Description

This invention relates to psychoactive drugs for use in treating depression and other nervous disorders.

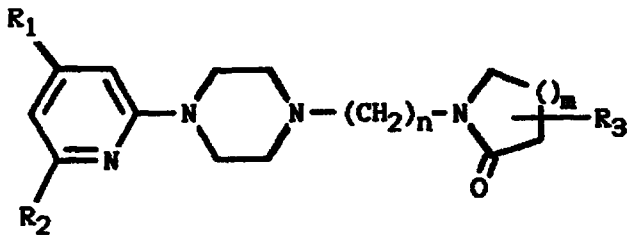
Although their mechanisms of action have not been fully elucidated, several drugs are known to be useful in the treatment of depressive, neurotic, or psychotic disorders. Drugs for treating depression (i.e. anti-depressants) include the well-known "tricyclics", characterized, chemically, by various tricyclic ring structures. One of these mood-elevating drugs, opipramol, also has neuroleptic ("antipsychotic") activity.

U.K. Patent GB 1,332,194 discloses, in Example 22, an agent having a 4-[6-(trifluoromethyl-2-pyridinyl)]-1-piperazinylalkyl group. This compound which displays tranquilizing action, however, possesses a cyclic imide moiety instead of a lactam group. Moreover, it has been found that the compounds of the present invention in comparison with said prior art compounds have either better oral activity or are devoid of dopaminergic activity.

U.K. Patent Application GB 2,023,594 discloses related compounds having antidepressant and antianxiety activity. These compounds, however, have pyrrolidinone-alkyl and piperidinone-alkyl groups, the alkyl moiety of which has 1-3 carbon atoms. It has now been found that these short chain compounds exhibit only marginal activity, and that therapeutically useful compounds have alkyl chains containing 4 or 5 carbon atoms.

5-Trifluoromethyl-2-pyridinyl imide derivatives, which are serotonin-1A ("5-HT_{1A}") receptor ligands with potential anxiolytic action, are also disclosed in Abou-Gharbia et al., "Polycyclic Aryl and Heteroarylpiperazinyl Imides as 5-HT_{1A} Receptor Ligands and Potential Anxiolytic Agents: Synthesis and Structure-Activity Relationship Studies", J. Med. Chem., 31(7), 1382-1392 (1988) at page 1386 (compound 25), at page 1387 (compound 37), and at page 1388 (compounds 48 and 56). The reported serotonin (5-HT_{1A}) binding levels for these compounds (e.g. 72% for compound 48 at a 1 µmol concentration), however, were too low for practical pharmaceutical use.

The invention relates to neuroleptic/antidepressant 4-[4- or 6-(trifluoromethyl)-2-pyridinyl]-1-piperazinylalkyl substituted lactam derivatives having the general structure of formula I:

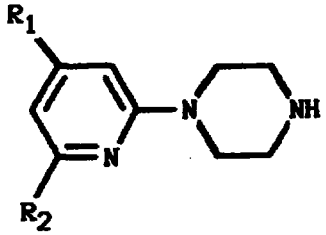


I

wherein one of the groups R_1 and R_2 is CF_3, and the other is hydrogen or CF_3;
R_3 is hydrogen or (1-4 C) alkyl;
n is an integer from 4 to 5; and
m is an integer from 1 to 2; or
pharmaceutically acceptable salts thereof.

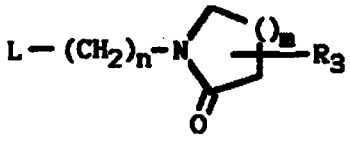
The invention also includes processes for making the compounds and their salts.

As more thoroughly described hereinafter, methods of making the compounds generally involve alkylating the terminal secondary amino portion of a 1-[4- or 6-(trifluoromethyl)-2-pyridinyl]piperazine derivative having formula II



II

wherein R_1 and R_2 have the previously given meanings, with a lactam having formula III



III

wherein R_3, n, and m have the previously given meanings, and L represents a leaving group. Suitable leaving groups are groups known as leaving group in alkylation reactions, such as halogens (especially chlorine, bromine, and iodine) or sulphonyl groups like the p-toluenesulphonyl and methanesulphonyl group.

