Novel benzodiazepine compounds, their preparation, intermediates employed in their preparation, and pharmaceutical compositions containing them.

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Description

This invention relates to novel compounds, process for preparing them and their use as pharmacocuticals.

Various tricyclic compounds with pharmaceutical properties have already been investigated and these have been mainly of the type that comprise two benzene nuclei; one such reference being U.S. Patent 4,097,597, Tricyclic compounds including a heterocyclic group have also been disclosed such as for example in German OLS 27 07 270. We have now discovered a new group of compounds having the following basic structure:

The compounds of the invention are of the following formula (I):

or an acid addition salt thereof; in which R¹, R², R³ and R⁴ independently represent hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₇ cycloalkyl, C₂₋₇ cycloalkyl C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, C₁₋₄ alkanoyl, nitro, amino, C₂₋₄ acylamino, cyano, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkythio, C₁₋₄ haloalkoxy or a group of the formula —SO₂N(R⁹)₂, —SO₃R⁸ or —SO₃R⁴ where R⁸ is C₁₋₄ alkyl, C₁₋₄ haloalkyl or phenyl optionally substituted with halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro; in which R⁹ is a group of the formula:

where R⁴ is hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₁₋₄ alkanoyl, benzyl, cyano or phenyl optionally substituted with halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro, where R⁵ is hydrogen, C₁₋₄ alkyl or phenyl optionally substituted with halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro, and where n is 0 or 1; in which R⁶ is hydrogen, C₁₋₁₀ alkyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, benzyl, C₁₋₄ alkanoyl, C₁₋₄ carboxyl or benzoyl; and in which R⁷ is one of the values of R⁶ or halogen, nitro, cyano, amino or C₁₋₄ acylamino.

Compounds of formula (I) have been found to possess useful biological properties and the invention includes a compound of formula (I) for use as a pharmaceutical and especially for use in the treatment of disorders of the central nervous system.

A particular group of compounds of formula (I) is one in which R¹, R² and R³ independently represent hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkythio, C₁₋₄ haloalkylsulphonyl or phenylsulphonyl, R⁴ is hydrogen, R⁵ is hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkyl C₁₋₄ alkyl or benzyl, R⁷ is hydrogen or C₁₋₄ alkyl, R⁸ is hydrogen or C₁₋₄ alkyl, C₂₋₄ cycloalkyl, C₂₋₄ cycloalkyl C₁₋₄ alkyl or benzyl, and R⁹ is hydrogen or C₁₋₄ alkyl.

A preferred group of compounds is one of the following formula (II):


or an acid addition salt thereof; in which R¹, R² and R³ independently represent hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ alkylthio or phenylsulphonyl. R⁴ is hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or benzyl, R⁵ is hydrogen or C₁₋₁₀ alkyl and R⁶ is hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or benzyl.

A preferred group of compounds of formula (II) is one in which R¹, R² and R³ independently represent hydrogen, halogen or C₁₋₄ haloalkyl, R⁴ is C₁₋₈ alkyl, C₂₋₇ cycloalkyl or C₂₋₇ cycloalkyl C₁₋₄ alkyl, R⁵ is hydrogen and R⁶, hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl C₁₋₄ alkyl or benzyl, the compounds in which R⁴ is hydrogen being useful as intermediates in the preparation of preferred compounds.

Within the scope of compounds defined in formula (II) there can be listed compounds of especial interest, namely, those having one or more of the following features

(a) R⁴ is a halogen substituent, such as fluorine, chlorine or bromine, and R¹ and R² are hydrogen.

(b) R⁴ and R² both represent halogen, especially fluorine or chlorine and R¹ is hydrogen.

(c) R⁴ is halogen, especially fluorine, and R¹ and R² are hydrogen.

(d) R⁴ is C₁₋₄ alkyl, especially methyl or ethyl

(e) R⁴ is hydrogen.

(f) R⁴ is methyl

Specific examples of preferred compounds include

7-Bromo-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b] [1,5]benzodiazepine

7-Chloro-2-ethyl-2,10-dihydro-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

7-Chloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

7,8-Dichloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

7-Fluoro-2-ethyl-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

7-Fluoro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

8-Fluoro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-b][1,5]benzodiazepine

In the above general formulae, the term “C₁₋₄ alkyl” means a straight or branched chain alkyl group containing 1 to 10 carbon atoms and is especially, for example, methyl, ethyl, isopropyl, propyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl. A preferred alkyl group is “C₁₋₄ alkyl”. The term “C₁₋₄ haloalkyl” means any such alkyl group substituted by one or more, preferably three halogen atoms, and is especially trifluoromethyl. The terms “C₁₋₄ alkoxy” and “C₁₋₄ alkylthio” mean any C₁₋₄ alkyl group attached through an oxygen or sulphur atom to a ring atom and “C₂₋₇ haloalkoxy” means a C₁₋₄ alkyl group substituted by one or more, preferably three halogen atoms and is especially trifluoromethoxy. The term “C₂₋₇ carboxalkoxy” means a C₁₋₄ alkoxy group attached via a carbonyl group to a ring atom. “C₂₋₇ Alkanoxy” includes the formyl group and groups of the formula R¹CO where R¹ is C₁₋₄ alkyl. The term “C₂₋₇ alkoxynyl” refers to groups such as vinyl, alky and butyl. The term “amino” indicates a group of formula —NH₂ and also substituted amino groups such as mono-C₁₋₄ alkylamino and di-C₁₋₄ alkylaminogroups. The term “C₂₋₄ acylamino” means an amino group substituted by a C₂₋₄ acyl group especially acetyl. “C₂₋₇ Cycloalkyl” means a saturated ring having 3 to 7 carbon atoms in the ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, which can, in the group “C₂₋₇ cycloalkyl C₁₋₄ alkyl”, be attached to the ring via an alkyl chain having 1 to 4 carbon atoms. The term “optionally substituted phenyl” means a phenyl group which is unsubstituted or substituted by one or more groups, for example, halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro. Specific examples of such substituents include chlorine, trifluoromethyl, methyl and methoxy.

As indicated above, the compounds of the invention are useful both in their free base and acid addition salt forms. The acid addition salts are preferably the pharmaceutically acceptable, non-toxic acid addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycolic, maleic hydroxymaleic, fumaric, malic, tartaric, citric or lactic acid, or organic sulphonic acids for example methane sulphonic, ethane sulphonic, 2-hydroxyethane sulphonic, toluene- p-sulphonic or naphthalene-2-sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts such as, for example, those with picric or oxalic acid, since they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterization or purification of the bases.

According to a further aspect of the invention there is provided a process for producing a compound of formula (II) or an acid addition salt thereof, which comprises

(a) reacting an amine of formula R¹H with a compound of formula (III)
where Q represents a radical capable of being split off with the hydrogen atom of the amine R^9H, optionally followed when R^9 or R^9 is hydrogen by reaction with a compound of the formula R^nX or R^nX respectively, X being a leaving group, and optionally followed when n is 0 by oxidation, or (b) ring-closing a compound of formula (IV)

 optionally followed when R^6 or R^7 is hydrogen by reaction with a compound of the formula R^nX or R^nX respectively, X being a leaving group, and optionally followed when n is 0 by oxidation.

