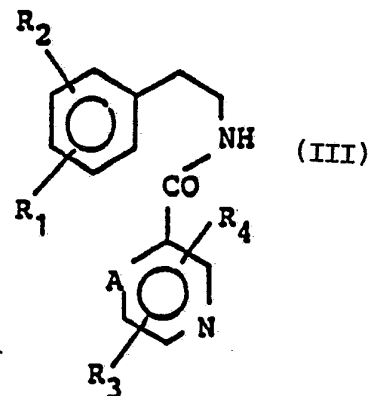
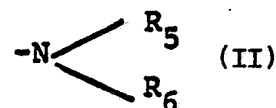
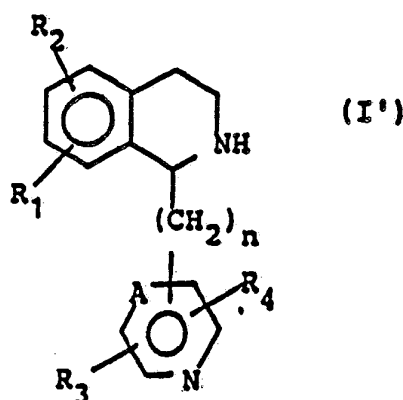
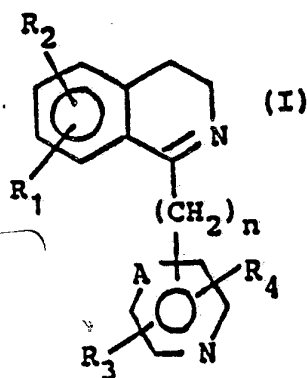




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<p>(21) International Application Number: PCT/FI87/00032 (22) International Filing Date: 12 March 1987 (12.03.87)</p> <p>(71) Applicant (for all designated States except US): HUH-TAMÄKI OY [FI/FI]; Käsämäkivägen 35, SF-20100 Åbo (FI).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : ALLONEN, Hannu [FI/FI]; Rajakivenkatu 26, SF-20720 Turku (FI). NIKANDER, Hannu [FI/FI]; Palomäki, SF-21330 Paattinen (FI).</p> <p>(74) Agent: LEITZINGER OY; Sandviksgatan 8, SF-00180 Helsingfors (FI).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), BG, BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent),</p>		<p>NL (European patent), NO, RO, SE (European patent), SU, US.</p> <p><b>Published</b> With international search report. In English translation (filed in Swedish).</p>

## (54) Title: ISOQUINOLINE DERIVATIVES, THEIR MANUFACTURE AND USE



## (57) Abstract

The invention relates to dihydro- and tetrahydroisoquinolines and their physiologically acceptable salts of formula (I) or (I'), in which formulae A is -CH= or -N=, n is 0 or 1, R<sub>1</sub> and R<sub>2</sub> are the same or different and designate H, halogen, OH, a C<sub>1</sub>-C<sub>4</sub> alkoxy, R<sub>3</sub> is H when R<sub>1</sub> and R<sub>2</sub> are H, or halogen or a C<sub>1</sub>-C<sub>6</sub> alkyl group, R<sub>4</sub> is halogen, a C<sub>1</sub>-C<sub>6</sub> alkyl group or designates an amino group of formula (II), where R<sub>5</sub> and R<sub>6</sub> are the same or different and designate H or a C<sub>1</sub>-C<sub>3</sub> alkyl group which can be substituted with a phenyl group substituted with one or two lower alkoxy, and R<sub>4</sub> can also be H when A is -N=. The invention also relates to a method for preparing same whereby an amide of formula (III), where R<sub>1</sub>-R<sub>4</sub> and A have the above significance, is cyclized with Lewis acid; and the use of compounds of the formula (I) or (I') or their physiologically acceptable derivatives or salts as therapeutical agents.

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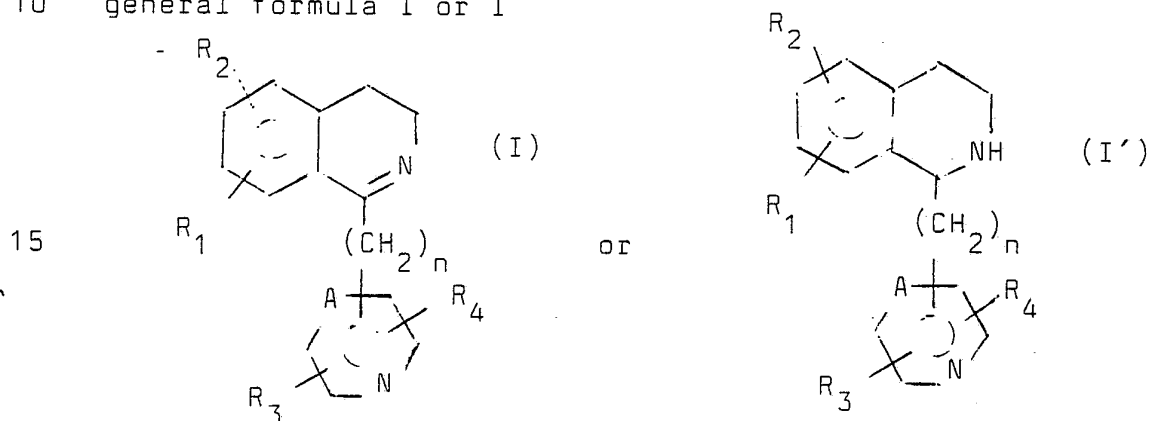
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Isoquinoline derivatives, their manufacture and use

Isoquinoline derivatives having a pyridyl group which includes  
 substitutes in the 1-position are described in Japanese publi-  
 cations (e.g. Yakugski Zasshi: 87(9), 1083 - 1088 (1967) and  
 in patent specifications JP 70 03,782, JP 68 08,277 and  
 5 Japan Tokyo Koho 58 26,350). The described compounds, however,  
 include solely non-substituted pyridyl groups or pyridyl methyl  
 groups.

This invention relates to 1-substituted isoquinolines of the  
 10 general formula I or I'



20 and their physiologically acceptable salts, and to methods for  
 preparing such isoquinolines and their use as therapeutic  
 substances (medicines).

In formula I and formula I'

25  $A = -CH=$  or  $-N=$   
 $n = 0$  or  $1$

$R_1$  and  $R_2$  are the same or different and designate hydrogen,  
 halogen, an hydroxyl group or a  $C_1-C_4$  alkoxy group,  
 30  $R_3 =$  hydrogen when  $R_1$  and  $R_2$  are hydrogen, or halogen, or a  
 $C_1-C_6$  alkyl group,  
 $R_4 =$  halogen,  $C_1-C_6$  alkyl or alkoxy group, or refers to an  
 amino group of the formula

