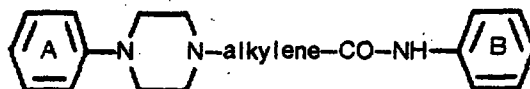


Description

The invention relates to N-piperazinylalkanoylanilides and pharmaceutically acceptable salts thereof, to processes for their production and to pharmaceutical compositions containing them.

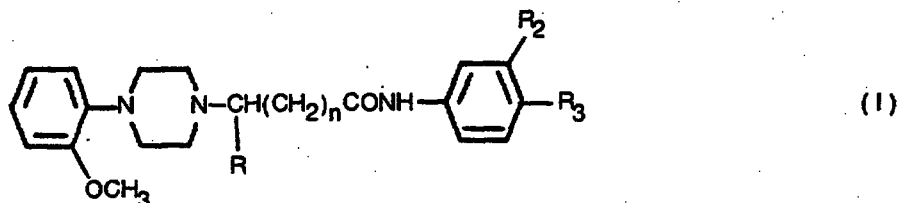
Compounds having the skeletal structure



are known to have antihypertensive properties. GB-A-912788 discloses those in which ring A is unsubstituted and ring B is mono-, di- or tri-methoxy substituted. These compounds combine the known antihypertensive properties of a fragment of the reserpine molecule with the central depressant activity and adrenergic blocking action of the piperazinyl moiety. GB-A-1166595 indicates that 2-substitution with e.g. nitro, cyano, sulpho, carboxy, carbalkoxy or carboxamido of ring B is essential and that ring A may be substituted, preferably 2-methoxylated. Additional alkoxy substitution of ring B is still highly preferred, retaining the reserpine-like structure. DE-A-2904799 discloses a specific β -blocking group, 3-alkylamino-2-hydroxy-propoxy, as a 2- or 4-substituent of ring B. Ring A is preferably unsubstituted.

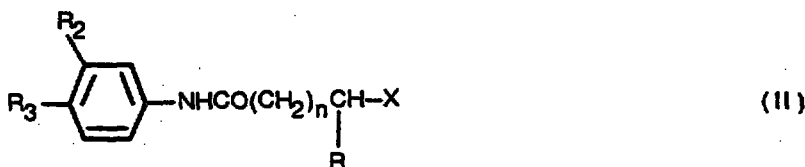
The invention is based upon the realisation of the single preferred substitution pattern for ring A together with a range of substituents for ring B which are remote from the alkoxy/alkyldioxy reserpine-like substituents previously preferred, mostly being attached through a sulphur atom and especially an oxygen-bearing sulphur atom.

The invention provides N-piperazinylalkanoylanilides of the general formula I



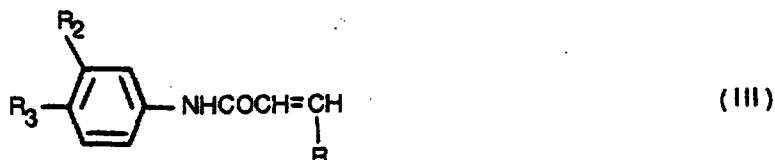
wherein n is 0, 1 or 2; R represents a hydrogen atom or an alkyl group; one of R_2 and R_3 represents a hydrogen atom and the other of R_2 and R_3 represents a hydroxyalkyl, alkylthio, alkylsulphonyl, alkylsulphinyl, alkanoyl, carbamoyl or guanidinosulphonyl group, or a group of the formula $SO_2NR_5R_6$ in which each of R_5 and R_6 independently represents a hydrogen atom or an alkyl, phenyl or alkanoyl group; or one of R_2 and R_3 represents a halogen atom and the other of R_2 and R_3 represents a sulphonamoyl group; and further provides their pharmaceutically acceptable acid addition salts. The term alkyl as used above, whether alone or in combination, refers to such groups having from 1 to 4 carbon atoms.

The invention also provides a process for the preparation of the N-piperazinylalkanoylanilides of the general formula I as above defined, the process comprising reacting a compound of the general formula II.



in which R , R_2 , R_3 and n have the meanings given above and X represents a halogen atom, with 1-(2-methoxyphenyl)-piperazine.

An alternative process for the preparation of the N-piperazinylalkanoylanilides of the general formula I in which n is 1 and R , R_2 and R_3 are as above defined, also within the scope of the invention, comprising reacting a compound of the general formula III



in which R , R_2 and R_3 have the meanings given above with 1-(2-methoxyphenyl)-piperazine.

Both reactions are carried out in the presence of a solvent, such as a ketone, a hydrocarbon, dimethylsulphoxide or a mixture thereof. When using dimethylsulphoxide, a reaction temperature of from 40° to 60°C is sufficient; in other cases the reflux temperature of the solvent is preferred. The compounds thus obtained may be purified according to methods known per se, and crystallized or recrystallized from

suitable solvents in purified form. The pharmaceutically acceptable salts according to the invention may be prepared from the bases in a conventional manner. Preferred pharmaceutically acceptable acid addition salts are those of hydrochloric, sulphuric, maleic, succinic, citric, methanesulphonic and toluenesulphonic acids.

- 5 The N-piperazinyalkanoylanilides and their salts according to the invention possess a valuable antihypertensive activity and a very low toxicity. Accordingly, the invention also provides a pharmaceutical composition comprising a compound of the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

10 The LD₅₀ of the compounds according to the invention was determined in the mouse *per os* following the method described by C. S. Weil (Biometrics, 8, 249, 1952). The results obtained are reported below.

