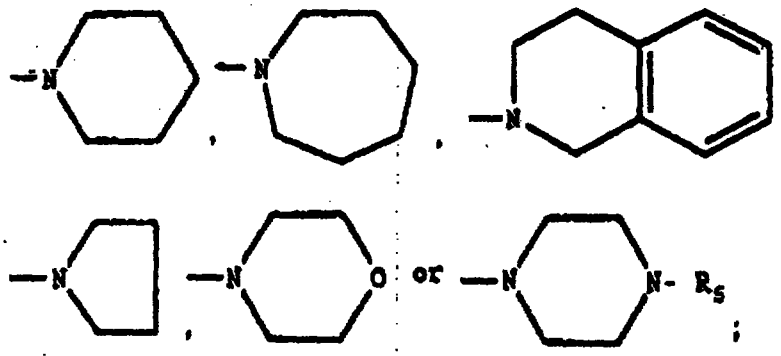
where

n is 0 or 1;
X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2 is hydrogen, loweralkyl, formyl or cyano;
R_3 is hydrogen or loweralkyl;
R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
or alternatively, $-NR_3R_4$ taken together constitutes

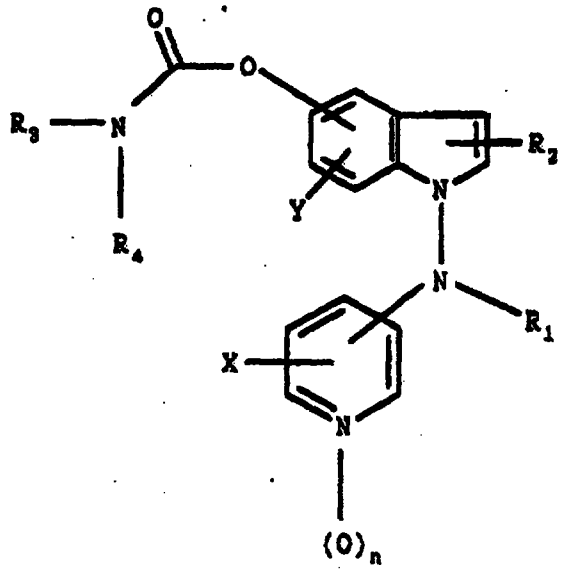


R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl,
which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

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☑ Description : paged 1 to paged 40
☑ Claim(s) : paged 40 to paged 44
☐ Drawing(s) : paged ..... to paged .....
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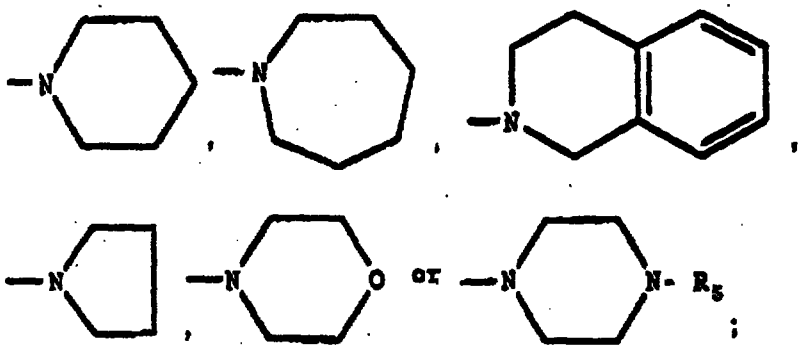
The present invention relates to compounds of Formula I a,



(Ia)

where

- n is 0 or 1;
- X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
- R_2 is hydrogen, loweralkyl, formyl or cyano;
- R_3 is hydrogen or loweralkyl;
- R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
  or alternatively, $-NR_3R_4$ taken together constitutes

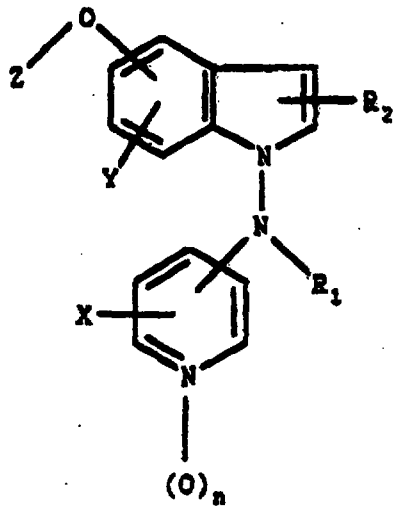


R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl,

which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

Also included within the scope of this invention are compounds depicted by the formula Ib below where the group Z is hydrogen, loweralkyl or benzyl, and other parameters are as defined above, which are useful as direct precursors to the target compounds of this invention having Formula Ia.

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(Ib)

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 8 carbon atoms. Examples of said loweralkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl, hexyl, heptyl and octyl.

The term cycloalkyl shall mean a cycloalkyl group of 3 to 7 carbon atoms.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term aryl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which being independently loweralkyl, loweralkoxy, halogen or trifluoromethyl.

The term heteroaryl shall mean furanyl, thienyl, pyrrolyl or pyridinyl.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all optical and geometric stereoisomers where such isomers exist.

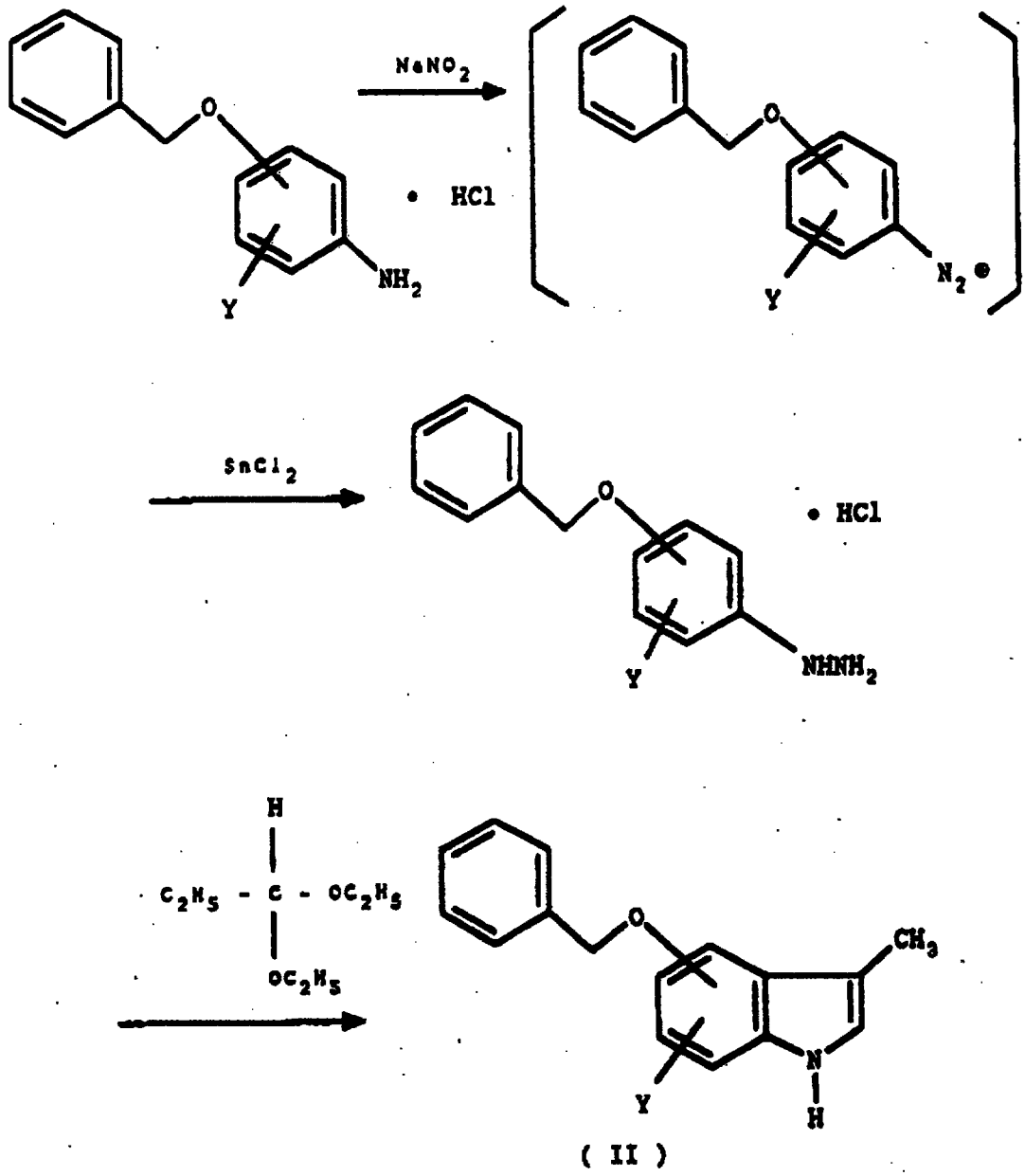
The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

Throughout the description of the synthetic steps, the notations n, X, Y and R_1 through R_5 shall have the respective meanings given above unless otherwise stated or indicated.

STEP A:

A benzyloxyaniline depicted below is allowed to react with $NaNO_2$ in a routine manner known to the art to afford the corresponding diazonium compound and the latter is reduced with $SnCl_2$ to afford the corresponding hydrazine compound, and thereafter the latter is allowed to react with the diethylacetal of propionaldehyde to afford the compound of Formula II. For details of the last reaction (Fisher indole synthesis), the reader is referred, for instance, to D. Keglevic et al., Chem. Absts. 56, 4710h.

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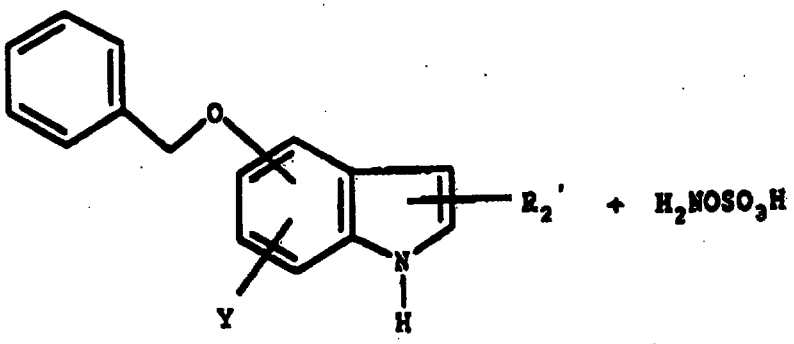
(II)

Where the 2-methylisomer of Compound II is desired, the above reaction is conducted in substantially the same manner as described above except that acetone is used instead of diethylacetal of propionaldehyde.

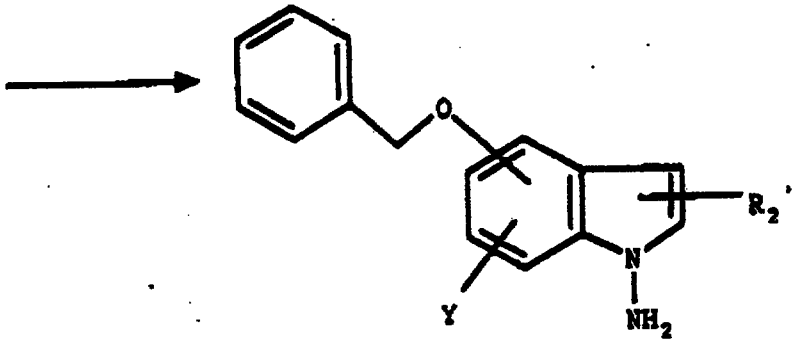
STEP B:

A compound of Formula III where R_2' is hydrogen or methyl is allowed to react with hydroxylamine-O-sulfonic acid in a routine manner known to the art to afford a compound of Formula IV. The starting compound of Formula III where R_2' is hydrogen is either available on the market or can be synthesized from known compounds according to methods known to the art.

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(III)

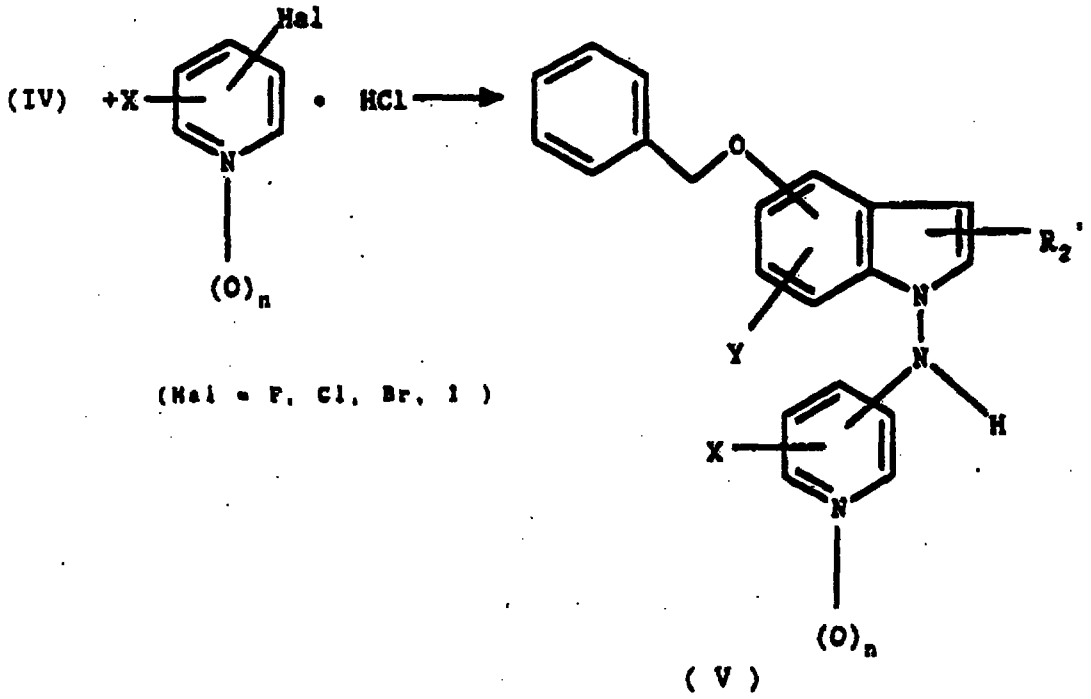


(IV)

STEP C:

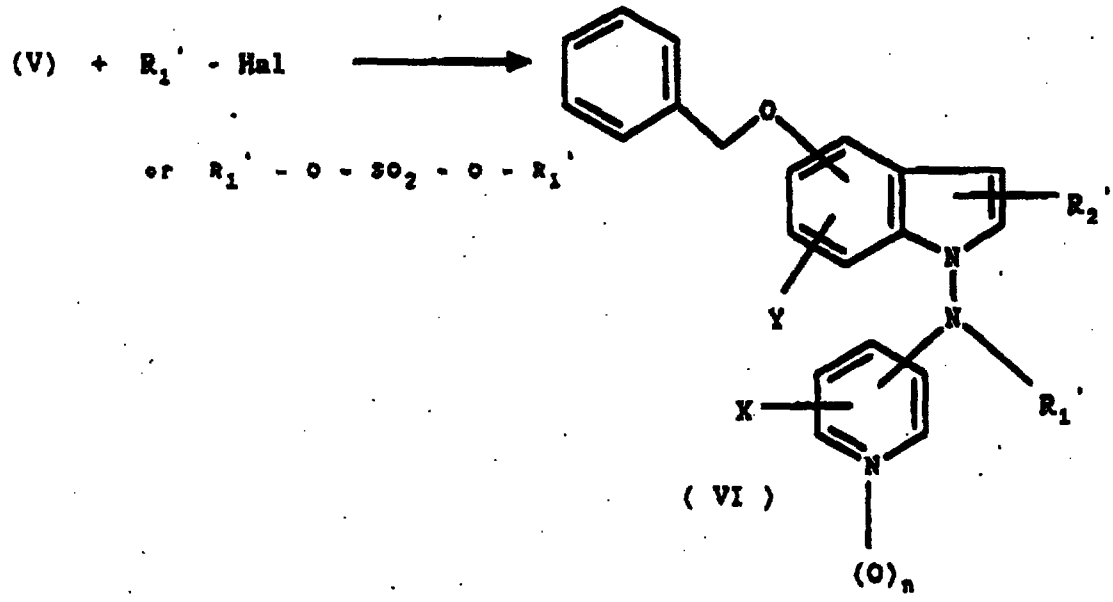
Compound IV is allowed to react with a halopyridine hydrochloride depicted below to afford a compound of Formula V. This reaction is typically conducted in a suitable solvent such as N-methyl-2-pyrrolidinone at a temperature of 20 to 200 °C.

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STEP D:

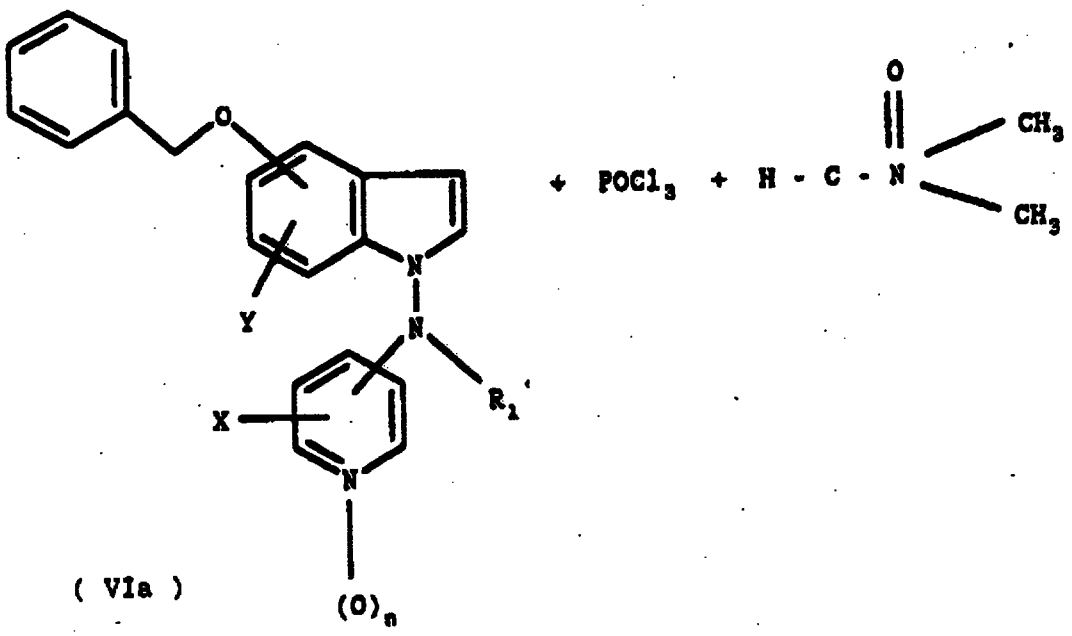
Compound V is allowed to react with a suitable base, such as sodium hydride or potassium t-butoxide, and the resultant anion is allowed to react with a halide of the formula R_1' - Hal where R_1' is loweralkyl, aryllowerallkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryllowerallkanoyl, heteroaryllowerallkyl or heteroaryllowerallkanoyl, and Hal is chlorine, bromine or iodine, or with a dilowerallkylsulfate of the formula R_1'-O-SO_2-O-R_1' where R_1' is loweralkyl, in a routine manner known to the art to afford a compound of Formula VI.

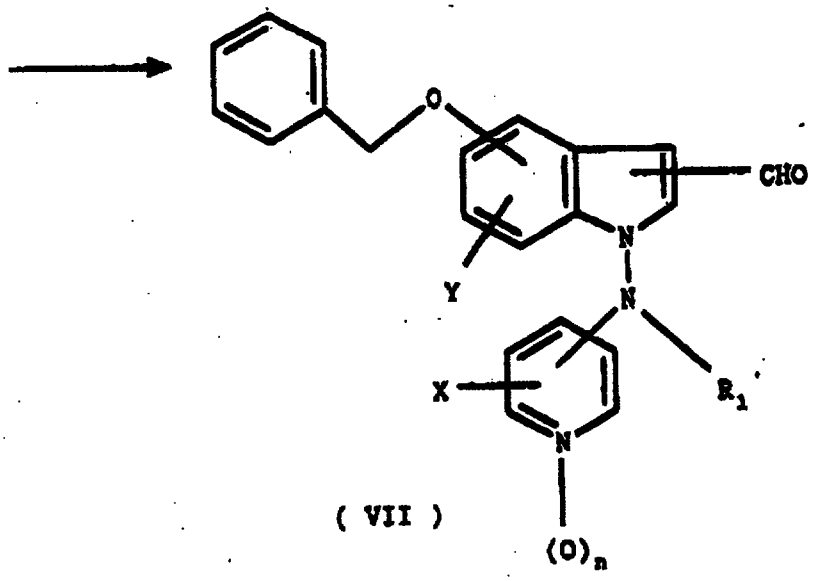


STEP E:

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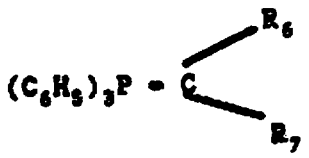
A compound of Formula VIa is allowed to react with phosphorus oxychloride and dimethylformamide in a routine manner known to the art to afford a compound of Formula VII.





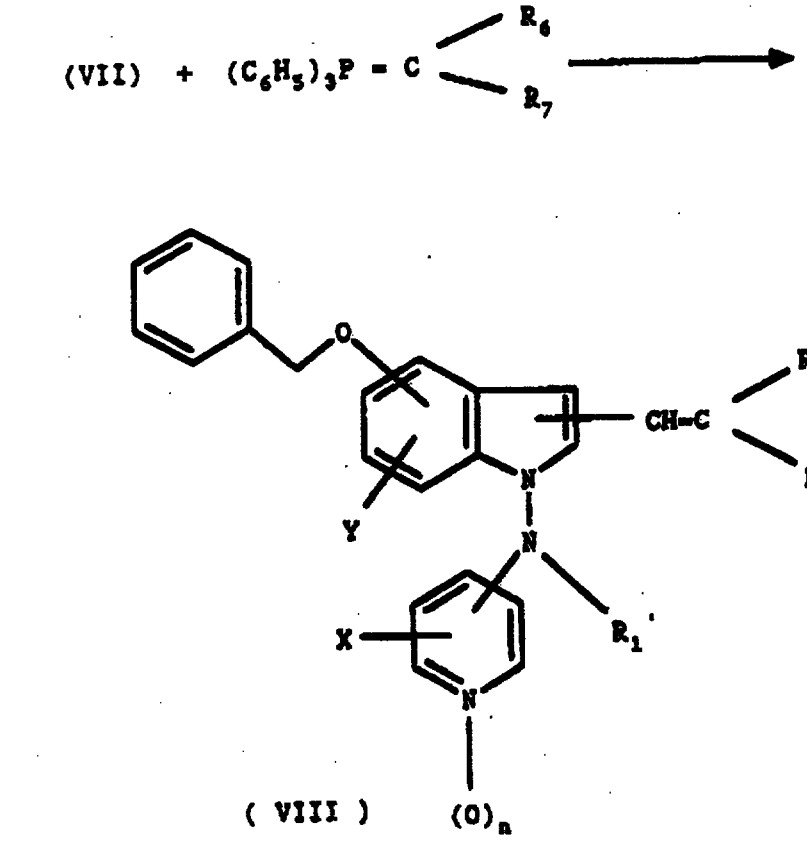
STEP F:

Compound VII is subjected to a Wittig reaction with an ylide of the formula

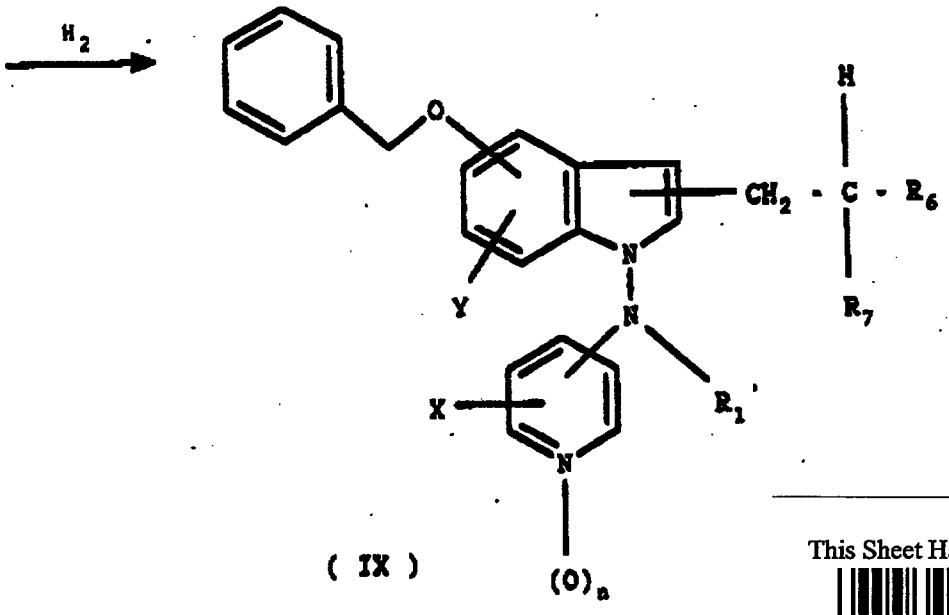


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where R_6 and R_7 are each independently hydrogen or loweralkyl in a routine manner known to the art to afford a compound of Formula VIII and thereafter the latter compound is reduced in a routine manner known to the art to afford a compound of Formula IX.



(VIII)



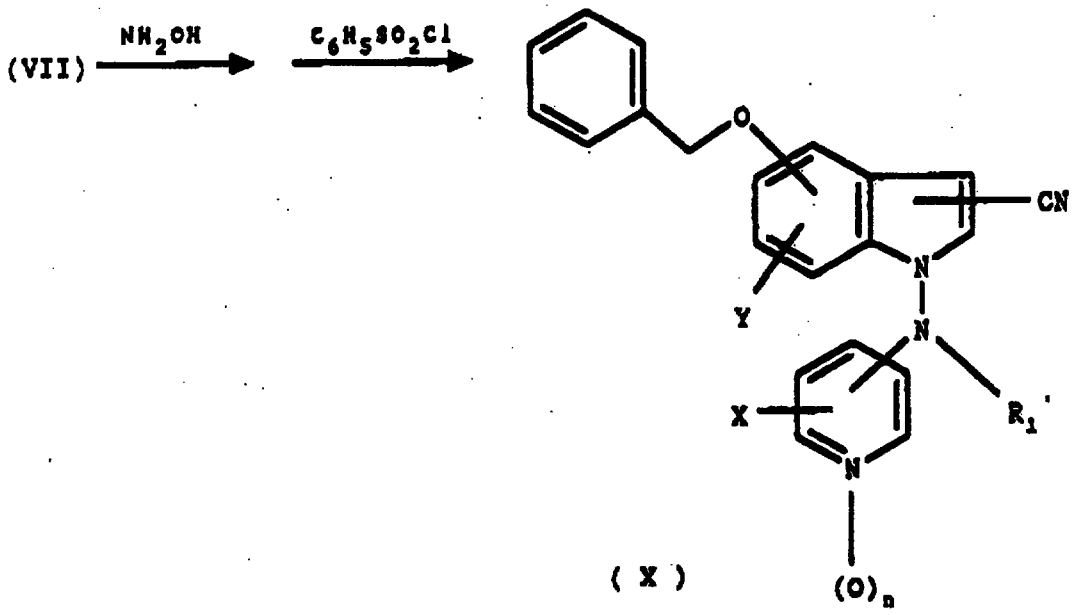
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STEP G:

Compound VII is allowed to react with hydroxylamine in a routine manner known to the art to afford a

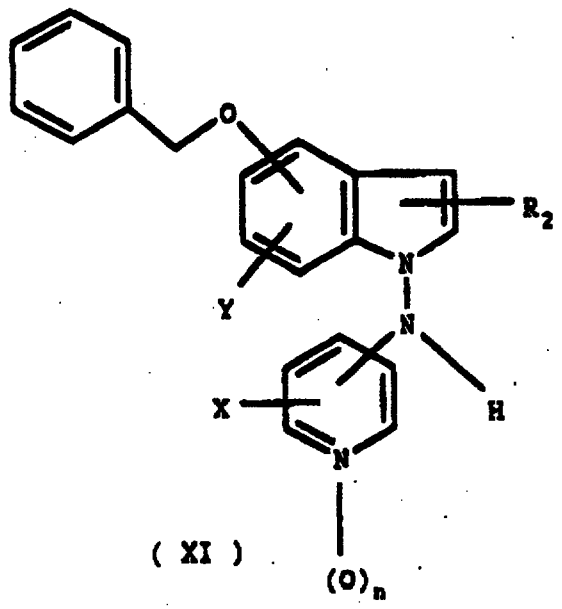
corresponding oxime and the latter is allowed to react with benzenesulfonyl chloride to afford a nitrile compound of Formula X. The second step is typically conducted in a suitable solvent such as tetrahydrofuran or p-dioxane at a temperature of about 60 to 100 °C.



(X)

STEP H:

In order to prepare a compound of Formula XI depicted below where R_2 is not hydrogen or methyl, it is convenient to adopt the following procedure.

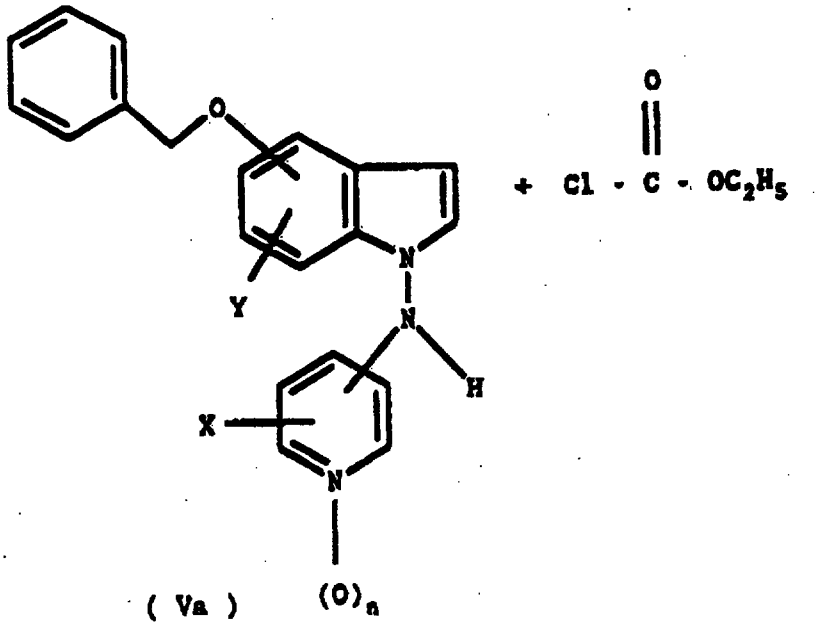


(R_2 = H or CH_3)

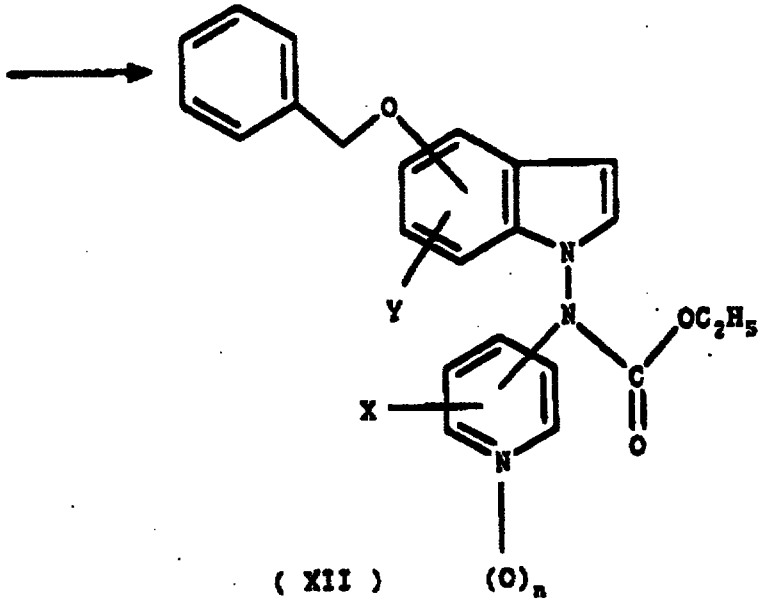
(XI)

Thus, a compound of Formula Va is allowed to react with ethyl chloroformate in a routine manner known to the art to afford an ethyl carbamate of Formula XII and thereafter the latter compound is subjected to one or more of STEPS E through G to afford a compound of Formula XIII. Subsequently, Compound XIII is hydrolyzed in a routine manner known to the art to afford Compound XI.

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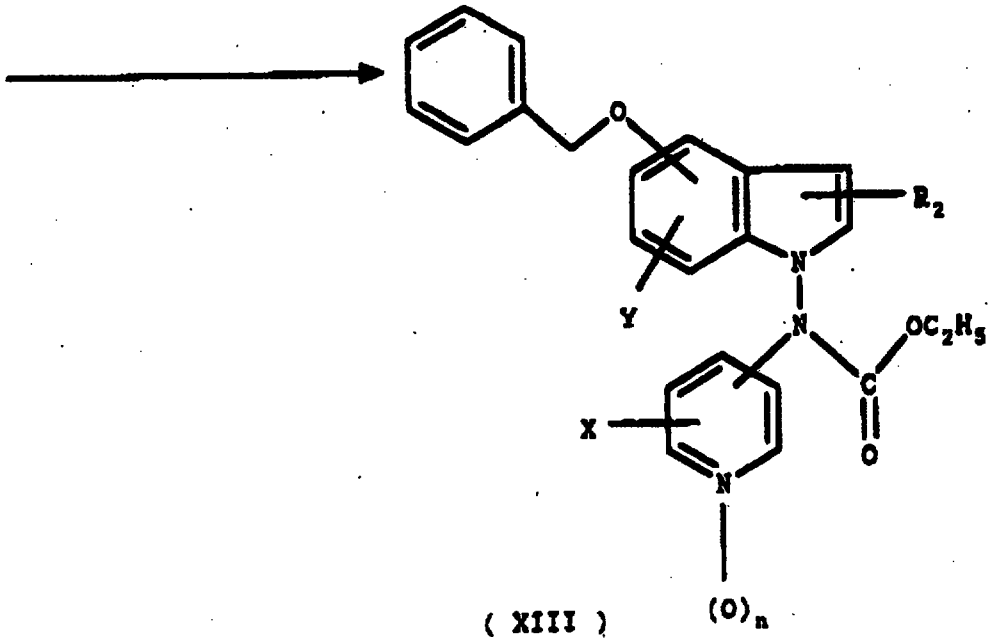
(Va)



(XII)

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One or more of STEPS E through G



(XIII)

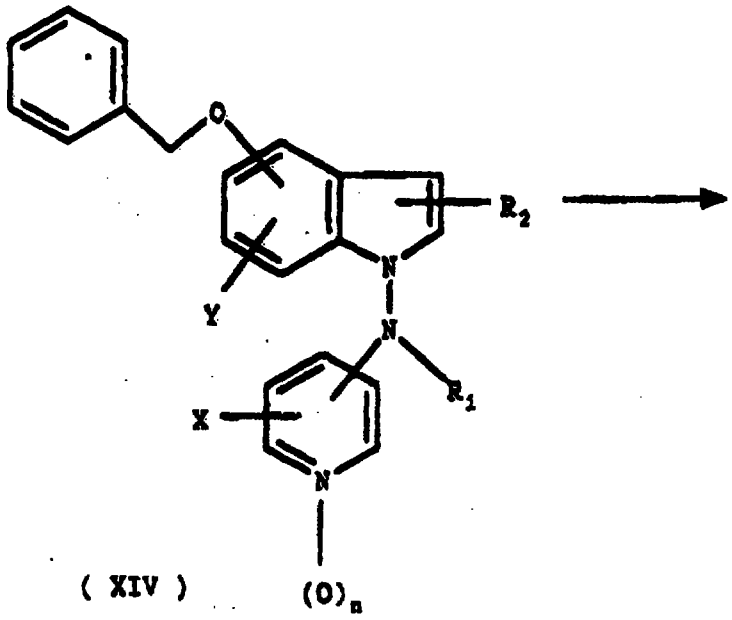
hydrolysis

(XI)

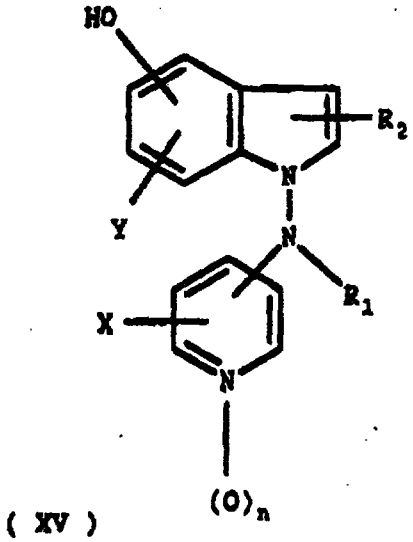
STEP I:

A compound of Formula XIV obtained from one of the foregoing STEPS is subjected to hydrogenolysis conducted in a routine manner known to the art to afford a compound of Formula XV.

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(XIV)



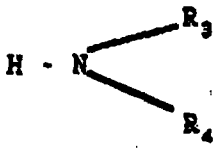
(XV)

In each of the foregoing STEPS A through I, the reactant molecule carries a benzyloxy group on the benzene portion thereof. However, the same reactions can also be accomplished in substantially the same manner as described above where the reactant molecule carries a loweralkoxy group instead of a benzyloxy group on the benzene portion thereof, except that in the case of STEP I, a cleavage reaction is utilized instead of hydrogenolysis. Said cleavage reaction is conducted in a routine manner known to the art, for instance, with the aid of 48% HBr, boron tribromide etherate, trimethylsilyl iodide or the sodium salt of ethyl mercaptan.

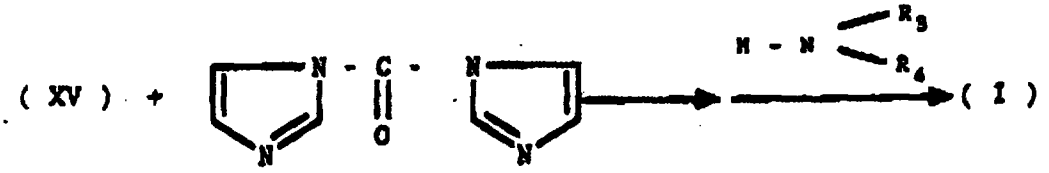
STEP J:

Compound XV is allowed to react with 1,1'-carbonyldiimidazole and the resultant reaction product is allowed to react with an amine of the formula

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in a routine manner known to the art to afford Compound I.



Typically, the first step is conducted in a suitable solvent such as tetrahydrofuran at room temperature. Typically, the second step is conducted by adding a suitable amount of the desired amine in glacial acetic acid to the reaction mixture.

Alternatively, where Compound I in which the group R_3 is hydrogen is desired, Compound XV is allowed to react with an isocyanate of the formula R_4 - NCO in a routine manner known to the art to afford Compound I.



The compounds of Formula I of the present invention are useful for the treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with central cholinergic innervation. This same innervation is suggested to be weakened in Alzheimer patients. We have determined in vitro inhibition of acetylcholinesterase activity in rat striatum.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in brain roughly correlates with cholinergic innervation and subfractionation shows the highest level in nerve terminals.

It is generally accepted that the physiological role of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinominetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AChE inhibitors may also be beneficial in the treatment of Alzheimer's dementia.

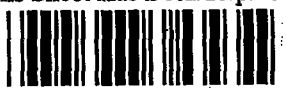
The method described below was used in this invention for assaying cholinesterase activity. This is a modification of the method of Ellman et al., Biochem. Pharmacol. 7, 88 (1961).

Procedure:

A. Reagents -

1. 0.05 M Phosphate buffer, pH 7.2

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(a) 6.85 g $NaH_2PO_4 \cdot H_2O$/100 ml distilled H_2O
(b) 13.40 g $Na_2HPO_4 \cdot 7H_2O$/100 ml distilled H_2O
(c) add (a) to (b) until pH reaches 7.2
(d) Dilute 1:10

2. Substrate in buffer
(a) 198 mg acetylthiocholine chloride (10 mM)
(b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)

3. DTNB in buffer
(a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
(b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)

4. A 2 mM stock solution of the test drug is made up in a suitable solvent and q.s. to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4}M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation -

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed 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 microliter aliquot of the homogenate is added to 1.0 milliter vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37° C.