The above processes are of a general type previously described in the literature (see standard treatises for references to acylation, alkylation, oxidation and ring closure) and suitable Q and X radicals and appropriate reaction conditions can be readily chosen.

It may be mentioned, for example, that in reaction (a) the radical Q can be hydroxy, thiol, an alkoxy or alkylthio group containing 1 to 4 carbon atoms, for example a methoxy or methylthio group, a halogen atom, especially a chlorine atom, an amino group or a mono- or dialkyl-substituted amino group, each alkyl substituent containing 1 to 4 carbon atoms. Preferably, Q is hydroxy, thiol, C_1-C_4 alkoxy, C_1-C_4 alkylthio, halogen or amino and it is especially preferred that Q is hydroxy, thiol or amino (NH_2). When Q is hydroxy or thiol, the intermediates of formula (III) exist predominantly in their amide and thioamide forms:

\[
\begin{align*}
\text{O} & \quad \text{or} \quad \text{S} \\
\text{NH} & \quad \text{C} \\
\end{align*}
\]

and when Q is amino the intermediates of formula (III) may also exist in the imino form:

\[
\begin{align*}
\text{NH} & \quad \text{C} \quad \text{NH} \\
\end{align*}
\]

When Q is hydroxy, and the compound of formula (III) is an amide, reaction (a) can be accomplished in the presence of titanium tetrachloride which has the ability to react with the amine of formula R^9H to form a metal amine complex. Other metal chlorides such as those of zirconium, hafnium or vanadium may also be employed. The reaction is preferably carried out in the presence of an acid binding agent such as a tertiary amine, for example, triethylamine. Alternatively, the reaction can be carried out using excess of the amine of formula R^9H to act as an acid-binding agent. A suitable organic solvent such as toluene or chlorobenzene can be used as reaction medium, although it has been found that the use of anisole is particularly desirable, at least as a co-solvent, in view of its ability to form a soluble complex with TiCl_4.

If desired, elevated temperatures, for example up to 200°C, can be used to expedite the reaction and a preferred temperature range for carrying out the reaction is from 100°C to 150°C.

The amidines of formula (III) (Q is NH_2), can be in a salt form for example as the hydrochloride, and they can be similarly reacted with amines of formula R^9H, optionally diluted with a solvent such as anisole, dimethylformamide or dimethylsulphoxide, and optionally using a catalyst such as TiCl_4 at a temperature range of 100°C to 150°C. Alternatively the amidine can be converted into the corresponding amide of formula (III) (Q is OH) by alkaline hydrolysis.

Thioamides of formula (III) (Q is SH), iminothiolothers, iminoethers or iminohalides, or other derivatives containing active Q radicals as specified above, tend to be more reactive towards the amine R^9H and can usually be reacted without the necessity for the presence of TiCl_4, but otherwise employing the same conditions of temperature and solvent.

In reaction (b) compounds of formula (IV) are ring-closed by employing, for example, the same conditions in terms of catalyst and solvent as those described above for reaction (a) and preferably at a temperature of 150°C to 200°C. The compounds of formula (IV) are conveniently prepared in situ without isolation.

When the compound prepared by reaction (a) or (b) is one in which R^6 or R^7 is hydrogen, it may be further reacted to provide other compounds of the invention. For example when R^6 is hydrogen, the compound can be reacted with R^nX by conventional alkylation or acylation type methods, X being a leaving group. The compound is dissolved in a suitable inert polar solvent such as acetonitrile or ethanol.
and the reagent of formula R^nX added, the reaction mixture then being heated under reflux in the presence of a base. The group X can be a suitable reactive atom such as chlorine, bromine or iodine, or a reactive group such as tosyl mesyl. Similarly, when R^n is hydrogen, the compound can be reacted with a reagent of formula R^nX in an inert solvent and in the presence of a base.

When the compound prepared by reaction (a) or (b) is one in which n is 0, it may be oxidised to provide other compounds of the invention, that is, the corresponding compound in which n is 1. Suitable oxidising agents include for example m-chloroperbenzoic acid and the reaction is preferably carried out in an inert solvent such as for example dichloromethane at a temperature of from −10°C to +10°C.

The compounds of formula (I) produced by the above processes may be isolated per se or may be converted to their corresponding acid addition salts using conventional methods.

The amides of formula (III) (Q is OH) can be prepared by a process which involves the ring-closure of an amino-ester of formula (V)

\[
\begin{align*}
\text{R}^2 & \quad \text{NH}_2 \\
\text{R}^3 & \quad \text{R}^4 \\
& \quad \text{N} \\
\text{R}^1 & \quad \text{CO}_2 \text{R}^{12} \\
& \quad \text{R}^7
\end{align*}
\]

(V)

where \( R^{12} \) is a C_4 alkyl group, employing for example sodium methylsulphinyl methanide in a suitable solvent such as dimethyl sulphoxide.

Alternatively amides of formula (III) (Q is OH) can be prepared by ring-closure of an amino-acid of formula (VI)

\[
\begin{align*}
\text{R}^2 & \quad \text{NH}_2 \\
\text{R}^3 & \quad \text{R}^4 \\
& \quad \text{N} \\
\text{R}^1 & \quad \text{CO}_2 \text{H} \\
& \quad \text{R}^7
\end{align*}
\]

(VI)

employing for example dicyclohexylcarbodiimide (DCC) in a suitable solvent such as tetrahydrofuran. These amino-acids can be obtained from the esters of formula (V) by basic hydrolysis using for example sodium hydroxide in ethanol.

The esters of formula (V) can be prepared by condensation of a pyrazole compound of formula

\[
\begin{align*}
\text{R}^{12} & \quad \text{O}_2 \text{C} \\
& \quad \text{H}_2 \text{N} \\
& \quad \text{N} \\
& \quad \text{NR}^6 \\
& \quad \text{R}^7
\end{align*}
\]

with an ortho-halonitribenzene of formula

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^1 \\
\text{R}^3 & \quad \text{NO}_2 \\
& \quad \text{R}^4 \\
& \quad \text{Z}
\end{align*}
\]

where Z is halogen, preferably fluorine, chlorine or bromine, in the presence of a base for example, sodium hydride in a solvent such as tetrahydrofuran or dimethylformamide, n-butyl lithium in tetrahydrofuran, potassium carbonate in dimethylsulphoxide or with a tetraalkylammonium salt in a two-phase system, to form a nitro ester of formula
which can be reduced to the amino ester of formula (V) catalytically, employing for instance hydrogen and palladium or chemically, employing for example, stannous chloride and hydrogen chloride in aqueous ethanol, or ammonium polysulphide.