In the following Table, the numbers under AC (active compound) indicate the compounds described in the corresponding Examples (thus "1" indicates the compound prepared in Example 1).

15 The antihypertensive activity was evaluated in male spontaneously hypertensive rats (SHR, Wister-Kyoto strain, 15-25 weeks old). The determination of blood pressure was performed by the indirect method (M. Gerold et al., Arzneim.-Forsch., 18, 1285, 1968). The animals were prewarmed in a heating chamber at a temperature from 35° to 37°C for a period of 15 minutes before administering the compounds. The compounds tested by oral route were dissolved or suspended in a 0.5% methylcellulose solution. Controls were given only the vehicle. Systolic blood pressure and heart rate were measured 1, 3, 5 and 7 hours after drug administration by means of a tail-cuff and the pulse pick-up method using a recorder.

20 In the Table the antihypertensive activity was expressed as ED₂₅, which is the drug dose producing in conscious SHR a 25% decrease in systolic blood pressure. The ED₂₅ was calculated from the linear regression of the dose-response curve. The tested compounds did not show any significant variation on the heart rate.

TABLE

AC	LD ₅₀ (mg/Kg) ^a os	ED ₂₅ (mg/Kg) ^a os
2	>3000	7.5
3	>3000	8.1
4	>3000	54.5
5	2200	58.5
6	537	69
7	>3000	8.7
8	>3000	100
9	>3000	100
14	>3000	60

a) All compounds were tested as hydrochloride, except for AC 2, 3 and 6 (tested as free bases).

Example 1

40 4-Sulphamoyl-γ-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide
(I: R=R₂=H, R₃=NH₂SO₂, n=2)

2.61 g of sodium carbonate and 4.8 g of 1-(2-methoxyphenyl)-piperazine dissolved in 25 ml of acetone were added to 6.9 g of 4-sulphamoyl-γ-chlorobutyryl-anilide in 25 ml of acetone. The whole was refluxed for 32 hours. At the end of the reaction, the solid thus formed was removed by the filtration and discarded.
45 The solvent was evaporated off in vacuo and the oily residue treated with diethyl ether until a solid was obtained. This solid was collected, dried and suspended in ethanol. Hydrogen chloride in ethanol was added until the pH was acid. The product thus obtained was collected and crystallized first from 90% ethanol and then from methanol to give the title compound as its hydrochloride.

Yield 3.82 g (32%), mp 235—237°C.

Example 2

4-Methylsulphonyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide
(I: R=R₂=H, R₃=CH₃SO₂, n=1)

2.02 g of 4-methylsulphonylacryloylanilide and 1.92 g of 1-(2-methoxyphenyl)-piperazine in 20 ml of toluene were refluxed for 4 hours. At the end of the reaction, after cooling, the solid thus formed was collected, dried and crystallized from 95% ethanol. After a long drying in vacuo at 100°C, 2.92 g (78%) of the title compound, melting at 142—143°C, was obtained.

Example 3

4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide
(I: R=R₂=H, R₃=NH₂SO₂, n=1)

A mixture comprising 2.26 g of 4-sulphamoylacryloylanilide and 2.01 g of 1-(2-methoxyphenyl)-piperazine in 60 ml of toluene was refluxed under stirring. After 8 hours, thin layer chromatography showed no starting materials. The crude product was collected, dried and crystallized from dioxane:water.
65 2.08 g (46%) of the title compound, as its dihydrate, melting at 180-181°C, was obtained. The product was

suspended in hot ethanol and hydrogen chloride in ethanol was added until the pH was acid. After cooling the solid was collected and crystallized from water to give the hydrochloride hydrate, mp 237—239°C.

Example 4

5 4-Carbamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=NH_2CO$, $n=1$)

A mixture comprising 1.9 g of 4-carbamoyl-acryloyl-anilide and 2.01 g of 1-(2-methoxyphenyl)-piperazine in 30 ml of dimethylsulphoxide was stirred for 8 hours at 50–60°C. The mixture was then poured in 150 ml of water and the solid thus precipitated was collected and crystallized from methanol:diethyl ether. The title compound was obtained. Mp 235–237°C, yield 2.88 g (75%). The corresponding hydrochloride, mp 246–249°C, was obtained as described in Example 3.

Example 5

15 4-Acetyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=COCH_3$, $n=1$)

Operating as described in Example 3, but using 4-acetyl-acryloyl-anilide in place of the 4-sulphamoyl-acryloyl-anilide, the title compound was obtained. The product was crystallized from ethyl acetate. Yield 77%, mp 138–140°C hydrochloride mp 232°C.

Using the appropriate acryloyl-anilide derivative and operating as described in Example 3, the following compound is obtained:

a) 4-methylthio-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide: yield 75%, mp, 165–166°C, crystallized from ethyl acetate. The corresponding hydrochloride hemihydrate melted at 210–211°C.

Example 6

25 4-(1-Hydroxyethyl)-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=CH_3CHOH$, $n=1$)

1.14 g of sodium borohydride were slowly added to 11.44 g of the compound of Example 5 in 200 ml of ethanol. The whole was stirred at room temperature for 8 hours. The solution thus formed was then acidified with dilute hydrochloric acid and subsequently neutralized with aqueous sodium carbonate. The ethanol was evaporated off in vacuo and the aqueous phase alkalized with aqueous sodium carbonate and then extracted with chloroform. The organic layers were dried on calcium chloride and the solvent was evaporated off in vacuo. The oily residue was purified on a silica gel column using a chloroform:methanol (97:3 by volume) mixture as eluent. The solvent was evaporated off and the residue was crystallized from toluene to give 5.61 g (48%) of the title compound, melting at 137–138°C.