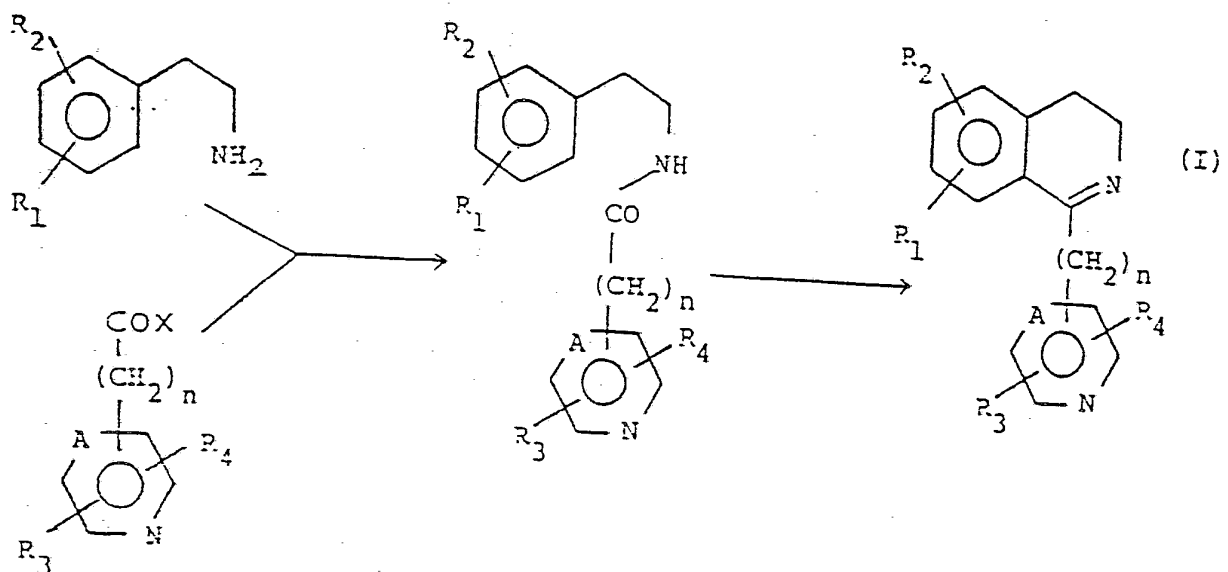


where  $R_5$  and  $R_6$  are the same or different and designate hydrogen or an alkyl group which has 1-3 carbon atoms and which can be substituted with a phenyl group substituted with one or two lower alkoxy, and  $R_4$  can also be hydrogen when  $A = -N=$ .

The compounds having formula 1 are of particular interest where  $n$  is 0,  $A$  designates the group  $-CH=$ ,  $R_1$  and  $R_2$  are hydrogen or an alkoxy group which has 1-3 carbon atoms, and  $R_3$  and  $R_4$  are hydrogen, halogen, or an alkoxy group having 1-4 carbon atoms.

The compounds of formula I can be produced according to the Bischler-Napieralskis reaction. In this reaction an amide is cyclized with Lewis acid. This amide has been produced from substituted 2-phenylethyl amine and a suitable pyridine carboxylic acid, an ester of a pyridine carboxylic acid or pyridine carboxylic acid chloride according to reactions described in the literature.

20 Bischler-Napieralskis reaction:



The condensing agent used in the reaction may suitably be phosphorus trichloride, phosphorus pentachloride, phosphorus

oxychloride, phosphorus pentoxide, boron trifluoride, tin tetrachloride, although strong mineral acids, such as sulphuric acid and polyphosphoric acid may also be used. Phosphorus oxychloride and phosphorus pentoxide are particularly suitable in this regard

5

Cyclization can be effected with or without a solvent. All solvents which will dissolve the reaction components and which have a sufficiently high boiling point can be used. Good solvents in this regard are, for instance, toluene, chloroform, actonitrile and xylene. The actual cyclizing agent, e.g. phosphorus oxychloride, may itself be used as a solvent.

10

The reaction temperature is not critical and the reaction can be carried out within a wide temperature range, although most suitably while warming or heating the system to the boiling point of the solvent.

15

Compounds which have the formula I and I' can also be produced by, for instance, the following methods, the reaction diagram of which have been shown in the appended common diagram page.

20

3.4-Dihydroisoquinolines (I) can also be produced, for instance by:

A) dehydrating corresponding to 1.2.3.4-tetrahydro derivatives (3) in the presence of, e.g. mercury acetate, N-bromosuccinimide or Freym-salt. (Bull. Chem. Soc. Japan 39, 2012 (1966)

25

J. Heterocyclic Chem. 21, 525 (1984)

30

J. Med. Chem. 25, 1240 (1982))

B) alkylating 1-haloisoquinolines (4) using a nickel phosphine complex as a catalyst. (Tetrahedron 38, 3354 (1982))

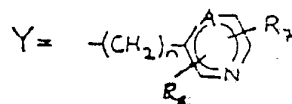
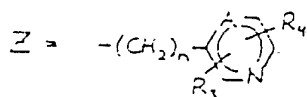
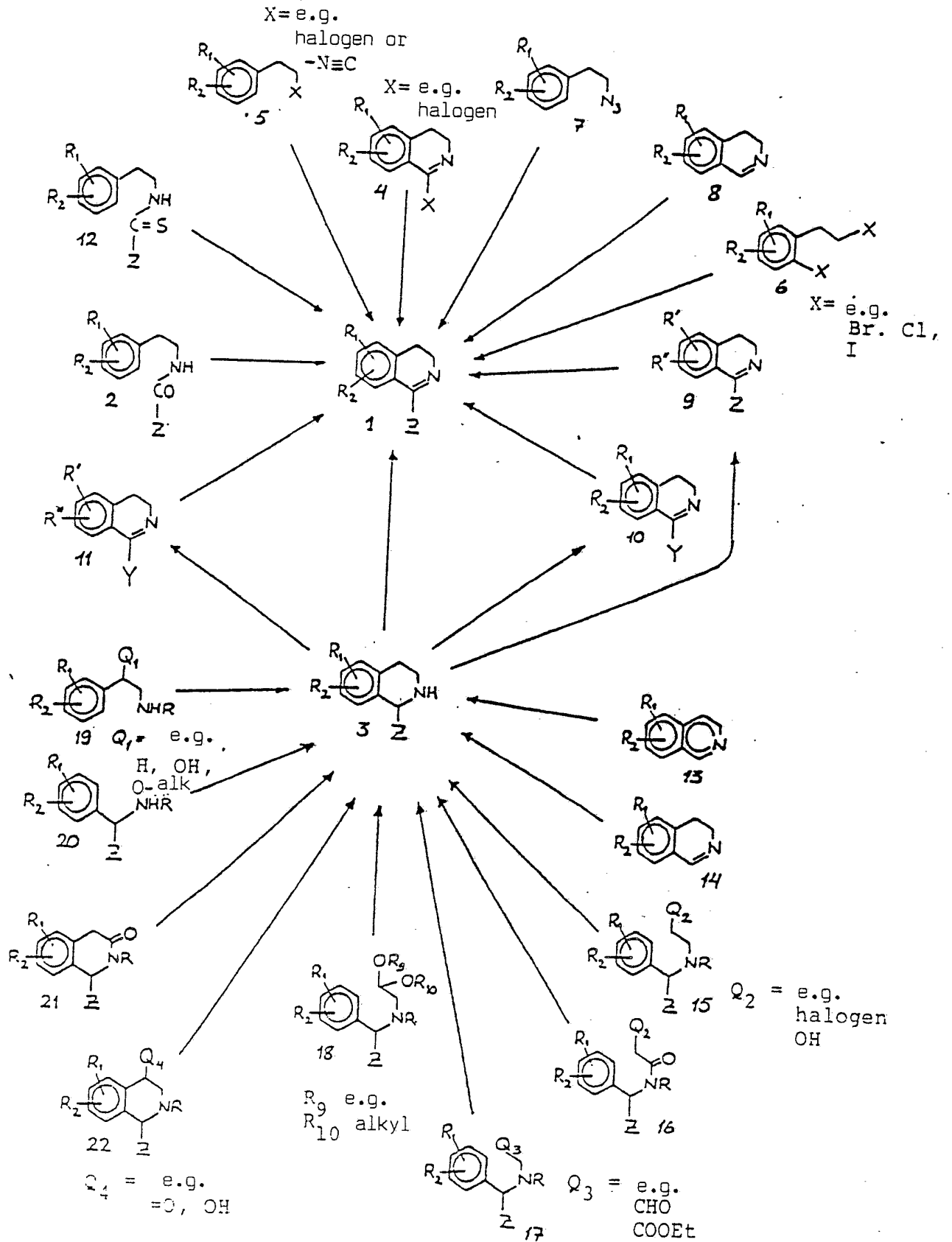
35

