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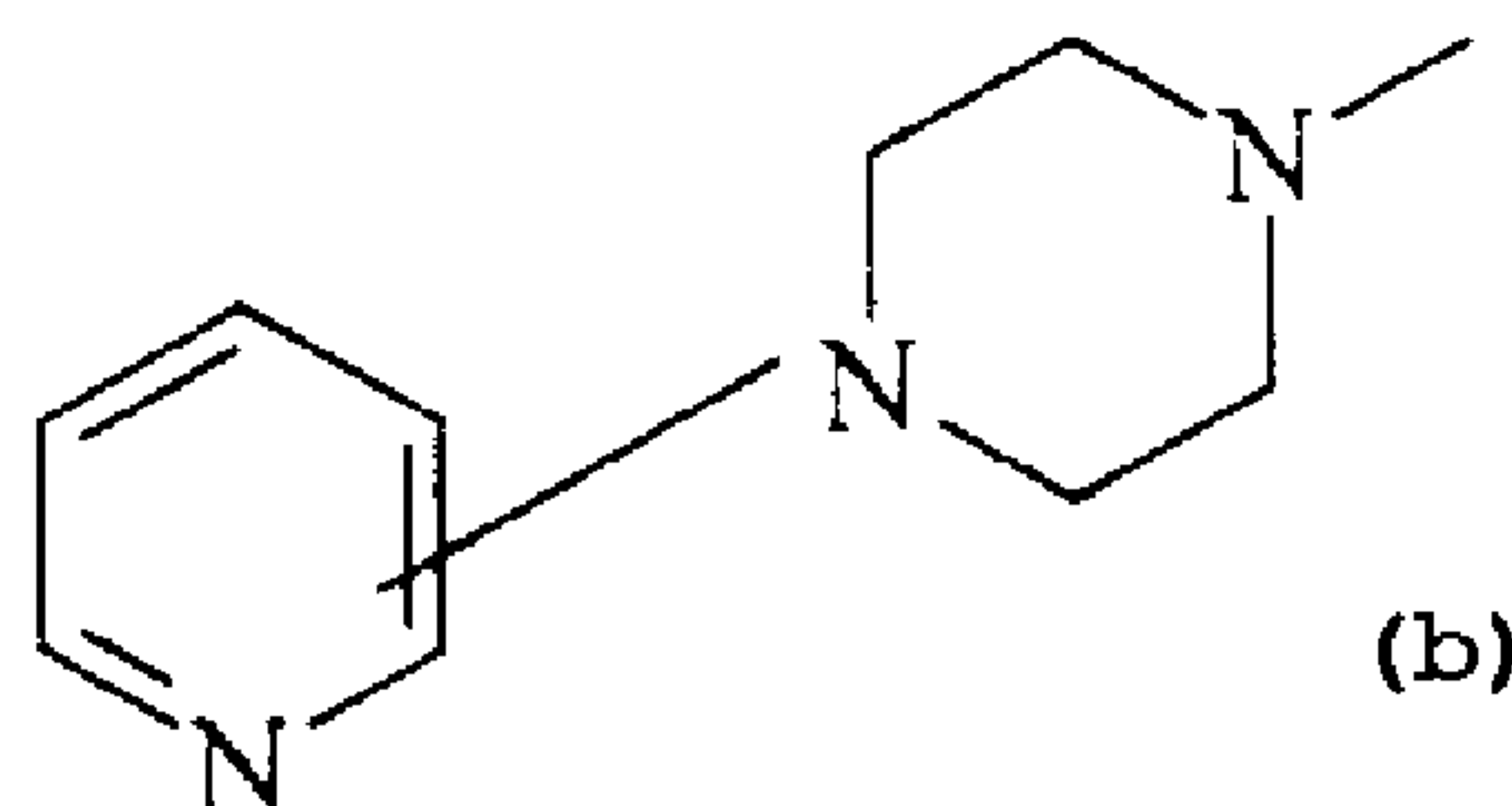
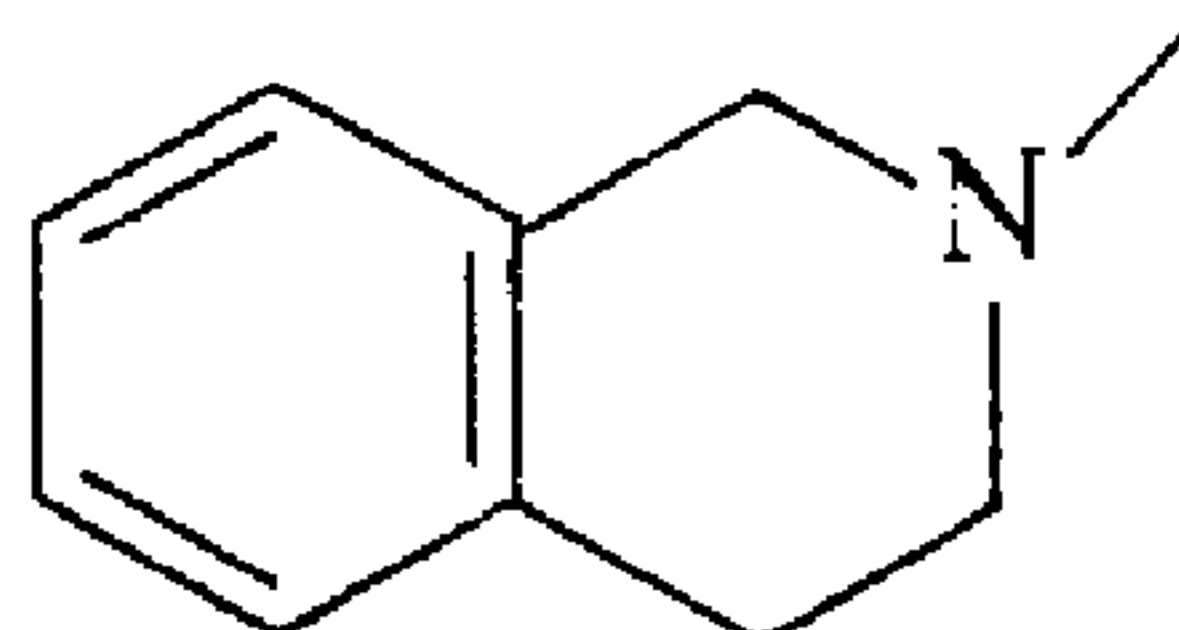
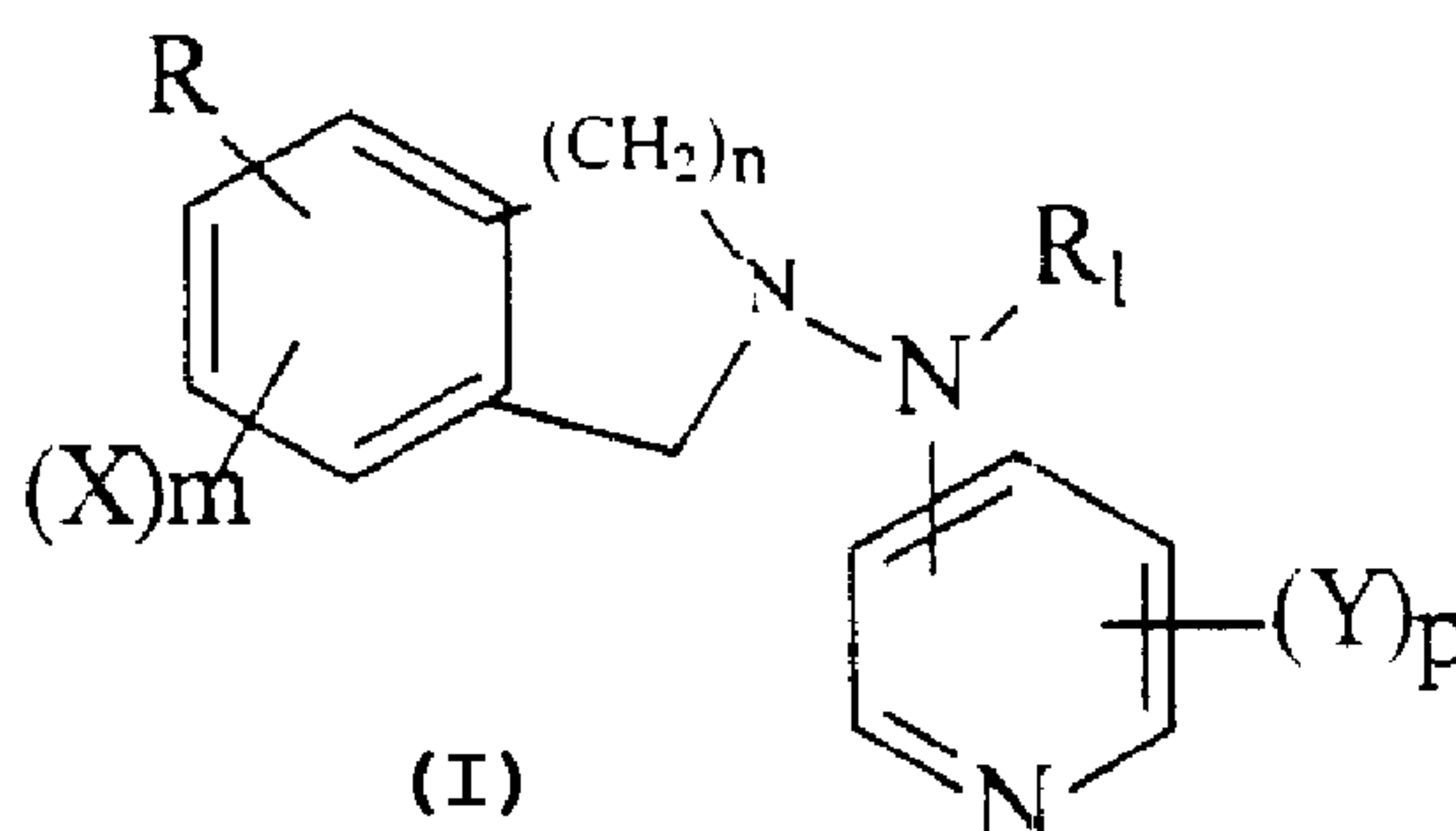
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(54) Titre : N-(PYRIDINYLAMINE)ISOINDOLINES ET COMPOSES ASSOCIES

(54) Title: N-(PYRIDINYLAMINO)ISOINDOLINES AND RELATED COMPOUNDS



(57) **Abrégé/Abstract:**

Novel N-(pyridinylamino)isoindolines of formula (I) and related compounds, intermediates and processes for the preparation thereof, and methods of relieving memory dysfunction and treating depression utilizing the N-(pyridinylamino)isoindolines and related compounds, the intermediates or compositions thereof are disclosed. Formula (I) R is hydrogen, a group of the formula R_2O- wherein R_2 is hydrogen, loweralkyl, benzyl, a group of the formula $(R_3)_3Si-$ wherein R_3 is loweralkyl, or a group of the formula R_4R_5NCO- wherein R_4 and R_5 are independently hydrogen, loweralkyl or benzyl; R_4 and R_5 taken together with the nitrogen atom to which they are attached form a group of formula (a) or a group of the formula (b); R_1 is hydrogen or loweralkyl; X is hydrogen, loweralkyl, halogen, hydroxy loweralkoxy, or trifluoromethyl; Y is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy, or trifluoromethyl; m is 1 or 2; n is 1, 2, or 3; p is 1 or 2; the optical isomers thereof; or the pharmaceutically acceptable salts thereof.



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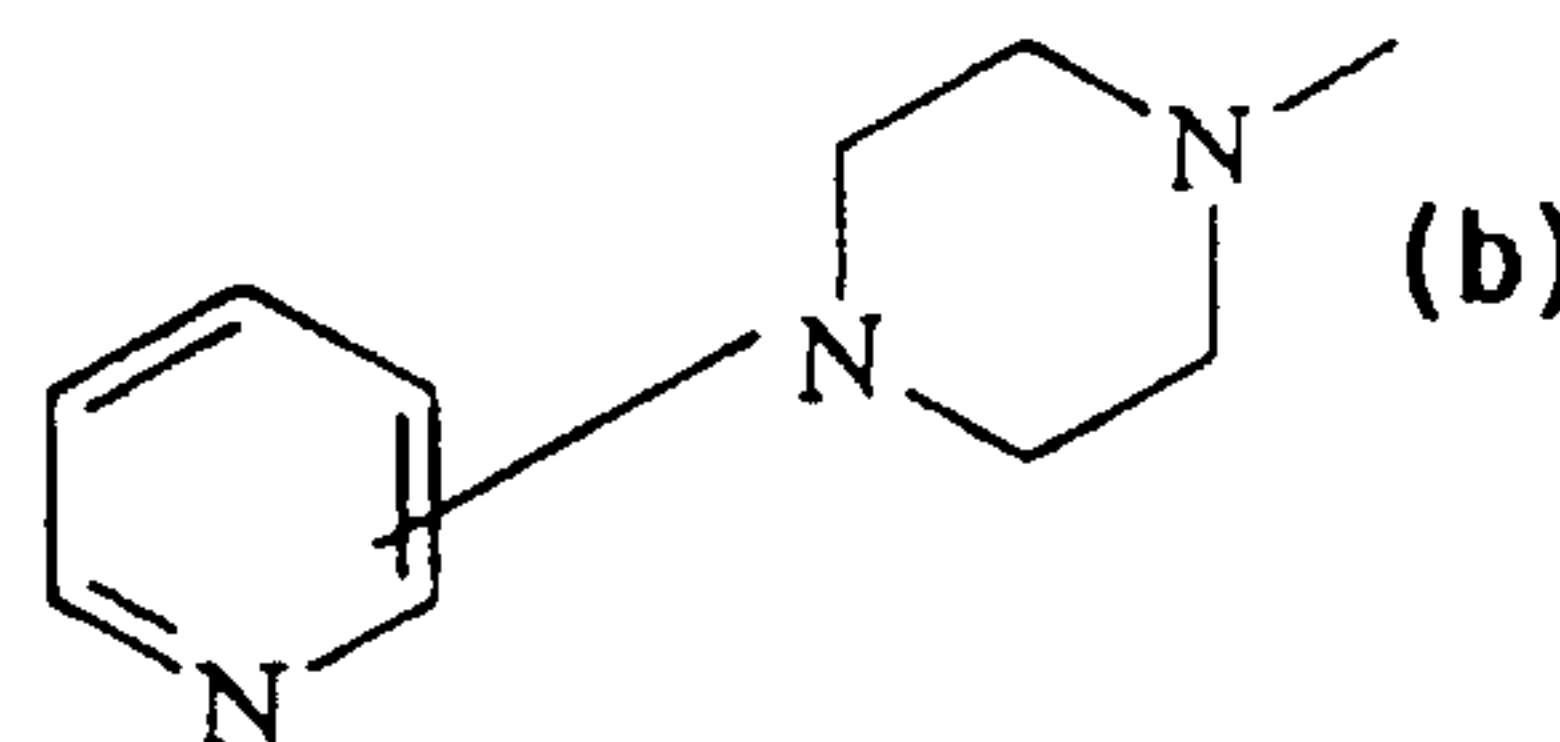
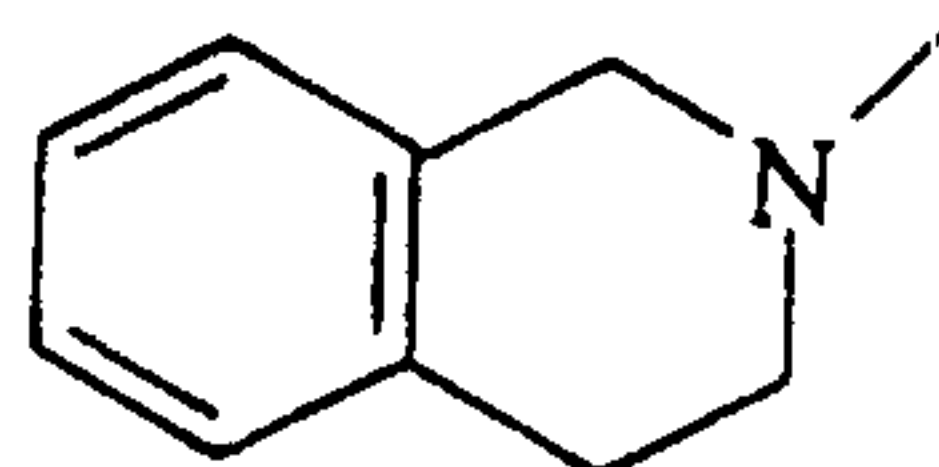
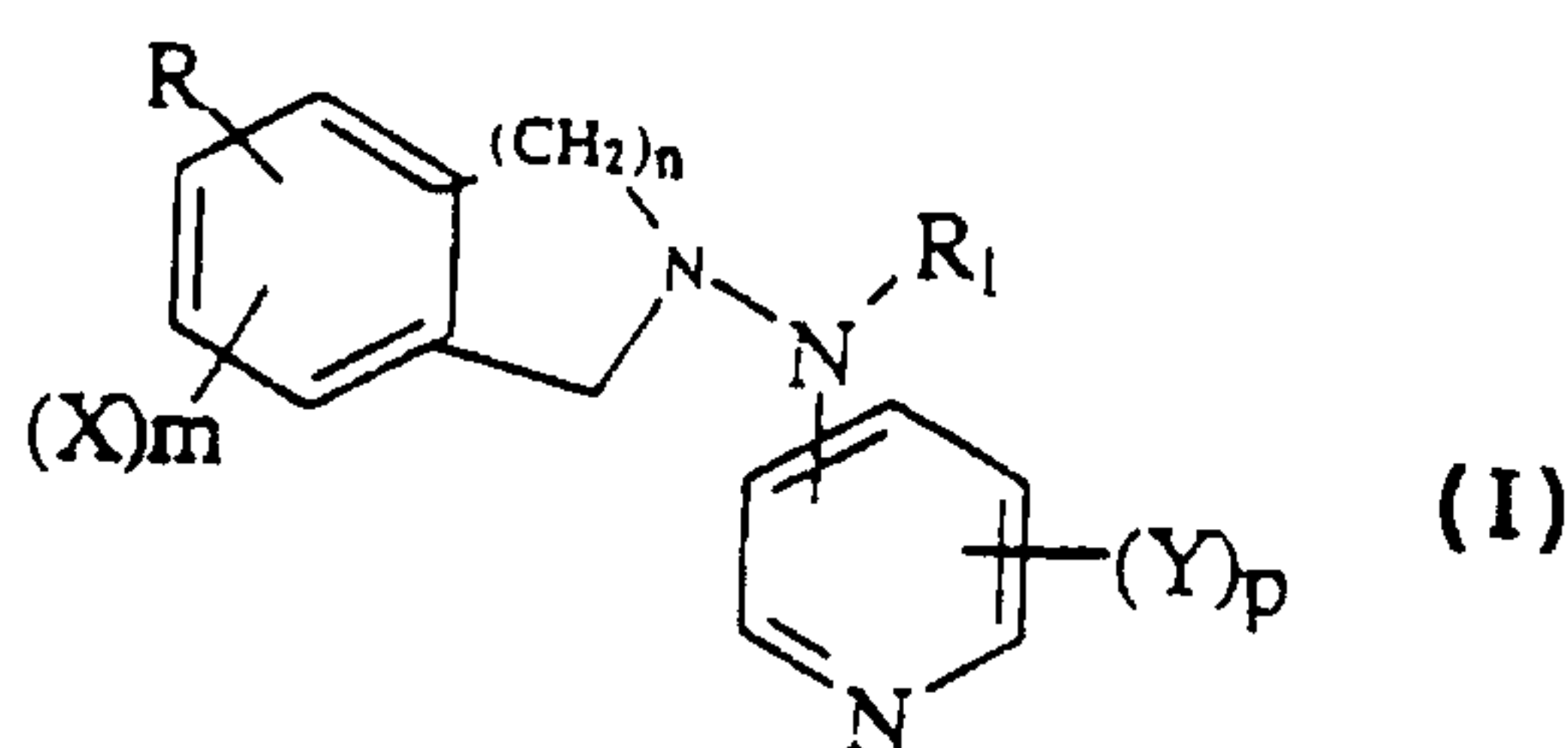
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(54) Title: N-(PYRIDINYLAMINO)ISOINDOLINES FOR TREATING ALZHEIMER'S AND DEPRESSION

**(57) Abstract**

Novel N-(pyridinylamino)isoindolines of formula (I) and related compounds, intermediates and processes for the preparation thereof, and methods of relieving memory dysfunction and treating depression utilizing the N-(pyridinylamino)isoindolines and related compounds, the intermediates or compositions thereof are disclosed. Formula (I) R is hydrogen, a group of the formula R₂O- wherein R₂ is hydrogen, loweralkyl, benzyl, a group of the formula (R₃)₃Si- wherein R₃ is loweralkyl, or a group of the formula R₄R₅NCO- wherein R₄ and R₅ are independently hydrogen, loweralkyl or benzyl; R₄ and R₅ taken together with the nitrogen atom to which they are attached form a group of formula (a) or a group of the formula (b); R₁ is hydrogen or loweralkyl; X is hydrogen, loweralkyl, halogen, hydroxy loweralkoxy, or trifluoromethyl; Y is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy, or trifluoromethyl; m is 1 or 2; n is 1, 2, or 3; p is 1 or 2; the optical isomers thereof; or the pharmaceutically acceptable salts thereof.

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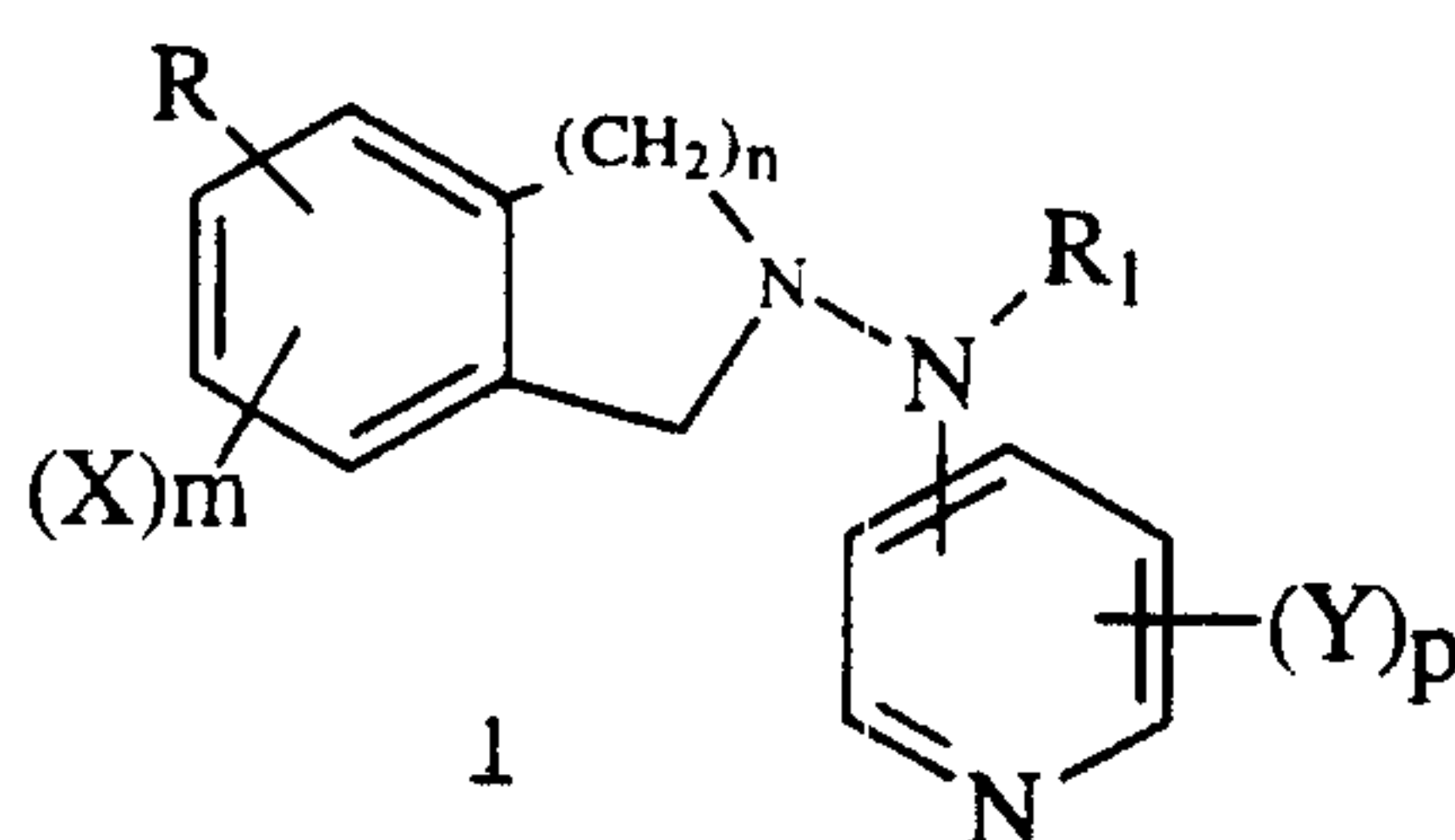
N-(PYRIDINYLAMINO)ISOINDOLINES AND RELATED COMPOUNDS

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SUMMARY OF THE INVENTION

The present invention relates to N-(pyridinylamino)isoindolines and related compounds. More particularly, the present invention relates to N-(pyridinylamino)isoindolines and related compounds of formula 1

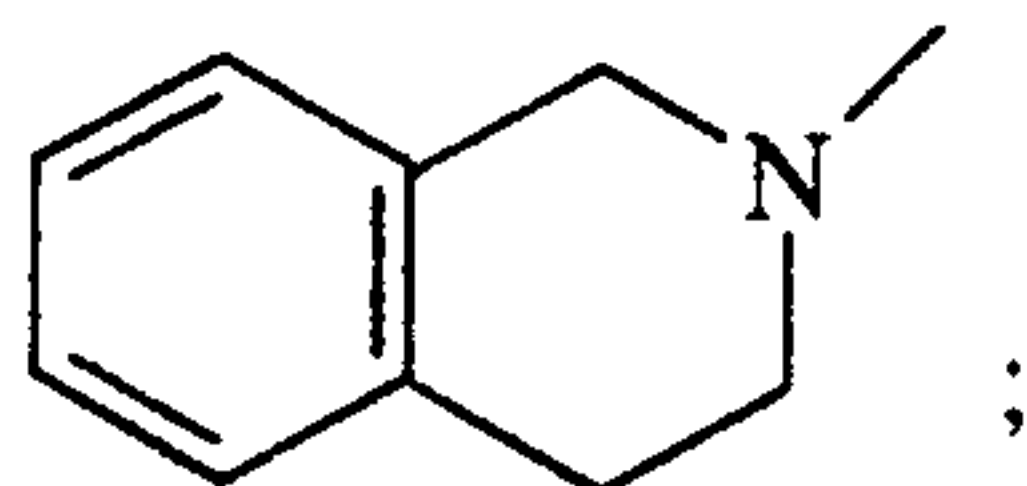
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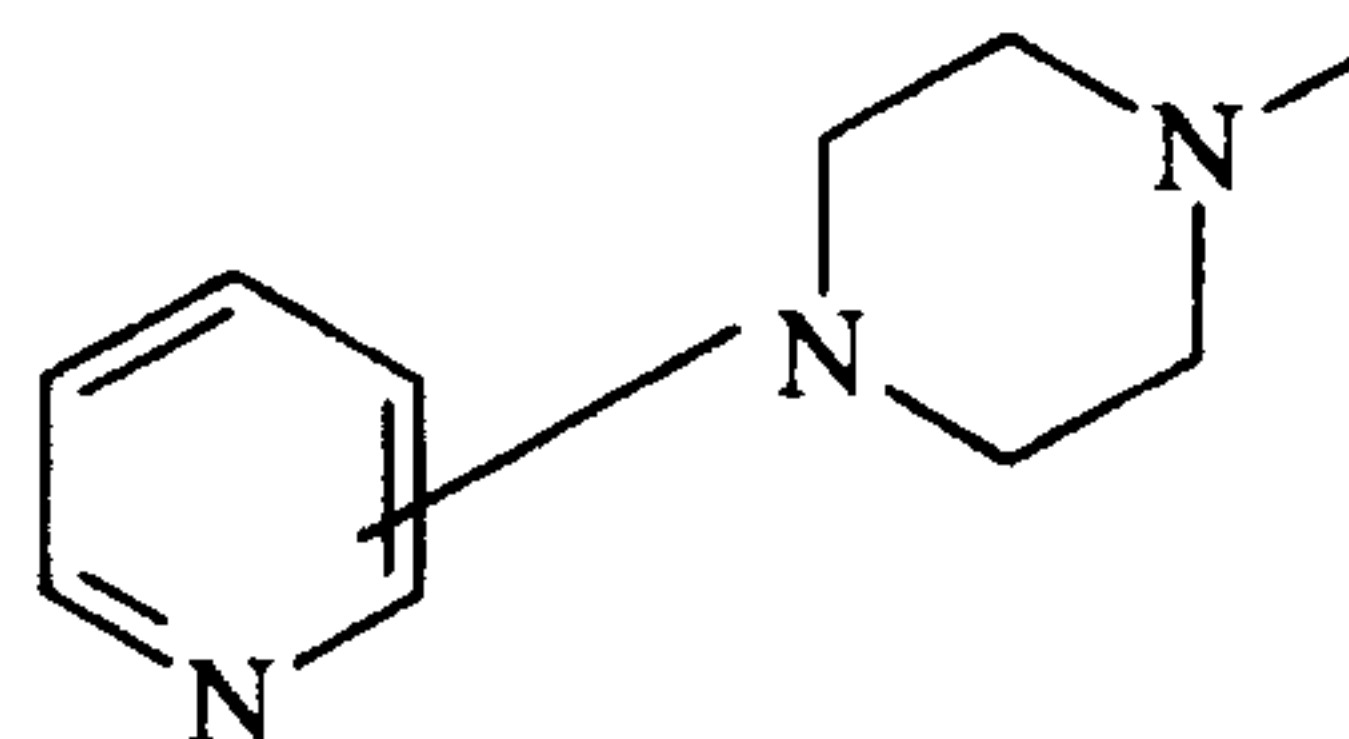
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wherein R is hydrogen, a group of the formula R_2O- wherein R_2 is hydrogen, loweralkyl, benzyl, a group of the formula $(R_3)_3Si-$ wherein R_3 is loweralkyl, or a group of the formula R_4R_5NCO- wherein R_4 and R_5 are independently hydrogen, loweralkyl or benzyl; R_4 and R_5 taken together with the nitrogen atom to which they are attached form a group of the formula

