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PATENT SPECIFICATION

(11) 1 517 971

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(52) Index at acceptance

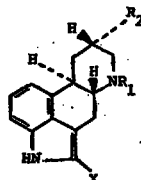
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 65X 678 72Y 777 790 79Y BC KA KF NS QF SC SD
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(54) 8 α -SUBSTITUTED ERGOLINE I DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides new compounds of formula I,



wherein

X is hydrogen, chlorine or bromine,

R₁ is methyl or ethyl, and

R₂ is CH₂—CN, or a group NR₃R₄,

wherein

R₃ is hydrogen or alkyl of 1 to 4 carbon atoms, and

R₄ is formyl, alkanoyl of 2 to 5 carbon atoms in the aggregate thereof,

alkoxycarbonyl of 2 to 5 carbon atoms in the aggregate thereof, mono- to

trihalogenalkoxycarbonyl of 3 to 5 carbon atoms in the aggregate thereof,

the alkoxy radical of which is substituted by halogen in a position other than α to the oxygen, or the radical SO₂R₅,

wherein

R₅ is alkyl of 1 to 4 carbon atoms, mono- to tri-halogenalkyl of 1 to 4 carbon atoms, phenyl, pyridyl, phenyl monosubstituted by halogen or alkoxy of 1 to 4 carbon atoms, or a group NR₆R₇,

wherein each of

R₆ and R₇ is independently hydrogen or alkyl of 1 to 4 carbon atoms, or

R₆ and R₇ together are one of the groups (CH₂)_n or (CH₂)₂—A—(CH₂)₂,

wherein

n is a number from 3 to 7, and

A is oxygen; sulphur; or nitrogen substituted by alkyl of 1 to 4 carbon atoms or phenyl,

with the proviso that when R₁ is methyl and X is hydrogen, then R₂ is other than cyanomethyl and other than N,N-dimethylsulphamoylamino,

X preferably signifies chlorine, especially hydrogen.

R_1 especially denotes methyl.

R_2 especially signifies hydrogen, methyl or ethyl, preferably hydrogen.

When the radical R_4 or R_5 has a halogen substituent, this signifies fluorine, chlorine or bromine. When the radical R_4 or R_5 is di- or trihalogenated, the halogen substituents of these radicals are preferably identical.

The preferred radicals R_4 are methoxycarbonyl, ethoxycarbonyl, (2,2,2-trihaloalkoxy)carbonyl or the group SO_2R_5 , preferably wherein R_5 is alkyl or phenyl.

Any halogen substituents in the radical R_4 especially signify fluorine or chlorine.

When R_6 is alkyl of 1 to 4 carbon atoms or mono- to tri-haloalkyl of 1 to 4 carbon atoms, these radicals preferably contain 1 or 2 carbon atoms.

When R_6 is phenyl monosubstituted by alkoxy of 1 to 4 carbon atoms, the alkoxy substituent especially contains 1 or 2, preferably 1 carbon atom.

R_7 preferably signifies methyl, phenyl, pyridyl or a group NR_8R_9 .

When both of R_6 and R_7 are alkyl of 1 to 4 carbon atoms, each of these groups preferably contains 1 or 2 carbon atoms.

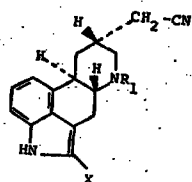
n is preferably 5.

A especially signifies oxygen, or nitrogen substituted by methyl or phenyl.

NR_8R_9 preferably signifies amino, dimethylamino, diethylamino or the 4-methyl-1-piperazinyl group.

Further, in accordance with the invention a compound of formula I may be obtained by a process comprising

a) producing a compound of formula Ia.