C) react a suitable phenethyl derivative (5), e.g. phenethyl halide, with a nitrile-tin tetrachloride complex (Chem. Ber. 94,199 (1961); Tetrah. Lett. 225 (1965)) or

phenethyl isocyanide with acyl halide  
(Tetrah. Lett. 5389 (1985))

- 5 D) reacting halogen-substituted aryl halogenides (6), e.g. a lithium compound obtained through a halogen metal exchange reaction with a suitable nitrile  
(Tetrah. Lett. 4145 (1977))
- 10 E) reacting phenylazide (7) with suitable nitriles in the presence of, e.g., nitrosonium ions  
(J. Heterocyclic Chem. 12, 263 (1975))
- F) effecting a Reissert reaction with dihydroisoquinoline (8)  
(Adv. Heterocyclic Chem. 24, 187 (1979))
- 15 G) converting in a suitable manner the ( $R'$ ,  $R''$ ) of the isoquinoline ring, or the substituent ( $Y$ ;  $R_7$ ,  $R_8$ ) of the 1-position or both substituents ( $R'$ ,  $R''$ ,  $R_7$ ,  $R_8$ ) in a substituted 3.4-dihydroisoquinoline (9, 10 and 11), e.g. by means of different substitution or elimination reactions
- 20 H) effecting a cyclo-desulphurizing reaction with thioamide (12) (Chem. Pharm. Bull. 14, 842 (1966))
- 1.2.3.4-Tetrahydro-isoquinolines (3) can be produced, e.g. by:
- 25 I) effecting a Grignard or Reissert reaction with isoquinolines (13) (Adv. Heterocyclic Chem. 24, 187 (1979); Chem. Pharm. Bull. 29, 1848 (1981); J. Org. Chem. 48, 1621 (1983))
- J) effecting, e.g., a Grignard reaction with 3.4-dihydroisoquinoline (14) (compare the references in I)
- 30 K) cyclizing benzyl amine or N-substituted benzyl amine (15, 16, 17, 20) (Helv. Chim. Acta 31, 914 (1948); Chem. Commun. 799 (1971); Tetrahedr. Lett. 1181 (1974); J. Heterocyclic Chem. 7, 91 (1970))
- L) cyclizing aminoacetals (18), amidoacetals or their reaction products (Org. Reaction 6, 191 (1951); Chem. Heterocyclic Compd. 38, 139 (1981))
- 35 M) departing from phenethyl amines or substituted phenethyl amines (19) (Chem. Heterocyclic Compd. 38, 139 (1981))
- N) e.g. reducing oxo- or hydroxy substituted isoquinolines (21, 22)

5



The compounds according to formula I are chemically basic and can be converted to any form physiologically acceptable acid addition salts with inorganic acids in a conventional manner. Suitable acids for binding salt are, for instance, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid and corresponding acids.

10 The pharmacological properties of the pyridyl derivatives

The activity of the pyridine derivatives have been examined in vitro with preparations of smooth muscles (guinea-pig trachea or windpipe preparations and the thoracic aorta of rabbits) and the cardiac atrium or auricle guinea-pigs preparations. These derivatives have been found to possess properties which widen their pharmacological use. The beta-adrenergic activity of those pyridyl derivatives which are most active pharmacologically have been measured with the aid of receptor binding processes carried out in vitro.

The comparison tests were carried out with compounds according to the present invention and with compounds known from Japanese patent specifications JP 68 08, 277 and JP 70 03, 782, and the publication entitled YAKUGAKI ZASSHI 87, 1083 (1967). These known compounds are:

- I. 1-(4-pyridylmethyl)-6.7-dimethoxy-3.4-dihydroisoquinoline
- II. 1-(4-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline
- 30 III. 1-(4-pyridyl)-6.7-dihydroxy-3.4-dihydroisoquinoline
- IV. 1-(4-pyridyl)-6-hydroxy-7-methoxy-3.4-dihydroisoquinoline
- V. 1-(4-pyridylmethyl)-6.7-dihydroxy-3.4-dihydroisoquinoline

35 1. The dilating effect on bronchi (bronchus dilation)

Since the bronchi of guinea-pigs are highly responsive to the contracting effect of the histamine on bronchi, guinea-pigs



of both sexes weighing from 300-400 g were used in the investigations (Duncin-Hartley, Pigment). Since tracheae are easier to separate and exhibit the same reactions as the bronchi to contracting and relaxing agents, trachea preparations were used in the tests instead of bronchi smooth or unstriated muscle.

The trachea of the dead animal was prepared and two zig-zag preparations were produced by a method according to Emmerson and Mackay (1979). The preparations were from 20 to 22 mm in length and were transferred to incubating dishes which contained nutrient solution oxidized with carbogen (Krebs-Henseleit). The solution had a pH of 7.4 and a temperature of 37°C. The other end of the preparation was attached to an isotonic myograph-indicator, which registered changes in length of the preparation during contraction and relaxation thereof. After 60 minutes 2  $\mu$ mole/l histamine were used to induce contraction of the smooth muscle, which constituted about 50-60% of the maximum response of the preparation. Subsequent hereto the relaxing action of the test and control compounds were examined by cumulative dosing of the test compound until maximum (100%) relaxation was reached. The response of the trachea preparation was measured isotonically. Using linear regression, there was calculated from the graphic presentation of the effect of the test doses the ED<sub>50</sub>-value, i.e. the concentration, which induces a 50%-relaxation of the maximum response for the contraction of smooth muscle caused by histamine. At least two measurements were taken with each compound, on average 4-5. The relaxation effects (ED<sub>50</sub>) in respect of the compound investigated have been combined in Table I below. The values recited are the average values of measurements made.

Table 1

The relaxing effect of the derivatives on the smooth muscle of guinea-pig tracheae, where contraction has been induced with histamines (2  $\mu$ mole/l) and which resulted in a 50-60%-contraction in relation to the maximum contraction of the preparation. ED<sub>50</sub> is the concentration of the examined derivative resulting in a 50%-reduction in the induced contraction, n designates the number of measurement/derivatives.

Derivative	Salt	n	ED <sub>50</sub> $\mu$ mole/l
1212	HCl	6	0.7
1209	HCl	9	1.2
1217	HCl	9	1.4
185	HCl	3	2.5
184	HCl	3	4.2
1219	HCl	3	4.4
1210	HCl	3	5.1
1208	HCl	5	6.0
183	HCl	2	9.4
1205	HCl	19	11.0
1224	HCl	3	11.0
1222	HCl	5	31.7
1218	HCl	4	36.0
1205	HBr	4	36.5
1216	HBr	3	48.4
1206	HBr	3	68.5
1207	HBr	2	68.9
1204	HCl	2	212.8
-----			
Comparison:			
I	HBr	4	21.1
II	HCl	4	32.8
III	HBr	2	53.3
IV	HBr	7	66.5
V	HBr	4	82.8
Papaverine	HCl	7	2.4
Theophylline	HCl	7	94.4

The test values show that the broncho-dilation effect of all derivatives, with the exception of 1204, are at least of the same magnitude as that of theophylline in vitro. The most active derivatives are 1217, 1209 and 1212. Their activity is from  
5 2 to 3 times greater than that of papaverine and from 60 to 135 times greater than that of theophylline. The results thus show that the compounds listed in the table had a pronounced bronchi-dilating effect when tested in vitro on the smooth muscle of guinea-pigs.