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; or a group of the formula



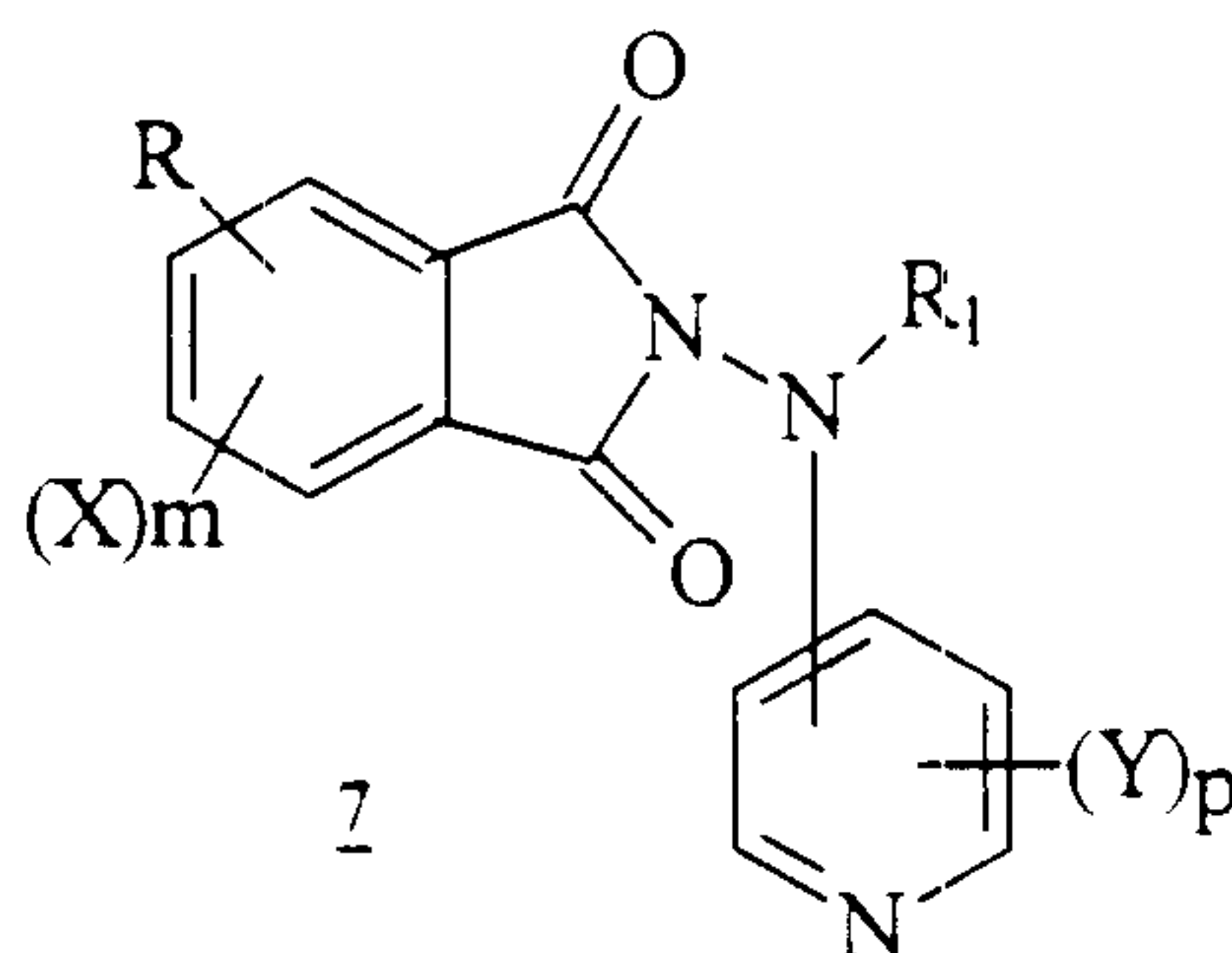
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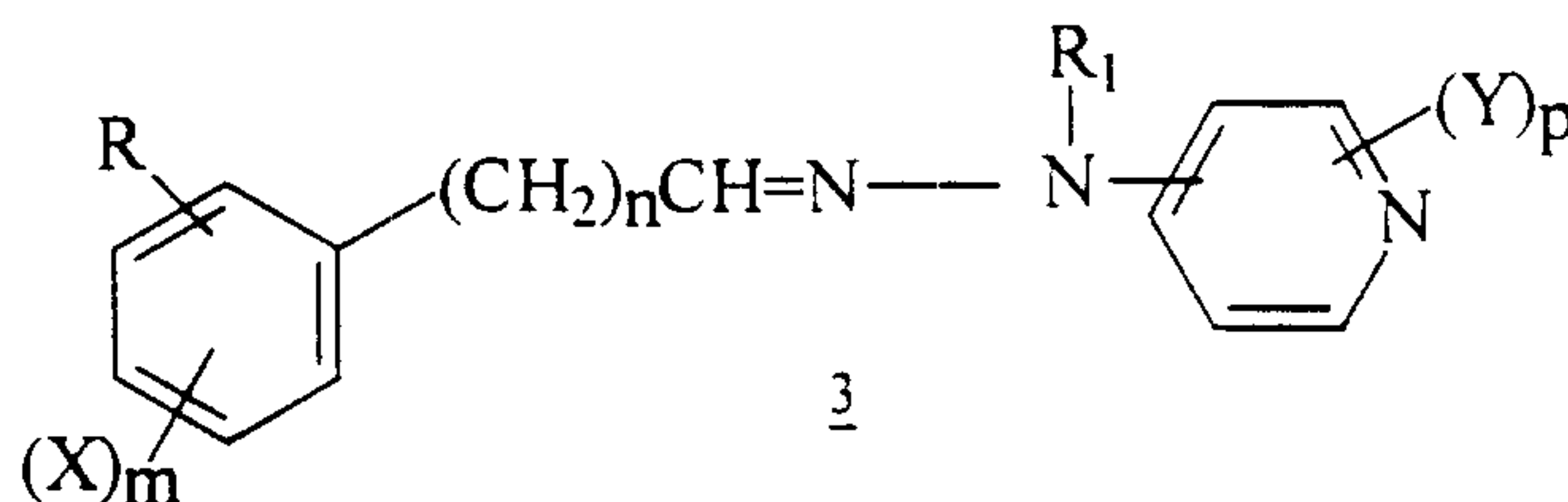
R_1 is hydrogen or loweralkyl; X is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; Y is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; m is 1 or 2; n is 1, 2, or 3; p is 1 or 2; the optical isomers thereof; or the pharmaceutically acceptable salts thereof, which are useful in relieving memory dysfunction and thus indicated in the treatment of Alzheimer's disease, as well as useful in the treatment of depression.

Preferred N-(pyridinylamino)isoindolines and related compounds are those wherein R is a group of the formula R_2O- wherein R_2 is a group of the formula R_4R_5NCO wherein R_4 and R_5 are as hereindescribed.

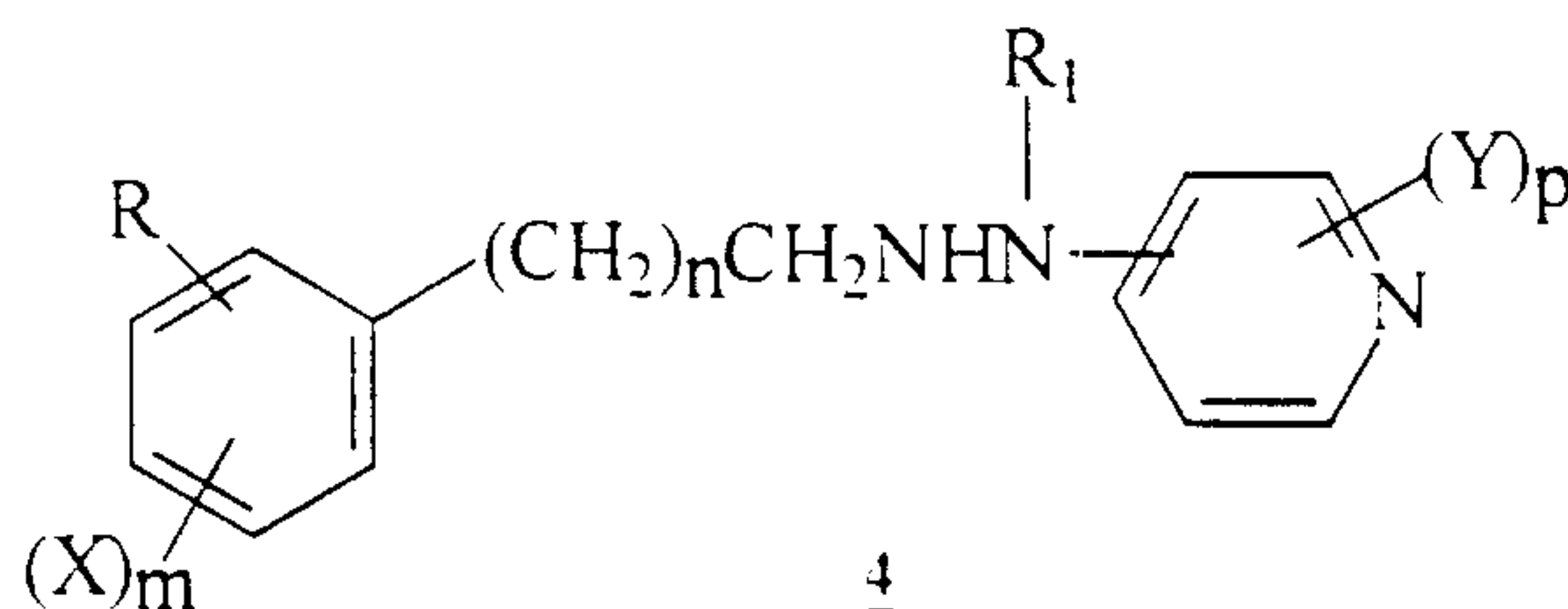
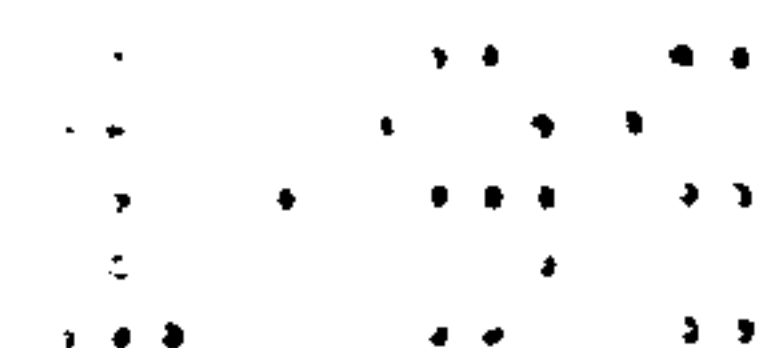
The present invention also relates to N-(pyridinylamino)phthalimides of formula 7



wherein R is R_2O- wherein R_2 is hydrogen or loweralkyl; R_1 is hydrogen or loweralkyl; X is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; Y is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; m and p are 1 or 2; the pharmaceutically acceptable salts thereof or the optical isomers thereof, N-(pyridinylamino)hydrazones of formula 3

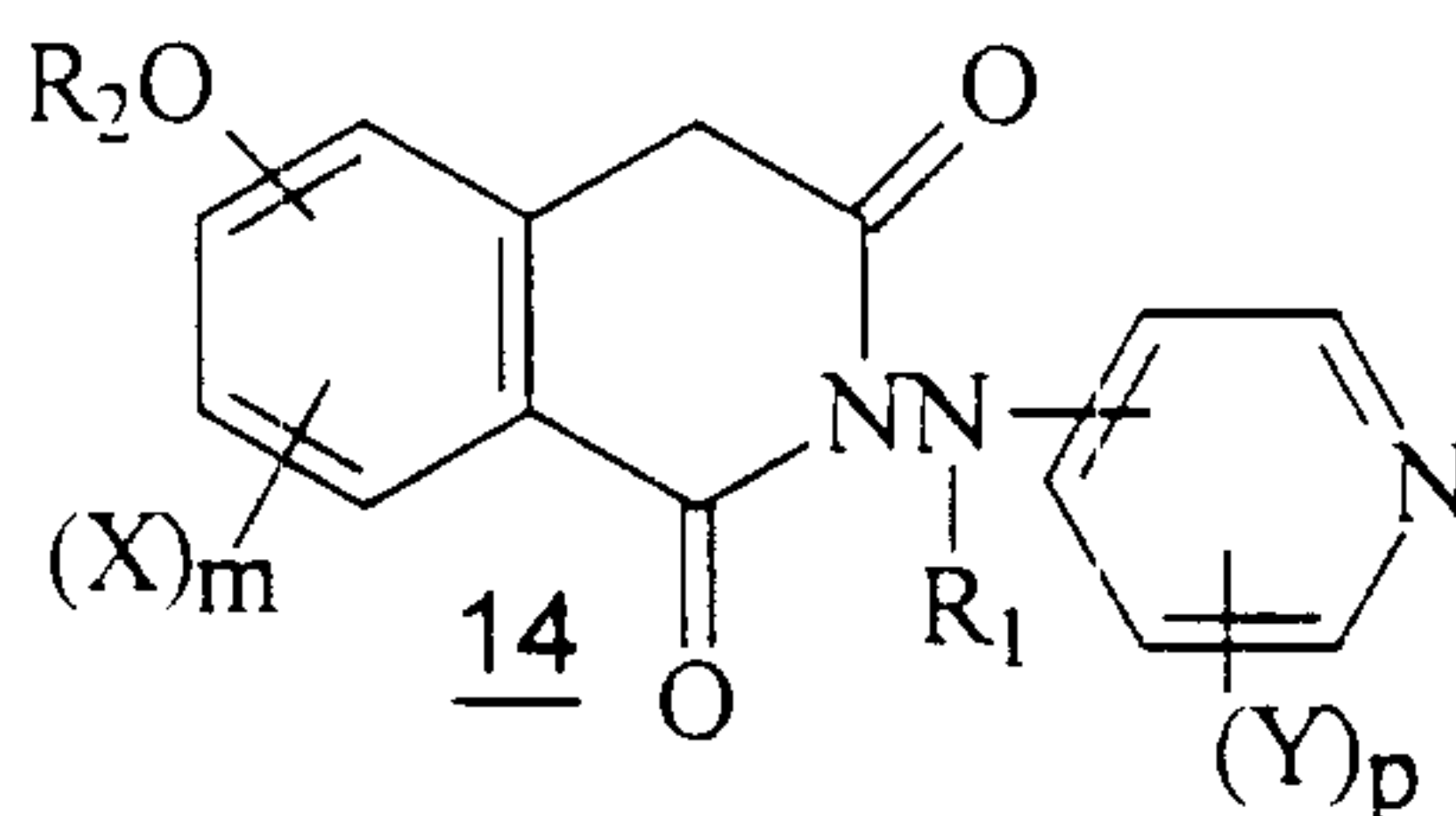


wherein R is hydrogen, a group of the formula R_2O- wherein R_2 is hydrogen, loweralkyl, benzyl or a group of the formula $(R_3)_3Si-$ wherein R_3 is loweralkyl; X is hydrogen, loweralkyl, hydroxy, loweralkoxy, halogen or trifluoromethyl; Y is hydrogen, loweralkyl, hydroxy, loweralkoxy, halogen or trifluoromethyl; n is 1, 2 or 3; or the optical isomers thereof, and N-(pyridinylamino)hydrazines of formula 4



wherein R is hydrogen, a group of the formula R_2O- wherein R_2 is hydrogen, loweralkyl, benzyl or a group of the formula $(R_3)_3Si-$ wherein R_3 is loweralkyl; X is hydrogen, loweralkyl, hydroxy, loweralkoxy, halogen or trifluoromethyl; Y is hydrogen, loweralkyl, hydroxy, loweralkoxy, halogen or trifluoromethyl; n is 1, 2 or 3; or the optical isomers thereof, which are useful as intermediates for the preparation of the present N-(pyridinylamino)isoindolines and related compounds.

In addition, the present invention relates to isoquinolindiones of formula 14



wherein R_2 is hydrogen or loweralkyl; R_1 is hydrogen or loweralkyl; X is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; Y is hydrogen, loweralkyl, halogen, hydroxy, loweralkoxy or trifluoromethyl; m and p are 1 or 2; or the optical isomers thereof, also useful for the synthesis of the N-(pyridinylamino)isoquinolines of the present invention and compounds related thereto.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the specification and appended claims, the term "alkyl" refers to a straight or branched chain hydrocarbon radical containing no saturation and having 1 to 8 carbon atoms. Examples of alkyl groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-hexyl, 3-hexyl, 4-heptyl, 2-octyl and the like. The term "alkoxy" refers to a monovalent substituent which consists of an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of alkoxy groups are methoxy, ethoxy, propoxy, 1-butoxy, 1-pentoxy, 3-hexoxy, 4-heptoxy, 2-octoxy and the like. The term "alkanol" refers to a compound formed by a combination of an alkyl group and hydroxy radical. Examples of

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alkanols are methanol, ethanol, 1- and 2-propanol, 2,2-dimethylethanol, hexanol, octanol and the like. The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acid are formic acid, acetic acid, propanoic acid, 2,2-dimethylpropanoic acid, hexanoic acid, octanoic acid and the like. The term "halogen" refers to a member of the family fluorine, chlorine, bromine, or iodine. The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to and including 6 carbon atoms.

The compounds of the present invention which lack an element of symmetry exist as optical antipodes and as the racemic forms thereof. The optical antipodes may be prepared from the corresponding racemic forms by standard optical resolution techniques, involving, for example, the separation of diastereomeric salts of those instant compounds characterized by the presence of a basic amino group and an optically active acid, or by synthesis from optically active precursors.

The present invention comprehends all optical isomers and racemic forms thereof of the compounds disclosed and claimed herein and the formulas of the compounds shown herein are intended to encompass all possible optical isomers of the compounds so depicted.

The novel N-(pyridinylamino)isoindolines and related compounds of the present invention are prepared by the processes delineated in Reaction Schemes, the tetrahydroisoquinolines and tetrahydroazepines shown therein, being the related compounds.

Entry into the N-(pyridinylamino)isoindoline series, that is, the series of compounds of formula 1, wherein n is 1, is gained by the sequence of reactions delineated in Reaction Scheme A. Condensation of a phthalic anhydride 5, which is commercially available or readily preparable, with an N-(pyridinyl)hydrazine of formula 6, affords an N-(pyridinyl)phthalimide 7 which is reduced to an N-(pyridinyl)isoindoline 8. The condensation is generally performed using a hydrohalide salt of the hydrazine 6, such as the hydrochloride salt, in an alkanoic acid, such as acetic acid, at the reflux temperature of the reaction medium, although reduced reaction temperatures may be employed.

The reduction of phthalimide 7 is accomplished by means of an alkali metal aluminum hydride in an ethereal solvent. Among alkali metal aluminum hydrides,

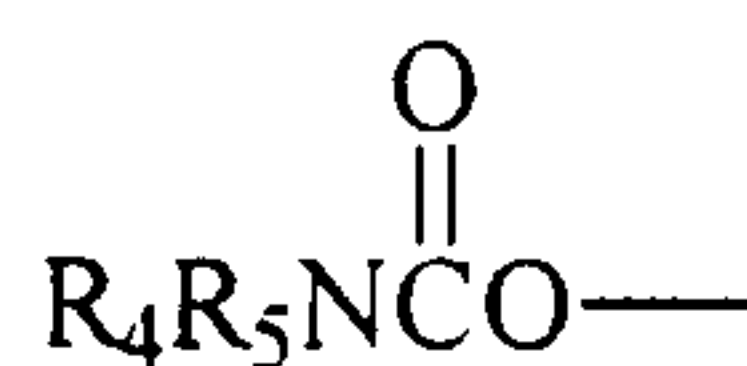


there may be mentioned lithium aluminum hydride, sodium aluminum hydride and potassium aluminum hydride. Among ethereal solvents there may be mentioned diethyl ether, 1,2-dimethoxyethane, methyl tert-butyl ether, 2-methoxyethyl ether, dioxane and tetrahydrofuran. Lithium aluminum hydride and tetrahydrofuran is the preferred reaction medium. The reduction temperature is not narrowly critical. While it is preferred to conduct the reduction at ambient temperature, the reduction may be conducted at either an elevated or reduced temperature consistent with the reaction medium.

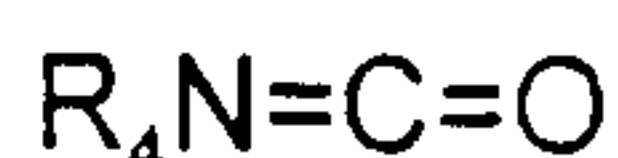
The conversion of phthalic anhydride 5 to isoindoline 8 may be carried out without characterization of the intermediate phthalimide 7 in essentially a one-pot reaction. For example, the condensation of a phthalic anhydride 5 with a hydrazine 6 may be conducted in acetic acid, and after the reaction is determined to be complete, the acetic acid is removed, the residue is triturated with an alkanol, such as 2-propanol, and the crude phthalimide 7 is reduced with lithium aluminum hydride in tetrahydrofuran.

Alternatively, entry into the N-(pyridinylamino)isoindoline series of compounds of formula 1 wherein n is 1 may be achieved by condensing a 1,2-dihalomethylbenzene 9 wherein Hal is chloro or bromo with a hydrazine 6 in a dipolar aprotic solvent, for example, dimethylacetamide, dimethylformamide, hexamethylphosphoramide, or dimethylsulfoxide in the presence of an acid acceptor, for example, pyridine, 4-dimethylaminopyridine, triethylamine or tripropylamine, at about ambient temperature, although reduced or elevated temperatures may be employed depending upon the selected reaction medium. Dimethylformamide is the preferred solvent; triethyl amine is the preferred acid acceptor.

To prepare a carbamoyloxy-N-(pyridinylamino)isoindoline 11 wherein R₄ and R₅ are as hereinmentioned, that is, to introduce the



moiety into the indoline, a hydroxy-N-(pyridinylamino)isoindoline 10 is treated with an isocyanate of formula 12



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wherein R_4 is loweralkyl in a suitable solvent such as acetonitrile in the presence of a catalytic amount of mild base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, at ambient temperature (although elevated temperatures may be employed) conditions providing the desired carbamate 11 wherein R_4 is loweralkyl and R_5 is hydrogen.

Treatment of a phenol 10 with a carbamoyl halide 13A



13A

wherein R_4 , R_5 and Hal are as hereindescribed in a suitable solvent such as a halocarbon (e.g., dichloromethane, trichloromethane, or 1,1- or 1,2-dichloroethane) in the presence of an acid acceptor such as trialkylamine (e.g., triethylamine or 4-dimethylaminopyridine) at the reflux temperature of the reaction medium (although reduced temperatures may be employed), also provides the desired carbamate 11, in this case, wherein R_4 and R_5 are loweralkyl.

In the event an N-(pyridinylamino)isoindoline 8 does not bear a phenolic hydroxyl group, that is, R_2 is not hydrogen, the group R_2O- must be cleaved prior to introduction of an aminocarbonyl (R_4R_5NCO) function. When R_2 is loweralkyl, the cleavage is effected by a hydrohalic acid, for example, hydrobromic acid at the reflux temperature of the reaction medium. Alternatively, the cleavage is effected by means of a boron trihalide such as boron tribromide in a halocarbon such as dichloromethane at ambient temperature. In the same vein, when R_2 is a group of the formula $(R_3)_3Si-$, the moiety R_2O- must be cleaved prior to formation of the carbamoyloxy function. The cleavage, in this case, is effected by tetra-n-butyl ammonium fluoride in an ethereal solvent, e.g., tetrahydrofuran at ambient temperature.

To gain entry into the N-(pyridinylamino)isoquinoline series, that is, the series of compounds where n is 2, a homophthalic anhydride 13 is condensed with a hydrazine 6 to provide an isoquinolinedione 14 which is reduced to an isoquinoline 15. The condensation and reduction are performed as described herein for the

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analogous processes in the isoindoline series, as are the cleavage and carbamylation reactions to provide phenol 18 and carbamate 19, respectively, as shown in reaction Scheme B.

Also, in a manner analogous to processes shown in Reaction Scheme A for conversion of a dihalomethylbenzene 9 to isoindoline 8 with hydrazine 6, a haloethylhalomethylbenzene 17 is converted to a tetrahydroisoquinoline 15 by hydrazine 6. Alternatively, entry into the N-(pyridinylamino)isoquinoline series is achieved by cyclizing a hydrazinoethylbenzene 16 with a halomethylalkyl ether of formula 20.

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wherein R₆ is loweralkyl in an alkanolic acid such as, for example, acetic acid at about 55°C to the reflux temperature of the reaction medium.

The hydrazinoethylbenzene 16 is prepared from phenylacetaldehyde 28, or the enol ether 29 thereof, by condensation with hydrazine 6 followed by reduction of the resulting hydrazone 30 by the processes described below for the synthesis of hydrazinopropylbenzene 23 (Scheme C).

In the event the phenolic hydroxyl group of a tetrahydroisoquinoline 15 is protected as a benzyloxy function, that is, is in the form of a group R₂O wherein R₂ is benzyl, the protected tetrahydroisoquinoline is debenzylated to phenol 18 by hydrogenation over, for example, a noble metal catalyst, such as palladium, preferably supported on carbon, at a pressure of about 55 psig in an alkanol such as methanol. In the event the hydroxyl group is present as an alkoxy function, the alkoxy function is cleaved by a boron trihalide as in the isoindoline series.

To gain access to the N-(pyridinylamino)azepinyl series, that is, the series of compounds of formula 1 wherein n is 2, a phenylpropionyl aldehyde 21 is condensed with a pyridinylhydrazine 6 to form a pyridinylhydrazone 22 which is reduced to a pyridinylhydrazine 23 and then cyclized with a halomethylalkylether 20 to a pyridinylaminoazepine 24. The condensation of an aldehyde 21 with a hydrazine 6 is effected in an alkanol, for example, methanol, ethanol, or 1- or 2- propanol, ethanol being preferred, in the presence of a drying agent to remove the formed water, for example, anhydrous magnesium sulfate at the reflux temperature of the reaction medium. The condensation temperature is not narrowly critical and a reaction

temperature from ambient to reflux may be employed.

The condensation of an aldehyde 21 with a hydrazine 6 to provide hydrazone 22 may be carried out with an enol ether 27 wherein R₇ is loweralkyl, the equivalent of an aldehyde 21. In this aspect, the condensation is accomplished in an alkanol such as methanol, ethanol, 1-, or 2-propanol in the presence of an organic acid such as methanesulfonic acid, benzenesulfonic acid or 4-methylbenzenesulfonic acid, conveniently at the reflux temperature of the condensation medium. Ethanol is the preferred alkanol; 4-methylbenzenesulfonic acid is the preferred organic acid. Reaction temperatures from ambient to the reflux temperature may be employed.

The reduction of hydrazone 22 to hydrazine 23 is conducted in an ethereal solvent utilizing an alkali metal aluminum hydride as the reducing agent. Among ethereal solvents are diethylether, 1,2-dimethoxyether, 2-methoxyethyl ether, dioxane or tetrahydrofuran. Among alkali metal aluminum hydride reducing agents are lithium aluminum hydride, sodium aluminum hydride, or potassium aluminum hydride. Lithium aluminum hydride and tetrahydrofuran are the preferred solvent and reducing agent. Ambient temperature is the preferred reduction temperature; the reduction may be performed at reduced or elevated temperatures, however.

The cyclization of a hydrazine 23 with a halomethylalkyl ether 20 is conducted as described herein.

The cleavage, if necessary, of the R₂O-moiety of 24 to a phenol 25 and the carbamylation of phenol 25 to a carbamate 26 are also conducted as hereindescribed.

As hereinbefore mentioned, the requisite starting materials for the preparation of the N-(pyridinylamino)isoindolines and related compounds of the present invention are either commercially available or preparable by processes described in the literature mentioned herein. As reported by P. A. Harland and P. Hodge in Synthesis, 223 (1982), condensation of cyclohexa-1, 3-dienes with dialkyl acetylene dicarboxylates followed by elimination of ethylene provides phthalates, which may be hydrolyzed and cyclized by conventional methods to phthalic anhydrides. Phthalic anhydrides are also prepared by oxidation of 1,2-dimethylbenzenes to 1,2-benzenedicarboxylic acids and dehydration to the anhydrides, as reported by B. V. Shetty in U. S. Patent 4,210,749 issued July 1, 1980. Phthalic anhydrides are also prepared via oxazolines as described herein.

The requisite 2-halomethylbenzyl halides, starting materials for the synthesis of the N-(pyridinylamino)isoindolines, are available from phthalic anhydrides by the processes disclosed by B. V. Shelty in U. S. Patent 4,210,749, as well as those described herein.

