hydrochloric acid mixture, and the precipitate obtained was then washed with ether and dried.

5.5 g of the compound of the title were thereby obtained in the form of a hydrochloride having a melting point M.p. of 178 °C

EXAMPLE 2 :

1-[4,5-bis(trifluoromethyl)-2-pyridinyl]piperazine

Working as described in Example 1, but starting with 10 g (0.04 mol) of 2-chloro-4,5-bis(trifluoromethyl)pyridine and 10.3 g (0.12 mol) of piperazine, the base having a boiling point B.p. _{0.04} of 100-102 °C was obtained, and then, after conversion to the hydrochloride, 7.8 g of the title compound.

EXAMPLE 3 :

1-(5-trifluoromethyl-2-pyridinyl)piperazine

Working as described in Example 1, but starting with 2-chloro-5-trifluoromethylpyridine, 10.4 g of the title compound were obtained in the form of a base having a boiling point B.p. _{0.05} of 91 °C.

The dihydrochloride obtained according to the usual methods has a melting point M.p. of 262 °C.

According to the same process, the compounds whose characteristics are given in Table I below were also obtained.

TABLE I

COMPOUND NO.			Base B.p. °C (mm Hg)	Hydrochloride M.p. °C
1 (Example 3)	5 CF ₃		91° (0.05 mm)	262° C
2	4 CF ₃		114-115° (0.35 mm)	224° C
3	5 CF ₃	6 Cl	118° (0.06 mm)	Decomposition
4 (Example 2)	4 CF ₃	5 CF ₃	100° (0.04 mm)	Decomposition
5 (Example 1)	5 CF ₃	3 Cl	101° (0.06 mm)	178° C

The activity of the compounds of the invention on the central nervous system was demonstrated by the pharmacological tests below, demonstrating the serotonergic activity and specifying the mode of action.

BINDING TEST

This test is carried out according to the protocol of PEROUTKA, S.J. ["Selective labelling of 5-HT_{1A} and 5HT_{1B} binding sites in bovine brain" BRAIN RESEARCH 344, p. 167-171 (1985)]. In this test, the affinity for 5HT_{1A} receptors is determined by the capacity of the compounds to displace [³H]-8-OH-DPAT from the membranes of the rat hippocampus; similarly, the affinity for 5HT_{1B} receptors is determined by the capacity of the compounds to displace [³H]-5HT from the membranes of the rat striatum.

The results recorded in Table II below show the p_{Ki} values calculated according to the abovementioned protocol.

PENILE ERECTION TEST

This test, carried out according to the protocol of BERENDSEN H.H.G. and BROEKKAMP C.L.E. ["Drug induced penile erections in rats: indication of serotonin 1B receptor mediation - EUROPEAN J. PHARMACOL. 135, 279-287 (1987)] enables the 5HT_{1B} agonist potentials of the various compounds to be assessed.

The results recorded in Table II below show the minimum dose in mg.kg⁻¹ administered subcutaneously which leads to an erection of the penis in rats, as well as the activity when administered orally.

TABLE II

COMPOUND NO.	BINDING p _{Ki}		ERECTION OF THE PENIS
	5HT _{1A}	5HT _{1B}	
1	<5.0	6.3	1 (>46 PO)
2	5.6	6.9	1 (2.2 PO)
3	5.6	7.0	0.46 (4.6 PO)
4	4.1	6.4	10 (2.2 PO)
5	5.4	6.3	4.6 (10 PO)

These results show that the compounds of the invention possess overall a greater affinity for 5HT_{1B} receptors than for 5HT_{1A} receptors.

Moreover, the toxicity of the compounds of the invention appears to be low: at an oral dose of 160 mg.kg⁻¹, no mortality is observed in mice.

These collective pharmacological properties hence enable the compounds of the invention to be applied in human therapy as a medicinal product for the treatment of disorders of the central nervous system, in particular as antidepressants.

In combination with customary pharmaceutical excipients, the compounds of the invention may be administered at daily doses of between 0.1 mg and 5 mg per kg of body weight. In human therapy, daily doses of between 10 mg and 150 mg, administered orally, will preferably be used.