10

## 2. Blood-vessel dilation effect (vasodilation)

The vasodilational effect of the pyridyl derivatives has been tested in vitro on thoracic aorta preparations from rabbits.

15

The tests were carried out on rabbits of both sexes and weighing from 2-2.5 kg (New Zealand White). The thoracic aorta of the dead animal was quickly prepared, removed and transferred to a petri-dish containing an oxidized Krebs-Hanseleit solution. A helical preparation (length 20-22 mm,  
20 breadth 2-3 mm) was then prepared in accordance with a method proposed by Furchgott & Bhadrakom (1953). Several preparations were obtained from a single thoracic aorta, and these preparations were transferred to an incubation dish containing an  
25 oxidized Krebs-Hanseleit solution (37°C, pH = 7.4) for investigation. The incubation dish had a volumetric capacity of 30 ml. One end of the preparation was attached to a bronchial tube and the other to an isotonic myograph indicator. The measuring results were obtained isototonically, after the tonus of the  
30 preparation had stabilized, a period of 60 minutes.

Contraction of the blood vessel was induced with noradrenaline, which was dosed to the incubation dish cumulatively, until the maximum contraction of the preparation was reached. Na<sub>3</sub>EDTA  
35 (10<sup>-5</sup> mole/l), which prevents premature inactivation of the noradrenaline, was also added to the Krebs-Hanseleit solution. The ED<sub>50</sub>-value of the noradrenaline for each preparation, i.e.

the amount of noradrenaline which results in a 50%-contraction of the preparation, was calculated with the aid of linear regression from the response curve drawn up for the noradrenaline dosing. This measurement was then repeated, by first  
 5 placing the derivative to be examined into the dish and allowing the derivative to react for a period of 10 minutes. A preparation response curve for the noradrenaline dosage was then drawn up, as in the earlier case. The dosage relationships were then determined in accordance with the following formula,  
 10 subsequent to calculating the  $ED_{50}$ -value of noradrenaline in the presence of the test derivatives:

$$ED_{50} \text{ noradrenaline} + \text{test derivative (antagonisten)} / ED_{50} \text{ noradrenaline.}$$

15

The formula shows at which test-derivative concentration a ratio in the proximity of 4 (four) is reached, i.e. how effectively each of the derivatives displaces the response curve for the dosing of noradrenaline to the right.

20

Table 2

The relaxing effect of the pyridyl derivatives on the smooth muscle of the thoracic aorta of a rabbit when contracting of the muscle preparation is induced with noradrenaline.

25

Derivative	Salt	Concentration $\mu\text{mole/l}$	Dosing ratio
185	HCl	0.1	3.9
1208	HCl	3.3	4.3
1209	HCl	3.3	3.7
30 1205	HCl	10.0	4.5
1218	HCl	33.0	4.1
1219	HCl	33.0	5.4
Papaverine	HCl	1.0	3.2

The above table refers to dosing ratios =

$$\frac{ED_{50} \text{ value for noradrenaline + test derivative}}{ED_{50} \text{ value for noradrenaline}}$$

The derivatives listed in the table displace the cumulative dosing curve of the noradrenaline to the right. The derivatives 185, 1208 and 1209 had an effect corresponding to that of the papaverine, the vasodilatory effect of the derivative 185 being ten times more effective than that of the papaverine. These derivatives also had a relaxing effect on the smooth muscle of the blood vessels.

### 3. The effect on adrenergic receptors

The beta-receptor activity of the most active bronchi-dilating derivatives 1209 and 1217 was measured by a receptor binding method in vitro with the aid of iodocyanopindolol (125 ICYP) as a radio-active ligand and lung membrane from guinea-pigs as the beta-receptor sources. The membrane receptor preparations or compounds were prepared by, and the actual bonding tests carried out in accordance with a method described by Engels working group (1981), although with certain minor modifications.

The radioligand (final concentration 39.5 pM) and the membrane suspension (40-100 µg protein) were incubated at 37°C for 60 minutes, either in the presence of propranolol (10 µM = unspecified bonding) or in the absence thereof (total bonding) to show specific bonding above 95% of the total bonding. The membrane ligand with bound ligands was isolated by filtration and the radioactivity calculated with a gamma counter. The ability of these compounds to compete with the radioligands for binding to the beta-receptors was determined by incubating the test derivative in different concentrations. The IC<sub>50</sub>-value indicates the test derivative concentration which inhibits 50%-bonding of the radioligand, this value being calculated by linear regression subsequent to a logit-log conversion of the binding results.

The  $IC_{50}$ -values calculated were  $1.2 \times 10^{-3} M$  in the case of 1209 and  $0.4 \times 10^{-3}$  in the case of 1217 and the Hill-constant deviated markedly from 1, and was 1.84 in the case of 1209 and 1.81 in the case of 127 when the correlation constants of the regression lines were 1.00 and 0.95 respectively. No appreciable binding to beta-3 receptors could be shown. The absence of effect on beta-adrenergic receptors was supported by the fact that propranolol ( $10^{-6} \mu M$ ) in vitro displaced the dosing curve for salbutamol relaxation in the guinea-pig trachea preparation to the right, while no such property was found in the case of 1217. Neither did the derivatives 1209, 1201, 1205, 1208, 1209 and 1210, cumulatively dosed (0.01 - 1  $\mu mole/l$ ) cause any clear change in the beat frequency in the guinea-pig auricle preparation in vitro, i.e. the derivatives do not have a beta-receptor stimulating or inhibiting effect. The isoprenaline, on the other hand, increased the beat frequency of the auricle preparation with a maximum change at a concentration of 1  $\mu mole/l$ .

The tests show that the pyridyl derivatives have a pronounced therapeutic effect on smooth muscle preparations. On the other hand, the derivatives have no effect on beta-adrenergic receptors. Certain comparison compounds, on the other hand, did have an effect on such receptors. Novel therapeutical properties are thus associated with the novel inventive derivatives.

#### References:

- Engel G, Hoyer D, Berthold R et al. (1981)  
Naunyn-Schmiedeberg's Arch Pharmacol 317, 227 - 285
- Emmerson J & Mackay D (1979)  
J Pharm Pharmacol 31, 798
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J Pharmacol Exp Ther 108, 129 - 143

Reitz A B, Sonveaux E, Rosenkranz R P et al. (1985)  
J Med Chem 28, 634 - 642

The invention will now be described in more detail with  
5 reference to the following working examples.

Example 1

Methyl-5-bromonicotinate

10 5-Bromonicotinic acid (10 g, 0.05 mole) was admixed with 100 ml  
methanol and the mixture heated to almost boiling point. 3.5 ml  
of thionylchloride were added to the mixture over a period  
of 15 minutes. The mixture was reflux boiled for 3 hours, and  
then cooled and the solvent removed under vacuum. The solid  
15 residue was redissolved in a small amount of methanol, neutra-  
lized with triethylamine and the solvents vaporized off. The  
ester was extracted from the evaporation residue with diisopropyl  
ether.

The yield was 10.7 g (99%).

20

Example 2

1-(5-Bromo-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline  
(1209)

25 A small amount of pyridine (0.3 ml) was added to a mixture of  
methyl-5-bromonicotinate (5 g, 0.023 mole) and homoveratryl  
amine (4.2 g, 0.023 mole) and the mixture heated to 100°C over  
a period of 4-5 hours. The resultant amide was not separated,  
but was used as such in future processes.