Example 7

40 4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide

(I: $R=CH_3$, $R_2=H$, $R_3=NH_2SO_2SO_2$, $n=1$)

7.2 g of 4-sulphamoyl-crotonylanilide and 6.33 g of 1-(2-methoxyphenyl)-piperazine in 20 ml of dimethylsulphoxide were stirred at 50°C for 6 hours. At the end of the reaction, the solution was cooled and poured into 100 ml of water. The precipitate thus formed was collected and dried. The crude product was dissolved in ethanol and hydrogen chloride in ethanol was added until the pH was acid. The title compound, as its hydrochloride, was collected, dried and crystallized from ethanol. Yield 6.16 g, mp 183–184°C.

Example 8

50 4-Acetylsulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=CH_3CONHSO_2$, $n=1$)

10.73 g of a raw 4-acetylsulphamoyl-acryloyl-anilide and 8.80 g of 1-(2-methoxyphenyl)-piperazine were stirred for 3 days at room temperature with 40 ml of dimethylsulphoxide.

The reaction was then carried out as described in Example 7, obtaining 9.24 g of the title compound, m.p. 193–195°C (crystallation from ethanol).

Example 9

55 3-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide hydrate

(I: $R=R_3=H$, $R_2=NH_2SO_2$, $n=1$)

6.78 g of 3-sulphamoyl-acryloyl-anilide and 6.60 g of 1-(2-methoxyphenyl)-piperazine in 120 ml of toluene were refluxed under stirring for 12 hours. At the end of the reaction, after cooling, the solid thus formed was collected, dried and crystallized twice from 70% ethanol. Yield 9.5 g of the title compound melting at 118–124°C.

Example 10

65 4-Methylsulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=CH_3NHSO_2$, $n=1$)

To 13.8 g of 4-methylsulphamoyl-β-chloro-propionylanilide in 100 ml of acetone, 5.3 g of sodium

carbonate and 10.57 g of 1-(2-methoxyphenyl)-piperazine in 100 ml of acetone were added under stirring. The mixture was refluxed for 9 hours and the solid thus formed collected by filtration. The solvent was then evaporated off giving 13.74 g (from ethanol) of the title compound, mp 168—169°C.

Example 11

4-Phenylsulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=PhNHSO_2$, $n=1$)

Operating as described in Example 10, but employing 16.9 g of phenylsulphamoyl-β-chloro-propionylanilide, refluxing for 20 hours, and crystallizing from methanol, 14.88 g of the desired compound were obtained, mp 197—201°C.

Example 12

4-Guanidinosulphonyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=guanidinosulphonyl$, $n=1$)

The reaction was carried out as described in Example 10, but employing 9.14 g of 4-guanidinosulphonyl-β-chloro-propionylanilide, 6.35 g of the piperazine derivative, 3.15 g of sodium carbonate and 75 ml of acetone. Reflux was carried on for 13 hours, then an excess of piperazine derivative (0.58 g) was added, and the mixture was refluxed for another 13 hours. Yield 6.84 g (from ethanol).

Example 13

4-Chloro-3-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=H$, $R_2=SO_2NH_2$, $R_3=Cl$, $n=1$)

5.49 g of 4,β-dichloro-3-sulphamoyl-propionylanilide, 2.10 g of sodium carbonate and 4.21 g of 1-(2-methoxyphenyl)-piperazine were refluxed under stirring for 18 hours in 30 ml of acetone. At the end of the reaction the mixture was cooled and the solid collected. The residue obtained from mother liquors was treated with ethyl acetate until a precipitate was obtained, and this was added to the first precipitate. The solid mixture was crystallized from dioxan, giving 6.71 g of the title compound, mp 191—193°C.

Example 14

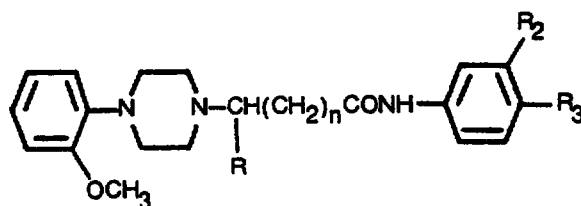
4-(Dimethylsulphamoyl)-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=SO_2N(CH_3)_2$, $n=1$)

Operating as described in Example 11, but employing 7.28 g of 4-(dimethylsulphamoyl)-β-chloro-propionylanilide, 2.64 g of sodium carbonate, 5.26 g of the piperazine derivative and 70 ml of acetone (reflux 10 hours), 8.35 g of the title compound were obtained (from dioxan), mp 178—179°C.

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

1. An N-piperazinylalkanoylanilide having the general formula I



(I)

wherein n is 0, 1 or 2; R represents a hydrogen atom or an alkyl group; one of R_2 and R_3 represents a hydrogen atom and the other of R_2 and R_3 represents a hydroxyalkyl, alkylthio, alkylsulphonyl, alkylsulphinyl, alkanoyl, carbamoyl or guanidinosulphonyl group, or a group of the formula $SO_2NR_5R_6$ in which each of R_5 and R_6 independently represents a hydrogen atom or an alkyl, phenyl or alkanoyl group; or some of R_2 and R_3 represents a halogen atom and the other of R_2 and R_3 represents a sulphamoyl group; each alkyl group referred to having from 1 to 4 carbon atoms; or a pharmaceutically acceptable acid addition salt of such an N-piperazinylalkanoylanilide.