C. Assay -

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

Instrument Settings

Kinetics Soft-Pac Module #598273 (10)
Program #6 Kindata:
Source - Vis
Wavelength - 412 nm
Sipper - none
Cuvettes - 2 ml cuvettes using auto 6-sampler
Blank - 1 for each substrate concentration
Interval time - 15 seconds (15 or 30 seconds for kinetics) Total time - 5 minutes (5 or 10 minutes for kinetics)
Plot - yes
Span - autoscale
Slope - increasing
Results - yes (gives slope)
Factor - 1

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

Blank:	0.8 ml Phosphate Buffer/DTNB
	0.8 ml Buffer/Substrate
Control:	0.8 ml Phosphate Buffer/DTNB/Enzyme
	0.8 ml Phosphate Buffer/Substrate
Drug:	0.8 ml Phosphate
Buffer/DTNB/Drug/Enzyme	0.8 ml Phosphate Buffer/Substrate

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 IC_{50} Determinations:

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Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration.

$$\% \text{ Inhibition} = \frac{\text{slope control} - \text{slope drug}}{\text{slope control}} \times 100$$

IC_{50} values are calculated from log-probit analysis

Results of this assay for some of the compounds of this invention and physostigmine (reference compound) are presented in Table 1.

TABLE 1

Compound	Inhibitory Concentration (μM) Brain AChE
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.0023
(S)-(-)-1-(propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate	30.21
Physostigmine	0.006

This utility is further demonstrated by the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay described below.

Dark Avoidance Assay

In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compound, resulting in a greater interval before re-entry into the dark compartment.

The results for an active compound are expressed as the percent of a group of animals in which the effect of scopolamine is blocked, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment.

Results of this assay for some of the compounds of this invention and those for tacrine and pilocarpine (reference compounds) are presented in Table 2.

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TABLE 2

Compound	Dose (mg/kg of body weight, s.c)	% of Animals with Scopolamine Induced Memory Deficit Reversal
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.35	21
Tacrine	0.63	13
Pilocarpine	5.0	13

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Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule 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 effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum 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 70% of the weight of the unit. 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 an oral dosage unit form contains between 1.0 - 300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweeting agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a 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 preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose 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 active compound, but may be varied between 0.5 and about 30% 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 inventions are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of 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 methyl parabens; 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 preparation can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-ethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-propylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-isopropylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-cyclohexylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-2-phenylethylcarbamate;
(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1-phenylethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-butylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-heptylcarbamate;

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1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-methylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-piperidinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-4-chlorophenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-heptylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-phenylmethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-
1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-heptylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-yl-methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-4-phenylpiperazin-1-ylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-morpholin-4-ylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate-N-oxide;
1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-(Methyl-4-pyridinylamino)-1H-indol-5-ol;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol;
3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole;
3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indo le;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethox y)-1H-indole;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol;
3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol;
1-(3-Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-5-phenylmethoxy-1H-indole;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-ol;
1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indol-3-carboxaldehyde;
3-Cyano-1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-(2-Phenylethyl-4-pyridinylamino)-1H-indol-5-ol; and
1-(2-Propynyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

Examples of this invention are presented below.

EXAMPLE 1

5-Phenylmethoxy-1H-indole-1-amine

To 5-phenylmethoxyindole (50 g) in 300 ml of dimethylformamide at ice bath temperature was added milled potassium hydroxide (62.72 g). Then hydroxylamine-O-sulfonic acid (32.93 g) was added portionwise, keeping the internal temperature below 20° C. After the addition was complete, the mixture was stirred for one hour, then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (71 g), which was eluted with dichloromethane on silica gel columns via HPLC. The desired fractions were concentrated to yield a solid (21.15 g). Of this material, 3.0 g was triturated with ether to yield a solid, 2.4 g, m.p. 126-128° C.

ANALYSIS:			
Calculated for $C_{15}H_{14}N_2O$:	75.60%C	5.92%H	11.76%N
Found:	75.54%C	5.97%H	11.87%N

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EXAMPLE 2

5-Phenylmethoxy-1-(4-pyridinylamino)-1H-indole

To 250 ml of N-methyl-2-pyrrolidinone was added 5-(phenylmethoxy)-1H-indole-1-amine (29.7 g) and the solution was heated to 80° C. Then 4-chloropyridine hydrochloride (20.55 g) was added portionwise and the mixture was stirred for three hours, cooled, poured into water, basified with aqueous sodium carbonate and extracted with toluene. The organic/aqueous mixture was filtered to yield a solid (39 g), which was triturated with ether to yield a solid (27 g). Of this material, 3.0 g was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 2.5 g, m.p. 143-145° C.

ANALYSIS:			
Calculated for $C_{20}H_{17}N_3O$:	76.17%C	5.44%H	13.32%N
Found:	75.82%C	5.43%H	13.21%N

EXAMPLE 3

1-(4-Pyridinylamino)-1H-indol-5-ol

To 0.8 g of 10% palladium on carbon in 10 ml of absolute ethanol was added a solution of 5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (4.0 g) in 240 ml of absolute ethanol and this was hydrogenated on a Parr apparatus for four hours at 50° C at 50 psig H_2. The mixture was cooled and filtered, and the filtrate was concentrated to yield an oil (4.2 g), which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.72 g). This material was eluted with 10% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a foam (1.8 g), which was recrystallized from ethyl acetate to yield a solid (1.5 g), m.p. 232-234° C.

ANALYSIS:			
Calculated for $C_{13}H_{11}N_3O$:	69.32%C	4.92%H	18.66%N
Found:	69.16%C	4.76%H	18.52%N

EXAMPLE 4

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole hydrochloride

5-(Phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (25 g) was slowly added to an ice-cooled solution of potassium tert-butoxide (11 g) in 250 mL tetrahydrofuran. Following the anion formation, a solution of dimethyl sulfate (12 g) in 25 mL tetrahydrofuran was slowly added so that the internal reaction temperature remained below 10° C. After one hour, the reaction mixture was stirred with water and extracted with ether. The organic layer was washed with water and saturated sodium chloride solution and thereafter dried (anhydrous magnesium sulfate), filtered and concentrated to afford a solid, 28 g. This solid was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 22 g of a solid, m.p. 118-121° C. An analytical sample was prepared by converting 1.5 g to the hydrochloride salt in methanol/ether to yield 1.6 g of crystals, m.p. 235-236° C (dec.).

ANALYSIS:			
Calculated for $C_{21}H_{20}ClN_3O$:	68.94%C	5.51%H	11.49%N
Found:	68.60%C	5.50%H	11.28%N

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EXAMPLE 5

1-(Methyl-4-pyridinylamino)-1H-indol-5-ol

A solution of 1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole (9 g) in 250 mL ethanol containing 0.6 g 10% palladium on activated charcoal was hydrogenated at 50 psi at 50° C for three hours via Parr hydrogenation apparatus. After cooling, the mixture was filtered through Celite and concentrated. The residue was eluted through silica with 5% methanol in dichloromethane via flash column chromatography to yield 6.2 g solid. A three gram portion was recrystallized from acetonitrile to yield 2.6 g solid, m.p. 191-193° C. This was again recrystallized from acetonitrile to yield 2.2 g crystals, m.p. 192-193° C.

ANALYSIS:			
Calculated for $C_{14}H_{13}N_3O$:	70.27%C	5.48%H	17.57%N
Found:	69.96%C	5.39%H	17.53%N

EXAMPLE 6

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

Methyl isocyanate (0.72 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing milled potassium carbonate (2 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield a solid 3.1 g. This was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 2.6 g solid, m.p. 186-188° C. This was recrystallized from 20% methanol in ether to yield 1.6 g of product, m.p. 186-188° C.

ANALYSIS:			
Calculated for $C_{16}H_{16}N_4O_2$:	64.85%C	5.44%H	18.91%N
Found:	64.85%C	5.58%H	18.73%N

EXAMPLE 7

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.2 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.7 g solid, m.p. 108-111° C. This was converted to the hydrochloride salt in methanol/ether to yield 3.3 g crystals, m.p. 232-234° C (dec.).

ANALYSIS:			
Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.89%C	6.34%H	14.88%N

EXAMPLE 8

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (1.7 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl

acetate via flash column chromatography to yield 3.8 g solid. This was recrystallized from acetonitrile to yield 3.2 g crystals, m.p. 179-181 °C.

ANALYSIS:			
Calculated for $C_{22}H_{20}N_4O_2$:	70.95%C	5.41%H	15.05%N
Found:	70.67%C	5.35%H	15.12%N

EXAMPLE 9

1-(Propyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole maleate

To potassium tert-butoxide (2.80 g) in 20 ml of tetrahydrofuran cooled to ice bath temperature was added dropwise a solution of 5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (6.5 g) in 60 ml of tetrahydrofuran. This mixture was stirred for 10 minutes and then a solution of 1-bromopropane (3.08 g) in 10 ml of tetrahydrofuran was added dropwise. The reaction was allowed to proceed for three hours at room temperature. The mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was removed to yield an oil (8.5 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (5.5 g). Of this material 1.0 g was dissolved in methanol and acidified with a methanol solution of maleic acid. After diluting with ether, the precipitate was collected to yield a solid 1.0 g, m.p. 118-119 °C.

ANALYSIS:			
Calculated for $C_{23}H_{23}N_3O \cdot C_4H_4O_4$:	68.48%C	5.75%H	8.67%N
Found:	68.29%C	5.72%H	8.86%N

EXAMPLE 10

1-(Propyl-4-pyridinylamino)-1H-indol-5-ol

To 0.3 g of 10% Pd/C in 10 ml of absolute ethanol was added 5-phenylmethoxy-1-(propyl-4-pyridinylamino)-1H-indole (3.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus for 48 hours at 50 °C and 50 psig H_2. The reaction mixture was then filtered and the filtrate concentrated to yield an oil (2.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (1.8 g) which was recrystallized from methanol/ether (1:1) to yield a solid 1.6 g, m.p. 214-216 °C.

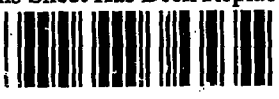
ANALYSIS:			
Calculated for $C_{16}H_{17}N_3O$:	71.89%C	6.41%H	15.72%N
Found:	71.78%C	6.41%H	15.61%N

EXAMPLE 11

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To 2.5 g of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g) followed by methyl isocyanate (0.56 ml). The reaction was allowed to proceed for half an hour. The reaction mixture was then filtered and the filtrate concentrated to yield a solid (2.9 g) which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.7 g) which was recrystallized from isopropyl ether to yield a solid 1.8 g, m.p. 158-159 °C.

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ANALYSIS:			
Calculated for $C_{18}H_{20}N_4O_2$:	66.65%C	6.22%H	17.27%N
Found:	66.83%C	6.10%H	17.18%N

EXAMPLE 12

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl ethylcarbamate hydrochloride

Ethyl isocyanate (1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL of tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.5 g of the product as a solid, m.p. 139-141 °C. This was converted to the hydrochloride salt in methanol/ether to yield 4.3 g of crystals, m.p. 209-211 °C (dec.).

ANALYSIS:			
Calculated for $C_{18}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.81%C	6.16%H	14.84%N

EXAMPLE 13

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl propylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then propyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 2 hours. The mixture was filtered and the filtrate was concentrated to yield an oil (2.8 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.5 g), m.p. 120-122 °C.

ANALYSIS:			
Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	67.87%C	6.89%H	15.93%N

EXAMPLE 14

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl isopropylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then isopropyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 4 hours. The mixture was filtered and the filtrate was concentrated to yield a solid (3.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.75 g), m.p. 131-133 °C.

ANALYSIS:			
Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	68.16%C	6.84%H	15.84%N

EXAMPLE 15

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1-(Propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.3 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as an oil. This material was converted to the hydrochloride salt in methanol/ether to yield 4 g of crystals, m.p. 178-180° C.

ANALYSIS:			
Calculated for $C_{21}H_{26}N_4O_2$*HCl:	62.60%C	6.75%H	13.91%N
Found:	62.52%C	6.71%H	13.84%N

EXAMPLE 16

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 50 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) portionwise, and the reaction was allowed to proceed for 24 hours. To this mixture was added glacial acetic acid (2.15 ml) followed by a solution of heptylamine (1.45 ml) in tetrahydrofuran which had been treated with 0.56 ml of acetic acid. The reaction mixture was then stirred for 21 hours. The mixture was diluted with water, basified with sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (4.5 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (2.8 g). This material was dissolved in 50 ml of pentane/ether (1:1) and the solution was concentrated to 15 ml, whereupon crystals precipitated out of the solution. These were collected to yield a solid (1.0 g), m.p. 83-85° C.

ANALYSIS:			
Calculated for $C_{24}H_{32}N_4O_2$:	70.56%C	7.90%H	13.72%N
Found:	70.33%C	7.69%H	13.63%N

EXAMPLE 17

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl cyclohexylcarbamate hydrochloride

Cyclohexyl isocyanate (1.7 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 167-169°. This solid was again eluted through silica with ethyl acetate via HPLC to yield 3.8 g of the product as a solid, m.p. 167-170° C. The product was converted to the hydrochloride salt in methanol/ether to yield 3.9 g of powder, m.p. 219-220° C (dec.).

ANALYSIS:			
Calculated for $C_{23}H_{28}N_4O_2$*HCl:	64.40%C	6.81%H	13.06%N
Found:	64.07%C	6.77%H	12.92%N

EXAMPLE 18

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1-(Propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (2 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 156-158° C. The product was recrystallized from acetonitrile to yield 3.8 g of crystals, m.p. 162-164° C.

ANALYSIS:			
Calculated for $C_{24}H_{24}N_4O_2$:	71.98%C	6.04%H	13.99%N
Found:	71.98%C	6.13%H	14.03%N

EXAMPLE 19

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 4-chlorophenylmethylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by 4-chlorophenylmethylamine (1.5 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.9 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (3.05 g), m.p. 149-151° C

ANALYSIS:			
Calculated for :	66.29%C	5.33%H	12.88%N
Found:	66.22%C	5.37%H	12.81%N

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EXAMPLE 20

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 2-phenylethylcarbamate hydrochloride

2-Phenylethyl isocyanate (2.1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3.5 g). After stirring three hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.7 g of the product as a solid. The product was converted to the hydrochloride salt in methanol/ether to yield 2.9 g of crystals, m.p. 144-146° C (dec.).

ANALYSIS:			
Calculated for $C_{25}H_{26}N_4O_2 \cdot HCl$:	66.58%C	6.04%H	12.43%N
Found:	66.60%C	5.94%H	12.38%N

EXAMPLE 21

(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.75 g) in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 0.912 g) followed by (S)-(-)-1-methylbenzyl isocyanate (0.97 g), and the reaction was allowed to proceed for one hour. The reaction mixture was filtered and the filtrate concentrated to yield an

oil (3.9 g) which was eluted with 5% methanol in dichloromethane (DCM) on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid 2.6 g, m.p. 78-80° C.

ANALYSIS:			
Calculated for $C_{25}H_{25}N_7O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.17%C	6.34%H	13.49%N

EXAMPLE 22

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethyl carbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by dimethylamine (40 wt % in water, 1.44 ml) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl., anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.5 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.5 g), m.p. 134-136° C.

ANALYSIS:			
Calculated for :	67.43%C	6.55%H	16.56%N
Found:	67.63%C	6.58%H	16.58%N

This Sheet Has Been Replace

EXAMPLE 23

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl piperidinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by piperidine (0.95 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.8 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.65 g).

ANALYSIS:			
Calculated for $C_{22}H_{25}N_4O_2$:	69.81%C	6.92%H	14.80%N
Found:	69.45%C	6.94%H	14.68%N

EXAMPLE 24

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 40 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 3.5 ml of glacial acetic acid was added to the reaction mixture. Then 1,2,3,4-tetrahydroisoquinoline (1.49 g) in 10 ml of tetrahydrofuran which had been acidified with 0.60 ml of glacial acetic acid was added to the reaction mixture dropwise. This was stirred for 24 hours and then the reaction mixture was quenched with water, basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and

dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (5.6 g) which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC The desired fractions were concentrated to yield an oil (4.2 g). This material was dissolved in pentane/ether (1:1), whereupon a solid precipitated out of the solution. This material was collected to yield a solid, 2.6 g, m.p. 141-143° C.

ANALYSIS:			
Calculated for $C_{26}H_{26}N_4O_2$:	73.21%C	6.15%H	13.14%N
Found:	73.12%C	6.22%H	12.95%N

EXAMPLE 25

1-(3-Fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole

To 250 ml 1-methyl-2-pyrrolidinone was added 5-phenylmethoxy-1H-indol-1-amine (27.3 g), and the mixture was heated to 80° C. Then, 4-chloro-3-fluoropyridine hydrochloride (22 g) was added, and the mixture was heated at 80° C for two hours. After cooling, the mixture was poured into 1 liter of ice-water, stirred for five minutes, and adjusted to pH 9 with milled K_2CO_3. The product was extracted with ethyl acetate (3X). The organic layer was washed with water (2X) and dried (saturated NaCl, anhydrous $MgSO_4$). After filtration, the filtrate was concentrated to give an oil, 48 g of which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on cooling, 32.2 g, m.p. 140° C. A sample of this material was recrystallized from ether, m.p. 157-159° C.

ANALYSIS:			
Calculated for $C_{20}H_{15}FN_3O$:	72.06%C	4.84%H	12.60%N
Found:	71.98%C	4.90%H	12.51%N

EXAMPLE 26

1-[(3-Fluoro-4-pyridinyl)propylamino]-5-phenylmethoxy-1H-indole hydrochloride

To 100 ml of dry DMF (dimethylformamide) was added 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (20.0 g), and the solution was cooled to 0° C. To this was added potassium t-butoxide (6.7 g), and the mixture was stirred at 0° C for ten minutes, and thereafter a solution of n-propylbromide (5.5 ml) in 10 ml dry DMF was added. After stirring at 0° C for thirty minutes and then at ambient temperature for two hours, the mixture was poured into 500 ml cold water, stirred for five minutes and extracted with ethyl acetate (3X). The organic layer was washed successively with water (2X) and saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give an oil, 23 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:2) via HPLC. The desired fractions were combined and concentrated to give an oil, 19.3 g. A 2.0 g sample of this oil was dissolved in 50 ml methanol, and the solution was acidified to pH 1 with ethereal HCl and diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g, m.p. 200° C (dec.).

ANALYSIS:			
Calculated for $C_{23}H_{22}FN_3O \cdot HCl$:	67.08%C	5.63%H	10.20%N
Found:	66.74%C	5.55%H	10.05%N

EXAMPLE 27

1-(3-Fluoro-4-pyridinylamino)-1H-indol-5-ol

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In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.0 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (5.0 g) in 200 ml ethanol. The mixture was shaken at 50° C under 50 psi hydrogen gas for two hours. After cooling, the mixture was filtered, and the filtrate was concentrated to give an oil (5.0 g) which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a crystalline solid, 3.5 g, m.p. 70-73° C.

ANALYSIS:			
Calculated for $C_{19}H_{10}FN_3O$:	64.19%C	4.14%H	17.28%N
Found:	64.06%C	4.30%H	16.93%N

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EXAMPLE 28

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol hydrochloride

In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.5 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-5-phenylmethoxy-1H-indole (15.0 g) in 200 ml ethanol. The mixture was shaken under 50 psi hydrogen gas for three hours at 50° C. Upon cooling, the mixture was filtered, and the filtrate was concentrated to give a solid, 11.4 g. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC, and the desired fractions were concentrated to give a solid, 8.5 g, m.p. 90-95° C. A 2.0 g sample of this material was dissolved in 50 ml methanol, the pH was adjusted to 1 with ethereal HCl, and the solution was diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g of the product, m.p. 218° C (dec.).

ANALYSIS:			
Calculated for $C_{15}H_{16}FN_3O \cdot HCl$:	59.72%C	5.33%H	13.06%N
Found:	59.30%C	5.36%H	12.62%N

EXAMPLE 29

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl methylcarbamate

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]- 1H-indol-5-ol (2.5 g) in 50 ml THF was added potassium carbonate (1.2 g), followed by methyl isocyanate (0.53 ml). After stirring at ambient temperature for three hours, the mixture was filtered, and the filtrate was concentrated to give a solid, 3.0 g, m.p. 165-166° C. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a solid, 2.7 g, m.p. 177-178° C.

ANALYSIS:			
Calculated for $C_{18}H_{19}FN_4O_2$:	63.14%C	5.59%H	16.37%N
Found:	63.27%C	5.68%H	16.23%N

EXAMPLE 30

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl butylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 50 ml tetrahydrofuran was added milled K_2CO_3 (1.1 g), followed by butyl isocyanate (0.9 ml). After stirring at ambient temperature for four hours, the mixture was filtered, and the filtrate was concentrated to give an oil, 5 g. This oil was eluted on a silica gel column with ethyl acetate/dichloromethane (1:4) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on standing, 2.7 g, m.p. 95-98° C.

This solid was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.9 g of a solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:10) to give the product as crystals, 2.4 g, m.p. 142°C (dec.).

ANALYSIS:			
Calculated for $C_{21}H_{25}FN_4O_2 \cdot HCl$:	59.92%C	6.23%H	13.31%N
Found:	60.31%C	6.26%H	13.31%N

EXAMPLE 31

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl heptylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 65 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.5 g), and the mixture was stirred at ambient temperature for four hours. The mixture was cooled with an ice bath, and thereafter glacial acetic acid (2.0 ml) was added, followed by a solution of heptylamine (2 ml) and acetic acid in tetrahydrofuran (20 ml).

After stirring at ambient temperature for twenty hours, the mixture was poured into 200 ml water, the pH adjusted to 8 with $NaHCO_3$ solution, and the product was extracted with ethyl acetate. The organic layer was washed successively with water and saturated NaCl solution, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to give an oil, 4.2 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC. The desired fractions were combined and concentrated to give an oil, 2.6 g. This oil was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.5 g of solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:4) to give crystals, 2.3 g, m.p., 246°C (dec.).

ANALYSIS:			
Calculated for $C_{24}H_{31}FN_4O_2 \cdot HCl$:	62.26%C	6.97%H	12.10%N
Found:	62.62%C	7.08%H	12.06%N

EXAMPLE 32

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine

p-Benzyloxyphenylhydrazine hydrochloride was prepared by the method of Mentzer, et al., [C.A. 48:33412]. Thus, p-benzyloxyaniline hydrochloride (72.6 g) was diazotized with conc. HCl (174 ml) and sodium nitrite (23.2 g) in water (40 ml) at 0°C. A solution of stannous chloride (169.3 g) in conc. HCl (435 ml) was added rapidly and the reaction mixture stirred for two hours. The solid product was filtered and washed with absolute ethanol, then partially dissolved in boiling methanol/ethanol (1:1) and filtered hot, yielding 52.5 g of p-benzyloxyphenylhydrazine hydrochloride.

The conversion of the above compound to 3-methyl-5-benzyloxyindole was conducted according to the method of Keglevic, et al. [C.A. 56:4710h]. Thus, the above hydrazine hydrochloride (34.0 g) was dissolved in 25% aqueous HOAc (1.4 L) at 80°C. Propionaldehyde diethyl acetal (22.1 ml) was then added and the reaction mixture stirred for 0.75 hour. Upon cooling to room temperature, ether was added to the reaction mixture and the layers were separated. The aqueous phase was extracted with ether (2x). The combined organics were washed with 5% aqueous NaOH until the aqueous extract was basic to litmus. The organic phase was then washed with brine and dried (K_2CO_3). Filtration and concentration afforded 29.0 g of 3-methyl-5-benzyloxyindole.

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine was prepared using the procedure of Somei, et al., [Tetrahedron Lett. No. 5, pp. 461-462, 1974]. Thus, to a solution of the above product (17.3 g) in dry DMF (260 ml) maintained at 0°C was added milled potassium hydroxide (20.5 g) under nitrogen. Hydroxylamine-O-sulfonic acid (10.7 g) was added portionwise (10% wt.) every ten minutes. After stirring for 1 hour at room temperature, water and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with

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brine and dried (K_2CO_3). Filtration and concentration gave the crude product.

Purification via preparative HPLC (silica gel, DCM) afforded 6.0 g of the desired product as a solid which was recrystallized from ether, m.p. 104-106 °C.

ANALYSIS:			
Calculated for $C_{16}H_{16}N_2O$:	76.16%C	6.39%H	11.10%N
Found:	75.86%C	6.37%H	10.87%N

EXAMPLE 33

3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (6.31 g) and 1-methyl-2-pyrrolidinone (109 ml) was added 4-chloropyridine hydrochloride (3.94 g). The resulting mixture was heated at 80 °C for 4-5 hours. Another batch of reaction was also carried out with the amine (2.94 g) and 4-chloropyridine hydrochloride (1.84 g) in nmp (50 ml) at 80 °C for 4 hours. The above reaction mixtures were poured together into dilute aqueous sodium bicarbonate and extracted with EtOAc (4x) and ether (1x). The combined organic layers were washed with water and brine followed by drying (K_2CO_3). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether/0-5% MeOH) afforded 7.55 g of the desired product. Recrystallization from EtOAc gave a solid, m.p. 167.5-169.5 °C.

ANALYSIS:			
Calculated for $C_{21}H_{19}N_3O$:	76.57%C	5.81%H	12.76%N
Found:	76.73%C	6.05%H	12.76%N

EXAMPLE 34

3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol

3-Methyl-5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (2.20 g) was subjected to hydrogenolysis in absolute ethanol (80 ml) with 10% Pd-C (0.26 g) at 50 psig hydrogen at 50 °C for 2 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. Concentration and recrystallization from methanol afforded 0.50 g of highly crystalline product, m.p. 239-241 °C (dec.).

ANALYSIS:			
Calculated for $C_{14}H_{13}N_3O$:	70.28%C	5.48%H	17.56%N
Found:	69.95%C	5.46%H	17.41%N

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EXAMPLE 35

3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole hemifumarate

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (7.78 g) and dimethylformamide (150 ml) maintained at 0 °C under nitrogen with stirring, was added sodium hydride (0.64 g, 97% purity). The resulting mixture was stirred at 0 °C for an additional 15 minutes at which time propyl bromide (2.25 ml) was added dropwise and the ice bath was removed. Stirring was continued at room temperature for 2-3 hours until complete reaction was observed by TLC (silica gel, ether). The reaction mixture was poured into water and the product extracted with EtoAc (3x) and ether (1x). The combined organic layers were washed successively with water (2x) and brine (2x), dried (K_2CO_3) and decolorized with activated carbon. Filtration and concentration gave the desired product (7.65 g) as an oil. The hemifumarate was prepared with 1.0 eq. fumaric acid in abs. ethanol. A highly crystalline solid resulted,

m.p. 165.5-167° C.

ANALYSIS:			
Calculated for $C_{24}H_{25}N_3O \cdot 0.5\ C_4H_4O_4$:	72.70%C	6.35%H	9.78%N
Found:	72.66%C	6.55%H	9.73%N

EXAMPLE 36

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol hemioxalate

The benzyl group of 3-methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole (7.80 g) was cleaved in a Parr hydrogenation apparatus in abs. EtOH (275 ml) over 10% Pd-C (0.80 g) at 50 psig and 50° C for 2-3 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. The combined filtrate was concentrated and the product purified via flash column chromatography (silica gel, 2% Et_3N/ether) affording 5.80 g of the product as an oil. Dissolving in absolute ethanol followed by addition of 1.0 eq of anhydrous oxalic acid (in abs. EtOH) resulted in formation of a solid, the hemioxalate, m.p. 235-237° C.

ANALYSIS:			
Calculated for $C_{17}H_{19}N_3O \cdot 0.5\ C_2H_2O_4$:	66.23%C	6.19%H	12.88%N
Found:	65.91%C	6.33%H	12.58%N

EXAMPLE 37

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.06 g) and tetrahydrofuran (49 ml) was added milled K_2CO_3 (1.06 g) followed by dropwise addition of methyl isocyanate (0.48 ml) at room temperature under nitrogen. Stirring was continued for 2.3 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.30 g of the desired carbamate as an oil. The product was crystallized from ether, m.p. 147-149° C.

ANALYSIS:			
Calculated for $C_{19}H_{22}N_4O_2$:	67.44%C	6.55%H	16.56%N
Found:	67.49%C	6.68%H	16.53%N

EXAMPLE 38

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.11 g) and tetrahydrofuran (50 ml) was added milled K_2CO_3 (1.09 g), followed by dropwise addition of butyl isocyanate (0.93 ml) at room temperature under nitrogen. Stirring was continued for 2.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.65 g of the desired carbamate as an oil. This oil was dissolved in a small amount of EtOAc and diluted with ether, whereupon the product crystallized as a white powder, m.p. 120-122° C.

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ANALYSIS:			
Calculated for $C_{22}H_{28}N_4O_2$:	69.45%C	7.42%H	14.72%N
Found:	69.67%C	7.44%H	14.68%N

EXAMPLE 39

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.23 g) and tetrahydrofuran (53 ml) was added 1,1'-carbonyldiimidazole (2.57 g) at room temperature with stirring under nitrogen. Stirring was continued for 96 hours, at which time acetic acid (1.54 ml) was added. To the resulting reaction mixture was added a solution consisting of heptyl amine (1.76 ml), acetic acid (0.71 ml) and THF (5 ml). After stirring for 24 hours, an additional solution of heptyl amine (1.17 ml), acetic acid (0.48 ml) and THF (5 ml) was added and stirring continued for 3 hours. The reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) afforded 1.60 g of the desired carbamate after recrystallization from ether/pentane, m.p. 102-104 °C.

ANALYSIS:			
Calculated for $C_{25}H_{34}N_4O_2$:	71.06%C	8.11%H	13.26%N
Found:	71.10%C	8.08%H	13.25%N

EXAMPLE 40

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.80 g) and tetrahydrofuran (43 ml) were added with stirring at room temperature milled potassium carbonate (0.93 g) and benzyl isocyanate (0.87 ml). Stirring was continued under nitrogen for 16 hours. The mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration followed by purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.28 g of the desired carbamate. Recrystallization from ether gave a highly crystalline solid, m.p. 149-151 °C.

ANALYSIS:			
Calculated for $C_{25}H_{26}N_4O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.39%C	6.73%H	13.92%N

EXAMPLE 41

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl, 1,2,3,4-tetrahydro-2-isoquinolylincarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.87 g) and tetrahydrofuran (40 ml) was added 1,1'-carbonyldiimidazole (1.92 g) at room temperature with stirring under nitrogen. Stirring was continued for 48 hours, at which time acetic acid (1.6 ml) was added. To the resulting reaction mixture was added a solution consisting of 1,2,3,4-tetrahydroisoquinoline (1.6 ml), acetic acid (0.76 ml) and THF (10 ml). After stirring for 16 hours, the reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) gave 2.41 g of the desired carbamate as a foam. The compound formed a white powder in ether/pentane, m.p. 160-162 °C.

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ANALYSIS:			
Calculated for $C_{27}H_{28}N_4O_2$:	73.61%C	6.41%H	12.72%N
Found:	73.57%C	6.38%H	12.61%N

EXAMPLE 42

1-[(3-Fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (4.81 g) and 1-methyl-2-pyrrolidinone (83 ml) was added 4-chloro-3-fluoro pyridine hydrochloride (3.20 g). The resulting mixture was heated at 80°C for 2 hours. Upon cooling to room temperature, dilute aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed successively with water (2x) and brine (1x), and thereafter dried ($MgSO_4$). Filtration and concentration gave the crude product. Purification via flash column chromatography (silica gel, 50% ethyl acetate/dichloromethane) afforded 4.0 g of the desired product as a solid, m.p. 210-213°C.

EXAMPLE 43

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole (3.76 g) and dimethylformamide (106 ml), cooled to 0°C under nitrogen with stirring, was added sodium hydride (0.29 g). The resulting mixture was stirred at 0°C for an additional 15 minutes, at which time 1-bromopropane (1.03 ml) was added dropwise and the ice bath removed. Stirring was continued at room temperature overnight, at which time the reaction appeared complete by TLC (silica gel, 50% ether/hexane). The reaction mixture was poured into water and the product extracted with EtoAc (3x). The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the crude product as an oil. Purification via preparative HPLC (silica gel, 30% EtOAc/hexane) afforded 2.80 g of the desired product as a solid which was recrystallized from ether, m.p. 94-96°C.

ANALYSIS:			
Calculated for $C_{24}H_{24}FN_3O$:	74.01%C	6.21%H	10.79%N
Found:	73.58%C	6.09%H	10.56%N

EXAMPLE 44

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol

The benzyl group of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole (15.82 g) was cleaved in a Parr hydrogenation apparatus in absolute ethanol (200 ml) over 10% Pd-C (1.58 g) at 50 psig and 50°C for 7.5 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with absolute ethanol. The combined filtrate was concentrated and the product purified via preparative HPLC (silica gel, 3:1 dichloromethane/EtOAc) affording 5.0 g of the desired product as an oil. Addition of EtOAc solidified the product which was recrystallized from EtOAc to give a solid, m.p. 157-160°C.

ANALYSIS:			
Calculated for $C_{17}H_{16}FN_3O$:	68.21%C	6.06%H	14.04%N
Found:	67.81%C	6.09%H	13.73%N

EXAMPLE 45

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl methylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of methyl isocyanate (0.46 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 50% EtOAc/dichloromethane) afforded 2.35 g of the desired carbamate as a solid. The product was recrystallized from ether, m.p. 163-164 °C.

ANALYSIS:			
Calculated for $C_{19}H_{21}FN_4O_2$:	64.03%C	5.94%H	15.72%N
Found:	63.84%C	6.10%H	15.55%N

EXAMPLE 46

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of butyl isocyanate (0.87 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, ether) afforded 2.3 g of the desired product as an oil. The product was crystallized from ether/pentane, m.p. 83-84 °C.

ANALYSIS:			
Calculated for $C_{22}H_{27}FN_4O_2$:	66.31%C	6.83%H	14.06%N
Found:	65.99%C	6.83%H	13.88%N

EXAMPLE 47

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl heptylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.54 g) and anhydrous tetrahydrofuran (57 ml) was added carbonyl diimidazole (2.75 g) under nitrogen with stirring. The resulting reaction mixture was stirred at room temperature for two days, at which time acetic acid (1.65 ml) was added followed by a solution of heptylamine (1.89 ml) in tetrahydrofuran (5 ml) and acetic acid (0.76 ml). After stirring for 24 hours, an additional equivalent of heptylamine (1.26 ml) in tetrahydrofuran (5 ml) and acetic acid (0.52 ml) was added. After an additional 24 hours the reaction was complete and the reaction mixture was poured into $NaHCO_3$ (aq.) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq.) and brine. Drying (Na_2SO_4), filtration and concentration gave a crude product. Purification via flash column chromatography (silica gel, 30% EtOAc/hexane) afforded 3.38 g of the desired product as an oil. Addition of ether and pentane solidified the product. The solid was filtered and washed with pentane, m.p. 90-93 °C.

ANALYSIS:			
Calculated for $C_{25}H_{33}FN_4O_2$:	68.16%C	7.55%H	12.72%N
Found:	67.87%C	7.35%H	12.60%N

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EXAMPLE 48

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl phenylmethylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-3-methyl-1H-indol-5-ol(2.66 g) in tetrahydrofuran (59 ml) was added milled potassium carbonate (1.29 g) followed by dropwise addition of benzyl isocyanate (1.21 ml) at room temperature under nitrogen. Stirring was continued for 17.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration afforded a crude product. Purification via flash column chromatography (silica gel, ether) afforded 3.34 g of the desired carbamate as a foam. This foam was dissolved in ether and the product crystallized as a solid. The solid was recrystallized from ether, m.p. 143-144° C.

ANALYSIS:			
Calculated for $C_{25}H_{25}FN_4O_2$:	69.42%C	5.83%H	12.96%N
Found:	69.44%C	5.83%H	12.84%N

EXAMPLE 49

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.51 g) in anhydrous tetrahydrofuran (56 ml) was added 1,1'-carbonyl diimidazole (2.72 g) at room temperature under nitrogen. After 24 hours the reaction appeared complete by TLC (silica gel, 60% EtOAc/hexane) and acetic acid (1.60 ml) was added to the reaction mixture followed by the dropwise addition of a solution of 1,2,3,4-tetrahydroisoquinoline (1.58 ml) in tetrahydrofuran (5.0 ml) and acetic acid (0.75 ml). After 72 hours, the reaction was not complete by TLC (60% EtOAc/dichloromethane) and an additional equivalent of 1,2,3,4-tetrahydroisoquinoline (1.05 ml) was added as a tetrahydrofuran (5.0 ml) and acetic acid (0.51 ml) solution. After 1.5 hours the reaction appeared complete and the mixture was poured into $NaHCO_3$ (aq) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq) and brine, and dried (Na_2SO_4). The organic phase was filtered and concentrated to give a crude product. Purification via flash column chromatography (silica gel., 30% EtOAc/dichloromethane) afforded 2.70 g of the desired product as an oil which solidified on standing. Recrystallization from ether (2x) gave a solid which was filtered and washed with ether, m.p. 157-160° C.

ANALYSIS:			
Calculated for $C_{27}H_{27}FN_4O_2$:	70.72%C	5.94%H	12.22%N
Found:	70.93%C	5.85%H	12.11%N

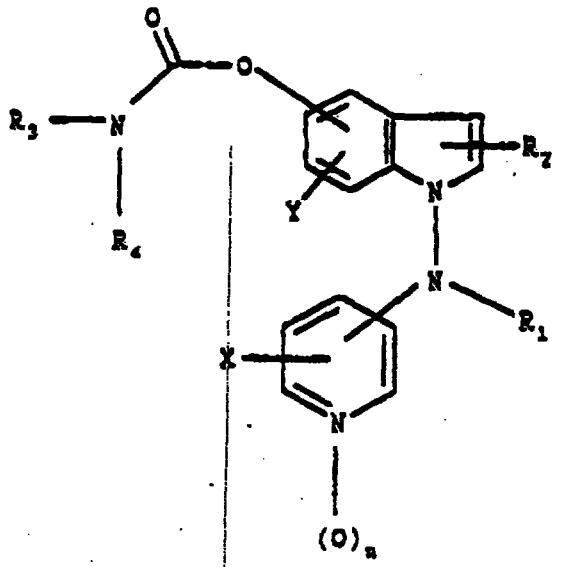
Claims

1. A compound of the formula Ia

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(Ia)

wherein

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

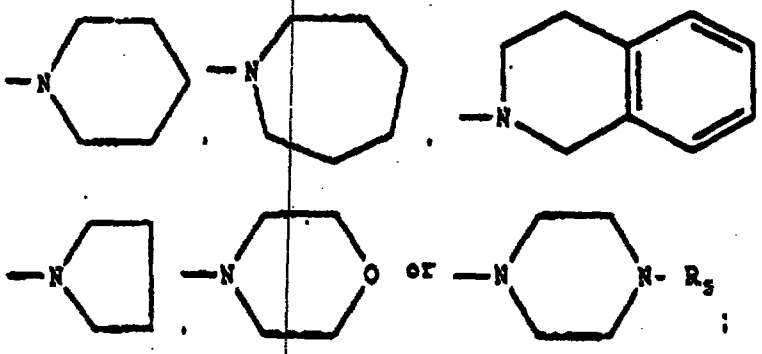
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;

R_2 is hydrogen, loweralkyl, formyl or cyano;

R_3 is hydrogen or loweralkyl;

R_4 is lowaralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;

or alternatively, $-NR_3R_4$ taken together constitutes



R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof.

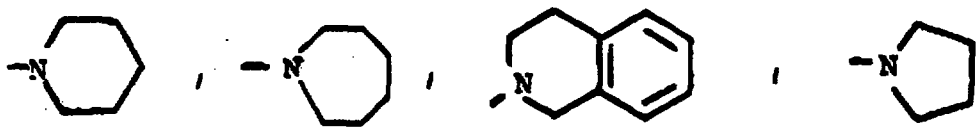
2. A compound of the formula Ia as defined in claim 1, wherein

n is 0,

X is hydrogen or halogen and Y is hydrogen.

