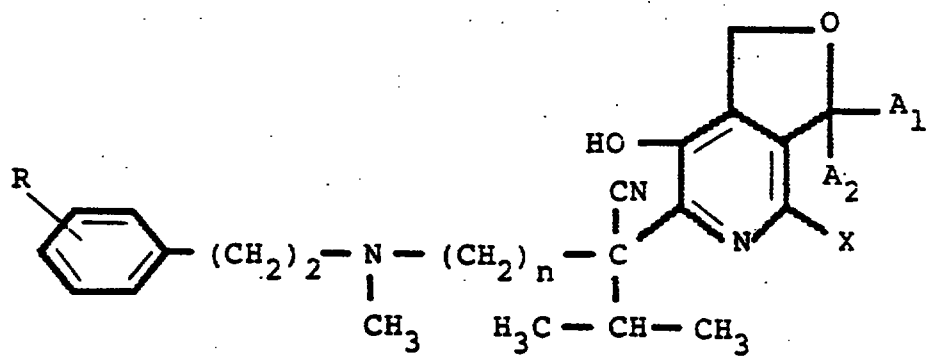
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Furo-(3,4-c)-pyridine Derivatives

The invention relates to new 6-phenethylaminoalkyl-7-hydroxy-furo-(3,4-c)-pyridine derivatives, to a process for their preparation and to therapeutic compositions containing them.

The invention provides 1,3-dihydro-6-[1-cyano-1-isopropyl-N-phenethyl-N-methyl-ω-aminoalkyl]-7-hydroxy-furo-(3,4-c)-pyridine derivatives of the general formula I :



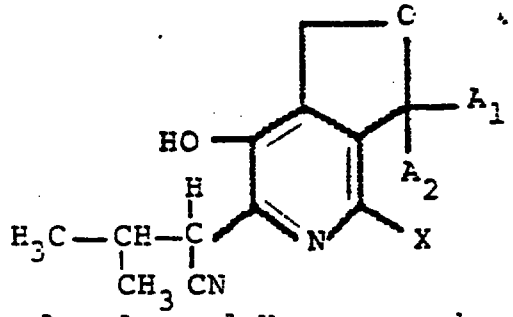
I

wherein each of A_1 and A_2 independently represents a hydrogen atom, a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenylalkyl group or a phenylalkenyl group, each of the groups represented by A_1 and A_2 being unsubstituted or being substituted by one or more chlorine or fluorine atoms, trifluoromethyl groups, alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms, alkylthio groups having from 1 to 5 carbon atoms, dialkylamino groups in which each alkyl group has from 1 to 5 carbon

atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy group has from 1 to 5 carbon atoms or α or β-(N-pyrrolidinyl)-alkoxy groups in which the alkoxy group has from 1 to 5 carbon atoms; R represents from one to three methoxy groups; n is 2,3,4 or 5; and X represents a hydrogen or chlorine atom; and further provides therapeutically acceptable salts of such compounds.

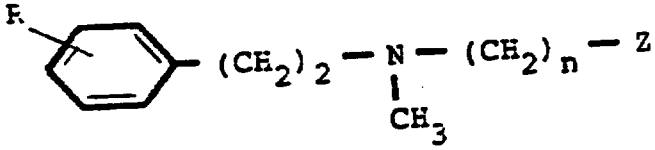
The compounds according to the invention are of interest for their therapeutical activity, principally in the field of calcium antagonism and serotoninergic receptors.

The invention also provides a process for the preparation of the compounds according to the invention, this process comprising reacting, in an organic solvent, a 6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)--pyridine derivative having the general formula II



II

wherein A_1, A_2 and X are as above defined with an N-methyl--N-phenethyl-ω-aminoalkyl halide of the general formula III

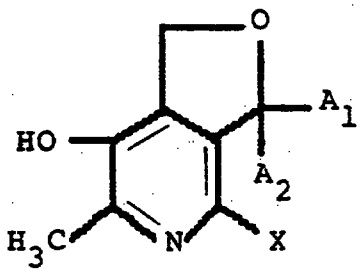


III

wherein R and n are as above defined and Z represents a halogen atom.

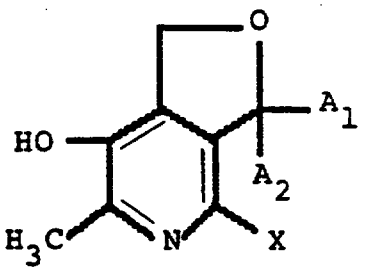
The furo-(3,4-c)-pyridine derivative II and the ω-aminoalkyl halide III are preferably reacted in stoichiometric proportions. The ω-aminoalkyl halide is preferably an ω-aminoalkyl chloride. The organic solvent is suitably dimethylsulphoxide, and the reaction temperature may be from 15° to 65°C.