Another method of preparation is the alkylation of the terminal secondary amino portion of the 1-[4- or 6-(trifluoromethyl)-2-pyridinyl)piperazine derivative having formula II, with a compound having the formula L-(CH_2)n-OH, wherein L and n have the previously given meanings, after which the hydroxy group is converted into a leaving group, as previously defined. The resulting synthon is then condensed in alkaline medium with 2-pyrrolidinone or with 2-piperidinone (δ-valerolactam), which are optionally provided with a (1-4 C) alkyl group (i.e. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl).

The novel compounds of formula I may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as HCl, HBr, HI, H_2SO_4, H_3PO_4, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, or ascorbic acid.

When R_3 is alkyl, the compounds of this invention possess a chiral carbon atom, and may therefore be obtained as a pure enantiomer, or as a mixture of enantiomers, among which the racemic mixture. Methods for obtaining the pure enantiomers are well known in the art, e.g. synthesis with chiral induction, crystallization of salts which are obtained from optically active acids and the racemic mixture, or chromatography using chiral columns.

The compounds of the present invention may be used in the treatment of mammals, including human beings. The compounds are then used medically to care for, or deal with, an existing problem. They may also be used prophylacticly to prevent the occurrence or reoccurrence of the behaviour. For example, the compounds are administered to exhibit undesirable (e.g. neurotic, psychotic, or depressive) behaviour. A sufficient amount of compound is administered on a mg/kg body mass basis, for a sufficient amount of time to decrease the undesirable behaviour.

The invention also includes the use of the described compounds in the manufacture of a medicament for the treatment and/or prevention of the occurrence or reoccurrence of psychotic, neurotic, and depressive disorders, or any of them.

Preferred compositions display improved preferential binding activity to the 5-HT_{1A} receptors over the 5-HT_{1B} receptor. Preferably the pK_i (binding constant) of the 5-HT_{1A} receptors will exceed the number 7, and most preferably exceed 8. The pK_i of the 5-HT_{1B} receptor will therefore be less than the pK_i of the 5-HT_{1A} receptor for a particular compound.

The compounds of formula I, wherein n is 4 and R_3 is hydrogen or (1-4 C) alkyl, are preferred. The group R_3 can be attached to any carbon atom of the cyclic amide moiety with the exception of the carbonyl carbon atom, but preferred, however, are the sites juxtapositioned to the nitrogen atom or the carbonyl group. More preferred are the compounds of formula I having n is 4, R_3 is hydrogen or methyl, and one of the groups R_1 and R_2 is hydrogen. Most preferred is the compound having formula I, wherein R_1 is CF_3, R_2 and R_3 are hydrogen, n is 4, and m is 1.

Administration of the described compounds is useful in the prevention and treatment of psychotic, neurotic and depressive disorders. For example, pharmaceutical compositions containing sufficient dosages of the active ingredients, either separately or with other active compounds, may be used to treat psychotic behaviour, neuroses, anxiety, depression, combinations of these disorders, or any other disease state susceptible to treatment by the described compounds.

The dosage administered will generally be dependent upon the kind of disorder to be treated, the type of patient involved, his age, health, weight, kind of concurrent treatment, if any, length and frequency of treatment and therapeutic ratio of the particular compound.

The dosage forms will be administered over varying durations. To treat psychotic behaviour, neuroses, anxiety, depression, or combinations of these disorders, the compounds are administered to a patient for a length of time sufficient to alleviate the symptoms associated with the disorders that the patient is suffering from. This time will vary, but periods of time exceeding two weeks are especially preferred. After the symptoms have been alleviated, the compound may then be discontinued to determine whether it is still required by the particular patient. Some patients may require a lifetime of treatment.

Illustratively, dosage levels of the administered active ingredients can be between 0.1 mg and 10 mg per kg of body mass. In human therapy, daily doses of between 1 mg and 1000 mg, administered orally, will preferably be used. The

pharmaceutical compositions containing the described compounds are preferably administered in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions and non-parenteral solutions or suspensions, containing suitable quantities of an active ingredient or its pharmaceutically acceptable salt. For oral administration, either solid or fluid unit dosage forms can be prepared.

Methods and compositions for making such dosage forms are well-known to those skilled in the art. For example, methods and compositions for making tablets and pills containing active ingredients, methods of making powders and their composition, and methods for making solutions, emulsions, suspensions, or extractions for parenteral and intravenous administration are described in the standard reference, Chase et al., Remington's Pharmaceutical Sciences, (16th ed., Mack Publishing Co., Easton, PA, U.S.A., 1980).

The term "unit dosage form" as used herein generally refers to physically discrete units suitable as unitary dosages for humans and animals, each containing a predetermined quantity of active material calculated to produce the desired psychotropic effect.