30

The oily amide was dissolved in 50 ml of toluene and 10 ml of  
phosphorus oxychloride were added to the solution. The mixture  
was boiled under reflux for four hours, cooled and the solvent  
decanted off. The tough residue was washed with hexane, to  
35 remove non-reacted phosphorus oxychloride, and dissolved in a  
25%-ethanol solution and was basified with an NaOH-solution.  
The product was extracted with diisopropyl ether.

The yield was 6.4 g.

m.p base 126 - 128<sup>o</sup>C (cryst. from isopropanol)

Ms: 237 (M), 315 (M-CH<sub>3</sub>OH)

5

NMR: (ppm)	3.76 s (3 H, MeO)	3.96 s (3 H, MeO)
	2.76 t (2 H, CH <sub>2</sub> )	3.84 t (2 H, CH <sub>2</sub> )
	6.70 s (1 H, ar.CH)	6.82 s (1 H, ar.CH)
	8.15 s (1 H, pyr.CH)	8.77 s (2 H, pyr.CH)

10

The following compounds were produced by the methods described in Examples 1 and 2.

Example 3

15 1-(2-Chloro-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline (1205)

---

The title compound was produced from methyl-2-chloronicotinate (6.8 g, 0.04 mole) and homoveratryl amine (7.8 g, 0.043 mole).

20

The yield was 9.7 g (crude product: 80% of the theoretical)

m.p. base 119.5 - 120.5<sup>o</sup>C

hydrochloride 209.5 - 211<sup>o</sup>C

25 Ms: 302 (M), 267 (M-Cl)

NMR: (ppm)	3.69 s (3 H, MeO)	3.95 s (3 H, MeO)
	2.81 t (2 H, CH <sub>2</sub> )	3.80 t (2 H, CH <sub>2</sub> )
	6.38 s (1 H, ar.CH)	6.78 s (1 H, ar.CH)
	7.37 m (1 H, pyr.CH)	7.82 d (1 H, pyr.CH)
	8.50 d (1 H, pyr.CH)	

30

Example 4

35 1-(6-Chloro-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline (1208)

---

The title compound was produced from methyl-6-chloronicotinate



(7.0 g, 0.041 mole) and homoveratryl amine (7.9 g, 0.044 mole).

The yield was 7.8 g (crude produce: 63% of the theoretical)

m.p. base 109 - 112.5°C

5 hydrochloride 197 - 198.5°C

Ms: 302 (M), 287 (M-Me), 271 (M-MeO), 267 (M-Cl)

10 NMR: (ppm)            3.76 s (3 H, MeO)            3.96 s (3 H, MeO)  
                           2.72 t (2 H, CH<sub>2</sub>)            3.84 t (2 H, CH<sub>2</sub>)  
                           6.69 s (1 H, ar.CH)            6.82 s (1 H, ar.CH)  
                           7.40 d (1 H, pyr.-CH)            7.95 d (1 H, pyr.CH)  
                           8.63 s (1 H, pyr.CH)            -

15 Example 5

1-(2-Chloro-3-pyridyl)-7-methoxy-3,4-dihydroisoquinoline (1224)

20 The title compound was produced from methyl-2-chloronicotinate (7.2 g, 0.044 mole) and 2-(4-methoxyphenyl)-ethylamine (8.5 g, 0.056 mole).

The yield was 6.6 g (crude product: 55% of the theoretical)  
 m.p. hydrochloride 206.5 - 208°C

25 Ms: 272 (M), 237 (M-Cl)

30 NMR: (ppm)            3.67 s (3 H, MeO)  
                           2.81 t (2 H, CH<sub>2</sub>)            3.87 t (2 H, CH<sub>2</sub>)  
                           6.42 d (1 H, ar.CH)            6.94 kv. (1 H, ar.CH)  
                           7.19 d (1 H, ar.CH)            7.37 kv. (1 H, pyr.CH)  
                           7.78 d (1 H, pyr.CH)            8.47 d (1 H, pyr.CH)

Example 6

1-(2-Chloro-3-pyridyl)-5-methoxy-3,4-dihydroisoquinoline (1222)

35

The title compound was prepared from methyl-2-chloronicotinate (7.5 g, 0.044 mole) and 2-(2-methoxyphenyl)-ethyl amine (8.5 g,

0.056 mole)

The yield was 6.6 g (crude product: 55% of the theoretical)  
m.p. hydrochloride 238 - 240°C

5

Ms: 272 (M), 237 (M-Cl)

NMR: (ppm)	3.89 s (3 H, MeO)	
	2.89 t (2 H, CH <sub>2</sub> )	3.87 t (2 H, CH <sub>2</sub> )
10	6.52 d (1 H, ar.CH)	6.97 d (1 H, ar.CH)
	7.17 t (1 H, ar.CH)	7.35 t (1 H, pyr.CH)
	7.78 d (1 H, pyr.CH)	8.47 d (1 H, pyr.CH)

Example 7

15 1-(5-Bromo-3-pyridyl)-7-methoxy-3,4-dihydroisoquinoline (1217)

The title compound was prepared from methyl-5-bromonicotinate  
(5.0 g, 0.023 mole) and 2-(4-methoxy phenyl)-ethyl amine (4.0 g,  
0.026 mole)

20

The yield was 5.2 g (71% of the theoretical)  
m.p. hydrochloride 203.5 - 206°C

Ms: 317 (M), 237 (M-Br), 285 (M-CH<sub>3</sub>OH)

25

NMR: (ppm)	3.70 s (3 H, MeO)	
	2.70 t (2 H, CH <sub>2</sub> )	3.80 t (2 H, CH <sub>2</sub> )
	7.10 s (1 H, ar.CH)	7.10 d (1 H, ar.CH)
	6.73 d (1 H, ar.CH)	8.08 s (1 H, pyr.CH)
30	8.67 s (2 H, pyr.CH)	

Example 8

1-(5-Bromo-3-pyridyl)-5-methoxy-3,4-dihydroisoquinoline (1218)

35 The title compound was produced from methyl-5-bromonicotinate  
(5.0 g, 0.023 mole) and 2-(2-methoxy phenyl)-ethyl amine (4.0 g,  
0.026 mole).

The yield was 3.7 g (51% of the theoretical)

m.p. base 133.5 - 135.5°C

hydrochloride 226 - 232°C

5 Ms: 317 (M), 285 (M-H-CH<sub>3</sub>O), 237 (M-Br)

NMR: (ppm)

	3.90 s (3 H, MeO)	
	2.79 t (2 H, CH <sub>2</sub> )	3.84 t (2 H, CH <sub>2</sub> )
	6.81 d (1 H, ar.CH)	7.03 d (1 H, ar.CH)
10	7.26 kv (1 H, ar.CH)	9.10 s (1 H, pyr.CH)
	8.73 s (1 H, pyr.CH)	8.73 s (1 H, pyr.CH)

#### Example 9

15 1-(2-Chloro-6-methyl-3-pyridyl)-6.7-dimethoxy-3.4-dihydro-  
isoquinoline (1210)

The title compound was produced from methyl-2-hydroxy-6-methylnicotinate (4.0 g, 0.024 mole) and homoveratryl amine (4.8 g, 0.026 mole).

20 (POCl<sub>3</sub> as condensing agent)

The yield was 4.0 g (crude product: 53% of the theoretical)

m.p. base 140 - 143°C

hydrochloride 206 - 208°C

25

Ms: 316 (M), 301 (M-Me), 281 (M-Cl)

NMR: (ppm)

	3.69 s (3 H, MeO)	3.94 s (3 H, MeO)
	2.80 t (2 H, CH <sub>2</sub> )	3.85 t (2 H, CH <sub>2</sub> )
30	6.44 s (1 H, ar.CH)	6.79 s (1 H, ar.CH)
	7.24 d (1 H, pyr.CH)	7.83 d (1 H, pyr.CH)
	2.63 s (3 H, Me)	

#### Example 10

35 1-(5-Bromo-3-pyridyl)-6.7-diethoxy-3.4-dihydroisoquinoline (1212)

The title compound was produced from methyl-5-bromonicotinate

(4.0 g, 0.0185 mole) and 2-(3,4-diethoxy phenyl)-ethyl amine (4.0 g, 0.019 mole).