Similarly, the amidines of formula (III) (Q is NH$_2$) can be prepared by condensation of a pyrazole of formula

with an ortho-halonitrobenzene as outlined above, followed by simultaneous reduction and ring-closure of the amide of formula (III) employing for example stannous chloride and hydrogen chloride in aqueous ethanol or, alternatively, by reduction with hydrogen and palladium or ammonium polysulphide followed by acid-catalysed ring closure.

Pyrazole starting materials used in the processes described above are either known compounds, see for example J. Am. Chem. Soc. (1956) 78 784; Helv. Chim. Acta (1958) 41 1052; Helv. Chim. Acta (1959) 42 349 and 763; German Patent 1,106,330 and British Patent 884,851; or can be prepared by conventional techniques from known compounds. The ortho-halonitrobenzene intermediates are either commercially available or can be simply prepared from commercially available substances.

Thioamides of formula (III) (Q is SH) can be prepared by treating a solution of the corresponding amide in anhydrous basic solvent such as for example pyridine with phosphorus pentasulphide. Similarly, the amides can be converted to iminothioethers, iminoethers or iminoaldehydes, or other derivatives containing active Q radicals, by treatment with conventional reagents such as for example in the case of an iminochloride, phosphorus pentachloride.

Compounds of formula (III) are novel and, in particular, those in which Q is hydroxyl, thiol or amino are included as an aspect of the invention.

In reaction (b), the compounds of formula (IV) are novel and they are included as a further aspect of this invention. They can be prepared in situ without isolation by reacting a compound of formula (V) with an amine of formula R$_3$H$_4$ such as by heating to a temperature between 30°C and 120°C, for example 100°C, in a suitable solvent such as for example anisole and employing TiCl$_4$ as catalyst, or by conventional methods from compounds of formula (V) or (VI).

It will be understood that electrophilic substitution on the aromatic nucleus can be carried out on compound of formulae (I), (III) (IV) in conventional manner to produce other derivatives. For instance, an amide of formula (III) can be acetylated using acetyl chloride and stannic chloride or halogenated employing for example N-chlorosuccinimide, to give the corresponding acetyl or chloro derivatives. Products of formula (I) in which R$_1$, R$_2$, R$_3$ or R$_4$ is amino can be acylated or alkylated in conventional manner to form the corresponding acylamino or alkylamino derivatives.

As an illustration of the preparation of representative compounds of the invention the following reaction scheme is given, in which various routes for preparing a 4-(4-alkyl-1-piperazinyl)-2,10-dihydropyrazolo[3,4-b][1,5] benzodiazepine are shown:
The compounds of the invention have useful central nervous system activity as demonstrated by well-known test procedures. In behavioural studies in mice, for instance, the compounds of the invention described in the following Examples were observed to produce hypothermia and activity decrease at a dose range of 12.5 to 200 mg/kg p.o. Preferred compounds have also been tested following chronic administration when a behavioural supersensitivity is produced by locally injected dopamine in a manner similar to that described in Psychopharmacologia (1975) 45 151—155. The activity profile observed in this test along with the lack of response in tests such as the production of catalepsy indicate that these compounds possess useful central nervous system activity and do not produce certain undesirable side effects. For some time it has been recognised that conventional central nervous system drugs can have undesirable characteristics and the potential absence of these side effects in compounds according to the invention represents a significant advance. In addition, compounds the invention possess unexpected anxiolytic activity as demonstrated by their profile in the test described in Neuropharmacology (1979) 18 689—695. The compounds of formula (I) and acid addition salts thereof are thus, potent centrally acting compounds with neuroleptic, sedative, relaxant, anxiolytic or anti-emetic properties. These properties, coupled with their low toxicity render them useful in the treatment of
mild anxiety states and certain kinds of psychotic conditions such as schizophrenia and acute mania.

The compounds of this invention are effective over a wide dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage required will normally fall within the range of 0.5 to 50 mg/kg per day, for example in the treatment of adult humans, dosages of from 5 to 500 mg per day may be used.

The compounds of the invention will normally be administered orally or by injection and, for this purpose, the compounds will usually be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula I or an acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, by formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions for parenteral use or as suppositories. Preferably the compositions are formulated in a dosage unit form, each dosage containing from 1 to 200 mg, more usually 5 to 100 mg, of the active ingredient.

The following Examples illustrate the invention:

Example 1
Ethyl 3-[4-fluoro-2-nitroanilino]-1-methylpyrazole-4-carboxylate
A solution of ethyl 3-aminoc-1-methylpyrazole-4-carboxylate (Helv. Chim. Acta (1959) 42 349) (17 g) in dry tetrahydrofuran (250 ml) was stirred under nitrogen at −10°C. n-Butyl lithium (75 ml of 1.84 molar solution in hexane) was added at −10 to −15°C. The mixture was stirred at −15°C for 10 minutes and a solution of 2,5-difluorotriphenylbenzene (16 g) in dry tetrahydrofuran (50 ml) was added at −15 to −10°C. The solution was warmed to room temperature and stirred for 1 hour. The ink-blue solution was poured into 500 ml of a 1:1 mixture of hydrochloric acid (2M) and ice-brine, extracted with chloroform (3 × 250 ml), washed with water (2 × 250 ml), dried with magnesium sulphate and evaporated to dryness. The brick-red residue was crystallised from ethanol (800 ml) to give the title compound having a m.p. of 162°C.

The following compounds were similarly prepared using the above process. In each case the recrystallisation solvent is given in parenthesis.

Ethyl 3-ethyl-3-[4,5-difluoro-2-nitroanilino]pyrazole-4-carboxylate, m.p. 141°C (isopropanol)
Ethyl 1-methyl-3-[4-fluoro-2-nitroanilino]pyrazole-4-carboxylate, m.p. 138°C (ethanol).
Ethyl 1-methyl-3-[2-nitro-4-trifluoromethylanilino]pyrazole-4-carboxylate, m.p. 158°C (isopropanol).
Ethyl 3-[5-fluoro-2-nitroanilino]-1-methylpyrazole-4-carboxylate, m.p. 165°C (ethanol).
Ethyl 3-[5-fluoro-2-nitroanilino]-1-[1-propyl]pyrazole-4-carboxylate, m.p. 109°C (ethanol).
Ethyl 3-[4-fluoro-2-nitroanilino]-1-[1-methyl]pyrazole-4-carboxylate, m.p. 106.5°C (ethanol).
Ethyl 3-[4-fluoro-2-nitroanilino]-1-[1-hexyl]pyrazole-4-carboxylate, m.p. 73°C (ethanol).
Ethyl 3-[2-nitroanilino]-1-methylpyrazole-4-carboxylate, m.p. 146°C (isopropanol).

Example 2
3-[4-Chloro-2-nitroanilino]-1-methylpyrazole-4-carbonitrile
3-Amino-1-methylpyrazole-4-carbonitrile (Helv. Chim. Acta (1959) 42 763) (3.66 g) was stirred in dry tetrahydrofuran (40 ml). Sodium hydride (50% oil dispersion, 2.28 g) was added and the mixture was stirred for 10 minutes. 2,5-Dichloronitrobenzene (5.76 g) was added and the solution stirred under nitrogen for 20 hours. Water was added dropwise to destroy excess sodium hydride, then the solution was poured on to a mixture of ice and dilute hydrochloric acid. After standing for 1 hour the brick-red precipitate was filtered, washed with water and dried. Crystallisation from ethanol-ethyl acetate afforded the product m.p. 205°C.