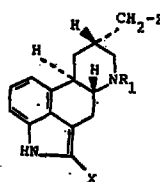


Ia

wherein

X and R_1 are as defined above, with the proviso that when R_1 is methyl X is other than hydrogen

by exchanging the radical Z for a cyano group in a compound of formula II,



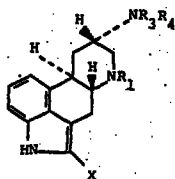
II

wherein

Z is a radical capable of being exchanged in a nucleophilic substitution reaction, and

X and R_1 are as defined above, or with the proviso that when R_1 is methyl X is other than hydrogen, or

b) producing a compound of formula Ib,

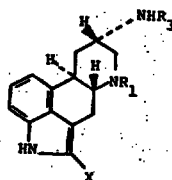


Ib

wherein

X, R_1 , R_2 , and R_3 are as defined above, with the proviso that when R_1 is methyl and X is hydrogen NR_3R_4 is other than N,N-dimethylsulphamyl-amino

by acylating a compound of formula III,



III

wherein

X, R₁ and R₂ are as defined above, with a reactive functional derivative of an acid R₄OH, wherein R₄ is as defined above with respect to formula Ib above.

The reaction of a compound of formula II for obtaining a compound of formula Ia [process a)] and the reaction of a compound of formula III to obtain a compound of formula Ib [process b)] may be effected in accordance with known methods.

The radical Z in the compounds of formula II may, for example, signify halogen such as chlorine or bromine, or an aliphatic or aromatic sulphonyloxy radical, preferably the mesyloxy or the *p*-tosyloxy radical. The reaction may, for example, be effected by reacting a compound of formula II with a cyano group donor, e.g. an alkali metal cyanide such as sodium or potassium cyanide.

The reaction is preferably effected in solution. It is convenient to use aprotic solvents such as dimethyl formamide, hexamethylphosphoric acid triamide or acetonitrile, if necessary in admixture with a small portion of water.

The reaction is preferably effected with heating, e.g. to 50–100°C.

Process b) is an N-acylation process. The following reactive functional derivatives of R₄OH may, for example, be used for the introduction of the radical R₄ in a compound of formula III: for the introduction of the formyl radical the mixed anhydride of formic acid with acetic acid, for the introduction of the remaining radicals R₄ a halide corresponding to the acid, e.g. the acid chloride or acid bromide, and for the introduction of an alkanoyl radical the corresponding anhydrides [(alkanoyl)₂O].

Process b) is conveniently effected in solution. Suitable solvents are, for example, methylene chloride and dioxane. When an anhydride is used as acylating agent it is also possible to use an excess of anhydride as solvent.

The reaction is generally conveniently effected at a reaction temperature between –10°C and about room temperature. However, the N-formylation with the mixed anhydride of acetic acid and formic acid is conveniently effected at a slightly elevated temperature, e.g. 40–60°C.

Process b) is conveniently effected in the presence of a tertiary base such as triethylamine, or preferably in the presence of pyridine or a homologue thereof.

The compounds obtained in accordance with processes a) and b) may be obtained in the form of a base or in the form of acid addition salts thereof. Acid addition salt forms may be produced from the free bases in known manner and *vice versa*.

The starting materials are known or may be produced in accordance with known methods, e.g. as described in the Examples.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade.

EXAMPLE 1.

6-ethyl-8α-cyano-methyl ergoline I

3.35 g (10 millimols) of 6-ethyl-8α-mesyloxymethyl ergoline I are dissolved in 20 cc of dimethyl formamide, and a solution of 3.25 g of potassium cyanide (50 millimols) in 4 cc of water is added. After standing at 80° for 48 hours, the reaction solution is poured into an excess of a 2N sodium carbonate solution, the precipitate is filtered off, dried in the air and subsequently chromatographed on 150 g of aluminium oxide activity II–III. The title compound is eluted with 0.2% of methanol in methylene chloride and crystallizes from methanol (M.P. 182°).