5 Homophthalic acids, the starting material for the preparation of the related N-(pyridinylamino)tetrahydroisoquinolines, are available from benzoic acids by conventional processes as described by H. K. Desai and R. N. Usgaonkar in the Journal of the Indian Chemical Society, 40, 239 (1963) and S. P. Inamdar and R. N. Usgaonkar in the Journal of the Indian Chemical Society, 43, 615 (1966).

10 2-(Haloethyl)benzyl halides, required for the preparation of the N-(pyridinylamino)tetrahydroisoquinolines of the present invention, are accessible by cleavage of isochromans with hydrohalic acids as described herein.

The phenylacetaldehyde and phenylpropionylaldehyde starting materials are prepared from phenylacetic acids or phenylpropionic acids, or the esters thereof, by
15 reduction to the corresponding carbinols and oxidation thereof to the desired aldehydes, as described herein and by methods reported by M. Elliott, et al., Pesticide Science, 18, 223 (1987).

The enol ether starting materials are prepared from the appropriate benzaldehyde by conventional methods utilizing
20 methoxymethyltriphenylphosphonium chloride in the presence of a base as reported in Synthesis, 796 (1975).

The N-(pyridinylamino)isoindolines and related compounds of the present invention are useful as agents for the relief of memory dysfunction, particularly dysfunctions associated with decreased cholinergic activity such as those found in
25 Alzheimer's disease. Relief of memory dysfunction activity is demonstrated in the in vitro inhibition of acetylcholinesterase assay, an assay for the determination of the ability of a drug to inhibit the inactivation of acetylcholine, a neurotransmitter implicated in the etiology of memory dysfunction and Alzheimer's dementia. In this assay, a modification of a test described by G. L. Ellman, et al., Biochemical
30 Pharmacology, 7, 88 (1961), the following reagents are prepared and employed:

1. 0.05 M Phosphate Buffer (pH 7.2)

A solution of monobasic sodium phosphate monohydrate (6.85 g) in distilled water (100 ml) is added to a solution of dibasic sodium phosphate heptahydrate (13.4

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g) and distilled water (100 ml) until a pH of 7.2 was attained. The solution was diluted 1 to 10 with distilled water.

2. Substrate in Buffer

The 0.05 m Phosphate Buffer (pH 7.2) was added to acetylthiocholine (198 mg) to a total volume of 100 ml, i.e., a quantity sufficient (gs) to 100 ml.

3. 5,5-Dithiobisnitrobenzoic acid in Buffer

The 0.05 m Phosphate Buffer (pH 7.2) was added to 5,5-dithiobisnitrobenzoic acid to a total volume of 100 ml, i.e., a quantity sufficient (gs) to 100 ml.

4. Stock Solution of Drug

A 2 millimolar stock solution of the test drug is prepared in a quantity sufficient of either acetic acid or dimethyl sulfoxide to volume with 5,5-dithiobisnitrobenzoic acid in Buffer. Stock Solution of Drug is serially diluted (1:10) so that the final cuvette concentration is 10^{-4} molar.

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighted and homogenized in 19 volumes (approximately 7 mg protein/ml) of 0.05 m Phosphate Buffer (pH 7.2) using a Potter-Elvehjem homogenizer. A 25 ml aliquot of this suspension is added to 1 ml of the vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37°C. Enzyme activity is measured with a Beckman DU-50 spectrophotometer with the following software and instrument settings:

1. Kinetics Soft-Pac[®] Module #598273;
2. Program #6 Kindata;
3. Source - Vis;
4. Wavelength - 412 nm;
5. Sipper - none;
6. Cuvettes - 2 ml cuvettes using auto 6-sampler;
7. Blank - 1 for each substrate concentration;
8. Interval time - 15 seconds (15 or 30 seconds for kinetics);
9. Total time - 5 minutes (5 to 10 minutes for kinetics);
10. Plot - yes;
11. Span - autoscale;
12. Slope - increasing;
13. Results - yes (gives slope); and

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14. Factor - 1.

Reagents are added to the blank and sample cuvettes as follows:

1. Blank: 0.8 ml 5.5-Dithiobisnitrobenzoic Acid
0.8 ml Substrate in Buffer
- 5 2. Control: 0.8 ml 5.5-Dithiobisnitrobenzoic Acid/Enzyme
0.8 ml Substrate in Buffer
3. Drug: 0.8 ml 5.5-Dithiobisnitrobenzoic Acid/Drug/Enzyme
0.8 ml Substrate in Buffer

10 Blank values are determined for each run to control for non-enzymatic hydrolysis of substrate and these values are automatically subtracted by the Kindata program available on kinetics soft-pac module. This program also calculates the rate of absorbance change for each cuvette.

For IC₅₀ Determinations

15 Substrate concentration is 10 millimolar diluted 1:2 in assay yielding final concentration of 5 millimolar. 5,5-dithiobisnitrobenzoic acid concentration is 0.5 millimolar yielding 0.25 millimolar final concentration.

$$\% \text{ Inhibition} = \frac{\text{Slope Control} - \text{Slope drug}}{\text{Slope Control}} \times 100$$

IC₅₀ values are calculated from log-probit analysis

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TABLE I

5	Compound	Inhibition of Acetylcholinesterase Activity IC ₅₀ (mM)
10	2,3-dihydro-2-[(N-2-pyridinyl)amino]-1H- isoindol-5-yl methyl carbamate	3.56
15	2,3-dihydro-2-[(N-2-pyridinyl)amino]-1H- isoindol-7-yl methyl carbamate	0.174
20	2,3-dihydro-2-(-4-pyridinylamino)-1H- isoindol-4-yl dimethylcarbamate	0.029
25	6-methoxy-2-(pyridin-4-yl-amino)-1,2,3,4- tetrahydro-isoquinolin-7-yl dimethyl carbamate	0.076
30	2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin- 6-yl dimethyl carbamate	12.71
35	2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin- 7-yl dimethyl carbamate	0.56
40	7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydro- isoquinolin-6-yl dimethyl carbamate	1.4
45	dimethyl-carbamic acid 2-((4-pyridinylamino)- 2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yl ester	0.34
50	tacrine (reference)	0.31

Relief of memory dysfunction is achieved when the present N-
(pyridinylamino)isoindolines and related compounds are administered to a subject
requiring such treatment as an effective oral, parenteral or intravenous dose of from

0.10 to 50 mg/kg of body weight per day. A particularly effective amount is about 10 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compounds. It is to be further understood that the dosages set forth herein are exemplary only and that they do not, to any extent, limit the scope or practice of the invention.

The N-(pyridinylamino)isoindolines and related compounds of the present invention are also useful as agents for treating depression. Depression treatment is demonstrated in the in vitro clonidine binding: α_2 -receptor assay, an assay for the determination of the ability of a drug to bind the clonidine α_2 -receptor, patterned after assays described by D. C. U'Prichard, et al., Molecular Pharmacology, 15, 47 (1979) and D. C. U'Prichard, et al., ibid, 13, 454, (1977).

The following reagents are prepared:

1. Tris buffer, pH 7.7

a. 57.2 g Tris hydrochloric acid

16.2 g Tris Base - q.s. to 1 liter (0.5 M Tris buffer, pH 7.7)

b. Make a 1:10 dilution in distilled H₂O (0.05 M Tris buffer, pH 7.7)

2. Tris buffer containing physiological ions

a. Stock Buffer

Sodium chloride 7.014 g

Potassium chloride 0.372 g

Calcium chloride 0.222 g - q.s. to 100 ml in 0.5

Tris buffer

Magnesium chloride 0.204 g

b. Dilute 1:10 in distilled H₂O. This yields 0.05 M Tris hydrochloric acid, pH 7.7; containing sodium chloride (120 mM), potassium chloride (5 mM), calcium chloride (2 mM) and magnesium chloride (1 mM)

3. [4-³H]-Clonidine hydrochloride (20-30 Ci/mmol) is obtained from New England Nuclear. For IC₅₀ determinations: ³H-clonidine is made up to a

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concentration of 120 nM and 50 ml of it is added to each tube (yields a final concentration of 3 nM in the 2 ml volume assay).

4. Clonidine hydrochloride is obtained from Boehringer Ingelheim. A stock solution of 0.1 mM clonidine is made up to determine nonspecific binding. This yields a final concentration of 1 mM in the assay (20 ml to 2 ml).
5. Test compounds. For most assays, a 1 mM stock solution is made up in a suitable solvent and serially diluted, such that the final concentration in the assay ranges from 10^{-5} to 10^{-8} M. Seven concentrations are used for each assay and higher or lower concentrations may be used, depending on the potency of the drug.

B. Tissue Preparation

Male Wistar rats are sacrificed by decapitation and the cortical tissue rapidly dissected. The tissue is homogenized in 50 volumes of 0.05 M Tris buffer, pH 7.7 (buffer 1b) with the Brinkman Polytron™, then centrifuged at 40,000 g for 15 minutes. The supernatant is discarded and the pellet rehomogenized in the original volume of 0.05 M Tris buffer, pH 7.7 and recentrifuged as before. The supernate is discarded and the final pellet rehomogenized in 50 volumes of Buffer 2b. This tissue suspension is then stored on ice. The final tissue concentration is 10 mg/ml. Specific binding is 1% of the total added ligand and 80% of total bound ligand.

C. Assay

100 ml	0.5 M Tris-physiological salts, pH 7.7 (buffer 2a)
830 ml	H ₂ O
20 ml	Vehicle (for total binding) or 0.1 mM clonidine (for nonspecific binding) or appropriate drug concentration
50 ml	³ H-clonidine stock
1000 ml	Tissue suspension

Tissue homogenates are incubated for 20 minutes at 25° C with 3 nM ³H-clonidine and varying drug concentrations, then immediately filtered under reduced pressure on Whatman™ GF/B filters. The filters are washed with three five ml volumes of ice-cold 0.05 M Tris buffer, pH 7.7, then transferred to scintillation vials. Ten ml of liquescent counting solution is added to each

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sample which is then counted by liquid scintillation spectroscopy. Specific clonidine is defined as the difference between total bound and that performed using log-probit analysis. The percent inhibition at each drug concentration is the mean of triplicate determinations.

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TABLE II

10	Compound	Inhibition of clonidine binding activity IC ₅₀ (mM)
	2,3-dihydro-N-2-pyridinyl-1H-isoindol-2-amine	7.58
15	2,3-dihydro-7-methoxy-N-2-pyridinyl-2H- isoindol-2-amine	2.79
	3,4-dihydro-N-4-pyridinyl-2(1H)-isoquinolinamine	0.084
	2,3-dihydro-N-4-pyridinyl-1H-isoindol-2-amine	0.064
20	1,4-dihydro-2-[(N-4-pyridinyl)amino]-3(2H)- isoquinolinone	3.88
25	2,3-dihydro-4-methoxy-N-(pyridinyl)-1H- isoindol-2-amine	0.035
	2,3-dihydro-N-methyl-N-(4-pyridinyl)-1H- isoindol-2-amine	0.08
30	2,3-dihydro-2-(-4-pyridinylamino)-1H-isoindol- 4-ol	0.034
	2,3-dihydro-2-(-4-pyridinylamino)-1H-isoindol- 4-yl dimethylcarbamate	3.82

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(7-methoxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl)-
4-pyridinylamine

2.67

amitriptyline (reference)

0.039

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Depression treatment is achieved when the present N-(pyridinylamino)isoindolines and related compounds are administered to a subject requiring such treatment as an effective oral, parenteral or intravenous dose of from 0.10 to 50 mg/kg of body weight per day. A particularly effective amount is about 10 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and that they do not, to any extent, limit the scope or practice of the invention.

Acetylcholinesterase inhibitors and clonidine binding inhibitors are known in the art as being useful as relievers of memory dysfunction and as antidepressants, respectively. (See V. Kumar in Alzheimer's Disease: Therapeutic Strategies, E. Giacobini and R. Becker Eds.; Birkhauser, Boston 1994, for memory dysfunction relief utility and K. F. Tipton in Biochemical and Pharmacological Aspects of Depression, K. F. Tipton and U.B.H. Youdin, Eds., Taylor and Francis, London 1989, for antidepressant utility).

Depression frequently attends memory dysfunction associated with Alzheimer's disease and responds to antidepressant intervention. Thus, the antidepressant component of the pharmacological properties of the compounds of the present invention provide both desirable effects in one chemical entity, providing both therapies in one administration, where indicated. See, for example, W. W. Pendlebury and P. R. Solomon, Neurobiology of Aging, 15, 287 (1994) at page 287, among others.

Effective amounts of the compounds of the invention may be administered to a subject by any one of various methods, for example orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while

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effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Preferred pharmaceutically acceptable addition salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid and the like, salts of monobasic carboxylic acids such as, for example, acetic acid, propionic acid and the like, salts of dibasic carboxylic acids such as, for example, maleic acid, fumaric acid, oxalic acid and the like, and salts of tribasic carboxylic acids such as, for example, carboxysuccinic acid, citric acid and the like.

The active compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the aforesaid compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 0.5% of active compounds, but may be varied depending upon the particular form and may conveniently be between 4% to about 75% of the weight of the unit. The amount of present compound in such composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 mg of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel™, corn starch and the like; a lubricant such as magnesium stearate or Sterotes™; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit is a capsule it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain

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preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purposes of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the aforesaid compound, but may be varied between 0.5 and about 50% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 mgs of the active compound.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or thyl parabensTM; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparations can be enclosed in ampules, disposable syringes or multiple vials made of glass or plastic.

Compounds of the present invention include:

- a. 2,3-dihydro-4-methyl-N-4-pyridinyl-1H-isoindol-2-amine;
- b. 2,3-dihydro-N-4-pyridinyl-4-trifluoromethyl-1H-isoindol-2-amine;
- c. (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-(3-methylpyridinyl)amine;
- d. (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-(3-methoxypyridinyl)amine;
- e. (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-(3-hydroxypyridinyl)amine;
- f. (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-(3-bromopyridinyl)amine;
- g. (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-(3-trifluoromethyl)amine;
- h. 2,3-dihydro-7-methoxy-N-2-(4-methylpyridinyl)-2H-isoindol-2-amine;
- i. 2,3-dihydro-7-methoxy-N-2-(4-methoxypyridinyl)-2H-isoindol-2-amine;
- j. 2,3-dihydro-7-methoxy-N-2-(4-hydroxypyridinyl)-2H-isoindol-2-amine;
- k. 2,3-dihydro-7-methoxy-N-2-(4-chloropyridinyl)-2H-isoindol-2-amine;
- l. 2,3-dihydro-7-methoxy-N-2-(4-trifluoromethylpyridinyl)-2H-isoindol-2-amine;
- m. N-[3-(3-methylphenyl)propylidene]-N'-(4-pyridinyl)hydrazine;

- n. N-[3-(3-hydroxyphenyl)propylidene]-N'-(4-pyridinyl)hydrazine;
o. N-[3-(3-trifluoromethyl)propylidene]-N'-(4-pyridinyl)hydrazine;
p. N-[2-(4-methylphenyl)ethyl]-N'-pyridin-4-yl hydrazine;
q. N-[2-(4-hydroxyphenyl)ethyl]-N'-pyridin-4-yl hydrazine;
5 r. N-[2-(4-trifluoromethyl)ethyl]-N'-pyridin-4-yl hydrazine;
s. 7-methyl-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione;
t. 7-chloro-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione;
u. 7-hydroxy-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione;
v. 7-trifluoromethyl-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione;
10 w. 7-methoxy-2-(2-methylpyridinyl-4-amino)-4H-isoquinoline-1,3-dione;
x. 7-methoxy-2-(2-bromopyridinyl-4-amino)-4H-isoquinoline-1,3-dione;
y. 7-methoxy-2-(3-hydroxypyridinyl-4-amino)-4H-isoquinoline-1,3-dione;
z. 7-methoxy-2-(3-methylpyridinyl-4-amino)-4H-isoquinoline-1,3-dione;
a'. 7-methoxy-2-(3-methoxypyridinyl-4-amino)-4H-isoquinoline-1,3-dione;
15 b'. 7-methoxy-2-(3-trifluoromethyl-4-pyridinyl)-4H-isoquinoline-1,3-dione.

The following examples further illustrates the invention. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the indicated meanings: "kg" refers to kilograms; "g" refers to grams; "mg" refers to milligrams; "μg" refers to micrograms; "mmol" refers to millimoles; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "cm" refers to centimeters; "M" refers to molar; "mM" refers to millimolar; "μM" refers to micromolar; "nM" refers to nanomolar; "eq" refers to equivalents; "N" refers to normal; "ppm" refers to parts per million; "δ" refers to parts per million down field from tetramethylsilane; "°C" refers to degrees Celsius; "°F" refers to degrees Fahrenheit; 25 "mm Hg" refers to millimeters of mercury; "kPa" refers to kilopascals; "psi" refers to pounds per square inch; "rpm" refers to revolutions per minute; "bp" refers to boiling point; "mp" refers to melting point; "dec" refers to decomposition; "HPLC" refers to high performance liquid chromatography; "h" refers to hours; "min" refers to minutes; 30 "sec" refers to seconds; "EtOAc" refers to ethyl acetate; "DCM" refers to dichloromethane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-

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dimethylformamide; "DMSO" refers to dimethyl sulfoxide; "LAH" refers to lithium aluminum hydride; "R_f" refers to retention factor; and "R_t" refers to retention time.

EXAMPLE 1

5 2,3-Dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-5-yl methyl carbamate.

2,3-Dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-5-ol (0.8 g) was suspended in acetonitrile (50 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 drops) was added, followed by methyl isocyanate (0.21 ml). The reaction mixture was stirred for about 15 mins and diluted with water and ethyl acetate. The organic layer was separated,
 10 washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using 50% methanol/ethyl acetate as the eluent. The appropriate fractions were collected to yield 0.6 g (60%) of product. Recrystallization of the product from ethyl acetate gave the analytical sample, mp 152-153°C.

15 Analysis:

Calculated for C ₁₅ H ₁₆ N ₄ O ₂ :	63.37%C	5.67%H	19.71%N
Found:	63.36%C	5.58%H	19.66%N

EXAMPLE 2

20 2,3-Dihydro-5-[[tris(1-methylethyl)silyl]oxy]-N-2-pyridinyl-1H-isoindol-2-amine.

Triethylamine (10.9 ml) was added to a solution of 1,2-dibromomethyl-4-[[tri(1-methylethyl)silyl]oxy]benzene (17 g) and 2-hydrazinopyridine (4.3 g) in dimethylformamide (300 ml), and the reaction mixture was stirred, under nitrogen, at ambient temperature for about 20 mins and then diluted with water and ethyl acetate.
 25 The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was triturated with ethyl acetate to yield 5.7 g (38%) of product. Recrystallization of the product from ethyl acetate gave the analytical sample mp 95-96°C.

Analysis:

30 Calculated for C ₂₂ H ₃₃ N ₃ OSi:	68.88%C	8.67%H	10.95%N
Found:	68.65%C	8.79%H	10.89%N

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EXAMPLE 32,3-Dihydro-N-2-pyridinyl-1H-isoindol-2-amine.

Triethylamine (10.5 ml) was added to a solution of alpha, alpha'-dibromo-o-xylene
5 (10 g) and 2-hydrazinopyridine (4.1 g) in dimethylformamide. The mixture was
stirred, under nitrogen, at ambient temperature for about 20 mins and diluted with
water and ethyl acetate. The organic layer was separated, washed with water and
brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated.
Trituration of the residue with ethyl acetate gave 3.8 g (48%) of product.

10 Recrystallization of the product from ethyl acetate afforded the analytical sample, mp
130-131°C.

Analysis:

Calculated for C ₁₃ H ₁₃ N ₃ :	73.91%C	6.20%H	19.89%N
Found:	73.86%C	6.16%H	20.01%N

3,4-Dihydro-N-2-pyridinyl-2-(1H)-isoquinolinamine.

Triethylamine (10.0 ml) was added to a solution of 1-bromomethyl-2-(2-
bromoethyl)benzene (10 g) and 2-hydrazinopyridine (3.9 g) in dimethylformamide
20 (250 ml), and the mixture was stirred, under nitrogen, at ambient temperature for
about 20 mins. The reaction mixture was diluted with water and ethyl acetate. The
organic layer was separated, washed with water and brine, dried over anhydrous
sodium sulfate, filtered, and the filtrate was concentrated. The residue was triturated
with ethyl acetate to afford 5.3 g (65%) of product. Recrystallization of the product
25 from ethyl acetate gave the analytical sample, mp 116-117°C.

Analysis:

Calculated for C ₁₄ H ₁₅ N ₃ :	74.64%C	6.71%H	18.65%N
Found:	74.36%C	6.57%H	18.65%N

EXAMPLE 52,3-Dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-5-ol hydrochloride.

Tetrabutylammonium fluoride (13.0 ml) was added to a solution of 1,3-dihydro-5-
5 [[tris(1-methylethyl)silyl]oxy]-N-2-pyridinyl-2H-isoindol-2-amine (5 g) in
tetrahydrofuran (250 ml), and the mixture was stirred, under nitrogen, at ambient
temperature for about 15 mins. The reaction mixture was diluted with water and ethyl
acetate and the organic layer was separated, washed with water and brine, dried
over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. Trituration
10 of the residue with ethyl acetate gave 1.8 g (61%) of product free base. The free
base was dissolved in methanol and methanolic hydrogen chloride was added. The
precipitate was collected and recrystallized from methanol/2-propanol to afford 0.40 g
(14%) of product, mp >250°C.

Analysis:

15	Calculated for C ₁₃ H ₁₄ ClN ₃ O:	59.21%C	5.35%H	15.93%N
	Found:	58.65%C	5.45%H	15.63%N

EXAMPLE 62,3-Dihydro-4-methoxy-N-2-pyridinyl-1H-isoindol-2-amine.

20 Triethylamine (18.6 ml) was added to a solution of 1,2-dibromomethyl-3-
methoxybenzene (19.6 g) and 2-hydrazinopyridine (7.27 g) in dimethylformamide
(300 ml), and the mixture was stirred, under nitrogen, at ambient temperature for
about 20 mins. The reaction mixture was diluted with water and ethyl acetate. The
organic layer was separated, washed with water and brine, dried over anhydrous
25 sodium sulfate, filtered, and the filtrate was concentrated. The residue was
chromatographed on silica, eluting with 5% methanol/ethyl acetate. The appropriate
fractions were collected and concentrated to yield 3.2 g (20%) of product. Trituration
with ethyl acetate gave the analytical sample, mp 123-124°C.

Analysis:

30	Calculated for C ₁₄ H ₁₅ N ₃ O:	69.69%C	6.27%H	17.41%N
	Found:	69.50%C	6.29%H	17.66%N

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EXAMPLE 72,3-Dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-4-ol hydrochloride.

2,3-Dihydro-7-methoxy-N-2-pyridinyl-2H-isoindol-2-amine (3.2 g) in dichloromethane
5 (25 ml) was added dropwise to a solution of boron tribromide (5.0 g) in
dichloromethane (50 ml), and the mixture was stirred for 1 hr. The reaction mixture
was quenched with water, basified with aqueous sodium bicarbonate solution, and
extracted with 2-propanol/chloroform. The organic extracts were dried over
anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue
10 was triturated with 2-propanol to give 1.8 g (60%) of product free base. The free
base was dissolved in methanol and acidified with methanolic hydrogen chloride. The
precipitate was recrystallized from hot methanol to afford (.53 g) of product, mp 241-
243°C.

Analysis:

15	Calculated for $C_{13}H_{14}ClN_3O$:	59.21%C	5.35%H	15.93%N
	Found:	59.16%C	5.18%H	15.67%N

EXAMPLE 82,3-Dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-4-yl methyl carbamate.

20 2,3-Dihydro-2-[N-2-pyridinyl)amino]-1H-isoindol-4-ol (0.9 g) was suspended in
acetonitrile (50 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 drops) was added,
followed by methyl isocyanate (0.23 ml). The reaction mixture was stirred for about
15 mins and diluted with water and ethyl acetate. The organic layer was separated
and washed with water and brine, dried over anhydrous sodium sulfate, filtered, and
25 the filtrate was concentrated. The residue was chromatographed on silica, eluting
with 5% methanol/ethyl acetate. The appropriate fractions were collected and
evaporated to yield 0.8 g (71%) of product. Recrystallization from chloroform gave
the analytical sample, mp 200-201°C.

Analysis:

30	Calculated for $C_{15}H_{16}N_4O_2$:	63.37%C	5.67%H	19.71%N
	Found:	63.19%C	5.59%H	19.48%N

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EXAMPLE 93,4-Dihydro-N-4-pyridinyl-2-(1H)-isoquinolinamine.

Homophthalic anhydride (5 g) and 4-hydrazinopyridine hydrochloride (4.5 g) were
5 suspended in glacial acetic acid (300 ml), and the mixture was heated under reflux
for 8 hrs. The reaction mixture was evaporated, and the residue was triturated with
2-propanol. The solid was collected by filtration and was dried to give 6.5 g of 2-[(N-
4-pyridinyl)amino]-1,3-(2H, 4H)isoindolindione hydrochloride.

1M lithium aluminum hydride in tetrahydrofuran (60.5 ml) was added dropwise to a
10 portion of the above solid (3.5 g) suspended in tetrahydrofuran (150 ml) at 0°C,
under nitrogen. The reaction mixture was warmed to ambient temperature and
stirred overnight, under nitrogen. The reaction mixture was added to ice water, with
stirring, and the mixture was extracted with 2-propanol/chloroform. The organic
extracts were washed with water and brine, dried over anhydrous sodium sulfate,
15 filtered, and the filtrate was concentrated. The residue was chromatographed on
silica, eluting with 5% methanol/chloroform. The appropriate fractions were collected
and evaporated to yield 1.2 g (32%) of product. The analytical sample was obtained
by recrystallization from ethyl acetate/diethyl ether and had mp 152-153°C.

Analysis:

20	Calculated for C ₁₄ H ₁₅ N ₃ :	74.64%C	6.71%H	18.65%N
	Found:	74.44%C	6.81%H	18.58%N

EXAMPLE 102,3-Dihydro-N-4-pyridinyl-1H-isoindol-2-amine hydrochloride.

25 Phthalic anhydride (5.1 g) and 4-hydrazinopyridine hydrochloride (5.0 g) were
suspended in glacial acetic acid (300 ml), and the mixture was heated under reflux
for 8 hrs. The reaction mixture was evaporated, and the residue was triturated with
2-propanol. The solid was collected and dried to give 8.0 g of N-(4-pyridinylamino)-
1H-isoindole.

30 1M lithium aluminum hydride in tetrahydrofuran (72.5 ml) was added dropwise to a
portion (4.0 g) of the above solid suspended in tetrahydrofuran (200 ml) at 0°C,
under nitrogen. The reaction mixture was warmed to ambient temperature, stirred
overnight, under nitrogen, and was added to ice water, with stirring. The mixture was

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extracted with 2-propanol/chloroform (1/4). The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 5% methanol/chloroform. The appropriate fractions were collected and evaporated to yield 1.3 g (36%) of product free base. The free base was dissolved in methanol, and methanolic hydrogen chloride was added. The precipitate was collected to give 0.25 g (5.8%) of product, mp 253-255°C.

Analysis:

Calculated for C ₁₃ H ₁₄ ClN ₃ :	63.03%C	5.70%H	16.96%N
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Found:	62.47%C	5.63%H	16.72%N
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EXAMPLE 111,4-Dihydro-2-[(N-4-pyridinyl)amino]-3-(2H)-isoquinolinone hydrochloride.

Homophthalic anhydride (5 g) and 4-hydrazinopyridine hydrochloride (4.5 g) were suspended in glacial acetic acid (300 ml) and the mixture was heated under reflux for 8 hrs. The reaction mixture was evaporated, and the residue was triturated with 2-propanol. The solid was collected and dried to give 6.5 g (%) of 2-[(N-4-pyridinyl)amine]-1,3-(2H,4H)-isoquinolinedione hydrochloride.

1M lithium aluminum hydride in tetrahydrofuran (60.5 ml) was added dropwise to a portion (3.5 g) of 2-[(N-4-pyridinyl)amine]-1,3-(2H,4H)-isoquinolinedione hydrochloride suspended in tetrahydrofuran (150 ml) at 0°C, under nitrogen. The solution was warmed to ambient temperature, stirred overnight under nitrogen, and added to ice water, with stirring. The mixture was extracted with 2-propanol/chloroform. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with 5% methanol/chloroform. The appropriate fractions were collected and evaporated to yield 0.6 g (16.0%) of product free base. The free base was dissolved in methanol, and methanolic hydrogen chloride was added. The precipitate was collected to yield 0.22 g (6%) of product, mp 213-214°C.

Analysis:

Calculated for C ₁₄ H ₁₄ ClN ₃ O:	60.98%C	5.12%H	15.24%N
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Found:	60.71%C	5.05%H	14.92%N
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EXAMPLE 125-Bromo-2-(4-pyridinylamino-isoindole-1,3-dione hydrochloride.

5 A solution of 5-bromophthalic anhydride (8.23 g), 4-hydrazinopyridine hydrochloride (5.2 g) in glacial acetic acid (180 ml) was heated under reflux for 6 hrs. The reaction mixture was allowed to cool to ambient temperature overnight. The precipitate was collected on a filter, washed with diethyl ether and dried *in vacuo* to give 8.32 g (65%) of product, mp >280°C.

Analysis:

10	Calculated for C ₁₃ H ₉ BrClN ₃ O ₂ :	44.03%C	2.56%H	11.85%N
	Found:	44.39%C	2.74%H	11.83%N

EXAMPLE 134-Methoxy-2-(4-pyridinylamino)isoindole-1,3-dione hydrochloride hydrate.