The 6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine derivatives II may be obtained from corresponding 6-methyl-7-hydroxy derivatives of the general formula IV, disclosed in our previous Patent No. 2092586 and Patent Applications Nos 2137618 and 2148292.



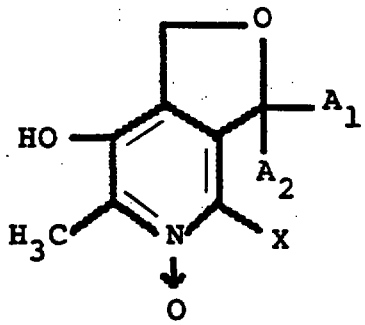
IV

wherein A_1, A_2 and X have the above meanings by the following sequence of reactions :

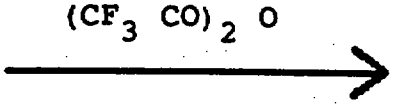


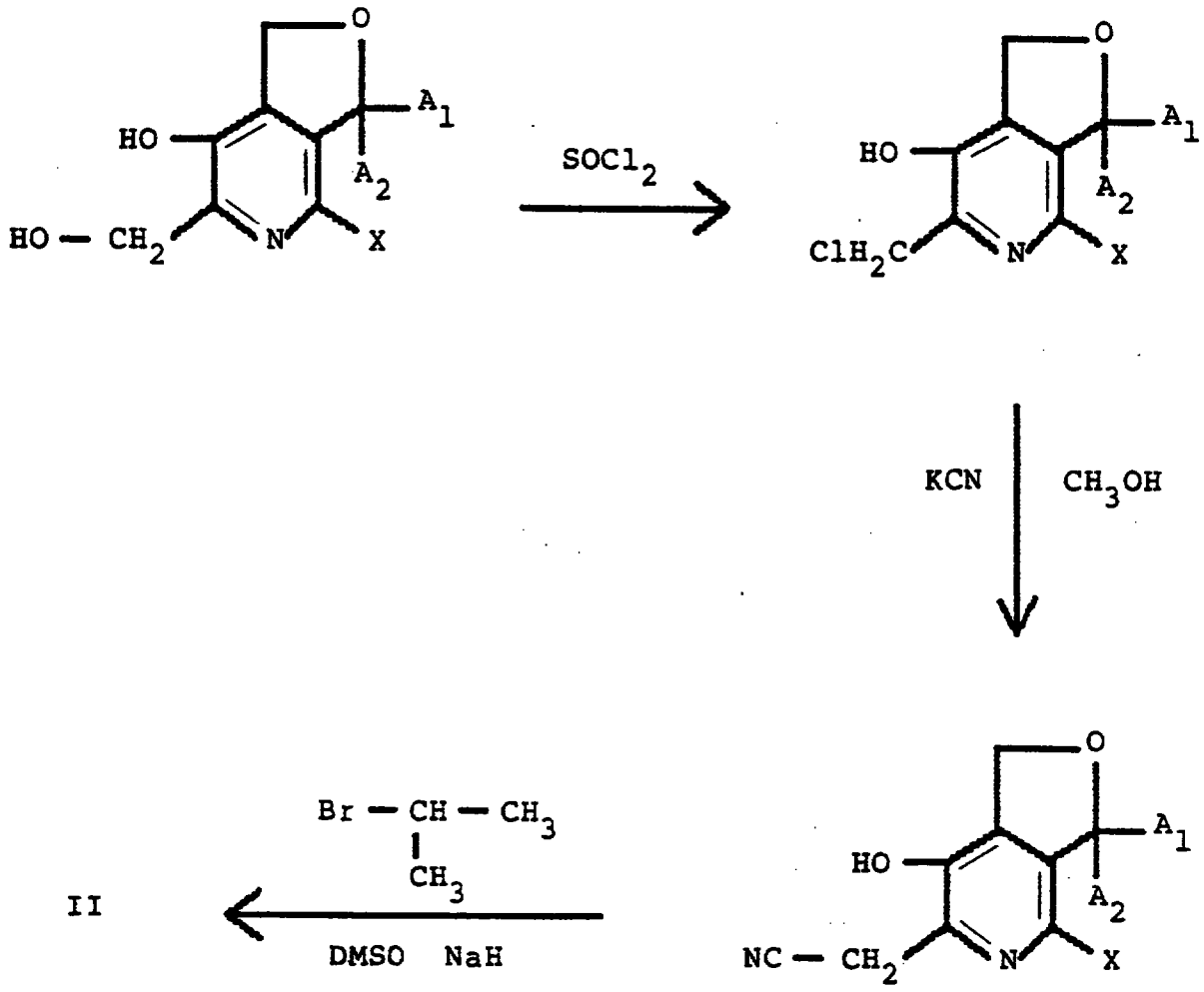
m-chloro peroxybenzoic acid





$(CF_3\ CO)_2\ O$





The preparation of one only of the starting compounds II, 1,3-dihydro-3-methyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine, is now described in detail, other starting materials being obtained by the same way.