The 6-ethyl-8α-mesyloxymethyl ergoline I, required as starting material, may be obtained as follows:

(a) 100 g of 6-demethyl-6-ethyl Δ^{7,8}-lysergic acid methyl ester are dissolved in 900 cc of dimethyl formamide while heating, dilution is effected with 1.5 litres of glacial acetic acid, and after the addition of 10 g of platinum oxide, hydrogenation

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is effected at +40—50° and normal pressure until the take up of hydrogen stops. The catalyst is filtered off and the filtrate is further hydrogenated under the above conditions after the addition of 5 g of platinum oxide. Working up is effected by filtering and evaporating the filtrate to dryness. The resulting resin is dissolved in 1.5 litres of methylene chloride containing 5% of methyl alcohol, the solution is stirred well with 20 g of active charcoal, filtration is effected, after cooling well, it is slowly covered with a layer of one litre a 2 N sodium carbonate solution and carefully shaken. The aqueous phase is again extracted twice with 500 cc of methylene chloride. After drying the organic phase over sodium sulphate and concentrating to about 1/5 of the original volume, dilution with about 500 cc of ether and scratching are effected. After standing at 0° for 2 hours, 6-demethyl-6-ethyl-9,10-dihydro-isolysergic acid methyl ester I crystallizes.

(b) 38 g of lithium aluminium hydride are suspended in 2.5 litres of absolute tetrahydrofuran under nitrogen, cooling is effected to 0°, and a solution of 200 g of the product of step a) in 2.5 litres of absolute tetrahydrofuran is added dropwise within 15 minutes while stirring vigorously. The reaction product is subsequently diluted with 2.5 litres of absolute tetrahydrofuran and stirred for a further 30 minutes. Working up is effected by the careful successive dropwise addition of 100 cc of ethyl acetate, 100 cc of methanol and 50 cc of water. Dilution is subsequently effected with 2 litres of 30% methanol in methylene chloride and filtration is effected. The residue is again boiled out 4 times with 1 litre amounts of 30% methanol in methylene chloride. After concentration and crystallization from methanol, the combined filtrates yield 6-demethyl-6-ethyl-9,10-dihydro-isolysergol I.

(c) 100 g of the product of step b) are suspended in 500 cc of absolute pyridine and 1.1 litres of absolute acetonitrile, and a solution of 80 cc of methane-sulphochloride in 200 cc of absolute acetonitrile is added dropwise at 0° while stirring. After removing the cooling bath, the reaction mixture is stirred for a further hour at room temperature, whereby a yellowish precipitate results. Working up is effected by again cooling to 0° and adding a 2 N ammonia solution until an alkaline reaction is obtained. After scratching, 6-ethyl-8 α -methane-sulphonyloxymethyl ergoline I crystallizes.

The following compound of formula Ia is obtained in a manner analogous to that described in process (a) above, by using the corresponding compound of formula II (Z=mesyloxy):

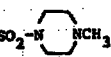
Ex. Nr.	X	R ₁	M.P.
2	Cl	CH ₃	of the hydrochloride 267—268°

EXAMPLE 3.

6-methyl-8 α -sulphamylamino ergoline I

10 millimols of 6-methyl-8 α -amino ergoline I are dissolved in a mixture of 200 cc of methylene chloride and 25 cc of absolute pyridine, and a solution of 25 millimols of sulphamyl chloride in 25 cc of methylene chloride is added dropwise with stirring at room temperature. After stirring for 12 hours, working up is effected as described in Example 1. The orange red crude base is chromatographed on a 50-fold quantity of silica gel, to purify the title compound.

The following compounds of formula Ib are obtained in a manner analogous to that described in Example 3, by acylating the corresponding compounds of formula III with the acid chloride:

Ex. Nr.	X	R ₁	R ₂	R ₄	M.P.
4	H	CH ₃	H	CO ₂ C ₂ H ₅	from 120° (dec.) base [α] _D ²⁰ = -29° (c = 0,35; dimethyl formamide)
5	H	CH ₃	H	CO ₂ CH ₃	of the hydrochloride: 279-280°
6	H	CH ₃	H	COC(CH ₃) ₃	of the base: 199-200°
7	H	CH ₃	H	CO ₂ CH ₂ CCl ₃	117-119°
8	H	CH ₃	H	SO ₂ NH-C(CH ₃) ₃	
9	H	CH ₃	H	SO ₂ - 	
10	H	CH ₃	H	SO ₂ - 	

EXAMPLE 11.