3. A compound of the formula Ia as defined in claim 2 wherein R_1 and R_2 are each independently H or loweralkyl.

4. A compound of the formula Ia as defined in claim 3 wherein R_3 is hydrogen, R_4 is loweralkyl, aryloweralkyl, cycloalkyl or alternatively $-NR_3R_4$ taken together constitutes



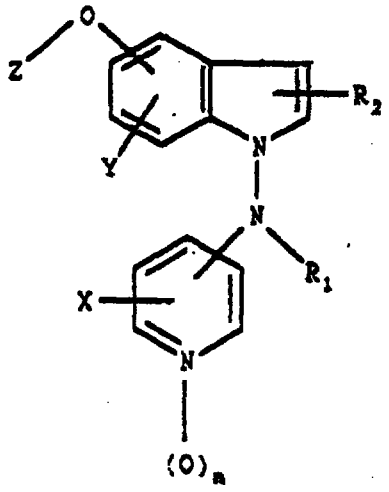
5. A compound as defined in claim 1, which is 1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate.

6. A compound as defined in claim 1, which is (S)-(-)-1-(propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate.

7. A pharmaceutical composition which comprises a compound as defined in claim 1 as the active ingredient and a suitable carrier therefor.

8. Use of a compound a defined in claim 1 for the preparation of a medicament having the activity of alleviating a memory dysfunction characterized by a cholinergic deficit.

9. A compound of the formula Ib



Ib

wherein

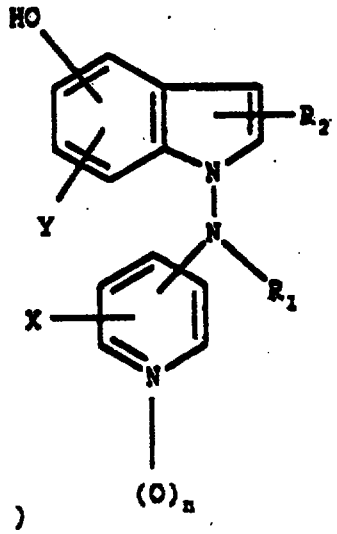
n is 0 or 1;
X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2 is hydrogen, loweralkyl, formyl or cyano;
Z is hydrogen, loweralkyl or benzyl

and all optical and geometrical stereoisomers and racemic mixtures thereof.

10. A compound of the formula Ib a defined in claim 7 wherein X is halogen or hydrogen, Y is hydrogen and R_1 and R_2 are each independently H or loweralkyl.

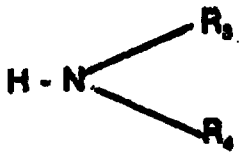
11. A process for the preparation of a compound of the formula Ia, as defined in claim 1, which comprises
a) reacting a compound of the formula XV

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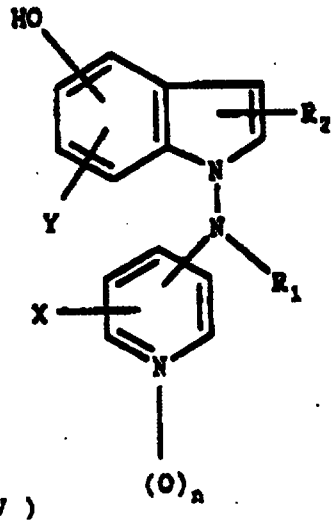
(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with 1,1'-carbonyldiimidazol to afford an intermediate which is treated with an amine of the formula



wherein R_3 and R_4 are defined as in claim 1, or

b) reacting a compound of the formula XV



(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with an isocyanate of the formula

R_4 - NCO

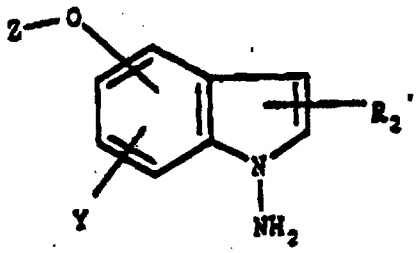
wherein R_4 is defined as above, to afford a compound of the formula Ia, where X, Y, R_1, R_2, R_4 and n are a defined above and R_3 is hydrogen.

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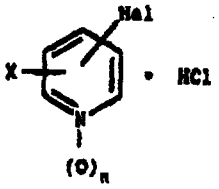
12.

a) A process for the preparation of a compound of the formula Ib according to claim 7, which comprises reacting a compound of the formula IV,



(IV)

wherein R_2 and Y are defined as in claim 7 with a halopyridine of the formula



wherein X and n are as defined in claim 7 and Hal is fluorine, chlorine, bromine or jodine, to afford a compound of the formula Ib, wherein X, Y, R_2 and n are a defined in claim 7, Z is benzyl or loweralkyl and R_1 is hydrogen,

b) optionally reacting a compound of the formula Ib as obtained in step a) with a suitable base of afford the corresponding anion, which is reacted with a halide of the formula

R_1 - Hal

wherein R_1 is defined as in claim 7, except hydrogen, and Hal is chlorine, bromine or jodine, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl and R_1 is defined as in claim 7, except hydrogen,

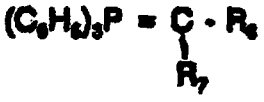
c) optionally reacting a compound of the formula Ib as obtained in step a) wherein R_2 is hydrogen with a suitable base to afford the corresponding anion, which is reacted with a diloweralkylsulfate of the formula

$R_1 - OSO_2 - OR_1$

wherein R_1 is loweralkyl to afford a compound of the formula Ib according to claim 7 wherein Z is benzyl or loweralkyl and R_1 is loweralkyl,

d) optionally reacting a compound of the formula Ib as obtained in step a), b) or c), wherein R_2 is hydrogen with phosphorus oxychloride and dimethylformamide to afford a compound of the formula Ib according to claim 7, wherein Z is benzyl or loweralkyl and R_2 is formyl,

e) optionally reacting a compound of the formula Ib as obtained in step d) with an ylide of the formula



wherein R_6 and R_7 are each independently hydrogen or loweralkyl, to afford a compound of the formula Ib wherein R_2 is loweralkenyl, which is reduced to afford a compound of the formula Ib,

according to claim 7 wherein Z is benzyl or loweralkyl and R_2 is loweralkyl.

f) optionally reacting a compound of the formula Ib as obtained in step d) with hydroxylamine to afford the corresponding oxime, which is treated with benzenesulfonyl chloride, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or lower alkyl and R_2 is the cyano group.

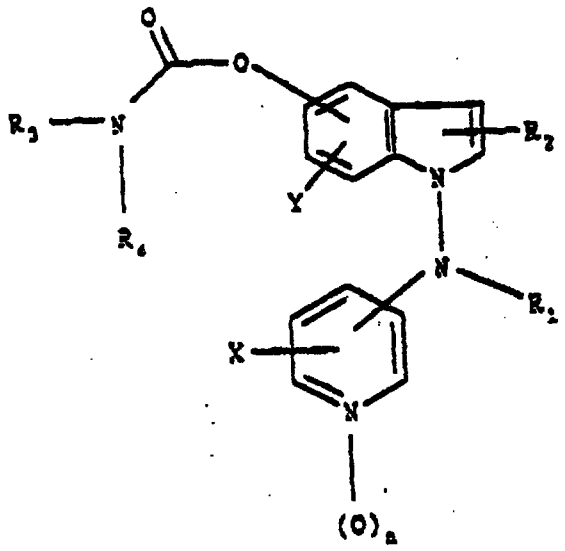
g) optionally reacting a compound of the formula Ib as obtained in step a) with ethyl chloroformate to afford the corresponding N-ethylcarbamate which is optionally treated as described in steps d), e) or f) to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl, R_1 is alkoxycarbonyl, and R_2 is formyl, loweralkyl or cyano.

h) optionally subjecting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is benzyl to a hydrogenolysis, to afford a compound of the formula Ib according to claim 7 wherein Z is hydrogen.

i) optionally reacting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is loweralkyl with a suitable cleavage reagent, such as HBr, borontribromide etherate, trimethylsilyl iodide or a sodium salt of ethylmercaptan, to afford a compound of the formula Ib according to claim 7, wherein Z is hydrogen.

Claims for the following Contracting States: ES, GR

1. A process for the preparation of compound of the formula Ia



(Ia)

wherein

n	is 0 or 1;
X	is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y	is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1	is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2	is hydrogen, loweralkyl, formyl or cyano;
R_3	is hydrogen or loweralkyl;
R_4	is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
	or alternatively, $-NR_3R_4$ taken together constitutes

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according to claim 7 wherein Z is benzyl or loweralkyl and R_2 is loweralkyl.

f) optionally reacting a compound of the formula Ib as obtained in step d) with hydroxylamine to afford the corresponding oxime, which is treated with benzenesulfonyl chloride, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or lower alkyl and R_2 is the cyano group.

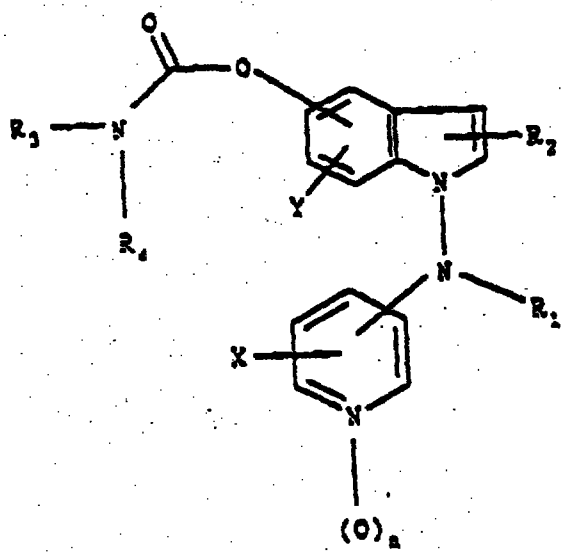
g) optionally reacting a compound of the formula Ib as obtained in step a) with ethyl chloroformate to afford the corresponding N-ethylcarbamate which is optionally treated as described in steps d), e) or f) to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl, R_1 is alkoxycarbonyl, and R_2 is formyl, loweralkyl or cyano.

h) optionally subjecting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is benzyl to a hydrogenolysis, to afford a compound of the formula Ib according to claim 7 wherein Z is hydrogen.

i) optionally reacting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is loweralkyl with a suitable cleavage reagent, such as HBr, borontribromide etherate, trimethylsilyl iodide or a sodium salt of ethylmercaptan, to afford a compound of the formula Ib according to claim 7, wherein Z is hydrogen.

Claims for the following Contracting States: ES, GR

1. A process for the preparation of compound of the formula Ia



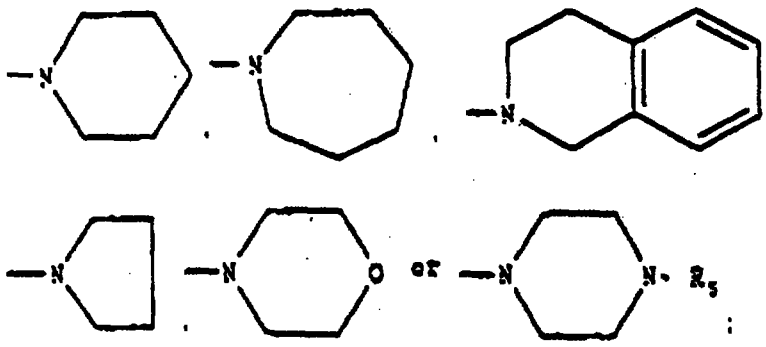
(Ia)

wherein

n is 0 or 1;
X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2 is hydrogen, loweralkyl, formyl or cyano;
R_3 is hydrogen or loweralkyl;
R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
or alternatively, $-NR_3R_4$ taken together constitutes

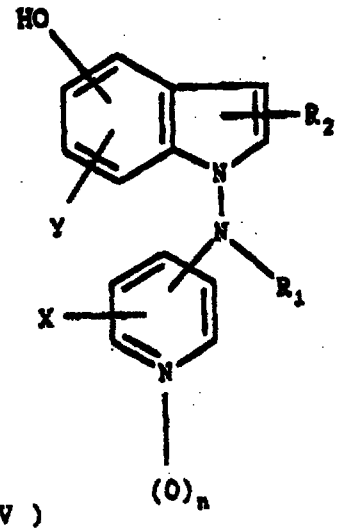
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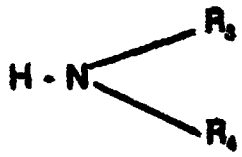
R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof, which comprises

a) reacting a compound of the formula XV



(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with 1,1'-carbonyldiimidazol to afford an intermediate which is treated with an amine of the formula

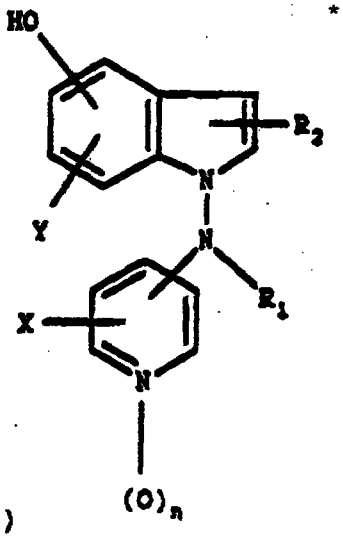


wherein R_3 and R_4 are defined as in claim 1, or

b) reacting a compound of the formula XV

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(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with an isocyanate of the formula

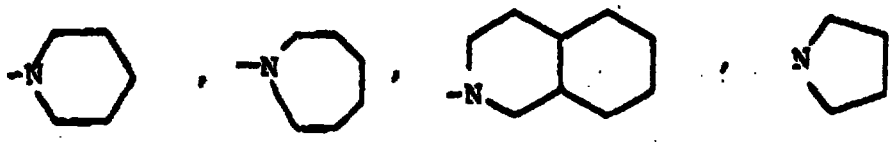
R_4 - NCO

wherein R_4 is defined as above, to afford a compound of the formula Ia, where X, Y, R_1, R_2, R_4 and n are as defined above and R_3 is hydrogen.

2. A process as defined in claim 1, wherein
   n is 0,
   X is hydrogen or halogen and Y is hydrogen.

3. A process as defined in claim 2, wherein R_1 and R_2 are each independently H or loweralkyl.

4. A process as defined in claim 3, wherein R_3 is hydrogen, R_4 is loweralkyl, arylloweralkyl, cycloalkyl or alternatively $-NR_3R_4$ taken together constitutes

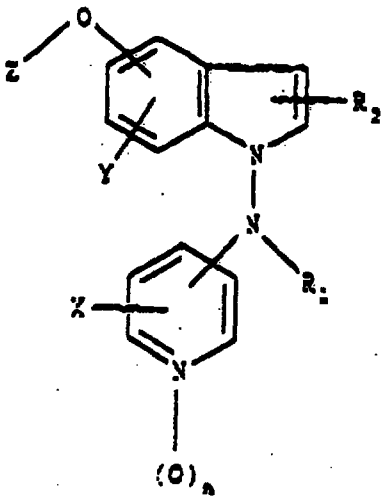


5. A process as defined in claim 1, wherein 1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate or a pharmaceutically acceptable acid addition salt thereof is prepared.

6. A process as defined in claim 1, wherein is (S)-(-)-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-1-phenylethylcarbamate or a pharmaceutically acceptable acid addition salt thereof is prepared.

7. A process for the preparation of a compound of the formula Ib

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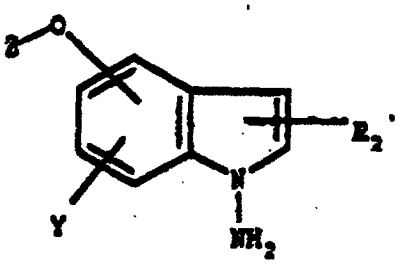
Ib

wherein

n is 0 or 1;
X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2 is hydrogen, loweralkyl, formyl or cyano;
Z is hydrogen, loweralkyl or benzyl

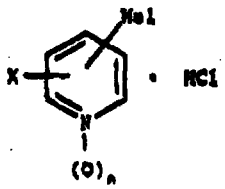
and all optical and geometrical stereoisomers and racemic mixtures thereof, which comprises

a) reacting a compound of the formula IV,



(IV)

wherein R_2 and Y are defined as in claim 7 with a halopyridine of the formula



wherein X and n are as defined in claim 7 and Hal is fluorine, chlorine, bromine or jodine, to afford a compound of the formula Ib, wherein X, Y, R_2 and n are as defined in claim 7, Z is bezyl or loweralkyl and R_1 is hydrogen,

b) optionally reacting a compound of the formula Ib as obtained in step a) with a suitable base of afford the corresponding anion, which is reacted with a halide of the formula

R_1 - Hal

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wherein R_1 is defined as in claim 7, except hydrogen, and Hal is chlorine, bromine or jodine, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl and R_1 is defined as in claim 7, except hydrogen,

c) optionally reacting a compound of the formula Ib as obtained in step a) wherein R_2 is hydrogen with a suitable base to afford the corresponding anion, which is reacted with a diloweralkylsulfate of the formula

$$R_1 - OSO_2 - OR_1$$

wherein R_1 is loweralkyl to afford a compound of the formula Ib according to claim 7 wherein Z is benzyl or loweralkyl and R_1 is loweralkyl,

d) optionally reacting a compound of the formula Ib as obtained in step a), b) or c), wherein R_2 is hydrogen with phosphorous oxychloride and dimethylformamide to afford a compound of the formula Ib according to claim 7, wherein Z is benzyl or loweralkyl and R_2 is formyl,

e) optionally reacting a compound of the formula Ib as obtained in step d) with an ylide of the formula

$$(C_6H_5)_3P = \underset{R_7}{\overset{}{C}} - R_6$$

wherein R_6 and R_7 are each independently hydrogen or loweralkyl, to afford a compound of the formula Ib wherein R_2 is loweralkenyl, which is reduced to afford a compound of the formula Ib, according to claim 7 wherein Z is benzyl or loweralkyl and R_2 is loweralkyl,

f) optionally reacting a compound of the formula Ib as obtained in step d) with hydroxylamine to afford the corresponding oxime, which is treated with benzenesulfonyl chloride, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or lower alkyl and R_2 is the cyano group.

g) optionally reacting a compound of the formula Ib as obtained in step a) with ethyl chloroformate to afford the corresponding N-ethylcarbamate which is optionally treated as described in steps d), e) or f) to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl, R_1 is alkoxycarbonyl, and R_2 is formyl, loweralkyl or cyano,

h) optionally subjecting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is benzyl to a hydrogenolysis, to afford a compound of the formula Ib according to claim 7 wherein Z is hydrogen.

i) optionally reacting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is loweralkyl with a suitable cleavage reagent, such as HBr, borontribromide etherate, trimethylsilyl iodide or a sodium salt of ethylmercaptan, to afford a compound of the formula Ib according to claim 7, wherein Z is hydrogen.

8. A process as defined in claim 7 wherein X is halogen or hydrogen, Y is hydrogen and R_1 and R_2 are each independently H or loweralkyl.

9. Use of a compound as defined in claim 1 for the preparation of a medicament having the activity of alleviating a memory dysfunction characterized by a cholinergic deficit.

10. A process for the preparation of a pharmaceutical compositions, which comprises mixing an effective amount of a compound as defined in claim 1 with a suitable carrier therefor.

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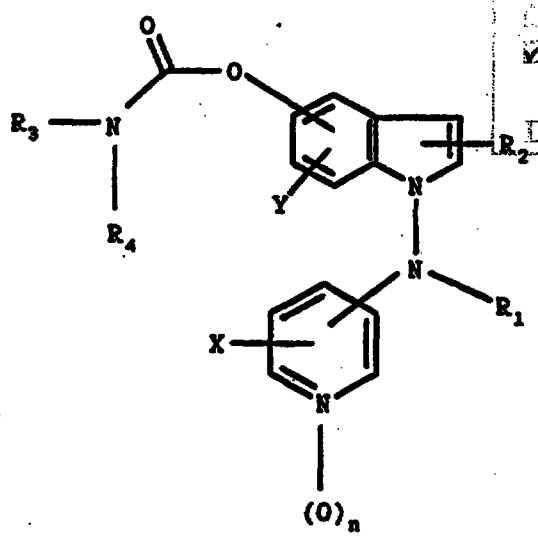
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1-(SUBSTITUTED PYRIDINYLAMINO)-1H-indol-5-YL SUBSTITUTED CARBAMATES, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS.

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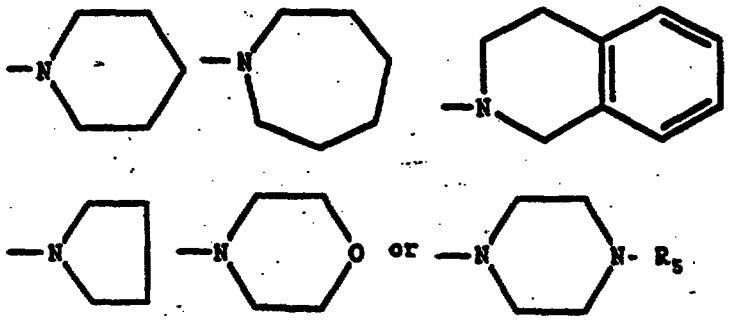
The present invention relates to compounds of Formula I a,



(Ia)

where

n is 0 or 1;
X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2 is hydrogen, loweralkyl, formyl or cyano;
R_3 is hydrogen or loweralkyl;
R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
or alternatively, $-NR_3R_4$ taken together constitutes

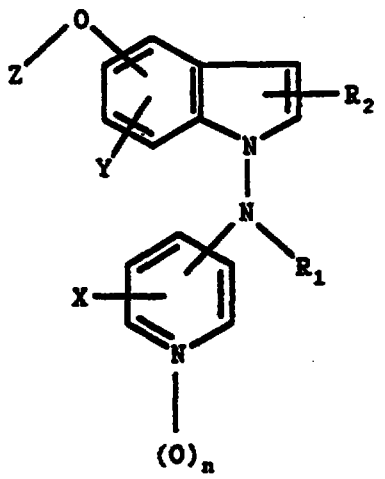


R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl, which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

Also included within the scope of this invention are compounds depicted by the formula Ib below where the group Z is hydrogen, loweralkyl or benzyl, and other parameters are as defined above, which are useful as direct precursors to the target compounds of this invention having Formula Ia.

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(Ib)

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 8 carbon atoms. Examples of said loweralkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl, hexyl, heptyl and octyl.

The term cycloalkyl shall mean a cycloalkyl group of 3 to 7 carbon atoms.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term aryl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which being independently loweralkyl, loweralkoxy, halogen or trifluoromethyl.

The term heteroaryl shall mean furanyl, thienyl, pyrrolyl or pyridinyl.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all optical and geometric stereoisomers where such isomers exist.

The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

Throughout the description of the synthetic steps, the notations n, X, Y and R_1 through R_5 shall have the respective meanings given above unless otherwise stated or indicated.

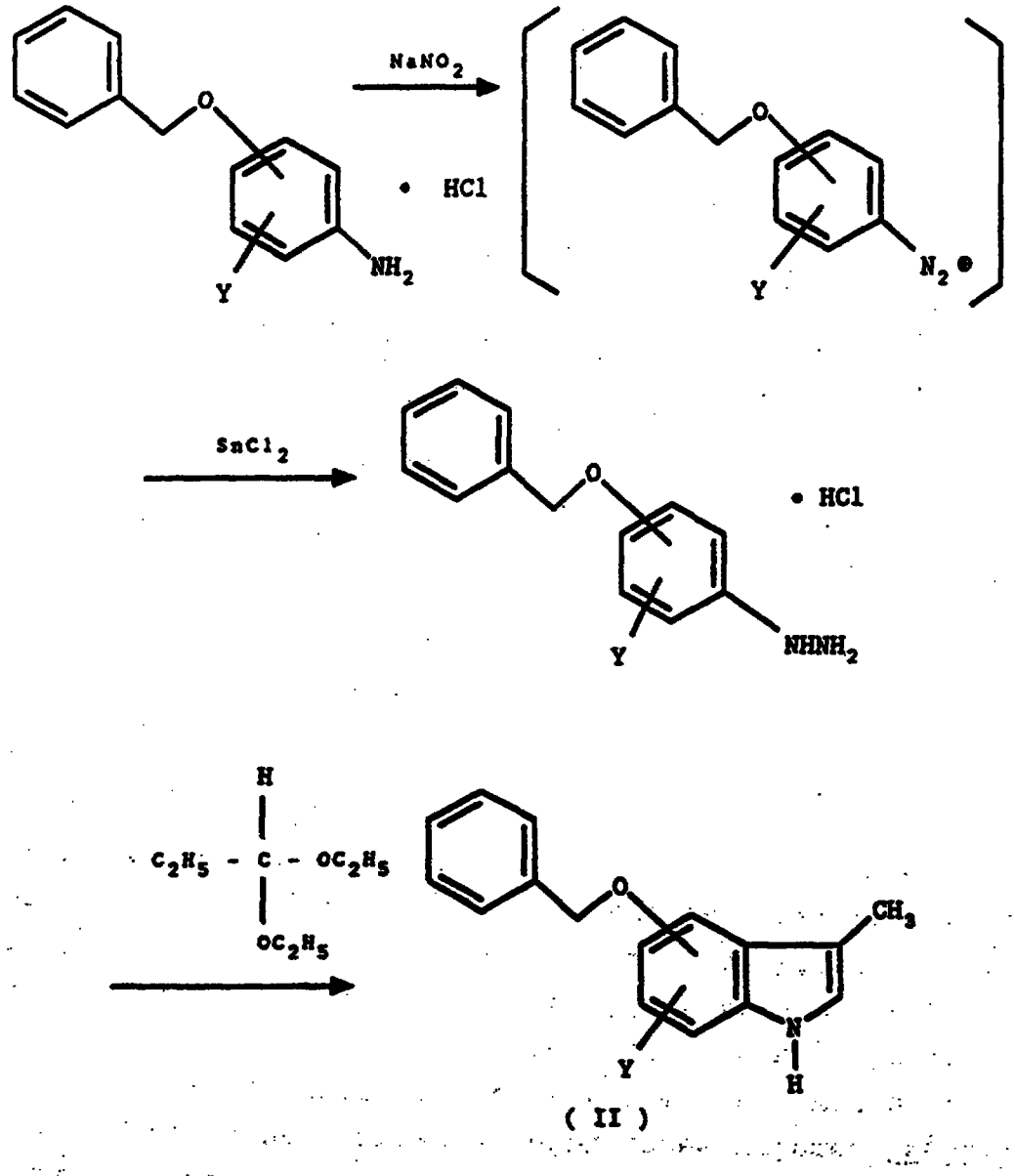
STEP A:

A benzyloxyaniline depicted below is allowed to react with $NaNO_2$ in a routine manner known to the art to afford the corresponding diazonium compound and the latter is reduced with $SnCl_2$ to afford the corresponding hydrazine compound, and thereafter the latter is allowed to react with the diethylacetal of propionaldehyde to afford the compound of Formula II. For details of the last reaction (Fisher indole synthesis), the reader is referred, for instance, to D. Keglevic et al., Chem. Absts. 56, 4710h.

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(II)

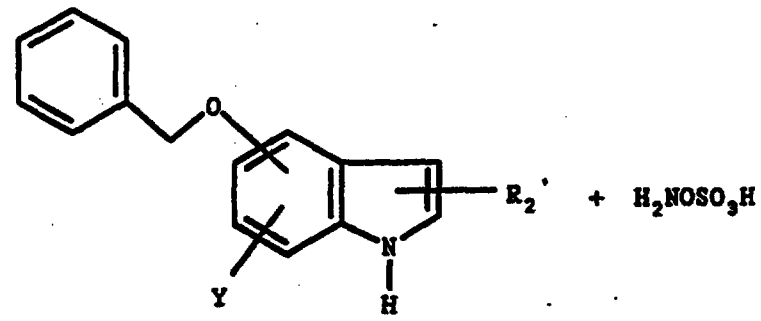
Where the 2-methylisomer of Compound II is desired, the above reaction is conducted in substantially the same manner as described above except that acetone is used instead of diethylacetal of propionaldehyde.

STEP B:

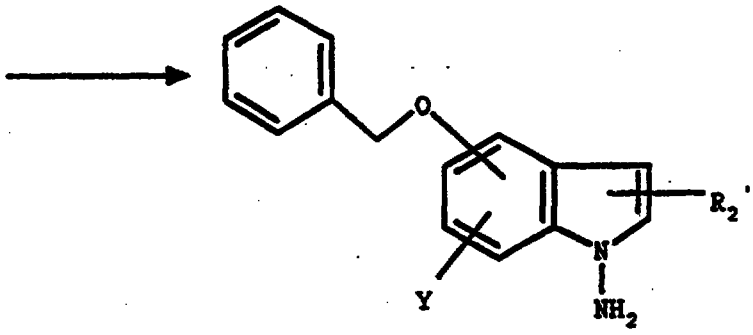
A compound of Formula III where R_2' is hydrogen or methyl is allowed to react with hydroxylamine-O-sulfonic acid in a routine manner known to the art to afford a compound of Formula IV. The starting compound of Formula III where R_2' is hydrogen is either available on the market or can be synthesized from known compounds according to methods known to the art.

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(III)



(IV)

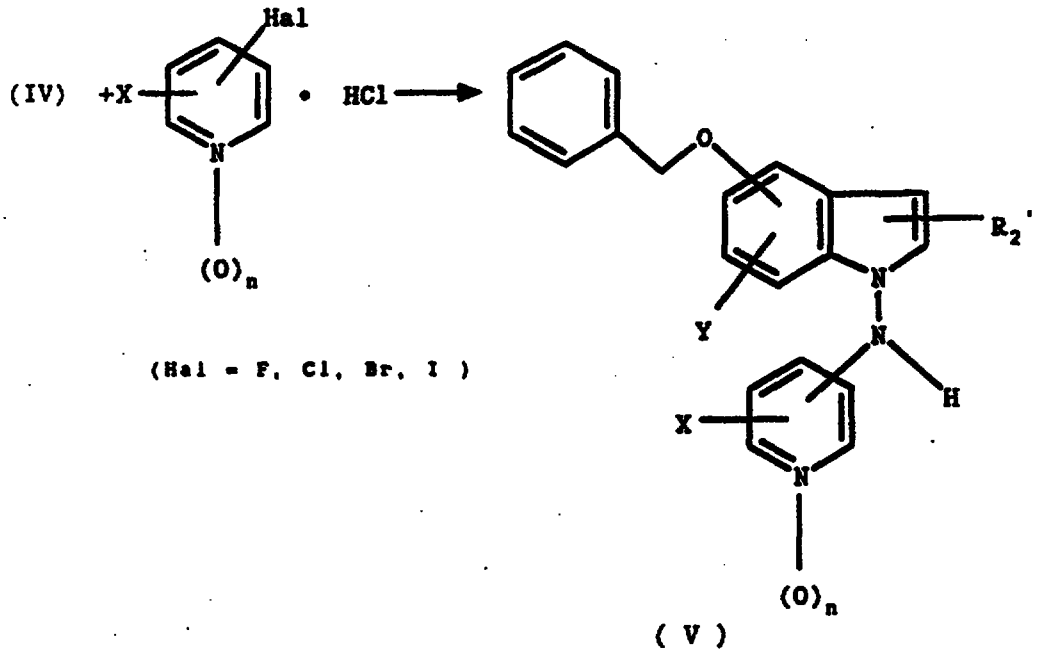
STEP C:

Compound IV is allowed to react with a halopyridine hydrochloride depicted below to afford a compound of Formula V. This reaction is typically conducted in a suitable solvent such as N-methyl-2-pyrrolidinone at a temperature of 20 to 200° C.

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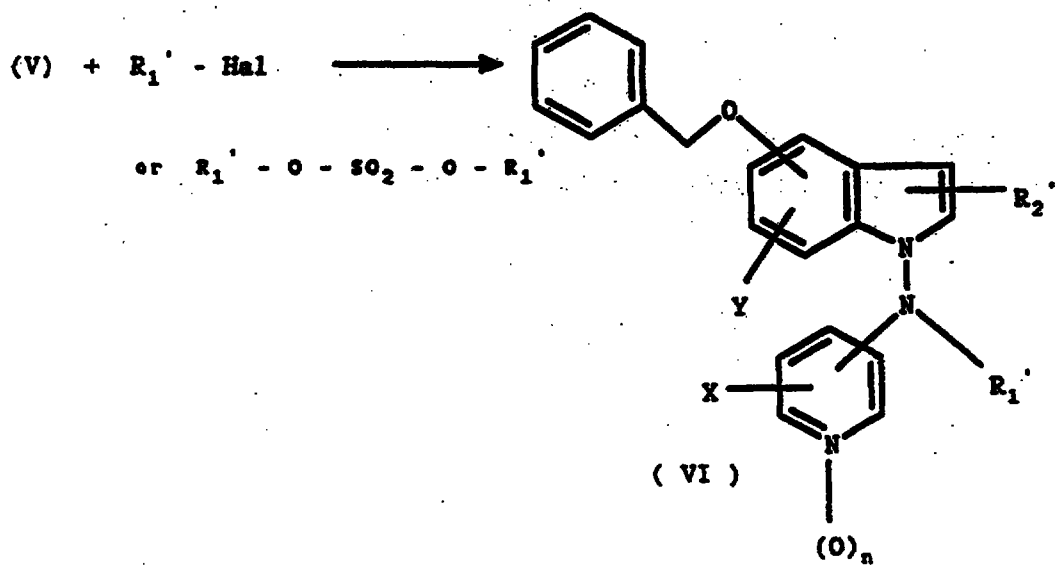


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STEP D:

Compound V is allowed to react with a suitable base, such as sodium hydride or potassium t-butoxide, and the resultant anion is allowed to react with a halide of the formula R_1' - Hal where R_1' is loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl, and Hal is chlorine, bromine or iodine, or with a diloweralkylsulfate of the formula R_1'-O-SO_2-O-R_1' where R_1' is loweralkyl, in a routine manner known to the art to afford a compound of Formula VI.

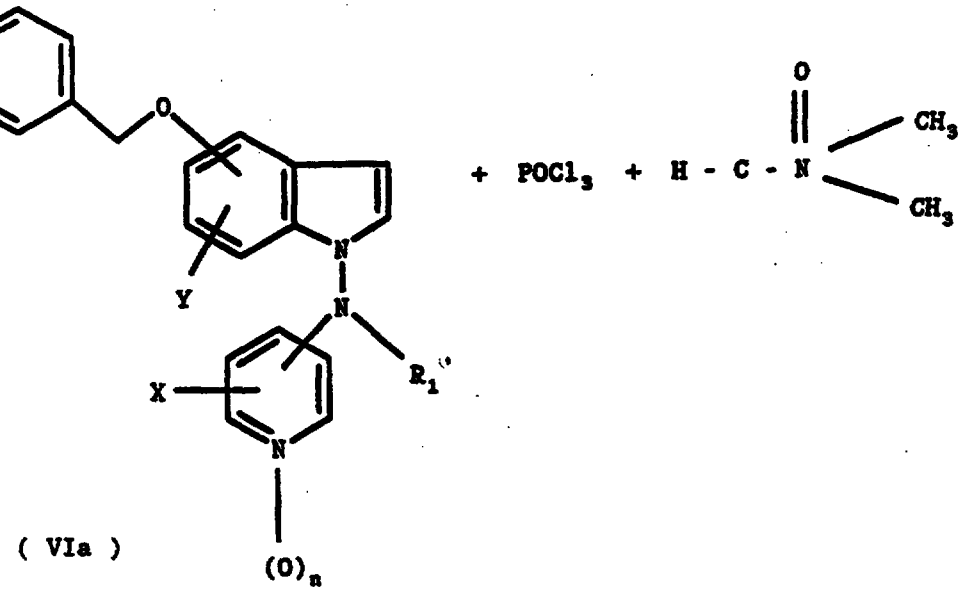


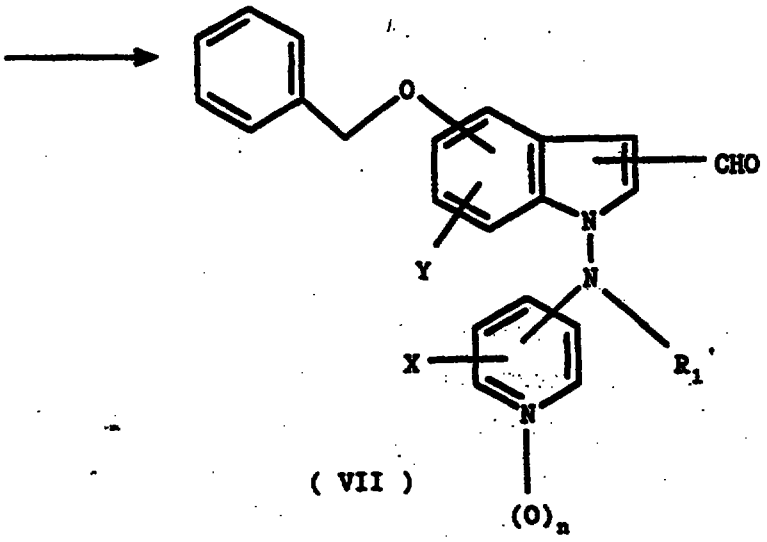
STEP E:

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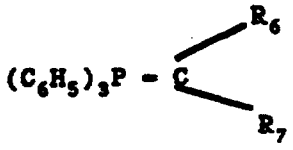
A compound of Formula VIa is allowed to react with phosphorus oxychloride and dimethylformamide in a routine manner known to the art to afford a compound of Formula VII.





STEP F:

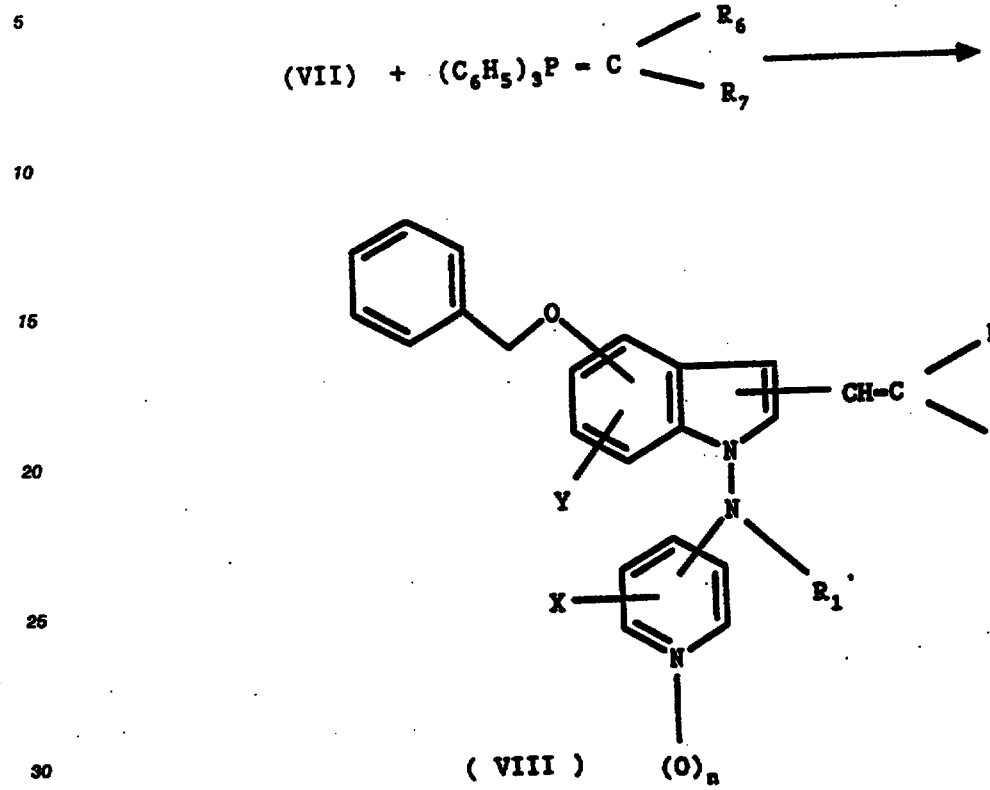
Compound VII is subjected to a Wittig reaction with an ylide of the formula



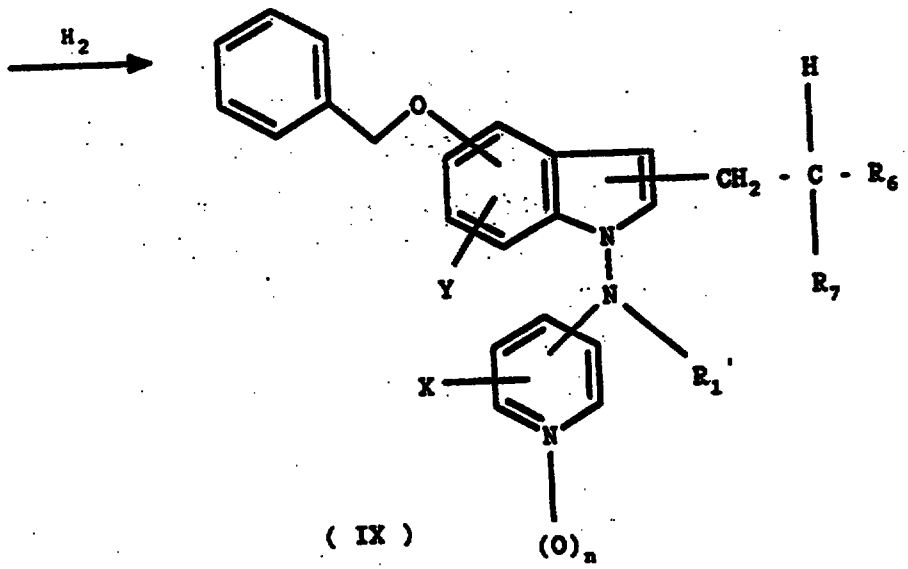
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where R_6 and R_7 are each independently hydrogen or loweralkyl in a routine manner known to the art to afford a compound of Formula VIII and thereafter the latter compound is reduced in a routine manner known to the art to afford a compound of Formula IX.