a) In a one litre reactor fitted with stirring, warming and cooling means, 18.2 g (0.11 mol) of 1,3-dihydro-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine were treated at 0°C, in the presence of 300 ml of methylene dichloride, with 22.5 g of m-chloroperoxybenzoic acid, slowly added. After stirring overnight at room temperature, there were added 150 ml of 10 % sodium sulphate solution. After stirring and decantation, the

product was washed with the same amount of sodium sulphate solution, twice with 150 ml of sodium bicarbonate solution and three times with 100 ml of water, and then dried over anhydrous sodium sulphate. On evaporation to dryness, there was obtained a beige precipitate which was washed with petroleum ether, hexane, then filtered and dried. Yield 18.9 g (95 %) of 1,3-dihydro-3,6-dimethyl-7-hydroxy-furo-(3,4-c)-pyridine-N-oxide.

b) In the same reactor as above, the 18.9 g of compound obtained in the previous step were treated at 0-5°C, in the presence of 175 ml of methylene dichloride, with 5 ml of trifluoroacetic anhydride added dropwise under stirring. The mixture was stirred overnight at room temperature, and then cooled and treated dropwise with 110 ml of methanol. After evaporation to dryness, the residue was taken up in 350 ml of chloroform, washed twice with 100 ml of 10 % sodium bicarbonate solution and three times with 150 ml of water and dried on anhydrous sodium sulphate. The chloroform was evaporated off and the residue was washed with diethyl ether and dried under reduced pressure. Yield 18 g (95 %) of 1,3-dihydro-3-methyl-6-hydroxymethyl-7-hydroxy-furo-(3,4-c)-pyridine.

c) In a two litre reactor fitted as above and under nitrogen circulation, the 18 g of the previously obtained compound were stirred with 350 ml of dry benzene ; there were slowly added 6 ml of thionyl chloride under stirring at room temperature. The resultant mixture was warmed at 70°C for one hour, leading to a yellow precipitate. This was separated off, washed with benzene and then with diethyl ether, and dissolved in 400 ml of methylene dichloride. The solution was washed with 10 % sodium bicarbonate solution until pH 8, washed with water, treated with carbon black, filtered, and concentrated up to crystallization. The product was separated off, washed twice with diethyl ether and dried, giving 19.2 g (yield 96 %)

of 1,3-dihydro-3-methyl-6-chloromethyl-7-hydroxy-furo-(3,4-c)-pyridine.

d) The 19.2 g of the compound obtained in the previous step were treated in a two litre reactor by 6.6 g of potassium cyanide in the presence of 0.8 litre of methanol at 28-30°C, under reflux for 18 hours. After separation, filtration, washing with chloroform, the solution was evaporated to dryness and the residue treated with pentane. There was thus obtained 17.5 g (95 %) of 1,3-dihydro-3-methyl-6-cyanomethyl-7-hydroxy-furo-(3,4-c)-pyridine.

e) Into the same reactor as above, and under nitrogen circulation, 4.27 g (0.09 mol) of 50 % sodium hydride in oil were poured, then washed in situ with hexane. There were poured 50 ml of dry dimethylsulphoxide and then, dropwise under stirring, the 17.5 g of the compound of previous step ; the mixture was stirred for one hour at room temperature and there was slowly added, under stirring 9.5 ml (0.12 mol) of isopropyl bromide. The reaction mixture was stirred for two hours at room temperature, then slowly poured onto icy water. After extraction with methylene dichloride and washing with water, there was obtained after filtration and concentration, a residue which was recrystallized from diethyl ether and dried. Yield 16.2 g (74 %) of compound II wherein A_1 stands for methyl and A_2 stands for hydrogen.

The invention further provides a therapeutical composition comprising a 1,3- dihydro-6-(1-cyano-1-isopropyl --N-phenethyl-N-methyl- ω -aminoalkyl)-7-hydroxy-furo-(3,4-c)-pyridine derivative of the general formula I as above defined or a therapeutically acceptable salt thereof in admixture with a therapeutically acceptable diluent or carrier.

The following examples illustrate the invention.