The yield was 4.2 g (60% of the theoretical)

5 m.p. base 96 - 99°C

hydrochloride 220 - 223.5°C

Ms: 375 (M), 330 (M-EtO), 346 (M-Et)

10 NMR: (ppm)

1.38 t (3 H, EtO)	1.50 t (3 H, EtO)
3.96 kv (2 H, EtO)	4.16 t (2 H, EtO)
2.73 t (2 H, CH <sub>2</sub> )	3.84 t (2 H, CH <sub>2</sub> )
6.71 s (1 H, ar.CH)	6.79 s (1 H, ar.CH)
8.12 s (1 H, pyr.CH)	8.74 s (2 H, pyr.CH)

15

Example 11

1-(2,6-Dichloro-4-pyridyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (183)

20 The title compound was produced from methyl-2,6-dichloronicotinate (2.5 g, 0.012 mole) and homoveratryl amine (2.8 g, 0.016 mole).

The yield was 3.2 g (79% of the theoretical)

25 m.p. base 117 - 120°C

hydrochloride 208 - 210.5°C

Ms: 336 (M), 301 (M-Cl)

30 NMR: (ppm)

3.79 s (3 H, MeO)	3.96 s (3 H, MeO)
2.73 t (2 H, CH <sub>2</sub> )	3.84 t (2 H, CH <sub>2</sub> )
6.62 s (1 H, ar.CH)	6.79 s (1 H, ar.CH)
7.50 d (2 H, pyr.CH)	

35 Example 12

1-(2-Pyrazyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (1206)

The title compound was produced from the methyl ester of

2-pyrazine carboxylic acid (7.3 g, 0.05 mole) and homoveratryl amine (10.9 g, 0.06 mole).

The yield was 9.5 g (63% of the theoretical)

5 m.p. hydrochloride 185 - 188<sup>o</sup>C

Ms: 269 (M), 254 (M-Me), 238 (M-MeO)

10 NMR: (ppm)      3.77 s (3 H, MeO)      3.80 s (3 H, MeO)  
                   2.73 t (2 H, CH<sub>2</sub>)      3.88 t (2 H, CH<sub>2</sub>)  
                   6.73 s (1 H, ar.CH)      7.05 s (1 H, ar.CH)  
                   8.58 s (2 H, pyr.CH)      9.12 s (1 H, pyr.CH)

Example 13

15 1-(5-n-Butyl-2-pyridyl)-6,7-dimethoxy-3,5-dihydroisoquinoline  
(1219)

---

20 The title compound was produced from the methyl ester of fusaric acid (4.5 g, 0.023 mole) and homoveratryl amid (5.0 g, 0.028 mole).

The yield was 4.6 g (62% of the theoretical)

m.p. base 116.5 - 119<sup>o</sup>C

hydrochloride 170.5 - 173<sup>o</sup>C

25

Ms: 324 (M), 309 (M-Me), 293 (M-MeO)

30 NMR: (ppm)      3.78 s (3 H, MeO)      3.93 s (3 H, MeO)  
                   2.71 t (2 H, CH<sub>2</sub>)      3.84 t (2 H, CH<sub>2</sub>)  
                   0.95 t (3 H, Bu-CH<sub>3</sub>)      1.39 kv (2 H, Bu-CH<sub>2</sub>)  
                   1.63 kv (2 H, Bu-CH<sub>2</sub>)      2.73 kv (2 H, Bu-CH<sub>2</sub>)  
                   6.75 s (1 H, ar.CH)      7.07 s (1 H, ar.CH)  
                   7.62 d (1 H, pyr.CH)      7.77 d (1 H, pyr.CH)  
                   8.47 s (1 H, pyr.CH)

35

Example 14

1-(2-(2'-(3,4-Dimethoxy phenyl)-ethyl amino)-6-chloro-4-pyridyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (184)

5 The title compound was produced from methyl-2,6-dichloro-isonicotinate (2.5 g, 0.012 mole) and homoveratryl amine (4.3 g, 0.024 mole)

10 The surplus amine used replaces the second chloro substitute in the isonicotinate.

The yield was 2.1 g (36% of the theoretical)  
m.p. hydrochloride 165 - 167°C

15 Ms: 481 (M), 330 (M- diMeO-Ph-CH<sub>2</sub>)

20	NMR: (ppm)	3.78 s (3 H, MeO)	3.97 s (3 H, MeO)
		2.74 t (2 H, CH <sub>2</sub> )	3.83 t (2 H, CH <sub>2</sub> )
		6.68 s (1 H, ar.CH)	6.82 s (1 H, ar.CH)
		6.72 s (1 H, pyr.CH)	7.12 s (1 H, pyr.CH)
		3.83 s (6 H, MeO)	2.60 t (2 H, CH <sub>2</sub> )
		3.68 t (2 H, CH <sub>2</sub> )	6.80 s (3 H, ar.CH)

Example 15

25 1-(2-(2'-(3,4-Dimethoxy phenyl)-ethyl-amino-3-pyridyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (1207)

30 The title compound was produced from methyl-2-chloronicotinate (3.4 g, 0.02 mole) and homoveratryl amine (7.2 g, 0.04 mole).

The yield was 2.0 g (22% of the theoretical)

m.p. - (decomposes)

Ms: 447 (M)

35	NMR: (ppm)	3.74 s (3 H, MeO)	3.95 s (3 H, MeO)
		2.89 t (2 H, CH <sub>2</sub> )	3.86 t (2 H, CH <sub>2</sub> )
		6.75 s (1 H, ar.CH)	6.80 s (1 H, ar.CH)

6.53 t (1 H, pyr.CH) 7.48 d (1 H, pyr.CH)  
 8.18 d (1 H, pyr.CH)  
 3.84 s (6 H, MeO) 2.61 t (2 H, CH<sub>2</sub>)  
 3.67 t (2 H, CH<sub>2</sub>) 6.78 s (3 H, ar.CH)

5

Example 16

1-(2-Chloro-6-methoxy-4-pyridyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline (185)

10 The title compound was produced from methyl-2-chloro-6-methoxyisonicotinate (1.8 g, 0.009 mole) and homoveratryl imine (2.0 g, 0.011 mole)

The yield was 2.2 g (74% of the theoretical)

15 m.p. base 116.5 - 120°C

hydrochloride 201 - 203°C

Ms: 332 (M), 301 (M-MeO), 297 (M-Cl)

20 NMR: (ppm) 3.78 s (3 H, MeO) 3.96 s (3 H, MeO)  
 3.98 s (s H, MeO)  
 2.73 t (2 H, CH<sub>2</sub>) 3.83 t (2 H, CH<sub>2</sub>)  
 6.69 s (1 H, ar.CH) 6.84 s (1 H, ar.CH)  
 6.77 s (1 H, pyr.CH) 7.14 s (2 H, pyr.CH)

25

Example 17

1-(5-Bromo-3-pyridyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1204)

30 The 1209 hydrochloride of the dihydro-derivative (2.0 g, 0.005 mole) was dissolved in methanol. The solution was cooled to 10 - 15°C and small quantities of sodium borohydride (0.5 g, 0.013 mole) were added over a period of 20 minutes, whereafter the mixture was stirred for two hours at 40°C, and then cooled  
 35 and acidified with a 10%-HCl solution. The solution was then evaporated off to leave hydrochloride.