The invention is further illustrated by the following examples.

EXAMPLE I

A. Method of making 1-(4-bromobutyl)-2-pyrrolidinone: To a suspension of 37 g of powdered KOH in 500 ml of tetrahydrofuran (THF) were added 25.2 g of tetraethylammonium bromide. Then, a solution of 51.6 g of 2-pyrrolidinone and 129.6 g of 1,4-dibromobutane in 100 ml of THF was added dropwise to the mixture. The mixture was heated and refluxed for 2 hours. The precipitate was filtered, and the THF evaporated. The residue was dissolved in dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue distilled to yield 51.2 g of 1-(4-bromobutyl)-2-pyrrolidinone (38.8% yield) having a boiling point of 120 °C at 0.05 mm Hg.

B. Method of making 1-[4-[4-[4-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-pyrrolidinone (E)-2-butenedioate (1:1) salt: 2.7 g of 1-(4-bromobutyl)-2-pyrrolidinone were mixed with 2.2 g of 1-[4-(trifluoromethyl)-2-pyridinyl]piperazine dissolved in 30 ml of butanol, after which 1.3 g of sodium carbonate were added. The mixture was refluxed for 2 hours, after which the precipitate was filtered and washed with butanol.

The solvent was evaporated and the residue was dissolved in dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. After evaporation of the solvent 3.4 g of 1-[4-[4-[4-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-pyrrolidinone were obtained. To make the monofumarate, 1 g of fumaric acid dissolved in absolute ethanol was mixed with the free base. The resulting compound was recrystallized twice from acetonitrile, after which 2.4 g (52% yield) of 1-[4-[4-[4-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-pyrrolidinone (E)-2-butenedioate (1:1) salt were obtained with a melting point of 140 °C.

EXAMPLE II

In a analogous manner as described in Example I was prepared:
1-[4-[4-[4-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-piperidinone. M.p. 64 °C.
1-[4-[4-[4-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-3-methyl-2-pyrrolidinone (E)-2-butenedioate (1:1) salt. M.p. 152 °C.

EXAMPLE III

Method of making 1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-pyrrolidinone (E)-2-butenedioate (1:1) salt: 9 g of 1-(4-bromobutyl)-2-pyrrolidinone and 7.6 g of 1-[6-(trifluoromethyl)-2-pyridinyl]-piperazine were mixed with 100 ml of butanol. 4.3 g of sodium carbonate were added, and the mixture is refluxed for 3 hours. The precipitate is filtered and washed with butanol, and the filtrate is then evaporated. The residue was dissolved in dichloromethane, washed with water, dried over anhydrous magnesium sulfate, after which the solvent was evaporated to obtain 12.5 g of 1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]-butyl]-2-pyrrolidinone.
To make the monofumarate, the free base was mixed with 3.9 g of fumaric acid in absolute ethanol. The resulting substance was recrystallized twice from absolute ethanol, after which 7.8 g (43.6% yield) of 1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-pyrrolidinone (E)-2-butenedioate (1:1) salt were obtained. M.p. 173 °C.

EXAMPLE IV

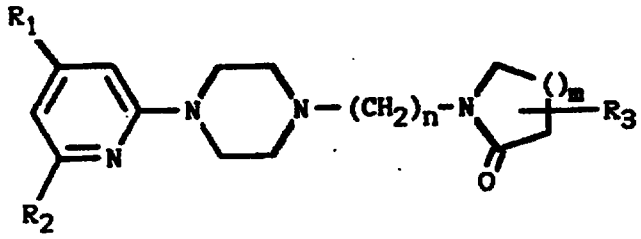
In a analogous manner as described in Example III were prepared:
1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-2-piperidinone (E)-2-butenedioate (2:3) salt. M.p. 154 °C.
1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-5-methyl-2-pyrrolidinone (E)-2-butenedioate (1:1) salt. M.p.

137 °C.
1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-3-methyl-2-pyrrolidinone (E)-2-butenedioate (1:1) salt.M.p. 125 °C.

Claims

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

1. A 4-[4- or 6-(trifluoromethyl)-2-pyridinyl]-1-piperazinylalkyl substituted lactam derivative having the general structure of formula I:



I

wherein one of the groups R_1 and R_2 is CF_3, and the other is hydrogen or CF_3;
R_3 is hydrogen or (1-4 C) alkyl;
n is an integer from 4 to 5; and
m is an integer from 1 to 2; or
pharmaceutically acceptable salts thereof.