(VIII)



(IX)

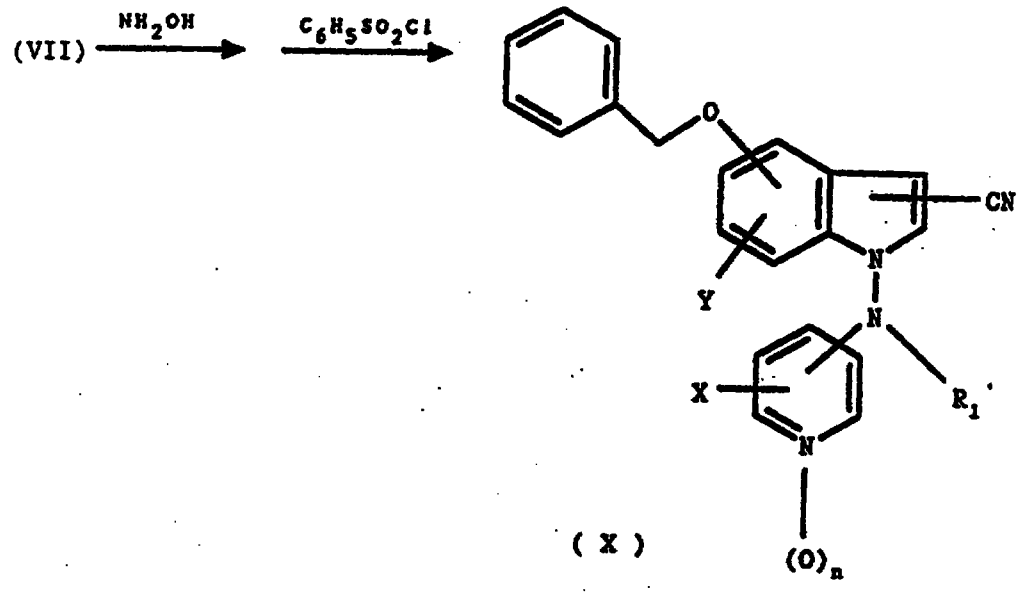
STEP G:

Compound VII is allowed to react with hydroxylamine in a routine manner known to the art to afford a

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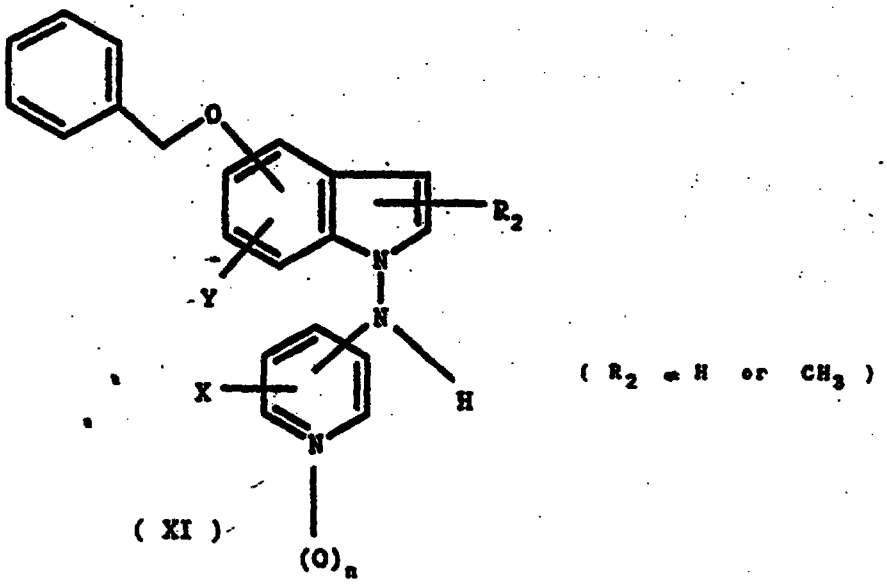
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corresponding oxime and the latter is allowed to react with benzenesulfonyl chloride to afford a nitrile compound of Formula X. The second step is typically conducted in a suitable solvent such as tetrahydrofuran or p-dioxane at a temperature of about 60 to 100 °C.



STEP H:

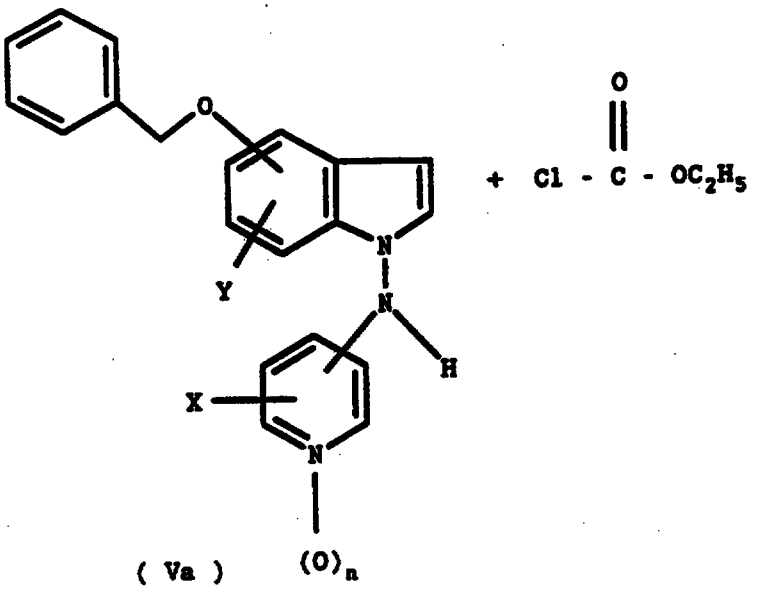
In order to prepare a compound of Formula XI depicted below where R_2 is not hydrogen or methyl, it is convenient to adopt the following procedure.



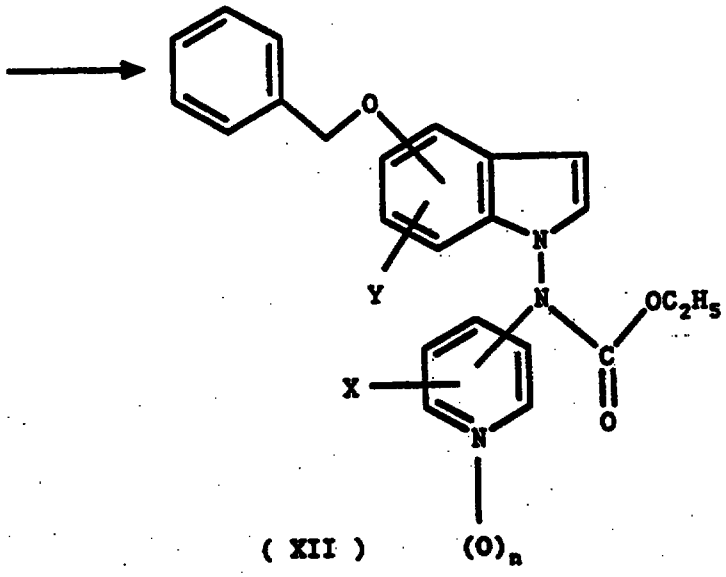
Thus, a compound of Formula Va is allowed to react with ethyl chloroformate in a routine manner known to the art to afford an ethyl carbamate of Formula XII and thereafter the latter compound is subjected to one or more of STEPS E through G to afford a compound of Formula XIII. Subsequently, Compound XIII is hydrolyzed in a routine manner known to the art to afford Compound XI.

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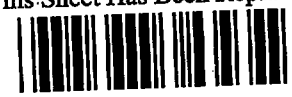


(Va)



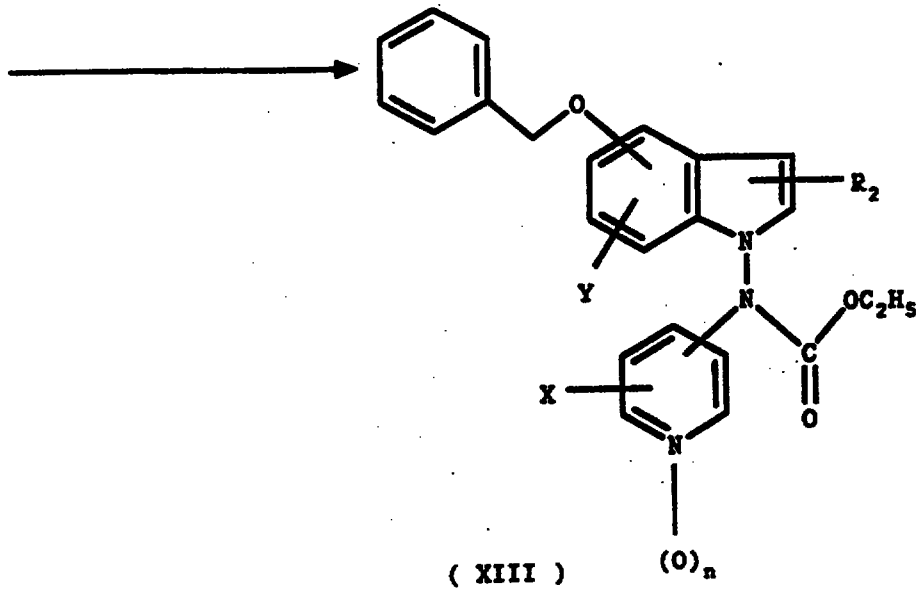
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One or more of STEPS E through G



(XIII)

hydrolysis

(XI)

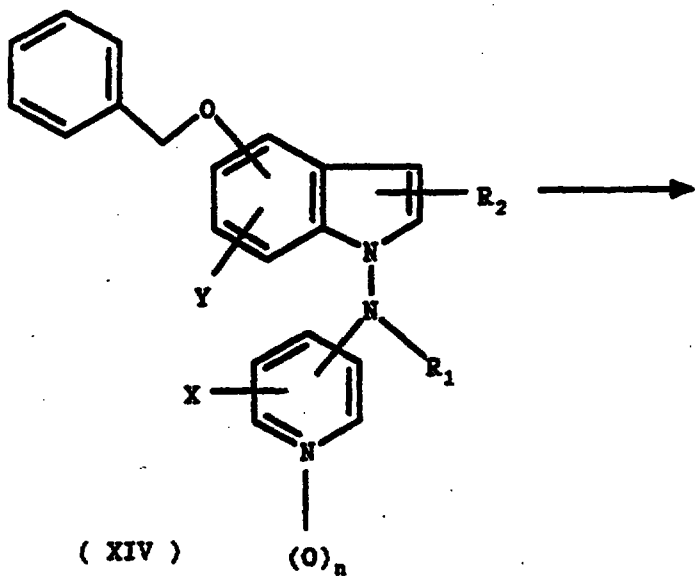
STEP I:

A compound of Formula XIV obtained from one of the foregoing STEPS is subjected to hydrogenolysis conducted in a routine manner known to the art to afford a compound of Formula XV.

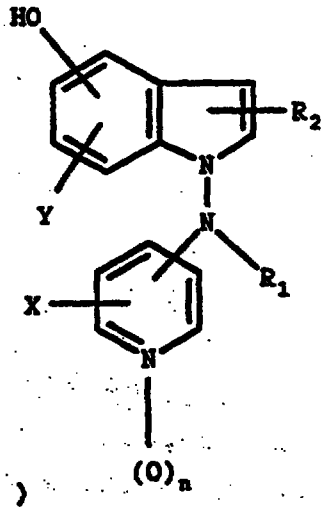
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(XIV)



(XV)

In each of the foregoing STEPS A through I, the reactant molecule carries a benzyloxy group on the benzene portion thereof. However, the same reactions can also be accomplished in substantially the same manner as described above where the reactant molecule carries a loweralkoxy group instead of a benzyloxy group on the benzene portion thereof, except that in the case of STEP I, a cleavage reaction is utilized instead of hydrogenolysis. Said cleavage reaction is conducted in a routine manner known to the art, for instance, with the aid of 48% HBr, boron tribromide etherate, trimethylsilyl iodide or the sodium salt of ethyl mercaptan.

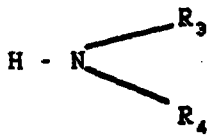
STEP J:

Compound XV is allowed to react with 1,1'-carbonyldiimidazole and the resultant reaction product is allowed to react with an amine of the formula

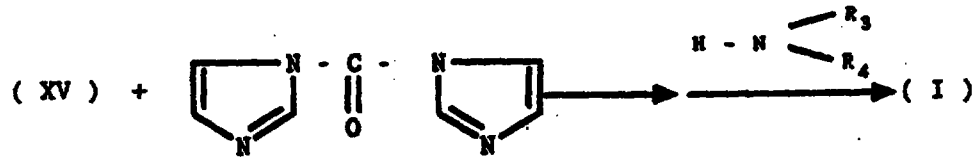
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in a routine manner known to the art to afford Compound I.



Typically, the first step is conducted in a suitable solvent such as tetrahydrofuran at room temperature. Typically, the second step is conducted by adding a suitable amount of the desired amine in glacial acetic acid to the reaction mixture.

Alternatively, where Compound I in which the group R_3 is hydrogen is desired, Compound XV is allowed to react with an isocyanate of the formula R_4 - NCO in a routine manner known to the art to afford Compound I.



The compounds of Formula I of the present invention are useful for the treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with central cholinergic innervation. This same innervation is suggested to be weakened in Alzheimer patients. We have determined in vitro inhibition of acetylcholinesterase activity in rat striatum.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in brain roughly correlates with cholinergic innervation and subfractionation shows the highest level in nerve terminals.

It is generally accepted that the physiological role of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinominetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AChE inhibitors may also be beneficial in the treatment of Alzheimer's dementia.

The method described below was used in this invention for assaying cholinesterase activity. This is a modification of the method of Ellman et al., Biochem. Pharmacol. 7, 88 (1961).

Procedure:

A. Reagents -

1. 0.05 M Phosphate buffer, pH 7.2

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(a) 6.85 g $NaH_2PO_4 \cdot H_2O$/100 ml distilled H_2O
(b) 13.40 g $Na_2HPO_4 \cdot 7H_2O$/100 ml distilled H_2O
(c) add (a) to (b) until pH reaches 7.2
(d) Dilute 1:10

2. Substrate in buffer
(a) 198 mg acetylthiocholine chloride (10 mM)
(b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)

3. DTNB in buffer
(a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
(b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)

4. A 2 mM stock solution of the test drug is made up in a suitable solvent and q.s. to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4}M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation -

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed 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 microliter aliquot of the homogenate is added to 1.0 milliter vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37° C.

C. Assay -

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

Instrument Settings

Kinetics Soft-Pac Module #598273 (10)
Program #6 Kindata:
Source - Vis
Wavelength - 412 nm
Sipper - none
Cuvettes - 2 ml cuvettes using auto 6-sampler
Blank - 1 for each substrate concentration
Interval time - 15 seconds (15 or 30 seconds for kinetics) Total time - 5 minutes (5 or 10 minutes for kinetics)
Plot - yes
Span - autoscale
Slope - increasing
Results - yes (gives slope)
Factor - 1

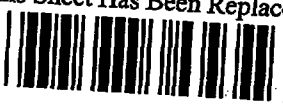
Reagents are added to the blank and sample cuvettes as follows:

Blank:	0.8 ml Phosphate Buffer/DTNB
	0.8 ml Buffer/Substrate
Control:	0.8 ml Phosphate Buffer/DTNB/Enzyme
	0.8 ml Phosphate Buffer/Substrate
Drug:	0.8 ml Phosphate
Buffer/DTNB/Drug/Enzyme	0.8 ml Phosphate Buffer/Substrate

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 IC_{50} Determinations:

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Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration.

$$\% \text{ Inhibition} = \frac{\text{slope control - slope drug}}{\text{slope control}} \times 100$$

IC_{50} values are calculated from log-probit analysis

Results of this assay for some of the compounds of this invention and physostigmine (reference compound) are presented in Table 1.

TABLE 1

Compound	Inhibitory Concentration (μM) Brain AChE
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.0023
(S)-(-)-1-(propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate	30.21
Physostigmine	0.006

This utility is further demonstrated by the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay described below.

Dark Avoidance Assay

In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compound, resulting in a greater interval before re-entry into the dark compartment.

The results for an active compound are expressed as the percent of a group of animals in which the effect of scopolamine is blocked, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment.

Results of this assay for some of the compounds of this invention and those for tacrine and pilocarpine (reference compounds) are presented in Table 2.

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TABLE 2

Compound	Dose (mg/kg of body weight, s.c)	% of Animals with Scopolamine Induced Memory Deficit Reversal
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.35	21
Tacrine	0.63	13
Pilocarpine	5.0	13

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Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule 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 effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum 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 70% of the weight of the unit. 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 an oral dosage unit form contains between 1.0 - 300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweeting agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a 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 preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose 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 active compound, but may be varied between 0.5 and about 30% 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 inventions are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of 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 methyl parabens; 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 preparation can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-ethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-propylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-isopropylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-cyclohexylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-2-phenylethylcarbamate;
(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1-phenylethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-butylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-heptylcarbamate;

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1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-methylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-piperidinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-4-chlorophenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-heptylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-phenylmethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-heptylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-yl-methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-4-phenylpiperazin-1-ylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-morpholin-4-ylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate-N-oxide;
1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-(Methyl-4-pyridinylamino)-1H-indol-5-ol;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol;
3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole;
3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indo le;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethox y)-1H-indole;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol;
3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol;
1-(3-Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-5-phenylmethoxy-1H-indole;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-ol;
1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indol-3-carboxaldehyde;
3-Cyano-1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;
1-(2-Phenylethyl-4-pyridinylamino)-1H-indol-5-ol; and
1-(2-Propynyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

Examples of this invention are presented below.

EXAMPLE 1

5-Phenylmethoxy-1H-indole-1-amine

To 5-phenylmethoxyindole (50 g) in 300 ml of dimethylformamide at ice bath temperature was added milled potassium hydroxide (62.72 g). Then hydroxylamine-O-sulfonic acid (32.93 g) was added portionwise, keeping the internal temperature below 20°C. After the addition was complete, the mixture was stirred for one hour, then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (71 g), which was eluted with dichloromethane on silica gel columns via HPLC. The desired fractions were concentrated to yield a solid (21.15 g). Of this material, 3.0 g was triturated with ether to yield a solid, 2.4 g, m.p. 126-128°C.

ANALYSIS:			
Calculated for $C_{15}H_{14}N_2O$:	75.60%C	5.92%H	11.76%N
Found:	75.54%C	5.97%H	11.87%N

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EXAMPLE 2

5-Phenylmethoxy-1-(4-pyridinylamino)-1H-indole

To 250 ml of N-methyl-2-pyrrolidinone was added 5-(phenylmethoxy)-1H-indole-1-amine (29.7 g) and the solution was heated to 80° C. Then 4-chloropyridine hydrochloride (20.55 g) was added portionwise and the mixture was stirred for three hours, cooled, poured into water, basified with aqueous sodium carbonate and extracted with toluene. The organic/aqueous mixture was filtered to yield a solid (39 g), which was triturated with ether to yield a solid (27 g). Of this material, 3.0 g was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 2.5 g, m.p. 143-145° C.

ANALYSIS:			
Calculated for $C_{20}H_{17}N_3O$:	76.17%C	5.44%H	13.32%N
Found:	75.82%C	5.43%H	13.21%N

EXAMPLE 3

1-(4-Pyridinylamino)-1H-indol-5-ol

To 0.8 g of 10% palladium on carbon in 10 ml of absolute ethanol was added a solution of 5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (4.0 g) in 240 ml of absolute ethanol and this was hydrogenated on a Parr apparatus for four hours at 50° C at 50 psig H_2. The mixture was cooled and filtered, and the filtrate was concentrated to yield an oil (4.2 g), which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.72 g). This material was eluted with 10% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a foam (1.8 g), which was recrystallized from ethyl acetate to yield a solid (1.5 g), m.p. 232-234° C.

ANALYSIS:			
Calculated for $C_{13}H_{11}N_3O$:	69.32%C	4.92%H	18.66%N
Found:	69.16%C	4.76%H	18.52%N

EXAMPLE 4

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole hydrochloride

5-(Phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (25 g) was slowly added to an ice-cooled solution of potassium tert-butoxide (11 g) in 250 mL tetrahydrofuran. Following the anion formation, a solution of dimethyl sulfate (12 g) in 25 mL tetrahydrofuran was slowly added so that the internal reaction temperature remained below 10° C. After one hour, the reaction mixture was stirred with water and extracted with ether. The organic layer was washed with water and saturated sodium chloride solution and thereafter dried (anhydrous magnesium sulfate), filtered and concentrated to afford a solid, 28 g. This solid was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 22 g of a solid, m.p. 118-121° C. An analytical sample was prepared by converting 1.5 g to the hydrochloride salt in methanol/ether to yield 1.5 g of crystals, m.p. 235-236° C (dec.).

ANALYSIS:			
Calculated for $C_{21}H_{20}ClN_3O$:	68.94%C	5.51%H	11.49%N
Found:	68.60%C	5.50%H	11.28%N

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EXAMPLE 5

1-(Methyl-4-pyridinylamino)-1H-indol-5-ol

A solution of 1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole (9 g) in 250 mL ethanol containing 0.6 g 10% palladium on activated charcoal was hydrogenated at 50 psi at 50° C for three hours via Parr hydrogenation apparatus. After cooling, the mixture was filtered through Celite and concentrated. The residue was eluted through silica with 5% methanol in dichloromethane via flash column chromatography to yield 6.2 g solid. A three gram portion was recrystallized from acetonitrile to yield 2.6 g solid, m.p. 191-193° C. This was again recrystallized from acetonitrile to yield 2.2 g crystals, m.p. 192-193° C.

ANALYSIS:			
Calculated for $C_{14}H_{13}N_3O$:	70.27%C	5.48%H	17.57%N
Found:	69.96%C	5.39%H	17.53%N

EXAMPLE 6

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

Methyl isocyanate (0.72 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing milled potassium carbonate (2 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield a solid 3.1 g. This was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 2.6 g solid, m.p. 186-188° C. This was recrystallized from 20% methanol in ether to yield 1.6 g of product, m.p. 186-188° C.

ANALYSIS:			
Calculated for $C_{16}H_{16}N_4O_2$:	64.85%C	5.44%H	18.91%N
Found:	64.85%C	5.58%H	18.73%N

EXAMPLE 7

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.2 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.7 g solid, m.p. 108-111° C. This was converted to the hydrochloride salt in methanol/ether to yield 3.3 g crystals, m.p. 232-234° C (dec.).

ANALYSIS:			
Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.89%C	6.34%H	14.88%N

EXAMPLE 8

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (1.7 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl

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acetate via flash column chromatography to yield 3.8 g solid. This was recrystallized from acetonitrile to yield 3.2 g crystals, m.p. 179-181 °C.

ANALYSIS:			
Calculated for $C_{22}H_{20}N_4O_2$:	70.95%C	5.41%H	15.05%N
Found:	70.67%C	5.35%H	15.12%N

EXAMPLE 9

1-(Propyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole maleate

To potassium tert-butoxide (2.80 g) in 20 ml of tetrahydrofuran cooled to ice bath temperature was added dropwise a solution of 5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (6.5 g) in 60 ml of tetrahydrofuran. This mixture was stirred for 10 minutes and then a solution of 1-bromopropane (3.08 g) in 10 ml of tetrahydrofuran was added dropwise. The reaction was allowed to proceed for three hours at room temperature. The mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was removed to yield an oil (8.5 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (5.5 g). Of this material 1.0 g was dissolved in methanol and acidified with a methanol solution of maleic acid. After diluting with ether, the precipitate was collected to yield a solid 1.0 g, m.p. 118-119 °C.

ANALYSIS:			
Calculated for $C_{23}H_{23}N_3O \cdot C_4H_4O_4$:	68.48%C	5.75%H	8.87%N
Found:	68.29%C	5.72%H	8.86%N

EXAMPLE 10

1-(Propyl-4-pyridinylamino)-1H-indol-5-ol

To 0.3 g of 10% Pd/C in 10 ml of absolute ethanol was added 5-phenylmethoxy-1-(propyl-4-pyridinylamino)-1H-indole (3.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus for 48 hours at 50 °C and 50 psig H_2. The reaction mixture was then filtered and the filtrate concentrated to yield an oil (2.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (1.8 g) which was recrystallized from methanol/ether (1:1) to yield a solid 1.6 g, m.p. 214-216 °C.

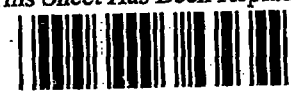
ANALYSIS:			
Calculated for $C_{16}H_{17}N_3O$:	71.89%C	6.41%H	15.72%N
Found:	71.78%C	6.41%H	15.61%N

EXAMPLE 11

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To 2.5 g of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g) followed by methyl isocyanate (0.56 ml). The reaction was allowed to proceed for half an hour. The reaction mixture was then filtered and the filtrate concentrated to yield a solid (2.9 g) which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.7 g) which was recrystallized from isopropyl ether to yield a solid 1.8 g, m.p. 158-159 °C.

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ANALYSIS:			
Calculated for $C_{18}H_{20}N_4O_2$:	66.65%C	6.22%H	17.27%N
Found:	66.83%C	6.10%H	17.18%N

EXAMPLE 12

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl ethylcarbamate hydrochloride

Ethyl isocyanate (1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL of tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.5 g of the product as a solid, m.p. 139-141° C. This was converted to the hydrochloride salt in methanol/ether to yield 4.3 g of crystals, m.p. 209-211° C (dec.).

ANALYSIS:			
Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.81%C	6.16%H	14.84%N

EXAMPLE 13

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl propylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then propyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 2 hours. The mixture was filtered and the filtrate was concentrated to yield an oil (2.8 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.5 g), m.p. 120-122° C.

ANALYSIS:			
Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	67.87%C	6.89%H	15.93%N

EXAMPLE 14

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl isopropylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then isopropyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 4 hours. The mixture was filtered and the filtrate was concentrated to yield a solid (3.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.75 g), m.p. 131-133° C.

ANALYSIS:			
Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	68.16%C	6.84%H	15.84%N

EXAMPLE 15

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1-(Propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.3 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as an oil. This material was converted to the hydrochloride salt in methanol/ether to yield 4 g of crystals, m.p. 178-180° C.

ANALYSIS:			
Calculated for $C_{21}H_{26}N_4O_2$*HCl:	62.60%C	6.75%H	13.91%N
Found:	62.52%C	6.71%H	13.84%N

EXAMPLE 16

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 50 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) portionwise, and the reaction was allowed to proceed for 24 hours. To this mixture was added glacial acetic acid (2.15 ml) followed by a solution of heptylamine (1.45 ml) in tetrahydrofuran which had been treated with 0.56 ml of acetic acid. The reaction mixture was then stirred for 21 hours. The mixture was diluted with water, basified with sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (4.5 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (2.8 g). This material was dissolved in 50 ml of pentane/ether (1:1) and the solution was concentrated to 15 ml, whereupon crystals precipitated out of the solution. These were collected to yield a solid (1.0 g), m.p. 83-85° C.

ANALYSIS:			
Calculated for $C_{24}H_{32}N_4O_2$:	70.56%C	7.90%H	13.72%N
Found:	70.33%C	7.69%H	13.63%N

EXAMPLE 17

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl cyclohexylcarbamate hydrochloride

Cyclohexyl isocyanate (1.7 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 167-169°. This solid was again eluted through silica with ethyl acetate via HPLC to yield 3.8 g of the product as a solid, m.p. 167-170° C. The product was converted to the hydrochloride salt in methanol/ether to yield 3.9 g of powder, m.p. 219-220° C (dec.).

ANALYSIS:			
Calculated for $C_{23}H_{28}N_4O_2$*HCl:	64.40%C	6.81%H	13.06%N
Found:	64.07%C	6.77%H	12.92%N

EXAMPLE 18

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1-(Propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (2 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 156-158 °C. The product was recrystallized from acetonitrile to yield 3.8 g of crystals, m.p. 162-164 °C.

ANALYSIS:			
Calculated for $C_{24}H_{24}N_4O_2$:	71.98%C	6.04%H	13.99%N
Found:	71.99%C	6.13%H	14.03%N

EXAMPLE 19

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 4-chlorophenylmethylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by 4-chlorophenylmethylamine (1.5 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.9 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (3.05 g), m.p. 149-151 °C

ANALYSIS:			
Calculated for :	66.29%C	5.33%H	12.88%N
Found:	66.22%C	5.37%H	12.81%N

EXAMPLE 20

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 2-phenylethylcarbamate hydrochloride

2-Phenylethyl isocyanate (2.1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3.5 g). After stirring three hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.7 g of the product as a solid. The product was converted to the hydrochloride salt in methanol/ether to yield 2.9 g of crystals, m.p. 144-146 °C (dec.).

ANALYSIS:			
Calculated for $C_{25}H_{26}N_4O_2 \cdot HCl$:	66.58%C	6.04%H	12.43%N
Found:	66.60%C	5.94%H	12.38%N

EXAMPLE 21

(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.75 g) in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 0.912 g) followed by (S)-(-)-1-methylbenzyl isocyanate (0.97 g), and the reaction was allowed to proceed for one hour. The reaction mixture was filtered and the filtrate concentrated to yield an

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oil (3.9 g) which was eluted with 5% methanol in dichloromethane (DCM) on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid 2.6 g, m.p. 78-80 °C.

ANALYSIS:			
Calculated for $C_{25}H_{26}N_7O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.17%C	6.34%H	13.49%N

EXAMPLE 22

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethyl carbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by dimethylamine (40 wt % in water, 1.44 ml) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl., anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.5 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.5 g), m.p. 134-136 °C.

ANALYSIS:			
Calculated for :	67.43%C	6.55%H	16.56%N
Found:	67.63%C	6.58%H	16.58%N

EXAMPLE 23

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl piperidinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by piperidine (0.95 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.65 g).

ANALYSIS:			
Calculated for $C_{22}H_{26}N_4O_2$:	69.81%C	6.92%H	14.80%N
Found:	69.45%C	6.94%H	14.68%N

EXAMPLE 24

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 40 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 3.5 ml of glacial acetic acid was added to the reaction mixture. Then 1,2,3,4-tetrahydroisoquinoline (1.49 g) in 10 ml of tetrahydrofuran which had been acidified with 0.60 ml of glacial acetic acid was added to the reaction mixture dropwise. This was stirred for 24 hours and then the reaction mixture was quenched with water, basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and

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dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (5.6 g) which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC The desired fractions were concentrated to yield an oil (4.2 g). This material was dissolved in pentane/ether (1:1), whereupon a solid precipitated out of the solution. This material was collected to yield a solid, 2.6 g, m.p. 141-143° C.

ANALYSIS:			
Calculated for $C_{25}H_{26}N_4O_2$:	73.21%C	6.15%H	13.14%N
Found:	73.12%C	6.22%H	12.95%N

EXAMPLE 25

1-(3-Fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole

To 250 ml 1-methyl-2-pyrrolidinone was added 5-phenylmethoxy-1H-indol-1-amine (27.3 g), and the mixture was heated to 80° C. Then, 4-chloro-3-fluoropyridine hydrochloride (22 g) was added, and the mixture was heated at 80° C for two hours. After cooling, the mixture was poured into 1 liter of ice-water, stirred for five minutes, and adjusted to pH 9 with milled K_2CO_3. The product was extracted with ethyl acetate (3X). The organic layer was washed with water (2X) and dried (saturated NaCl, anhydrous $MgSO_4$). After filtration, the filtrate was concentrated to give an oil, 46 g of which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on cooling, 32.2 g, m.p. 140° C. A sample of this material was recrystallized from ether, m.p. 157-159° C.

ANALYSIS:			
Calculated for $C_{20}H_{16}FN_3O$:	72.06%C	4.84%H	12.60%N
Found:	71.98%C	4.90%H	12.51%N

EXAMPLE 26

1-[(3-Fluoro-4-pyridinyl)propylamino]-5-phenylmethoxy-1H-indole hydrochloride

To 100 ml of dry DMF (dimethylformamide) was added 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (20.0 g), and the solution was cooled to 0° C. To this was added potassium t-butoxide (6.7 g), and the mixture was stirred at 0° C for ten minutes, and thereafter a solution of n-propylbromide (5.5 ml) in 10 ml dry DMF was added. After stirring at 0° C for thirty minutes and then at ambient temperature for two hours, the mixture was poured into 500 ml cold water, stirred for five minutes and extracted with ethyl acetate (3X). The organic layer was washed successively with water (2X) and saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give an oil, 23 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:2) via HPLC. The desired fractions were combined and concentrated to give an oil, 19.3 g. A 2.0 g sample of this oil was dissolved in 50 ml methanol, and the solution was acidified to pH 1 with ethereal HCl and diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g, m.p. 200° C (dec.).

ANALYSIS:			
Calculated for $C_{23}H_{22}FN_3O \cdot HCl$:	67.06%C	5.63%H	10.20%N
Found:	66.74%C	5.55%H	10.05%N

EXAMPLE 27

1-(3-Fluoro-4-pyridinylamino)-1H-indol-5-ol

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In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.0 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (5.0 g) in 200 ml ethanol. The mixture was shaken at 50° C under 50 psi hydrogen gas for two hours. After cooling, the mixture was filtered, and the filtrate was concentrated to give an oil (5.0 g) which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a crystalline solid, 3.5 g, m.p. 70-73° C.

ANALYSIS:			
Calculated for $C_{13}H_{10}FN_3O$:	64.19%C	4.14%H	17.28%N
Found:	64.06%C	4.30%H	16.93%N

EXAMPLE 28

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol hydrochloride

In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.5 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-5-phenylmethoxy-1H-indole (15.0 g) in 200 ml ethanol. The mixture was shaken under 50 psi hydrogen gas for three hours at 50° C. Upon cooling, the mixture was filtered, and the filtrate was concentrated to give a solid, 11.4 g. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC, and the desired fractions were concentrated to give a solid, 8.5 g, m.p. 90-95° C. A 2.0 g sample of this material was dissolved in 50 ml methanol, the pH was adjusted to 1 with ethereal HCl, and the solution was diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g of the product, m.p. 218° C (dec.).

ANALYSIS:			
Calculated for $C_{16}H_{16}FN_3O \cdot HCl$:	59.72%C	5.33%H	13.06%N
Found:	59.30%C	5.36%H	12.62%N

EXAMPLE 29

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl methylcarbamate

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]- 1H-indol-5-ol (2.5 g) in 50 ml THF was added potassium carbonate (1.2 g), followed by methyl isocyanate (0.53 ml). After stirring at ambient temperature for three hours, the mixture was filtered, and the filtrate was concentrated to give a solid, 3.0 g, m.p. 165-166° C. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a solid, 2.7 g, m.p. 177-178° C.

ANALYSIS:			
Calculated for $C_{18}H_{19}FN_4O_2$:	63.14%C	5.59%H	16.37%N
Found:	63.27%C	5.68%H	16.23%N

EXAMPLE 30

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl butylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 50 ml tetrahydrofuran was added milled K_2CO_3 (1.1 g), followed by butyl isocyanate (0.9 ml). After stirring at ambient temperature for four hours, the mixture was filtered, and the filtrate was concentrated to give an oil, 5 g. This oil was eluted on a silica gel column with ethyl acetate/dichloromethane (1:4) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on standing, 2.7 g, m.p. 95-98° C.

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This solid was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.9 g of a solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:10) to give the product as crystals, 2.4 g, m.p. 142°C (dec.).

ANALYSIS:			
Calculated for $C_{21}H_{25}FN_4O_2$*HCl:	59.92%C	6.23%H	13.31%N
Found:	60.31%C	6.26%H	13.31%N

EXAMPLE 31

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl heptylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 65 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.5 g), and the mixture was stirred at ambient temperature for four hours. The mixture was cooled with an ice bath, and thereafter glacial acetic acid (2.0 ml) was added, followed by a solution of heptylamine (2 ml) and acetic acid in tetrahydrofuran (20 ml).

After stirring at ambient temperature for twenty hours, the mixture was poured into 200 ml water, the pH adjusted to 8 with $NaHCO_3$ solution, and the product was extracted with ethyl acetate. The organic layer was washed successively with water and saturated NaCl solution, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to give an oil, 4.2 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC. The desired fractions were combined and concentrated to give an oil, 2.6 g. This oil was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.5 g of solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:4) to give crystals, 2.3 g, m.p., 246°C (dec.).

ANALYSIS:			
Calculated for $C_{24}H_{31}FN_4O_2$*HCl:	62.26%C	6.97%H	12.10%N
Found:	62.62%C	7.08%H	12.06%N

EXAMPLE 32

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine

p-Benzyloxyphenylhydrazine hydrochloride was prepared by the method of Mentzer, et al., [C.A. 48:33412]. Thus, p-benzyloxyaniline hydrochloride (72.6 g) was diazotized with conc. HCl (174 ml) and sodium nitrite (23.2 g) in water (40 ml) at 0°C. A solution of stannous chloride (169.3 g) in conc. HCl (435 ml) was added rapidly and the reaction mixture stirred for two hours. The solid product was filtered and washed with absolute ethanol, then partially dissolved in boiling methanol/ethanol (1:1) and filtered hot, yielding 52.5 g of p-benzyloxyphenylhydrazine hydrochloride.

The conversion of the above compound to 3-methyl-5-benzyloxyindole was conducted according to the method of Keglevic, et al. [C.A. 56:4710h]. Thus, the above hydrazine hydrochloride (34.0 g) was dissolved in 25% aqueous HOAc (1.4 L) at 80°C. Propionaldehyde diethyl acetal (22.1 ml) was then added and the reaction mixture stirred for 0.75 hour. Upon cooling to room temperature, ether was added to the reaction mixture and the layers were separated. The aqueous phase was extracted with ether (2x). The combined organics were washed with 5% aqueous NaOH until the aqueous extract was basic to litmus. The organic phase was then washed with brine and dried (K_2CO_3). Filtration and concentration afforded 29.0 g of 3-methyl-5-benzyloxyindole.

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine was prepared using the procedure of Somei, et al., [Tetrahedron Lett. No. 5, pp. 461-462, 1974]. Thus, to a solution of the above product (17.3 g) in dry DMF (260 ml) maintained at 0°C was added milled potassium hydroxide (20.5 g) under nitrogen. Hydroxylamine-O-sulfonic acid (10.7 g) was added portionwise (10% wt.) every ten minutes. After stirring for 1 hour at room temperature, water and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with

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brine and dried (K_2CO_3). Filtration and concentration gave the crude product.