15 A solution of 3-methoxyphthalic anhydride (14.30 g), 4-hydrazinopyridine hydrochloride (11.12 g) and glacial acetic acid (75 ml) was heated under reflux overnight, with stirring. The reaction mixture was cooled to ambient temperature, the precipitate was collected and washed with ether and the filtrate was evaporated. The residue was crystallized from ethanol, and the combined crops were dried at 60°C
20 under vacuum to give 19.8 g (80%) of product. The analytical sample was prepared by recrystallization from ethanol and had mp 203-205°C.

Analysis:

25	Calculated for C ₁₄ H ₁₄ ClN ₃ O ₄ :	51.94%C	4.36%H	12.98%N
	Found:	52.33%C	4.34%H	12.84%N

EXAMPLE 145-Hydroxy-2-(4-pyridinylamino)isoindole-1,3-dione hydrochloride.

30 A solution of 5-acetoxypthalic anhydride (3.03 g), 4-hydrazinopyridine hydrochloride (2.04 g) and glacial acetic acid (15 ml) was heated under reflux, under nitrogen, for 4 hrs, with stirring. The reaction mixture was cooled to ambient temperature, the precipitate was collected, washed with water and dried at 60°C under vacuum overnight. Trituration with hot absolute ethanol gave 2.3 g (56%) of product, mp >260°C.

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Analysis:

Calculated for C ₁₃ H ₁₀ ClN ₃ O ₃ :	53.53%C	3.46%H	14.41%N
Found:	53.51%C	3.29%H	14.23%N

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EXAMPLE 155-Bromo-2,3-dihydro-N-4-pyridinyl-1H-isoindol-2-amine hydrochloride.

Lithium aluminum hydride (11.8 g) was added portionwise to a suspension of 5-bromo-2-(4-pyridinylamino-1(H)-isoindole-1,3(2H)-dione hydrochloride (22.2 g) in tetrahydrofuran (625 ml). The reaction mixture was stirred at ambient temperature for 18 hrs, sodium sulfate decahydrate was added, filtered, and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica, eluting with triethyl amine, methanol and ethyl acetate. The appropriate fractions were collected and evaporated to provide 12.2 g (67%) of product, free base. A portion of the product free base (500 mg) was dissolved in methanol and treated with methanolic hydrochloride. Ether was added and the mixture was evaporated. The residue was recrystallized from methanol to give the analytical sample, mp 240°-265°C (dec).

Analysis:

Calculated for C ₁₃ H ₁₃ BrClN ₃ :	47.80%C	4.01%H	12.86%N
Found:	48.03%C	3.85%H	12.83%N

20

EXAMPLE 162,3-Dihydro-4-methoxy-N-(-4-pyridinyl)-1H-isoindol-2-amine.

A mixture of lithium aluminum hydride (9.96 g) in dry tetrahydrofuran (150 ml) was stirred at ambient temperature, under nitrogen, as 4-methoxy-2-(4-pyridinylamino)isoindole-1,3-dione hydrochloride monohydrate (17.0 g) was added in portions. The reaction mixture was stirred, under nitrogen, at ambient temperature overnight and sodium sulfate decahydrate was added in portions, with cooling. The precipitate was collected, washed with ethyl acetate, and the filtrate was evaporated. The residue was chromatographed on silica, eluting with 8-10% methanol-dichloromethane. The appropriate fractions were collected and concentrated. The residue was crystallized, then recrystallized from ethyl acetate to give 7.2 g (57%) of product, mp 144-146°C.

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Analysis:

Calculated for C ₁₄ H ₁₅ N ₃ O:	69.69%C	6.27%H	17.41%N
Found:	69.67%C	6.31%H	17.39%N

5

EXAMPLE 17N-[3-(3-Methoxyphenyl)propylidene]-N'-(4-pyridinyl)hydrazine hydrochloride.

A slurry of 3-(3-methoxyphenyl)propionaldehyde (6.46 g), 4-hydrazinopyridine hydrochloride (6.30 g) and magnesium sulfate (5 g) in ethanol (75 ml) was heated under reflux, under nitrogen, with stirring, for 45 mins. The reaction mixture was filtered, the filter cake was washed with ethyl acetate, and the filtrate was concentrated *in vacuo*. The residue was triturated with ethyl acetate to give 7 g (61%) of product, mp 155-156°C.

Analysis:

15	Calculated for C ₁₅ H ₂₁ ClN ₃ O ₁ :	61.75%C	6.22%H	14.40%N
	Found:	61.35%C	6.15%H	14.27%N

EXAMPLE 182,3-Dihydro-N-methyl-N-(4-pyridinyl)-1H-isoindol-2-amine hydrochloride.

A solution of phthalic anhydride (2.53 g) and 1-methyl-1-(4-pyridinyl)hydrazine (2.0 g) in glacial acetic acid (10 ml) was heated under reflux, under nitrogen, 4 hrs, with stirring. The reaction mixture was evaporated, and the residue was azeotroped with heptane, dried under high vacuum to give 2-(4-pyridinylmethylamino)isoindole-1,3-dione. To a slurry of 2-(4-pyridinylmethylamino)isoindole-1,3-dione in tetrahydrofuran (75 ml) was added lithium aluminum hydride (3.08 g), in portions. The reaction mixture was stirred, under nitrogen, at ambient temperature overnight and sodium sulfate decahydrate was added in portions, with cooling. The precipitate was collected, washed with ethyl acetate, and the filtrate was evaporated. The residue was chromatographed on silica, eluting with 5-8% methanol/dichloromethane. The appropriate fractions were collected and evaporated. The residue was dissolved in absolute ethanol and concentrated hydrochloric acid was added. The precipitate was recrystallized from ethanol to give 720 mg (17%) of product, mp >260°C.

29

Analysis:

Calculated for $C_{14}H_{16}ClN_3$:	64.24%C	6.16%H	16.05%N
Found:	64.03%C	6.19%H	16.01%N

5

EXAMPLE 192,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol hydrobromide.

10 A solution of 2,3-dihydro-4-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine (6.10 g) in 48% hydrobromic acid (50 ml) was heated under reflux for 4 hrs, with stirring. The reaction mixture was cooled to about 10°C and filtered. The filtrate was washed with cold water and dried under vacuum at 80°C to give 6.1 g (78%) of product. The analytical sample was obtained by recrystallization from water (dried at 80°C under vacuum) and had mp 249-252°C (dec).

Analysis:

15	Calculated for $C_{13}H_{13}N_3O \cdot HBr$:	50.67%C	4.58%H	13.63%N
	Found:	50.51%C	4.58%H	13.42%N

EXAMPLE 205-Hydroxy-2-(4-pyridinylmethylamino)isoindole-1,3-dione hydrochloride hemihydrate.

20 A solution of 5-acetoxypthalic anhydride (15.65 g), 1-methyl-1-(4-pyridinyl)hydrazine (8.90 g) and glacial acetic acid (60 ml) was heated under reflux, under nitrogen, for 4 hrs, with stirring. The reaction mixture was cooled to ambient temperature, the precipitate was collected and washed with ether. Trituration of the residue with absolute ethanol gave 16.2 g (83%) of product. Two grams of the residue were
25 dissolved in absolute ethanol, treated with concentrated hydrochloric acid and cooled. The precipitate was collected and recrystallized from absolute ethanol (2 times) to give 1.4 g of product, mp >260°C, as the analytical sample.

Analysis:

	Calculated for $C_{14}H_{11}N_3O_3 \cdot HCl \cdot 0.5H_2O$:	53.43%C	4.16%H	13.35%N
30	Found:	53.46%C	4.16%H	13.37%N

EXAMPLE 21

N-[2-(3-Methoxy-4-benzyloxyphenyl)-ethylidene]-N'-pyridin-4-yl-hydrazine hydrochloride.

- 5 To a stirred solution of 1-benzyloxy-2-methoxy-4-(2-methoxyvinyl)benzene (11.0 g), 4-hydrazinopyridine hydrochloride (6.6 g), and ethanol (150 ml) was added p-toluene sulfonic acid (0.39 g). The reaction mixture was stirred under reflux for 2 hrs and concentrated *in vacuo*. Recrystallization of the residue from methanol/ether gave 9.48 g (61%) of product, mp 154-155°C.

10 Analysis:

Calculated for C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂ :	65.71%C	5.78%H	10.95%N
Found:	65.47%C	5.81%H	10.81%N

EXAMPLE 22

15 2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl dimethylcarbamate.

- To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.20 g), triethylamine (1.18 g) and chloroform (35 ml), was added dimethylcarbamyl chloride (0.68 g) with stirring, at ambient temperature, under nitrogen. The reaction mixture was heated under reflux for 3 hrs, poured into dilute sodium bicarbonate solution (100 ml), and the layers were separated. The aqueous phase was extracted with chloroform, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated. The residue was chromatographed on silica, eluting with 10-15% methanol/dichloromethane. The appropriate fractions were collected and concentrated to give 953 mg (60%) of product. Recrystallization from dichloromethane-heptane gave the analytical sample, mp 183-185°C.
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- 25

Analysis:

Calculated for C ₁₆ H ₁₈ N ₄ O ₂ :	64.41%C	6.08%H	18.78%N
Found:	63.90%C	6.06%H	18.64%N

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EXAMPLE 23

N-[3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propylidene]-N'-pyridin-4-yl-hydrazine hydrochloride.

5 To a solution of ethyl 3-(4-hydroxy-3-methoxyphenyl)propionate (20.0 g) in dimethylformamide (150 ml) was added t-butyldimethylsilylchloride (16.1 g) followed by imidazole (14.7 g). The reaction mixture was stirred for 2 hrs at ambient temperature, poured into water (1 l) and extracted with ethyl acetate (200 ml) followed by petroleum ether (500 ml). The combined organic extracts were dried
10 over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo* to afford 33.0 g of ethyl 3-(4-t-butyldimethylsilyloxy-3-methoxyphenyl)propionate as a colorless oil.

To a slurry of lithium aluminum hydride (3.6 g) in tetrahydrofuran (200 ml) at 0°C was added dropwise a solution of ethyl 3-(4-t-butyldimethylsilyloxy-3-methoxyphenyl)propionate in tetrahydrofuran (100 ml). The reaction mixture was
15 stirred for 1 hr at 0°C and sodium sulfate decahydrate was added. Ethyl acetate (500 ml) was added, and the mixture was filtered over celite™. The filtrate was concentrated *in vacuo* to give 22.75 g of 3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propan-1-ol. To a slurry of pyridinium chlorochromate (25.0 g) in dichloromethane (250 ml) at room temperature was added a solution of 3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propan-1-ol in dichloromethane (100 ml).
20 The reaction mixture was stirred for 1 hr and filtered through a bed of florisil™. The filtrate was concentrated *in vacuo* to afford 17.0 g of 3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propionyl aldehyde. To a solution of 3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propionylaldehyde (10 g) in ethanol (100 ml) was added
25 4-hydrazinopyridine hydrochloride salt (5.4 g) followed by magnesium sulfate (5 g). The solution was heated under reflux for 1 hr, then filtered hot. The filtrate was concentrated *in vacuo* to afford 9.03 g (67%) of product, mp 147-149°C.

Analysis:

30	Calculated for C ₂₁ H ₃₂ ClN ₃ O ₂ Si:	59.76%C	7.64%H	9.96%N
	Found:	58.99%C	7.67%H	10.39%N

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EXAMPLE 24

[7-Methoxy-8-tert-butyldimethylsilyloxy-1,3,4,5-tetrahydrobenzo[c]azepine-2-yl]-pyridine-4-yl-amine.

5 To a solution of N-[3-(3-methoxy-4,6-butyldimethylsilyloxyphenyl)propylidene]-N'-pyridin-4-yl-hydrazine (5.81 g) in tetrahydrofuran (150 ml) was added lithium aluminum hydride in small portions at ambient temperature. The reaction mixture was stirred for 1.5 hrs at ambient temperature, sodium sulfate decahydrate was added. Ethyl acetate was added, and the mixture was filtered over celite. The filtrate
10 was concentrated *in vacuo* to afford 5.81 g (75%) of N-[3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propyl]-N'-pyridin-4-yl hydrazine.

To a solution of N-[3-(3-methoxy-4-t-butyldimethylsilyloxyphenyl)propyl]-N'-pyridin-4-yl hydrazine in glacial acetic acid (50 ml) was added chloromethyl methyl ether (1.42 g). The reaction mixture was stirred overnight, then partitioned between 10%
15 aqueous sodium hydroxide (500 ml) and ethyl acetate (500 ml). The organic extract was separated, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with dichloromethane/methanol (9:1). The appropriate fractions were collected and evaporated to afford 3.61 g (60%) of product, mp 149-150°C.

20 Analysis:

Calculated for C ₂₂ H ₃₃ N ₃ O ₂ Si:	66.13%C	8.32%H	10.52%N
Found:	66.23%C	8.47%H	10.37%N

EXAMPLE 25

25 (7-Methoxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl)-4-pyridinylamine 0.2 hydrate.

To a solution of (N-[3-(3-methoxy phenyl)propylidene]-N-4-pyridinyl)hydrazine (12.0 g) in acetic acid (90 ml) was added a solution of chloromethyl methyl ether in acetic acid (10 ml). The reaction mixture was stirred overnight, under nitrogen, at ambient temperature, then heated at 50°C for one hr. The reaction mixture was extracted
30 with ethyl acetate, and the extract was washed with 10% sodium hydroxide solution and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 10% methanol:dichloromethane. The appropriate fractions were collected and concentrated to give 9.22 g (95%) of product. The analytical sample was prepared

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by recrystallization from dichloromethane, heptane and ether and had mp 120-121°C.

Analysis:

Calculated for $C_{16}H_{19}N_3O \cdot 0.2 H_2O$:	70.41%C	7.16%H	15.39%N
Found:	70.69%C	7.03%H	15.63%N

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EXAMPLE 267-Methoxy-2-(pyridin-4-yl-amino)-1,2,3,4-tetrahydroisoquinolin-6-ol-dihydrochloride.

A solution of (6-benzyloxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)pyridin-4-ylamine (2.0 g) in ethanol (75 ml) was slowly added to Degussa 5% palladium-on-carbon (0.1 g). The mixture was hydrogenated overnight at ambient temperature in a Parr Shaker at 55 psi. The reaction mixture was filtered through a pad of celite and the pad was washed with ethanol. The filtrate was concentrated, and the residue was purified by Chromatotron chromatography (5% methanol/ethyl acetate). The appropriate fractions were collected and concentrated. The residue was dissolved in hot methanol. Ethanolic hydrochloric acid was added and the precipitate was collected to yield 0.25 g (13%) of product, mp 194-195°C.

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Analysis:

Calculated for $C_{15}H_{17}N_3O_2 \cdot 2HCl \cdot 0.39H_2O$:	51.28%C	5.69%H	11.96%N
Found:	51.52%C	5.76%H	11.53%N

20

EXAMPLE 27(3,4-Dihydro-6-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine hydrochloride.

Lithium aluminum hydride (0.55 g) was added portionwise to a suspension of N-[2-(3-methoxyphenyl)ethylidene]-N'-pyridin-4-yl hydrazone (2.0 g) in tetrahydrofuran (36 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 1 hr, sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was concentrated to give 1.73 g of N-[2-(3-methoxyphenyl)ethyl]-N'-pyridin-4-yl hydrazine. A solution of N-[2-(3-methoxyphenyl)ethyl]-N'-pyridin-4-yl hydrazine (0.85 g) and chloromethyl methyl ether (0.31 g) in acetic acid (15 ml) was heated at 55°C for 1.5 hrs, and the mixture was cooled to 0°C. Sodium hydroxide solution (15%) was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was dissolved in methanol

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and methanolic hydrogen chloride and then ether were added to give 0.31 g (30%) of product, mp 199-200°C.

Analysis:

Calculated for $C_{15}H_{17}Cl_{18}N_3O$: 61.75%C 6.22%H 14.40%N

5 Found: 61.41%C 6.21%H 14.31%N

EXAMPLE 28

(7-Methoxy-1,3,4,5-tetrahydrobenzo[c]azepin-4-yl)methyl-1-pyridin-4-yl-amine.

To a solution of 3-(3-methoxyphenyl)propionaldehyde (9.75 g) in ethanol (100 ml)
 10 was added 4-(1-methylhydrazino)pyridine (9.80 g) and magnesium sulfate (10 g).
 The reaction mixture was heated under reflux for 1 hr, filtered hot, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and evaporated to give 10.4 g (65%) of N-[3-(3-methoxyphenyl)propylidene]-N'-pyridinyl-
 15 4-yl hydrazine. To a slurry of lithium aluminum hydride (3.38 g) in tetrahydrofuran (40 ml) was added N-[3-(3-methoxyphenyl)propylidene]-N'-pyridin-4-yl hydrazine (8.0 g) in small portions. The reaction mixture was stirred for 1 hr at ambient temperature, and sodium sulfate decahydrate was added. The slurry was diluted with ethyl acetate, and the mixture was filtered through celite. The filtrate was concentrated *in vacuo* to
 20 give 6.16 g (76%) of N-[3-(3-methoxyphenyl)propyl]-N'-pyridin-4-yl hydrazine.
 To a solution of N-[3-(3-methoxyphenyl)propyl]-N'-pyridin-4-yl hydrazine (6.0 g) in acetic acid was added chloromethyl methyl ether (2 ml) in one portion. The reaction mixture was stirred at ambient temperature for 1 hr, and at 50°C for 2 hrs. The solution was then allowed to cool to ambient temperature, stirred overnight, and
 25 ethyl acetate (500 ml) was added. The organic phase was washed with aqueous 10% sodium hydroxide, separated, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and evaporated to give 5.2 g (83%) of product, mp 163-165°C.

30 Analysis:

Calculated for $C_{17}H_{21}N_3O$: 72.06%C 7.47%H 14.83%N

Found: 71.89%C 7.46%H 14.72%N

35

EXAMPLE 29N-[3-(Phenyl)propylidene]-N'-(4-pyridinyl)hydrazine hydrochloride.

To a solution of hydrocinnamaldehyde (5.0 g) in ethanol (50 ml) was added 4-hydrazinopyridine (5.9 g) followed by magnesium sulfate (5 g). The reaction mixture was heated under reflux for 2.5 hrs, filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with hot ethyl acetate and filtered to give 9.0 g (92%) of product. Recrystallization from ethyl acetate and methanol gave the analytical sample, mp 204-205°C.

Analysis:

Calculated for C ₁₄ H ₁₆ ClN ₃ :	64.24%C	6.16%H	16.05%N
Found:	63.99%C	6.10%H	15.88%N

EXAMPLE 306-Methoxy-2-(pyridin-4-ylamino)-1,2,3,4-tetrahydro-isoquinolin-7-yl-dimethyl carbamate.

To a stirred solution of 6-(methoxy-7-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)pyridin-4-yl-amine (1.07 g) triethylamine (1.2 ml) and chloroform (35 ml), dimethylcarbamy chloride (0.44 ml) was added. The reaction mixture was heated under reflux for 2 hrs, with stirring, poured into saturated sodium bicarbonate solution (100 ml) and extracted with chloroform. The combined organic extracts were concentrated *in vacuo*, and the residue was chromatographed on silica gel eluting with 20% methanol/dichloromethane. The appropriate fractions were collected and concentrated *in vacuo* to yield 0.310 g (23%) of product, mp 176-177°C.

Analysis:

Calculated for C ₁₈ H ₂₂ N ₄ O ₃ ·0.33H ₂ O:	62.05%C	6.56%H	16.08%N
Found:	61.85%C	6.45%H	15.43%N

EXAMPLE 312-(4-Pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-6-yl dimethyl carbamate.

Dimethyl carbamoyl chloride (0.50 g) was added dropwise to an ambient temperature mixture of (6-hydroxy-1,2,3,4-tetrahydro-1H-isoquinolin-2-yl)-4'-pyridinylamine (0.93 g) and triethylamine (0.85 g) in chloroform (25 ml). The reaction mixture was heated

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under reflux for 4 hrs, cooled and poured into saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated to give 0.97 g (%) of product. The product was chromatographed on silica gel using a chromatotron, eluting with 2% triethylamine/23% methanol/75% ethyl acetate. The appropriate fractions were collected and evaporated to provide 0.34 g (28%) of the analytical sample, mp 208-211°C.

Analysis:

10	Calculated for C ₁₇ H ₂₀ N ₄ O ₂ :	65.37%C	6.45%H	17.94%N
	Found:	64.87%C	6.40%H	17.66%N

EXAMPLE 32

N'-[3-(4-methoxyphenyl)propylidene]-N-methyl-N-pyridin-4-yl hydrazine hydrochloride.

To a solution of 3-(methoxyphenyl)propionaldehyde (6.0 g) in ethanol (50 ml) was added 1-methyl-1-(4-pyridyl)hydrazine (4.5 g) followed by anhydrous magnesium sulfate (5 g). The reaction mixture was heated under reflux, with stirring for 1 hr, filtered hot, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and concentrated to afford 6.4 g (57%) of product, mp 163-165°C.

Analysis:

	Calculated for C ₁₆ H ₂₀ ClN ₃ O:	62.84%C	6.59%H	13.74%N
25	Found:	63.00%C	6.47%H	13.51%N

EXAMPLE 33

N-[2-(4-Benzoyloxyphenyl)ethylidene]-N'-pyridin-4-ylhydrazine hydrochloride monohydrate.

A mixture of 1-benzoyloxy-4-(2-methoxyvinyl)benzene (16.9 g), 4-hydrazinopyridine hydrochloride (11.3 g) and *p*-toluenesulfonic acid (0.68 g) in ethanol (200 ml) was heated under reflux for 5 hrs, with stirring. The reaction mixture was cooled, filtered, and the filtrate was concentrated *in vacuo*. The residue crystallized to give 15.75 g

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(63%) of product, mp 203-205°C.

Analysis:

Calculated for $C_{20}H_{19}N_3O \cdot H_2O \cdot HCl$:	64.60%C	5.96%H	11.30%N
Found:	64.53%C	5.88%H	11.46%N

5

EXAMPLE 34N-[2-(4-benzyloxyphenyl)ethyl]-N'-pyridin-4-yl-hydrazine hydrochloride.

Lithium aluminum hydride (0.43 g) was added portionwise to a suspension of N-[2-(4-benzyloxyphenyl)ethylidene]-N'-pyridin-4-ylhydrazine hydrochloride (2.0 g) in tetrahydrofuran (28 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 1 hr, and sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was evaporated to provide 1.66 g of product free base. A portion (0.66 g) of the free base was dissolved in hot ethanol, and methanolic hydrogen chloride was added. The precipitate was collected to provide 0.38 g (48%) of product, mp 231-233°C.

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Analysis:

Calculated for $C_{20}H_{21}N_3O \cdot HCl$:	67.50%C	6.23%H	11.81%N
Found:	67.27%C	6.12%H	11.64%N

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EXAMPLE 357-(Benzyloxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine.

Lithium aluminum hydride (2.76 g) was added portionwise to a suspension of N-[2-(4-benzyloxyphenyl)ethyl]-N'-pyridin-4-yl hydrazone hydrochloride (12.87 g) in tetrahydrofuran (180 ml), at 0°C. The reaction mixture was stirred at ambient temperature for 18 hrs, and sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was evaporated to provide 11.0 g of N-[2-(4-benzyloxyphenyl)ethyl]-N'-pyridin-4-yl hydrazine. A solution of N-[2-(4-benzyloxyphenyl)ethyl]-N'-pyridin-4-yl hydrazine and chloromethyl methyl ether (3.04 g) in acetic acid (140 ml) was heated under reflux for 1 hr and then poured into ice. Sodium hydroxide solution (50%) was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using a high performance

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chromatography system, eluting with 10% methanol/ethyl acetate. The appropriate fractions were collected and evaporated to yield 8.1 g (71%) of product, mp 138-140°C.

Analysis:

5	Calculated for C ₂₁ H ₂₁ N ₃ O:	76.11%C	6.39%H	12.68%N
	Found:	75.45%C	6.45%H	12.64%N

EXAMPLE 362-(4-Pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-yl dimethyl carbamate.

10 Dimethyl carbamoyl chloride (0.80 g) was added dropwise to a mixture of 2-(pyridin-4-yl amino)-1,2,3,4-tetrahydroisoquin-7-ol (1.5 g) and triethylamine (1.83 g) in chloroform (65 ml) at ambient temperature. The reaction mixture was heated under reflux for 5 hrs, allowed to cool and poured into saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted with
 15 dichloromethane. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using a Chromatotron, eluting with 2% triethylamine/23% methanol/75% ethyl acetate. The appropriate fractions were collected and evaporated to provide 1.65 g (85%) of product. Recrystallization from
 20 methanol gave the analytical sample, mp 204-205°C.

Analysis:

	Calculated for C ₁₇ H ₂₀ N ₄ O ₂ :	65.37%C	6.45%H	17.94%N
	Found:	65.02%C	6.40%H	18.16%N

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EXAMPLE 377-Methoxy-2(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-6-yl dimethyl carbamate.

Dimethyl carbamoyl chloride (0.81 ml) was added dropwise to a mixture of 7-methoxy-2-(pyridin-4-yl amino)-1,2,3,4-tetrahydroisoquin-6-ol (92 g) and triethylamine (2.3 ml) in chloroform (75 ml) at ambient temperature. The reaction mixture was
 30 heated under reflux for 0.5 hr, stirred overnight at ambient temperature and was added to sodium bicarbonate solution and chloroform. The layers were separated and the organic extract was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was

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chromatographed on silica gel, eluting with 1% triethylamine, 5% methanol, 94% ethyl acetate; ended with 1% triethylamine, 20% methanol, 79% ethyl acetate. The appropriate fractions were collected and evaporated to yield 2.1 g (83%) of product, mp 210°C.

5 Analysis:

Calculated for C ₁₈ H ₂₂ N ₄ O ₃ :	63.14%C	6.48%H	16.36%N
Found:	62.88%C	6.47%H	16.04%N

EXAMPLE 38

10 N-[3-(4-methoxyphenyl)propylidene]-N'-(4-pyridyl) hydrazine hydrochloride hemihydrate.

To a solution of 3-(4-methoxyphenyl)propionaldehyde (5.0 g) in ethanol (100 ml) was added 4-hydrazinopyridine hydrochloride (4.42 g), followed by magnesium sulfate (5 g). The solution was heated under reflux for 1 hr, cooled to ambient temperature and
 15 filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over silica gel eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and concentrated to afford 7.2 g (81%) of product, mp 164-165°C.

Analysis:

20 Calculated for C ₁₅ H ₁₈ ClN ₃ O·0.5 H ₂ O:	59.90%C	6.37%H	13.97%N
Found:	60.00%C	6.13%H	14.39%N

EXAMPLE 39

25 [7-Methoxy-8-hydroxy-1,3,4,5-tetrahydrobenzo[c]azepine-2-yl]pyridin-4-yl amine hydrochloride 0.25 hydrate.

To a solution of [7-methoxy-8-t-butyldimethylsilyloxy-1,3,4,5-tetrahydrobenzo[c]azepine-2yl]pyridin-4-yl-amine (7.84 g) in tetrahydrofuran (100 ml) at 0°C was added 1 M tetrabutylammonium fluoride (23.5 ml) in tetrahydrofuran. The reaction mixture was allowed to warm to ambient temperature, stirred overnight and
 30 dichloromethane (500 ml) was added. The organic extracts were washed with water, separated, dried over anhydrous magnesium sulfate, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with dichloromethane:methanol (8:1). The appropriate fractions were collected and

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concentrated. The residue was dissolved in methanol (30 ml), and concentrated hydrochloric acid was added. The solution was concentrated *in vacuo*. The residue was crystallized from dichloromethane-methanol to afford 1.6 g (25%) of product, mp 199-210°C.

5 Analysis:

Calculated for $C_{16}H_{20}ClN_3O_2 \cdot 0.25 H_2O$:	58.89%C	6.33%H	12.88%N
Found:	58.82%C	6.70%H	12.46%N

EXAMPLE 40

10 (1.3-Dihydroisoindol-2-yl)-(3-fluoropyridin-4-yl)amine hydrochloride.

To a stirred solution of phthalic anhydride (1.76 g) in acetic acid (45 ml), 3-fluoro-4-hydrazinopyridine (1.52 g) was added. The reaction mixture was heated under reflux for 1 hr and concentrated *in vacuo* to give 3.88 g of 2-(3-fluoro-pyridin-4-ylamino)-isoindole-1,3-dione. To a stirred solution of 2-(3-fluoropyridin-4-ylamino)isoindole-1,3-dione (3.88 g) in tetrahydrofuran (125 ml) at 0°C, lithium aluminum hydride (2.86 g) was added. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1 day. Sodium sulfate decahydrate was added, and the mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was chromatographed on a silica gel eluting with ethyl acetate. The appropriate fractions were collected and concentrated to yield 1.28 g (37%) of product free base. A portion of the free base was dissolved in methanol, and ethereal hydrogen chloride was added. The precipitate was collected and recrystallized from methanol to yield 0.200 g of product, mp 200-202°C.

Analysis:

25 Calculated for $C_{13}H_{13}ClFN_3$:	58.76%C	4.93%H	15.81%N
Found:	58.66%C	5.15%H	15.54%N

EXAMPLE 41

30 Dimethylcarbamic acid-2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yl ester hydrochloride 0.25 hydrate.

To a solution of (7-methoxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl)-4-pyridinylamine in dichloromethane (50 ml) was added boron tribromide (3.9 ml) at 0°C. The reaction mixture was stirred for 2 hrs at ambient temperature, methanol was added, and the

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mixture was concentrated *in vacuo* to afford (7-hydroxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl-4-pyridinylamine hydrobromide. (7-Hydroxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl-4-pyridinylamine hydrobromide was neutralized with sodium bicarbonate solution to afford 1.3 g of (7-hydroxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl-4-pyridinylamine. To a solution of (7-hydroxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl-4-pyridinylamine (1.2 g) in chloroform (30 ml) was added dimethyl carbamyl chloride (0.48 ml) followed by triethylamine (1.43 ml). The reaction mixture was heated under reflux, with stirring, for 2 hrs, allowed to cool to ambient temperature, and dichloromethane (200 ml) was added. The organic extract was washed with saturated sodium bicarbonate (100 ml), dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and concentrated. The residue was dissolved in methanol, acidified with concentrated hydrochloric acid, and concentrated *in vacuo*. The residue was triturated with petroleum ether and filtered to give 0.72 g (44%) of product, mp 100-110°C.