Example 1

1,3-dihydro-3-methyl-6-[1-cyano-1-isopropyl-3-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine

$R = (OCH_3)_2$ $n = 2$ $X = H$ $A_1 = CH_3$ $A_2 = H$

Into the same reactor as in step (e) above, and under nitrogen circulation, 4.8 g (0.1 mol) of 50 % sodium hydride in oil were poured and then washed in situ with hexane. 150 ml of dry dimethylsulphoxide was then poured into the reactor followed, slowly under stirring, by 21.8 g (0.1 mol) of 1,3-dihydro- 3-methyl-6- (1-cyano-2-methyl-propyl) -7-hydroxy-furo-(3,4-c)-pyridine. The mixture was stirred for one hour at room temperature and there was slowly added, under stirring, 26 g (0.10 mol) of N-(3,4-dimethoxy-phenethyl)-N-methyl-2-aminoethyl chloride dissolved in 100 ml of dry dimethylsulphoxide. The reaction mixture was stirred for two hours at room temperature, and then slowly poured on icy water. After extraction with methylene dichloride, washing with water and treatment with hydrochloric acid, there was obtained after filtration and concentration a residue, which was recrystallized from diethyl ether and dried. Yield 23 g (47 %) of a white crystalline powder melting at 167°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{26}H_{35}N_3O_4$, HCl.

Example 2

1,3-dihydro-3-phenyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine

$R = (OCH_3)_2$ $n = 2$ $X = Cl$ $A_1 = C_6H_5$ $A_2 = H$

(16)

The method of example 1 was repeated with 1,3-dihydro-3-phenyl-4-chloro-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 2-aminoethyl chloride at 35-40°C. Yield was 31.5 g (54 %) of a white powder melting at 187-190°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{31}H_{36}N_3O_4Cl$, HCl.

Example 3

1,3-dihydro-3-methyl-3-α-furyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 2 X = H A_1 = CH_3 A_2 = α-furyl

The method of example 1 was repeated with 1,3-dihydro-3-methyl-3-α-furyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 2-aminoethyl chloride at room temperature. Yield was 22 g (39.5 %) of a white product melting at 173-175°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{30}H_{37}N_3O_5$, HCl.

Example 4

1,3-dihydro-3-propyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

R = $(OCH_3)_2$ n = 3 X = Cl A_1 = propyl A_2 = H

The method of example 1 was repeated but with 1,3-dihydro-3-propyl-4-chloro-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and N-(3,4-dimethoxy-phenethyl)-N-methyl-3-aminopropyl chloride at 50°C but without final acidic treatment. Yield was 30.7 g (58 %) of a white product melting at 144°C (Tottoli), elemental analysis of which showed a perfect correspondence with the formula $C_{29}H_{40}N_3O_4Cl$.

Example 5

1,3-dihydro-3-phenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = phenyl A_2 = H

The method of example 4 was repeated but with 1,3-dihydro-3-phenyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 65°C ; final acidic treatment was with oxalic acid. Yield 26 g (42 %) of a yellow powder melting at 186-190°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{32}H_{39}N_3O_4$, $C_2H_2O_4$.

Example 6

1,3-dihydro-3-p-fluorophenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = p-fluorophenyl A_2 = H

The method of example 5 was repeated, the only change being that the first starting material was 1,3-dihydro-3-p-fluorophenyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine. Yield was 40 g (63 %) of a white powder melting at 182°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{32}H_{38}N_3O_4F$, $C_2H_2O_4$.

Example 7

1,3-dihydro-3-p-trifluoromethylphenyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_3$ n = 3 X = Cl A_1 = p-CF_3-phenyl A_2 = H

The method of example 1 was repeated but starting with 1,3-dihydro-3-p-trifluoromethylphenyl-4-chloro-6-(1-cyano- 2 -methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and N-(3,4,5-trimethoxy-phenethyl)-N-methyl-3-aminopropyl chloride at 35°C. Yield was 34.7 g (51 %) of a yellowish product melting at 204-207°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{34}H_{39}N_3O_4ClF_3$, HCl.

Example 8

1,3-dihydro-3-p-methoxyphenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = p-methoxyphenyl A_2 = H

The method of example 4 was repeated but starting with 1,3-dihydro-3-p-methoxy-phenyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 60°C. Yield was 20 g (36 %) of a white powder melting at 214-217°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{33}H_{41}N_3O_5$.

Example 9

1,3-dihydro-3-(p-[N-pyrrolidinyl-methoxy]-phenyl)-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-amino butyl] -7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H

A_1 = p-(N-pyrrolidinyl-methoxy)-phenyl A_2 = H

The method of example 5 was repeated but starting with 1,3-dihydro-3-(p-[N-pyrrolidinyl-methoxy]-phenyl)-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 45°C. Yield was 33 g (46 %) of a pale beige powder melting at 169-171°C (Tottoli), elemental

analysis of which showed a very good correspondence with the formula $C_{37}H_{48}N_4O_5$, $C_2H_2O_4$.