The compounds according to the invention can be processed to pharmaceutical preparations for enteral administration, local application or parenteral administration by mixing with suitable auxiliaries. A suitable form for administration is a tablet, pill, powder, capsule, paste, spray, sirup, ointment, suppository, solution, suspension or emulsion. For instance, the following pharmaceutical dosage forms were prepared:

Tablet	
1-(5-trifluoromethyl-2-pyridinyl)piperazine dihydrochloride	50 mg
hydroxypropyl cellulose (HPC)	7,5 mg
corn starch	25 mg
magnesium stearate	1,25 mg
aerosil	2,5 mg
lactose	to 250 mg

The active principle, lactose and corn starch were mixed. An aqueous HPC solution was added and the mass was granulated in several minutes. The resulting mass was dried, sieved and aerosil and magnesium stearate were added. After mixing the mass was compressed to form tablets each weighting 250 mg.

Injectable preparation	
1-(4-trifluoromethyl-2-pyridinyl)piperazine	15 mg
NaOH/HCl	to pH 5
mannitol	to isotonic
water for injections	to 1 ml
dissolve the components, adjust to volume and pH.	

Freeze-dried injectable preparations

The same components as for the injectable preparation were dissolved and adjusted to pH 5, and the solution was freeze-dried.

Capsule	
active component	50 mg
HPC	3 mg
corn starch	15 mg
magnesium stearate	1,5 mg
lactose	to 150 mg

The components were processed as for the tablet and the resulting mass was filled into capsules.

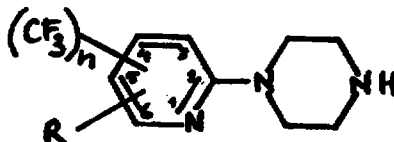
Suppository	
compound of example 1	5 mg
whitepsol 558	500 mg

The wax was melted and the active compound was dissolved therein.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

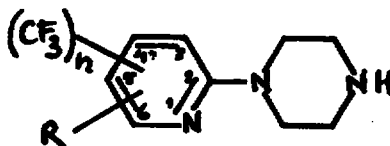
1. A pharmaceutical composition containing a compound of the formula



in which $n=1$ or 2 , for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF₃, or its pharmaceutically acceptable salts.

2. Pharmaceutical composition according to Claim 1, characterized in that the compound denotes 1-(5-trifluoromethyl-2-pyridinyl)piperazine or one of its salts.
3. Pharmaceutical composition according to Claim 1, characterized in that the compound denotes 1-(4-trifluoromethyl-2-pyridinyl)piperazine or one of its salts.

4. Compounds of the formula

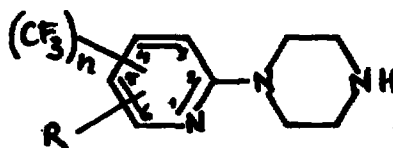


in which $n=1$ or 2 , for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF₃, and their pharmaceutically acceptable salts, with the proviso that R denotes a halogen when only one trifluoromethyl substituent is present.

5. Compound according to Claim 4, characterized in that it denotes 1-(3-chloro-5-trifluoromethyl-2-pyridinyl) -piperazine, 1-[4,5-bis(trifluoromethyl)-2-pyridinyl] -piperazine, 1-(5-trifluoromethyl-6-chloro-2-pyridinyl)-piperazine, or one of their salts.
6. Process for obtaining the compounds according to Claim 4 or 5, characterized in that a suitably substituted 2-halopyridine is treated with an excess of piperazine.
7. Process for obtaining the compounds according to Claim 4 or 5, characterized in that a suitably substituted 2-halopyridine is treated with a piperazine in which one of the NH groups is protected by a cleavable group.
8. Process to Claim 6 or 7, characterized in that the substituted 2-halopyridine is a substituted 2-chloropyridine.



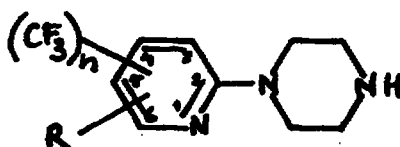
9. Use of compounds of formula



in which $n=1$ or 2, for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF₃, or their pharmaceutically acceptable salts, for the preparation of a medicament with activity for the treatment of disorders of the central nervous system.