Analysis:

Calculated for $C_{18}H_{23}ClN_4O_2 \cdot 0.25H_2O$: 58.85%C 6.45%H 15.25%N

Found: 58.75%C 6.32%H 15.34%N

EXAMPLE 422-(3-Fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole.

To a slurry of 3-fluoro-4-methoxybenzoic acid (30.0 g) in toluene (100 ml) was added thionyl chloride (25 ml). The reaction was heated under reflux for 2 hrs and then distilled. The residue was dried under high vacuum to give 32 g of 3-fluoro-4-methoxybenzyl chloride. To a solution of 2-amino-2-methyl-1-propanol (35 ml) in dichloromethane (200 ml) was added a solution of the 3-fluoro-4-methoxybenzoyl chloride in dichloromethane (150 ml). The reaction mixture was stirred for 1 hr at ambient temperature, dichloromethane (500 ml) was added, and washed with 2N hydrochloric acid (1 l). The layers were separated and the organic extract was dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. To the residue was added thionyl chloride (25 ml) at 0°C. The reaction mixture was stirred for 30 min, diethyl ether (200 ml) was added, and the mixture was

stirred for 10 min. The supernatant was decanted. 10% Sodium hydroxide solution was added, and the mixture was extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo* to give 36 g (91%) of product, mp 59-60°C.

5 Analysis:

Calculated for C ₁₂ H ₁₄ FNO ₂ :	64.56%C	6.32%H	6.27%N
Found:	64.35%C	6.35%H	6.11%N

EXAMPLE 43

10 2,3-Dihydro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine.

A mixture of 5-methoxyisobenzofuran-1,3-dione (33.0 g), 4-pyridinylhydrazine hydrochloride (25.7 g) and glacial acetic acid (100 ml) was heated overnight, under reflux, under nitrogen, with stirring. Water (100 ml) was added, and the mixture was evaporated and dried *in vacuo*. The residue was triturated with acetone, the acetone
 15 decanted, and the residue was triturated with methanol to give 16.1 g of 5-methoxy-2-(4-pyridinylamino)isoindol-1,3-dione. To a mixture of lithium aluminum hydride (6.00 g) and dry tetrahydrofuran (150 ml) at ambient temperature, under nitrogen, 5-methoxy-2-(4-pyridinylamino)isoindol-1,3-dione hydrochloride (16.1 g) was added in portions, with stirring. The reaction mixture was stirred at room temperature, under
 20 nitrogen, 4 hrs, and sodium sulfate decahydrate was added in portions. The mixture was filtered through a bed of celite, the filter cake was washed thoroughly with ethyl acetate, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with 7% methanol-dichloromethane followed by 185:14:1 dichloromethane:methanol:ammomium hydroxide. The appropriate
 25 fractions were collected and concentrated. The residue was crystallized from ethanol to give 5.8 (46%) of product, mp 166-167°C.

Analysis:

Calculated for C ₁₄ H ₁₅ N ₃ O:	69.69%C	6.27%H	17.41%N
Found:	69.69%C	6.34%H	17.37%N4

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EXAMPLE 44

7-Methoxy-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione.
hydrochloride hemihydrate

5 A solution of 7-methoxyisochroman-1,3-dione (4.50 g), 4-hydrazinopyridine hydrochloride (3.25 g) and glacial acetic acid (35 ml) was heated under reflux, under nitrogen, for 4 hrs, with stirring. The reaction mixture was allowed to cool to ambient temperature, and the precipitate was collected and washed with ether. The filter cake was recrystallized from absolute ethanol, dried at 100°C under vacuum to give 1.55 g
10 (21%) of product, mp 218-223°C.

Analysis:

Calculated for C ₁₅ H ₁₃ N ₃ O ₃ ·0.5 H ₂ O:	54.80%C	4.60%H	12.78%N
Found:	54.34%C	4.54%H	12.73%N

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EXAMPLE 45

2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl-1,2,3,4-tetrahydroisoquinolin-2-ylcarbamate hydrochloride.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.50 g), triethylamine (1.47 g) and chloroform (20 ml) at ambient temperature, under nitrogen,
20 1,2,3,4-tetrahydroisoquinolin-2-ylcarbamyl chloride (1.55 g) in chloroform (10 ml) was added with stirring. The reaction mixture was heated under reflux for 1 hr, poured into dilute sodium bicarbonate solution (100 ml), and the layers were separated. The aqueous phase was extracted with chloroform, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in*
25 *vacuo*. The residue was chromatographed on silica, eluting with 10-15% methanol-dichloromethane, and then on silica, eluting with 90:9:1 dichloromethane:methanol:ammonium hydroxide. The appropriate fractions were collected and concentrated to give 1.78 g (70%) of product, free base. The free base was dissolved in absolute ethanol, and
30 concentrated hydrochloric acid was added. The solution was cooled, the precipitate was collected, recrystallized from absolute ethanol and dried under vacuum at 80°C to give 950 mg (34%) of product, mp 242-245°C.

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Analysis:

Calculated for C ₂₃ H ₂₃ ClN ₄ O ₂ :	65.32%C	5.48%H	13.25%N
Found:	65.06%C	5.39%H	13.15%N

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EXAMPLE 462,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-5-ol hydrobromide.

A solution of 2,3-dihydro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine (5.25 g) in 48% hydrobromic acid (35 ml) was heated under reflux for 5 hrs, with stirring. The reaction mixture was cooled to about 10°C and filtered. The filter cake was washed with cold water and dried under vacuum in an oven at 80°C to give 4.8 g (72%) of product. The product was recrystallized from water and dried under vacuum at 80°C to give 3.1 g (46%) of the analytical sample, mp 261-264°C.

Analysis:

Calculated for C ₁₃ H ₁₄ BrN ₃ O:	50.67%C	4.58%H	13.63%N
Found:	50.81%C	4.37%H	13.60%N

EXAMPLE 472-[Methyl(pyridin-4-yl)amino]-1,2,3,4-tetrahydro-isoquinolin-6-ol.

A mixture of 6-benzyloxy-3,4-dihydro-1H-isoquinoline-2-yl-N-methyl-4-pyridinylamine (5.1 g) and 5% palladium-on-carbon (1.0 g) in methanol (75 ml) was shaken on a Parr hydrogenation apparatus at ambient temperature and an initial pressure of 55 psi for 2 hrs. An additional 1 g of catalyst was added, and the mixture was shaken for an additional 4 hrs at an initial pressure of 55 psi. The reaction mixture was filtered through a pad of celite, the pad was washed with methanol, and the filtrate was concentrated to give 3.45 g (92%) of product. Recrystallization from methanol provided the analytical sample, mp 263-266°C.

Analysis:

Calculated for C ₁₅ H ₁₇ N ₃ O:	70.56%C	6.71%H	16.46%N
Found:	70.38%C	6.66%H	16.57%N

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EXAMPLE 48

(6-Fluoro-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine.

Lithium aluminum hydride (4.5 g) was added portionwise to a suspension of the N-[2-(3-fluoro-5-methoxyphenyl)ethylidene]-N'-4-hydrazine hydrochloride (16.8 g) in tetrahydrofuran (300 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 1 hr, and sodium sulfate decahydrate was added. The mixture was filtered and was concentrated to provide 15.1 g of N-[2-(3-fluoro-5-methoxyphenyl)ethyl]-N-pyridin-4-yl hydrazine.

A solution of N-[2-(3-fluoro-5-methoxyphenyl)ethyl]-N-pyridin-4-yl hydrazine (15.1 g) and chloromethyl methyl ether (5.3 g) in acetic acid (240 ml) was heated under reflux for 2 hrs and then cooled to 0°C. 50% Sodium hydroxide solution was added, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was recrystallized from methanol to provide 3.5 g (23%) of product, mp 216-218°C.

Analysis:

Calculated for C ₁₅ H ₁₆ FN ₃ O:	65.92%C	5.90%H	15.37%N
Found:	65.65%C	5.83%H	15.29%N

EXAMPLE 49

Dimethylcarbamic acid-7-methoxy-2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl ester hydrochloride.

To a solution of [7-methoxy-8-hydroxy-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl]-4-pyridinylamine hydrochloride 0.25 hydrate (500 mg) in chloroform (10 ml) was added dimethylcarbamyl chloride (170 µl) and triethylamine (0.75 ml). The reaction mixture was heated under reflux for 3 hrs, then cooled to room temperature, and dichloromethane (200 ml) and saturated sodium bicarbonate solution (100 ml) were added. The aqueous phase was extracted with dichloromethane (2 x 5 ml), the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and concentrated. The residue was dissolved in methanol (5 ml), and

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concentrated hydrochloric acid was added. The mixture was concentrated *in vacuo*, and the residue was crystallized from diethyl ether-dichloromethane to give 320 mg (52%) of product, mp 95-110°C.

Analysis:

5	Calculated for C ₁₉ H ₂₅ ClN ₄ O ₃ :	58.09%C	6.41%H	14.26%N
	Found:	57.68%C	6.36%H	14.45%N

EXAMPLE 50N-[2-(2-Bromo-5-methoxyphenyl)ethylidene]-N'-pyridin-4-yl-hydrazine.

- 10 A mixture of 4-bromo-1-methoxy-3-(2-methoxyvinyl)benzene (42.3 g), 4-hydrazinopyridine (27.6 g), and p-toluenesulfonic acid (3.3 g) in ethanol (500 ml) was heated under reflux overnight, with stirring. The reaction mixture was filtered, and the filtrate was concentrated to about 50% of its initial volume. The precipitate was collected to give 5.5 g of product, as the hydrochloride salt, and the filtrate was
- 15 concentrated. Saturated sodium hydrogen carbonate solution was added to the residue and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on a Waters LC2000 instrument, gradient eluting with: 1% ethylamine/2% methanol/97% ethyl acetate/1% triethylamine acid/5%
- 20 methanol/94% ethyl acetate. The appropriate fractions were collected and concentrated to yield 4.9 g (8.8%) of product, mp 142°C.

Analysis:

Calculated for C ₁₄ H ₁₄ BrN ₃ O:	52.52%C	4.41%H	13.12%N
Found:	52.57%C	4.42%H	13.03%N

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EXAMPLE 51(5-Bromo-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine.

- Lithium aluminum hydride (1.3 g) was added portionwise to a suspension of N-[2-bromo-5-methoxyphenyl)ethylidene]-N-pyridin-4-ylhydrazone hydrochloride (8.4 g) in
- 30 tetrahydrofuran (450 ml) at 0°C. The reaction mixture was stirred overnight at ambient temperature. Sodium sulfate decahydrate was added, and the mixture was filtered. The filtrate was concentrated, and the residue was chromatographed on a Waters™ C2000 instrument, gradient eluting with: 1% triethylamine/2% methanol/97%

ethyl acetate; 1% triethylamine/5% methanol/94% ethyl acetate. The appropriate fractions were collected and concentrated to yield 6.9 g (91%) of N-[3-(2-bromo-5-methoxyphenyl)propyl]-N'-pyridin-4-yl hydrazine.

A solution of N-[3-(2-bromo-5-methoxyphenyl)propyl]-N'-pyridin-4-yl hydrazine (96.6 g), chloromethyl methyl ether (1.7 ml) and acetic acid (400 ml) was heated under reflux for 1 hr. The reaction mixture was cooled, poured onto ice, and saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on a Waters LC2000 instrument, gradient eluting with 1% triethylamine/4% methanol/95% ethyl acetate. The appropriate fractions were collected and concentrated to provide 5.5 g (80%) of product, mp 172-173°C.

Analysis:

Calculated for C ₁₅ H ₁₆ BrN ₃ O:	53.91%C	4.83%H	12.57%N
Found:	54.04%C	4.73%H	12.53%N

EXAMPLE 52

(3,4-Dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine.

A mixture of 5-bromo-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl-4-pyridinylamine (0.8 g), ethanol (75 ml) and 5% palladium-on-carbon (0.1 g) was hydrogenated at 55 psi overnight in a Parr shaker at ambient temperature. The reaction mixture was filtered through a pad of celite, the pad was washed with methanol, and the filtrate was concentrated. Aqueous sodium hydrogen carbonate was added to the residue, and the mixture was extracted with ethyl acetate. The extracts were dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel on a Chromatotron, eluting with 1% triethylamine/5% methanol/94% ethyl acetate. The appropriate fractions were collected and concentrated. The residue was crystallized in hot ethyl acetate to give 0.25 g (41%) of product, mp 170-171°C.

Analysis:

Calculated for C ₁₅ H ₁₇ N ₃ O:	70.56%C	6.71%H	16.46%N
Found:	70.39%C	6.74%H	16.35%N

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EXAMPLE 53N-[2-(2-fluoro-5-methoxy-phenyl)ethylidene]-N'-pyridin-4-yl-hydrazine hydrochloride.

To a solution of 1-fluoro-4-methoxy-2-(2-methoxyvinyl)benzene (20 g) and 4-hydrazinopyridine hydrochloride (17.7 g) in ethanol (300 ml), p-toluene sulfonic acid (3.13 g) was added, with stirring. The reaction mixture was stirred under reflux for 2 hrs, filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from methanol to yield 13.24 g (41%) of product, mp 219-220°C.

Analysis:

Calculated for C ₁₄ H ₁₅ ClN ₃ O:	56.86%C	5.11%H	14.21%N
10 Found:	56.65%C	5.09%H	14.11%N

EXAMPLE 54N-[2-(4-methoxy-3-methyl-phenyl)ethylidene]-N'-pyridin-4-ylhydrazine hydrochloride.

To a solution of 1-methoxy-2-methyl-4-(2-methoxyvinyl)benzene (17 g) and 4-hydrazinopyridine hydrochloride (15.4 g) in ethanol (300 ml), p-toluenesulfonic acid (2.7 g) was added, with stirring. The reaction mixture was stirred under reflux for 2 hrs, filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from methanol to yield 10.9 g (39%) of product, mp 224-226 °C.

Analysis:

20 Calculated for C ₁₅ H ₁₈ ClN ₃ O:	61.75%C	6.22%H	14.40%N
Found:	61.72%C	6.18%H	14.41%N

EXAMPLE 556-Fluoro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-ol hydrobromide.

25 Boron tribromide (8.8 g) was added dropwise to a solution of 6-fluoro-7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinoline (2.9 g) in dichloromethane (200 mL) at -78°C. The dry ice bath was removed, and the suspension was stirred at ambient temperature for 3 hrs. The reaction mixture was cooled to -78°C, and methanol (100 mL) was added. The mixture was stirred at ambient temperature for 1 hr and concentrated *in vacuo*. The residue was washed with methanol/ethyl ether and recrystallized from 2-propanol/ethyl acetate to give 0.61 g (17%) of product, mp 244-245°C (dec).

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Analysis:

Calculated for $C_{14}H_{15}BrFN_3O$:	49.43%C	4.44%H	12.35%N
Found:	49.41%C	4.32%H	12.16%N

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EXAMPLE 566-Fluoro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-yl dimethyl carbamate.

Dimethyl carbamoyl chloride (0.46 g) was added dropwise to a mixture of 6-fluoro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinoline-7-ol hydrobromide (1.5 g) and triethylamine (1.87 g) in chloroform (50 mL) at ambient temperature. The reaction mixture was heated under reflux for 3 hrs, cooled and poured into saturated sodium bicarbonate solution. The layers were separated, and the organic extract was extracted with dichloromethane. The extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on a Chromatotron, eluting with 2% triethylamine/23% methanol/75% ethyl acetate. The appropriate fractions were collected and concentrated to provide 0.93 g (79%) of product. The product was dissolved in ethyl acetate and the solution was washed with 10% sodium hydroxide solution. The layers were separated, and the organic layer was concentrated *in vacuo*. Recrystallization of the residue from methanol gave the analytical sample, mp 174-175°C.

Analysis:

Calculated for $C_{17}H_{19}FN_4O_2$:	61.81%C	5.80%H	16.96%N
Found:	61.41%C	5.67%H	16.91%N

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EXAMPLE 57(8-Chloro-4-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine.

Lithium aluminum hydride (3.3 g) was added portionwise to a suspension of N-[2-(5-chloro-2-methoxyphenyl)ethylidene]-N-pyridin-4-ylhydrazine hydrochloride (13.4 g) in tetrahydrofuran (215 mL) at 0°C. The reaction mixture was stirred at ambient temperature for 2 hrs, and sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was concentrated to provide 11.8 g of N-[2-(5-chloro-2-methoxyphenyl)ethyl]-N-pyridine-4-ylhydrazine, as an oil.

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A solution of N-[2-(5-chloro-2-methoxyphenyl)ethyl]-N-pyridine-4-ylhydrazine (11.8 g) and chloromethyl methyl ether (3.8 g) in acetic acid (170 mL) was heated under reflux for 2 hrs and then cooled to 0°C. Sodium hydroxide solution (50 %) was added, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 10% methanol/ethyl acetate. The appropriate fractions were collected and concentrated to provide 6.54 g (52%) of product. Recrystallization from ethyl acetate provided the analytical sample, mp 152-154°C (dec).

10 Analysis:

Calculated for C ₁₅ H ₁₆ ClN ₃ O:	62.18%C	5.57%H	14.50%N
Found:	61.95%C	5.63%H	14.24%N

EXAMPLE 58

15 8-Chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-4-yl dimethyl carbamate.

Dimethyl carbamoyl chloride (0.54 g) was added dropwise to a mixture of (8-chloro-4-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-4-pyridinyl amine (1.5 g), triethylamine (2.1 g) and dimethylaminopyridine (0.10 g) in chloroform (56 mL), at ambient temperature. The reaction mixture was heated under reflux for 5 hrs, cooled and poured into saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on a Chromatotron, eluting with 2% triethylamine/23% methanol/75% ethyl acetate. The appropriate fractions were collected and concentrated to provide 0.64 g (44%) of product. Recrystallization from ethyl acetate gave (0.4 g) analytical sample (0.4 g), mp 193-194°C.

Analysis:

Calculated for C ₁₇ H ₁₉ ClN ₄ O ₂ :	58.87%C	5.52%H	16.15%N
Found:	58.73%C	5.47%H	16.17%N

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EXAMPLE 595-Bromo-2-(pyridin-4-yl)amino-1,2,3,4-tetrahydroisoquinolin-8-ol.

To a slurry of 5-bromo-8-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinoline
5 (2.9 g) in dichloromethane (25 ml) was cooled to -78°C, and boron tribromide (2.5 ml)
was added. The reaction mixture was warmed to ambient temperature, stirred for 1.5
hrs, cooled to -78°C, and methanol (50 ml) was added. The mixture was evaporated
to dryness *in vacuo*, and the residue was triturated with methanol/ethyl ether. The
solid was collected to yield product 2.1 g (60.3%) as the hydrobromide salt. The
10 mother liquors were basified with aqueous sodium hydrogen carbonate and extracted
into 4:1 chloroform /2-propanol. The layers were separated, and the organic layer
was concentrated. The residue was chromatographed over silica gel, eluting with 1%
triethylamine, 5% methanol, 94% ethyl acetate; ending with 1% triethylamine, 20%
methanol, 79% ethyl acetate. The appropriate fractions were collected and
15 concentrated to yield 0.8 g (26%) of product. Trituration with methanol gave the
analytical sample, mp 255-256°C.

Analysis:

Calculated for C ₁₄ H ₁₄ BrN ₃ O:	52.52%C	4.41%H	13.12%N
Found:	52.18%C	4.66%H	12.67%N

20

EXAMPLE 605-Bromo-2-(4-Pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate.

Dimethyl carbamoyl chloride (0.66 ml) was added dropwise to a mixture of
5-bromo-2-(pyridin-4-yl)amino-1,2,3,4-tetrahydro isoquinolin-8-ol (2.1 g) and
25 triethylamine (5 ml) in chloroform (50 ml), at ambient temperature. The reaction
mixture was heated under reflux for 0.5 hr, stirred at ambient temperature overnight,
and sodium bicarbonate solution and chloroform were added. The layers were
separated and the organic layer was washed with water and brine, dried over
anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The
30 residue was chromatographed on silica gel, eluting with 1% triethylamine, 5%
methanol, 94% ethyl acetate to 1% triethylamine, 20% methanol, 79% ethyl acetate.
The appropriate fractions were collected and evaporated to yield 0.7 g (34%) of
product. Recrystallization from methanol gave the analytical sample, mp 182-183°C.

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Analysis:

Calculated for C ₁₇ H ₁₉ BrN ₄ O ₂ :	52.19%C	4.89%H	14.32%N
Found:	52.19%C	4.67%H	14.15%N

5

EXAMPLE 61(5-Benzyloxy-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine.

Lithium aluminum hydride (4.3 g) was added portionwise at 0°C to a suspension of N-[2-(2-benzyloxy-5-methoxyphenyl)ethylidene]-N-pyridin-4-ylhydrazine (13.2 g) in tetrahydrofuran (330 mL). The reaction mixture was stirred overnight at ambient
10 temperature, and sodium sulfate decahydrate was added. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 1% triethylamine/2% methanol/97% ethyl acetate and 1% triethylamine/5% methanol/94% ethyl acetate. The appropriate fractions were collected and concentrated to yield product 12.0 g of
15 N-[2-(2-benzyloxy-5-methoxyphenyl)ethyl]-N-pyridinyl-4-hydrazine.
A solution of N-[2-(2-benzyloxy-5-methoxyphenyl)ethyl]-N-pyridinyl-4-hydrazine (12.0 g) and chloromethyl methyl ether (2.9 ml) in acetic acid (150 ml) was heated under reflux for 1 hr. The reaction mixture was cooled, poured onto ice, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The
20 combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed eluting with 1% triethylamine/2% methanol/97% ethyl acetate to 1% triethylamine/4% methanol/95% ethyl acetate. The appropriate fractions were collected and evaporated to provide 5.8 g (46.4 %) of product. Recrystallization
25 from ethyl acetate gave the analytical sample, mp 151-152°C.

Analysis:

Calculated for C ₂₂ H ₂₃ N ₃ O ₂ :	73.11%C	6.41%H	11.63%N
Found:	72.84%C	6.38%H	11.57%N

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EXAMPLE 625-Fluoro-2-(pyridin-4-ylamino)-1,2,3,4-tetrahydroisoquinolin-8-ol hydrobromide.

To a solution of

- 5 (5-fluoro-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-pyridin-4-yl-amine (4.82 g) and dichloromethane (100 ml) at -78° C, boron tribromide (5.5 ml) was added, with stirring. The reaction mixture was warmed to ambient temperature, stirred for 3 hrs, and methanol (100 ml) was added. The mixture was stirred for 1 hr and concentrated *in vacuo*. The residue was recrystallized from 2-propanol to yield 4.45
- 10 g (74%) of product, mp 266°C.

Analysis:

Calculated for C ₁₄ H ₁₅ BrFN ₃ O:	49.43%C	4.44%H	12.35%N
Found:	49.34%C	4.30%H	12.33%N

15

EXAMPLE 632-(4-Pyridinylamino)-2,3,4,5-tetrahydro-1H-Benzo[c]azepine-7,8-diol Hydrochloride.

To a solution of [7-methoxy-8-hydroxy-1,3,4,5-tetrahydrobenzo

[c]azepine-2-yl]pyridin-4-ylamine hydrochloride (1.0 g) in dichloromethane (10 mL) was slowly added boron tribromide (2.32 g), at 0° C. The reaction mixture was

20 allowed to warm to ambient temperature, stirred overnight, methanol was added, and the solution was concentrated *in vacuo*. The residue was washed with saturated sodium bicarbonate solution and filtered. The filtrate crystallized. The precipitate was collected, washed with hydrochloric acid, and recrystallized from ethyl acetate-methanol to afford 425 mg (45%) of product. Trituration with hot

25 dichloromethane gave the analytical sample, mp 240°C (decomp.).

Analysis:

Calculated for C ₁₅ H ₁₈ ClN ₃ O ₂ :	58.54%C	5.89%H	13.65%N
Found:	58.00%C	5.78%H	13.54%N

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EXAMPLE 64

2-(4-Pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate fumarate.
5-Bromo-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate
5 (0.22 g) was dissolved in ethanol (10 ml) and slowly added to 10%
palladium-on-carbon (0.022 g). The mixture was hydrogenated at 50 psi overnight in
a parr shaker at ambient temperature. The reaction mixture was filtered through a
pad of Celite, and the pad was washed with methanol. The filtrate was concentrated.
The residue was basified with sodium hydrogen carbonate solution and extracted
10 with ethyl acetate. The extracts were dried over anhydrous magnesium sulfate,
filtered, and the filtrate was concentrated. The residue was chromatographed on a
Chromatotron, eluting with 1% triethylamine/5% methanol/94% ethyl acetate. The
appropriate fractions were collected and concentrated. The residue was dissolved in
hot methanol, and fumaric acid, dissolved in methanol, was added. The mixture was
15 concentrated to one-half of its original volume, and several drops of ethyl ether were
added. The precipitate was collected and dried to give 0.12 g (69%) of product, mp
201-202°C.

Analysis:

Calculated for C ₂₁ H ₂₄ N ₄ O ₆ :	58.87%C	5.65%H	13.08%N
20 Found:	58.56%C	5.64%H	12.87%N

EXAMPLE 65

8-Methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-5-ol hydrochloride.
(5-Benzyloxy-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine (2.5 g) was
25 dissolved in methanol (60 ml) and slowly added to 10% palladium-on-carbon (0.4 g).
Cyclohexene (14.5 ml) was added, and the mixture was heated under reflux, under
nitrogen, for 4 hrs. The reaction mixture was filtered through a pad of Celite, and the
pad was washed with methanol. The filtrate was concentrated, and the residue was
dissolved in a small amount of 2-propanol. Ethanolic hydrochloric acid was added
30 until the solution was acidic. The precipitate was collected to yield product 0.32 g
(15.1%) mp 274-276°C (dec). The mother liquor was basified with sodium
bicarbonate solution and extracted with 2-propanol/chloroform (1:4). The layers were
separated, and the organic layer was washed with water and brine, dried over

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anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica dioxide, eluting with 1% triethylamine, 5% methanol, 94% ethyl acetate to 1% triethylamine, 20% methanol, 79% ethyl acetate to yield 1.4 g (90% overall yield) of product.

5 Analysis:

Calculated for C ₁₅ H ₁₈ ClN ₃ O ₂ :	58.54%C	5.89%H	13.65%N
Found:	58.31%C	5.95%H	13.37%N

EXAMPLE 66

10 (7-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine.

To a mixture of lithium aluminum hydride (1.42 g) and dry tetrahydrofuran (50 ml), under nitrogen 7-methoxy-2-(4-pyridinylamino)-4H-isoquinoline-1,3-dione hydrochloride hemihydrate (4.10 g) was added in portions, with rapid stirring, at ambient temperature. The reaction mixture was stirred at ambient temperature,
 15 under nitrogen, for 4 hrs, and sodium sulfate decahydrate was added in portions. The mixture was filtered through a bed of celite, the filter cake washed thoroughly with ethyl acetate, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with 7% methanol-dichloromethane followed by 185:14:1 dichloromethane:methanol:ammonium hydroxide. The appropriate
 20 fractions were collected and evaporated. Absolute ethanol was added to the residue, the precipitate was collected and dried under vacuum at 80°C overnight to give 300 mg (9%) of product, mp 188-189°C.

Analysis:

Calculated for C ₁₅ H ₁₇ N ₃ O:	70.56%C	6.71%H	16.46%N
25 Found:	70.08%C	6.59%H	16.26%N

EXAMPLE 67

2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl dimethylcarbamate.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-5-ol (1.20 g),
 30 triethylamine (1.18 g) and chloroform (10 ml), dimethylcarbamoyl chloride (681 mg) in chloroform (10 ml) was added dropwise, with stirring, under nitrogen, at ambient temperature,. The reaction mixture was heated under reflux for 2 hrs, poured into dilute sodium bicarbonate solution and the layers were separated. The aqueous

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phase was extracted with chloroform, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica, eluting with 10-15% methanol-dichloromethane. The appropriate fractions were collected and concentrated. The residue was chromatographed over silica, eluting with 7% methanol:dichloromethane followed by 185:14:1 dichloromethane:methanol:ammonium hydroxide. The appropriate fractions were collected and concentrated to give 1.15 g (73%) of product. Recrystallization from ethyl acetate gave 550 mg (35%) of product, (dried under vacuum at 80°C) mp 134-135°C.

Analysis:

Calculated for C ₁₆ H ₁₈ N ₄ O ₂ :	64.41%C	6.08%H	18.78%N
Found:	64.08%C	6.00%H	18.53%N

15

EXAMPLE 682,3-Dihydro-5-fluoro-N-(4-pyridinyl)-1H-isoindol-2-amine hydrochloride 1/8 hydrate.