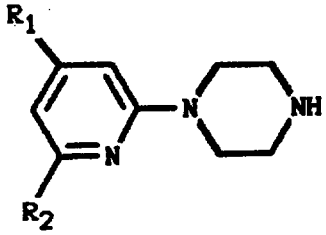
2. The compound of claim 1, wherein n is 4, and R_3 is hydrogen or (1-4 C) alkyl, or pharmaceutically acceptable salts thereof.

3. The compound of claim 1 wherein n is 4, R_3 is hydrogen or methyl, and one of the groups R_1 and R_2 is hydrogen, or pharmaceutically acceptable salts thereof.

4. The compound of claim 1 wherein R_1 is CF_3, R_2 and R_3 are hydrogen, n is 4, and m is 1, or pharmaceutically acceptable salts thereof.

5. A method of making the compound of claim 1 comprising

a) alkylating the terminal secondary amino portion of a 1-[4- or 6-(trifluoromethyl)-2-pyridinyl)piperazine derivative having formula II



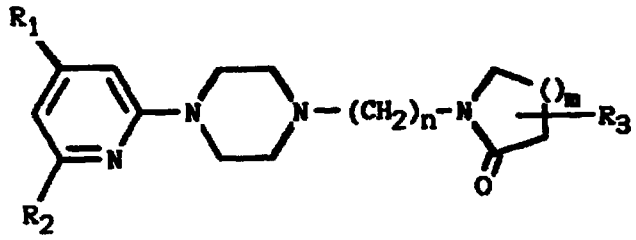
II

137 °C.
1-[4-[4-[6-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl]butyl]-3-methyl-2-pyrrolidinone (E)-2-butenedioate (1:1) salt.M.p. 125 °C.

Claims

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

1. A 4-[4- or 6-(trifluoromethyl)-2-pyridinyl]-1-piperazinylalkyl substituted lactam derivative having the general structure of formula I:



I

wherein one of the groups R_1 and R_2 is CF_3, and the other is hydrogen or CF_3;
R_3 is hydrogen or (1-4 C) alkyl;
n is an integer from 4 to 5; and
m is an integer from 1 to 2; or
pharmaceutically acceptable salts thereof.

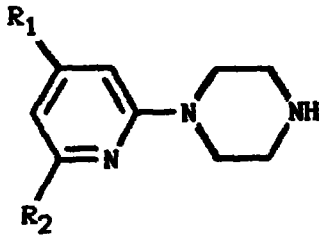
2. The compound of claim 1, wherein n is 4, and R_3 is hydrogen or (1-4 C) alkyl, or pharmaceutically acceptable salts thereof.

3. The compound of claim 1 wherein n is 4, R_3 is hydrogen or methyl, and one of the groups R_1 and R_2 is hydrogen, or pharmaceutically acceptable salts thereof.

4. The compound of claim 1 wherein R_1 is CF_3, R_2 and R_3 are hydrogen, n is 4, and m is 1, or pharmaceutically acceptable salts thereof.

5. A method of making the compound of claim 1 comprising

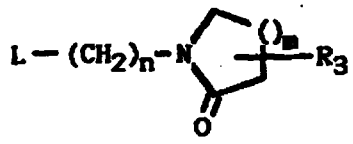
a) alkylating the terminal secondary amino portion of a 1-[4- or 6-(trifluoromethyl)-2-pyridinyl)piperazine derivative having formula II



II

* C L M S *

wherein R_1 and R_2 have the meanings given in claim 1, with a lactam having formula III



III

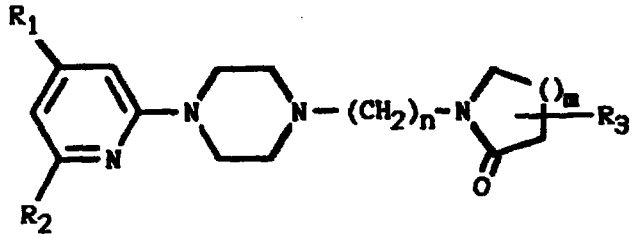
wherein R_3, n, and m have the meanings given in claim 1, and L represents a leaving group; or

b) alkylating the terminal secondary amino portion of said 1-[4- or 6-(trifluoromethyl)-2-pyridinyl]-piperazine derivative with a compound having the formula $L-(CH_2)_n-OH$, wherein L and n have the meanings given in claim 1, after which the hydroxy group is converted into a leaving group, as previously defined, and the resulting synthon is condensed in alkaline medium with 2-pyrrolidinone or with 2-piperidinone (δ-valerolactam), which are optionally provided with a (1-4 C) alkyl group; after which the compound obtained is optionally converted into a pharmaceutically acceptable salt.