The yield was 2.0 g (95% of the theoretical)  
m.p. (HCl salt) 208 - 210°C

Ms: 349 (M), 348 (M-1), 317 (M-CH<sub>3</sub>OH)

5

NMR: (ppm)      3.63 s (3 H, MeO)      3.85 s (3 H, MeO)  
                  3.0 - 3.3 (5 H, CH<sub>2</sub>, CH)  
                  6.30 s (1 H, ar.CH)      6.81 s (1 H, ar.CH)  
                  8.26 s (1 H, pyr.CH)      8.71 s (1 H, pyr.CH)  
10               8.82 s (1 H, pyr.CH)

Example 18

1-(2-Hydroxy-6-methyl-3-pyridyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline (1220)

15

Homoveratryl amine (12.7 g, 0.07 mole) methyl-2-hydroxy-6-methylnicotinate (10.5 g, 0.07 mole) and pyridine (0.5 g) were heated for 5 hours at 130°C. The mixture was cooled and dissolved in 100 ml of xylene. 20 g of phosphorus pentoxide were added to the solution and the mixture boiled under reflux for 4 hours and then cooled. The solvent was decanted and the solidified residue dissolved carefully in 100 ml of water. The solution was basified with an ammonium solution and extracted with chloroform. The solvent was evaporated off to leave a 9 g crude-product residue (43%).

20

m.p. base 192 - 196°C

hydrochloride 207 - 213°C

Ms: 298 (M), 283 (M-Me), 267 (M-MeO)

30

NMR: (ppm)      3.77 s (3 H, MeO)      3.94 s (3 H, MeO)  
                  2.33 s (3 H, Me)  
                  2.76 t (2 H, CH<sub>2</sub>)      3.75 s (2 H, CH<sub>2</sub>)  
                  6.74 s (1 H, ar.CH)      6.86 s (1 H, ar.CH)  
35               6.31 d (1 H, pyr.CH)      7.69 d (1 H, pyr.CH)



Example 191-(2-Chloro-3-pyridyl)-6.7-dihydroxy-3.4-dihydroisoquinoline (1215)

5 The hydrochloride (5 g, 0.15 mole) of 1-(2-Chloro-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline was dissolved in 40 ml of an HBr-solution (48%). The solution was boiled in a nitrogen atmosphere for 5 hours and the solvent then evaporated off in a vacuum environment. The product was crystallized from an  
10 ethanol-ethyl-acetate mixture.

The yield was 2.8 g (43% of the theoretical; HBr-salt)  
m.p. hydrobromide 219 - 223°C

15 Ms: 274 (M)

NMR (ppm)            2.89 t (2 H, CH<sub>2</sub>)            3.84 t (2 H, CH<sub>2</sub>)  
                          6.60 (1 H, ar.CH)            6.75 (1 H, ar.CH)  
                          6.97 kv (1 H, pyr.CH)        8.18 d (1 H, pyr.CH)  
20                            8.57 d (1 H, pyr.CH)

Example 201-(2-Pyrazyl)-6.7-dihydroxy-3.4-dihydroisoquinoline (1216)

25 The product was produced from corresponding dimethoxy derivative 1206 (5 g, 0.015 mole) as recited in Example 19.

The yield was 5.3 g (88% of the theoretical; HBr-salt)  
m.p. hydrobromide 212.5 - 215°C

30 Ms: 385 (silylated; mole.w. 241 + 2\* (CH<sub>3</sub>)<sub>3</sub>Si)

NMR: (ppm)            3.16 t (2 H, CH<sub>2</sub>)            4.01 t (2 H, CH<sub>2</sub>)  
                          6.99 s (1 H, ar.CH)            7.13 s (1 H, ar.CH)  
                          8.98 s (1 H, pyr.CH)        9.01 s (1 H, pyr.CH)  
35                            9.16 s (1 H, pyr.CH)

Example 21

1-(5-Bromo-3-pyridyl)-6.7-dihydroxy-3.4-dihydroisoquinoline  
(1221)

5 The product was produced from corresponding dimethoxy derivative 1209 (2.4 g, 0.006 mole) as recited in Example 19.

The yield was 2.4 g (83% of the theoretical; HBr-salt)  
m.p. hydrobromide 286 - 290°C

10

Ms: 319 (M)

NMR: (ppm)      3.10 t (2 H, CH<sub>2</sub>)      3.98 t (2 H, CH<sub>2</sub>)  
                  6.88 s (1 H, ar.CH)      6.98 s (1 H, ar.CH)  
15                   8.43 s (1 H, pyr.CH)      8.87 s (1 H, pyr.CH)  
                  8.98 s (1 H, pyr.CH)

Example 22

20 1-(2-Aminomethyl-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline (1221)

The 2-chloro-3-pyridyl derivative (1205) (1.5 g, 0.005 mole) was dissolved in an ethanol solution of methyl amine (3 g methyl amine in 30 ml ethanol). The solution was boiled in a  
25 closed bomb at 140°C for 15 hours. The solvent and non-reacted amine were evaporated off, and the product was isolated from the evaporation residue by flash-chromatography (the column material was silicagel Merck, 230 - 400 mesh) and the eluate was toluene-acetone (1:1).

30

The yield was 1.1 g (74% of the theoretical)  
m.p. 231 - 234.5°C (HCl-salt)

Ms: 297 (M), 296 (M-1), 282 (M-Me), 266 (M-MeO)

5	NMR: (ppm)	3.87 s (3 H, MeO)	3.70 s (3 H, MeO)
		3.02 d (3 H, Me)	
		2.58 t (2 H, CH <sub>2</sub> )	3.75 t (2 H, CH <sub>2</sub> )
		6.70 s (1 H, ar.CH)	6.73 s (1 H, ar.CH)
		6.45 kv (1 H, pyr.CH)	7.42 kv (1 H, pyr.CH)
		8.10 kv (1 H, pyr.CH)	

10 NMR - the spectrum was obtained with the aid of a 200 MHz  
Bruker-spectrometer with CDCl<sub>3</sub> as the solvent.

10 Example 23

1-(5-Bromo-3-pyridyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-  
quinoline (Pictet-Spengler)

15 5-Bromo-3-pyridine carboxaldehyd (5.5 g, 0.03 mole ) was  
dissolved in ethanol. Homoveratryl amine (5.4 g, 0.03 mole)  
was added to the solution, whereafter the solution was heated  
in a water bath until the major part of the ethanol had vapou-  
rized. Cooling of the residue resulted in a crystallized  
20 product. The Schiff base obtained was dissolved in a minor  
quantity of methylene chloride, and the solution was added  
slowly to a hot (80 - 90°C) 20%-HCl-solution and boiled with  
reflux for 30 minutes. Subsequent to cooling in ice, the  
crystallized product was filtered-off, i.e. the hydrochloride  
25 of the tetrahydroisoquinoline.