The following compounds were similarly prepared. In each case the recrystallisation solvent is given in parenthesis.

3-[4-iodo-2-nitroanilino]-1-methylpyrazole-4-carbonitrile, m.p. 212°C (ethanol-ethyl acetate)
3-[5-Chloro-2-nitroanilino]-1-methylpyrazole-4-carbonitrile, m.p. 187°C (ethanol-ethyl acetate)
3-[4,5-Dichloro-2-nitroanilino]-1-methylpyrazole-4-carbonitrile, m.p. 225°C. (ethanol-ethyl acetate)
3-[4-Bromo-2-nitroanilino]-1-methylpyrazole-4-carbonitrile, m.p. 208°C (ethanol-ethyl acetate)
3-[4-Trifluoromethyl-2-nitroanilino]-1-methylpyrazole-4-carbonitrile, m.p. 183°C—184°C (ethanol)
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3-(4-Chloro-2-nitroanilino)-1-ethylpyrazole-4-carbonitrile, m.p. 172°C (ethanol-ethylacetate)
3-(4-Chloro-2-nitroanilino)-1-(2-methyl-1-propyl)pyrazole-4-carbonitrile, m.p. 151°C (ethanol)
3-(4-Chloro-2-nitroanilino)-1-cyclopentylpyrazole-4-carbonitrile, m.p. 145°C (ethanol)
3-(4-Fluoro-2-nitroanilino)-1-methylpyrazole-4-carbonitrile, m.p. 174°C (ethanol)
3-(3-Chloro-2-nitroanilino)-1-methylpyrazole-4-carbonitrile, m.p. 190°C (ethanol)
1-methyl-3-(2,4-dinitroanilino)pyrazole-4-carbonitrile, m.p. 224°C (ethanol-ethyl acetate)

Example 3

Ethyl 1,5-dimethyl-3-(4-fluoro-2-nitroanilino)pyrazole-4-carboxylate

Ethyl 3-amino-1,5-dimethylpyrazole-4-carboxylate (5.5 g), 2,5-difluorotoluene (6.6 g) and anhydrous potassium carbonate (8.9 g), were stirred in dimethylsulphoxide (60 ml) under dry nitrogen at 70°C for 20 hours. The mixture was poured on to 300 ml of ice-cold dilute hydrochloric acid, extracted with chloroform (3x), washed with water (2x), dried with magnesium sulphate and the solvent evaporated under reduced pressure. The yellow-brown residue was crystallised from ethanol to give the title compound having a m.p. of 174°C.

Example 4

1-Methyl-3-(2-nitroanilino)pyrazole-4-carbonitrile

3-Amino-1-methylpyrazole-4-carbonitrile (Helv. Chim. Acta (1959) 42, 763) (7.5 g) and 2-fluorotoluene (8.4 g) were stirred in toluene (120 ml) with Adogen 464 (3.0 g) and potassium carbonate (18.5 g) at 60°C. 50% Sodium hydroxide solution (0.1 ml) was added and the mixture was heated under reflux for 2 hours. The mixture was poured on to dilute hydrochloric acid, extracted, the aqueous layer washed with toluene and the combined extracts washed twice with water. After evaporation the residue was crystallised from ethanol (750 ml) to give the title compound, m.p. 172°C.

Example 5

Ethyl 3-(2-amino-4-trifluoromethylanilino)-1-methylpyrazole-4-carboxylate

Ethyl 1-methyl-3-(2-nitro-4-trifluoromethylanilino)pyrazole-4-carboxylate (9.2 g) was hydrogenated at 60 p.s.i. in a mixture of ethyl acetate (200 ml) and ethanol (50 ml) over 10% palladium on charcoal (1.0 g). The catalyst was removed by filtration, the solvent evaporated and the residue crystallised from carbon tetrachloride to give the title compound m.p. 162°C.

The following compounds were similarly prepared and used in Examples 10 and 13 without purification.

Ethyl 3-(2-amino-4-fluoroanilino)-1-methylpyrazole-4-carboxylate.
Ethyl 3-(2-amino-4-fluoroanilino)-1,5-dimethylpyrazole-4-carboxylate.
Ethyl 3-(2-amino-4-fluoroanilino)-1-ethylpyrazole-4-carboxylate.
Ethyl 3-(2-amino-5-fluoroanilino)-1-methylpyrazole-4-carboxylate.
Ethyl 3-(2-amino-4,5-difluoroanilino)-1-methylpyrazole-4-carboxylate.
Ethyl 3-(2-amino-4-fluoroanilino)-1-(1-propyl)pyrazole-4-carboxylate.
Ethyl 3-(2-amino-4-fluoroanilino)-1-(1-methylthyl)pyrazole-4-carboxylate.
Ethyl 3-(2-amino-4-fluoroanilino)-1-(1-hexyl)pyrazole-4-carboxylate.
Ethyl 3-(2-aminoanilino)-1-methylpyrazole-4-carboxylate.

Example 6

3-(2-Amino-4-nitroanilino)-1-methylpyrazole-4-carbonitrile

1-Methyl-3-(2,4-dinitroanilino)pyrazole-4-carbonitrile (2.88 g) was stirred in a mixture of 0.88 ammonia solution (60 ml), water (90 ml) and ethanol (60 ml) under reflux whilst a slow stream of hydrogen sulphide gas was bubbled through for 2 hours. The mixture was cooled, filtered and the residue crystallised from ethyl acetate-n-hexane to give the title compound m.p. 204°C.

Example 7

4-Methyl-1-(3-[2-amino-4-trifluoromethylanilino]-1-methylpyrazole-4-carbonylpiperazine

Ethyl 3-(2-amino-4-trifluoromethylanilino)-1-methylpyrazole-4-carboxylate (4.75 g) was stirred in a mixture of N-methylpiperazine (25 ml) and anisole (65 ml). A solution of titanium tetrachloride (4.2 ml) in anisole (20 ml) was added and the mixture was stirred under nitrogen at 65°C for 30 minutes. A mixture of isopropanol (25 ml) and 0.88 ammonia solution (25 ml) was added and the stirred mixture cooled to 25°C. The precipitate was removed by filtration, washing with ethyl acetate. The combined filtrates were washed with water (3x), dried over magnesium sulphate, the solvent evaporated and the residue crystallised from acetonitrile to give the title compound m.p. 170°C.

Other examples of this type were prepared in situ and cyclised as in Example 13.