6. The use of the compound of claims 1-4 for the manufacture of a medicament for the treatment of neurotic, psychotic, or depressive behaviour.

Claims for the following Contracting States : ES, GR

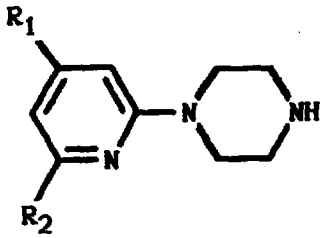
1. A method of making 4-[4- or 6-(trifluoromethyl)-2-pyridinyl]-1-piperazinylalkyl substituted lactam derivatives having the general structure of formula I:



I

wherein one of the groups R_1 and R_2 is CF_3, and the other is hydrogen or CF_3;
R_3 is hydrogen or (1-4 C) alkyl;
n is an integer from 4 to 5; and
m is an integer from 1 to 2; or
pharmaceutically acceptable salts thereof, comprising

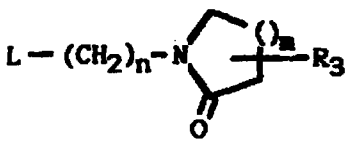
a) alkylating the terminal secondary amino portion of a 1-[4- or 6-(trifluoromethyl)-2-pyridinyl]piperazine derivative having formula II



II

* C L M S *

wherein R_1 and R_2 have the previously given meanings, with a lactam having formula III



III

wherein R_3, n, and m have the previously given meanings, and L represents a leaving group; or

b) alkylating the terminal secondary amino portion of said 1-[4- or 6-(trifluoromethyl)-2-pyridinyl]-piperazine derivative with a compound having the formula L-$(CH_2)_n$-OH, wherein L and n have the previously given meanings, after which the hydroxy group is converted into a leaving group, as previously defined, and the resulting synthon is condensed in alkaline medium with 2-pyrrolidinone or with 2-piperidinone (δ-valerolactam), which are optionally provided with a (1-4 C) alkyl group; after which the compound obtained is optionally converted into a pharmaceutically acceptable salt.

2. The method according to claim 1, wherein n is 4, and R_3 is hydrogen or (1-4 C) alkyl.

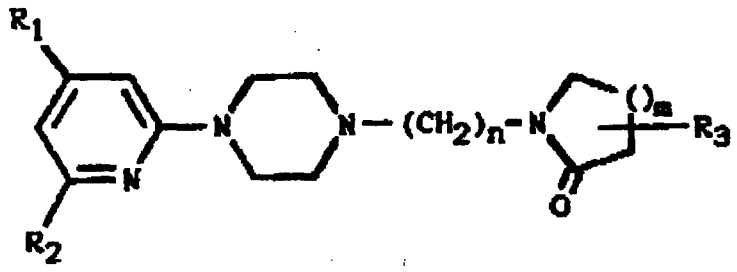
3. The method according to claim 1 wherein n is 4, R_3 is hydrogen or methyl, and one of the groups R_1 and R_2 is hydrogen.

4. The method according to claim 1 wherein R_1 is CF_3, R_2 and R_3 are hydrogen, n is 4, and m is 1.

Patentansprüche

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

1. 4-[4- oder 6-(Trifluormethyl)-2-piridinyl]-1-piperazinylalkyl substituierte Laktam-Derivate mit der generellen Struktur der Formel I:



I

worin eine der Gruppen R_1 und R_2 CF_3 ist, und die andere Wasserstoff oder CF_3;
R_3 Wasserstoff oder (1-4 C) Alkyl ist;
n eine ganze Zahl von 4 bis 5 ist; und
m eine ganze Zahl von 1 bis 2 ist;
oder pharmazeutisch annehmbare Salze davon.

2. Die Verbindung nach Anspruch 1, worin n 4 ist und R_3 Wasserstoff oder (1-4 C) Alkyl ist, oder pharmazeutisch annehmbare Salze davon.