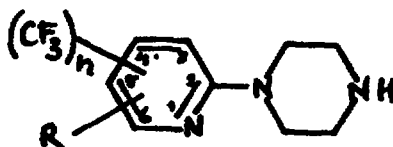
Claims for the following Contracting States : ES, GR

1. A process for the manufacture of a pharmaceutical composition containing a compound of the formula



in which $n=1$ or 2, for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF₃, or its pharmaceutically acceptable salts, characterized in that the compound is mixed with suitable auxiliaries.

2. The process according to claim 1, wherein the pharmaceutical composition containing 1-(5-trifluoromethyl-2-pyridinyl)piperazine or one of its salts is prepared.
3. The process according claim 1, wherein the pharmaceutical composition containing 1-(4-trifluoromethyl-2-pyridinyl)piperazine or one of its salts is prepared.
4. A process for the preparation of compounds of the formula



in which $n=1$ or 2, for $n=1$ the trifluoromethyl substituent is at the 4-position or at the 5-position of the pyridinyl ring and for $n=2$ at the 4- and 5-position of the pyridinyl ring, and the substituent R denotes either hydrogen or a halogen substituent at position(s) of the pyridinyl ring not occupied by CF₃, and their pharmaceutically acceptable salts, with the proviso that R denotes a halogen when only one trifluoromethyl substituent is present, characterized in that a suitably substituted 2-halopyridine is treated with an excess of piperazine.

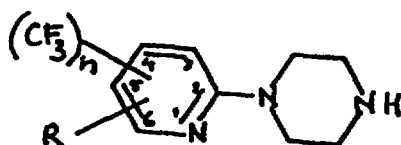


5. The process according to claim 4, wherein one of the NH groups of the piperazine is protected by a cleavable group.
6. The process according to claim 4 or 5, wherein the compound 1-(3-chloro-5-trifluoromethyl-2-pyridinyl)-piperazine, or 1-[4,5-bis(trifluoromethyl)-2-pyridinyl]-piperazine, or 1-(5-trifluoromethyl-6-chloro-2-pyridinyl)-piperazine, or one of their salts is prepared.
7. The process according to claim 4 or 5, wherein the substituted 2-halopyridine is a substituted 2-chloropyridine.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

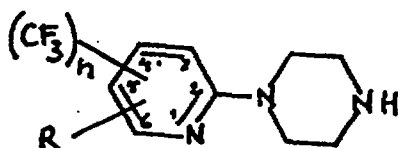
1. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel



in welcher n = 1 oder 2 ist, wobei für n = 1 der Trifluormethylsubstituent in Stellung 4 oder 5 des Pyridinylringes ist und für n = 2 in der 4- und 5-Stellung des Pyridinylringes ist, und der Substituent R entweder Wasserstoff oder einen Halogensubstituenten in Stellung(en) des Pyridinylringes, welcher nicht durch CF₃ besetzt sind, bedeutet, oder eines ihrer pharmazeutisch annehmbaren Salze.

2. Pharmazeutische Zusammensetzung gemäss Anspruch 1, dadurch gekennzeichnet, dass die Verbindung 1-(5-Trifluormethyl-2-pyridinyl)-piperazin oder eines ihrer Salze bedeutet.
3. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, dass die Verbindung 1-(4-Trifluormethyl-2-pyridinyl)-piperazin oder eines ihrer Salze bedeutet.

4. Verbindungen der Formel

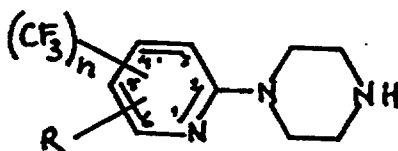


in welcher n = 1 oder 2 ist, wobei für n = 1 der Trifluormethylsubstituent in Stellung 4 oder in Stellung 5 des Pyridinylringes ist, und für n = 2 in der 4- und 5-Stellung des Pyridinylringes ist, und der Substituent R entweder Wasserstoff oder einen Halogensubstituenten in Stellung(en) des Pyridinylringes, welche nicht durch CF₃ besetzt sind, bedeutet, und ihre pharmazeutisch annehmbaren Salze, unter der Voraussetzung, dass R ein Halogen bedeutet, wenn nur ein Trifluormethylsubstituent zugegen ist.