Example 8

4-Amino-7-chloro-2,10-dihydro-2-methyl-pyrazole [3,4-b] [1,5] benzodiazepine

To 1-methyl-3-(4-chloro-2-nitroanilino)pyrazole-4-carbonitrile (16 g) stirred in ethanol (500 ml) was added a solution of anhydrous stannous chloride (33.1 g) in concentrated hydrochloric acid (176 ml). The mixture was heated under reflux for 2 hours, cooled, filtered and crystallised from methyl-
ated spirits (1 litre) to give the title compound as its hydrochloride salt m.p. > 260°C. 2.0 g of the hydrochloride salt was partitioned between dilute ammonia solution and chloroform. The organic phase was washed with water, dried with magnesium sulphate, evaporated and the residue crystallised from chloroform-n-hexane to give the title compound as the free base m.p. 240°C.

The following compounds were similarly prepared and used as the hydrochlorides without purification as in Example 15.
4-Amino-2,10-dihydro-7-iodo-2-methylpyrazolo[3,4-b] [1,5] benzodiazepine
4-Amino-8-chloro-2,10-dihydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7,8-dichloro-2,10-dihydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7-bromo-2,10-dihydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-2,10-dihydro-7-trifluoromethyl-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7-chloro-2-ethyl-2,10-dihydropyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7-chloro-2,10-dihydro-2-(2-methyl-1-propyl)pyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7-chloro-2-cyclopentyl-2,10-dihydropyrazolo [3,4-b] [1,5] benzodiazepine
4-Amino-7-fluoro-2,10-dihydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine.

Example 9
4-Amino-2,10-dihydro-2-methyl-7-nitropyrazolo [3,4-b] [1,5] benzodiazepine hydrochloride

Example 10
3-(2-Amino-4-nitroanilino)-1-methylpyrazole-4-carbonitrile (250 mg) was heated under reflux in a mixture of isopropanol (10 ml) and concentrated hydrochloric acid (1 ml) for 20 hours. The solution was evaporated under reduced pressure and the residue crystallised from methylated spirits to give the title compound m.p. > 260°C.

Example 11
7-Fluoro-2,4,5,10-tetrahydropyrazolo [3,4-b] [1,5] benzodiazepin-4-one
A solution of sodium methyl sulphinyl methane was generated by stirring sodium hydride (50% oil dispersion, 1.5 g) in dry dimethylsulphoxide (15 ml) at 65°C until gas evolution ceased. A solution of ethyl 3-(2-amino-4-fluoroanilino)-1-methylpyrazole-4-carboxylate (2.7 g) dissolved in dry dimethyl sulphoxide (5 ml) was added dropwise and the mixture stirred at 65°C for 20 minutes. The mixture was poured on to excess ice-water, filtered and dried to give the title compound which was crystallised from chloroform-hexane m.p. 264°C.

Example 12
7-Chloro-2,4,5,10-tetrahydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine-4-thione
7-Chloro-2,4,5,10-tetrahydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine-4-one (7.2 g) was added to a stirred solution of phosphorous pentasulphide (6.5 g) in anhydrous pyridine (145 ml). The mixture was heated under reflux for 1.5 hours, poured on to ice, and the precipitate crystallised from chloroform methanol to yield the title compound m.p. > 260°C.

Example 13
2-Ethyl-7-fluoro-2,10-dihydro-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine

Ethyl 3-(2-amino-4-fluoroanilino)-1-ethylpyrazole-4-carboxylate (2.64 g) was dissolved in a mixture of N-methyl piperazine (12.5 ml) and anisole (50 ml). Titanium tetrachloride (3 ml) in anisole (12 ml) was added, dropwise, and the stirred solution was heated at reflux under an atmosphere of dry nitrogen for 24 hours. The mixture was cooled to 60°C and a mixture of isopropanol (10 ml) and 0.88 ammonia solution (10 ml) cautiously added. This mixture was allowed to cool to room temperature over 1 hour, then filtered through a pad of Celite (registered Trade Mark), whilst washing with ethyl acetate. The filtrate was washed with water (3x), dried over magnesium sulphate and the solvent removed. The residue was filtered through a short column of Florisil (registered Trade Mark), eluting with ethyl acetate. After removal of solvent the title product was crystallised from acetonitrile m.p. 181°C.

The following compounds were similarly prepared:
7-Fluoro-2,10-dihydro-2,3-dimethyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 234°C (acetonitrile)
7-Chloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 107—109°C (acetonitrile)
8-Fluoro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 192°C (acetonitrile)

10
Example 14

7-Fluoro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine and citrate salt.

7-Fluoro-2,4,5,10-tetrahydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepin-4-one (0.95 g) was stirred in a mixture of N-methylpiperazine (10 ml) and anisole (15 ml). A solution of titanium tetrachloride (0.55 ml) in anisole (10 ml) was added and the mixture stirred under nitrogen at 130°C for 2 hours. The mixture was poured on to ice-dilute ammonia solution and extracted into methylene chloride. The extract was washed with water (3x), dried and evaporated. The residue was chromatographed on Florisoril (registered trade mark) eluting with ethyl acetate and crystallised from acetonitrile, m.p. 192°C.

The citrate salt was prepared by adding a solution of citric acid in ethanol to a solution of the title compound in a 1:1 mixture of ethanol and ethyl acetate m.p. 138°C (softens).

Example 15

2,10-Dihydro-7-iodo-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine

To a mixture of N-methylpiperazine (10 ml), dimethylsulphoxide (25 ml) and toluene (25 ml) through which nitrogen had been bubbled for 30 minutes was added 4-amino-2,10-dihydro-7-iodo-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine hydrochloride (3.84 g). The stirred mixture was heated under nitrogen at 120°C for 20 hours. The mixture was cooled to 60°C and water (25 ml) added. The residue was filtered, dried and crystallised from chloroform-n-hexane m.p. 113°C.

The following compounds were similarly prepared:

8-Chloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 221°C (chloroform-n-hexane).

7,8-Dichloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 158°C (acetonitrile).

7-Bromo-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 162°C (acetonitrile).

2,10-Dihydro-7-trifluoromethyl-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 129—130°C (ethyl acetate-hexane).

7-Chloro-2-ethyl-2,10-dihydro-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 155°C (acetonitrile).

7-Chloro-2,10-dihydro-4-(4-methyl-1-piperazinyl)-2-(2-methyl-1-propyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 161°C (acetonitrile).

7-Chloro-2-cyclopentyl-2,10-dihydro-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 151°C (acetonitrile).

7-Fluoro-2,10-dihydro-2-methyl-4-(1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 183—185°C (acetonitrile).

6-Chloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine, m.p. 214°C (chloroform-n-hexane).

Example 16

7-Chloro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine

7-Chloro-2,4,5,10-tetrahydro-2-methyl-4-(4-methyl-1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine-4-thione (0.265 g) was heated under reflux in N-methylpyrroldine (3 ml) for 20 hours. The cooled mixture was dissolved in 1M hydrochloric acid, washed with ethyl acetate (2X), basified with 0.88 ammonia and extracted into dichloromethane. The extract was washed with water, dried with magnesium sulphate and evaporated to leave a residue which was crystallised from chloroform-n-hexane m.p. 173—175°C.