A mixture of 4-fluorophthalic anhydride (5.99 g), 4-pyridinylhydrazine hydrochloride (5.00 g), and glacial acetic (30 ml) acid was stirred under reflux, under nitrogen, for 4 hrs. The reaction mixture was evaporated, and the residue was azeotroped with heptane. The residue was dried *in vacuo* to give 4-fluoro-2-(4-pyridinylamino)-isoindol-1,3-dione. To a mixture of lithium aluminum hydride (3.91 g) and dry tetrahydrofuran (100 ml), 2,3-dihydro-5-fluoro-2-(4-pyridinylamino)isoindole-1,3-dione hydrochloride was added in portions with rapid stirring, under nitrogen, at ambient temperature. The reaction mixture was stirred under nitrogen, overnight, at ambient temperature, and sodium sulfate decahydrate was added in portions. The mixture was filtered through a bed of celite, the filter cake was washed with ethyl acetate and concentrated *in vacuo*. The residue was chromatographed over silica gel, eluting with 7% methanol-dichloromethane, followed by 185:14:1 dichloromethane:methanol:ammonium hydroxide. The appropriate fractions were collected and evaporated. The residue was dissolved in absolute ethanol, excess concentrated hydrochloric acid was added, and the mixture was evaporated. The residue was crystallized from absolute ethanol to give 550 mg (6%) of product, (dried

under vacuum at 80°C overnight), mp 235-240°C (decomp).

Analysis:

Calculated for $C_{13}H_{12}N_3 \cdot HCl \cdot 1/8H_2O$:	58.27%C	4.98%H	15.68%N
Found:	58.11%C	4.91%H	15.96%N

5

EXAMPLE 69

2,3-Dihydro-4-fluoro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine.

To a solution of 2-(3-fluoro-4-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (34.0 g) in dry tetrahydrofuran (300 ml) sec-butyllithium (140 ml of a 1.3 M solution in cyclohexane) was added dropwise at -78°C with stirring, under nitrogen. The reaction mixture was stirred 15 mins, and carbon dioxide was bubbled below the surface. The reaction was stirred for 1 hr and water added dropwise. The mixture was basified with 10% sodium hydroxide solution and extracted with ethyl acetate. The aqueous extract was cooled to 0°C and an equal volume of concentrated hydrochloric acid was added dropwise. The solution was stirred, under reflux overnight, cooled and the solid collected. The solid was washed with cold water and dried *in vacuo* to give 26.6 g of 3-fluoro-4-methoxyphthalic acid.

A mixture of 3-fluoro-4-methoxyphthalic acid (26.6 g) in acetic anhydride (100 ml) was stirred, under reflux, under nitrogen, for 4 hrs. The reaction mixture was cooled to -60°C and filtered. The solid was collected, washed with ether and dried *in vacuo* to give 19.9 g (67%) of 3-fluoro-4-methoxyphthalic anhydride, mp 128-130°C.

A mixture of 3-fluoro-4-methoxyphthalic anhydride (10.0 g) and 4-hydrazinopyridine hydrochloride (7.42 g) in glacial acetic acid (50 ml) was stirred, under reflux, under nitrogen, for 4 hrs and stirred at ambient temperature overnight. The solid was collected, washed with ether and dried *in vacuo* at 80°C overnight to give 10.6 g (64%) of 4-fluoro-5-methoxy-2-(4-pyridinylamino)isoindol-1,3-dione.

To a mixture of lithium aluminum hydride (3.72 g) and dry tetrahydrofuran (100 ml), 4-fluoro-5-methoxy-2-(4-pyridinylamino)isoindole-1,3-dione hydrochloride (10.60 g) was added in portions with rapid stirring, under nitrogen, at ambient temperature.

The reaction mixture was stirred at ambient temperature, under nitrogen, for 3 hrs, and sodium sulfate decahydrate was added in portions. The mixture was filtered through a bed of celite, the filter pad was washed with ethyl acetate, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel,

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eluting with 7% methanol-dichloromethane followed by 185:14:1 dichloromethane:methanol:ammonium hydroxide. The residue was crystallized from absolute ethanol to give 3.2 g (8%) of product, (dried under vacuum at 80°C overnight) mp 206-210°C.

5 Analysis:

Calculated for C ₁₄ H ₁₄ FN ₃ O:	64.85%C	5.44%H	16.21%N
Found:	64.61%C	5.30%H	16.18%N

EXAMPLE 70

10 2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-5-yl
1,2,3,4-tetrahydroisoquinolin-2-ylcarbamate 1/4 hydrate.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-5-ol (1.50 g), triethylamine (1.47 g), and chloroform (15 ml), 1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl chloride (1.55 g) in chloroform (10 ml) was
 15 added dropwise with stirring, under nitrogen, at ambient temperature. The reaction mixture was stirred under reflux for 3 hrs, at ambient temperature overnight and poured into dilute sodium bicarbonate solution. The layers were separated. The aqueous phase was extracted with chloroform, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in*
 20 *vacuo*. The residue was chromatographed on silica, eluting with 7% methanol-dichloromethane followed by 185:14:1 dichloromethane-methanol-ammonium hydroxide. The appropriate fractions were collected and evaporated. The residue was recrystallized from ethanol-toluene to give 800 mg (31%) of product, mp 162-163°C.

25 Analysis:

Calculated for C ₂₃ H ₂₂ N ₄ O ₂ · 1/4H ₂ O:	70.66%C	5.80%H	14.33%N
Found:	70.63%C	5.36%H	14.17%N

EXAMPLE 71

30 2,3-Dihydro-4-fluoro-2-(-4-pyridinylamino)-1H-isoindol-5-ol hydrobromide.

A solution of 2,3-dihydro-4-fluoro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine (3.25 g) in 48% hydrobromic acid (25 ml) was stirred, under reflux, for 5 hrs. The reaction mixture was diluted with water and stirred at ambient temperature overnight.

The mixture was cooled to approximately 10°C and filtered. The filter cake was washed with cold water and dried under vacuum at 80°C to give 2.8 g (69%) of product. Recrystallization from water gave the analytical sample, mp. >250°C, dried at 80°C under vacuum.

5 Analysis:

Calculated for $C_{13}H_{13}BrFN_3O$:	47.87%C	4.02%H	12.88%N
Found:	47.82%C	3.85%H	12.81%N

EXAMPLE 72

10 2-(4-Pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-ol.

A mixture of 7-benzyloxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinoline (5.68 g) and 5% palladium-on-carbon (1.1 g) in methanol (85 mL) was shaken on a parr hydrogenation apparatus at ambient temperature, starting at an initial pressure of 55 psi. After 2 hrs an additional 1.1 g of catalyst was added, the pressure was
 15 increased to 55 psi, and the mixture was shaken for an additional 5 hrs. An additional 0.75 g of catalyst was added, the pressure was increased to 55 psi, and the mixture was shaken until hydrogen uptake ceased. The reaction mixture was filtered through a pad of Celite, and the pad was washed with methanol. Concentration of the filtrate gave 3.4 g (82%) of product. Recrystallization from
 20 ethanol gave the analytical sample, mp 236-239°C (dec).

Analysis:

Calculated for $C_{14}H_{15}N_3O$:	69.69%C	6.27%H	17.41%N
Found:	69.37%C	6.18%H	17.16%N

25

EXAMPLE 73

8-Chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-5-ol hydrobromide.

Boron tribromide (12.7 g) was added dropwise to a solution of (8-chloro-5-methoxy-3,4-dichloro-1H-isoquinolin-2-yl)-4-pyridinylamino (4.46 g) in dichloromethane (155 mL) at -78°C. The reaction mixture was stirred at ambient
 30 temperature for 3 hrs. The mixture was cooled to -78°C, and methanol (100 mL) was added. The mixture was stirred at ambient temperature for 1 hr and concentrated *in vacuo*. The residue was washed with methanol/ethyl ether to provide 4.6 g of product. A sample (2.5 g) was recrystallized from methanol to give 0.86 g (34%) of

the analytical sample of the product, mp>260°C.

Analysis:

Calculated for C ₁₄ H ₁₅ BrClN ₃ O:	47.15%C	4.24%H	11.78%N
Found:	46.76%C	4.06%H	11.46%N

5

EXAMPLE 74

(5-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine dihydrochloride.

Lithium aluminum hydride (4.9 g) was added portionwise to a suspension of N-[2-(2-methoxyphenyl)ethylidene]-N-pyridine-4-yl hydrazine hydrochloride (18.1 g) in tetrahydrofuran (325 mL), at 0°C. The reaction mixture was stirred at ambient temperature for 4 hrs, and sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was concentrated to provide 16.4 g of N-[2-(2-methoxyphenyl)ethyl]-N-pyridin-4-ylhydrazine. A solution of N-[2-(2-methoxyphenyl)ethyl]-N-pyridin-4-ylhydrazine (16.4 g) and chloromethyl methyl ether (5.76 g) in acetic acid (260 mL) was heated, under reflux, for 2 hrs, and the mixture was cooled to 0°C. Sodium hydroxide solution (50%) was added, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with 10% methanol/ethyl acetate. The appropriate fractions were collected and concentrated to provide 9.4 g (57%) of product as the free base. The product free base was dissolved in methanol and ethereal hydrogen chloride was added. The precipitate was collected to give 1.0 g of product, mp 181-187°C (dec).

Analysis:

Calculated for C ₁₅ H ₁₉ Cl ₂ N ₃ O:	54.89%C	5.83%H	12.80%N
Found:	54.90%C	5.78%H	12.75%N

EXAMPLE 75

(7-Benzyloxy-5-bromo-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine hydrochloride.

Lithium aluminum hydride (5.4 g) was added portionwise at 0°C to a suspension of N-[2-(4-benzyloxy-2-bromo-5-methoxyphenyl)ethylidene]-N-pyridin-4-ylhydrazine hydrochloride (26.0 g) in tetrahydrofuran (360 mL). The reaction mixture was stirred

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at ambient temperature for 3 hrs, and sodium sulfate decahydrate was added. The mixture was filtered, and the filtrate was concentrated to provide 24.3 g of N-[2-(4-benzyloxy-2-bromo-5-methoxyphenyl)ethyl]-N-pyridine-4-ylhydrazine.

A solution of N-[2-(4-benzyloxy-2-bromo-5-methoxyphenyl)ethyl]-N-pyridine-4-yl

5 hydrazine (24.3 g) and chloromethyl methyl ether (5.0 g) in acetic acid (225 mL) was heated under reflux for 2 hrs and cooled to 0°C. Sodium hydroxide solution (50%) was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was triturated with ethyl
10 acetate. The solid was collected and the filtrate was concentrated. The residue was chromatographed on silica, eluting with 10% methanol/ethyl acetate. The appropriate fractions were collected and concentrated to provide 8.1 g (33%) of product. The solid was dissolved in methanol and ethereal hydrogen chloride was added. The precipitate was collected to give the analytical sample, mp 235-237°C (dec).

15 Analysis:

Calculated for C ₂₂ H ₂₃ ClBrN ₃ O ₂ :	55.42%C	4.86%H	8.81%N
Found:	55.32%C	4.74%H	8.64%N

EXAMPLE 76

20 N-[2-(3-Fluoro-4-methoxyphenyl)ethylidene]-N'-pyridin-4-yl-hydrazine hydrochloride.

A mixture of 2-fluoro-1-methoxy-4-(2-methoxyvinyl)benzene (20.0 g), 4-hydrazinopyridine (17.6 g), p-toluenesulfonic acid (1.0 g) and ethanol (mL) was heated under reflux for 6 hrs. The reaction mixture was cooled, filtered, and concentrated *in vacuo*. The residue was triturated with a mixture of methanol and
25 ether. The solid was collected to give 18.1 g (55%) of product. Recrystallization from ethanol gave the analytical sample, mp 189-191°C.

Analysis:

Calculated for C ₁₄ H ₁₅ ClFN ₃ O:	56.86%C	5.11%H	14.21%N
Found:	56.79%C	4.96%H	14.14%N

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EXAMPLE 772-(5-Chloro-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole.

To a solution of 5-chloro-o-anisic acid (50 g) in toluene (100 mL) was added thionyl chloride (50 mL). The reaction mixture was heated under reflux for 2 hrs and distilled using a short path distillation apparatus to give 5-chloro-o-anisyl chloride, which was used in the next step. To a solution of 2-amino-2-methyl-1-propanol (38 mL) in dichloromethane (200 mL) was added a solution of 5-chloro-o-anisyl chloride in dichloromethane (150 mL) dropwise. The reaction mixture was stirred at ambient temperature for 1 hr, dichloromethane was added and the mixture was washed with 2 N hydrochloric acid. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo* to give N-(2-(1-hydroxy-2-methylpropyl)-5-chloro-2-methoxy benzamide, which was used in the next step. To N-(2-(1-hydroxy-2-methylpropyl)-5-chloro-2-methoxy benzamide was added thionyl chloride (40 mL) at 0° C. The reaction mixture was stirred for 30 min, warmed to ambient temperature, diluted with diethyl ether (200 mL), and the mixture was stirred for 10 mins. The mixture was decanted, 10% sodium hydroxide solution was added, and the mixture was extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo* to afford 41 g (64%) of product, mp 50-51° C.

Analysis:

Calculated for C ₁₂ H ₁₄ ClNO ₂ :	60.13%C	5.89%H	5.84%N
Found:	60.03%C	5.90%H	5.77%N

EXAMPLE 784-Chloro-7-methoxyisobenzofuran-1,3-dione.

To a solution of 2-(5-chloro-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (40.0 g) in tetrahydrofuran (250 mL) was added s-butyllithium (154 mL) at -78° C. The solution was stirred for 45 mins, and carbon dioxide was bubbled into the solution for 2 hrs. Water and ethyl acetate (500 mL) were added and the mixture was washed with 10% sodium hydroxide solution (500 mL). The aqueous phase was acidified with conc hydrochloric acid, and the mixture was heated under reflux for 12 hrs, cooled, and concentrated *in vacuo* to 1/3 the original volume. The precipitate was

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collected, washed with water and dried under vacuum to afford 3.43 g (10%) of product, mp 192-193°C.

Analysis:Calculated for C₉H₅ClO₄:

50.85%C 2.37%H

5 Found:

50.85%C 2.22%H

EXAMPLE 792,3-Dihydro-4-chloro-7-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine.

To a slurry of 4-chloro-7-methoxyisobenzofuran-1,3-dione (3.3 g) in acetic acid (25 mL) was added 4-hydrazinopyridine hydrochloride (2.25 g). The reaction mixture was heated under reflux for 3 hrs, cooled to 0°C, diluted with ethyl acetate and filtered. The filtrate was evaporated. The residue was dried to afford 4.24 g of 4-chloro-7-methoxyphthalimide.

To a solution of 4-chloro-7-methoxyphthalimide (4.24 g) in tetrahydrofuran (50 mL) was added lithium aluminum hydride (1.38 g) in small portions, at ambient temperature. The reaction mixture was stirred for 3 hrs, and sodium sulfate decahydrate was added. The mixture was diluted with ethyl acetate (200 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over silica gel, eluting with dichloromethane:methanol (9:1). The appropriate fractions were collected and evaporated to afford 1.75 g of product, free base. The product free base was dissolved in a minimum amount of ethanol and conc hydrochloric acid was added. Ethyl acetate and heptane were added to afford 1.38 g of product, mp 229-230°C.

Analysis:25 Calculated for C₁₄H₁₅Cl₂N₃O:

53.86%C 4.84%H 13.46%N

Found:

53.80%C 4.60%H 13.41%N

EXAMPLE 80

30 2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl N-benzyl-N-methylcarbamate hydrochloride hemihydrate.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.50 g), triethylamine (1.47 g) and chloroform (15 ml), N-benzyl-N-methylcarbamyl chloride (1.55 g) in chloroform (10 ml) was added dropwise, with stirring, at ambient

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temperature, under nitrogen. The reaction mixture was stirred under reflux for 3 hrs, at ambient temperature overnight and poured into dilute sodium bicarbonate solution (100 ml). The layers were separated. The aqueous phase was extracted with chloroform and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica, eluting with 7% methanol-dichloromethane followed by 185:14:1 methanol-dichloromethane-ammonium hydroxide. The appropriate fractions were collected and concentrated to give 1.35 g of product, free base. The product free base was dissolved in absolute ethanol and hydrogen chloride was added. Ether was added, and the mixture was cooled. The precipitate was collected to give 650 mg (23%) of product, mp 128-132°C.

Analysis:

Calculated for C ₂₂ H ₂₃ ClN ₄ O ₂ :	62.93%C	5.76%H	13.34%N
Found:	62.96%C	5.57%H	13.45%N

EXAMPLE 81N-[2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)ethylidene]-N'-pyridin-4-yl-hydrazine hydrochloride.

A mixture of 5-benzyloxy-2-bromo-4-methoxy-3-(2-methoxyvinyl)benzene (42.1 g), 4-hydrazinopyridine hydrochloride (19.0 g), p-toluenesulfonic acid (0.23 g) and ethanol (350 ml) was heated under reflux overnight, with stirring. The reaction mixture was cooled and filtered. Recrystallization of the precipitate from methanol yielded 40.2 g, (72.2%) of product, mp 232-233°C.

Analysis:

Calculated for C ₂₁ H ₂₁ BrClN ₃ O ₂ :	54.50%C	4.57%H	9.08%N
Found:	54.36%C	4.41%H	8.95%N

EXAMPLE 82(3,4-Dihydro-8-benzyloxy-5-bromo-7-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine fumarate.

Lithium aluminum hydride (10.7 g) was added portionwise at 0°C to a suspension of N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)ethylidene]-N-pyridin-4-ylhydrazine hydrochloride (39.4 g) in tetrahydrofuran (1 L). The reaction mixture was stirred

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overnight at ambient temperature, and sodium sulfate decahydrate was added. The mixture was filtered and the filtrate was concentrated to provide (27.7 g) of N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)ethyl]-N-pyridin-4-yl)hydrazine.

A solution of

- 5 N-[2-(5-benzyloxy-2-bromo-4-methoxyphenyl)ethyl]-N-pyridin-4-ylhydrazine (27.7 g) and chloromethyl methyl ether (5.4 ml) in acetic acid (400 ml) was heated under reflux for 1.5 hrs, under nitrogen. The reaction mixture was cooled and poured onto ice. 2 N Sodium hydroxide solution was added to neutrality, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water
10 and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with 1% triethylamine/2% methanol/97% ethyl acetate 1% triethylamine/4% methanol/95% ethyl acetate. The appropriate fractions were collected and evaporated to provide 12.5 g of product (44% overall yield). The fumarate salt was prepared from methanol
15 and fumaric acid and had mp 186-187°C.

Analysis:

Calculated for C ₂₆ H ₂₆ BrN ₃ O ₆ :	56.12%C	4.71%H	7.55%N
Found:	55.78%C	4.23%H	7.29%N

20

EXAMPLE 83

7-Methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-ol hydrobromide.

- (8-Benzyloxy-5-bromo-3,4-dihydro-7-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine)
(11 g) was dissolved in ethanol (250 ml) and slowly added to 5%
palladium-on-carbon (2.2 g). The mixture was hydrogenated at 55 psi overnight in a
25 parr shaker at ambient temperature. The reaction mixture was filtered through a pad of Celite, and the pad was washed well with methanol. The filtrate was concentrated, and the precipitate was collected and dried to give 8.3 g, 94.6% of product, mp 235-236°C.

Analysis:

30 Calculated for C ₁₅ H ₁₈ BrN ₃ O ₂ :	51.15%C	5.15%H	11.93%N
Found:	51.07%C	4.93%H	11.82%N

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EXAMPLE 84

7-Methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate fumarate.

5 Dimethyl carbamoyl chloride (0.6 ml) was added dropwise to a mixture of 7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinoline-8-ol) hydrobromide (1.5 g) and triethylamine (2.5 ml) in chloroform (75 ml) at ambient temperature. The reaction mixture was heated under reflux overnight, cooled, and diluted with sodium bicarbonate solution and chloroform. The layers were separated and the organic
10 layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with 1% triethylamine, 5% methanol, 94% ethyl acetate to 1% triethylamine, 20% methanol, 79% ethyl acetate. The appropriate fractions were collected and concentrated to yield 1.1 g (75%) of product. The fumarate was
15 prepared from fumaric acid and methanol and had mp 176-177°C.

Analysis:

Calculated for C ₂₂ H ₂₆ N ₄ O ₇ :	57.64%C	5.72%H	12.22%N
Found:	57.53%C	5.72%H	12.04%N

20

EXAMPLE 85

2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl diethylcarbamate hydrochloride.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.50 g), triethylamine (1.47 g) and chloroform (15 ml), diethylcarbamyl chloride (1.07 g) in chloroform (10 ml) was added dropwise, with stirring at ambient temperature, under
25 nitrogen. The reaction mixture was stirred under reflux for 5 hrs, at ambient temperature overnight, and poured into dilute sodium bicarbonate solution (100 ml). The layers were separated. The aqueous phase was extracted with chloroform, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was flash chromatographed
30 (silica), eluting with 7% methanol-dichloromethane followed by 185:14:1 dichloromethane-methanol-ammonium hydroxide. The appropriate fractions were collected and evaporated. The residue was dissolved in absolute ethanol and treated with excess ethereal hydrogen chloride. The precipitate was recrystallized

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from ethanol-ether to give 1.20 g (50%) of product, mp 213-215°C (dec).

Analysis:

Calculated for C ₁₈ H ₂₃ ClN ₄ O ₂ :	59.58%C	6.39%H	15.44%N
Found:	59.48%C	6.47%H	15.06%N

5

EXAMPLE 86

2,3-Dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl dimethylcarbamate hydrochloride.

To a mixture of 2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-ol
 10 hydrobromide (600 mg), triethylamine (614 mg), and chloroform (10 ml),
 dimethylcarbamy l chloride (237 mg) in chloroform (5 ml) was added dropwise, with
 stirring at ambient temperature, under nitrogen. The reaction mixture was stirred
 under reflux for 5 hrs, at ambient temperature overnight and poured into dilute
 sodium bicarbonate solution (100 ml). The layers were separated. The aqueous
 15 phase was extracted with chloroform, and the combined organic layers were dried
 over anhydrous magnesium sulfate, filtered, and the filtrate was evaporated *in vacuo*.
 The residue was flash chromatographed (silica), eluting with 7%
 methanol-dichloromethane followed by 185:14:1
 dichloromethane-methanol-ammonium hydroxide. The appropriate fractions were
 20 collected and evaporated. The residue was dissolved in absolute ethanol and excess
 ethereal hydrogen chloride was added. Ether was added and the solution was
 cooled. The precipitate was collected to give 450 mg (69%) of product, mp
 250-252°C (dec).

Analysis:

25	Calculated for C ₁₆ H ₁₈ ClFN ₄ O ₂ :	54.47%C	5.14%H	15.88%N
	Found:	54.30%C	5.08%H	15.60%N

EXAMPLE 87

2,3-Dihydro-4-chloro-2-(4-pyridinylamino)-1H-isoindol-7-ol dihydrobromide.

30 To a solution of 2,3-dihydro-4-chloro-7-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine
 hydrochloride (1.12 g) in dichloromethane (10 mL) was added boron tribromide (1.0
 mL) at 0°C. The solution was warmed to ambient temperature and stirred for 3
 days. Methanol was added, and the mixture was filtered to give 1.2 g (79%) of

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product, mp >240°C (decomp).

Analysis:

Calculated for C ₁₃ H ₁₄ ClBr ₂ N ₃ O:	36.87%C	3.33%H	9.92%N
Found:	36.29%C	3.15%H	9.70%N

5

EXAMPLE 88

2,3-Dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl

1,2,3,4-tetrahydroisoquinolin-2-ylcarbamate hydrochloride.

To a mixture of 2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-ol
 10 hydrobromide (655 mg), triethylamine (671 mg), and chloroform (10 ml),
 1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl chloride (471 mg) in chloroform (5 ml) was
 added dropwise, with stirring at ambient temperature, under nitrogen. The reaction
 mixture was stirred under reflux for 5 hrs, at ambient temperature overnight and
 poured into dilute sodium bicarbonate solution (100 ml). The layers were separated.
 15 The aqueous phase was extracted with chloroform, and the combined organic layers
 were dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in*
vacuo. The residue was flash chromatographed (silica), eluting with 7%
 methanol-dichloromethane followed by 185:14:1
 dichloromethane-methanol-ammonium hydroxide to give 800 mg of product. The
 20 appropriate fractions were collected and evaporated. The residue was dissolved in
 absolute ethanol and excess ethereal hydrogen chloride was added. Ether was
 added and the mixture was cooled. The precipitate was collected to give 750 mg
 (85%) of product, mp >260°C.

Analysis:

25 Calculated for C ₂₃ H ₂₂ FN ₄ O ₂ :	62.66%C	5.03%H	12.71%N
Found:	62.22%C	4.99%H	12.59%N

EXAMPLE 89

2-(4-pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-5-ol hydrobromide monohydrate.

30 Boron tribromide (22.6 g) was added dropwise to a solution of
 4-methoxy-3,4-dihydro-1H-isoquinoline-2-yl-4-pyridinylamine (7.0 g) in
 dichloromethane (275 mL) at -78°C. The dry ice bath was removed, and the
 suspension was stirred at ambient temperature for 3 hrs. The reaction mixture was

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cooled to -78°C , methanol (150 mL) was added, and the mixture was stirred at ambient temperature for 1 hr and concentrated *in vacuo*. The residue was washed with methanol/ethyl ether to provide 8.4 g (95%) of product. Recrystallization from 2-propanol gave the analytical sample, mp $248-252^{\circ}\text{C}$ (dec).

5 Analysis:

Calculated for $\text{C}_{14}\text{H}_{18}\text{BrN}_3\text{O}_2$:	49.42%C	5.33%H	12.35%N
Found:	49.16%C	4.96%H	12.10%N

EXAMPLE 9010 3,4-Dihydro-1H-isoquinolin-2-carboxylic acid-7-methoxy-2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl ester hydrochloride.

To a solution of

[7-methoxy-8-hydroxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-pyridin-4-yl amine hydrochloride (500 mg) in chloroform (10 mL) was added

15 1,2,3,4-tetrahydroisoquinoline-2-yl carbonyl chloride (362 mg) followed by triethylamine (0.75 mL). The reaction mixture was heated under reflux for 3 hrs, cooled to ambient temperature, diluted with dichloromethane (200 mL), and the mixture was washed with saturated sodium bicarbonate solution. The organic phase was separated, dried under anhydrous magnesium sulfate, filtered, and the filtrate
20 was concentrated *in vacuo*. The residue was flash chromatographed over silica gel, eluting with chloroform:methanol (9:1). The appropriate fractions were collected and evaporated. The residue was dissolved in methanol and conc hydrochloric acid was added. The precipitate was collected and crystallized from ethyl acetate-petroleum ether to give 230 mg of product, mp $> 100^{\circ}\text{C}$ (dec).

25 Analysis:

Calculated for $\text{C}_{26}\text{H}_{29}\text{ClN}_4\text{O}_3$:	64.93%C	6.08%H	11.65%N
Found:	64.48%C	6.02%H	11.21%N

EXAMPLE 9130 2,3-Dihydro-4-chloro-2-(4-pyridylamino)-1H-isoindol-7-yl dimethyl carbamate hydrochloride.

To a solution of 2,3-dihydro-4-chloro-2-(4-pyridinylamino)-1H-isoindol-7-ol dihydrobromide (600 mg) in chloroform (10 mL), dimethylcarbonyl chloride (156 mL)

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followed by triethylamine (0.68 mL) was added. The reaction mixture was heated under reflux for 4 hrs, cooled to ambient temperature and stirred for two days.

Dichloromethane (100 mL) was added and the solution was washed with saturated sodium bicarbonate solution. The organic phase was separated, dried over

5 anhydrous magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*.

The residue was flash chromatographed over silica gel, eluting with 10% methanol in dichloromethane. The residue was dissolved in methanol and conc hydrochloric acid was added. The mixture was concentrated in vacuo, the precipitate was collected and recrystallized from dichloromethane-methanol to give 285 mg (54%) of product,
10 >200°C (dec).

Analysis:

Calculated for C₁₆H₁₇ClN₄O₂ HCl: 52.05%C 4.91%H 15.17%N

Found: 51.88%C 4.59%H 15.04%N

15

EXAMPLE 92

2,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl 4-(2-pyridinyl)-1-piperazinyl-carbamate 1/4 hydrate.

To a mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.50 g),

triethylamine (1.47 g) and chloroform (15 ml), 4-(2-pyridinyl)-1-piperazinylcarbonyl

20 chloride (1.79 g) in chloroform (10 ml) was added dropwise, with stirring at ambient temperature, under nitrogen. The reaction mixture was heated under reflux for 3 hrs, stirred at ambient temperature, under nitrogen, overnight and poured into dilute sodium bicarbonate solution. The layers were separated. The aqueous phase was extracted with chloroform, and the combined organic layers were dried over

25 anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was flash chromatographed on silica, 185:14:1

dichloromethane:methanol:ammonium hydroxide. The appropriate fractions were collected and evaporated. The residue was chromatographed (silica), eluting with

192:7:1 ethyl acetate:methanol:ammonium hydroxide. The appropriate fractions

30 were collected and evaporated to give 450 mg (16%) of product. Recrystallization from ethyl acetate-ether gave the analytical sample, mp 98-101°C.

Calculated for $C_{23}H_{24}N_6O_2 \cdot 1/4H_2O$:	65.62%C	5.87%H	19.96%N
Found:	65.70%C	5.49%H	20.07%N

2,3-Dihydro-4-fluoro-2-(-4-pyridinylamino)-1H-isoindol-5-ol hydrobromide.

A solution of 2,3-dihydro-4-fluoro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine (3.25 g, 12.53 mmol) in 25 ml of 48% hydrobromic acid is stirred at reflux for five hours. The reaction is diluted with 25 ml of water and allowed to stir at room temperature overnight. The mixture is cooled to approximately 10°C and filtered. The solid is washed with cold water and dried under vacuum in an oven at 80°C to give 2.8 g (69%) of the hydrobromide as tan crystals. 500 mg of this material is recrystallized from water and dried under vacuum at 80°C to give 300 mg (60% recovery) of white crystals, m.p. >250°C.