Example 10

1,3-dihydro-3-methyl-3-butyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = CH_3 A_2 = butyl

The method of example 5 was repeated but with 1,3-dihydro-3-methyl-3-butyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 30°C. Yield was 27 g (44 %) of a white powder melting at 158°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{31}H_{45}N_3O_4$, $C_2H_2O_4$.

Example 11

1,3-dihydro-3-methyl-3-phenyl-6-[1-cyano-1-isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_3$ n = 3 X = H A_1 = CH_3 A_2 = phenyl

The method of example 7 was repeated but with 1,3-dihydro-3-methyl-3-phenyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at room temperature. Yield was 40 g (66 %) of a yellowish product melting at 188-189°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{36}H_{43}N_3O_5$, HCl.

Example 12

1,3-dihydro-3-methyl-3-α-thienyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = CH_3 A_2 = α-thienyl

The method of example 8 was repeated but starting with 1,3-dihydro-3-methyl-3-α-thienyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 55°C. Yield was 29.1 g (53 %) of a white powder melting at 147-149°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{31}H_{39}N_3O_4S$.

Example 13

1,3-dihydro-3-vinyl-3-(p-methylthio-phenyl)-4-chloro-6-[1-cyano-1-isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_3$ n = 3 X = Cl A_1 = vinyl

A_2 = p-methylthio-phenyl

The method of example 7 was repeated but starting with 1,3-dihydro-3-vinyl-3-(p-methylthio-phenyl)-4-chloro-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride at 60°C. Yield was 40.7 g (58 %) of a pale yellow product melting at 176-178°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{36}H_{44}N_3O_5SCl$, HCl.

Example 14

1,3-dihydro-3-phenyl-3-(p-diethylaminoethoxy-phenyl)-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 3 X = H A_1 = phenyl

A_2 = p-diethylaminoethoxy-phenyl

The method of example 5 was repeated but with 1,3-dihydro-3-phenyl-3-(p - diethylaminoethoxy - phenyl)-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 3-aminopropyl chloride, at 40°C but acidic treatment was with hydrochloric acid. Yield was 30.5 g (41 %) of a white powder melting at 143-146°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{43}H_{54}N_4O_5$, HCl.

Example 15

1,3-dihydro-3-ethyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-5-aminopentyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 4 X = H A_1 = ethyl A_2 = H

The method of example 1 was repeated but with 1,3-dihydro-3-ethyl - 4 - chloro-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c) - pyridine and N - (3,4 - dimethoxy - phenethyl)-N-methyl-4-aminobutyl chloride at 55°C. Yield was 26 g (46 %) of a pale yellow powder melting at 218°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{29}H_{40}N_3O_4Cl$, HCl.

Example 16

1,3-dihydro-3,3-diphenyl-4-chloro-6-[1-cyano-1-isopropyl-N, (m,m,p-trimethoxy-phenethyl)-N-methyl-5-aminopentyl -7-hydroxy-furo-(3,4-c)-pyridine

$R = (OCH_3)_3$ $n = 4$ $X = Cl$ $A_1 = A_2 =$ phenyl

The method of example 15 was repeated but with 1,3-dihydro-3,3-diphenyl-4-chloro-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and N-(3,4,5-trimethoxy-phenethyl)-N-methyl-4-aminobutyl chloride at 65°C. Yield was 44.6 g (62 %) of a yellow powder melting at 169°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{40}H_{46}N_3O_5Cl$, HCl.

Example 17

1,3-dihydro-3,3-di(p-chlorophenyl)-6-[1-cyano-1-isopropyl-N, (m,p-dimethoxy-phenethyl)-N-methyl-5-aminopentyl] -7-hydroxy-furo-(3,4-c)-pyridine

$R = (OCH_3)_2$ $n = 4$ $X = H$ $A_1 = A_2 =$ p-chlorophenyl

The method of example 15 was repeated but with 1,3-dihydro-3,3-di(p-chlorophenyl)-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 4-aminobutyl chloride, at 25°C. Yield was 39.2 g (54 %) of a white product melting at 200-202°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{39}H_{43}N_3O_4Cl_2$.

Example 18

1,3-dihydro-3-methyl-6-[1-cyano-1-methyl-N-(m,m,p-trimethoxy -phenethyl)-N-methyl-6-aminohexyl] -7-hydroxy-furo-(3,4-c)-pyridine

$R = (OCH_3)_3$ $n = 5$ $X = H$ $A_1 =$ methyl $A_2 = H$

The method of example 4 was repeated but with 1,3-dihydro-3-methyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and N-(3,4,5-trimethoxy-phenethyl)-N-methyl-5-aminopentyl chloride at 40°C. Yield was 35.7 g (68 %) of a pale yellow product melting at 213-215°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{30}H_{43}N_3O_5$.