5. Verbindung nach Anspruch 4, dadurch gekennzeichnet, dass sie 1-(3-Chlor-5-trifluormethyl-2-pyridinyl)-piperazin, 1-[4,5-Bis-(trifluormethyl)-2-pyridinyl]-piperazin, 1-(5-Trifluormethyl-6-chlor-2-pyridinyl)-piperazin oder eines ihrer Salze ist.
6. Verfahren zur Herstellung der Verbindungen gemäss Anspruch 4 oder 5, dadurch gekennzeichnet, dass ein auf geeignete Weise substituiertes 2-Halogenpyridin mit einem Ueberschuss an Piperazin behandelt wird.



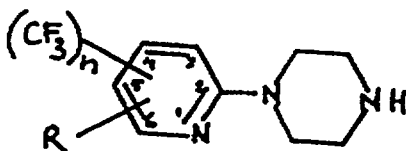
7. Verfahren zur Herstellung der Verbindungen gemäss Anspruch 4 oder 5, dadurch gekennzeichnet, dass ein auf geeignete Weise substituiertes 2-Halogenpyridin mit einem Piperazin behandelt wird, in welchem eine der NH-Gruppen durch eine abspaltbare Gruppe geschützt ist.
8. Verfahren nach Anspruch 6 oder 7, dadurch gekennzeichnet, dass das substituierte 2-Halogenpyridin ein substituiertes 2-Chlorpyridin ist.
9. Verwendung von Verbindungen der Formel



in welcher $n = 1$ oder 2 ist, wobei, wenn $n = 1$ ist, der Trifluormethylsubstituent in Stellung 4 oder in Stellung 5 des Pyridinyrings ist und für $n = 2$ in der 4- und 5-Stellung des Pyridinyrings ist, und der Substituent R entweder Wasserstoff oder einen Halogensubstituenten in Stellung(en) des Pyridinyrings, welcher nicht durch CF_3 besetzt sind, darstellt, oder deren pharmazeutisch annehmbaren Salzen, zur Herstellung eines Medikaments mit Wirksamkeit für die Behandlung von Störungen des Zentralnervensystems.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren für die Herstellung einer pharmazeutischen Zusammensetzung, welche eine Verbindung der Formel

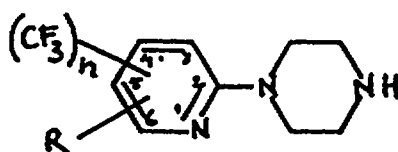


enthält, in welcher $n = 1$ oder 2 ist, wobei für $n = 1$ der Trifluormethylsubstituent in Stellung 4 oder in Stellung 5 des Pyridinyrings ist, und für $n = 2$ in der 4- und 5-Stellung des Pyridinyrings, und der Substituent R entweder Wasserstoff oder einen Halogensubstituenten in Stellung(en) des Pyridinyrings, welche nicht durch CF_3 besetzt sind, bedeutet, oder ihre pharmazeutisch annehmbaren Salze, dadurch gekennzeichnet, dass die Verbindung mit geeigneten Hilfsstoffen vermischt wird.

2. Verfahren nach Anspruch 1, in welchem die pharmazeutische Zusammensetzung hergestellt wird, welche 1-(5-Trifluormethyl-2-pyridinyl)-piperazin oder eines ihrer Salze enthält.
3. Verfahren nach Anspruch 1, in welchem die pharmazeutische Zusammensetzung hergestellt wird, welche 1-(5-Trifluormethyl-2-pyridinyl)-piperazin oder eines ihrer Salze enthält.