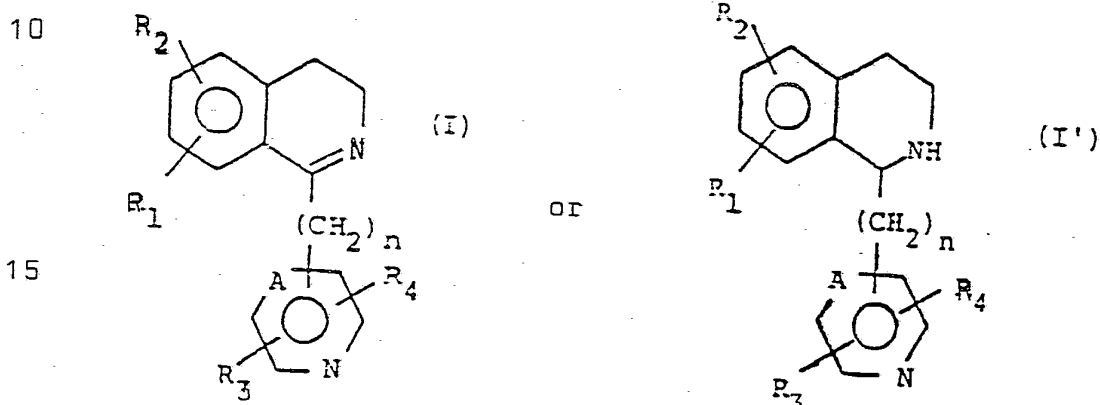
The yield was 5.9 g (56% of the theoretical)  
m.p. hydrochloride 208 - 210.5°C.

30 NMR- and the mass spectrum corresponded to the values recited  
in Example 17

CLAIMS

1. Therapeutically useful dihydro- and tetrahydroisoquinolines and their physiologically suitable salts, characterized in that they have the formula I or I'

5



20 in which formulae

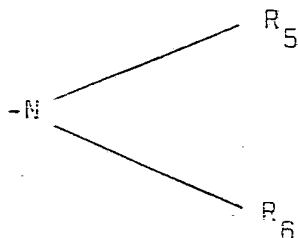
A = -CH= or -N=

n = 0 or 1

25 R<sub>1</sub> and R<sub>2</sub> are the same or different and designate hydrogen, halogen, an hydroxyl group or an alkoxy group having 1-4 carbon atoms,

R<sub>3</sub> = hydrogen when R<sub>1</sub> and R<sub>2</sub> are hydrogen, or halogen, or an alkyl group having 1-6 carbon atoms,

30 R<sub>4</sub> = halogen, an alkyl or alkoxy group having 1-6 carbon atoms, or designates an amino group of the formula



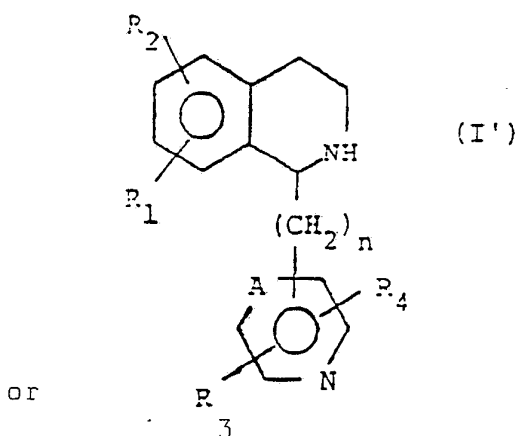
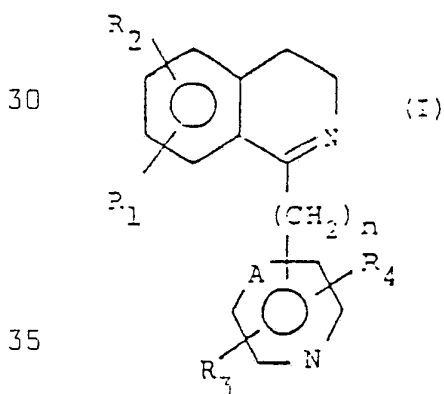
where  $R_5$  and  $R_6$  are the same or different and designate hydrogen or an alkyl group which has 1-3 carbon atoms and which can be substituted with one or two lower alkoxy, and  $R_4$  can also be hydrogen when A is  $-N=$ .

5

2. A compound according to Claim 1, characterized in that in the formula I or I'  $n$  is 0, A designates the group  $-CH=$ ,  $R_1$  and  $R_2$  are hydrogen or an alkoxy group having 1-3 carbon atoms, and  $R_3$  and  $R_4$  are hydrogen, halogen or an alkyl group or alkoxy group having 1-4 carbon atoms.

3. A compound according to Claim 1 or 2 said compound being: 1-(2-chloro-6-methoxy-4-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline, 1-(6-chloro-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline, 1-(5-bromo-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline, 1-(2-chloro-6-methyl-3-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline, 1-(5-bromo-3-pyridyl)-7-methoxy-3.4-dihydroisoquinoline, 1-(5-n-butyl-2-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline, 1-(5-bromo-3-pyridyl)-6.7-diethoxy-3.4-dihydroisoquinoline, or 1-(2-(2'-(3.4-dimethoxy phenyl)-ethyl amino)-6-chloro-4-pyridyl)-6.7-dimethoxy-3.4-dihydroisoquinoline.

4. A method for preparing physiologically active isoquinoline derivatives of the formula I or I'



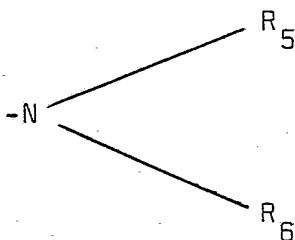
and their physiologically acceptable salts, in which formula  
 $A = -CH=$  or  $-N=$

$n = 0$  or  $1$

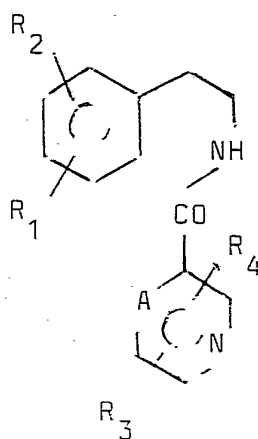
$R_1$  and  $R_2$  are the same or different and designate hydrogen,  
 5 halogen, an hydroxyl group or an alkoxy group having 1-4  
 carbon atoms,

$R_3 =$  hydrogen when  $R_1$  and  $R_2$  are hydrogen, or halogen, or  
 an alkyl group having 1-6 carbon atoms,

10  $R_4 =$  halogen, an alkyl group or alkoxy group having 1-6  
 carbon atoms, or designates an amino group of the formula



where  $R_5$  and  $R_6$  are the same or different and designate  
 hydrogen or an alkyl group which has 1-3 carbon atoms and  
 20 which can be substituted with a phenyl group substituted  
 with one or two lower alkoxy groups, and  $R_4$  can also be hydrogen  
 when  $A$  is  $-N=$ , characterized in that an amide of the formula

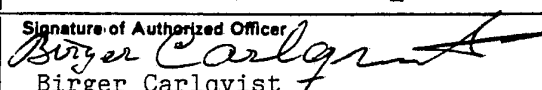


35 where  $R_1 - R_4$  and  $A$  have the above significance, are cyclized  
 with Lewis acid.

5. The use of compounds having the formula I or I' or their physiologically suitable derivatives or salts as therapeutical agents.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/FI87/00032

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC <span style="float: right;">4</span>		
C 07 D 401/04, 401/06		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC 1	C 07 d 57/00	
IPC 2-4	C 07 D 401/04, 401/06	
US C1	260:283--289; 546:139-151	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
SE, NO, DK, FI classes as above		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	DK, B, 123 413 (Dr KARL THOMAE GMBH) 19 June 1972	1-3, 5
X	DE, A1, 1 795 787 (PFIZER INC) 10 April 1975 & NL, 6714762 GB, 1199768 CH, 510032 BE, 705970 DE, 1695593 CH, 535768 FR, 8470 FR, 8481 FR, 8482 US, 3812127 AT, 293390 US, 3594480	1-3, 5
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<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1987-10-08	1987 -10- 1 2	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Birger Carlqvist	