Example 19

1,3-dihydro-3-α-furyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-6-aminohexyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 5 X = H A_1 = α-furyl A_2 = H

The method of example 5 was repeated but with 1,3-dihydro-3-α-furyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and N-(3,4-dimethoxy-phenethyl)-N-methyl-5-aminopentyl chloride at 30°C. Yield was 26 g (41 %) of a white product melting at 154-155°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{32}H_{41}N_3O_5$, $C_2H_2O_4$.

Example 20

1,3-dihydro-3,3-dimethyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-6-aminohexyl]-7-hydroxy-furo-(3,4-c)-pyridine

R = $(OCH_3)_2$ n = 5 X = H $A_1 = A_2 = CH_3$

The method of example 19 was repeated but with 1,3-dihydro-3,3-dimethyl-6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine and the same 5-aminopentyl chloride, at 50°C. Yield was 36 g (60 %) of a white crystalline product melting at 189-191°C, elemental analysis of which showed a very good correspondence with the formula $C_{30}H_{43}N_3O_4$, $C_2H_2O_4$.

TOXICITY

Acute toxicity was researched, per os on rats and mice. Preliminary tests showed that no LD_{50} was inferior to 650 mg/kg.

PHARMACOLOGY

The interest of the compounds of the invention has been evidenced by various tests.

A) Isolated rabbit aorta strips treated by various contracturing agents.

This experiment was conducted along the lines of the methods described by FURCHGOTT R.F. and BHADRAKOM S., J. Pharmac. Exp. Therapeut., 1953, 108, 129-143, VAN ROSSUM J.M., Arch. Int. Pharmacodyn. Ther., 1963, 143; 299-330; and ARUNLAKSHANA, O. and SCHILD, H.O., 1959, Brit. J. Pharmac. 14, 48-58, using noradrenaline (NE), serotonine (5-HT), histamine (HIST) KCl and angiotensine II as agonists.

The compounds of the invention were compared to verapamil on these agonists and showed a similar range of action, with significant and generally comparable values of PA_2 (for NE, 5-HT and HIST) or of IC_{50} (for KCl or angiotensine); however, they appear 5 to 10 times more active on 5-HT (average value for the compounds of the invention: 1.35×10^{-8} compared with 7×10^{-8} for verapamil). These compounds are competitive antagonists of the 5-HT receptor.

B) Experimental ulcer induced by dimaprit.

23 batches each of 5 male Sprague Dawley rats (150-200 g) were treated as follows:

Batches 1 - 20 : The rats of each of these batches received 25 mg/kg per os of one of the compounds of the invention, suspended in 1 ml of physiologic serum.

Batches 21 and 22 : The rats of these batches received 1 ml of physiologic serum.

Batch 23 : The rats of this batch received 25 mg/kg of ranitidine, as reference compound, suspended in 1 ml of physiologic serum.

30 minutes after this administration, all batches except batch 23, received, ip, 175 mg/kg of dimaprit (1-dimethylamino-3-amidino-propane).

Four hours after this treatment, the animals were killed and the ulcers counted. Batch 21 was a blank control and batch 22 the ulceration control. Results were given in percentage of protection compared with ulceration control. Protection by ranitidine was 39 %, whereas protection for the compounds of the invention was from 37 to 52.4%.

C) Diuresis on rats

The diuretic activity has been researched on rats in comparison with a well known diuretic, furosemide, verapamil and a control ; diuresis, elimination of Na^+, K^+ and of uric acid were determined on the compounds of the examples.

This experiment was conducted on batches each of 8 Wistar male rats (180-200 g) deprived from food and drink 16 hours before the experiment and during the same.

At zero time, each animal received, orally, in 2.5 ml/100 g of physiologic serum, 50 mg/kg of the compound to be tested. Rats are placed in individual metabolic cages and

urines are collected for 6 hours. Na^+, K^+ and uric acid are dosed by usual methods. One batch was used as control (physiologic serum only), one for furosemide at 20 mg/kg, one for verapamil and one for each of the tested compounds, all at 50 mg/kg. The results are reported in the following table from which it clearly appears that the compounds of the invention are mild diuretics with a K^+ retention and a good Na^+ elimination. For uric acid, elimination is better in some cases than that of furosemide.

In the table, V is the volume of urine collected in 6 hours (in ml), Na^+ and K^+ are given in mEq/6 hours and uric acid in mMoles/6 hours. The figures are the average values of the animals of each batch. The percentages appearing in the column are by reference to control. The tested compounds are identified by the number of the corresponding example.