2. An N-piperazinylalkanoylanilide according to claim 1 wherein n is 1, each of R and R_2 represents a hydrogen atom, and R_3 represents a carbamoyl, acetyl, methylthio, 1-hydroxyethyl, acetylsulphamoyl, methylsulphamoyl, phenylsulphamoyl, guanidinosulphonyl or dimethylsulphamoyl group.

3. 4-Methylsulphonyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.

4. 4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.

5. 4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide.

6. Any one of the following N-piperazinylalkanoylanilides according to claim 1, namely 3-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide, 4-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide or 4-chloro-3-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.



carbonate and 10.57 g of 1-(2-methoxyphenyl)-piperazine in 100 ml of acetone were added under stirring. The mixture was refluxed for 9 hours and the solid thus formed collected by filtration. The solvent was then evaporated off giving 13.74 g (from ethanol) of the title compound, mp 168—169°C.

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Operating as described in Example 10, but employing 16.9 g of phenylsulphamoyl-β-chloro-propionylanilide, refluxing for 20 hours, and crystallizing from methanol, 14.88 g of the desired compound were obtained, mp 197—201°C.

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The reaction was carried out as described in Example 10, but employing 9.14 g of 4-guanidinosulphonyl-β-chloro-propionylanilide, 6.35 g of the piperazine derivative, 3.15 g of sodium carbonate and 75 ml of acetone. Reflux was carried on for 13 hours, then an excess of piperazine derivative (0.58 g) was added, and the mixture was refluxed for another 13 hours. Yield 6.84 g (from ethanol).

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5.49 g of 4,β-dichloro-3-sulphamoyl-propionylanilide, 2.10 g of sodium carbonate and 4.21 g of 1-(2-methoxyphenyl)-piperazine were refluxed under stirring for 18 hours in 30 ml of acetone. At the end of the reaction the mixture was cooled and the solid collected. The residue obtained from mother liquors was treated with ethyl acetate until a precipitate was obtained, and this was added to the first precipitate. The solid mixture was crystallized from dioxan, giving 6.71 g of the title compound, mp 191—193°C.

Example 14

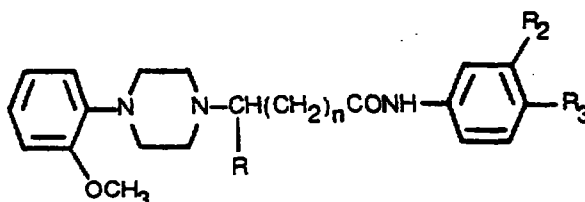
4-(Dimethylsulphamoyl)-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide

(I: $R=R_2=H$, $R_3=SO_2N(CH_3)_2$, $n=1$)

Operating as described in Example 11, but employing 7.28 g of 4-(dimethylsulphamoyl)-β-chloro-propionylanilide, 2.64 g of sodium carbonate, 5.26 g of the piperazine derivative and 70 ml of acetone (reflux 10 hours), 8.35 g of the title compound were obtained (from dioxan), mp 178—179°C.

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

1. An N-piperazinylalkanoylanilide having the general formula I



(I)

wherein n is 0, 1 or 2; R represents a hydrogen atom or an alkyl group; one of R_2 and R_3 represents a hydrogen atom and the other of R_2 and R_3 represents a hydroxyalkyl, alkylthio, alkylsulphonyl, alkylsulphinyl, alkanoyl, carbamoyl or guanidinosulphonyl group, or a group of the formula $SO_2NR_5R_6$ in which each of R_5 and R_6 independently represents a hydrogen atom or an alkyl, phenyl or alkanoyl group; or some of R_2 and R_3 represents a halogen atom and the other of R_2 and R_3 represents a sulphamoyl group; each alkyl group referred to having from 1 to 4 carbon atoms; or a pharmaceutically acceptable acid addition salt of such an N-piperazinylalkanoylanilide.

2. An N-piperazinylalkanoylanilide according to claim 1 wherein n is 1, each of R and R_2 represents a hydrogen atom, and R_3 represents a carbamoyl, acetyl, methylthio, 1-hydroxyethyl, acetylsulphamoyl, methylsulphamoyl, phenylsulphamoyl, guanidinosulphonyl or dimethylsulphamoyl group.

3. 4-Methylsulphonyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.

4. 4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.

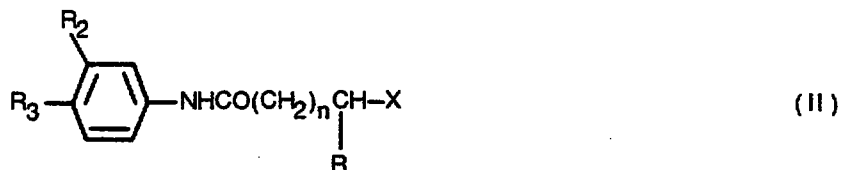
5. 4-Sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide.

6. Any one of the following N-piperazinylalkanoylanilides according to claim 1, namely 3-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide, 4-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilide or 4-chloro-3-sulphamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilide.