6-methyl-8α-formylamino ergoline I

2.41 g (10 millimols) of 6-methyl-8α-amino ergoline I are dissolved in 5 cc of formic acid, and 5 cc of acetic anhydride are added dropwise at 50-60° while stirring. After stirring for one hour, gas evolution stops; cooling is subsequently effected to 0°, and the reaction mixture is carefully neutralized with 4 N potassium hydroxide solution, and extraction is effected with chloroform containing methanol. After drying and concentrating the organic phases by evaporation, the title compound crystallizes from ethanol, and is obtained in pure form after recrystallization from methylene chloride/ethanol.

[α]_D²⁰ = +23° (c=0.3, pyridine).

EXAMPLE 12.

6-methyl-8α-pivaloylamino ergoline I

The process is effected in a manner analogous to that described in Example 6, except that pivalic acid anhydride is used in place of pivalic acid chloride as acylating agent, whereby the title compound, having a M.P. of 199 to 200°, is obtained.

The compounds of formula I exhibit pharmacological activity. In particular, the compounds exhibit central dopaminergic stimulant activity, as indicated in standard tests, for example according to the principles of U. Ungerstedt Acta Physiol. Scand. Suppl. (1971) 367, 69-93, by an induction of contralateral turning in rats lesioned unilaterally in the substantia nigra by 6-hydroxydopamine and by an induction of dose dependent stereotyped sniffing, licking and biting behaviour in the rat according to the following test:

Rats, 180-222 g, are placed in Perspex (Registered Trade Mark) cylinders of 30 cm diameter on a wire grid floor. After 30 minutes to allow acclimatisation to the cage, the rats are injected with the compound under investigation. The

behaviour of the rats is observed for 2 minutes at 30 minute intervals for 2 hours and then at 60 minute intervals for 2 hours and then at 60 minute intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Naylor and Olley [Euro J. Pharmac. 18, 83-94 (1972)].

The scores and criteria are as follows:

1. Intermittent sniffing
2. Persistent sniffing, occasional licking
3. Licking, occasional biting
4. Intense and persistent biting

The compounds are, therefore, indicated for use as central dopaminergic stimulant agents, for example, for treating Morbus Parkinson. For this use as indicated dose from 0.5 to 100 mg, especially 1-50 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.1 to 50 mg, or in sustained release form.

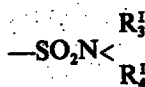
The compounds additionally exhibit prolactin secretion inhibition activity as indicated in standard tests, for example, in rats by an inhibition of ovum implantation as follows:

The compound under investigation is administered to female rats 5 days after coitus and shown to be sperm positive according to the vaginal smear test. The rats are sacrificed on day 12 and their uteri are examined by means of the Salewski reaction for proof that the nidations process has been interrupted [Arch. exp. Path. Pharm. 247, 367 (1967)].

The compounds are, therefore, indicated for use as prolactin secretion inhibitor agents. For this use an indicated daily dose is from 0.05 to 10 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.01 to 5 mg, or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner, so as to be, for example, a solution or a tablet.

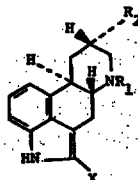
In one group of compounds of formula I as defined above R_2 is CH_2CN . In another group of compounds R_2 is $-\text{NHR}$, wherein R is formyl, alkanoyl, alkoxy carbonyl or



wherein R_2 and R_1 are alkyl or together are $-(\text{CH}_2)_n-$, wherein n is from 3 to 5. In yet another group of compounds X is H, R_1 is CH_3 and R_2 is H.