Purification via preparative HPLC (silica gel, DCM) afforded 6.0 g of the desired product as a solid which was recrystallized from ether, m.p. 104-106 °C.

ANALYSIS:			
Calculated for $C_{16}H_{16}N_2O$:	76.16%C	6.39%H	11.10%N
Found:	75.86%C	6.37%H	10.87%N

EXAMPLE 33

3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (6.31 g) and 1-methyl-2-pyrrolidinone (109 ml) was added 4-chloropyridine hydrochloride (3.94 g). The resulting mixture was heated at 80 °C for 4-5 hours. Another batch of reaction was also carried out with the amine (2.94 g) and 4-chloropyridine hydrochloride (1.84 g) in nmp (50 ml) at 80 °C for 4 hours. The above reaction mixtures were poured together into dilute aqueous sodium bicarbonate and extracted with EtOAc (4x) and ether (1x). The combined organic layers were washed with water and brine followed by drying (K_2CO_3). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether/0-5% MeOH) afforded 7.55 g of the desired product. Recrystallization from EtOAc gave a solid, m.p. 167.5-169.5 °C.

ANALYSIS:			
Calculated for $C_{21}H_{19}N_3O$:	76.57%C	5.81%H	12.76%N
Found:	76.73%C	6.05%H	12.76%N

EXAMPLE 34

3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol

3-Methyl-5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (2.20 g) was subjected to hydrogenolysis in absolute ethanol (80 ml) with 10% Pd-C (0.26 g) at 50 psig hydrogen at 50 °C for 2 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. Concentration and recrystallization from methanol afforded 0.50 g of highly crystalline product, m.p. 239-241 °C (dec.).

ANALYSIS:			
Calculated for $C_{14}H_{13}N_3O$:	70.28%C	5.48%H	17.56%N
Found:	69.95%C	5.46%H	17.41%N

EXAMPLE 35

3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole hemifumarate

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (7.78 g) and dimethylformamide (150 ml) maintained at 0 °C under nitrogen with stirring, was added sodium hydride (0.64 g, 97% purity). The resulting mixture was stirred at 0 °C for an additional 15 minutes at which time propyl bromide (2.25 ml) was added dropwise and the ice bath was removed. Stirring was continued at room temperature for 2-3 hours until complete reaction was observed by TLC (silica gel, ether). The reaction mixture was poured into water and the product extracted with EtoAc (3x) and ether (1x). The combined organic layers were washed successively with water (2x) and brine (2x), dried (K_2CO_3) and decolorized with activated carbon. Filtration and concentration gave the desired product (7.65 g) as an oil. The hemifumarate was prepared with 1.0 eq. fumaric acid in abs. ethanol. A highly crystalline solid resulted.

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m.p. 165.5-167° C.

ANALYSIS:			
Calculated for $C_{24}H_{25}N_3O$*0.5 $C_4H_4O_4$:	72.70%C	6.35%H	9.78%N
Found:	72.66%C	6.55%H	9.73%N

EXAMPLE 36

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol hemioxalate

The benzyl group of 3-methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole (7.80 g) was cleaved in a Parr hydrogenation apparatus in abs. EtOH (275 ml) over 10% Pd-C (0.80 g) at 50 psig and 50° C for 2-3 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. The combined filtrate was concentrated and the product purified via flash column chromatography (silica gel, 2% Et_3N/ether) affording 5.80 g of the product as an oil. Dissolving in absolute ethanol followed by addition of 1.0 eq of anhydrous oxalic acid (in abs. EtOH) resulted in formation of a solid, the hemioxalate, m.p. 235-237° C.

ANALYSIS:			
Calculated for $C_{17}H_{19}N_3O$*0.5 $C_2H_2O_4$:	66.23%C	6.19%H	12.88%N
Found:	65.91%C	6.33%H	12.58%N

EXAMPLE 37

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.06 g) and tetrahydrofuran (49 ml) was added milled K_2CO_3 (1.06 g) followed by dropwise addition of methyl isocyanate (0.48 ml) at room temperature under nitrogen. Stirring was continued for 2.3 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.30 g of the desired carbamate as an oil. The product was crystallized from ether, m.p. 147-149° C.

ANALYSIS:			
Calculated for $C_{19}H_{22}N_4O_2$:	67.44%C	6.55%H	16.56%N
Found:	67.49%C	6.68%H	16.53%N

EXAMPLE 38

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.11 g) and tetrahydrofuran (50 ml) was added milled K_2CO_3 (1.09 g), followed by dropwise addition of butyl isocyanate (0.93 ml) at room temperature under nitrogen. Stirring was continued for 2.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.65 g of the desired carbamate as an oil. This oil was dissolved in a small amount of EtOAc and diluted with ether, whereupon the product crystallized as a white powder, m.p. 120-122° C.

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ANALYSIS:			
Calculated for $C_{22}H_{28}N_4O_2$:	69.45%C	7.42%H	14.72%N
Found:	69.67%C	7.44%H	14.68%N

EXAMPLE 39

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.23 g) and tetrahydrofuran (53 ml) was added 1,1'-carbonyldiimidazole (2.57 g) at room temperature with stirring under nitrogen. Stirring was continued for 96 hours, at which time acetic acid (1.54 ml) was added. To the resulting reaction mixture was added a solution consisting of heptyl amine (1.76 ml), acetic acid (0.71 ml) and THF (5 ml). After stirring for 24 hours, an additional solution of heptyl amine (1.17 ml), acetic acid (0.48 ml) and THF (5 ml) was added and stirring continued for 3 hours. The reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) afforded 1.60 g of the desired carbamate after recrystallization from ether/pentane, m.p. 102-104°C.

ANALYSIS:			
Calculated for $C_{25}H_{34}N_4O_2$:	71.06%C	8.11%H	13.26%N
Found:	71.10%C	8.08%H	13.25%N

EXAMPLE 40

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.60 g) and tetrahydrofuran (43 ml) were added with stirring at room temperature milled potassium carbonate (0.93 g) and benzyl isocyanate (0.87 ml). Stirring was continued under nitrogen for 16 hours. The mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration followed by purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.28 g of the desired carbamate. Recrystallization from ether gave a highly crystalline solid, m.p. 149-151°C.

ANALYSIS:			
Calculated for $C_{25}H_{26}N_4O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.39%C	6.73%H	13.92%N

EXAMPLE 41

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl, 1,2,3,4-tetrahydro-2-isoquinolylincarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.67 g) and tetrahydrofuran (40 ml) was added 1,1'-carbonyldiimidazole (1.92 g) at room temperature with stirring under nitrogen. Stirring was continued for 48 hours, at which time acetic acid (1.6 ml) was added. To the resulting reaction mixture was added a solution consisting of 1,2,3,4-tetrahydroisoquinoline (1.6 ml), acetic acid (0.76 ml) and THF (10 ml). After stirring for 16 hours, the reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) gave 2.41 g of the desired carbamate as a foam. The compound formed a white powder in ether/pentane, m.p. 160-162°C.

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ANALYSIS:			
Calculated for $C_{27}H_{28}N_4O_2$:	73.61%C	6.41%H	12.72%N
Found:	73.57%C	6.38%H	12.61%N

EXAMPLE 42

1-[(3-Fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (4.81 g) and 1-methyl-2-pyrrolidinone (83 ml) was added 4-chloro-3-fluoro pyridine hydrochloride (3.20 g). The resulting mixture was heated at 80° C for 2 hours. Upon cooling to room temperature, dilute aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed successively with water (2x) and brine (1x), and thereafter dried ($MgSO_4$). Filtration and concentration gave the crude product. Purification via flash column chromatography (silica gel, 50% ethyl acetate/dichloromethane) afforded 4.0 g of the desired product as a solid, m.p. 210-213° C.

EXAMPLE 43

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole (3.76 g) and dimethylformamide (108 ml), cooled to 0° C under nitrogen with stirring, was added sodium hydride (0.29 g). The resulting mixture was stirred at 0° C for an additional 15 minutes, at which time 1-bromopropane (1.03 ml) was added dropwise and the ice bath removed. Stirring was continued at room temperature overnight, at which time the reaction appeared complete by TLC (silica gel, 50% ether/hexane). The reaction mixture was poured into water and the product extracted with EtoAc (3x). The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the crude product as an oil. Purification via preparative HPLC (silica gel, 30% EtOAc/hexane) afforded 2.80 g of the desired product as a solid which was recrystallized from ether, m.p. 94-96° C.

ANALYSIS:			
Calculated for $C_{24}H_{24}FN_3O$:	74.01%C	6.21%H	10.79%N
Found:	73.58%C	6.09%H	10.56%N

EXAMPLE 44

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol

The benzyl group of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole (15.82 g) was cleaved in a Parr hydrogenation apparatus in absolute ethanol (200 ml) over 10% Pd-C (1.58 g) at 50 psig and 50° C for 7.5 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with absolute ethanol. The combined filtrate was concentrated and the product purified via preparative HPLC (silica gel, 3:1 dichloromethane/EtOAc) affording 5.0 g of the desired product as an oil. Addition of EtOAc solidified the product which was recrystallized from EtOAc to give a solid, m.p. 157-160° C.

ANALYSIS:			
Calculated for $C_{17}H_{18}FN_3O$:	68.21%C	6.06%H	14.04%N
Found:	67.81%C	6.09%H	13.73%N

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EXAMPLE 45

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl methylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of methyl isocyanate (0.46 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 50% EtOAc/dichloromethane) afforded 2.35 g of the desired carbamate as a solid. The product was recrystallized from ether, m.p. 163-164° C.

ANALYSIS:			
Calculated for $C_{19}H_{21}FN_4O_2$:	64.03%C	5.94%H	15.72%N
Found:	63.84%C	6.10%H	15.55%N

EXAMPLE 46

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of butyl isocyanate (0.87 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, ether) afforded 2.3 g of the desired product as an oil. The product was crystallized from ether/pentane, m.p. 83-84° C.

ANALYSIS:			
Calculated for $C_{22}H_{27}FN_4O_2$:	66.31%C	6.83%H	14.06%N
Found:	65.99%C	6.83%H	13.88%N

EXAMPLE 47

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl heptylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.54 g) and anhydrous tetrahydrofuran (57 ml) was added carbonyl diimidazole (2.75 g) under nitrogen with stirring. The resulting reaction mixture was stirred at room temperature for two days, at which time acetic acid (1.65 ml) was added followed by a solution of heptylamine (1.89 ml) in tetrahydrofuran (5 ml) and acetic acid (0.76 ml). After stirring for 24 hours, an additional equivalent of heptylamine (1.26 ml) in tetrahydrofuran (5 ml) and acetic acid (0.52 ml) was added. After an additional 24 hours the reaction was complete and the reaction mixture was poured into $NaHCO_3$ (aq.) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq.) and brine. Drying (Na_2SO_4), filtration and concentration gave a crude product. Purification via flash column chromatography (silica gel, 30% EtOAc/hexane) afforded 3.38 g of the desired product as an oil. Addition of ether and pentane solidified the product. The solid was filtered and washed with pentane, m.p. 90-93° C.

ANALYSIS:			
Calculated for $C_{25}H_{33}FN_4O_2$:	68.16%C	7.55%H	12.72%N
Found:	67.87%C	7.35%H	12.60%N

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EXAMPLE 48

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl phenylmethylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-3-methyl-1H-indol-5-ol(2.66 g) in tetrahydrofuran (59 ml) was added milled potassium carbonate (1.29 g) followed by dropwise addition of benzyl isocyanate (1.21 ml) at room temperature under nitrogen. Stirring was continued for 17.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration afforded a crude product. Purification via flash column chromatography (silica gel, ether) afforded 3.34 g of the desired carbamate as a foam. This foam was dissolved in ether and the product crystallized as a solid. The solid was recrystallized from ether, m.p. 143-144° C.

ANALYSIS:			
Calculated for $C_{25}H_{25}FN_4O_2$:	69.42%C	5.83%H	12.96%N
Found:	69.44%C	5.83%H	12.84%N

EXAMPLE 49

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.51 g) in anhydrous tetrahydrofuran (56 ml) was added 1,1'-carbonyl diimidazole (2.72 g) at room temperature under nitrogen. After 24 hours the reaction appeared complete by TLC (silica gel, 60% EtOAc/hexane) and acetic acid (1.60 ml) was added to the reaction mixture followed by the dropwise addition of a solution of 1,2,3,4-tetrahydroisoquinoline (1.58 ml) in tetrahydrofuran (5.0 ml) and acetic acid (0.75 ml). After 72 hours, the reaction was not complete by TLC (60% EtOAc/dichloromethane) and an additional equivalent of 1,2,3,4-tetrahydroisoquinoline (1.05 ml) was added as a tetrahydrofuran (5.0 ml) and acetic acid (0.51 ml) solution. After 1.5 hours the reaction appeared complete and the mixture was poured into $NaHCO_3$ (aq) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq) and brine, and dried (Na_2SO_4). The organic phase was filtered and concentrated to give a crude product. Purification via flash column chromatography (silica gel., 30% EtOAc/dichloromethane) afforded 2.70 g of the desired product as an oil which solidified on standing. Recrystallization from ether (2x) gave a solid which was filtered and washed with ether, m.p. 157-160° C.

ANALYSIS:			
Calculated for $C_{27}H_{27}FN_4O_2$:	70.72%C	5.94%H	12.22%N
Found:	70.93%C	5.85%H	12.11%N

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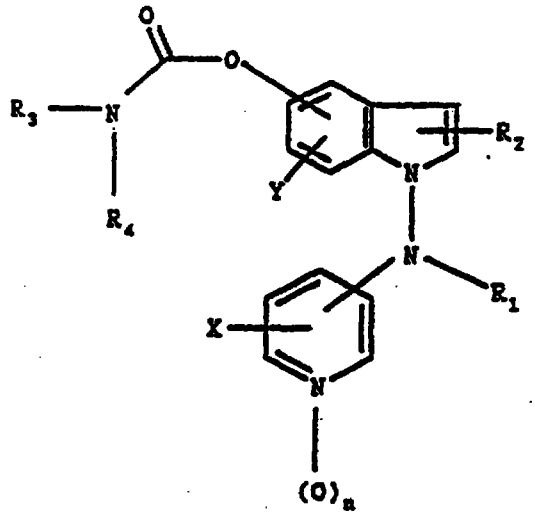
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Claims

1. A compound of the formula Ia

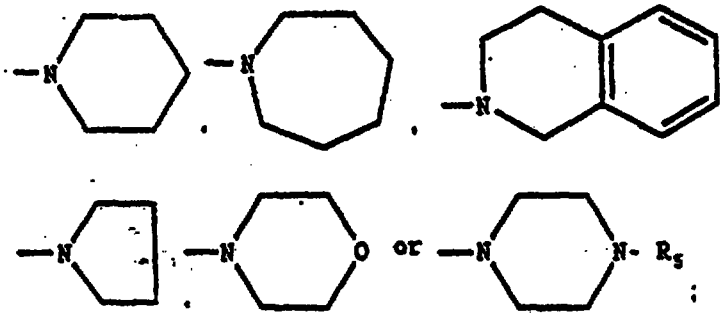


(Ia)

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wherein

- n is 0 or 1;
- X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
- R_2 is hydrogen, loweralkyl, formyl or cyano;
- R_3 is hydrogen or loweralkyl;
- R_4 is lowaralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
- or alternatively, $-NR_3R_4$ taken together constitutes



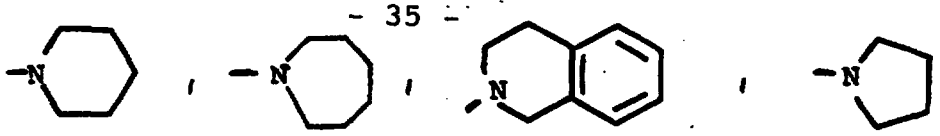
- R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof.

2. A compound of the formula Ia as defined in claim 1, wherein
   - n is 0,
   - X is hydrogen or halogen and Y is hydrogen.

3. A compound of the formula Ia as defined in claim 2 wherein R_1 and R_2 are each independently H or loweralkyl.

4. A compound of the formula Ia as defined in claim 3 wherein R_3 is hydrogen, R_4 is loweralkyl, aryloweralkyl, cycloalkyl or alternatively $-NR_3R_4$ taken together constitutes

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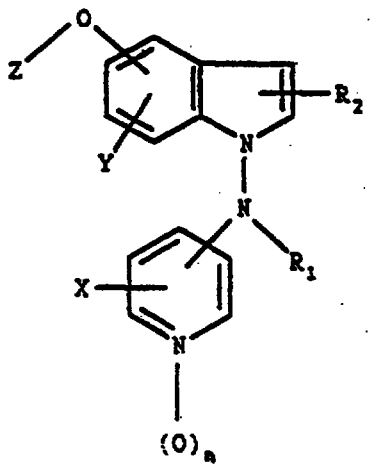
5. A compound as defined in claim 1, which is 1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate.

6. A compound as defined in claim 1, which is (S)-(-)-1-(propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate.

7. A pharmaceutical composition which comprises a compound as defined in claim 1 as the active ingredient and a suitable carrier therefor.

8. Use of a compound a defined in claim 1 for the preparation of a medicament having the activity of alleviating a memory dysfunction characterized by a cholinergic deficit.

9. A compound of the formula Ib



Ib

wherein

n	is 0 or 1;
X	is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
Y	is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
R_1	is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
R_2	is hydrogen, loweralkyl, formyl or cyano;
Z	is hydrogen, loweralkyl or benzyl

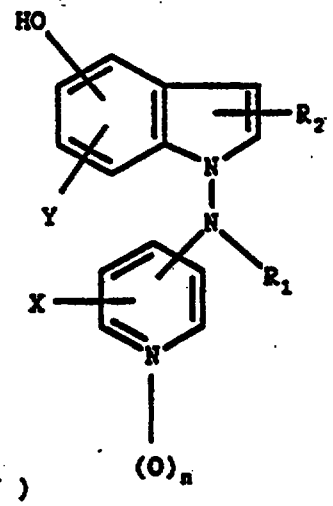
and all optical and geometrical stereoisomers and racemic mixtures thereof.

10. A compound of the formula Ib a defined in claim 7 wherein X is halogen or hydrogen, Y is hydrogen and R_1 and R_2 are each independently H or loweralkyl.

11. A process for the preparation of a compound of the formula Ia, as defined in claim 1, which comprises
a) reacting a compound of the formula XV

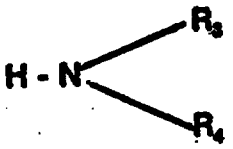
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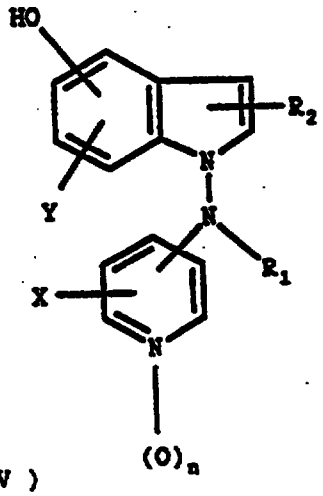
(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with 1,1'-carbonyldiimidazol to afford an intermediate which is treated with an amine of the formula



wherein R_3 and R_4 are defined as in claim 1, or

b) reacting a compound of the formula XV



(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with an isocyanate of the formula

R_4 - NCO

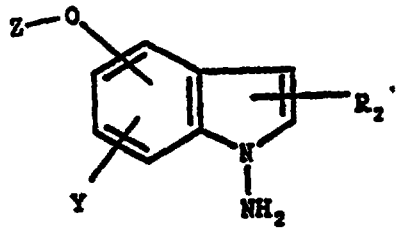
wherein R_4 is defined as above, to afford a compound of the formula Ia, where X, Y, R_1, R_2, R_4 and n are a defined above and R_3 is hydrogen.

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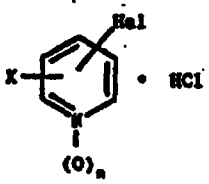
12.

a) A process for the preparation of a compound of the formula Ib according to claim 7, which comprises reacting a compound of the formula IV,



(IV)

wherein R_2 and Y are defined as in claim 7 with a halopyridine of the formula



wherein X and n are as defined in claim 7 and Hal is fluorine, chlorine, bromine or jodine, to afford a compound of the formula Ib, wherein X, Y, R_2 and n are a defined in claim 7, Z is benzyl or loweralkyl and R_1 is hydrogen,

b) optionally reacting a compound of the formula Ib as obtained in step a) with a suitable base of afford the corresponding anion, which is reacted with a halide of the formula

R_1 - Hal

wherein R_1 is defined as in claim 7, except hydrogen, and Hal is chlorine, bromine or jodine, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl and R_1 is defined as in claim 7, except hydrogen,

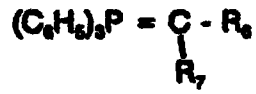
c) optionally reacting a compound of the formula Ib as obtained in step a) wherein R_2 is hydrogen with a suitable base to afford the corresponding anion, which is reacted with a diloweralkylsulfate of the formula

$R_1 - OSO_2 - OR_1$

wherein R_1 is loweralkyl to afford a compound of the formula Ib according to claim 7 wherein Z is benzyl or loweralkyl and R_1 is loweralkyl,

d) optionally reacting a compound of the formula Ib as obtained in step a), b) or c), wherein R_2 is hydrogen with phosphorus oxychloride and dimethylformamide to afford a compound of the formula Ib according to claim 7, wherein Z is benzyl or loweralkyl and R_2 is formyl,

e) optionally reacting a compound of the formula Ib as obtained in step d) with an ylide of the formula



wherein R_6 and R_7 are each independently hydrogen or loweralkyl, to afford a compound of the formula Ib wherein R_2 is loweralkenyl, which is reduced to afford a compound of the formula Ib.

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according to claim 7 wherein Z is benzyl or loweralkyl and R_2 is loweralkyl.

f) optionally reacting a compound of the formula Ib as obtained in step d) with hydroxylamine to afford the corresponding oxime, which is treated with benzenesulfonyl chloride, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or lower alkyl and R_2 is the cyano group.

g) optionally reacting a compound of the formula Ib as obtained in step a) with ethyl chloroformate to afford the corresponding N-ethylcarbamate which is optionally treated as described in steps d), e) or f) to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl, R_1 is alkoxycarbonyl, and R_2 is formyl, loweralkyl or cyano,

h) optionally subjecting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is benzyl to a hydrogenolysis, to afford a compound of the formula Ib according to claim 7 wherein Z is hydrogen.

i) optionally reacting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is loweralkyl with a suitable cleavage reagent, such as HBr, borontribromide etherate, trimethylsilyl iodide or a sodium salt of ethylmercaptan, to afford a compound of the formula Ib according to claim 7, wherein Z is hydrogen.

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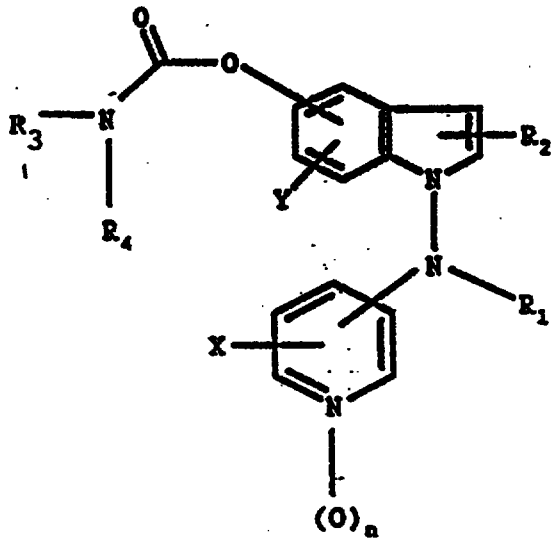
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1-(SUBSTITUTED PYRIDINYLAMINO)-1H-INDOL-5-YL SUBSTITUTED CARBAMATES, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS.

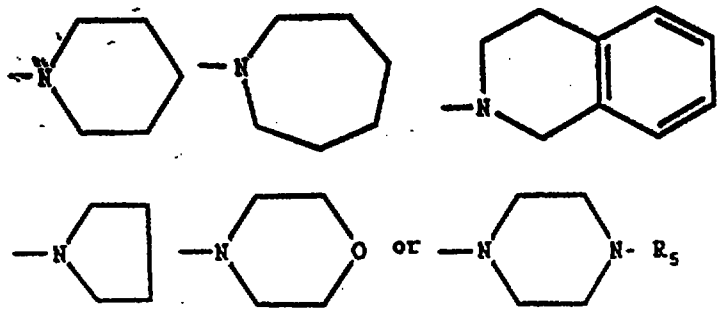
ABSTRACT

There are disclosed various compounds of the formula below,



where

- n is 0 or 1;
- X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;
- R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;
- R_2 is hydrogen, loweralkyl, formyl or cyano;
- R_3 is hydrogen or loweralkyl;
- R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;
  or alternatively, $-NR_3R_4$ taken together constitutes



R_5 being hydrogen, loweralkyl, aryl, aryloweralkyl, heteroaryl or heteroaryloweralkyl,

which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

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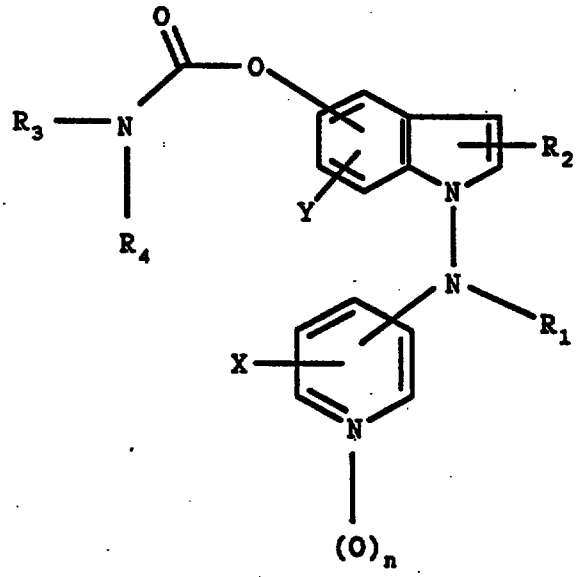
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☐ Drawing(s) : paged ..... to paged .....
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1-(Substituted pyridinylamino)-1H-indol-5-yl Substituted Carbamates, a process and intermediates for their preparation and their use as medicaments

The present invention relates to compounds of Formula I a,



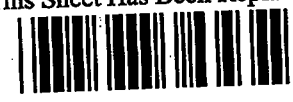
(Ia)

where

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

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Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

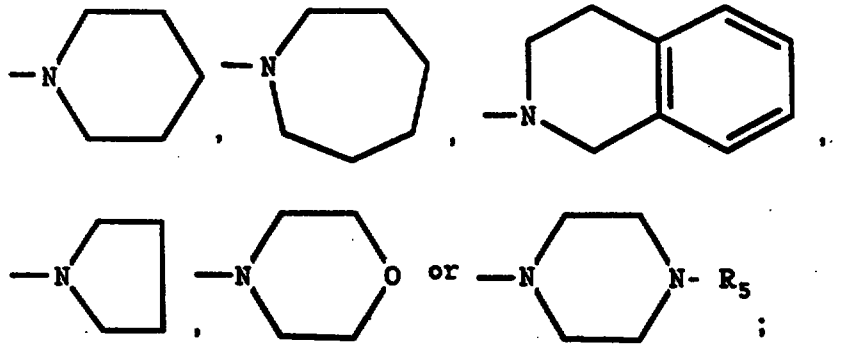
R_1 is hydrogen, loweralkyl, arylloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, arylloweralkanoyl, heteroarylloweralkyl or heteroarylloweralkanoyl;

R_2 is hydrogen, loweralkyl, formyl or cyano;

R_3 is hydrogen or loweralkyl;

R_4 is loweralkyl, arylloweralkyl, cycloalkyl, aryl or heteroaryl;

or alternatively, $-NR_3R_4$ taken together constitutes



R_5 being hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl,

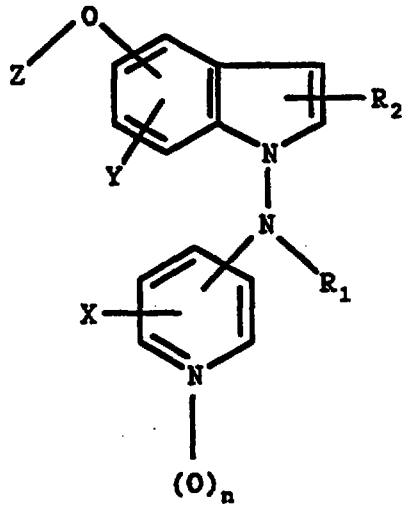
which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

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Also included within the scope of this invention are compounds depicted by the formula Ib below where the group Z is hydrogen, loweralkyl or benzyl, and other parameters are as defined above, which are useful as direct precursors to the target compounds of this invention having Formula Ia.



(Ib)

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 8 carbon atoms. Examples of said loweralkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and

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straight- and branched-chain pentyl, hexyl, heptyl and octyl.

The term cycloalkyl shall mean a cycloalkyl group of 3 to 7 carbon atoms.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term aryl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which being independently loweralkyl, loweralkoxy, halogen or trifluoromethyl.

The term heteroaryl shall mean furanyl, thienyl, pyrrolyl or pyridinyl.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all optical and geometric stereoisomers where such isomers exist.

The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

Throughout the description of the synthetic steps, the notations n, X, Y and R_1 through R_5 shall have the respective meanings given above unless otherwise stated or indicated.

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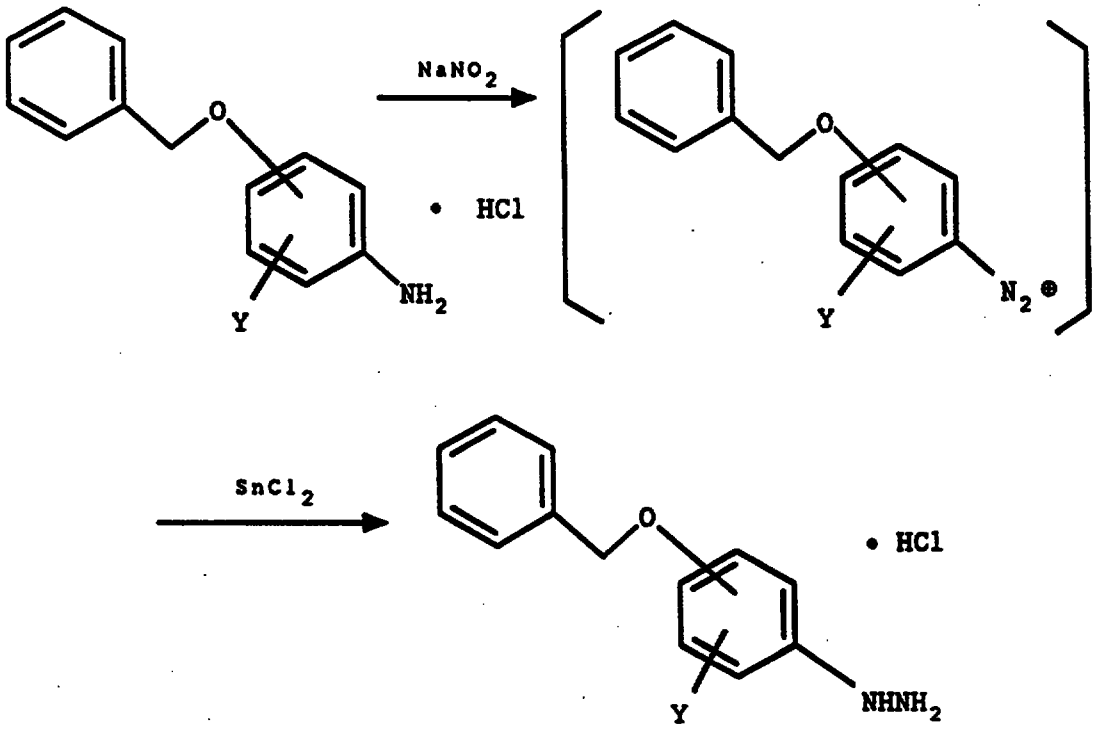


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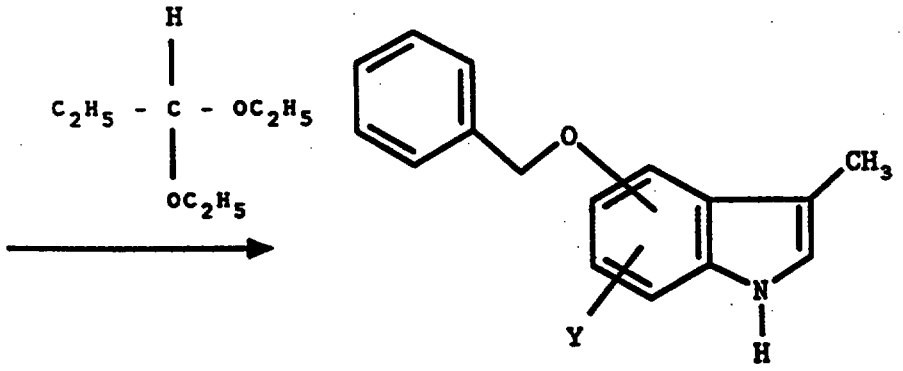
STEP A:

A benzyloxyaniline depicted below is allowed to react with $NaNO_2$ in a routine manner known to the art to afford the corresponding diazonium compound and the latter is reduced with $SnCl_2$ to afford the corresponding hydrazine compound, and thereafter the latter is allowed to react with the diethylacetal of propionaldehyde to afford the compound of Formula II. For details of the last reaction (Fisher indole synthesis), the reader is referred, for instance, to D. Keglevie et al., Chem. Absts. 56, 4710h.



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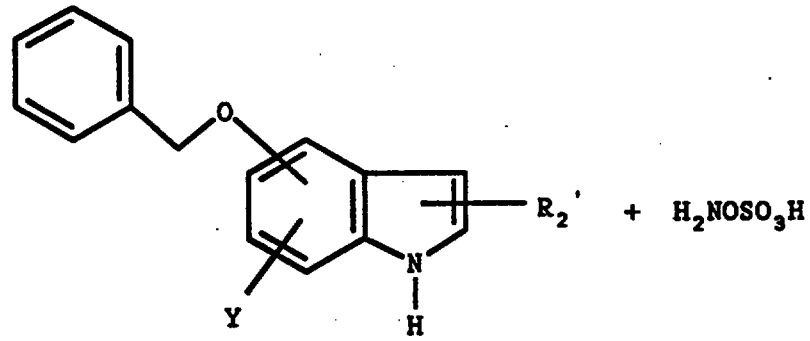
Where the 2-methylisomer of Compound II is desired, the above reaction is conducted in substantially the same manner as described above except that acetone is used instead of diethylacetal of propionaldehyde.

STEP B:

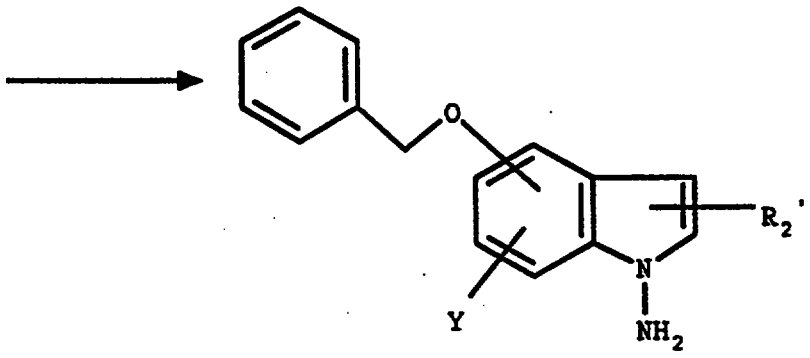
A compound of Formula III where R_2' is hydrogen or methyl is allowed to react with hydroxylamine-O-sulfonic acid in a routine manner known to the art to afford a compound of Formula IV. The starting compound of Formula III where R_2' is hydrogen is either available on the market or can be synthesized from known compounds according to methods known to the art.

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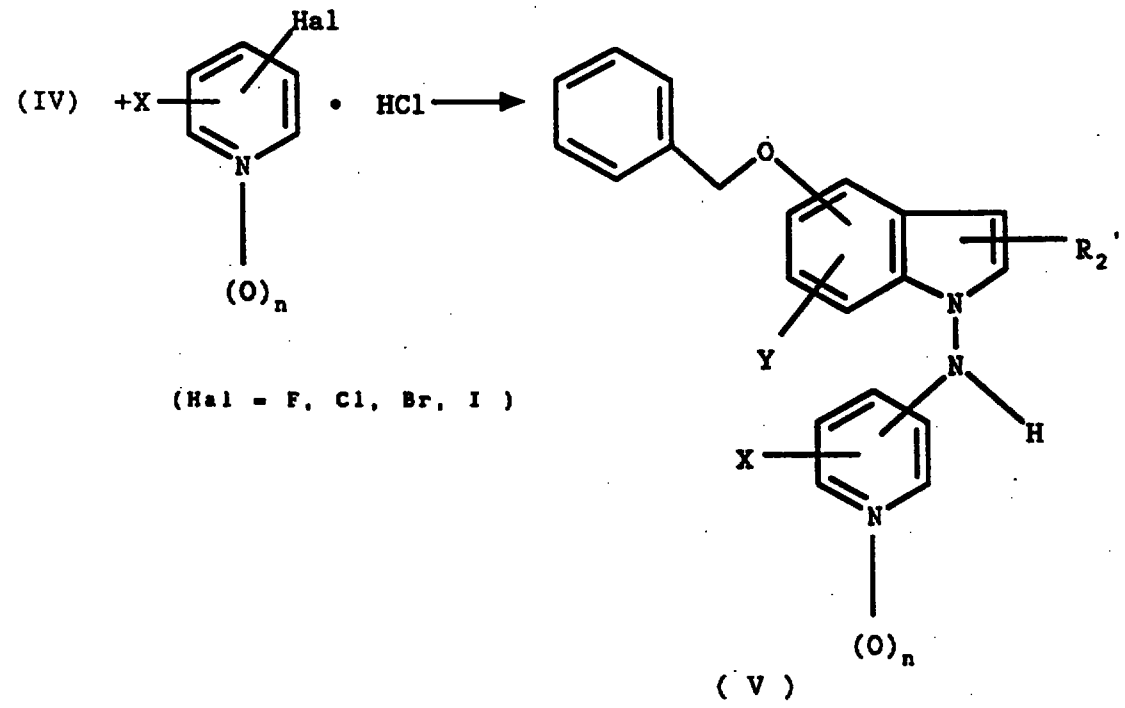
(IV)

STEP C:

Compound IV is allowed to react with a halopyridine hydrochloride depicted below to afford a compound of Formula V. This reaction is typically conducted in a suitable solvent such as N-methyl-2-pyrrolidinone at a temperature of 20 to 200°C.