15

7. A process for the preparation of an N-piperazinyalkanoylanilide according to claim 1, the process comprising reacting a compound having the general formula II



10 wherein R, R₂, R₃ and n are as defined in claim 1 and X represents a halogen atom with 1-(2-methoxyphenyl)-piperazine in the presence of a solvent.

8. A method for the preparation of an N-piperazinyalkanoylanilide having the general formula I wherein R, R₂ and R₃ are as defined in claim 1 and n is 1, the process comprising reacting a compound having the general formula III



20 with 1-(2-methoxyphenyl)-piperazine in the presence of a solvent.

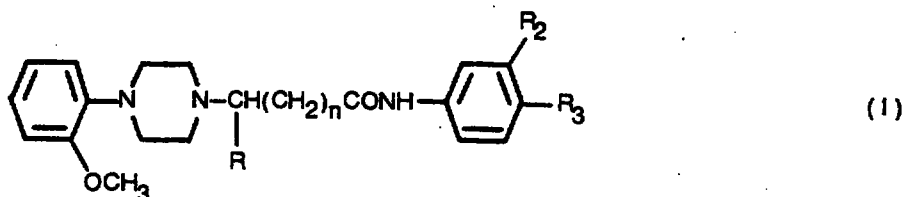
9. A process according to claim 7 or claim 8 in which the solvent is dimethylsulphoxide and the reaction is carried out at from 40°C to 60°C.

10. A process according to claim 7 or claim 8 in which the solvent is a ketone or a hydrocarbon and the reaction is carried out under reflux.

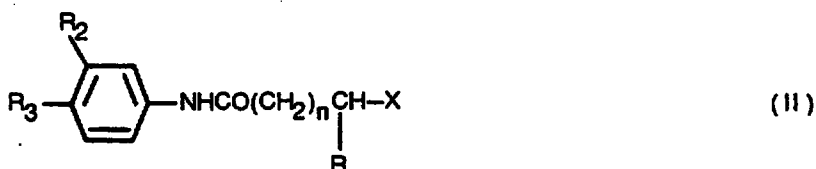
11. A pharmaceutical composition comprising an N-piperazinyalkanoylanilide according to claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

30 Claims for the Contracting State: AT

1. A process for the preparation of an N-piperazinyalkanoylanilide having the general formula I

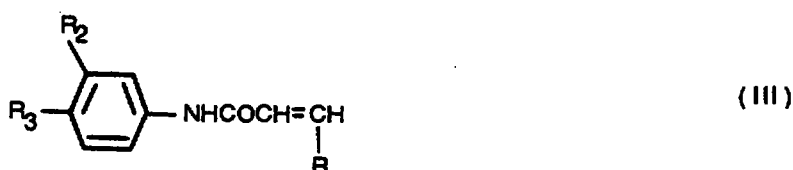


40 wherein n is 0, 1 or 2; R represents a hydrogen atom or an alkyl group; one of R₂ and R₃ represents a hydrogen atom and the other R₂ and R₃ represents a hydroxyalkyl, alkylthio, alkylsulphonyl, alkylsulphinyl, alkanoyl, carbamoyl or guanidosulphonyl group, or a group of the formula SO₂NR₅R₆ in which each of R₅ and R₆ independently represents a hydrogen atom or an alkyl, phenyl or alkanoyl group; or one of R₂ and R₃ represents a halogen atom and the other of R₂ and R₃ represents a sulphonamoyl group; each alkyl group referred to having from 1 to 4 carbon atoms; the process comprising reacting a compound having the general formula II



55 wherein R, R₂, R₃ and n are as defined in this claim and X represents a halogen atom with 1-(2-methoxyphenyl)-piperazine in the presence of a solvent.

2. A method for the preparation of an N-piperazinyalkanoylanilide having the general formula I wherein R, R₂ and R₃ are as defined in claim 1 and n is 1, the process comprising reacting a compound having the general formula III





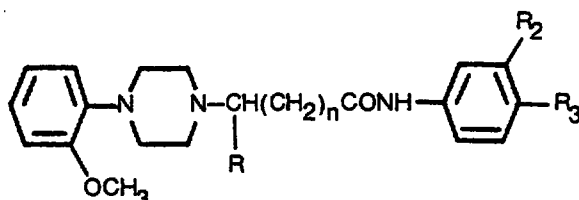
with 1-(2-methoxyphenyl)-piperazine in the presence of a solvent.

3. A process according to claim 1 or claim 2 in which the solvent is dimethylsulphoxide and the reaction is carried out at from 40°C to 60°C.

4. A process according to claim 1 or claim 2 in which the solvent is a ketone or a hydrocarbon and the reaction is carried out under reflux.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI NL SE

1. Ein Piperazinyalkanoylanilid der allgemeinen Formel I



(I)

worin n 0, 1 oder 2 ist, R ein Wasserstoffatom oder eine Alkylgruppe bedeutet, einer der beiden Substituenten R₂ und R₃ ein Wasserstoffatom und der andere eine Hydroxyalkyl-, Alkylthio-, Alkylsulfonyl-, Alkylsulfinyl-, Alkanoyl-, Carbamoyl- oder Guanidinosulfonylgruppe oder eine Gruppe der Formel SO₂NR₅R₆ bedeutet, in welcher jedes R₅ und R₆ unabhängig ein Wasserstoffatom oder eine Alkyl-, Phenyl- oder Alkanoylgruppe darstellt, oder einer der Substituenten R₂ und R₃ ein Halogenatom bedeutet und der andere eine Sulfamoylgruppe darstellt, wobei jede angegebene Alkylgruppe 1 bis 4 C-Atome aufweist, oder ein pharmazeutisch anwendbares Salz eines solchen N-Piperazinyalkanoylanilids.