PRESENTATION - POSOLOGY

For oral use, the compounds of the invention may be presented in 50 mg dosage units associated with an appropriate diluent or carrier, in tablet, gelatine capsules or in suspension - Posology is of 1 or 2 units per diem.

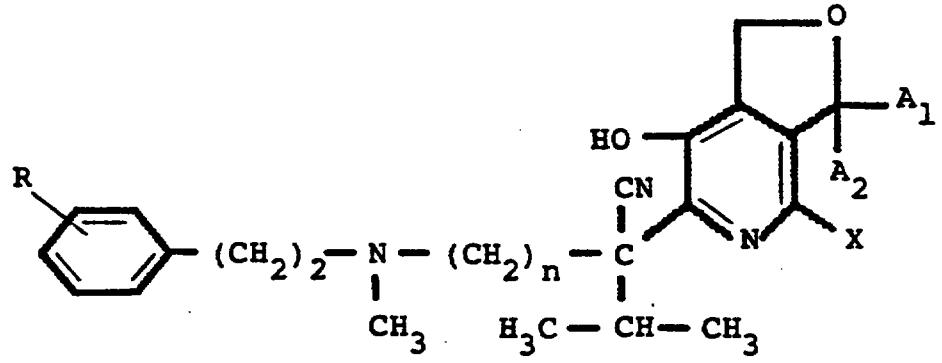
For iv route, phials contain 10 mg of active compound and posology is 1 or 2 phials per diem.

T A B L E

COMPOUND	V	K^+	Na^+	Uric acid
CONTROL	0.52	74.4	116.5	1.56
FUROSEMIDE	2.86 (+ 450 %)	138.1 (+ 85.6 %)	455.6 (+ 291 %)	2.01 (+ 28.8 %)
VERAPAMIL	0.68 (+ 31 %)	86.5 (+ 16.3 %)	193.3 (+ 65.9 %)	2.13 (+ 36.5 %)
1	1.32 (+ 154 %)	76.5 (- 8.4 %)	309.8 (+ 94 %)	2.05 (+ 32.3 %)
5	0.85 (+ 63.5 %)	69.7 (- 6.3 %)	225.8 (+ 93.8 %)	2.08 (+ 33.5 %)
6	0.60 (+ 15.4 %)	34.4 (- 53.8 %)	200.1 (+ 72.5 %)	1.71 (+ 9 %)
9	0.56 (+ 7.7 %)	74.5 (0 %)	150.1 (+ 28.8 %)	1.77 (+ 13.5 %)
12	0.71 (+ 36.5 %)	68.3 (- 8.2 %)	160 (+ 37.3 %)	1.89 (+ 21 %)
15	0.82 (+ 58.4 %)	76.6 (+ 3 %)	236.5 (+ 103 %)	1.83 (+ 17.5 %)
18	1.49 (+ 187.2 %)	72 (- 3.2 %)	311.7 (+ 167.6 %)	2.20 (+ 41.1 %)
19	0.95 (+ 82.5 %)	49.5 (- 33.4 %)	195.5 (+ 67.8 %)	1.85 (+ 18.4 %)

CLAIMS:

1. A furo -(3,4-c)-pyridine derivative having the general formula



wherein each of A_1 and A_2 independently represents a hydrogen atom, a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenylalkyl group or a phenylalkenyl group, each of the groups represented by A_1 and A_2 being unsubstituted or being substituted by one or more chlorine or fluorine atoms, trifluoromethyl groups, alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms, alkylthio groups having from 1 to 5 carbon atoms, dialkylamino groups in which each alkyl group has from 1 to 5 carbon atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy group has from 1 to 5 carbon atoms or α or β - (N-pyrrolidinyl)-alkoxy groups in which the alkoxy group has from 1 to 5 carbon atoms ; R represents from one to three methoxy groups ; n is 2,3,4 or 5 ; and X represents a hydrogen or chlorine atom ; or a therapeutically acceptable salt of such a compound.

* C L M S *

2. 1,3-dihydro-3-methyl-6-[1-cyano-1-isopropyl-3-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine.

3. 1,3-dihydro-3-phenyl-4-chloro-6- [1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine.

4. 1,3-dihydro-3-methyl-3-α-furyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-3-aminopropyl]-7-hydroxy-furo-(3,4-c)-pyridine.

5. 1,3-dihydro-3-propyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

6. 1,3-dihydro-3-phenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

7. 1,3-dihydro-3-p-fluorophenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

8. 1,3-dihydro-3-p-trifluoromethylphenyl-4-chloro-6-[1-cyano-1-isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

9. 1,3-dihydro-3-p-methoxyphenyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

10. 1,3-dihydro-3-(p-[N-pyrrolidinyl-methoxy]-phenyl)-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

11. 1,3-dihydro-3-methyl-3-butyl-6-[1-cyano-1-isopropyl-N--(m,p-dimethoxy-phenethyl)-N-methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

12. 1,3-dihydro-3-methyl-3-phenyl-6-[1-cyano-1-isopropyl--N-(m,m,p-trimethoxy-phenethyl)-N-methyl-4-aminobutyl]--7-hydroxy-furo-(3,4-c)-pyridine.