Example 17

4-(4-Cyclopropylmethyl-1-piperazinyl)-7-fluoro-2-methyl-2,10-dihydro-2-methylpyrazolo [3,4-b] [1,5] benzodiazepine

A solution of 7-fluoro-2,10-dihydro-2-methyl-4-(1-piperazinyl)pyrazolo [3,4-b] [1,5] benzodiazepine (1.0 g), bromomethylcyclopropane (0.5 g) and triethylamine (0.0375 g) in acetonitrile (30 ml) was stirred at ambient temperature for 20 hours. The solution was poured into water and the product extracted with chloroform (3X). The organic extract was washed with saturated brine and water, dried over magnesium sulphate, the solvent removed and the residue crystallised from ethyl acetate to give
the title compound m.p. 186—189°C 4-(4-Benzyl-1-piperazinyl-7-fluoro-2,10-dihydro-2-methyl-
pyrazolo [3,4-b] [1,5] benzodiazepine was similarly prepared, m.p. 241—245°C (ethyl acetate-diethyl ether).

Example 18
4-(7-Fluoro-2,10-dihydro-2-methyl-pyrazolo [3,4-b] [1,5] benzodiazepin-4-yl)-1-methyl piperazine-1-
oxide monohydrate

7-Fluoro-2,10-dihydro-2-methyl-4-(4-methyl-1-piperazinyl)-pyrazolo [3,4-b] [1,5] benzo-
diazepine (2.0 g) was stirred in dichloromethane (50 ml) at 0—5°C whilst m-chloroperbenzoic acid
(1.5 g) was added in portions. The solution was stirred for 30 minutes then filtered through a column of
basic alumina, eluting with 9:1 chloroform:methanol to give, after removal of the solvent and crystal-
lisation from acetonitrile-diethyl ether, the title compound m.p. 228°C.

The following formulations were prepared employing 7-fluoro-2,10-dihydro-2-methyl-4-(4-
methyl-1-piperazinyl) pyrazolo [3,4-b] [1,5] benzodiazepine as the active ingredient. Formulations con-
taining other active ingredients of the invention can be prepared in a similar manner.

Example 19
Tablets each containing 10 mg of active ingredient were made up as follows

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>10 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>45 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>1 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100 mg</strong></td>
</tr>
</tbody>
</table>

The active ingredient, starch and cellulose were passed through a No. 44 mesh B.S. sieve and
mixed thoroughly. The solution of polyvinylpyrrolidone was mixed with the resultant powders which
were then passed through a No. 12 mesh B.S. sieve. The granules so produced were dried at 50—60°C
and passed through a No. 16 mesh B.S. sieve. The sodium carboxymethyl starch, magnesium stearate
and talc, previously passed through a No. 60 mesh B.S. sieve, were then added to the granules which,
after mixing, were compressed on a tablet machine to yield tablets each weighing 100 mg.

Example 20
Capsules each containing 20 mg of medicament were made as follows

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>20 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>89 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>89 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200 mg</strong></td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch and magnesium stearate were passed though a No. 44
mesh B.S. sieve and filled into hard gelatin capsules in 200 mg quantities.

Example 21

Suppositories each containing 25 mg of active ingredient were made as follows

<table>
<thead>
<tr>
<th>Medicament</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fatty acid</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>glycerides to</td>
<td></td>
</tr>
</tbody>
</table>

The active ingredient was passed through a No. 60 mesh B.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture was then poured into a suppository mould of nominal 2 g capacity and allowed to cool.

Example 22

Suspensions each containing 5 mg of medicament per 5 ml dose were made as follows

<table>
<thead>
<tr>
<th>Medicament</th>
<th>5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium carboxymethyl</td>
<td>50 mg</td>
</tr>
<tr>
<td>cellulose</td>
<td></td>
</tr>
<tr>
<td>Syrup</td>
<td>1.25 ml</td>
</tr>
<tr>
<td>Benzoic acid solution</td>
<td>0.10 ml</td>
</tr>
<tr>
<td>Flavour</td>
<td>q.s.</td>
</tr>
<tr>
<td>Colour</td>
<td>q.s.</td>
</tr>
<tr>
<td>Purified water to</td>
<td>5 ml</td>
</tr>
</tbody>
</table>

The medicament was passed through a No. 44 mesh B.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavour and colour were diluted with some of the water and added, with stirring. Sufficient water was then added to produce the required volume.

Claims

1. A compound of the formula

or an acid addition salt thereof;
in which R¹, R², R³ and R⁴ independently represent hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, C₁₋₄ alkanoyl, nitro, amino, C₂₋₄ acylamino, cyano, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkythio, C₁₋₄ haloalkoxy or a group of the formula —SO₂N(R⁹)₂, —SO₃R⁸ or —SO₃R⁸ where R⁸ is C₁₋₄ alkyl, C₁₋₄ haloalkyl or phenyl optionally substituted with halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro; in which R⁹ is a group of the formula

where R⁹ is hydrogen, C₁₋₄ alkyl, C₂₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₁₋₄ alkanoyl, benzyl, cyano or phenyl optionally substituted with halogen, C₁₋₄ haloalkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy or nitro, where R¹⁰ is hydrogen, C₁₋₄ alkyl or phenyl optionally substituted with halogen,
C_{1-4} haloalkyl, C_{1-4} alkyl, C_{1-4} alkoxy or nitro, and where n is 0 or 1: in which R^6 is hydrogen, C_{1-10} alkenyl, C_{2-7} cycloalkyl, C_{2-7} cycloalkyl C_{1-4} alkyl, C_{1-4} haloalkyl, benzyl, C_{1-6} alkanoyl, C_{1-4} carboxalkoxy or benzoyl; and in which R^1 is one of the values of R^6 or halogen, nitro, cyano, amino or C_{1-4} acylamino.

2. A compound according to claim 1 in which R^1, R^2 and R^3 independently represent hydrogen, C_{1-4} alkyl, C_{2-7} alkenyl, halogen, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} cycloalkyl, C_{1-4} alkoxy or phenylsulphonyl, R^6 is hydrogen, C_{1-4} alkythio, C_{1-4} cycloalkyl C_{1-4} alkyl or benzyl, and R^1 is hydrogen or C_{1-4} alkyl.

3. A compound according to claim 2 of the formula

in which R^1, R^2 and R^3 independently represent hydrogen, C_{1-4} alkyl, C_{2-7} alkenyl, halogen, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} alkythio or phenylsulphonyl, R^6 is hydrogen, C_{1-10} alkyl, C_{2-7} cycloalkyl, C_{2-7} cycloalkyl C_{1-4} alkyl or benzyl, R^1 is hydrogen or C_{1-10} alkyl and R^6 is hydrogen, C_{1-4} alkyl, C_{2-7} cycloalkyl, C_{2-7} cycloalkyl C_{1-4} alkyl or benzyl.

4. A compound according to claim 3 in which R^1, R^2 and R^3 independently represent hydrogen, halogen or C_{1-4} haloalkyl, R^6 is C_{1-4} alkyl, C_{2-7} cycloalkyl or C_{2-7} cycloalkyl C_{1-4} alkyl, R^1 is hydrogen and R^6 is hydrogen, C_{1-4} alkyl, C_{2-7} cycloalkyl C_{1-4} alkyl or benzyl.