2. Ein N-Piperazinyalkanoylanilid nach Anspruch 1, wobei n = 1 ist, jedes R und R₂ ein Wasserstoffatom bedeutet und R₃ eine Carbamoyl-, Acetyl-, Methylthio-, 1-Hydroxyäthyl-, Acetylsulfamoyl-, Methylsulfamoyl-, Phenylsulfamoyl-, Guanidinosulfonyl- oder Dimethylsulfamoylgruppe darstellt.

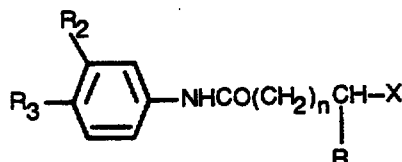
3. 4-Methylsulfonyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilid.

4. 4-Sulfamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-propionylanilid.

5. 4-Sulfamoyl-β-[4-(2-methoxyphenyl)-1-piperazinyl]-butyrylanilid.

6. Eines der folgenden N-Piperazinyalkanoylanilide nach Anspruch 1, insbesondere 3 - Sulfamoyl - β - [4 - (2 - methoxyphenyl) - 1 - piperazinyl] - propionylanilid, 4 - Sulfamoyl - γ - [4 - (2 - methoxyphenyl) - 1 - piperazinyl] - butyrylanilid oder 4 - Chlor - 3 - sulfamoyl - β - [4 - (2 - methoxyphenyl) - 1 - piperazinyl] - propionylanilid.

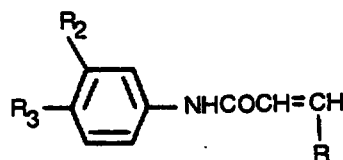
7. Verfahren zur Herstellung eines N-Piperazinyalkanoylanilids nach Anspruch 1, dadurch gekennzeichnet, dass eine Verbindung der allgemeinen Formel II



(II)

worin R, R₂, R₃ und n wie in Anspruch 1 definiert sind und X ein Halogenatom bedeutet, mit 1-(2-Methoxyphenyl)-piperazin in Gegenwart eines Lösungsmittels zur Reaktion gebracht wird.

8. Verfahren zur Herstellung eines N-Piperazinyalkanoylanilids der allgemeinen Formel I, in welcher R, R₂ und R₃ wie in Anspruch 1 definiert sind und n = 1 ist, dadurch gekennzeichnet, dass eine Verbindung der allgemeinen Formel III



(III)

mit 1-(2-Methoxyphenyl)-piperazin in Gegenwart eines Lösungsmittels zur Reaktion gebracht wird.

9. Verfahren nach Anspruch 7 oder Anspruch 8, wobei das Lösungsmittel Dimethylsulfoxid ist und die Reaktion von 40°C bis 60°C durchgeführt wird.

10. Verfahren nach Anspruch 7 oder Anspruch 8, wobei das Lösungsmittel ein Keton oder ein Kohlenwasserstoff ist und die Reaktion unter Rückfluss durchgeführt wird.

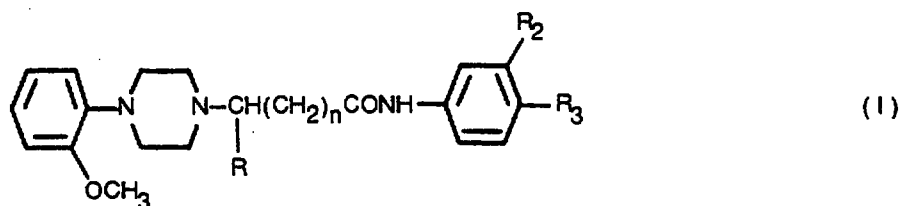
11. Eine pharmazeutische Zubereitung enthaltend ein N-Piperazinyalkanoylanilid nach Anspruch 1 oder ein pharmazeutisch anwendbares Salz davon in Mischung mit einem pharmazeutisch anwendbaren Verdünnungsmittel oder Trägerstoff.



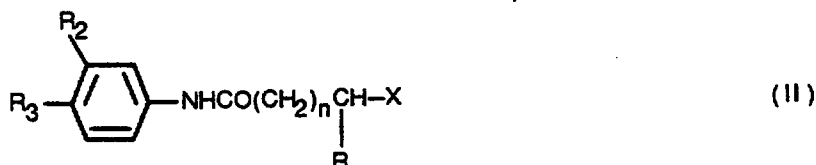
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Patentansprüche für die Vertragsstaat: AT