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(Hal = F, Cl, Br, I)

(V)

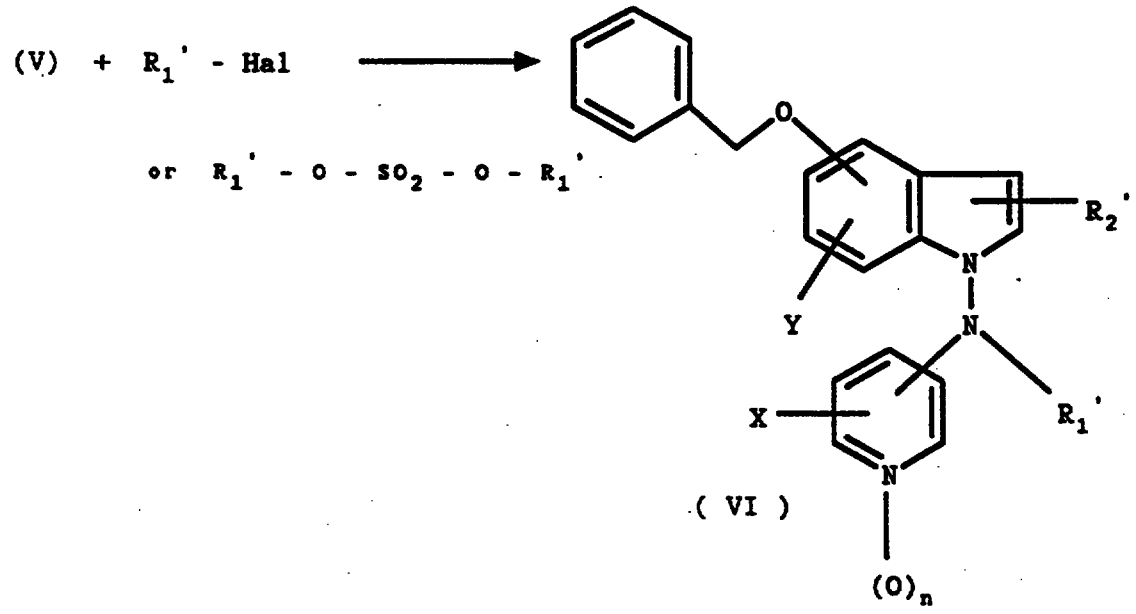
STEP D:

Compound V is allowed to react with a suitable base, such as sodium hydride or potassium t-butoxide, and the resultant anion is allowed to react with a halide of the formula R_1'- Hal where R_1' is loweralkyl, arylloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, arylloweralkanoyl, heteroarylloweralkyl or heteroarylloweralkanoyl, and Hal is chlorine, bromine or iodine, or with a diloweralkylsulfate of the formula R_1'-O-SO_2-O-R_1' where R_1' is loweralkyl, in a routine

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manner known to the art to afford a compound of Formula VI.

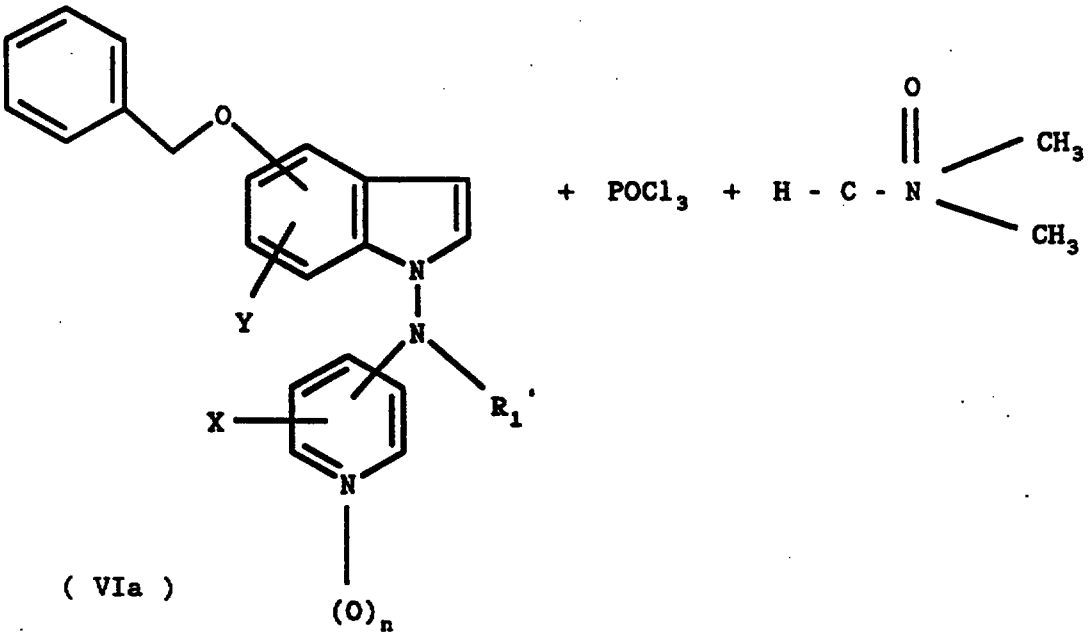


STEP E:

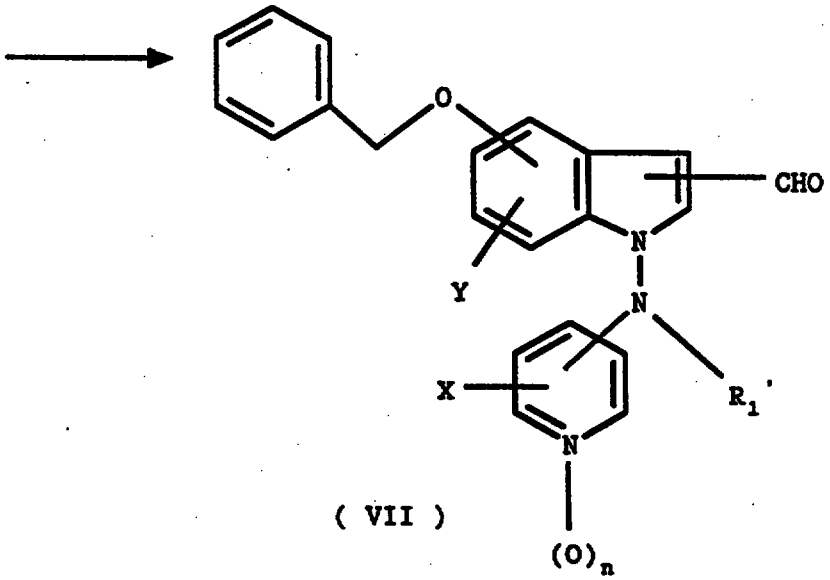
A compound of Formula VIa is allowed to react with phosphorus oxychloride and dimethylformamide in a routine manner known to the art to afford a compound of Formula VII.

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(VIa)



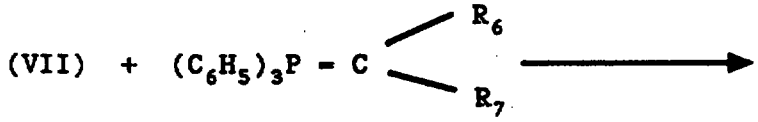
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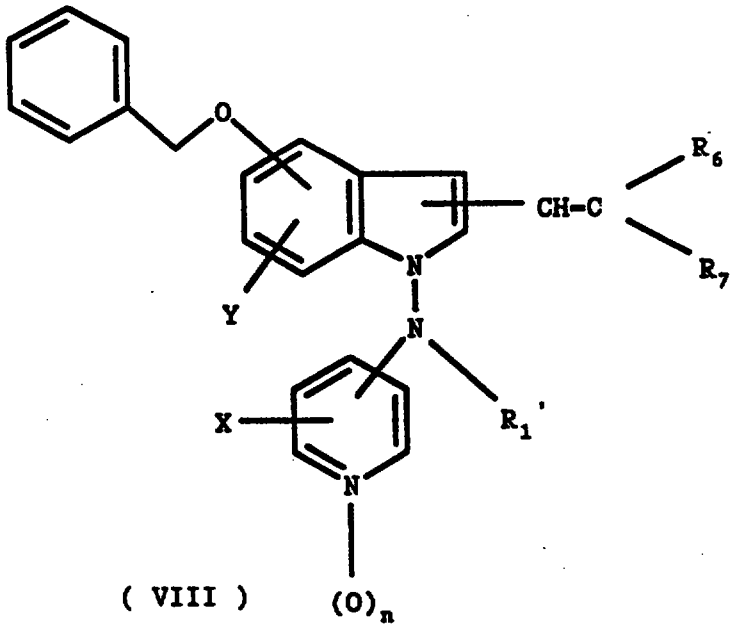
STEP F:

Compound VII is subjected to a Wittig reaction with an ylide of the formula $(C_6H_5)_3P = C(R_6)(R_7)$ where R_6 and R_7 are each independently hydrogen or loweralkyl in a routine manner known to the art to afford a compound of Formula VIII and thereafter the latter compound is reduced in a routine manner known to the art to afford a compound of Formula IX.

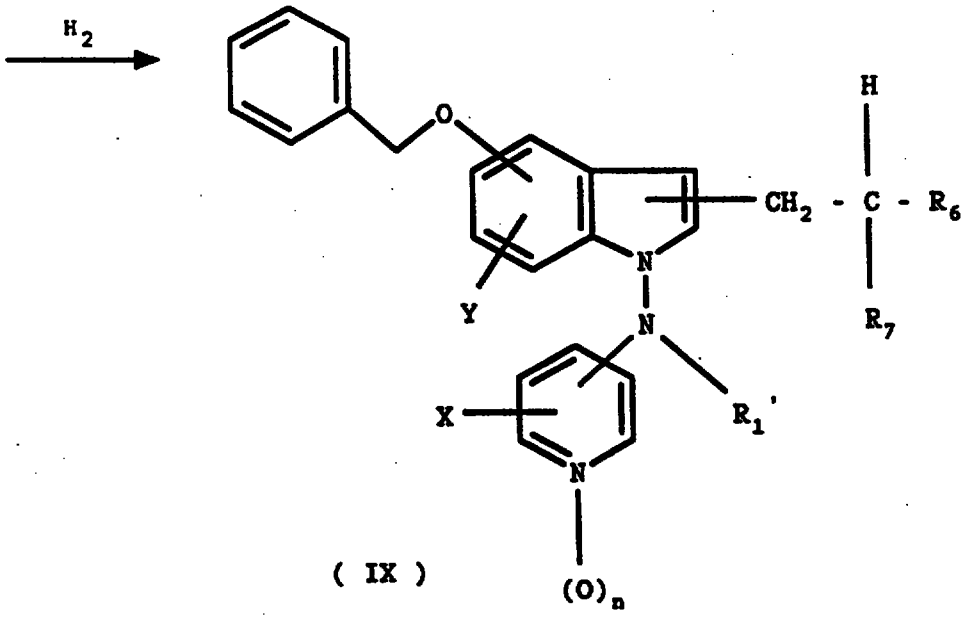


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(VIII)



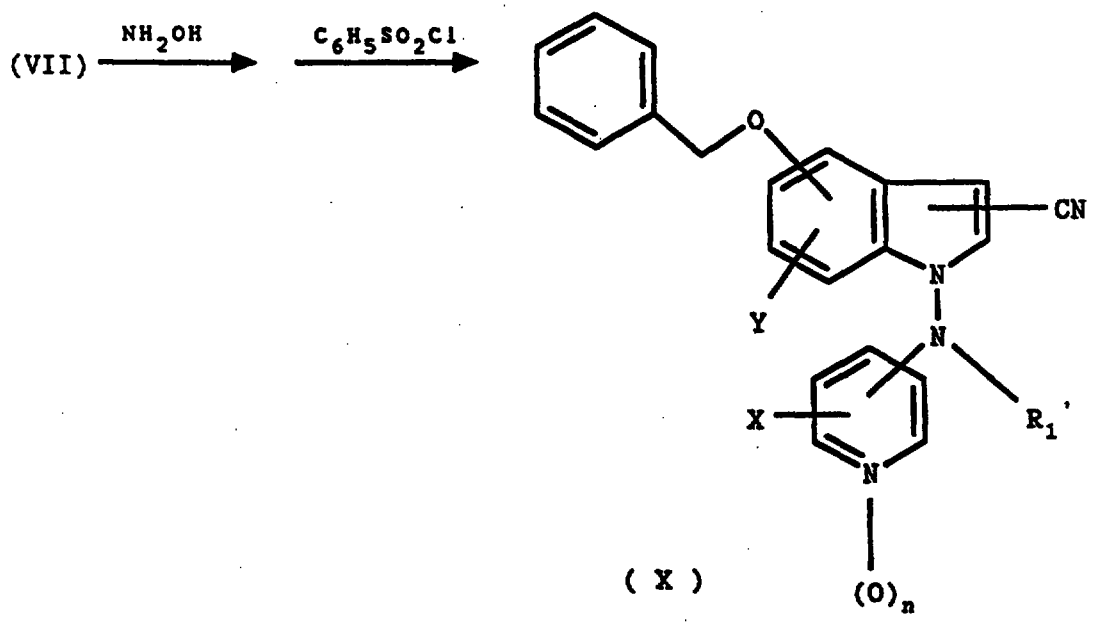
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STEP G:

Compound VII is allowed to react with hydroxylamine in a routine manner known to the art to afford a corresponding oxime and the latter is allowed to react with benzenesulfonyl chloride to afford a nitrile compound of Formula X. The second step is typically conducted in a suitable solvent such as tetrahydrofuran or p-dioxane at a temperature of about 60 to 100°C.



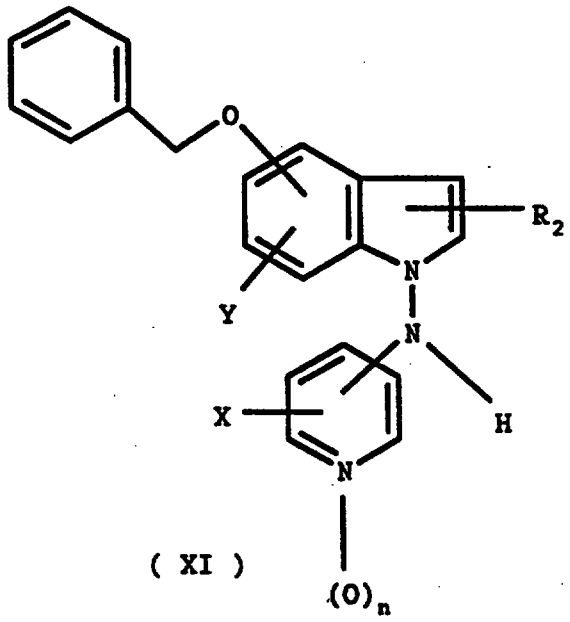
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STEP H:

In order to prepare a compound of Formula XI depicted below where R_2 is not hydrogen or methyl, it is convenient to adopt the following procedure.



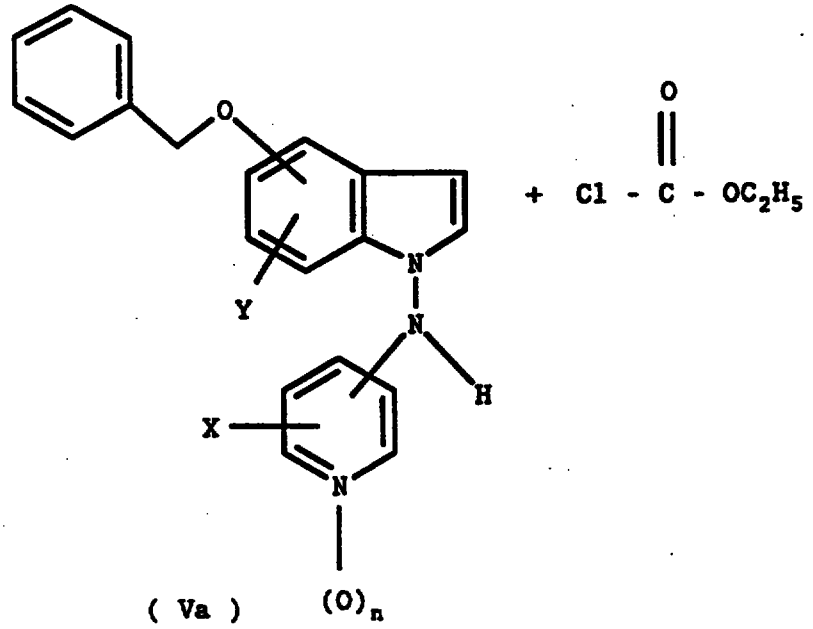
(XI)

(R_2 ≠ H or CH_3)

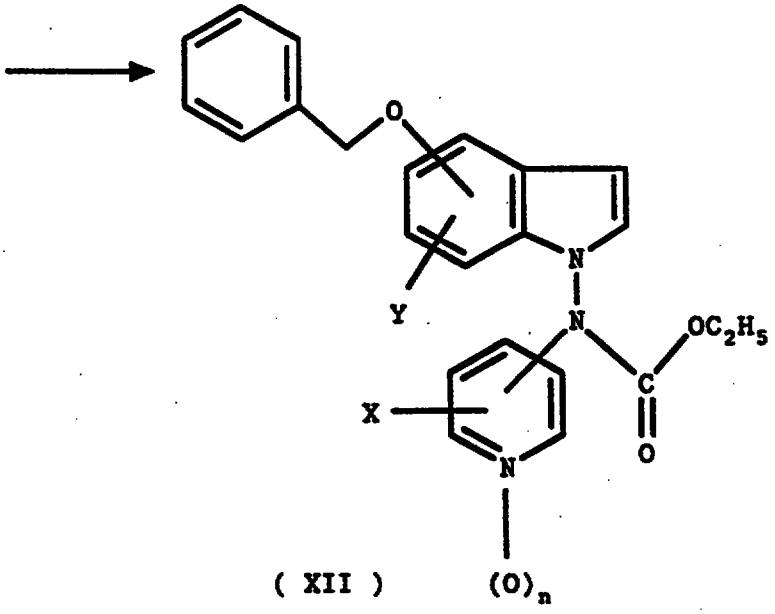
Thus, a compound of Formula Va is allowed to react with ethyl chloroformate in a routine manner known to the art to afford an ethyl carbamate of Formula XII and thereafter the latter compound is subjected to one or more of STEPS E through G to afford a compound of Formula XIII. Subsequently, Compound XIII is hydrolyzed in a routine manner known to the art to afford Compound XI.

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(Va)

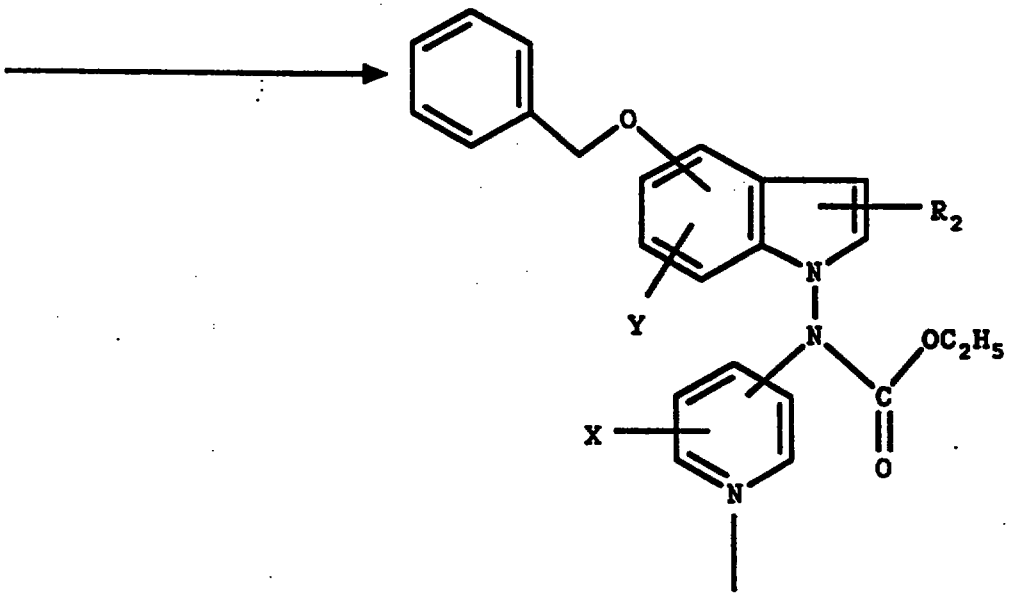


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One or more of STEPS E through G



(XIII)

hydrolysis

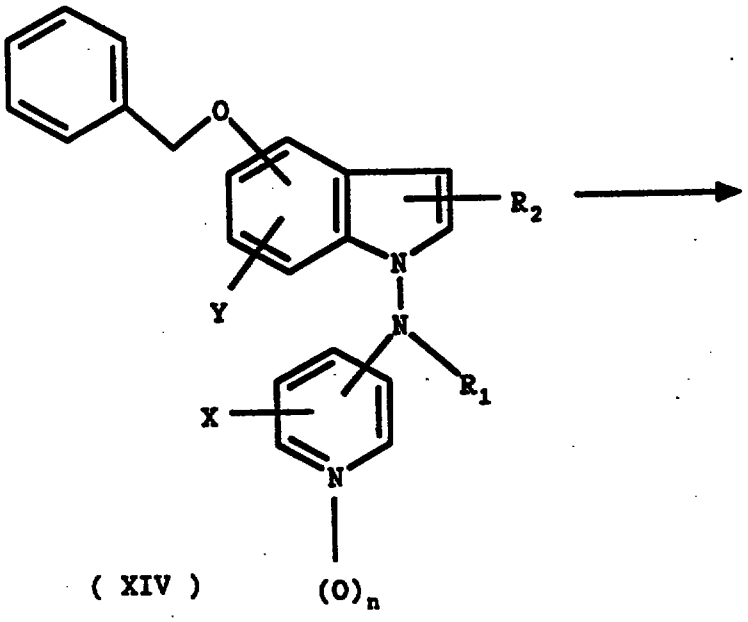
(XI)

STEP I:

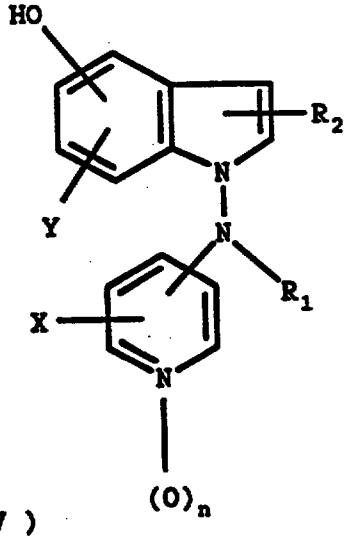
A compound of Formula XIV obtained from one of the foregoing STEPS is subjected to hydrogenolysis conducted in a routine manner known to the art to afford a compound of Formula XV.

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(XIV)



(XV)

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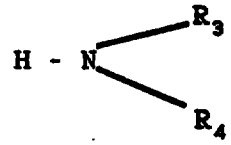
AMENDMENT SHEET

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In each of the foregoing STEPS A through I, the reactant molecule carries a benzyloxy group on the benzene portion thereof. However, the same reactions can also be accomplished in substantially the same manner as described above where the reactant molecule carries a loweralkoxy group instead of a benzyloxy group on the benzene portion thereof, except that in the case of STEP I, a cleavage reaction is utilized instead of hydrogenolysis. Said cleavage reaction is conducted in a routine manner known to the art, for instance, with the aid of 48% HBr, boron tribromide etherate, trimethylsilyl iodide or the sodium salt of ethyl mercaptan.

STEP J:

Compound XV is allowed to react with 1,1'-carbonyldiimidazole and the resultant reaction product is allowed to react with an amine of the formula

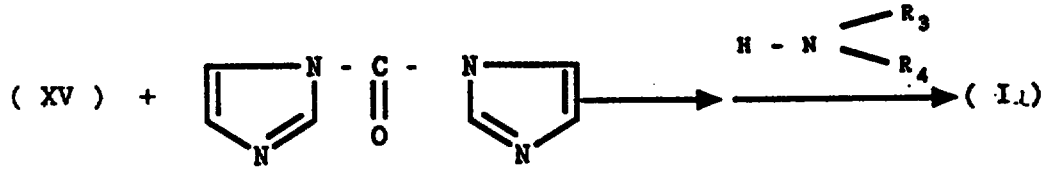


in a routine manner known to the art to afford Compound I.

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Typically, the first step is conducted in a suitable solvent such as tetrahydrofuran at room temperature. Typically, the second step is conducted by adding a suitable amount of the desired amine in glacial acetic acid to the reaction mixture.

Alternatively, where Compound I in which the group R_3 is hydrogen is desired, Compound XV is allowed to react with an isocyanate of the formula R_4 - NCO in a routine manner known to the art to afford Compound I.



The compounds of Formula I of the present invention are useful for the treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and

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thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

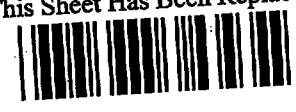
Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with central cholinergic innervation. This same innervation is suggested to be weakened in Alzheimer patients. We have determined in vitro inhibition of acetylcholinesterase activity in rat striatum.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in brain roughly correlates with cholinergic innervation and subfractionation shows the highest level in nerve terminals.

It is generally accepted that the physiological role

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of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinominetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AChE inhibitors may also be beneficial in the treatment of Alzheimer's dementia.

The method described below was used in this invention for assaying cholinesterase activity. This is a modification of the method of Ellman et al., Biochem. Pharmacol. 7, 88 (1961).

Procedure:

A. Reagents -

1. 0.05 M Phosphate buffer, pH 7.2
   (a) 6.85 g $NaH_2PO_4 \cdot H_2O$/100 ml distilled H_2O
   (b) 13.40 g $Na_2HPO_4 \cdot 7H_2O$/100 ml distilled H_2O
   (c) add (a) to (b) until pH reaches 7.2
   (d) Dilute 1:10
2. Substrate in buffer
   (a) 198 mg acetylthiocholine chloride (10 mM)

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(b) q.s. to 100 ml with 0.05 M phosphate buffer,

pH 7.2 (reagent 1)

3. DTNB in buffer

(a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)

(b) q.s. to 100 ml with 0.05 M phosphate buffer,

pH 7.2 (reagent 1)

4. A 2 mM stock solution of the test drug is made up in a suitable solvent and q.s. to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4}M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. <u>Tissue Preparation</u> -

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed and homogenized in 19 volumes (approximately 7 mg

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protein/ml) of 0.05 M phosphate buffer, pH 7.2 using a Potter-Elvehjem homogenizer. A 25 microliter aliquot of the homogenate is added to 1.0 milliter vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37°C.

C. Assay -

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

Instrument Settings

Kinetics Soft-Pac Module #598273 (10)
Program #6 Kindata:
Source - Vis
Wavelength - 412 nm
Sipper - none
Cuvettes - 2 ml cuvettes using auto 6-sampler
Blank - 1 for each substrate concentration
Interval time - 15 seconds (15 or 30 seconds

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for kinetics)

Total time - 5 minutes (5 or 10 minutes for kinetics)

Plot - yes

Span - autoscale

Slope - increasing

Results - yes (gives slope)

Factor - 1

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

Blank:	0.8 ml Phosphate Buffer/DTNB
	0.8 ml Buffer/Substrate
Control:	0.8 ml Phosphate Buffer/DTNB/Enzyme
	0.8 ml Phosphate Buffer/Substrate
Drug:	0.8 ml Phosphate Buffer/DTNB/Drug/Enzyme
	0.8 ml Phosphate Buffer/Substrate

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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 IC_{50} Determinations:

Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration.

$$\% \text{ Inhibition} = \frac{\text{slope control} - \text{slope drug}}{\text{slope control}} \times 100$$

IC_{50} values are calculated from log-probit analysis

Results of this assay for some of the compounds of this invention and physostigmine (reference compound) are presented in Table 1.

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TABLE 1

Compound	Inhibitory Concentration (μM) Brain AChE
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.0023
(S)-(-)-1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl 1-phenylethylcarbamate	30.21
Physostigmine	0.006

This utility is further demonstrated by the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay described below.

Dark Avoidance Assay

In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to

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cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compound, resulting in a greater interval before re-entry into the dark compartment.

The results for an active compound are expressed as the percent of a group of animals in which the effect of scopolamine is blocked, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment.

Results of this assay for some of the compounds of this invention and those for tacrine and pilocarpine (reference compounds) are presented in Table 2.

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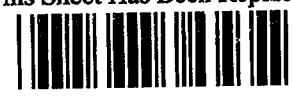
TABLE 2

Compound	Dose (mg/kg of body weight, s.c)	% of Animals with Scopolamine Induced Memory Deficit Reversal
1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl methylcarbamate	0.35	21
Tacrine	0.63	13
Pilocarpine	5.0	13

Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule 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 effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic,

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sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum 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 70% of the weight of the unit. 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 an oral dosage unit form contains between 1.0 - 300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or

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gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweeting agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a 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 preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose 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 active

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compound, but may be varied between 0.5 and about 30% 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 inventions are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of 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 methyl parabens; 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 preparation can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;

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compound, but may be varied between 0.5 and about 30% 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 inventions are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

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Examples of the compounds of this invention include:

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;

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1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-methylcarbamate;

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-butylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-piperidinylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-4-chlorophenylmethylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethylcarbamate;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-heptylcarbamate;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-phenylmethylcarbamate;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-heptylcarbamate;

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-

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1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;

1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-yl-methylcarbamate;

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-4-phenylpiperazin-1-ylcarbamate;

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-morpholin-4-ylcarbamate;

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate-N-oxide;

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

1-(Methyl-4-pyridinylamino)-1H-indol-5-ol;

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol;

3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole;

3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole;

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol;

3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol;

1-(3-Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

1-[Methyl-(3-methyl-4-pyridinyl)amino]-5-phenylmethoxy-1H-

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indole;

1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-ol;

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indol-3-carboxaldehyde;

3-Cyano-1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

1-(2-Phenylethyl-4-pyridinylamino)-1H-indol-5-ol; and

1-(2-Propynyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole;

Examples of this invention are presented below.

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EXAMPLE 1

5-Phenylmethoxy-1H-indole-1-amine

To 5-phenylmethoxyindole (50 g) in 300 ml of dimethylformamide at ice bath temperature was added milled potassium hydroxide (62.72 g). Then hydroxylamine-O-sulfonic acid (32.93 g) was added portionwise, keeping the internal temperature below 20°C. After the addition was complete, the mixture was stirred for one hour, then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (71 g), which was eluted with dichloromethane on silica gel columns via HPLC. The desired fractions were concentrated to yield a solid (21.15 g). Of this material, 3.0 g was triturated with ether to yield a solid, 2.4 g, m.p. 126-128°C.

ANALYSIS:

Calculated for $C_{15}H_{14}N_2O$:	75.60%C	5.92%H	11.76%N
Found:	75.54%C	5.97%H	11.87%N

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EXAMPLE 2

5-Phenylmethoxy-1-(4-pyridinylamino)-1H-indole

To 250 ml of N-methyl-2-pyrrolidinone was added 5-(phenylmethoxy)-1H-indole-1-amine (29.7 g) and the solution was heated to 80°C. Then 4-chloropyridine hydrochloride (20.55 g) was added portionwise and the mixture was stirred for three hours, cooled, poured into water, basified with aqueous sodium carbonate and extracted with toluene. The organic/aqueous mixture was filtered to yield a solid (39 g), which was triturated with ether to yield a solid (27 g). Of this material, 3.0 g was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 2.5 g, m.p. 143-145°C.

ANALYSIS:

Calculated for $C_{20}H_{17}N_3O$:	76.17%C	5.44%H	13.32%N
Found:	75.82%C	5.43%H	13.21%N

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EXAMPLE 3

1-(4-Pyridinylamino)-1H-indol-5-ol

To 0.8 g of 10% palladium on carbon in 10 ml of absolute ethanol was added a solution of 5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (4.0 g) in 240 ml of absolute ethanol and this was hydrogenated on a Parr apparatus for four hours at 50°C at 50 psig H_2. The mixture was cooled and filtered, and the filtrate was concentrated to yield an oil (4.2 g), which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.72 g). This material was eluted with 10% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a foam (1.8 g), which was recrystallized from ethyl acetate to yield a solid (1.5 g), m.p. 232-234°C.

ANALYSIS:

Calculated for $C_{13}H_{11}N_3O$:	69.32%C	4.92%H	18.66%N
Found:	69.16%C	4.76%H	18.52%N

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EXAMPLE 4

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole hydrochloride

5-(Phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (25 g) was slowly added to an ice-cooled solution of potassium tert-butoxide (11 g) in 250 mL tetrahydrofuran. Following the anion formation, a solution of dimethyl sulfate (12 g) in 25 mL tetrahydrofuran was slowly added so that the internal reaction temperature remained below 10°C. After one hour, the reaction mixture was stirred with water and extracted with ether. The organic layer was washed with water and saturated sodium chloride solution and thereafter dried (anhydrous magnesium sulfate), filtered and concentrated to afford a solid, 28 g. This solid was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 22 g of a solid, m.p. 118-121°C. An analytical sample was prepared by converting 1.5 g to the hydrochloride salt in methanol/ether to yield 1.5 g of crystals, m.p. 235-236°C (dec.).

ANALYSIS:

Calculated for $C_{21}H_{20}ClN_3O$:	68.94%C	5.51%H	11.49%N
Found:	68.60%C	5.50%H	11.28%N

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EXAMPLE 5

1-(Methyl-4-pyridinylamino)-1H-indol-5-ol

A solution of 1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole (9 g) in 250 mL ethanol containing 0.6 g 10% palladium on activated charcoal was hydrogenated at 50 psi at 50°C for three hours via Parr hydrogenation apparatus. After cooling, the mixture was filtered through Celite and concentrated. The residue was eluted through silica with 5% methanol in dichloromethane via flash column chromatography to yield 6.2 g solid. A three gram portion was recrystallized from acetonitrile to yield 2.6 g solid, m.p. 191-193°C. This was again recrystallized from acetonitrile to yield 2.2 g crystals, m.p. 192-193°C.

ANALYSIS:

Calculated for $C_{14}H_{13}N_3O$:	70.27%C	5.48%H	17.57%N
Found:	69.96%C	5.39%H	17.53%N

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EXAMPLE 6

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

Methyl isocyanate (0.72 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing milled potassium carbonate (2 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield a solid 3.1 g. This was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 2.6 g solid, m.p. 186-188°C. This was recrystallized from 20% methanol in ether to yield 1.6 g of product, m.p. 186-188°C.

ANALYSIS:

Calculated for $C_{16}H_{16}N_4O_2$:	64.85%C	5.44%H	18.91%N
Found:	64.85%C	5.58%H	18.73%N

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EXAMPLE 7

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.2 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.7 g solid, m.p. 108-111°C. This was converted to the hydrochloride salt in methanol/ether to yield 3.3 g crystals, m.p. 232-234°C (dec.).

ANALYSIS:

Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.89%C	6.34%H	14.88%N

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EXAMPLE 8

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (1.7 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.8 g solid. This was recrystallized from acetonitrile to yield 3.2 g crystals, m.p. 179-181°C.

ANALYSIS:

Calculated for $C_{22}H_{20}N_4O_2$:	70.95%C	5.41%H	15.05%N
Found:	70.67%C	5.35%H	15.12%N

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EXAMPLE 9

1-(Propyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole maleate

To potassium tert-butoxide (2.80 g) in 20 ml of tetrahydrofuran cooled to ice bath temperature was added dropwise a solution of 5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (6.5 g) in 60 ml of tetrahydrofuran. This mixture was stirred for 10 minutes and then a solution of 1-bromopropane (3.08 g) in 10 ml of tetrahydrofuran was added dropwise. The reaction was allowed to proceed for three hours at room temperature. The mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was removed to yield an oil (8.5 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (5.5 g). Of this material 1.0 g was dissolved in methanol and acidified with a methanol solution of maleic acid. After diluting with ether, the precipitate was collected to yield a solid 1.0 g, m.p. 118-119°C.

ANALYSIS:

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Calculated for $C_{23}H_{23}N_3O \cdot C_4H_4O_4$: 68.48%C 5.75%H 8.87%N

Found: 68.29%C 5.72%H 8.86%N

EXAMPLE 10

1-(Propyl-4-pyridinylamino)-1H-indol-5-ol

To 0.3 g of 10% Pd/C in 10 ml of absolute ethanol was added 5-phenylmethoxy-1-(propyl-4-pyridinylamino)-1H-indole (3.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus for 48 hours at 50°C and 50 psig H_2. The reaction mixture was then filtered and the filtrate concentrated to yield an oil (2.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (1.8 g) which was recrystallized from methanol/ether (1:1) to yield a solid 1.6 g, m.p. 214-216°C.

ANALYSIS:

Calculated for $C_{16}H_{17}N_3O$: 71.89%C 6.41%H 15.72%N

Found: 71.78%C 6.41%H 15.61%N

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EXAMPLE 11

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To 2.5 g of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g) followed by methyl isocyanate (0.56 ml). The reaction was allowed to proceed for half an hour. The reaction mixture was then filtered and the filtrate concentrated to yield a solid (2.9 g) which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.7 g) which was recrystallized from isopropyl ether to yield a solid 1.8 g, m.p. 158-159°C.

ANALYSIS:

Calculated for $C_{18}H_{20}N_4O_2$:	66.65%C	6.22%H	17.27%N
Found:	66.83%C	6.10%H	17.18%N

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EXAMPLE 12

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl ethylcarbamate hydrochloride

Ethyl isocyanate (1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL of tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.5 g of the product as a solid, m.p. 139-141°C. This was converted to the hydrochloride salt in methanol/ether to yield 4.3 g of crystals, m.p. 209-211°C (dec.).

ANALYSIS:

Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87%C	6.18%H	14.95%N
Found:	60.81%C	6.16%H	14.84%N

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EXAMPLE 13

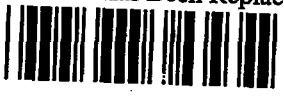
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl propylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then propyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 2 hours. The mixture was filtered and the filtrate was concentrated to yield an oil (2.8 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.5 g), m.p. 120-122°C.

ANALYSIS:

Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	67.87%C	6.89%H	15.93%N

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EXAMPLE 14

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl isopropylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then isopropyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 4 hours. The mixture was filtered and the filtrate was concentrated to yield a solid (3.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.75 g), m.p. 131-133°C.

ANALYSIS:

Calculated for $C_{20}H_{24}N_4O_2$:	68.16%C	6.86%H	15.90%N
Found:	68.16%C	6.84%H	15.84%N

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EXAMPLE 15

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.3 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as an oil. This material was converted to the hydrochloride salt in methanol/ether to yield 4 g of crystals, m.p. 178-180°C.

ANALYSIS:

Calculated for $C_{21}H_{26}N_4O_2 \cdot HCl$:	62.60%C	6.75%H	13.91%N
Found:	62.52%C	6.71%H	13.84%N

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EXAMPLE 16

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 50 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) portionwise, and the reaction was allowed to proceed for 24 hours. To this mixture was added glacial acetic acid (2.15 ml) followed by a solution of heptylamine (1.45 ml) in tetrahydrofuran which had been treated with 0.56 ml of acetic acid. The reaction mixture was then stirred for 21 hours. The mixture was diluted with water, basified with sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (4.5 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (2.8 g). This material was dissolved in 50 ml of pentane/ether (1:1) and the solution was concentrated to

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15 ml, whereupon crystals precipitated out of the solution. These were collected to yield a solid (1.0 g), m.p. 83-85°C.

ANALYSIS:

Calculated for $C_{24}H_{32}N_4O_2$:	70.56%C	7.90%H	13.72%N
Found:	70.33%C	7.69%H	13.63%N

EXAMPLE 17

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl cyclohexylcarbamate hydrochloride

Cyclohexyl isocyanate (1.7 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 167-169°. This solid was again eluted through silica with ethyl acetate via HPLC to yield 3.8 g of the product as a solid, m.p. 167-170°C. The product was converted to the hydrochloride salt in methanol/ether to yield 3.9 g of powder, m.p. 219-220°C

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(dec.).

ANALYSIS:

Calculated for $C_{23}H_{28}N_4O_2 \cdot HCl$:	64.40%C	6.81%H	13.06%N
Found:	64.07%C	6.77%H	12.92%N

EXAMPLE 18

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (2 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 156-158°C. The product was recrystallized from acetonitrile to yield 3.8 g of crystals, m.p. 162-164°C.

ANALYSIS:

Calculated for $C_{24}H_{24}N_4O_2$:	71.98%C	6.04%H	13.99%N
Found:	71.99%C	6.13%H	14.03%N

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EXAMPLE 19

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 4-chlorophenylmethylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by 4-chlorophenylmethylamine (1.5 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.9 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (3.05 g), m.p. 149-151°C

ANALYSIS:

Calculated for :	66.29%C	5.33%H	12.88%N
Found:	66.22%C	5.37%H	12.81%N

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EXAMPLE 20

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 2-phenylethylcarbamate hydrochloride

2-Phenylethyl isocyanate (2.1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3.5 g). After stirring three hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.7 g of the product as a solid. The product was converted to the hydrochloride salt in methanol/ether to yield 2.9 g of crystals, m.p. 144-146°C (dec.).

ANALYSIS:

Calculated for $C_{25}H_{26}N_4O_2 \cdot HCl$:	66.58%C	6.04%H	12.43%N
Found:	66.60%C	5.94%H	12.38%N

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EXAMPLE 21

(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.75 g) in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 0.912 g) followed by (S)-(-)-1-methylbenzyl isocyanate (0.97 g), and the reaction was allowed to proceed for one hour. The reaction mixture was filtered and the filtrate concentrated to yield an oil (3.9 g) which was eluted with 5% methanol in dichloromethane (DCM) on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid 2.6 g, m.p. 78-80°C.