5. A compound according to claim 4 in which R^2 is halogen and R^1 and R^3 are hydrogen, or R^2 and R^3 are halogen and R^1 is hydrogen, R^6 is methyl or ethyl, R^1 is hydrogen and R^6 is methyl.

6. A pharmaceutical composition comprising a compound according to either of claims 1 and 2 associated with a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising a compound according to any of claims 3 to 5 associated with a pharmaceutically acceptable carrier.

8. A process for preparing a compound according to any of claims 1 to 5 which comprises

(a) reacting an amine of formula R^3NH with a compound of formula

where Q represents a radical capable of being split off with the hydrogen atom of the amine R^3NH, optionally followed when R^6 or R^1 is hydrogen by reaction with a compound of the formula R^7X or R^9X respectively, X being a leaving group, and optionally followed when n is 0 by oxidation, or

(b) ring-closing a compound of formula

optionally followed when R^6 or R^1 is hydrogen by reaction with a compound of the formula R^7X or R^9X respectively, X being a leaving group, and optionally followed when n is 0 by oxidation.

9. An intermediate compound of formula
0.027 390

Where R¹, R², R³, R⁴, R⁶ and R⁷ are as defined in claim 1, and Q is hydroxyl, thiol or amino.
10. A compound according to any of claims 1 to 5, for use as a pharmaceutical.
11. A compound according to any of claims 1 to 5, for use in the treatment of disorders of the central nervous system.

Revendications

1. Compose de formule:

ou un de ses sels d’addition d’acide;

formule dans laquelle R¹, R², R³ et R⁴ représentent chacun indépendamment l’un de l’autre un atome d’hydrogène, un groupe alkyle en C₁–C₄, un groupe alcènyle en C₂–C₄, un groupe cycloalkyle en C₃–C₇, un groupe cycloalkyl (en C₃–C₇) alkyle en C₁–C₅, un atome d’halogène, un groupe haloalkyle en C₆–C₁₂, un groupe alcancyle en C₁–C₄, un groupe nitro, un groupe amino, un groupe acyl (en C₁–C₄) amino, un groupe cyano, un groupe hydroxy, un groupe alcoxy en C₁–C₄, un groupe alkyl (en C₁–C₄) thio, un groupe haloalcoxy en C₁–C₄ ou un groupe de formule —SO₂N(R⁵), —SO₃R⁶, où R⁶ représente un groupe alkyle en C₁–C₄, un groupe haloalkyle en C₁–C₄ ou un groupe phényle éventuellement substitué par un atome d’halogène, par un groupe haloalkyle en C₁–C₄, par un groupe alkyle en C₁–C₄, par un groupe alcoxy en C₁–C₄ ou par un groupe nitro, R⁶ représente un groupe de formule:

2. Composé suivant la revendication 1, dans lequel R¹, R² et R³ représentent chacun indépendamment l’un de l’autre un atome d’hydrogène, un groupe alkyle en C₁–C₄, un groupe alcènyle en C₂–C₄, un atome d’halogène, un groupe haloalkyle en C₁–C₄, un groupe nitro, un groupe alcoxy en C₁–C₄, un groupe haloalcoxy en C₁–C₄, un groupe alkyl(thio, un groupe haloalkyl(thio, un groupe sulfonyle ou un groupe phényl-sulfonyle, R⁶ représente un atome d’hydrogène, R⁷ représente un atome d’hydrogène, un groupe alkyle en C₁–C₅, un groupe cyano, un groupe amino ou un groupe acyl (en C₁–C₄) amino.

3. Composé suivant la revendication 2 répondant à la formule:
dans laquelle R¹, R² et R³ représentent chacun indépendamment l’un de l’autre un atome d’hydrogène, un groupe alkyle en C₁⁻C₅, un groupe alcényle en C₂⁻C₄, un atome d’halogène, un groupe haloalkyle en C₁⁻C₅, un groupe nitro, un groupe alcoxy en C₁⁻C₄, un groupe alkyle(thio ou un groupe phényl-sulfonyle). R⁴ représente un atome d’hydrogène, un groupe alkyle en C₅⁻C₁₀, un groupe cycloalkyle en C₅⁻C₁₂ ou un groupe benzyle. R⁵ représente un atome d’hydrogène ou un groupe alkyle en C₁⁻C₅.

4. Composé suivant la revendication 3, dans lequel R¹, R² et R³ représentent chacun indépendamment l’un de l’autre en atome d’hydrogène, un atome d’halogène ou un groupe haloalkyle en C₁⁻C₅. R⁴ représente un groupe alkyle en C₁⁻C₅, un groupe cycloalkyle en C₅⁻C₁₂ ou un groupe cycloalkyl(thio ou un groupe phényl-sulfonyle). R⁴ représente un atome d’hydrogène et R⁵ représente un atome d’hydrogène ou un groupe alkyle en C₁⁻C₅, un groupe cycloalkyl(thio ou un groupe phényl-sulfonyle). R⁶ représente un groupe méthyle ou un groupe éthyle. R⁷ représente un atome d’hydrogène ou un groupe méthyle.

5. Composé suivant la revendication 4, dans lequel R² représente un atome d’halogène, R¹ et R³ représentent chacun un atome d’hydrogène ou R² et R³ représentent chacun un atome d’halogène et R¹ représente un atome d’hydrogène, R⁵ représente un groupe méthyle ou un groupe éthyle. R⁷ représente un atome d’hydrogène et R⁵ représente un groupe méthyle.

6. Composition pharmaceutique comprenant un composé suivant l’une quelconque des revendications 1 et 2 en association avec un support pharmaceutiquement acceptable.

7. Composition pharmaceutique comprenant un composé suivant l’une quelconque des revendications 3 à 5 en association avec un support pharmaceutiquement acceptable.

8. Procédé de préparation d’un composé suivant l’une quelconque des revendications 1 à 5, caractérisé en ce qu’il comprend les étapes qui consistent à :
   (a) faire réagir une amine de formule R⁶H avec un composé de formule :

   R²
   R¹
   N = C
   N
   H
   Q
   R⁷

   dans laquelle Q représente un radical capable d’être séparé avec l’atome d’hydrogène de l’amine R⁶H, cette réaction étant éventuellement suivie, lorsque R² ou R³ est un atome d’hydrogène, d’une réaction avec un composé de formule R⁶X ou R⁷X respectivement, X étant un groupe qui s’éloigne, cette réaction étant éventuellement suivie, lorsque n est égal à O, d’une oxydation, ou
   (b) cycliser un composé de formule :

   R²
   R¹
   R⁴
   N
   H
   NH₂
   CO₅
   R⁷
   R³
   NR₆

   cette cyclisation étant éventuellement suivie, lorsque R² ou R³ est un atome d’hydrogène, d’une réaction avec un composé de formule R⁶X ou R⁷X respectivement, X étant un groupe qui s’éloigne, cette réaction étant éventuellement suivie, lorsque n est égal à O, d’une oxydation.