1. Verfahren zur Herstellung eines N-Piperazinyalkanoylanilids der allgemeinen Formel I

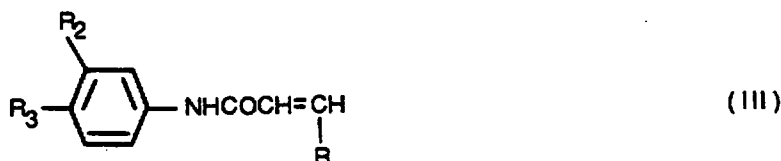


worin n 0, 1 oder 2 ist, R ein Wasserstoffatom oder eine Alkylgruppe bedeutet, einer der beiden Substituenten R₂ und R₃ ein Wasserstoffatom und der andere eine Hydroxyalkyl-, Alkylthio-, Alkylsulfonyl-, Alkylsulfinyl-, Alkanoyl-, Carbamoyl- oder Guanidinosulfonylgruppe oder eine Gruppe der Formel SO₂NR₅R₆ bedeutet, in welcher jedes R₅ und R₆ unabhängig ein Wasserstoffatom oder eine Alkyl-, Phenyl- oder Alkanoylgruppe darstellt, oder einer der Substituenten R₂ und R₃ ein Halogenatom bedeutet und der andere eine Sulfamoylgruppe darstellt, wobei jede angegebene Alkylgruppe 1 bis 4 C-Atome aufweist, dadurch gekennzeichnet, dass eine Verbindung der allgemeinen Formel II



worin R, R₂, R₃ und n wie in diesen Anspruch definiert sind und X ein Halogenatom darstellt mit 1-(2-Methoxyphenyl)-piperazin in Gegenwart eines Lösungsmittels zur Reaktion gebracht wird.

2. Verfahren zur Herstellung eines N-Piperazinyalkanoylanilids der allgemeinen Formel I, worin R, R₂ und R₃ wie in Anspruch 1 definiert sind und n = 1 ist, dadurch gekennzeichnet, dass eine Verbindung der allgemeinen Formel III



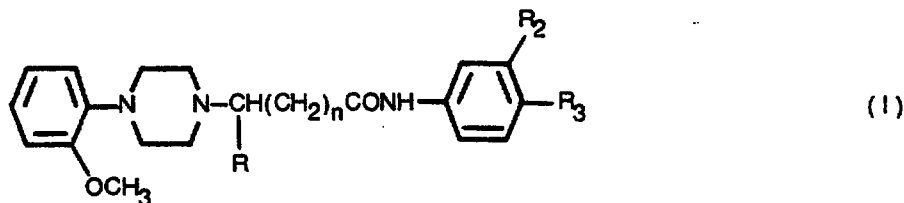
mit 1-(2-Methoxyphenyl)-piperazin in Gegenwart eines Lösungsmittels zur Reaktion gebracht wird.

3. Verfahren nach Anspruch 1 oder Anspruch 2, wobei das Lösungsmittel Dimethylsulfoxid ist und die Reaktion von 40°C bis 60°C durchgeführt wird.

4. Verfahren nach Anspruch 1 oder Anspruch 2, wobei das Lösungsmittel ein Keton oder ein Kohlenwasserstoff ist und die Reaktion unter Rückfluss durchgeführt wird.

45 **Revendications pour les Etats contractants: BE CH DE FR GB IT LI NL SE**

1. Un pipérazino-N-alcanoylanilide de formule générale I



dans laquelle

n = 0, 1 ou 2;

R représente un atome d'hydrogène ou un groupement alcoyle;

l'un des groupements R₂ et R₃ représente un atome d'hydrogène et l'autre, un groupement hydroxyalcoyle, alcoylsulfo, alcoylsulfonyl, alcoylsulfinyle, alcanoyl, carbamoyl ou guanidinosulfonyl ou encore un groupement de formule SO₂NR₅R₆ dans laquelle R₅ et R₆ représentent, chacun de façon indépendante, un atome d'hydrogène ou un alcoyle, un groupement phényle ou alcanoyl; ou bien R₂ et R₃ représentent, l'un un atome d'halogène et l'autre, un groupement sulfamoyl; chaque groupement alcoyle cité ayant de 1 à 4 atomes de carbone; ou un sel d'addition acide pharmaceutiquement acceptable d'un tel pipérazino-N-alcanoylanilide.



2. Un pipérazino-N-alcanoylanilide selon la revendication 1, dans lequel $n = 1$, chacun des substituants R et R_2 représentant un atome d'hydrogène et R_3 représentant un groupement carbamoyle, acétyle, méthylsulfo, hydroxy-1 éthyle, acétylsulfamoyle, méthylsulfamoyle, phénylsulfamoyle, guanidinosulfonyle ou diméthylsulfamoyle.

3. Méthylsulfonyl-4 β -[(méthoxy-2-phényle)-4 pipérazinyl-1] propionylanilide.

4. Sulfamoyl-4 β -[(méthoxy-2 phényle)-4 pipérazinyl-1] propionylanilide.

5. Sulfamoyl-4 β -[(méthoxy-2 phényle)-4 pipérazinyl-1] butyrylanilide.

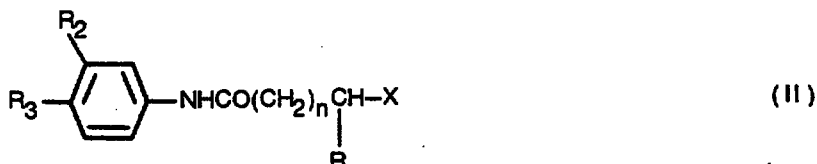
6. L'un des pipérazino-N-alcanoylanilides suivants selon la revendication 1, c'est-à-dire:

sulfamoyl-3- β -[(méthoxy-2 phényle)-4 pipérazinyl-1] propionylanilide,

sulfamoyl-4 γ -[(méthoxy-2 phényle)-4 pipérazinyl-1] butyrylanilide,

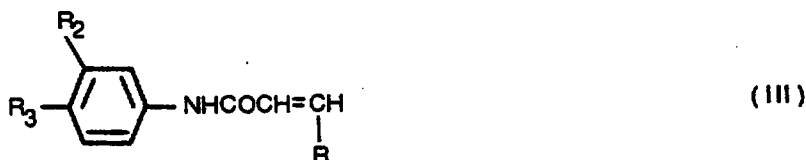
chloro-4 sulfamoyl-3 β -[(méthoxy-2 phényle)-4 pipérazinyl-1] propionylanilide.