Calc. for $C_{13}H_{12}FN_3O \cdot HBr$:	47.87%C	4.02%H	12.88%N
Found:	47.82%C	3.85%H	12.81%N

2-(4-Pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-7-ol.

A mixture of benzyl ether (5.68 g, 17.1 mmol) and 5% palladium on carbon (1.1 g, 50 % water by weight , Degussa type) in 85 mL of methanol is shaken on a Parr hydrogenation apparatus at room temperature starting at 55 psi. After 2 hr an additional 1.1 g of catalyst is added, the pressure is returned to 55 psi, and the mixture is shaken for an additional 5 hr. An additional 0.75 g of catalyst is added, the pressure is again returned to 55 psi and the mixture shaken until hydrogen uptake ceases. The reaction mixture is filtered through a pad of Celite and the pad is washed with a copious amount of methanol. Concentration of the filtrate provides 3.4 g (82%) of a white solid. Recrystallization from ethanol provides 1.73 g (42%) of a solid, mp=236-239°C(dec).

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Analysis:

Calc. for C ₁₄ H ₁₅ N ₃ O::	69.69%C	6.27%H	17.41%N
Found:	69.37%C	6.18%H	17.16%N

EXAMPLE 958-Chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-5-ol hydrobromide.

Boron tribromide (12.7g, 50.7 mmol) is added dropwise to a solution of the methyl ether (4.46g, 15.4 mmol) in 155 mL of dichloromethane at -78°C. The dry ice bath is removed and the suspension is stirred at room temperature for 3 hr. The reaction mixture is cooled to -78°C and quenched by the addition of 100 mL of methanol. This mixture is stirred at room temperature for 1 hr, and then the volatiles are removed *in vacuo*. The solid residue is washed with methanol/ethyl ether to provide 4.6 g of an orange solid. A sample (2.5 g) is recrystallized from methanol providing 0.86 g (34%) of a solid, mp>260°C.

Analysis:

Calc. for C ₁₄ H ₁₅ BrClN ₃ O::	47.15%C	4.24%H	11.78%N
Found:	46.76%C	4.06%H	11.46%N

EXAMPLE 96(4-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine dihydrochloride.

Lithium aluminum hydride (4.9g, 130 mmol) is added portionwise to a 0°C suspension of the hydrazone hydrochloride (18.1g, 65.1 mmol) in 325 mL of THF. The resulting mixture is stirred at room temperature for 4 hr, and then the excess LAH is destroyed by the careful addition of sodium sulfate decahydrate. Filtration and concentration of the filtrate provides 16.4 g of hydrazine as an oil which is used in the subsequent reaction without purification.

A solution of the hydrazine (65.1 mmol) and chloromethyl methyl ether (5.76 g, 71.6 mmol) in 260 mL of acetic acid is heated at reflux for 2 hr, and then the mixture is cooled to 0°C. The acetic acid is neutralized with 50 % sodium hydroxide solution, and the product is extracted into ethyl acetate. The combined organic layers are washed with water and brine, dried over MgSO₄, filtered and concentrated to leave

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16.1 g of crude product as a tan foam. Purification on a Waters LC 2000 chromatography system, eluting with 10% methanol/ethyl acetate provides 9.4 g (57%) of product as a foam. 2.4 g of the foam are dissolved in methanol and acidified with ethereal HCl solution. A solid slowly crystallizes. Filtration gives 1.0 g of product mp=181-187°C (dec).

Analysis:

Calc. for C ₁₅ H ₁₇ N ₃ O• 2HCl:	54.89%C	5.83%H	12.80%N
Found:	54.90%C	5.78%H	12.75%N

EXAMPLE 97

(6-Benzyloxy-4-bromo-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine hydrochloride.

Lithium aluminum hydride (5.4g, 143 mmol) is added portionwise to a 0°C suspension of the hydrazone hydrochloride (26.0g, 56.2 mmol) in 360 mL of THF.

The resulting mixture is stirred at room temperature for 3 hr, and then the excess LAH is destroyed by the careful addition of sodium sulfate decahydrate. Filtration and concentration of the filtrate provides 24.3 g of hydrazine as an oil which is used in the subsequent reaction without purification.

A solution of the hydrazine (56.2 mmol) and chloromethyl methyl ether (5.0 g, 61.8 mmol) in 225 mL of acetic acid is heated at reflux for 2 hr, and then the mixture is cooled to 0°C. The acetic acid is neutralized with 50 % sodium hydroxide solution, and the product is extracted into ethyl acetate. The combined organic layers are washed with water and brine, dried over MgSO₄, filtered and concentrated to leave 18.1 g of crude product as a tan solid. Recrystallization from ethyl acetate gives 4.6 g (19%) of a solid. Purification of the residue obtained by concentration of the filtrate on a Waters LC 2000 chromatography system, eluting with 10% methanol/ethyl acetate provides 8.1 g (33%) of product as a solid. 1.0 g of the recrystallized material is dissolved in methanol and acidified with ethereal HCl solution. A solid slowly crystallizes. Filtration gives 0.3 g of product mp=235-237°C (dec).

Analysis:

Calc. for C ₂₂ H ₂₂ BrN ₃ O ₂ • HCl :	55.42%C	4.86%H	8.81%N
Found:	55.32%C	4.74%H	8.64%N

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EXAMPLE 982,3-Dihydro-4-chloro-7-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine.

To a slurry of 3.3 g (15.5 mmol) of 4-chloro-7-methoxy-isobenzofuran-1,3-dione in 25 mL of acetic acid is added 2.25 g (15.5 mmol) of 4-hydrazinopyridine hydrochloride in one portion. The mixture is warmed under reflux for 3 h, cooled to 0°C, diluted with ethyl acetate and filtered. The yellow solid is dried to afford 4.24 g of the phthalimide which is used without further purification.

To a solution of 4.24 g (12.4 mmol) of the aforementioned phthalimide in 50 mL of tetrahydrofuran at room temperature is added 1.38 g (37.4 mmol) of lithium aluminum hydride in small portions. The mixture is stirred for 3 h, then quenched with sodium sulfate decahydrate. The mixture is diluted with 200 mL of ethyl acetate and filtered. The filtrate is concentrated *in vacuo* and the residue is chromatographed over silica gel (eluted with DCM:MeOH = 9:1) to afford 1.75 g of the isoindoline product as an orange oil. The oil is dissolved in a minimum amount of ethanol and acidified with conc. HCl. The hydrochloride salt is crystallized by adding ethyl acetate followed by heptane to afford 1.38 g of the product as dark red crystals, mp 229-230°C

Analysis:

Calc. for C ₁₄ H ₁₅ Cl ₂ N ₃ O:	53.86%C	4.84%H	13.46%N
Found:	53.80%C	4.60%H	13.41%N

EXAMPLE 992,3-Dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl N-benzyl-N-methylcarbamate hydrochloride hemihydrate.

A mixture of 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol (1.50 g, 6.60 mmoles), 2.2 equivalents of triethylamine (1.47 g, 14.52 mmoles) 15 ml of chloroform is stirred at room temperature under nitrogen as 1.2 equivalents of N-benzyl-N-methylcarbonyl chloride (1.55 g, 7.92 mmoles) in 10 ml of chloroform is added dropwise. The reaction is stirred at reflux for three hours, then at room temperature overnight. The mixture is poured into 100 ml of dilute sodium bicarbonate solution and separated. The aqueous phase is extracted with chloroform and the combined organic layers are dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue is

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purified by flash chromatography (silica; 7% MeOH-DCM followed by 185:14:1 DCM-MeOH-NH₄OH) to give 1.35 g of brown oil. The oil is dissolved in absolute ethanol and treated with excess ethereal HCl. The addition of more ether and cooling gives 650 mg (23%) of tan crystals, m.p. 128-132°C (gas evolution). The moisture content is confirmed by Karl-Fischer titration (2.15% calculated, 1.95% found).

Analysis:

Calc. for C ₂₂ H ₂₂ N ₄ O ₂ • HCl • 1/2H ₂ O:	62.93%C	5.76%H	13.34%N
Found:	62.96%C	5.57%H	13.45%N

EXAMPLE 100

(3,4-Dihydro-8-benzyloxy-5-bromo-7-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine fumarate.

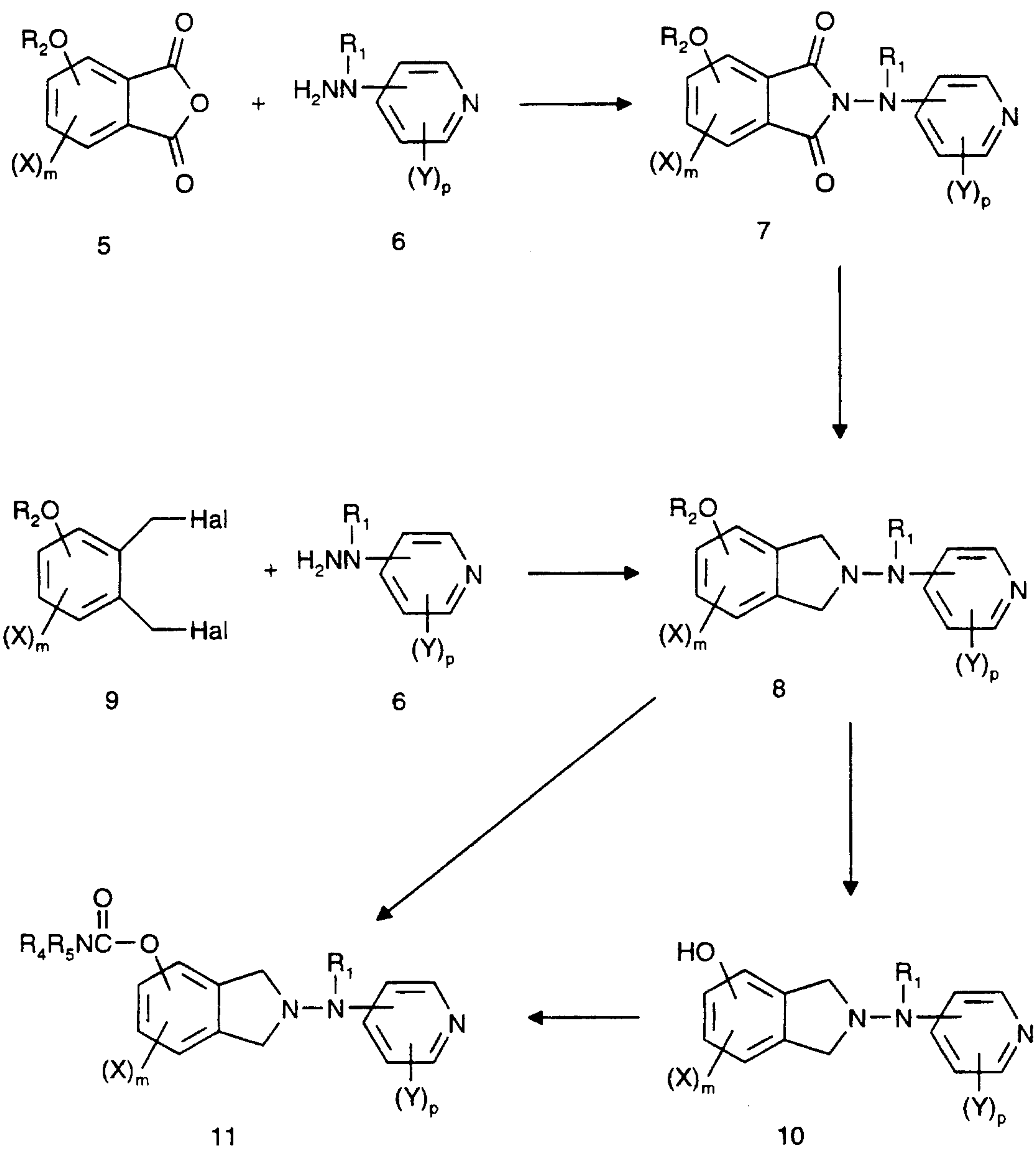
Lithium aluminum hydride (10.7g, 282 mmol, 3.3 eq) is added portionwise to a 0°C suspension of the hydrazone hydrochloride (39.4g, 85.2 mmol) in THF (1L). The resulting mixture is stirred overnight at room temperature. The excess LAH is subsequently destroyed by the careful addition of sodium sulfate decahydrate. Filtration and concentration of the filtrate provides the crude hydrazine (27.7g, 76%, 2003-134-A, pure by TLC) which is used without further purification.

A solution of the hydrazine (27.7g, 64.7 mmol) and chloromethyl methyl ether (5.4 ml, 71.2 mmol, 1.1 eq) in acetic acid (400 ml) is refluxed 1.5 hours under nitrogen. The mixture is subsequently cooled and poured onto ice. This acidic mixture is carefully neutralized with 2 N sodium hydroxide solution and extracted with ethyl acetate. The combined organic extracts containing the product are washed with water and brine, dried over MgSO₄, filtered and concentrated to leave the crude product as an oil. Purification on a Waters LC2000 chromatography system (gradient elution with 1%triethylamine/ 2%methanol/97%EtOAc → 1%triethylamine/4%methanol/95%EtOAc) provides the product (12.5g,mmol, 44%, overall yield after 2 steps =33 %, pure by TLC) as an oil. The analytically pure product, m.p.= 186-7°C, is precipitated from methanol as the fumarate salt.

Analysis:

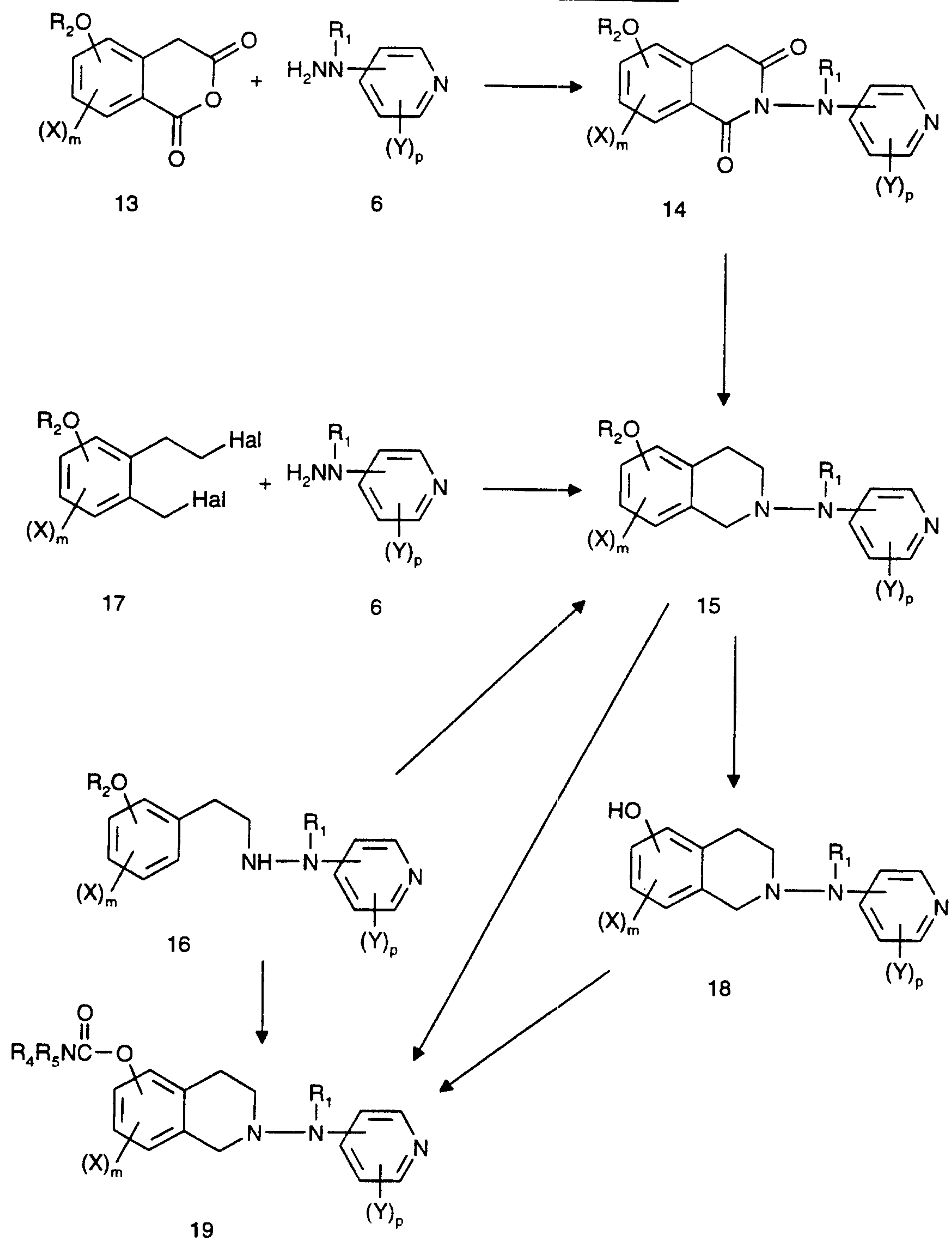
Calc. for C ₂₆ H ₂₆ BrN ₃ O ₆	56.12%C	4.71%H	7.55%N
Found:	55.78%C	4.23%H	7.29%N

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REACTION SCHEME A

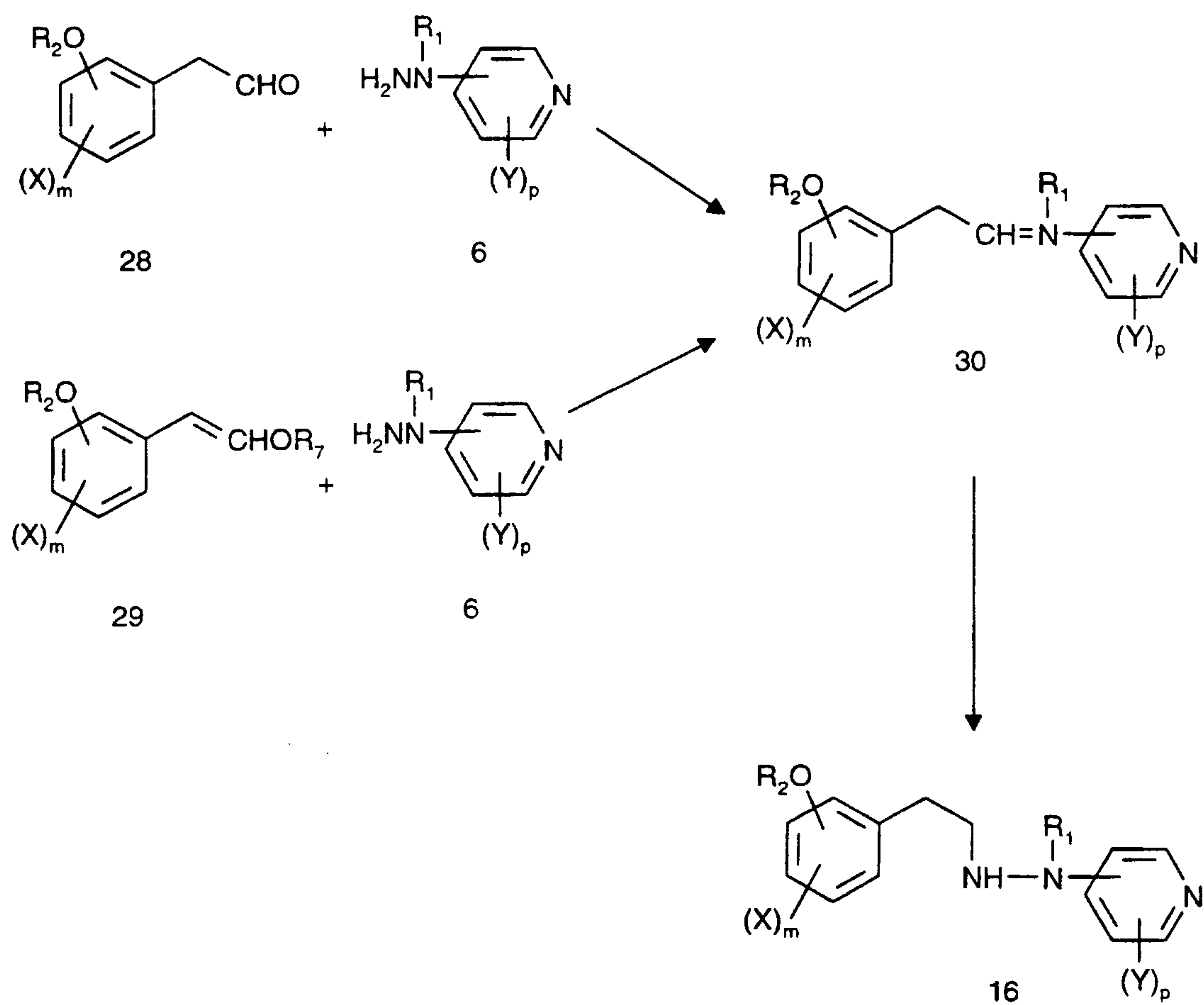


wherein R_1 , R_2 , R_4 , R_5 , X , Y , m and P are as herein described.

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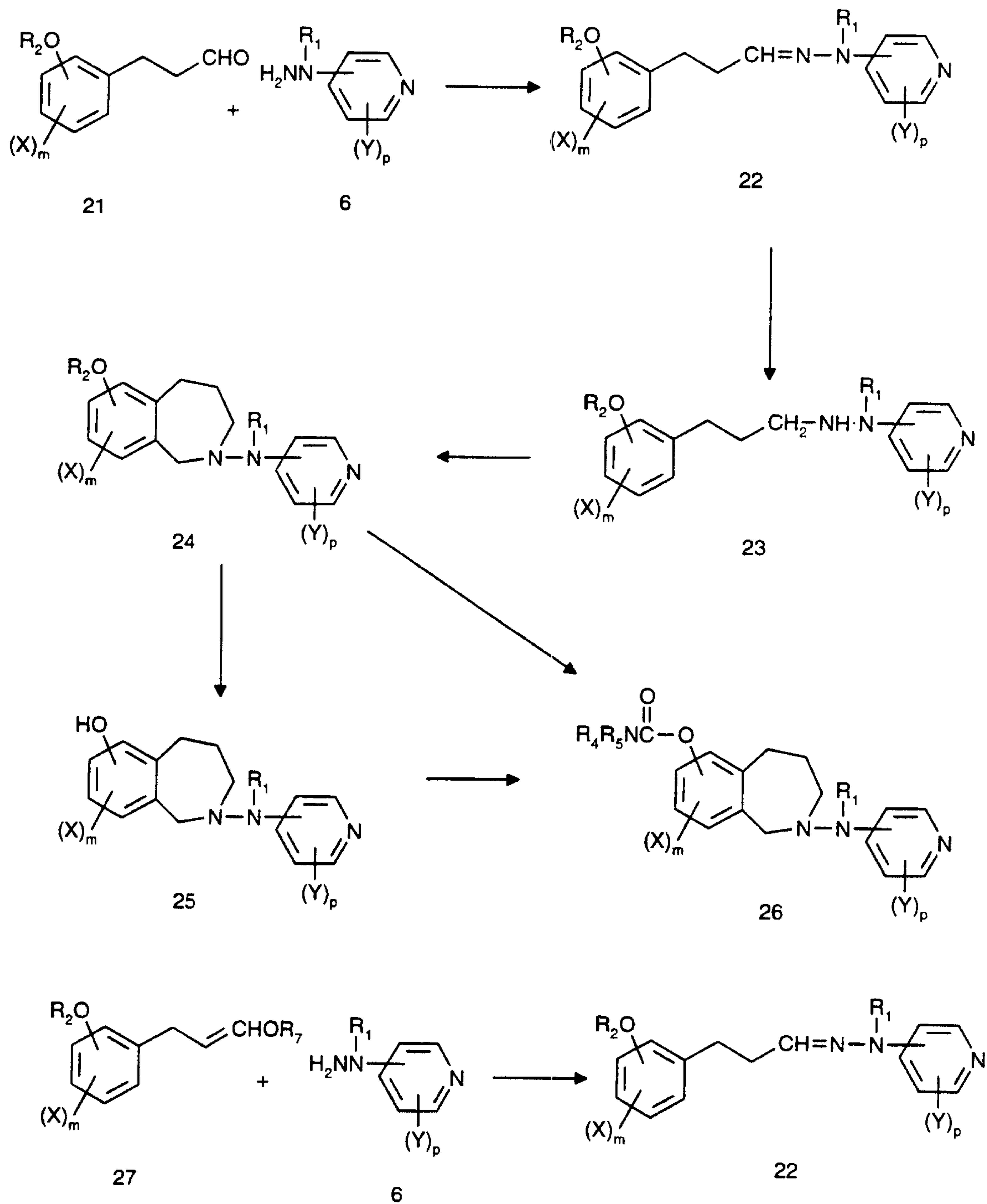
REACTION SCHEME B

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REACTION SCHEME B CONTINUED

wherein R_1 , R_2 , R_4 , R_5 , R_7 , X , Y , m and P are as herein described.

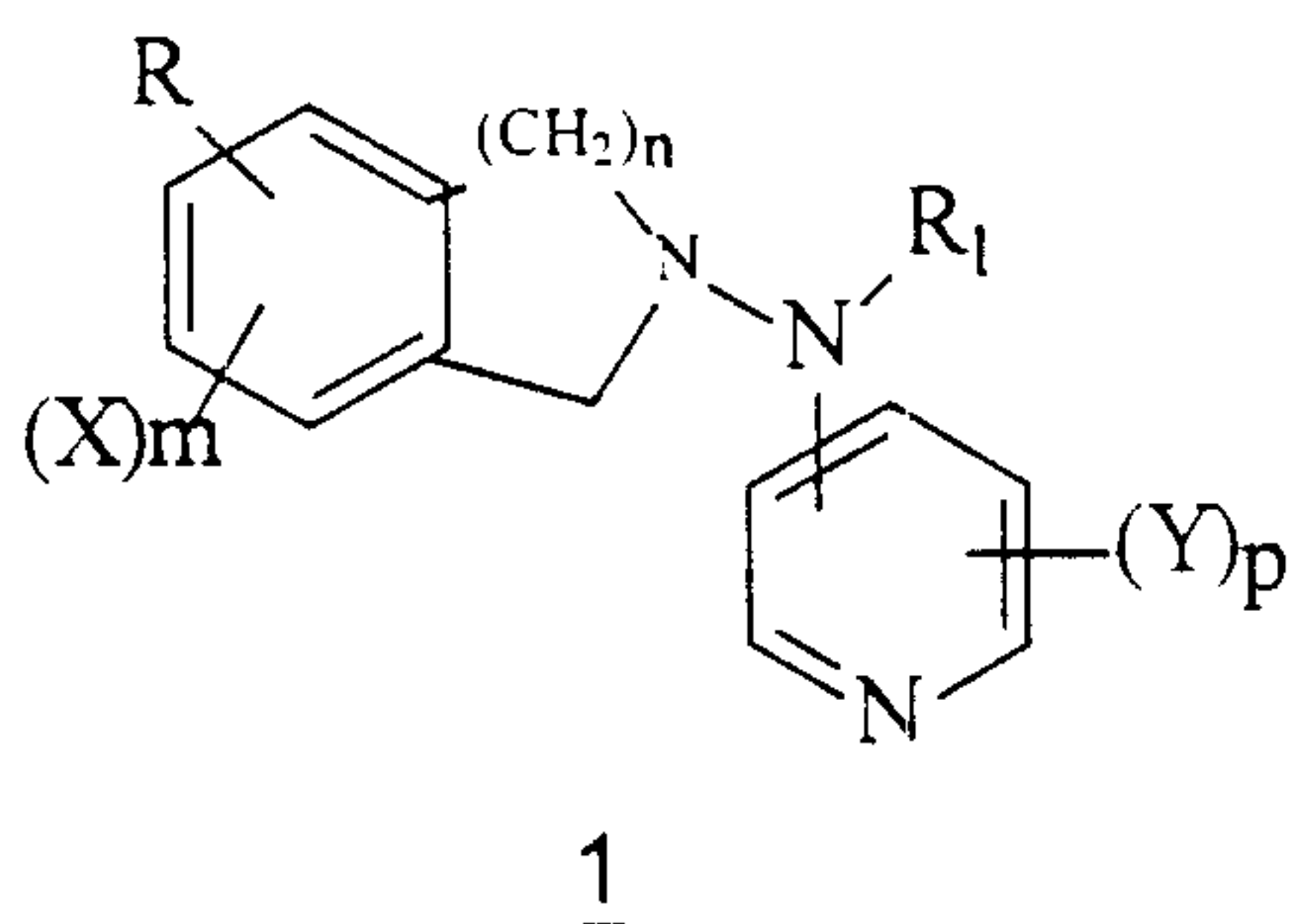
85

REACTION SCHEME C

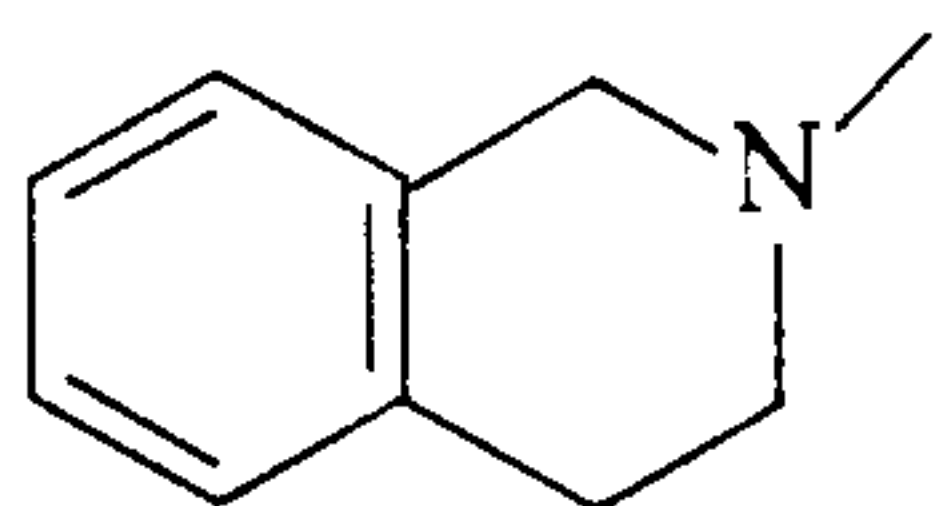
wherein R_1 , R_2 , R_4 , R_5 , R_7 , X , Y , m and P are as herein described.