4. Verfahren zur Herstellung von Verbindungen der Formel



in welcher $n = 1$ oder 2 ist, wobei für $n = 1$ der Trifluormethylsubstituent in Stellung 4 oder in Stellung 5 des Pyridinylringes ist und für $n = 2$ in der 4- und 5-Stellung des Pyridinylringes, und der Substituent R entweder Wasserstoff oder einen Halogensubstituenten in Stellung(en) des Pyridinylringes, welche nicht durch CF₃ besetzt sind, bedeutet, und ihren pharmazeutisch annehmbaren Salzen, unter der Bedingung, dass R ein Halogen bedeutet, wenn nur ein Trifluormethylsubstituent zugegen ist, dadurch gekennzeichnet, dass ein auf geeignete Weise substituiertes 2-Halogenpyridin mit einem Ueberschuss an Piperazin behandelt wird.

5. Verfahren nach Anspruch 4, in welchem eine der NH-Gruppen des Piperazins durch eine abspaltbare Gruppe geschützt ist.

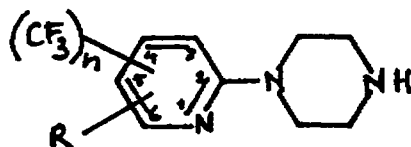
6. Verfahren nach Anspruch 4 oder 5, in welchem die Verbindung 1-(3-Chlor-5-trifluormethyl-2-pyridinyl)-piperazin oder 1-[4,5-Bis-(trifluormethyl)-2-pyridinyl]-piperazin oder 1-(5-Trifluormethyl-6-chlor-2-pyridinyl)-piperazin oder eines ihrer Salze ist, hergestellt wird.

7. Verfahren nach Anspruch 4 oder 5, in welchem das substituierte 2-Halogenpyridin ein substituiertes 2-Chlorpyridin ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composition pharmaceutique contenant un composé de formule:



dans laquelle:

n est égal à 1 ou 2, pour $n = 1$, le substituant trifluorométhyle est en position 4- ou en position 5- sur le cycle pyridinyle et pour $n = 2$, le substituant trifluorométhyle est en position 4- et 5- sur le cycle pyridinyle, et

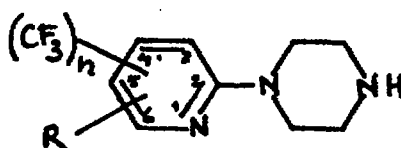
le substituant R représente soit un atome d'hydrogène, soit un atome d'halogène qui se trouve sur le cycle pyridinyle aux positions non occupées par CF₃, ou ses sels pharmaceutiquement acceptables.

2. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le composé correspond à la 1-(5-trifluorométhyl-2-pyridinyl)pipérazine ou à l'un de ses sels.

3. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le composé correspond à la 1-(4-trifluorométhyl-2-pyridinyl)pipérazine ou à l'un de ses sels.



4. Composés de formule:



dans laquelle:

n est égal à 1 ou 2, pour n=1, le substituant trifluorométhyle est en position 4- ou en position 5- sur le cycle pyridinyle et pour n=2, le substituant trifluorométhyle est en position 4- et 5- sur le cycle pyridinyle, et

le substituant R représente soit un atome d'hydrogène, soit

un atome d'halogène qui se trouve sur le cycle pyridinyle aux positions non occupées par CF₃,

et ses sels pharmaceutiquement acceptables, à la condition que R représente un atome d'halogène lorsque seulement un substituant trifluorométhyle est présent.

5. Composé selon la revendication 4, caractérisé en ce qu'il représente :

1-(3-chloro-5-trifluorométhyl-2-pyridinyl)pipérazine,

1-[4,5-bis(trifluorométhyl)-2-pyridinyl]pipérazine,

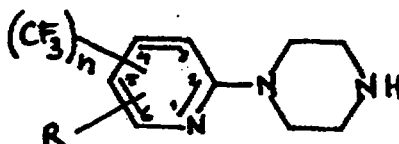
1-(5-trifluorométhyl-6-chloro-2-pyridinyl)pipérazine, ou l'un de ses sels.

6. Procédé d'obtention des composés selon la revendication 4 ou 5, caractérisé en ce qu'une 2-halopyridine substituée de façon appropriée est traitée à l'aide d'un excès de pipérazine.