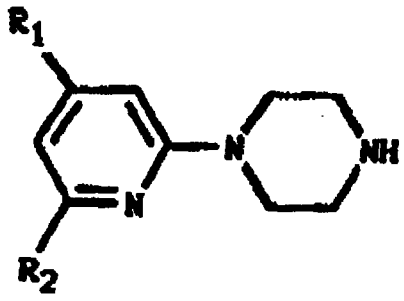
3. Die Verbindung nach Anspruch 1, worin n 4 ist, R_3 Wasserstoff oder Methyl und eine der Gruppen R_1 und R_2 Wasserstoff ist, oder pharmazeutisch annehmbare Salze davon.

4. Die Verbindung nach Anspruch 1 wobei, R_1 CF_3 ist, R_2 und R_3 Wasserstoffe sind, n 4 ist und m 1 ist, oder parmazeutisch annehmbare Salze davon

5. Ein Verfahren für die Herstellung der Verbindung nach Anspruch 1, umfassend

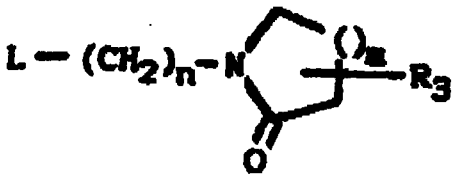
* C L M S *

a) die Alkylierung der endständigen sekundären Aminogruppe eines 1-[4- oder 6-(trifluormethyl) -2-piridinyl]-1-piperazin-Derivates der Formel II



II

worin R_2 und R_2 die in Anspruch 1 gegebenen Bedeutungen besitzen mit einem Laktam der Formel III



III

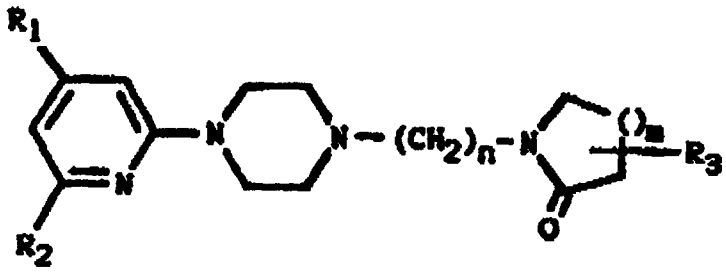
worin R_3, n und m die in Anspruch 1 gegebenen Bedeutungen besitzen und L eine abgehende Gruppe darstellt; oder

b) die Alkylierung der endständigen sekundären Aminogruppe des genannten 1-[4- oder 6-(Trifluormethyl)-2-piridinyl]-1-piperazin-Derivates mit einer Verbindung der Formel L-$(CH_2)_n$-OH, worin L und n die in Anspruch 1 gegebenen Bedeutungen besitzen, wonach die Hydroxygruppe in eine abgehende Gruppe umgewandelt wird, wie vorhergehend definiert, und das resultierende Synthon in alkalischem Medium mit 2- Pyrrolidinon oder mit 2-Piperidinon (δ-Valerolaktam) kondensiert wird, die gegebenenfalls mit einer (1-4 C)-Alylgruppe versehen sind; wonach die erhaltene Verbindung gegebenenfalls in ein pharmazeutisch annehmbares Salz umgewandelt wird.

6. Die Vervendung der Verbindung nach den Ansprüchen 1-4 für die Herstellung eines Medikamentes für die Behandlung neurotischen, psychotischen oder depressiven Verhaltens.

Patentansprüche für folgende Vertragsstaaten : ES, GR

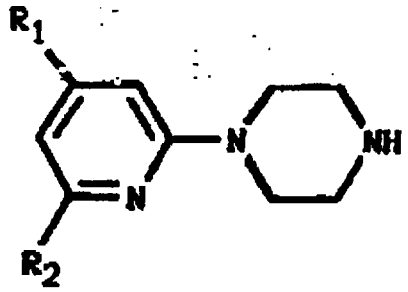
1. Ein Verfahren für die Herstellung von mit 4-[4- oder 6-(Trifluormethyl)-2-piridinyl]-1-piperazinylalkyl substituierten Laktam-Derivaten mit der generellen Struktur der Formel I:



worin eine der Gruppen R_1 und R_2 CF_3 ist und die andere Wasserstoff oder CF_3 ist;
R_3 Wasserstoff oder (1-4 C) Alkyl ist;
n eine ganze Zahl von 4 bis 5 ist; und
m eine ganze Zahl von 1 bis 2; oder parmazeutisch annehmbaren Salzen davon ist, umfassend:

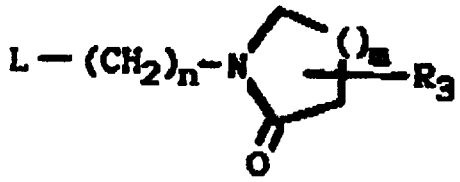
* C L M S *

a) die Alkylierung der endständigen sekundären Aminogruppe eines 1-[4- oder 6-(Trifluormethyl) -2-piridinyl]-1-piperazin-Derivates der Formel II



II

worin R_2 und R_2 die in vorhergehend gegebenen Bedeutungen besitzen mit einem Laktam der Formel III



III

worin R_3, n und m die vorhergehend gegebenen Bedeutungen besitzen und L eine abgehende Gruppe darstellt; oder

b) die Alkylierung der endständigen sekundären Aminogruppe des genannten 1-[4- oder 6-(Trifluormethyl) -2-piridinyl]-1-piperazin-Derivates mit einer Verbindung der Formel L-$(CH_2)_n$-OH, wobei L und n die vorhergehend gegebenen Bedeutungen besitzen wonach die Hydroxygruppe in eine abgehende Gruppe umgewandelt wird, wie vorhergehend definiert, und das resultierende Synthon in alkalischem Medium mit 2- Pyrrolidinon oder mit 2-Piperidinon (δ-Valerolaktam) kondensiert wird, die gegebenenfalls mit einer (1-4 C)-Alylgruppe versehen sind; wonach die erhaltene Verbindung gegebenenfalls in ein pharmazeutisch annehmbares Salz umgewandelt wird.

2. Das Verfahren gemäss Anspruch 1, worin n 4 ist und R_3 Wasserstoff oder (1-4 C)Alkyl ist.

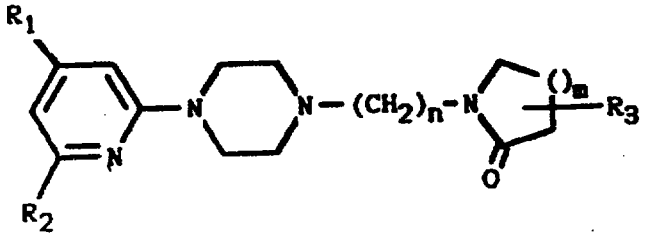
3. Das Verfahren gemäss Anspruch 1, worin n 4 ist, R_3 Wasserstoff oder Methyl ist und eine der Gruppen R_1 und R_2 Wasserstoff ist.

4. Das Verfahren gemäss Anspruch 1, worin R_1 CF_3 ist, R_2 und R_3 Wasserstoffe sind, n 4 ist und m 1 ist.

Revendications

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

1. Dérivé de lactame substitué par un groupe 4- [4- ou 6-(trifluorométhyl)-2-pyridinyl]-1-pipérazinylalkyle répondant à la formule générale développée I:



I

* C L M S *

dans laquelle l'un des groupes R_1 et R_2 est CF_3 et l'autre est un atome d'hydrogène ou un groupe CF_3;
R_3 est un atome d'hydrogène ou un radical alkyle en (C_1-C_4);
n est un nombre entier de 4 à 5; et
m est un nombre entier de 1 à 2; ou
les sels pharmaceutiquement acceptables en dérivant.

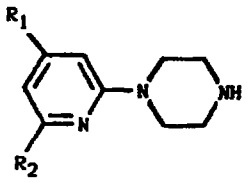
2. Le dérivé selon la revendication 1, dans lequel n est égal à 4, et R_3 est un atome d'hydrogène ou un radical alkyle en C_1 à C_4, ou les sels pharmaceutiquement acceptables en dérivant.

3. Le dérivé selon la revendication 1, dans lequel n est égal à 4, R_3 est un atome hydrogène ou un radical méthyle, et l'un des groupes R_1 et R_2 est un atome d'hydrogène, ou les sels pharmaceutiquement acceptables en dérivant.

4. Le dérivé selon la revendication 1 dans lequel R_1 est un groupe CF_3, R_2 et R_3 sont des atomes d'hydrogène, n est égal à 4, et m est égal à 1 ou les sels pharmaceutiquement acceptables en dérivant.