ANALYSIS:

Calculated for $C_{25}H_{26}N_7O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.17%C	6.34%H	13.49%N

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EXAMPLE 22

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethyl carbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by dimethylamine (40 wt % in water, 1.44 ml) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl., anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.5 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.5 g), m.p. 134-136°C.

ANALYSIS:

Calculated for :	67.43%C	6.55%H	16.56%N
Found:	67.63%C	6.58%H	16.58%N

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EXAMPLE 23

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl piperidinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by piperidine (0.95 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.65 g).

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ANALYSIS:

Calculated for $C_{22}H_{26}N_4O_2$:	69.81%C	6.92%H	14.80%N
Found:	69.45%C	6.94%H	14.68%N

EXAMPLE 24

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 40 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 3.5 ml of glacial acetic acid was added to the reaction mixture. Then 1,2,3,4-tetrahydroisoquinoline (1.49 g) in 10 ml of tetrahydrofuran which had been acidified with 0.60 ml of glacial acetic acid was added to the reaction mixture dropwise. This was stirred for 24 hours and then the reaction mixture was quenched with water, basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (5.6 g) which was eluted with 5% methanol/dichloromethane on a silica gel

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column via HPLC The desired fractions were concentrated to yield an oil (4.2 g). This material was dissolved in pentane/ether (1:1), whereupon a solid precipitated out of the solution. This material was collected to yield a solid, 2.6 g, m.p. 141-143°C.

ANALYSIS:

Calculated for $C_{26}H_{26}N_4O_2$:	73.21%C	6.15%H	13.14%N
Found:	73.12%C	6.22%H	12.95%N

EXAMPLE 25

1-(3-Fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole

To 250 ml 1-methyl-2-pyrrolidinone was added 5-phenylmethoxy-1H-indol-1-amine (27.3 g), and the mixture was heated to 80°C. Then, 4-chloro-3-fluoropyridine hydrochloride (22 g) was added, and the mixture was heated at 80°C for two hours. After cooling, the mixture was poured into 1 liter of ice-water, stirred for five minutes, and adjusted to pH 9 with milled K_2CO_3. The product was extracted with ethyl acetate (3X). The organic layer was washed with water (2X) and dried (saturated NaCl, anhydrous $MgSO_4$). After filtration, the

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filtrate was concentrated to give an oil, 46 g of which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on cooling, 32.2 g, m.p. 140°C. A sample of this material was recrystallized from ether, m.p. 157-159°C.

ANALYSIS:

Calculated for $C_{20}H_{16}FN_3O$:	72.06%C	4.84%H	12.60%N
Found:	71.98%C	4.90%H	12.51%N

EXAMPLE 26

1-[(3-Fluoro-4-pyridinyl)propylamino]-5-phenylmethoxy-1H-indole hydrochloride

To 100 ml of dry DMF (dimethylformamide) was added 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (20.0 g), and the solution was cooled to 0°C. To this was added potassium t-butoxide (6.7 g), and the mixture was stirred at 0°C for ten minutes, and thereafter a solution of n-propylbromide (5.5 ml) in 10 ml dry DMF was added. After stirring at 0°C for thirty minutes and then at ambient temperature for two hours, the mixture was poured into 500 ml cold water, stirred for five minutes and

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extracted with ethyl acetate (3X). The organic layer was washed successively with water (2X) and saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give an oil, 23 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:2) via HPLC. The desired fractions were combined and concentrated to give an oil, 19.3 g. A 2.0 g sample of this oil was dissolved in 50 ml methanol, and the solution was acidified to pH 1 with ethereal HCl and diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g, m.p. 200°C (dec.).

ANALYSIS:

Calculated for $C_{23}H_{22}FN_3O \cdot HCl$: 67.06%C 5.63%H 10.20%N

Found: 66.74%C 5.55%H 10.05%N

EXAMPLE 27

1-(3-Fluoro-4-pyridinylamino)-1H-indol-5-ol

In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.0 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-(3-fluoro-4-pyridinylamino)-

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5-phenylmethoxy-1H-indole (5.0 g) in 200 ml ethanol. The mixture was shaken at 50°C under 50 psi hydrogen gas for two hours. After cooling, the mixture was filtered, and the filtrate was concentrated to give an oil (5.0 g) which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a crystalline solid, 3.5 g, m.p. 70-73°C.

ANALYSIS:

Calculated for $C_{13}H_{10}FN_3O$:	64.19%C	4.14%H	17.28%N
Found:	64.06%C	4.30%H	16.93%N

EXAMPLE 28

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol hydrochloride

In a 500 ml Parr hydrogenation bottle, 10% Pd/C (1.5 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-5-phenylmethoxy-1H-indole (15.0 g) in 200 ml ethanol. The mixture was shaken under 50 psi hydrogen gas for three hours at 50°C. Upon cooling, the mixture was filtered,

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and the filtrate was concentrated to give a solid, 11.4 g. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC, and the desired fractions were concentrated to give a solid, 8.5 g, m.p. 90-95°C. A 2.0 g sample of this material was dissolved in 50 ml methanol, the pH was adjusted to 1 with ethereal HCl, and the solution was diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g of the product, m.p. 218°C (dec.).

ANALYSIS:

Calculated for $C_{16}H_{16}FN_3O \cdot HCl$: 59.72%C 5.33%H 13.06%N

Found: 59.30%C 5.36%H 12.62%N

EXAMPLE 29

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl methylcarbamate

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]- 1H-indol-5-ol (2.5 g) in 50 ml THF was added potassium carbonate (1.2 g), followed by methyl isocyanate (0.53 ml). After stirring at ambient temperature for three hours, the mixture was filtered, and the filtrate was concentrated to give a

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solid, 3.0 g, m.p. 165-166°C. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1:1) via HPLC. The desired fractions were combined and concentrated to give a solid, 2.7 g, m.p. 177-178°C.

ANALYSIS:

Calculated for $C_{18}H_{19}FN_4O_2$: 63.14%C 5.59%H 16.37%N

Found: 63.27%C 5.68%H 16.23%N

EXAMPLE 30

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl butylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 50 ml tetrahydrofuran was added milled K_2CO_3 (1.1 g), followed by butyl isocyanate (0.9 ml). After stirring at ambient temperature for four hours, the mixture was filtered, and the filtrate was concentrated to give an oil, 5 g. This oil was eluted on a silica gel column with ethyl acetate/dichloromethane (1:4) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on standing, 2.7 g, m.p. 95-98°C.

This solid was dissolved in ether, the pH was

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adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.9 g of a solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:10) to give the product as crystals, 2.4 g, m.p. 142°C (dec.).

ANALYSIS:

Calculated for $C_{21}H_{25}FN_4O_2 \cdot HCl$: 59.92%C 6.23%H 13.31%N

Found: 60.31%C 6.26%H 13.31%N

EXAMPLE 31

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl heptylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 65 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.5 g), and the mixture was stirred at ambient temperature for four hours. The mixture was cooled with an ice bath, and thereafter glacial acetic acid (2.0 ml) was added, followed by a solution of heptylamine (2 ml) and acetic acid in tetrahydrofuran (20 ml).

After stirring at ambient temperature for twenty

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hours, the mixture was poured into 200 ml water, the pH adjusted to 8 with $NaHCO_3$ solution, and the product was extracted with ethyl acetate. The organic layer was washed successively with water and saturated NaCl solution, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to give an oil, 4.2 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1:3) via HPLC. The desired fractions were combined and concentrated to give an oil, 2.6 g. This oil was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.5 g of solid, m.p. 140°C (dec.). This material was recrystallized from ethyl acetate/ether (1:4) to give crystals, 2.3 g, m.p., 246°C (dec.).

ANALYSIS:

Calculated for $C_{24}H_{31}FN_4O_2 \cdot HCl$:	62.26%C	6.97%H	12.10%N
Found:	62.62%C	7.08%H	12.06%N

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EXAMPLE 32

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine

p-Benzyloxyphenylhydrazine hydrochloride was prepared by the method of Mentzer, et al., [C.A. 48:33412]. Thus, p-benzyloxyaniline hydrochloride (72.6 g) was diazotized with conc. HCl (174 ml) and sodium nitrite (23.2 g) in water (40 ml) at 0°C. A solution of stannous chloride (169.3 g) in conc. HCl (435 ml) was added rapidly and the reaction mixture stirred for two hours. The solid product was filtered and washed with absolute ethanol, then partially dissolved in boiling methanol/ethanol (1:1) and filtered hot, yielding 52.5 g of p-benzyloxyphenylhydrazine hydrochloride.

The conversion of the above compound to 3-methyl-5-benzyloxyindole was conducted according to the method of Keglevic, et al. [C.A. 56:4710h]. Thus, the above hydrazine hydrochloride (34.0 g) was dissolved in 25% aqueous HOAc (1.4 L) at 80°C. Propionaldehyde diethyl acetal (22.1 ml) was then added and the reaction mixture stirred for 0.75 hour. Upon cooling to room temperature, ether was added to the reaction mixture and the layers were separated. The aqueous phase was extracted with

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ether (2x). The combined organics were washed with 5% aqueous NaOH until the aqueous extract was basic to litmus. The organic phase was then washed with brine and dried (K_2CO_3). Filtration and concentration afforded 29.0 g of 3-methyl-5-benzyloxyindole.

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine was prepared using the procedure of Somei, et al., [Tetrahedron Lett. No. 5, pp. 461-462, 1974]. Thus, to a solution of the above product (17.3 g) in dry DMF (260 ml) maintained at 0°C was added milled potassium hydroxide (20.5 g) under nitrogen. Hydroxylamine-O-sulfonic acid (10.7 g) was added portionwise (10% wt.) every ten minutes. After stirring for 1 hour at room temperature, water and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with brine and dried (K_2CO_3). Filtration and concentration gave the crude product.

Purification via preparative HPLC (silica gel, DCM) afforded 6.0 g of the desired product as a solid which was recrystallized from ether, m.p. 104-106°C.

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ANALYSIS:

Calculated for $C_{16}H_{16}N_2O$:	76.16%C	6.39%H	11.10%N
Found:	75.86%C	6.37%H	10.87%N

EXAMPLE 33

3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (6.31 g) and 1-methyl-2-pyrrolidinone (109 ml) was added 4-chloropyridine hydrochloride (3.94 g). The resulting mixture was heated at 80°C for 4-5 hours. Another batch of reaction was also carried out with the amine (2.94 g) and 4-chloropyridine hydrochloride (1.84 g) in nmp (50 ml) at 80°C for 4 hours. The above reaction mixtures were poured together into dilute aqueous sodium bicarbonate and extracted with EtOAc (4x) and ether (1x). The combined organic layers were washed with water and brine followed by drying (K_2CO_3). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether/0-5% MeOH) afforded 7.55 g of the desired product. Recrystallization from EtOAc gave a solid, m.p.

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167.5-169.5°C.

ANALYSIS:

Calculated for $C_{21}H_{19}N_3O$:	76.57%C	5.81%H	12.76%N
Found:	76.73%C	6.05%H	12.76%N

EXAMPLE 34

3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol

3-Methyl-5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (2.20 g) was subjected to hydrogenolysis in absolute ethanol (80 ml) with 10% Pd-C (0.26 g) at 50 psig hydrogen at 50°C for 2 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. Concentration and recrystallization from methanol afforded 0.50 g of highly crystalline product, m.p. 239-241°C (dec.).

ANALYSIS:

Calculated for $C_{14}H_{13}N_3O$:	70.28%C	5.48%H	17.56%N
Found:	69.95%C	5.46%H	17.41%N

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EXAMPLE 35

3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole hemifumarate

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (7.78 g) and dimethylformamide (150 ml) maintained at 0°C under nitrogen with stirring, was added sodium hydride (0.64 g, 97% purity). The resulting mixture was stirred at 0°C for an additional 15 minutes at which time propyl bromide (2.25 ml) was added dropwise and the ice bath was removed. Stirring was continued at room temperature for 2-3 hours until complete reaction was observed by TLC (silica gel, ether). The reaction mixture was poured into water and the product extracted with EtOAc (3x) and ether (1x). The combined organic layers were washed successively with water (2x) and brine (2x), dried (K_2CO_3) and decolorized with activated carbon. Filtration and concentration gave the desired product (7.65 g) as an oil. The hemifumarate was prepared with 1.0 eq. fumaric acid in abs. ethanol. A highly crystalline solid resulted, m.p. 165.5-167°C.

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ANALYSIS:

Calculated for $C_{24}H_{25}N_3O \cdot 0.5\ C_4H_4O_4$: 72.70%C 6.35%H 9.78%N

Found: 72.66%C 6.55%H 9.73%N

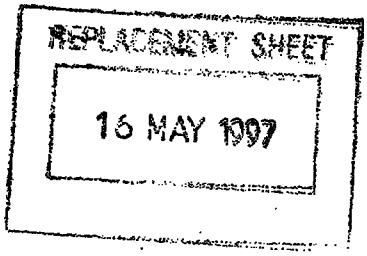
EXAMPLE 36

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol hemioxalate

The benzyl group of 3-methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole (7.80 g) was cleaved in a Parr hydrogenation apparatus in abs. EtOH (275 ml) over 10% Pd-C (0.80 g) at 50 psig and 50°C for 2-3 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. The combined filtrate was concentrated and the product purified via flash column chromatography (silica gel, 2% Et_3N/ether) affording 5.80 g of the product as an oil. Dissolving in absolute ethanol followed by addition of 1.0 eq of anhydrous oxalic acid (in abs. EtOH) resulted in formation of a solid, the hemioxalate, m.p. 235-237°C.

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ANALYSIS:

Calculated for $C_{17}H_{19}N_3O \cdot 0.5\ C_2H_2O_4$: 66.23%C 6.19%H 12.88%N

Found: 65.91%C 6.33%H 12.58%N

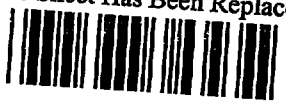
EXAMPLE 37

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.06 g) and tetrahydrofuran (49 ml) was added milled K_2CO_3 (1.06 g) followed by dropwise addition of methyl isocyanate (0.48 ml) at room temperature under nitrogen. Stirring was continued for 2.3 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.30 g of the desired carbamate as an oil. The product was crystallized from ether, m.p. 147-149°C.

ANALYSIS:

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Calculated for $C_{19}H_{22}N_4O_2$:	67.44%C	6.55%H	16.56%N
Found:	67.49%C	6.68%H	16.53%N

EXAMPLE 38

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.11 g) and tetrahydrofuran (50 ml) was added milled K_2CO_3 (1.09 g), followed by dropwise addition of butyl isocyanate (0.93 ml) at room temperature under nitrogen. Stirring was continued for 2.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.65 g of the desired carbamate as an oil. This oil was dissolved in a small amount of EtOAc and diluted with ether, whereupon the product crystallized as a white powder, m.p. 120-122°C.

ANALYSIS:

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Calculated for $C_{22}H_{28}N_4O_2$:	69.45%C	7.42%H	14.72%N
Found:	69.67%C	7.44%H	14.68%N

EXAMPLE 39

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.23 g) and tetrahydrofuran (53 ml) was added 1,1'-carbonyldiimidazole (2.57 g) at room temperature with stirring under nitrogen. Stirring was continued for 96 hours, at which time acetic acid (1.54 ml) was added. To the resulting reaction mixture was added a solution consisting of heptyl amine (1.76 ml), acetic acid (0.71 ml) and THF (5 ml). After stirring for 24 hours, an additional solution of heptyl amine (1.17 ml), acetic acid (0.48 ml) and THF (5 ml) was added and stirring continued for 3 hours. The reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$).

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Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) afforded 1.60 g of the desired carbamate after recrystallization from ether/pentane, m.p. 102-104°C.

ANALYSIS:

Calculated for $C_{25}H_{34}N_4O_2$:	71.06%C	8.11%H	13.26%N
Found:	71.10%C	8.08%H	13.25%N

EXAMPLE 40

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.80 g) and tetrahydrofuran (43 ml) were added with stirring at room temperature milled potassium carbonate (0.93 g) and benzyl isocyanate (0.87 ml). Stirring was continued under nitrogen for 16 hours. The mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration followed by purification via flash column chromatography (silica gel, 2% Et_3N/EtOAc) afforded 2.28 g of the desired

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carbamate. Recrystallization from ether gave a highly crystalline solid, m.p. 149-151°C.

ANALYSIS:

Calculated for $C_{25}H_{26}N_4O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.39%C	6.73%H	13.92%N

EXAMPLE 41

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl, 1,2,3,4-tetrahydro-2-isoquinolylincarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.67 g) and tetrahydrofuran (40 ml) was added 1,1'-carbonyldiimidazole (1.92 g) at room temperature with stirring under nitrogen. Stirring was continued for 48 hours, at which time acetic acid (1.6 ml) was added. To the resulting reaction mixture was added a solution consisting of 1,2,3,4-tetrahydroisoquinoline (1.6 ml), acetic acid (0.76 ml) and THF (10 ml). After stirring for 16 hours, the reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$).

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Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether) gave 2.41 g of the desired carbamate as a foam. The compound formed a white powder in ether/pentane, m.p. 160-162°C.

ANALYSIS:

Calculated for $C_{27}H_{28}N_4O_2$:	73.61%C	6.41%H	12.72%N
Found:	73.57%C	6.38%H	12.61%N

EXAMPLE 42

1-[(3-Fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (4.81 g) and 1-methyl-2-pyrrolidinone (83 ml) was added 4-chloro-3-fluoro pyridine hydrochloride (3.20 g). The resulting mixture was heated at 80°C for 2 hours. Upon cooling to room temperature, dilute aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed successively with water (2x) and brine (1x), and thereafter dried ($MgSO_4$). Filtration and

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concentration gave the crude product. Purification via flash column chromatography (silica gel, 50% ethyl acetate/dichloromethane) afforded 4.0 g of the desired product as a solid, m.p. 210-213°C.

EXAMPLE 43

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole (3.76 g) and dimethylformamide (108 ml), cooled to 0°C under nitrogen with stirring, was added sodium hydride (0.29 g). The resulting mixture was stirred at 0°C for an additional 15 minutes, at which time 1-bromopropane (1.03 ml) was added dropwise and the ice bath removed. Stirring was continued at room temperature overnight, at which time the reaction appeared complete by TLC (silica gel, 50% ether/hexane). The reaction mixture was poured into water and the product extracted with EtOAc (3x). The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the crude product as an oil. Purification via preparative

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HPLC (silica gel, 30% EtOAc/hexane) afforded 2.80 g of the desired product as a solid which was recrystallized from ether, m.p. 94-96°C.

ANALYSIS:

Calculated for $C_{24}H_{24}FN_3O$:	74.01%C	6.21%H	10.79%N
Found:	73.58%C	6.09%H	10.56%N

EXAMPLE 44

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol

The benzyl group of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole (15.82 g) was cleaved in a Parr hydrogenation apparatus in absolute ethanol (200 ml) over 10% Pd-C (1.58 g) at 50 psig and 50°C for 7.5 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with absolute ethanol. The combined filtrate was concentrated and the product purified via preparative HPLC (silica gel, 3:1 dichloromethane/EtOAc) affording 5.0 g of the desired product as an oil. Addition of EtOAc solidified the product which was recrystallized from EtOAc to give a

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solid, m.p. 157-160°C.

ANALYSIS:

Calculated for $C_{17}H_{18}FN_3O$:	68.21%C	6.06%H	14.04%N
Found:	67.81%C	6.09%H	13.73%N

EXAMPLE 45

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl methylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of methyl isocyanate (0.46 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 50% EtOAc/dichloromethane) afforded 2.35 g of the desired carbamate as a solid. The product was recrystallized from ether, m.p. 163-164°C.

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ANALYSIS:

Calculated for $C_{19}H_{21}FN_4O_2$:	64.03%C	5.94%H	15.72%N
Found:	63.84%C	6.10%H	15.55%N

EXAMPLE 46

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of butyl isocyanate (0.87 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, ether) afforded 2.3 g of the desired product as an oil. The product was crystallized from ether/pentane, m.p. 83-84°C.

ANALYSIS:

Calculated for $C_{22}H_{27}FN_4O_2$:	66.31%C	6.83%H	14.06%N
Found:	65.99%C	6.83%H	13.88%N

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EXAMPLE 47

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl heptylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.54 g) and anhydrous tetrahydrofuran (57 ml) was added carbonyl diimidazole (2.75 g) under nitrogen with stirring. The resulting reaction mixture was stirred at room temperature for two days, at which time acetic acid (1.65 ml) was added followed by a solution of heptylamine (1.89 ml) in tetrahydrofuran (5 ml) and acetic acid (0.76 ml). After stirring for 24 hours, an additional equivalent of heptylamine (1.26 ml) in tetrahydrofuran (5 ml) and acetic acid (0.52 ml) was added. After an additional 24 hours the reaction was complete and the reaction mixture was poured into $NaHCO_3$ (aq.) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq.) and brine. Drying (Na_2SO_4), filtration and concentration gave a crude

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product. Purification via flash column chromatography (silica gel, 30% EtOAc/hexane) afforded 3.38 g of the desired product as an oil. Addition of ether and pentane solidified the product. The solid was filtered and washed with pentane, m.p. 90-93°C.

ANALYSIS:

Calculated for $C_{25}H_{33}FN_4O_2$:	68.16%C	7.55%H	12.72%N
Found:	67.87%C	7.35%H	12.60%N

EXAMPLE 48

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl phenylmethylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-3-methyl-1H-indol-5-ol (2.66 g) in tetrahydrofuran (59 ml) was added milled potassium carbonate (1.29 g) followed by dropwise addition of benzyl isocyanate (1.21 ml) at room temperature under nitrogen. Stirring was continued for 17.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration afforded a crude product.

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Purification via flash column chromatography (silica gel, ether) afforded 3.34 g of the desired carbamate as a foam. This foam was dissolved in ether and the product crystallized as a solid. The solid was recrystallized from ether, m.p. 143-144°C.

ANALYSIS:

Calculated for $C_{25}H_{25}FN_4O_2$:	69.42%C	5.83%H	12.96%N
Found:	69.44%C	5.83%H	12.84%N

EXAMPLE 49

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl 1,2,3,4-tetrahydro-2-isoquinolinylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.51 g) in anhydrous tetrahydrofuran (56 ml) was added 1,1'-carbonyl diimidazole (2.72 g) at room temperature under nitrogen. After 24 hours the reaction appeared complete by TLC (silica gel, 60% EtOAc/hexane) and acetic acid (1.60 ml) was added to the reaction mixture followed by the dropwise addition of a solution of 1,2,3,4-tetrahydroisoquinoline (1.58 ml) in tetrahydrofuran (5.0 ml) and acetic acid

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(0.75 ml). After 72 hours, the reaction was not complete by TLC (60% EtOAc/dichloromethane) and an additional equivalent of 1,2,3,4-tetrahydroisoquinoline (1.05 ml) was added as a tetrahydrofuran (5.0 ml) and acetic acid (0.51 ml) solution. After 1.5 hours the reaction appeared complete and the mixture was poured into $NaHCO_3$ (aq) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq) and brine, and dried (Na_2SO_4). The organic phase was filtered and concentrated to give a crude product. Purification via flash column chromatography (silica gel., 30% EtOAc/dichloromethane) afforded 2.70 g of the desired product as an oil which solidified on standing. Recrystallization from ether (2x) gave a solid which was filtered and washed with ether, m.p. 157-160°C.

ANALYSIS:

Calculated for $C_{27}H_{27}FN_4O_2$:	70.72%C	5.94%H	12.22%N
Found:	70.93%C	5.85%H	12.11%N

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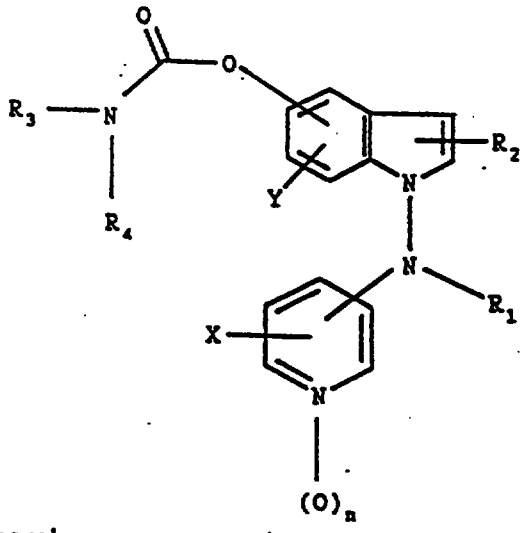
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Claims:

1. A compound of the formula Ia



(Ia)

wherein

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

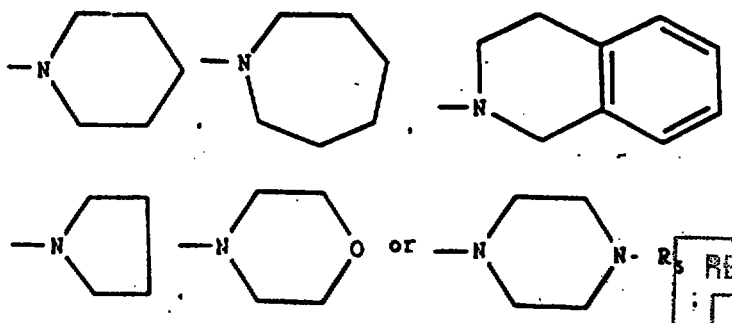
R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;

R_2 is hydrogen, loweralkyl, formyl or cyano;

R_3 is hydrogen or loweralkyl;

R_4 is loweralkyl, aryloweralkyl, cycloalkyl, aryl or heteroaryl;

or alternatively, $-NR_3R_4$ taken together constitutes



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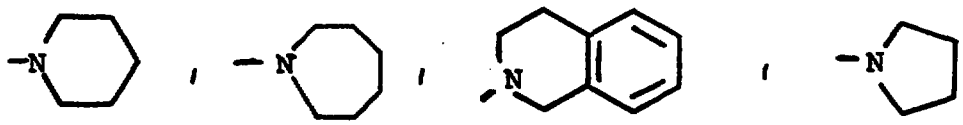
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R_5 being hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof.

2. A compound of the formula Ia as defined in claim 1, wherein
n is 0,
X is hydrogen or halogen and Y is hydrogen.

3. A compound of the formula Ia as defined in claim 2 wherein R_1 and R_2 are each independently H or loweralkyl.

4. A compound of the formula Ia as defined in claim 3 wherein R_3 is hydrogen, R_4 is loweralkyl, arylloweralkyl, cycloalkyl or alternatively $-NR_3R_4$ taken together constitutes



5. A compound as defined in claim 1, which is 1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate.

6. A compound as defined in claim 1, which is (S)-(-)-1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl 1-phenylethylcarbamate.

7. A pharmaceutical composition which comprises a compound as defined in claim 1 as the active ingredient and a suitable carrier therefor.

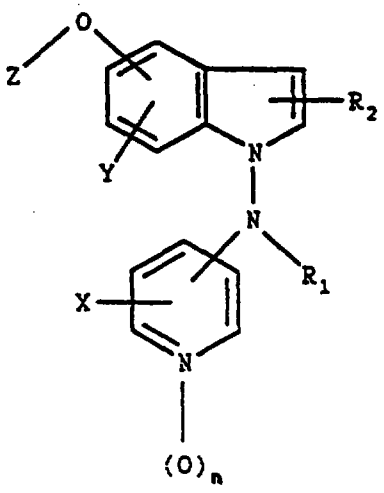
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8. Use of a compound as defined in claim 1 for the preparation of a medicament having the activity of alleviating a memory dysfunction characterized by a cholinergic deficit.

9. A compound of the formula Ib



Ib

wherein

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

R_1 is hydrogen, loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl;

R_2 is hydrogen, loweralkyl, formyl or cyano;

Z is hydrogen, loweralkyl or benzyl

and all optical and geometrical stereoisomers and racemic mixtures thereof.

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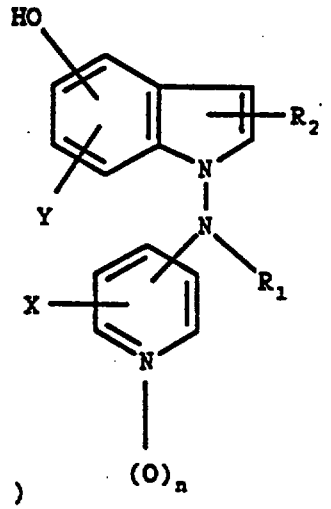
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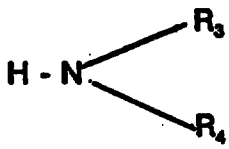
10. A compound of the formula Ib as defined in claim 7 wherein X is halogen or hydrogen, Y is hydrogen and R_1 and R_2 are each independently H or loweralkyl.

11. A process for the preparation of a compound of the formula Ia, as defined in claim 1, which comprises
a) reacting a compound of the formula XV



(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with 1,1'-carbonyldiimidazol to afford an intermediate which is treated with an amine of the formula



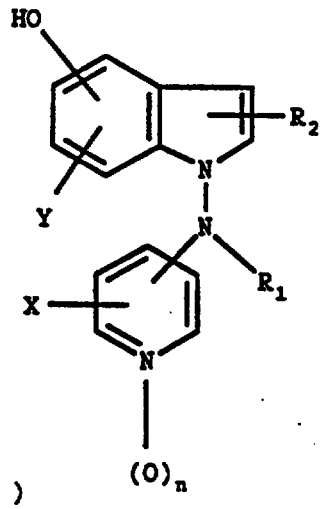
wherein R_3 and R_4 are defined as in claim 1, or

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b) reacting a compound of the formula XV



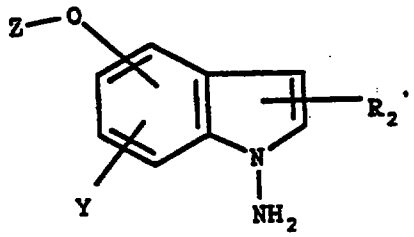
(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with an isocyanate of the formula

$$R_4 - NCO$$

wherein R_4 is defined as above, to afford a compound of the formula Ia, where X, Y, R_1, R_2, R_4 and n are as defined above and R_3 is hydrogen.

12. a) A process for the preparation of a compound of the formula Ib according to claim 7, which comprises reacting a compound of the formula IV,



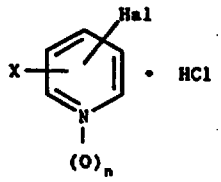
(IV)

wherein R_2 and Y are defined as in claim 7 with a halopyridine of the formula

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wherein X and n are as defined in claim 7 and Hal is fluorine, chlorine, bromine or jodine, to afford a compound of the formula Ib, wherein X, Y, R_2 and n are as defined in claim 7, Z is benzyl or loweralkyl and R_1 is hydrogen,

b) optionally reacting a compound of the formula Ib as obtained in step a) with a suitable base of afford the corresponding anion, which is reacted with a halide of the formula

$$R_1 - Hal$$

wherein R_1 is defined as in claim 7, except hydrogen, and Hal is chlorine, bromine or jodine, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl and R_1 is defined as in claim 7, except hydrogen,

c) optionally reacting a compound of the formula Ib as obtained in step a) wherein R_2 is hydrogen with a suitable base to afford the corresponding anion, which is reacted with a diloweralkylsulfate of the formula

$$R_1 - OSO_2 - OR_1$$

wherein R_1 is loweralkyl to afford a compound of the formula Ib according to claim 7 wherein Z is benzyl or loweralkyl and R_1 is loweralkyl,

d) optionally reacting a compound of the formula Ib as obtained in step a), b) or c), wherein R_2 is hydrogen with phosphorus oxychloride and dimethylformamide to afford a compound of the formula Ib according to claim 7, wherein Z is benzyl or loweralkyl and R_2 is formyl,

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e) optionally reacting a compound of the formula Ib as obtained in step d) with an ylide of the formula

$$(C_6H_5)_3P = \underset{\underset{R_7}{|}}{C} - R_6$$

wherein R_6 and R_7 are each independently hydrogen or loweralkyl, to afford a compound of the formula Ib wherein R_2 is loweralkenyl, which is reduced to afford a compound of the formula Ib, according to claim 7 wherein Z is benzyl or loweralkyl and R_2 is loweralkyl.

f) optionally reacting a compound of the formula Ib as obtained in step d) with hydroxylamine to afford the corresponding oxime, which is treated with benzenesulfonyl chloride, to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or lower alkyl and R_2 is the cyano group.

g) optionally reacting a compound of the formula Ib as obtained in step a) with ethyl chloroformate to afford the corresponding N-ethylcarbamate which is optionally treated as described in steps d), e) or f) to afford a compound of the formula Ib, according to claim 7, wherein Z is benzyl or loweralkyl, R_1 is alkoxycarbonyl, and R_2 is formyl, loweralkyl or cyano,

h) optionally subjecting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is benzyl to a hydrogenolysis, to afford a compound of the formula Ib according to claim 7 wherein Z is hydrogen.

i) optionally reacting a compound of the formula Ib as obtained from one of the foregoing steps a) to g), wherein Z is loweralkyl with a suitable cleavage reagent, such as HBr, borontribromide etherate, trimethylsilyl iodide or a sodium salt of ethylmercaptan, to afford a compound of the formula Ib according to claim 7, wherein Z is hydrogen.

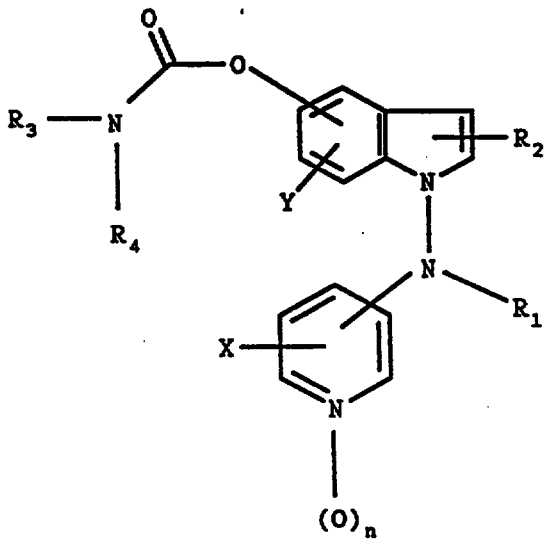
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1-(SUBSTITUTED PYRIDINYLAMINO)-1H-INDOL-5-YL SUBSTITUTED CARBAMATES, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

ABSTRACT

There are disclosed various compounds of the formula below,



where

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

R_1 is hydrogen, loweralkyl, arylloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, arylloweralkanoyl, heteroarylloweralkyl or heteroarylloweralkanoyl;

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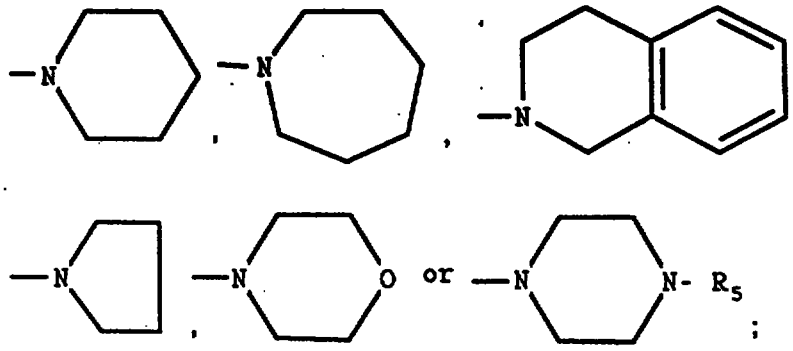
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R_2 is hydrogen, loweralkyl, formyl or cyano;

R_3 is hydrogen or loweralkyl;

R_4 is loweralkyl, arylloweralkyl, cycloalkyl, aryl or heteroaryl;

or alternatively, $-NR_3R_4$ taken together constitutes



R_5 being hydrogen, loweralkyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl,

which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

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☑ Claim(s) : paged 48 to paged 51
☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged 52 to paged 53

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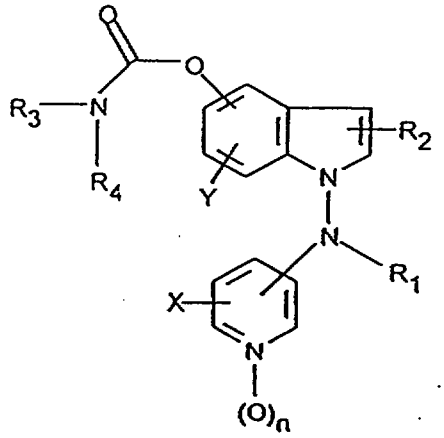
1-(SUBSTITUTED PYRIDINYLAMINO)-1H-INDOL-5-YL SUBSTITUTED CARBAMATES, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS.

The present invention relates to 1-(Substituted pyridinylamino)-1H-indol-5-yl substituted carbamates, a process for their preparation and their use as medicaments

EP-A-287 982 discloses 1-pyridylaminoindole derivatives useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit, as antidepressants and analgesics in which the benzo moiety is unsubstituted or substituted with groups such as alkoxy, halogen and nitro.

EP-A-253 372 discloses 1, 2, 3, 3a, 8, 8a-hexahydro-3a, 8 (and 1, 3a, 8)-Di (and Tri) methyl-pyrrolo[2,3-b]indoles which are useful as memory-enhancing and analgesic agents.

The present invention relates to compounds of formula I a,



(Ia)

wherein

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, (C_1-C_8)alkyl, or (C_1-C_8)alkoxy;

Y is hydrogen, halogen, nitro, amino, trifluoromethyl, (C_1-C_8)alkyl, or (C_1-C_8)alkoxy;

R_1 is hydrogen, (C_1-C_8)alkyl, phenyl(C_1-C_8)alkyl, up to C_8 alkenyl, up to C_8 alkynyl, (C_1-C_8)alkanoyl, phenyl(C_1-C_8)-alkanoyl, heteroaryl(C_1-C_8)alkyl or

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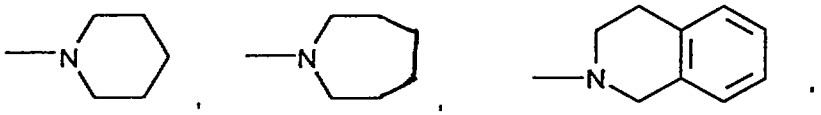
heteroaryl(C_1-C_8)alkanoyl, where phenyl is optionally substituted with 1 or 2 substituents selected from: (C_1-C_8)alkyl, (C_1-C_8)-alkoxy, halogen or trifluoromethyl, and heteroaryl is furanyl, thienyl, pyrrolyl or pyridinyl;

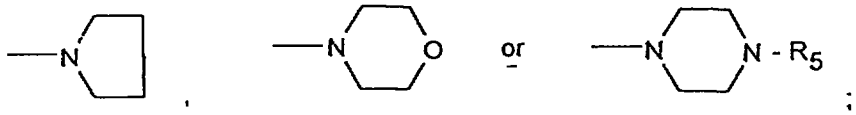
R_2 is hydrogen, (C_1-C_8)alkyl, formyl or cyano;

R_3 is hydrogen or (C_1-C_8)-alkyl;

R_4 is (C_1-C_8)alkyl, phenyl(C_1-C_8)-alkyl, cyclo(C_3-C_7)-alkyl, phenyl, where phenyl in each case is optionally substituted with 1 or 2 substituents selected from: (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, halogen or trifluoromethyl, or R_4 is a heteroaryl selected from: furanyl, thienyl, pyrrolyl and pyridinyl;

or alternatively, $-NR_3R_4$ taken together constitutes





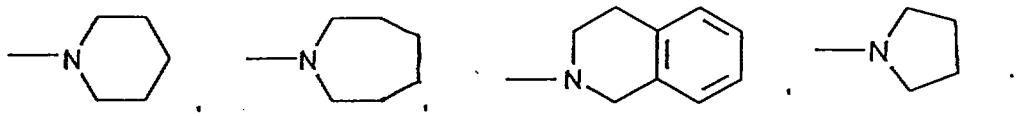
R_5 being hydrogen, (C_1-C_8)-alkyl, phenyl, phenyl(C_1-C_8)alkyl, heteroaryl or heteroaryl(C_1-C_8)alkyl, where phenyl in each case is optionally substituted with 1 or 2 substituents selected from: (C_1-C_8)alkyl, (C_1-C_8)alkoxy, halogen or trifluoromethyl, and heteroaryl in each case is furanyl, thienyl, pyrrolyl or pyridinyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof;

which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.