7. Un procédé pour la préparation d'un pipérazino-N-alcanoylanilide selon la revendication 1, ce procédé consistant à faire réagir un composé de formule générale II



dans laquelle R , R_2 , R_3 et n sont tels que définis dans la revendication 1 et où X représente un atome d'halogène, avec la (méthoxy-2 phényle)-1 pipérazine, en présence d'un solvant.

8. Une méthode pour la préparation d'un pipérazino-N-alcanoylanilide de formule générale I dans laquelle R , R_2 et R_3 sont tels que définis dans la revendication 1 avec $n = 1$, ce procédé consistant à faire réagir un composé de formule générale III:



avec de la (méthoxy-2 phényle)-1 pipérazine en présence d'un solvant.

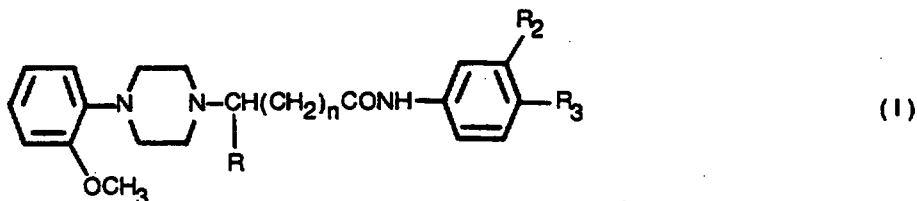
9. Un procédé, selon la revendication 7 ou la revendication 8, dans lequel le solvant est du diméthylsulfoxyde et la réaction est effectuée à une température comprise entre 40°C et 60°C.

10. Un procédé, selon la revendication 7 ou la revendication 8, dans lequel le solvant est une cétone ou un hydrocarbure et la réaction est effectuée au reflux.

11. Une composition pharmaceutique comprenant un pipérazino-N-alcanoylanilide selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci en mélange avec un excipient ou diluant pharmaceutiquement acceptable.

Revendications pour l'Etat contractant: AT

1. Un procédé pour la préparation d'un pipérazino-N-alcanoylanilide de formule générale I



dans laquelle

$n = 0, 1$ ou 2 ;

R représente un atome d'hydrogène ou un groupement alcoyle;

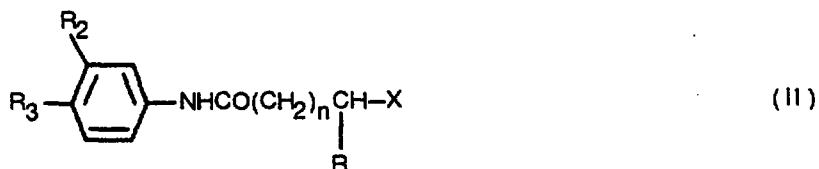
l'un des groupements R_2 et R_3 représente un atome d'hydrogène et l'autre, un groupement hydroxyalcoyle, alcoylsulfo, alcoylsulfonyl, alcoylsulfinyl, alcanoyl, carbamoyl ou guanidinosulfonyl ou encore un groupement de formule $SO_2NR_5R_6$ dans laquelle R_5 et R_6 représentent, chacun de façon indépendante, un atome d'hydrogène ou un alcoyle, un groupement phényle ou alcanoyl; ou bien R_2 et R_3 représentent, l'un un atome d'halogène et l'autre, un groupement sulfamoyl; chaque groupement alcoyle cité ayant de 1 à 4

atomes de carbone; ce procédé consistant à faire réagir un composé de formule générale II



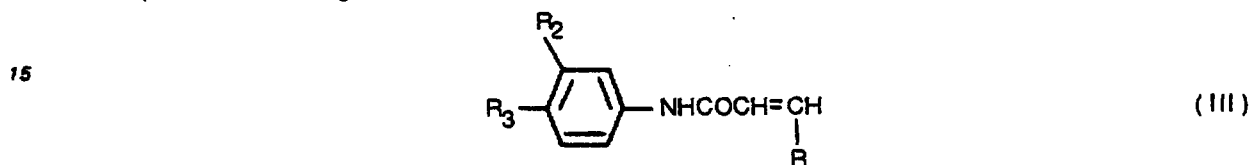
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dans laquelle R, R₂, R₃ et n sont tels que définis dans la présente revendication et X représente un atome un atome d'halogène avec de la (méthoxy-2-phényle)-1 pipérazine en présence d'un solvant.

- 10 2. Une méthode pour la préparation d'une pipérazino-N-alcanoylanilide de formule générale I dans laquelle R, R₂ et R₃ sont tels que définis dans la revendication 1 et n = 1, ce procédé consistant à faire réagir un composé de formule générale III



20 avec de la (méthoxy-2 phényle)-1 pipérazine en présence d'un solvant.

3. Un procédé selon la revendication 1 ou la revendication 2, dans lequel le solvant est du diméthylsulfoxyde et la réaction est effectuée à une température comprise entre 40°C et 60°C.

4. Un procédé selon la revendication 1 ou la revendication 2, dans lequel le solvant est une cétone ou un hydrocarbure et la réaction est effectuée au reflux.