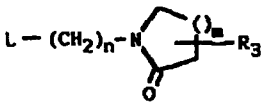
5. Le procédé de préparation du composé selon la revendication 1 comprenant

a) l'alkylation de la portion amino secondaire terminale d'un dérivé 1- [4- ou 6-(trifluorométhyl)-2-pyridinyl] pipérazine répondant à la formule II:



II

dans laquelle R_1 et R_2 sont tels que définis dans la revendication 1, avec un lactame répondant à la formule III:



III

dans laquelle R_3, n et m sont tels que définis dans la revendication 1, et L représente un groupe partant; ou

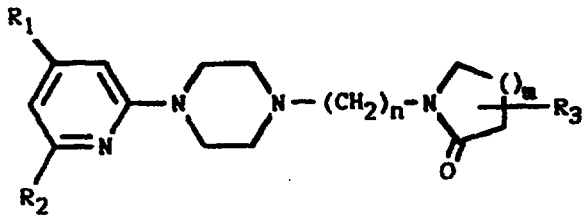
b) l'alkylation de la portion amino secondaire terminale dudit dérivé 1- [4- ou 6-(trifluorométhyl)-2-pyridinyl] - pipérazine par un composé de formule L-$(CH_2)_n$-OH, dans laquelle L et n sont tels que définis dans la revendication 1, suivie de la conversion du groupe hydroxy en un groupe partant, tel que défini, ci-dessus et condensation de l'intermédiaire résultant, en milieu alcalin, avec de la 2-pyrrolidinone ou avec de la 2-pipéridinone (δ-valérolactame), qui sont éventuellement porteurs d'un groupe alkyle en (C_1-C_4); puis conversion du composé obtenu, éventuellement, en un sel pharmaceutiquement acceptable.

6. Utilisation du dérivé selon les revendications 1-4 pour la préparation d'un médicament pour le traitement d'un comportement névrotique, psychotique ou dépressif.

* C L M S *

Revendications pour les Etats contractants suivants : ES, GR

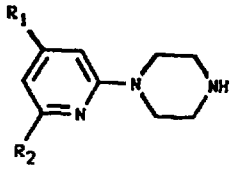
1. Procédé de préparation d'un dérivé de lactame substitué par un groupe 4-[4- ou 6-(trifluorométhyl)-2-pyridinyl]-1-pipérazinylalkyle répondant à la formule générale développée I:



I

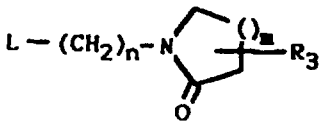
dans laquelle l'un des groupes R_1 et R_2 est CF_3 et l'autre est un atome d'hydrogène ou un groupe CF_3;
R_3 est un atome d'hydrogène ou un radical alkyle en C_1 à C_4;
n est un nombre entier de 4 à 5; et
m est un nombre entier de 1 à 2; ou
les sels pharmaceutiquement acceptables en dérivant, comprenant

a) l'alkylation de la portion amino secondaire terminal d'un dérivé 1-[4- ou 6-(trifluorométhyl)-2-pyridinyl] pipérazine ayant la formule II:



II

dans laquelle R_1 et R_2 sont tels que définis ci-dessus, avec un lactame répondant à la formule III:



III

dans laquelle R_3, n et m sont tels que définis ci-dessus, et L représente un groupe partant; ou
b) l'alkylation de la portion amino secondaire terminale dudit dérivé 1-[4- ou 6-(trifluorométhyl)-2-pyridinyl] - pipérazine par un composé de formule L-$(CH_2)_n$-OH, dans laquelle L et n sont tels que définis ci-dessus, suivi de la conversion du groupe hydroxy en un groupe partant, tel que défini ci-dessus, et condensation de l'intermédiaire résultant, en milieu alcalin, avec de la 2-pyrrolidinone ou avec de la 2-pipéridinone (δ-valérolactame), éventuellement porteurs d'un groupe alkyle en (C_1-C_4); puis conversion du composé obtenu, éventuellement, en un sel pharmaceutiquement acceptable.

2. Le procédé selon la revendication 1, dans lequel n est égal à 4, et R_3 est un atome d'hydrogène ou un radical alkyle en (C_1-C_4).

3. Le procédé selon la revendication 1, dans lequel n est égal à 4, R_3 est un atome hydrogène ou un radical méthyle, et l'un des groupes R_1 et R_2 est un atome d'hydrogène.

4. Le procédé selon la revendication 1 dans lequel R_1 est un groupe CF_3, R_2 et R_3 sont des atomes d'hydrogène, n est égal à 4, et m est égal à 1.

* C L M S *