WHAT WE CLAIM IS:-

1. A process for the production of a compound of formula I,



wherein

- X is hydrogen, chlorine or bromine,
- R_1 is methyl or ethyl, and
- R_2 is CH_2CN , or a group NR_1R_2 ,

wherein

- R_1 is hydrogen or alkyl of 1 to 4 carbon atoms, and
- R_2 is formyl, alkanoyl of 2 to 5 carbon atoms in the aggregate thereof, alkoxy carbonyl of 2 to 5 carbon atoms in the aggregate thereof, mono- to trihalogenalkoxy carbonyl of 3 to 5 carbon atoms in the aggregate thereof,

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behaviour of the rats is observed for 2 minutes at 30 minute intervals for 2 hours and then at 60 minute intervals for 2 hours and then at 60 minute intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Naylor and Olley [Euro J. Pharmac. 18, 83-94 (1972)].

The scores and criteria are as follows:

1. Intermittent sniffing
2. Persistent sniffing, occasional licking
3. Licking, occasional biting
4. Intense and persistent biting

The compounds are, therefore, indicated for use as central dopaminergic stimulant agents, for example, for treating Morbus Parkinson. For this use as indicated dose from 0.5 to 100 mg, especially 1-50 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.1 to 50 mg, or in sustained release form.

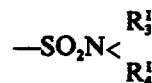
The compounds additionally exhibit prolactin secretion inhibition activity as indicated in standard tests, for example, in rats by an inhibition of ovum implantation as follows:

The compound under investigation is administered to female rats 5 days after coitus and shown to be sperm positive according to the vaginal smear test. The rats are sacrificed on day 12 and their uteri are examined by means of the Salewski reaction for proof that the nidations process has been interrupted [Arch. exp. Path. Pharm. 247, 367 (1967)].

The compounds are, therefore, indicated for use as prolactin secretion inhibitor agents. For this use an indicated daily dose is from 0.05 to 10 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.01 to 5 mg, or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner, so as to be, for example, a solution or a tablet.

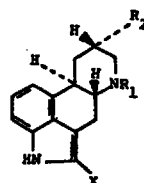
In one group of compounds of formula I as defined above R_2 is CH_2CN . In another group of compounds R_2 is $-\text{NHR}$, wherein R is formyl, alkanoyl, alkoxy-carbonyl or



wherein R_3 and R_4 are alkyl or together are $-(\text{CH}_2)_n-$, wherein n is from 3 to 5. In yet another group of compounds X is H, R_1 is CH_3 and R_2 is H.

WHAT WE CLAIM IS:-

1. A process for the production of a compound of formula I,

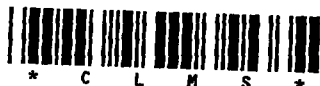


wherein

X is hydrogen, chlorine or bromine,
 R_1 is methyl or ethyl, and
 R_2 is CH_2CN , or a group NR_3R_4 ,

wherein

R_3 is hydrogen or alkyl of 1 to 4 carbon atoms, and
 R_4 is formyl, alkanoyl of 2 to 5 carbon atoms in the aggregate thereof, alkoxy-carbonyl of 2 to 5 carbon atoms in the aggregate thereof, mono- to trihalogenalkoxy-carbonyl of 3 to 5 carbon atoms in the aggregate thereof,



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the alkoxy radical of which is substituted by halogen in a position other than α to the oxygen, or the radical SO_2R_s ,

wherein

R_s is alkyl of 1 to 4 carbon atoms, mono- to tri-halogenalkyl of 1 to 4 carbon atoms, phenyl, pyridyl, phenyl monosubstituted by halogen or alkoxy of 1 to 4 carbon atoms, or a group NR_6R_7 ,

wherein each of

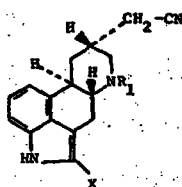
R_6 and R_7 is independently hydrogen or alkyl of 1 to 4 carbon atoms, or R_6 and R_7 together are one of the groups $(\text{CH}_2)_n$ or $(\text{CH}_2)_2\text{—A—}(\text{CH}_2)_2$,

n is a number from 3 to 7, and

A is oxygen; sulphur; or nitrogen substituted by alkyl of 1 to 4 carbon atoms or phenyl,

with the proviso that when R_s is methyl and X is hydrogen, then R_s is other than cyanomethyl and other than N,N -dimethylsulphamoylamino, which comprises