9. Composé intermédiaire de formule :

   R²
   R¹
   N = C
   N
   H
   Q
   R⁷
   R³
   NR₆

   dans laquelle R¹, R², R³, R⁴, R⁵ et R⁷ ont les significations définies dans la revendication 1 et Q représente un groupe hydroxy, un groupe thiol ou un groupe amino.

10. Composé suivant l’une quelconque des revendications 1 à 5 en vue de l’utiliser comme produit pharmaceutique.
11. Composé suivant l’une quelconque des revendications 1 à 5 en vue de l’utiliser pour le traitement des troubles du système nerveux central.

**Patentansprüche**

1. Verbindung mit der Formel

![Chemical Structure Image]

oder ein Säureadditionssalt davon;

worin R¹, R², R³ und R⁴ unabhängig Wasserstoff, C₃₋₄-Alkyl, C₃₋₄-Alkenyl, C₃₋₄-Cycloalkyl, C₃₋₄-Cycloalkyl-C₃₋₄-alkyl, Halogen, C₃₋₄-Halogenalkyl, C₃₋₄-Alkanoyl, Nitro, Amino, C₂₋₅-Acylaminino, Cyano, Hydroxyl, C₁₋₄-Alkoxy, C₁₋₄-Alkythio, C₁₋₄-Alkylthioalkoxy oder eine Gruppe der Formel —SO₂N(R⁵)₂, —SO₂R⁶ oder —SO₂R⁶—SO₂R⁶ bedeutet, worin R⁵, R⁶—Alkyl, C₃₋₄-Halogenalkyl oder Phenyl gegebenenfalls substituiert mit Halogen, C₃₋₄-Halogenalkyl, C₁₋₄-Alkyl, C₁₋₄-Alkoxy oder Nitro ist, worin R⁶ eine Gruppe der Formel

![Chemical Structure Image]

ist, worin R⁶ Wasserstoff, C₁₋₄-Alkyl, C₃₋₄-Cycloalkyl, C₃₋₄-Cycloalkyl-C₁₋₄-alkyl, C₁₋₄-Halogenalkyl, C₃₋₄-Alkenyl, C₁₋₄-Alkanoyl, Benzyl, Cyano oder Phenyl gegebenenfalls substituiert mit Halogen, C₁₋₄-Halogenalkyl, C₃₋₄-Alkyl, C₁₋₄-Alkoxy oder Nitro ist, worin R⁶ Wasserstoff, C₁₋₄-Alkyl oder Phenyl gegebenenfalls substituiert mit Halogen, C₁₋₄-Halogenalkyl, C₃₋₄-Alkyl, C₁₋₄-Alkoxy oder Nitro ist, und worin n 0 oder 1 ist; worin R⁶ Wasserstoff, C₁₋₄-Alkenyl, C₃₋₄-Cycloalkyl, C₃₋₄-Cycloalkyl-C₁₋₄-alkyl, C₁₋₄-Halogenalkyl, Benzyl C₁₋₄-Alkanoyl, C₁₋₄-Carbalkoxy oder Benzyl ist; und worin R⁷ eine der Bedeutungen von R⁶ oder Halogen, Nitro, Cyano, Amino oder C₁₋₄-Acylaminino ist.


3. Verbindung nach Anspruch 2, mit der Formel

![Chemical Structure Image]

worin R¹, R² und R³ unabhängig Wasserstoff, C₁₋₄-Alkyl, C₃₋₄-Alkenyl, Halogen, C₁₋₄-Halogenalkyl, Nitro, C₁₋₄-Alkoxy, C₁₋₄-Alkythio oder Phenylsulfonyl sind, R⁶ Wasserstoff, C₁₋₄-Alkenyl, C₃₋₄-Cycloalkyl, C₃₋₄-Cycloalkyl-C₁₋₄-alkyl oder Benzyl ist, R⁷-Wasserstoff oder C₁₋₄-Alkenyl ist, R⁸ Wasserstoff, C₁₋₄-Alkyl, C₃₋₄-Cycloalkyl, C₃₋₄-Cycloalkyl-C₁₋₄-alkyl oder Benzyl ist.


5. Verbindung nach Anspruch 4, worin R⁶ Halogen ist und R⁷ und R³ Wasserstoff sind oder R² und R³ Halogen sind und R¹ Wasserstoff ist, R⁶ Methyl oder Ethyl ist, R⁷ Wasserstoff ist und R⁸ Methyl ist.

6. Pharmazeutische Zusammensetzung enthaltend eine Verbindung gemäß einem der Ansprüche 1 und 2 in Verbindung mit einem pharmazeutisch brauchbaren Träger.
0 027 390

7. Pharmazeutische Zusammensetzung enthaltend eine Verbindung gemäß einem der Ansprüche 3 bis 5 zusammen mit einem pharmazeutisch brauchbaren Träger.

8. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 5 durch (a) Reaktion eines Amins der Formel \( R^6 H \) mit einer Verbindung der Formel

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^1 \\
\text{R}^3 & \quad \text{N} = \text{C} \\
\text{R}^4 & \quad \text{N} \\
\text{R}^5 & \quad \text{H}
\end{align*}
\]

worin \( Q \) einen Rest darstellt der mit dem Wasserstoffatom des Amins \( R^6 H \) abgespalten werden kann, worauf gegebenenfalls, wenn \( R^8 \) oder \( R^9 \) Wasserstoff sind, die Reaktion mit einer Verbindung der Formel \( R^8 X \) bzw. \( R^9 X \) folgt, wobei \( X \) eine austretende Gruppe ist, und gegebenenfalls, wenn \( n \) die Bedeutung von 0 hat, eine Oxidation folgt, oder

(b) Ringschluß einer Verbindung der Formel

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^1 \\
\text{R}^3 & \quad \text{NH}_2 \\
\text{R}^4 & \quad \text{N} \\
\text{R}^5 & \quad \text{COR}^6 \\
\text{R}^7 & \quad \text{N} \\
\text{R}^8 & \quad \text{R}^9
\end{align*}
\]

gegebenenfalls, falls \( R^8 \) oder \( R^9 \) Wasserstoff ist, gefolgt von der Reaktion mit einer Verbindung der Formel \( R^8 X \) bzw. \( R^9 X \), wobei \( X \) eine austretende Gruppe ist, und gegebenenfalls gefolgt von einer Oxidation, wenn \( n \) 0 ist.

9. Zwischenprodukt-Verbindung der Formel

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^1 \\
\text{R}^3 & \quad \text{N} = \text{C} \\
\text{R}^4 & \quad \text{N} \\
\text{R}^5 & \quad \text{H}
\end{align*}
\]

worin \( \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 \) und \( \text{R}^7 \) wie in Anspruch 1 definiert sind und \( Q \) Hydroxyl, Thiol oder Amino darstellt.

10. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung als Pharmaceuticum.

11. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung bei der Behandlung von Erkrankungen des Zentralen Nervensystems.