7. Procédé d'obtention des composés selon la revendication 4 ou 5, caractérisé en ce qu'une 2-halopyridine substituée de façon appropriée est traitée à l'aide de pipérazine dans laquelle l'un des groupes NH est protégé par un groupe clivable.

8. Procédé selon la revendication 6 ou 7, caractérisé en ce que la 2-halopyridine substituée est une 2-chloropyridine substituée.

9. Utilisation des composés de formule:



dans laquelle:

n est égal à 1 ou 2, pour n=1, le substituant trifluorométhyle est en position 4- ou en position 5- sur le cycle pyridinyle et pour n=2, le substituant trifluorométhyle est en position 4- et 5- sur le cycle pyridinyle, et

le substituant R représente soit un atome d'hydrogène, soit

un atome d'halogène qui se trouve sur le cycle

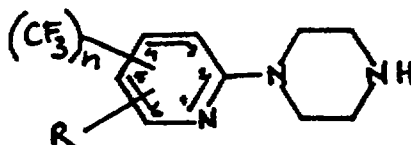
pyridinyle aux positions non occupées par CF₃,

ou leurs sels pharmaceutiquement acceptables, pour la préparation d'un médicament actif dans le traitement des troubles du système nerveux central.



Revendications pour les Etats contractants suivant : ES, GR

1. Procédé de préparation d'une composition pharmaceutique contenant un composé de formule:



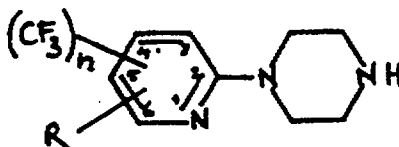
dans laquelle:

n est égal à 1 ou 2, pour n=1, le substituant trifluorométhyle est en position 4- ou en position 5- sur le cycle pyridinyle et pour n=2, le substituant trifluorométhyle est en position 4- et 5- sur le cycle pyridinyle, et le substituant R représente soit un atome d'hydrogène, soit un atome d'halogène qui se trouve sur le cycle pyridinyle aux positions non occupées par CF₃, ou ses sels pharmaceutiquement acceptables, caractérisé en ce que le composé est mélangé avec des auxiliaires appropriés.

2. Procédé selon la revendication 1, dans lequel est fabriquée la composition pharmaceutique contenant la 1-(5-trifluorométhyl-2-pyridinyl)pipérazine ou l'un de ses sels.

3. Procédé selon la revendication 1, caractérisé en ce que l'on prépare la composition pharmaceutique contenant la 1-(4-trifluorométhyl-2-pyridinyl)pipérazine ou l'un de ses sels.

4. Procédé de préparation des composés de formule:



dans laquelle:

n est égal à 1 ou 2, pour n=1, le substituant trifluorométhyle est en position 4- ou en position 5- sur le cycle pyridinyle et pour n=2, le substituant trifluorométhyle est en position 4- et 5- sur le cycle pyridinyle, et le substituant R représente soit un atome d'hydrogène, soit un atome d'halogène qui se trouve sur le cycle pyridinyle aux positions non occupées par CF₃, et ses sels pharmaceutiquement acceptables, à condition que R représente un halogène lorsque seulement un substituant trifluorométhyle est présent, caractérisé en ce que une 2-halopyridine substituée de façon appropriée convenable est traitée avec un excès de pipérazine.

5. Procédé selon la revendication 4, caractérisé en ce que l'un des groupes NH de la pipérazine est protégé par un groupe clivable.

6. Procédé selon la revendication 4 ou 5, caractérisé en ce que le composé 1-(3-chloro-5-trifluorométhyl-2-pyridinyl)pipérazine ou 1-[4,5-bis(trifluorométhyl)-2-pyridinyl]pipérazine, ou 1-(5-trifluorométhyl-6-chloro-2-pyridinyl)pipérazine, ou l'un de ses sels est préparé.

7. Procédé selon la revendication 4 ou 5, caractérisé en ce que la 2-halopyridine substituée est une 2-chloro-pyridine substituée.