WHAT IS CLAIMED IS:

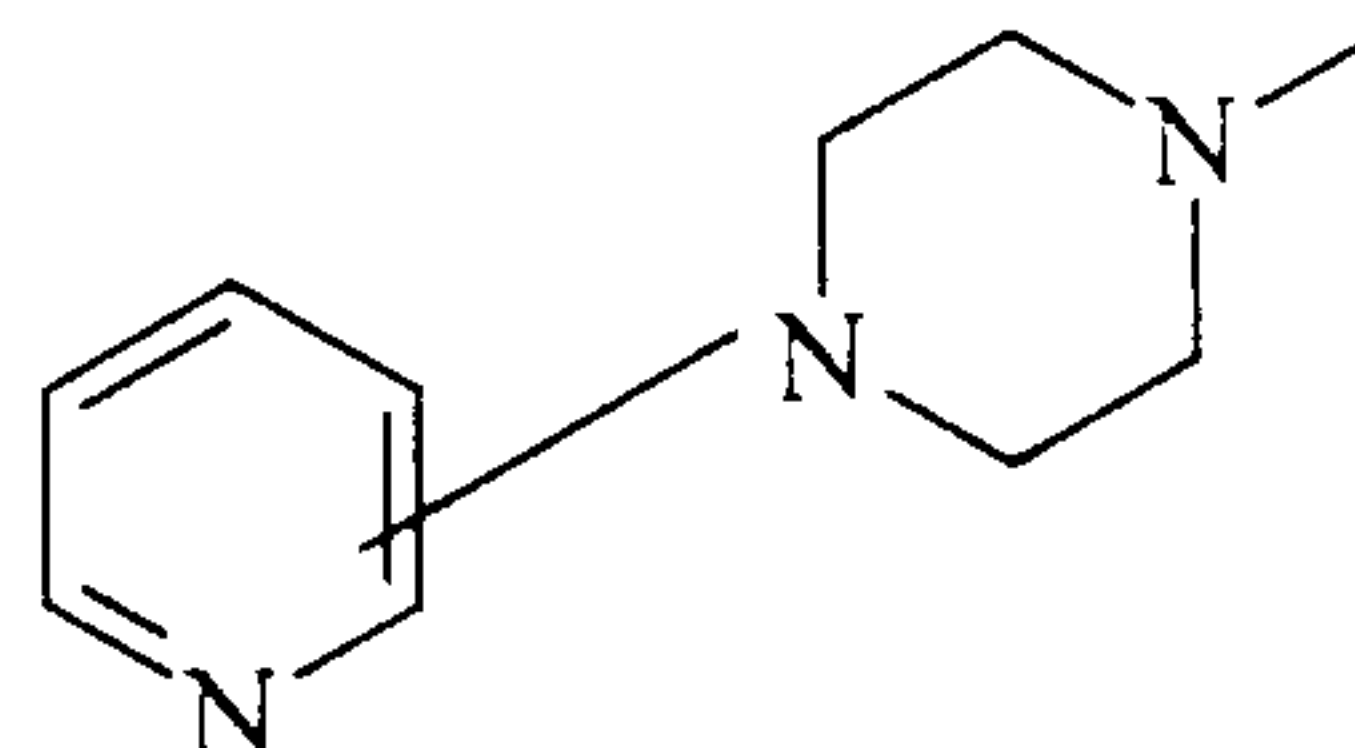
1. A compound of the formula 1



wherein R is hydrogen, a group of the formula R_2O- wherein R_2 is hydrogen, C_1-C_6 alkyl, benzyl, a group of the formula $(R_3)_3Si-$ wherein R_3 is C_1-C_6 alkyl, or a group of the formula R_4R_5NCO- wherein R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl or benzyl; R_4 and R_5 taken together with the nitrogen atom to which they are attached form a group of the formula



or a group of the formula



R_1 is hydrogen or C_1-C_6 alkyl; X is hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_6 alkoxy, or trifluoromethyl; Y is hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_6 alkoxy, or trifluoromethyl; m is 1 or 2; n is 1, 2, or 3; p is 1 or 2; the optical isomers thereof; or the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R is a group of the formula R_2O- wherein R_2 is a group of the formula R_4R_5NCO- .

3. A compound according to claim 2 which is selected from the group consisting of;

2,3-dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-5-yl methyl carbamate;
 2,3-dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-4-yl methyl carbamate;
 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl dimethylcarbamate;
 6-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-yl



dimethylcarbamate;

2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-6-yl dimethyl carbamate;

2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-yl dimethyl carbamate;

7-methoxy-2(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-6-yl dimethyl

5 carbamate;

dimethylcarbamic acid 2-((4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yl ester hydrochloride 0.25 hydrate;

dimethylcarbamic acid 7-methoxy-2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl ester; and

10 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl-1,2,3,4-tetrahydroisoquinolin-2-yl carbamate.

4. A compound according to claim 1 which is selected from the group consisting of;

15 [7-methoxy-8-tert-butyldimethylsilyloxy-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl]pyridin-4-yl amine;

2,3-dihydro-N-2-pyridinyl-1H-isoindol-2-amine;

3,4-dihydro-N-2-pyridinyl-2(1H)-isoquinolinamine;

2,3-dihydro-2-[(N-2-pyridinyl)amino]-1H-isoindol-5-ol;

20 2,3-dihydro-4-methoxy-N-2-pyridinyl-2H-isoindol-2-amine;

2,3-dihydro-2-[N-2-pyridinyl)amino]-1H-isoindol-7-ol;

3,4-dihydro-N-4-pyridinyl-2(1H)-isoquinolinamine;

2,3-dihydro-N-4-pyridinyl-1H-isoindol-2-amine;

4-bromo-2,3-dihydro-N-4-pyridinyl-1H-isoindol-2-amine;

25 2,3-dihydro-4-methoxy-N-(pyridinyl)-1H-isoindol-2-amine;

2,3-dihydro-N-methyl-N-(4-pyridinyl)-1H-isoindol-2-amine;

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-ol;

(7-methoxy-1,3,4,5-tetrahydro-2-benzo[c]azepinyl)-4-pyridinylamine;

7-methoxy-2-(pyridin-4-yl amino)-1,2,3,4-tetrahydro-isoquinolin-6-ol;

30 (3,4-dihydro-6-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine;

(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-4-yl)-methyl-1-pyridin-4-yl-amine;

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(7-benzyloxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;
[7-methoxy-8-hydroxy-1,3,4,5-tetrahydrobenzo[c]azepine-2-yl]pyridin-4-
ylamine;
(2,3-dihydro-(1H)-isoindol-2-yl)-(3-fluoro-pyridin-4-yl)amine;
5 2,3-dihydro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine;
2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-5-ol;
2-[methyl-(pyridin-4-yl)amino]-1,2,3,4-tetrahydro-isoquinolin-6-ol;
(6-fluoro-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;
(5-bromo-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine; and
10 (3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine.

5. Use of an effective amount of a compound of claim 1 or a
pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical
composition useful in the treatment of relieving memory dysfunction in mammals.

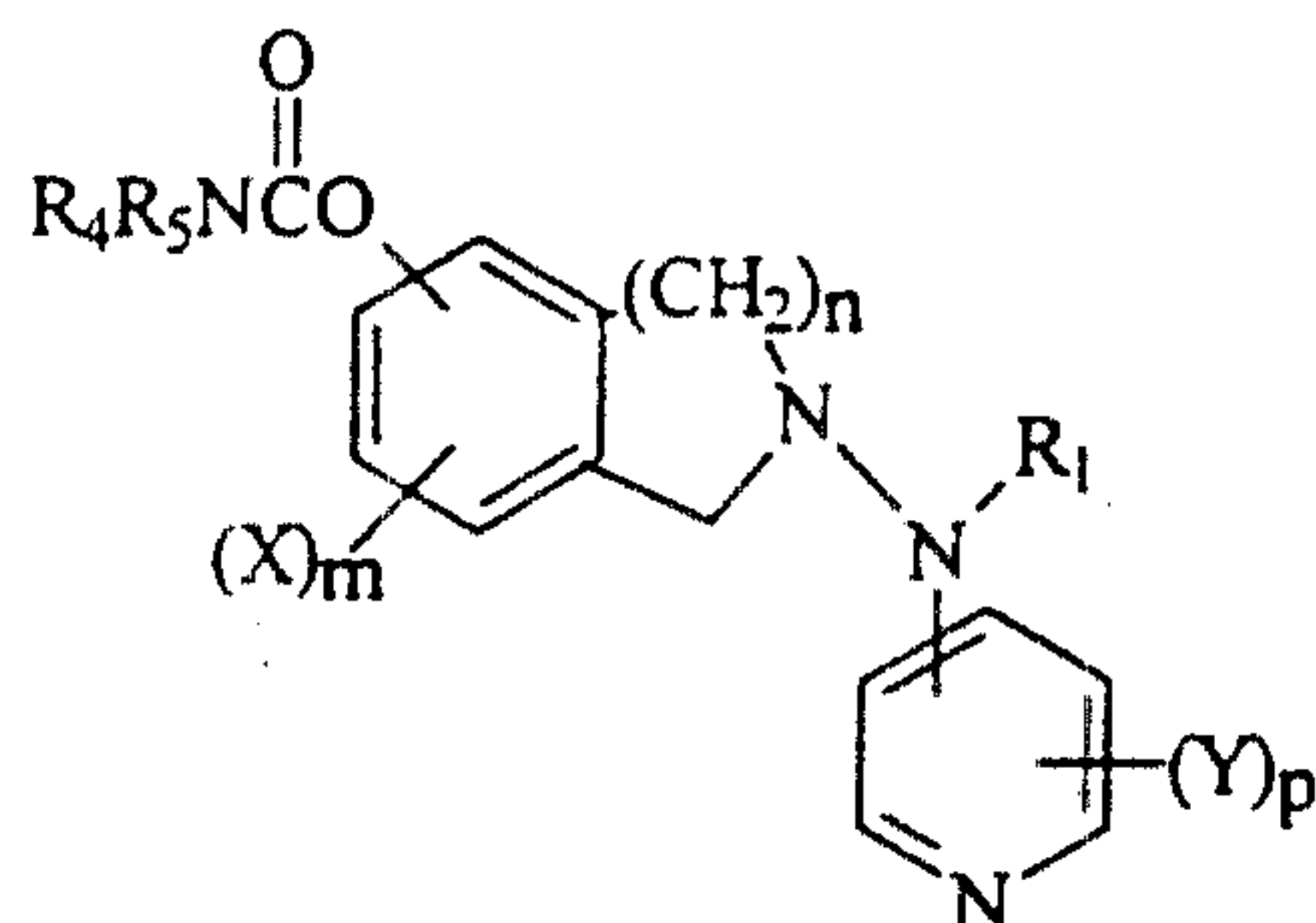
15 6. A memory dysfunction relieving composition comprising an adjuvant and
as the active ingredient, a memory dysfunction relieving effective amount of a
compound of claim 1.

20 7. Use of an effective amount of a compound of claim 1 or a
pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical
composition useful in the treatment of depression in mammals.

25 8. A depression treating composition comprising an adjuvant and as the
active ingredient, a depression treating effective amount of a compound of claim 1.

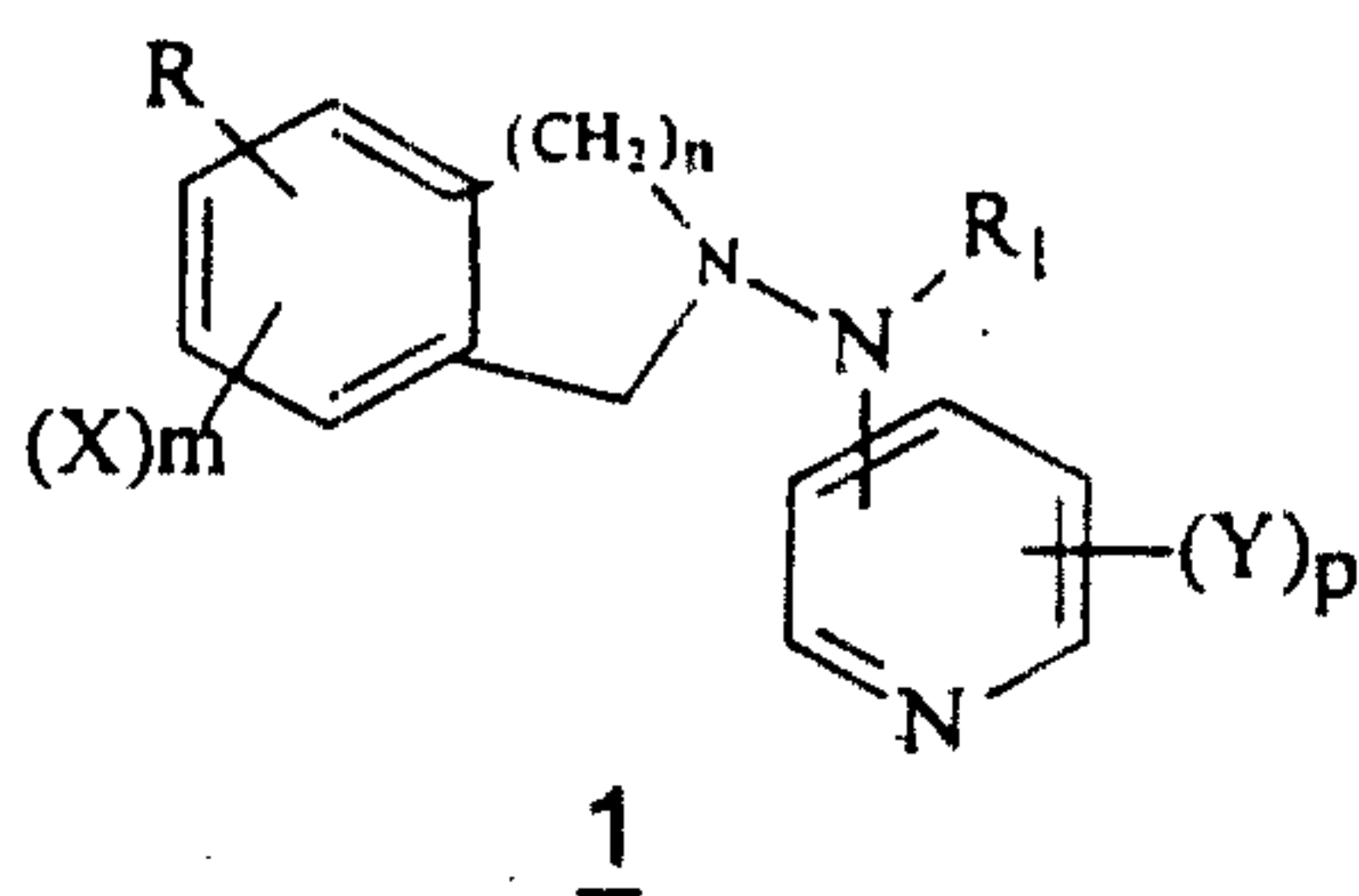
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9. A process for the preparation of a compound of the formula 1,

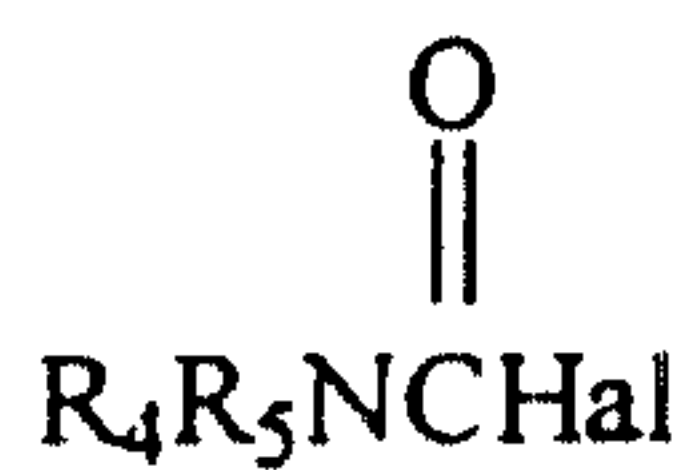


1, where $R = R_4R_5NCOO-$

wherein R is R_4R_5NCOO- , as claimed in claim 1, which comprises reacting a compound of the formula 1, wherein R is hydroxyl



with a compound of the formula



wherein R_1 , R_4 , R_5 , X, Y, m, n, and p are as defined in claim 1 and Hal is chloro or bromo.

10. The process of claim 9 wherein a solvent is employed.

11. The process of claim 10 wherein the solvent is a halocarbon.

12. The process of claim 11 wherein the halocarbon is chloroform.

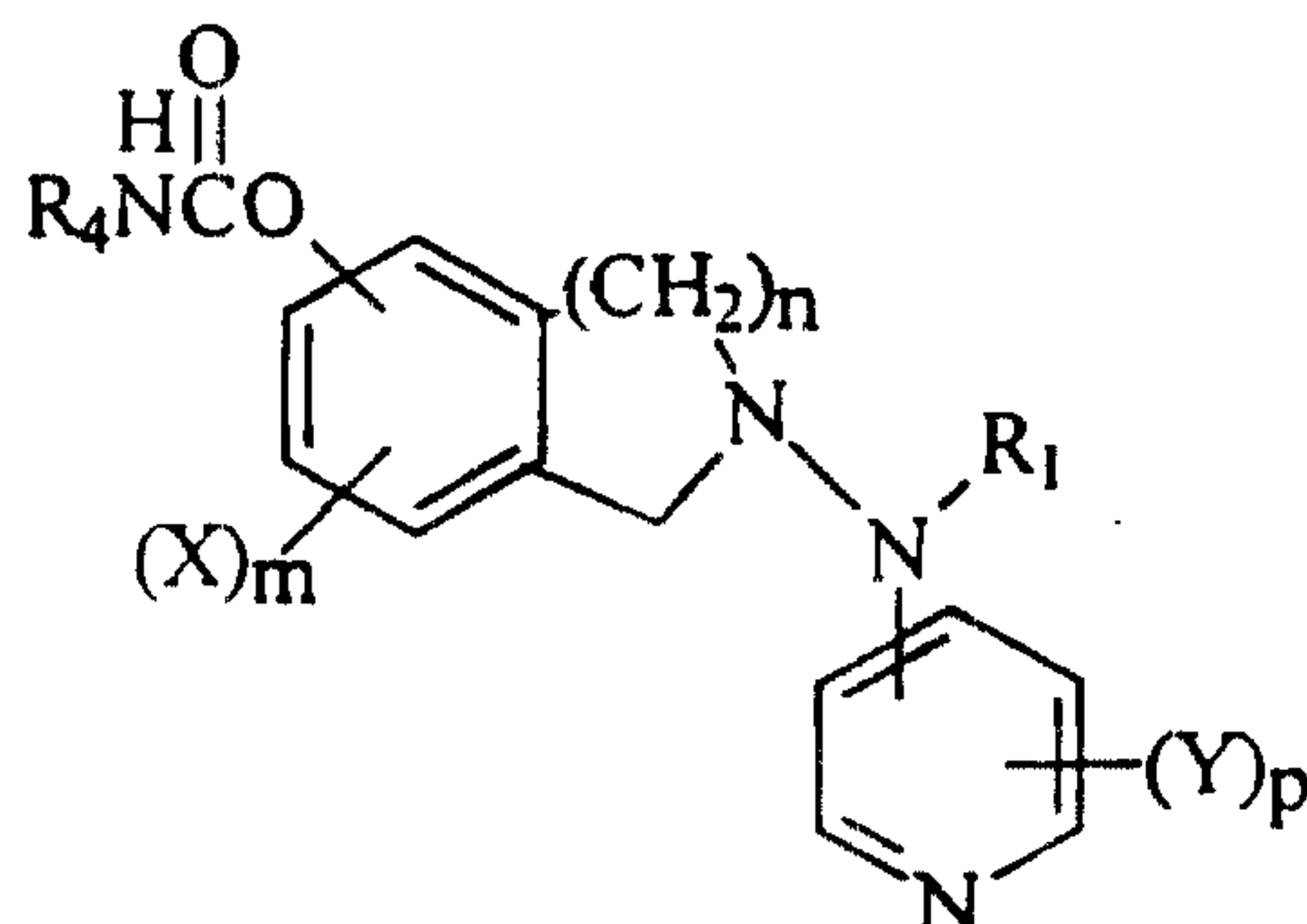
13. The process of claim 9 wherein an acid acceptor is employed.

14. The process of claim 13 wherein the acid acceptor is a tertiary amine.

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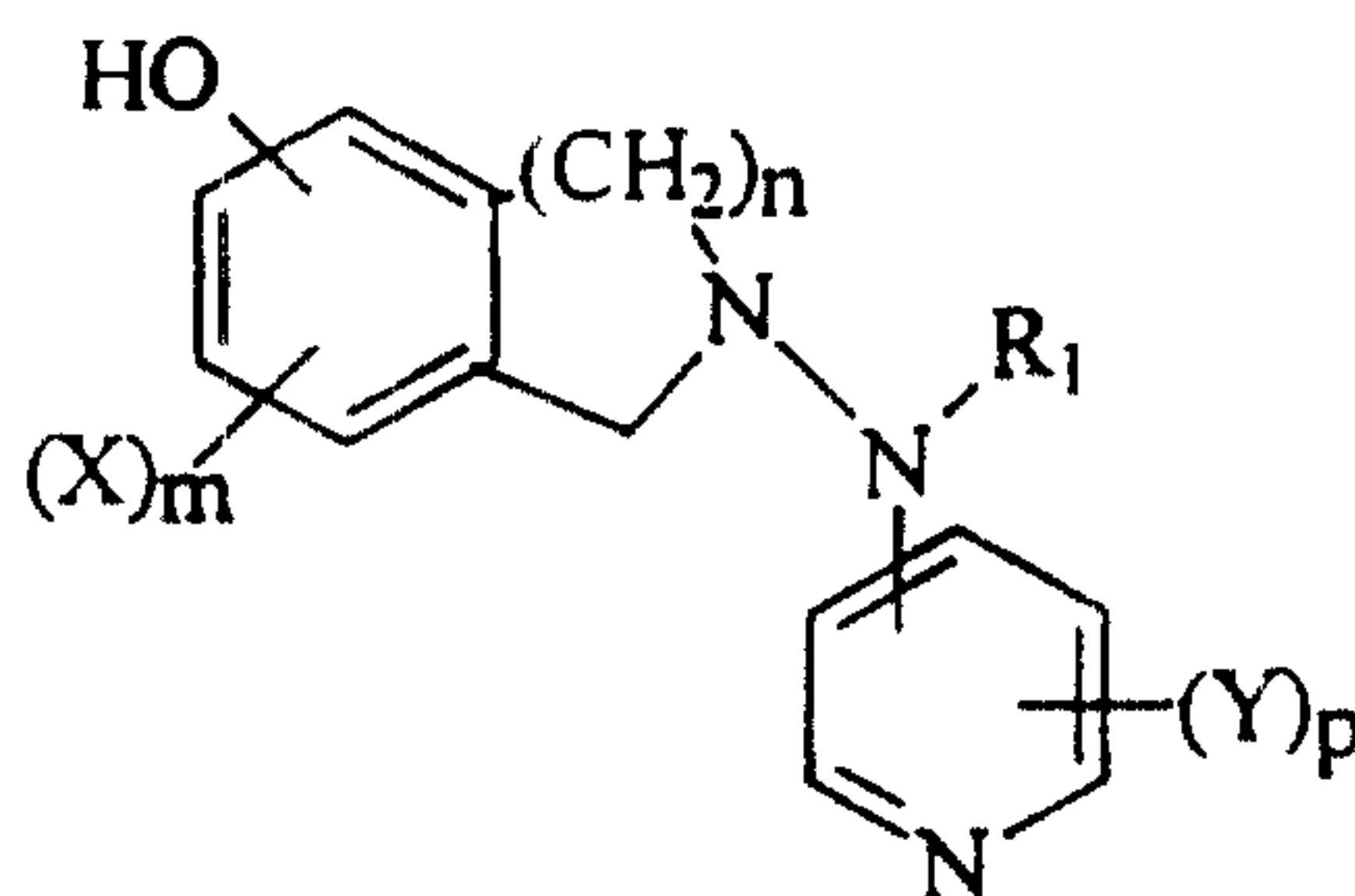
15. The process of claim 14 wherein the tertiary amine is triethylamine.

16. A process for the preparation of a compound of the formula 1,



1, where R = R₄HNCOO-

wherein R is R₄HNCOO-, as claimed in claim 1, which comprises reacting a compound of the formula 1, wherein R is hydroxyl



1, where R = OH

with a compound of the formula



wherein R₁, R₄, X, Y, m, n, and p are as defined in claim 1.

17. The process of claim 16 wherein a solvent is employed.

18. The process of claim 17 wherein the solvent is acetonitrile.

19. The process of claim 16 wherein a base is employed.

20. The process of claim 19 wherein the base is 1,8-diazabicyclo[5.4.0]undec-7-ene.

21. Use of an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition useful in the simultaneous treatment of depression and memory dysfunction in mammals suffering from memory dysfunction and depression.

5

22. A simultaneous depression treating and memory dysfunction relieving composition comprising an adjuvant and as the active ingredient, a depression treating and memory dysfunction relieving effective amount of a compound of claim 1.

10

23. A compound according to claim 1 which is selected from the group consisting of;

6-fluoro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-ol;

6-fluoro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-yl dimethyl carbamate;

15

(8-chloro-4-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;

8-chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-4-yl dimethyl carbamate;

5-bromo-2-(pyridin-4-yl)amino-1,2,3,4-tetrahydroisoquinolin-8-ol;

5-bromo-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl

20

carbamate;

(5-benzyloxy-3,4-dihydro-8-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine;

5-fluoro-2-(pyridin-4-ylamino)-1,2,3,4-tetrahydroisoquinolin-8-ol;

2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepine-7,8-diol;

2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate;

25

8-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-5-ol;

(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl dimethylcarbamate;

2,3-dihydro-5-fluoro-N-(4-pyridinyl)-1H-isoindol-2-amine;

2,3-dihydro-4-fluoro-5-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine;

30

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-5-yl 1,2,3,4-tetrahydroisoquinolin-2-ylcarbamate; 2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-ol;

2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-7-ol;

8-chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-5-ol;

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(4-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;

(6-benzyloxy-4-bromo-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine;

2,3-dihydro-4-chloro-7-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine;

5 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl N-benzyl-N-methylcarbamate;

(3,4-dihydro-8-benzyloxy-5-bromo-7-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine;

7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-ol;

10 7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl carbamate;

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl diethylcarbamate;

2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl dimethylcarbamate;

2,3-dihydro-4-chloro-2-(4-pyridinylamino)-1H-isoindol-7-ol;

15 2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl 1,2,3,4-tetrahydroisoquinolin-2-ylcarbamate;

2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-5-ol;

3,4-dihydro-1H-isoquinolin-2-carboxylic acid-7-methoxy-2-(4-pyridinylamino)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl ester;

20 2,3-dihydro-4-chloro-2-(4-pyridylamino)-1H-isoindol-7-yl dimethyl carbamate;

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl 4-(2-pyridinyl)-1-piperazinylcarbamate;

2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-ol hydrobromide;

2-(4-pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-7-ol;

25 8-chloro-2-(4-pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-5-ol hydrobromide;

(4-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine dihydrochloride;

(6-benzyloxy-4-bromo-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-4-pyridinylamine hydrochloride;

2,3-dihydro-4-chloro-7-methoxy-N-(4-pyridinyl)-1H-isoindol-2-amine;

30 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl N-benzyl-N-methylcarbamate hydrochloride hemihydrate;

(3,4-dihydro-8-benzyloxy-5-bromo-7-methoxy-1H-isoquinolin-2-yl)-4-pyridinylamine fumarate;

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7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-ol
hydrobromide;

7-methoxy-2-(4-pyridinylamino)-1,2,3,4-tetrahydroisoquinolin-8-yl dimethyl
carbamate fumarate;

5 2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl diethylcarbamate
hydrochloride;

2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl dimethylcarbamate
hydrochloride;

2,3-dihydro-4-chloro-2-(4-pyridinylamino)-1H-isoindol-7-ol dihydrobromide;

10 2,3-dihydro-4-fluoro-2-(4-pyridinylamino)-1H-isoindol-5-yl 1,2,3,4-
tetrahydroisoquinolin-2-ylcarbamate hydrochloride;

2-(4-pyridinylamino)-1,2,3,4-tetrahydro-isoquinolin-5-ol hydrobromide
monohydrate;

15 3,4-dihydro-1H-isoquinolin-2-carboxylic acid-7-methoxy-2-(4-pyridinylamino)-
2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl ester hydrochloride;

2,3-dihydro-4-chloro-2-(4-pyridylamino)-1H-isoindol-7-yl dimethyl carbamate
hydrochloride; and

2,3-dihydro-2-(4-pyridinylamino)-1H-isoindol-4-yl 4-(2-pyridinyl)-1-piperazinyl-
carbamate 1/4 hydrate.

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