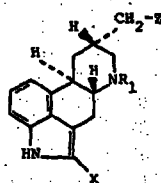
a) producing a compound of formula Ia,



Ia

wherein

X and R_1 are as defined above, with the proviso that when R_1 is methyl X is other than hydrogen by exchanging the radical Z for a cyano group in a compound of formula II,



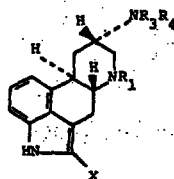
II

wherein

Z is a radical capable of being exchanged in a nucleophilic substitution reaction, and

X and R_1 are as defined above, with the proviso that when R_1 is methyl X is other than hydrogen, or

b) producing a compound of formula Ib,



Ib

wherein

X , R_1 , R_3 and R_4 are as defined above, with the proviso that when R_1 is methyl and X is hydrogen NR_3R_4 is other than N,N -dimethylsulphamyl-amino,

by acylating a compound of formula III,

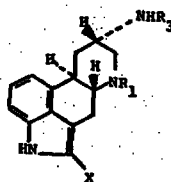
1A



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III

wherein

X, R₁ and R₂ are as defined above, with a reactive functional derivative of an acid R₄OH, wherein R₄ is as defined above with respect to formula Ib above.

2. A process for the production of a compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

3. A compound of formula I, whenever produced by a process according to claim 1 or 2.

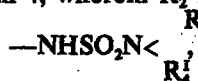
4. A compound of formula I, as defined in claim 1.

5. A compound of claim 4, wherein R₂ is —CH₂CN.

6. A compound of claim 4, wherein R₂ is —NR₃R₄, wherein R₃ and R₄ are as defined in claim 1.

7. A compound of claim 4, wherein R₂ is —NHR, wherein R is formyl or alkanoyl or alkoxy-carbonyl as defined in claim 1.

8. A compound of claim 4, wherein R₂ is



wherein R₃^I and R₄^I are alkyl of 1 to 4 carbon atoms or together —[CH₂]_n—, wherein n is from 3 to 5.

9. A compound of claim 4, wherein X is hydrogen.

10. A compound of claim 4, wherein X is chlorine.

11. A compound of claim 4, wherein X is bromine.

12. A compound of claim 4, wherein R₁ is methyl.

13. A compound of claim 4, wherein R₁ is ethyl.

14. A compound of claim 4, wherein R₄ is formyl or alkanoyl, Alkoxy-carbonyl or halogenalkoxy-carbonyl as defined in claim 1.

15. A compound of claim 4, wherein R₄ is SO₂R₅.

16. A compound of claim 15, wherein R₅ is NR₆R₇.

17. 6-Methyl-8α-formylamino ergoline I.

18. 6-Methyl-8α-pivaloylamino ergoline I.

19. The compound of claim 5, wherein X is Cl and R₁ is CH₃.

20. The compound of claim 5, wherein X is H and R₁ is C₂H₅.

21. A compound of claim 4, wherein X is H, R₁ is CH₃, and R₂ is H.

22. The compound of claim 21, wherein R₄ is CO₂C₂H₅.

23. The compound of claim 21, wherein R₄ is CO₂CH₃.

24. The compound of claim 21, wherein R₄ is COC(CH₃)₃.

25. The compound of claim 21, wherein R₄ is CO₂CH₂CCl₃.

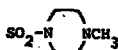
26. The compound of claim 21, wherein R₄ is SO₂NH₂.

27. The compound of claim 21, wherein R₄ is SO₂NH—C(CH₃)₃.

28. The compound of claim 21, wherein R₄ is



29. The compound of claim 21, wherein R₄ is



30. A compound according to any one of claims 4 to 29 in free base form.

31. A compound according to any one of claims 4 to 29 in acid addition salt form.



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32. A pharmaceutical composition comprising a compound according to any one of claims 4 to 29 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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