13. 1,3-dihydro-3-methyl-3-α-thienyl-6-[1-cyano-1--isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-4-amino-butyl]-7-hydroxy-furo-(3,4-c)-pyridine.

14. 1,3-dihydro-3-vinyl-3-(p-methylthio-phenyl)-4-chloro--6-[1-cyano-1-isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N--methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

15. 1,3-dihydro-3-phenyl-3-(p-diethylaminoethoxy-phenyl)-6--[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N--methyl-4-aminobutyl]-7-hydroxy-furo-(3,4-c)-pyridine.

16. 1,3-dihydro-3-ethyl-4-chloro-6-[1-cyano-1-isopropyl--N-(m,p-dimethoxy-phenethyl)-N-methyl-5-aminopentyl]--7-hydroxy-furo-(3,4-c)-pyridine.

17. 1,3-dihydro-3,3-diphenyl-4-chloro-6-[1-cyano-1--isopropyl-N-(m,m,p-trimethoxy-phenethyl)-N-methyl-5--aminopentyl-7-hydroxy-furo-(3,4-c)-pyridine.

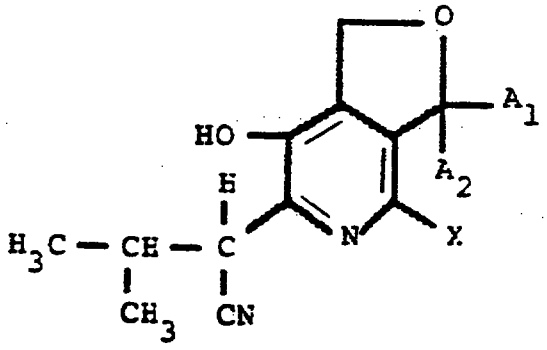
18. 1,3-dihydro-3,3-di(p-chlorophenyl)-6-[1-cyano-1--isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-5-amino-pentyl]-7-hydroxy-furo-(3,4-c)-pyridine.

19. 1,3-dihydro-3-methyl-6-[1-cyano-1-methyl-N-(m,m,p--trimethoxy-phenethyl)-N-methyl-6-aminohexyl]-7-hydroxy--furo-(3,4-c)-pyridine.

20. 1,3-dihydro-3-α-furyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-6-aminohexyl]-7-hydroxy-furo-(3,4-c)-pyridine.

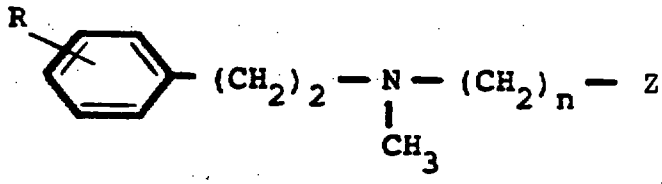
21. 1,3-dihydro-3,3-dimethyl-6-[1-cyano-1-isopropyl-N-(m,p-dimethoxy-phenethyl)-N-methyl-6-aminohexyl]-7-hydroxy-furo-(3,4-c)-pyridine.

22. A process for the preparation of a furo-(3,4-c)-pyridine derivative according to claim 1, the process comprising reacting, in an organic solvent, a 6-(1-cyano-2-methyl-propyl)-7-hydroxy-furo-(3,4-c)-pyridine derivative having the general formula II



II

wherein A_1, A_2 and X are as defined in claim 1 with an ω-aminoalkyl halide having the general formula III



III

wherein R and n are as defined in claim 1 and Z represents a halogen atom.

23. A process according to claim 22 in which the furo-(3,4-c)-pyridine derivative II and the ω-aminoalkyl halide III are reacted in stoichiometric proportions.

24. A process according to claim 22 or claim 23 in which the ω-aminoalkyl halide is an ω-aminoalkyl chloride.

25. A process according to any of claims 22 to 24 in which the organic solvent is dimethylsulphoxide.

26. A process according to any of claims 22 to 25 in which the reaction is conducted at from 15° to 65°C.

27. A process for the preparation of a furo-(3,4-c)--pyridine derivative according to claim 1, the process being substantially as described herein with reference to any of the Examples.

28. A therapeutic composition comprising a furo-(3,4-c)--pyridine derivative according to claim 1 or a therapeutically acceptable salt of such a compound in admixture with a therapeutically acceptable diluent or carrier.