In the compound of formula Ia above, preferably n is 0, X is hydrogen or halogen and Y is hydrogen. More preferably, R_1 and R_2 are each independently H or (C_1-C_8)alkyl. Even more preferably, R_3 is hydrogen, R_4 is (C_1-C_8)alkyl, phenyl-(C_1-C_8)alkyl, where phenyl is optionally substituted as indicated above, cyclo(C_3-

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C_7)alkyl, or $-NR_3R_4$ taken together constitute



Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims.

The term lower or (C_1-C_8)alkyl shall mean a straight or branched alkyl group having from 1 to 8 carbon atoms. Examples of said (C_1-C_8)alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl, hexyl, heptyl and octyl.

The term cyclo (C_3-C_7)alkyl shall mean a cycloalkyl group of 3 to 7 carbon atoms.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term aryl or phenyl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which being independently (C_1-C_8)alkyl, (C_1-C_8)alkoxy, halogen or trifluoromethyl.

The term heteroaryl shall mean furanyl, thienyl, pyrrolyl or pyridinyl.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all optical and geometric stereoisomers where such isomers exist.

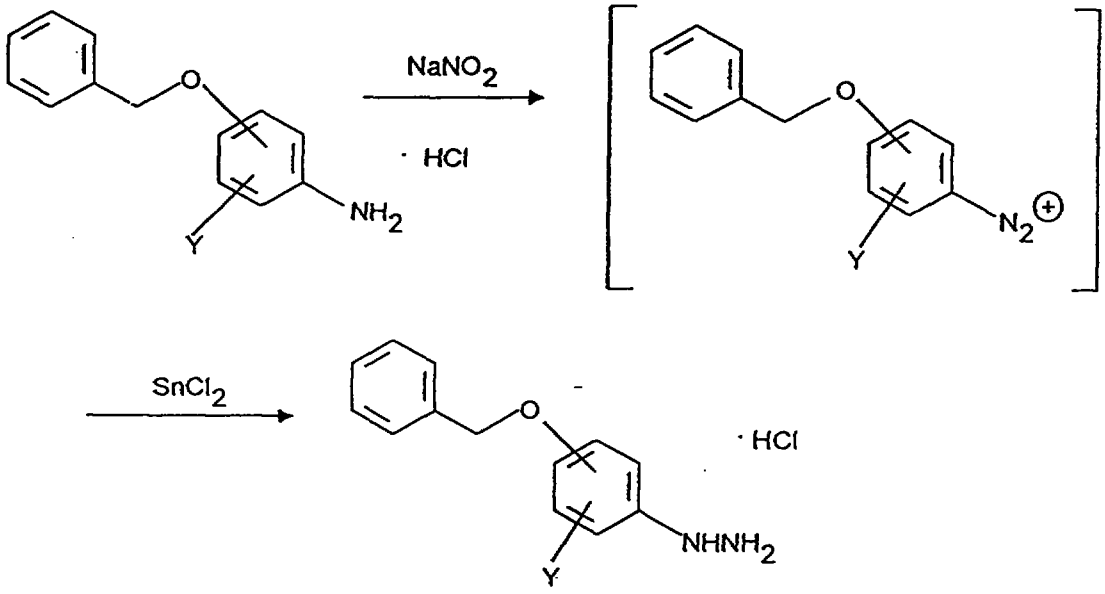
The compounds of this invention are prepared by utilizing one or more of the synthetic steps described below.

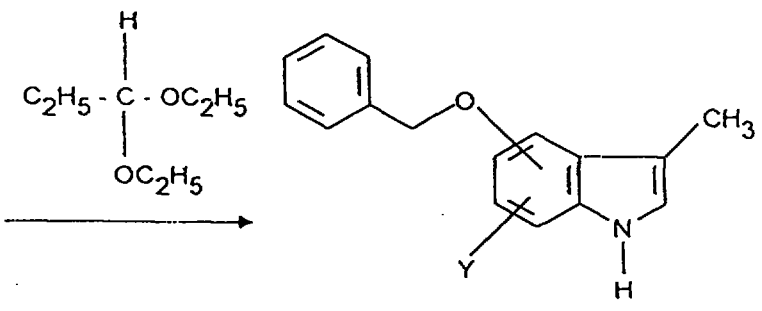
Throughout the description of the synthetic steps, the notations n, X, Y and R_1 through R_5 shall have the respective meanings given above unless otherwise stated or indicated.

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Step A:

A benzyloxyaniline depicted below is allowed to react with $NaNO_2$ in a routine manner known to the art to afford the corresponding diazonium compound and the latter is reduced with $SnCl_2$ to afford the corresponding hydrazine compound, and thereafter the latter is allowed to react with the diethylacetal of propionaldehyde to afford the compound of Formula II. For details of the last reaction (Fisher indole synthesis), the reader is referred, for instance, to D. Keglevic et al., Chem. Absts. 56, 4710h.





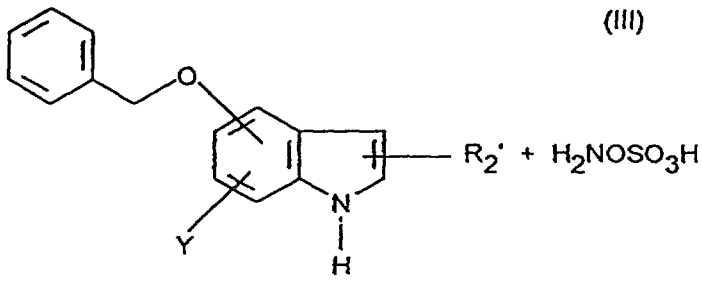
(II)

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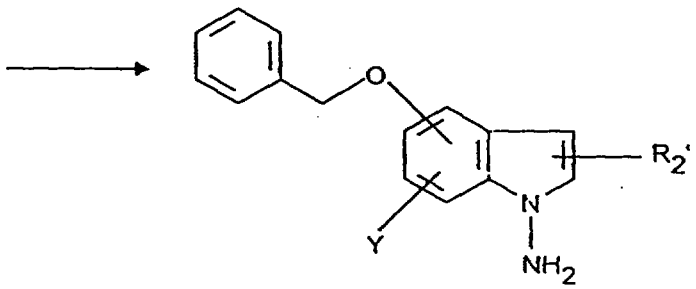
Where the 2-methylisomer of Compound II is desired, the above reaction is conducted in substantially the same manner as described above except that acetone is used instead of diethylacetal of propionaldehyde.

Step B:

A compound of Formula III where R_2' is hydrogen or methyl is allowed to react with hydroxylamine-O-sulfonic acid in a routine manner known to the art to afford a compound of Formula IV. The starting compound of Formula III where R_2' is hydrogen is either available on the market or can be synthesized from known compounds according to methods known to the art.



(III)

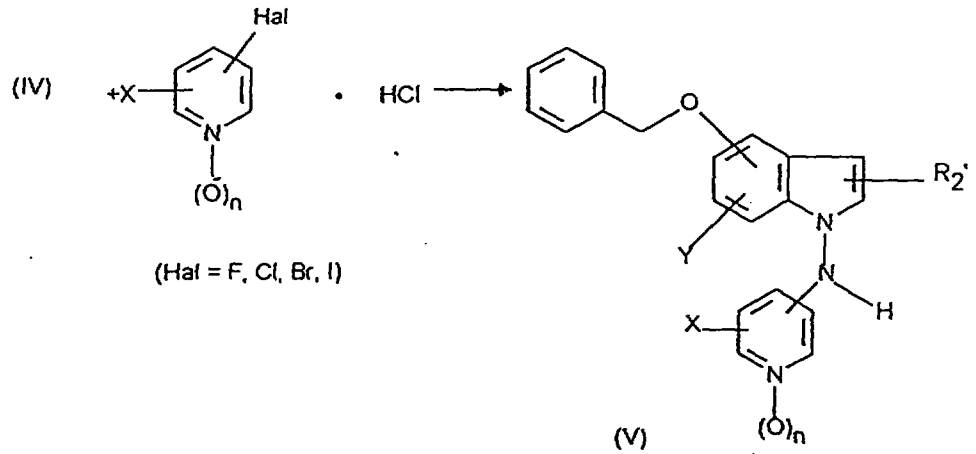


(IV)

Step C:

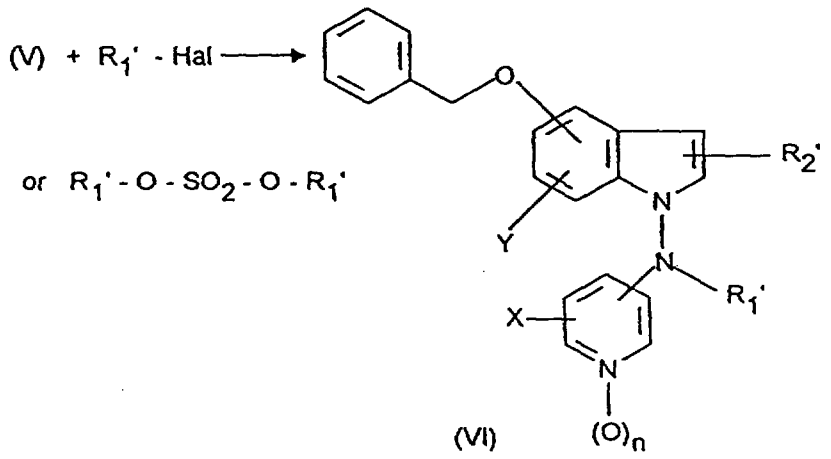
Compound IV is allowed to react with a halopyridine hydrochloride depicted below to afford a compound of Formula V. This reaction is typically conducted in a suitable solvent such as N-methyl-2-pyrrolidinone at a temperature of 20 to 200°C.

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Step D:

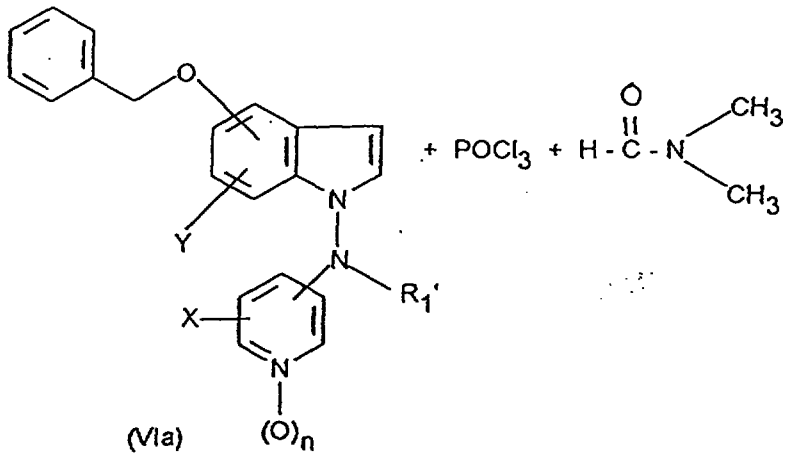
Compound V is allowed to react with a suitable base, such as sodium hydride or potassium t-butoxide, and the resultant anion is allowed to react with a halide of the formula R_1'- Hal where R_1' is loweralkyl, aryloweralkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryloweralkanoyl, heteroaryloweralkyl or heteroaryloweralkanoyl, and Hal is chlorine, bromine or iodine, or with a diloweralkylsulfate of the formula R_1'-O-SO2-O-R_1' where R_1' is loweralkyl, in a routine manner known to the art to afford a compound of Formula VI.



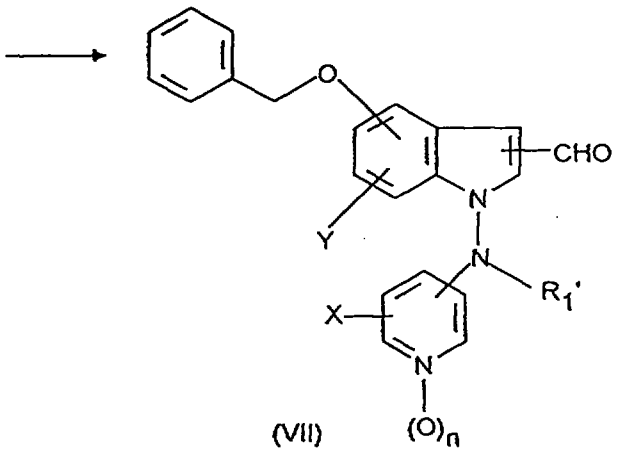
Step E:

A compound of Formula VIa is allowed to react with phosphorus oxychloride and dimethylformamide in a routine manner known to the art to afford a compound of Formula VII.

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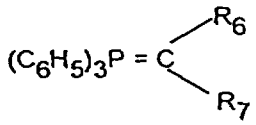
(VIa)



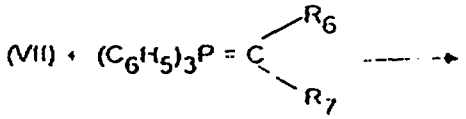
(VII)

Step F:

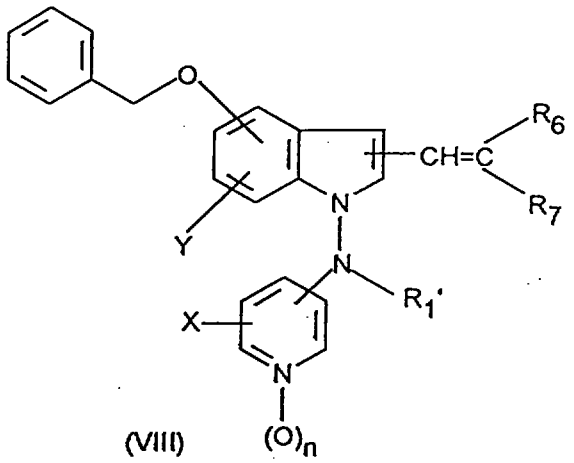
Compound VII is subjected to a Wittig reaction with an ylide of the formula



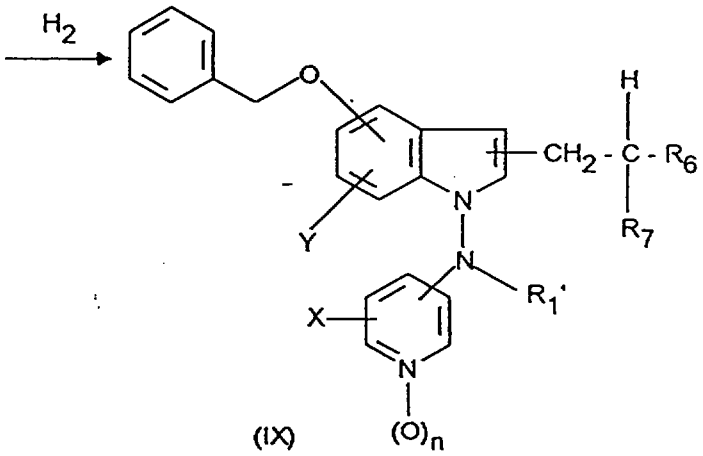
where R_6 and R_7 are each independently hydrogen or loweralkyl in a routine manner known to the art to afford a compound of Formula VIII and thereafter the latter compound is reduced in a routine manner known to the art to afford a compound of Formula IX.



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(VIII)

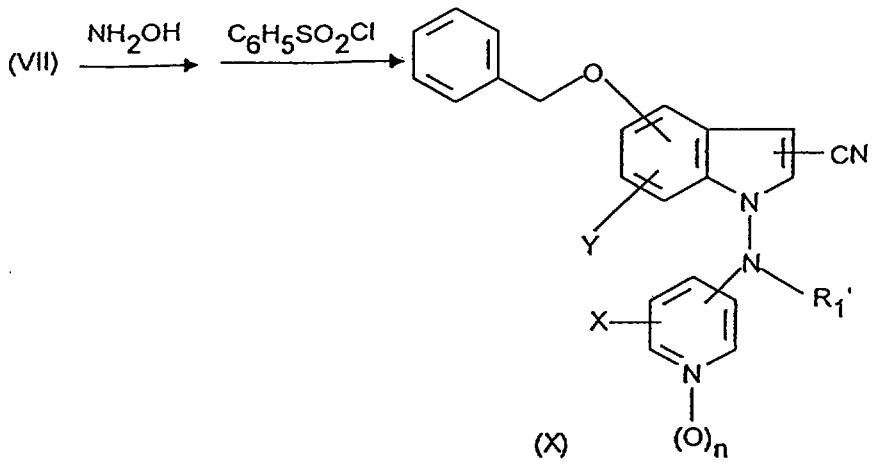


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Step G:

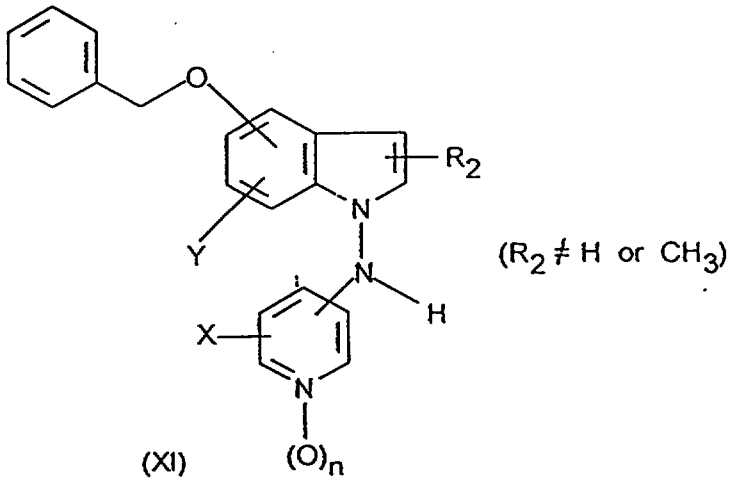
Compound VII is allowed to react with hydroxylamine in a routine manner known to the art to afford a corresponding oxime and the latter is allowed to react with benzenesulfonyl chloride to afford a nitrile compound of Formula X. The second step is typically conducted in a suitable solvent such as tetrahydrofuran or p-dioxane at a temperature of about 60 to 100°C.

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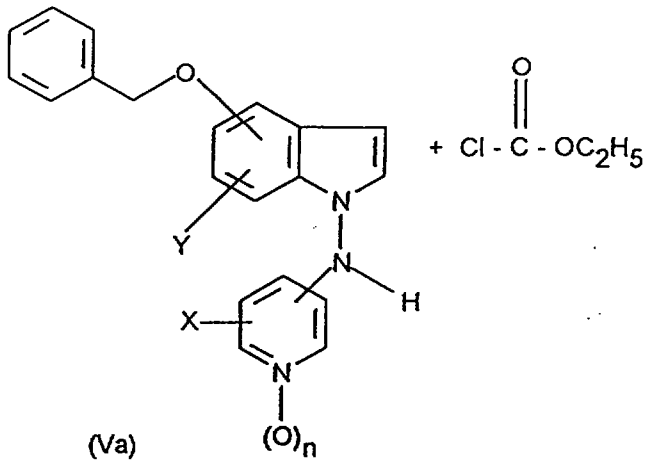
Step H:

In order to prepare a compound of Formula XI depicted below where R_2 is not hydrogen or methyl, it is convenient to adopt the following procedure.

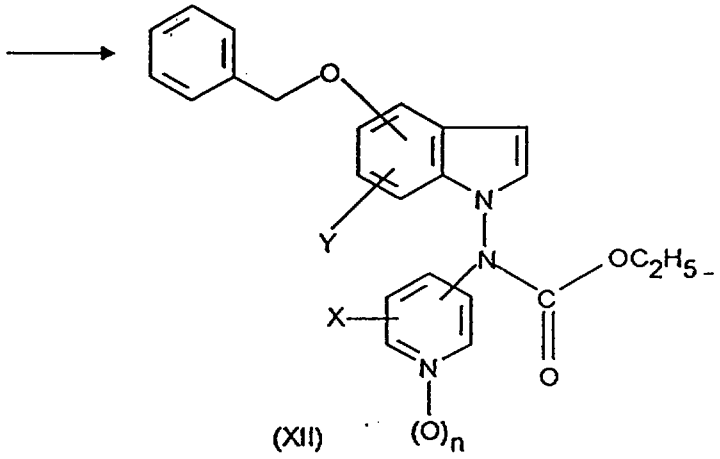


Thus, a compound of Formula Va is allowed to react with ethyl chloroformate in a routine manner known to the art to afford an ethyl carbamate of Formula XII and thereafter the latter compound is subjected to one or more of STEPS E through G to afford a compound of Formula XIII. Subsequently, Compound XIII is hydrolyzed in a routine manner known to the art to afford Compound XI.

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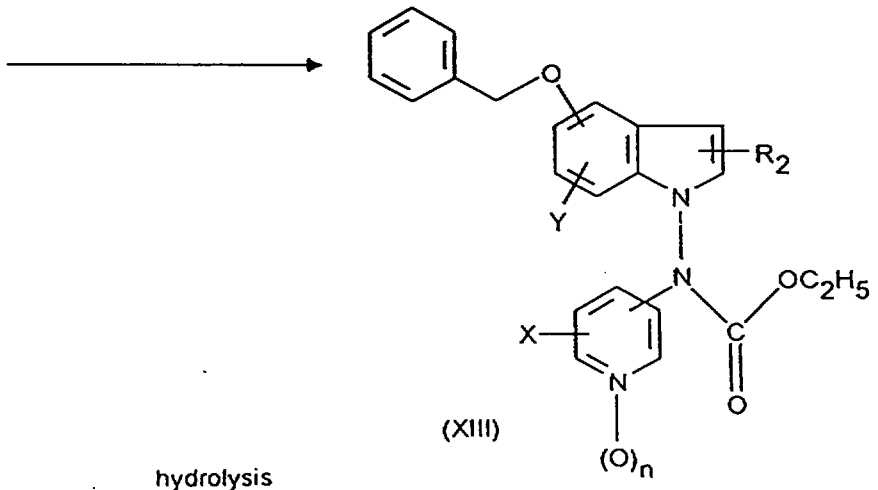


(Va)



(XII)

One or more of Steps E through G



(XIII)

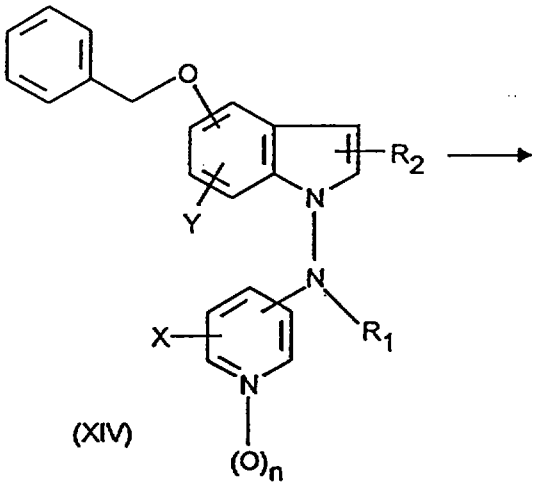
hydrolysis

(XI)

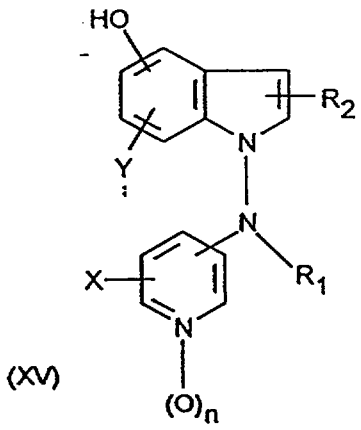
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Step I:

A compound of Formula XIV obtained from one of the foregoing STEPS is subjected to hydrogenolysis conducted in a routine manner known to the art to afford a compound of Formula XV.



(XIV)



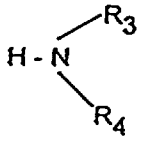
(XV)

In each of the foregoing STEPS A through I, the reactant molecule carries a benzyloxy group on the benzene portion thereof. However, the same reactions can also be accomplished in substantially the same manner as described above where the reactant molecule carries a loweralkoxy group instead of a benzyloxy group on the benzene portion thereof, except that in the case of STEP I, a cleavage reaction is utilized instead of hydrogenolysis. Said cleavage reaction is conducted in a routine manner known to the art, for instance, with the aid of 48 % HBr, boron tribromide etherate, trimethylsilyl iodide or the sodium salt of ethyl mercaptan.

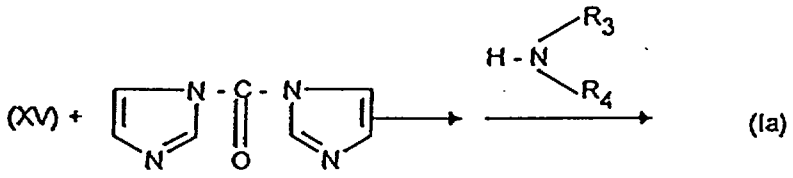
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Step J:

Compound XV is allowed to react with 1,1'-carbonyldiimidazole and the resultant reaction product is allowed to react with an amine of the formula



in a routine manner known to the art to afford Compound Ia.



Typically, the first step is conducted in a suitable solvent such as tetrahydrofuran at room temperature. Typically, the second step is conducted by adding a suitable amount of the desired amine in glacial acetic acid to the reaction mixture.

Alternatively, where Compound Ia in which group R_3 is hydrogen is desired, Compound XV is allowed to react with an isocyanate of the formula R_4 - NCO in a routine manner known to the art to afford Compound Ia.

$$(XV) + R_4 - NCO \rightarrow (Ia)\ (R_3=H)$$

The compounds of Formula Ia of the present invention are useful for the treatment various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with

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central cholinergic innervation. This same innervation is suggested to be weakened in Alzheimer patients. We have determined in vitro inhibition of acetylcholinesterase activity in rat striatum.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in brain roughly correlates with cholinergic innervation and subfractionation shows the highest level in nerve terminals.

It is generally accepted that the physiological role of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinominetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AchE inhibitors may also be beneficial in the treatment of Alzheimer's dementia.

The method described below was used in this invention for assaying cholinesterase activity. This is a modification of the method of Ellman et al., Biochem. Pharmacol. 7, 88 (1961).

Procedure:

A. Reagents -

1. 0.05 M Phosphate buffer, pH 7.2
   (a) 6.85 g NaH2PO4|H2O/100 ml distilled H_2O
   (b) 13.40 g Na2HPO4|7H2O/100 ml distilled H_2O
   (c) add (a) to (b) until pH reaches 7.2
   (d) Dilute 1:10
2. Substrate in buffer
   (a) 198 mg acetylthiocholine chloride (10 mM)
   (b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)

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3. DTNB in buffer
   (a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
   (b) q.s. to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)
4. A 2 mM stock solution of the test drug is made up in a suitable solvent and q.s. to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4} M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation -
Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed 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 microliter aliquot of the homogenate is added to 1.0 milliliter vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37°C.

C. Assay -
Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

Instrument Settings
Kinetics Soft-Pac Module #598273 (10)
Program #6 Kindata:
Source - Vis
Wavelength - 412 nm
Sipper - none
Cuvettes - 2 ml cuvettes using auto 6-sampler
Blank - 1 for each substrate concentration
Interval time - 15 seconds (15 or 30 seconds for kinetics)
Total time - 5 minutes (5 or 10 minutes for kinetics)
Plot - yes

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Span - autoscale

Slope - increasing

Results - yes (gives slope)

Factor - 1

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

Blank: 0.8 ml Phosphate Buffer/DTNB
0.8 ml Buffer/Substrate

Control: 0.8 ml Phosphate Buffer/DTNB/Enzyme
0.8 ml Phosphate Buffer/Substrate

Drug: 0.8 ml Phosphate Buffer/DTNB/Drug/Enzyme
0.8 ml Phosphate Buffer/Substrate

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 IC_{50} Determinations:

Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration.

$$\% \text{ Inhibition} = \frac{\text{slope control - slope drug}}{\text{slope control}} \times 100$$

IC_{50} values are calculated from log-probit analysis

Results of this assay for some of the compounds of this invention and

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physostigmine (reference compound) are presented in Table 1.

TABLE 1

Compound	Inhibitory Concentration (μM) Brain AChE
1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate	0.0023
(S)-(-)-1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl 1-phenylethylcarbamate	30.21
Physostigmine	0.006

This utility is further demonstrated by the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay described below.

Dark Avoidance Assay

In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compound, resulting in a greater interval before re-entry into the dark compartment.

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The results for an active compound are expressed as the percent of a group of animals in which the effect of scopolamine is blocked, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment.

Results of this assay for a compound of this invention and those for tacrine and pilocarpine (reference compounds) are presented in Table 2.

TABLE 2

Compound	Dose (mg/kg of body weight, s.c)	% of Animals with Scopolamine Induced Memory Deficit Reversal
1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl methylcarbamate	0.35	21
Tacrine	0.63	13
Pilocarpine	5.0	13

Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule 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 effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the

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invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets.

For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum 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 70% of the weight of the unit. 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 an oral dosage unit form contains between 1.0 - 300 milligrams of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweeting agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a 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 preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and

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non-toxic in the amounts used.

For the purpose 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 active compound, but may be varied between 0.5 and about 30% 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 inventions are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of 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 methyl parabens; 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 preparation can be enclosed in isposable syringes or multiple dose vials made of glass or plastic.

Examples of the compounds of this invention include:

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-methylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-ethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-propylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-isopropylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-cyclohexylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl- phenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-2-phenylethylcarbamate;
(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1-phenylethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-butylcarbamate;

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1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-heptylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-methylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-methylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-butylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-piperidinylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl- 4-chlorophenylmethylcarbamate;
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-heptylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-phenylmethylcarbamate;
1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-heptylcarbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolinyl carbamate;
3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate;
1-[Methyl-(3-methyl-4-pyridinyl)amino]-1H-indol-5-yl-methylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-4-phenylpiperazin-1-ylcarbamate;
1-(Methyl-4-pyridinylamino)-1H-indol-5-yl-morpholin-4-ylcarbamate; and
1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate-N-oxide.

Examples of this invention are presented below.

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Example 1

5-Phenylmethoxy-1H-indole-1-amine

To 5-phenylmethoxyindole (50 g) in 300 ml of dimethylformamide at ice bath temperature was added milled potassium hydroxide (62.72 g). Then hydroxylamine-O-sulfonic acid (32.93 g) was added portionwise, keeping the internal temperature below 20°C. After the addition was complete, the mixture was stirred for one hour, then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (71 g), which was eluted with dichloromethane on silica gel columns via HPLC. The desired fractions were concentrated to yield a solid (21.15 g). Of this material, 3.0 g was triturated with ether to yield a solid, 2.4 g, m.p. 126-128°C.

Analysis:

Calculated for $C_{15}H_{14}N_{20}$:	75.60 % C	5.92 % H	11.76 % N
Found:	75.54 % C	5.97 % H	11.87 % N

Example 2

5-Phenylmethoxy-1-(4-pyridinylamino)-1H-indole

To 250 ml of N-methyl-2-pyrrolidinone was added (phenylmethoxy)-1H-indole-1-amine (29.7 g) and the solution was heated to 80°C. Then 4-chloropyridine hydrochloride (20.55 g) was added portionwise and the mixture was stirred for three hours, cooled, poured into water, basified with aqueous sodium carbonate and extracted with toluene. The organic/aqueous mixture was filtered to yield a solid (39 g), which was triturated with ether to yield a solid (27 g). Of this material, 3.0 g was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid, 2.5 g, m.p. 143-145°C.

Analysis:

Calculated for $C_{20}H_{17}N_{30}$:	76.17 % C	5.44 % H	13.32 % N

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Found:	75.82 % C	5.43 % H	13.21 % N

Example 3

1-(4-Pyridinylamino)-1H-indol-5-ol

To 0.8 g of 10% palladium on carbon in 10 ml of absolute ethanol was added a solution of 5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (4.0 g) in 240 ml of absolute ethanol and this was hydrogenated on a Parr apparatus for four hours at 50°C at 34.5×10^4 Pa (50 psig) H_2. The mixture was cooled and filtered, and the filtrate was concentrated to yield an oil (4.2 g), which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.72 g). This material was luted with 10 % methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a foam (1.8 g), which was recrystallized from ethyl acetate to yield a solid (1.5 g), m.p. 232-234°C.

Analysis:

Calculated for $C_{13}H_{11}N_{30}$:	69.32 % C	4.92 % H	18.66 % N
Found:	69.16 % C	4.76 % H	18.52 % N

Example 4

1-(Methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole hydrochloride

5-(Phenylmethoxy)-1-(4-pyridinylamino)-1H-indole (25 g) was slowly added to an ice-cooled solution of potassium tert-butoxide (11 g) in 250 mL tetrahydrofuran. Following the anion formation, a solution of dimethyl sulfate (12 g) in 25 mL tetrahydrofuran was slowly added so that the internal reaction temperature remained below 10°C. After one hour, the reaction mixture was stirred with water and extracted with ether. The organic layer was washed with water and saturated sodium chloride solution and thereafter dried (anhydrous magnesium sulfate), filtered and concentrated to afford a solid, 28 g. This solid was eluted through silica with 5% methanol in dichloromethane via HPLC to yield 22 g of a solid, m.p.

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118-121°C. An analytical sample was prepared by converting 1.5 g to the hydrochloride salt in methanol/ether to yield 1.5 g of crystals, m.p. 235-236°C (dec.).

Analysis:

Calculated for $C_{21}H_{20}ClN_{30}$:	68.94 % C	5.51 % H	11.49 % N
Found:	68.60 % C	5.50 % H	11.28 % N

Example 5

1-(Methyl-4-pyridinylamino)-1H-indol-5-ol

A solution of 1-(methyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole (9 g) in 250 mL ethanol containing 0.6 g 10% palladium on activated charcoal was hydrogenated at 34.5 x 10^4 Pa (50 psi) at 50°C for three hours via Parr hydrogenation apparatus. After cooling, the mixture was filtered through Celite and concentrated. The residue was eluted through silica with 5% methanol in dichloromethane via flash column chromatography to yield 6.2 g solid. A three gram portion was recrystallized from acetonitrile to yield 2.6 g solid, m.p. 191-193°C. This was again recrystallized from acetonitrile to yield 2.2 g crystals, m.p. 192-193°C.

Analysis:

Calculated for $C_{14}H_{13}N_{30}$:	70.27 % C	5.48 % H	17.57 % N
Found:	69.96 % C	5.39 % H	17.53 % N

Example 6

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

Methyl isocyanate (0.72 g) was added to a solution of (methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing milled potassium carbonate (2 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield a solid 3.1 g. This was eluted through

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silica with 5% methanol in dichloromethane via HPLC to yield 2.6 g solid, m.p. 186-188°. This was recrystallized from 20 % methanol in ether to yield 1.6 g of product, m.p. 186-188°C.

Analysis:

Calculated for $C_{16}H_{16}N_4O_2$:	64.85 % C	5.44 % H	18.91 % N
Found:	64.85 % C	5.58 % H	18.73 % N

Example 7

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.2 g) was added to a solution of (methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.7 g solid, m.p. 108-111°C. This was converted to the hydrochloride salt in methanol/ether to yield 3.3 g crystals, m.p. 232-234°C (dec.).

Analysis:

Calculated for $C_{19}H_{22}N_4O_2$|HCl:	60.87 % C	6.18 % H	14.95 % N
Found:	60.89 % C	6.34 % H	14.88 % N

Example 8

1-(Methyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (1.7 g) was added to a solution of 1-(methyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring three hours at ambient temperature the mixture was filtered and concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 3.8 g solid. This was recrystallized from acetonitrile to yield 3.2 g crystals, m.p. 179-181°C.

Analysis:

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Calculated for $C_{22}H_{20}N_4O_2$:	70.95 % C	5.41 % H	15.05 % N
Found:	70.67 % C	5.35 % H	15.12 % N

Example 9

1-(Propyl-4-pyridinylamino)-5-phenylmethoxy-1H-indole maleate

To potassium tert-butoxide (2.80 g) in 20 ml of tetrahydrofuran cooled to ice bath temperature was added dropwise a solution of 5-phenylmethoxy-1-pyridinylamino)-1H-indole (6.5 g) in 60 ml of tetrahydrofuran. This mixture was stirred for 10 minutes and then a solution of 1-bromopropane (3.08 g) in 10 ml of tetrahydrofuran was added dropwise. The reaction was allowed to proceed for three hours at room temperature. The mixture was then poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. MgSO4). After filtration, the solvent was removed to yield an oil (8.5 g) which was eluted with ethyl acetate on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (5.5 g). Of this material 1.0 g was dissolved in methanol and acidified with a methanol solution of maleic acid. After diluting with ether, the precipitate was collected to yield a solid 1.0 g, m.p. 118-119°C.
Analysis:

Calculated for $C_{23}H_{23}N_3O \cdot C_4H_4O_4$:	68.48 % C	5.75 % H	8.87 % N
Found:	68.29 % C	5.72 % H	8.86 % N

Example 10

1-(Propyl-4-pyridinylamino)-1H-indol-5-ol

To 0.3 g of 10% Pd/C in 10 ml of absolute ethanol was added 5-phenylmethoxy-1-(propyl-4-pyridinylamino)-1H-indole (3.0 g) in 240 ml of ethanol and this was hydrogenated on a Parr apparatus for 48 hours at 50°C and 34.5 x 10^4 Pa (50 psig) H_2. The reaction mixture was then filtered and the filtrate concentrated to yield an oil (2.2 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (1.8 g)

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which was recrystallized from methanol/ether (1:1) to yield a solid 1.6 g, m.p. 214-216°C.

Analysis:

Calculated for $C_{16}H_{17}N_{30}$:	71.89 % C	6.41 % H	15.72 % N
Found:	71.78 % C	6.41 % H	15.61 % N

Example 11

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate

To 2.5 g of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g) followed by methyl isocyanate (0.56 ml). The reaction was allowed to proceed for half an hour. The reaction mixture was then filtered and the filtrate concentrated to yield a solid (2.9 g) which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (2.7 g) which was recrystallized from isopropyl ether to yield a solid 1.8 g, m.p. 158-159°C.

Analysis:

Calculated for $C_{18}H_{20}N_4O_2$.	66.65 % C	6.22 % H	17.27 % N
Found:	66.83 % C	6.10 % H	17.18 % N

Example 12

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl ethylcarbamate hydrochloride

Ethyl isocyanate (1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL of tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.5 g of the product as a solid, m.p. 139-141°C. This was converted to the hydrochloride salt in methanol/ether to yield 4.3 g of crystals, m.p. 209-211°C (dec.).

Analysis:

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Calculated for $C_{19}H_{22}N_4O_2 \cdot HCl$:	60.87 % C	6.18 % H	14.95 % N
Found:	60.81 % C	6.16 % H	14.84 % N

Example 13

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl propylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H- indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then propyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 2 hours. The mixture was filtered and the filtrate was concentrated to yield an oil (2.8 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.5 g), m.p. 120-122°C.

Analysis:

Calculated for $C_{20}H_{24}N_4O_2$:	68.16 % C	6.86 % H	15.90 % N
Found:	67.87 % C	6.89 % H	15.93 % N

Example 14

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl isopropylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.1 g) in 50 ml of tetrahydrofuran was added potassium carbonate (milled, 1.3 g). Then isopropyl isocyanate (0.67 g) was added and the reaction mixture was stirred for 4 hours. The mixture was filtered and the filtrate was concentrated to yield a solid (3.2 g), which was eluted with 5% methanol/dichloromethane on a silicagel column via HPLC. The desired fractions were concentrated to yield an oil which solidified on standing (2.75 g), m.p. 131-133°C.

Analysis:

Calculated for $C_{20}H_{24}N_4O_2$:	68.16 % C	6.86 % H	15.90 % N
Found:	68.16 % C	6.84 % H	15.84 % N

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Example 15

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl butylcarbamate hydrochloride

Butyl isocyanate (1.3 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as an oil. This material was converted to the hydrochloride salt in methanol/ether to yield 4 g of crystals, m.p. 178-180°C.

Analysis:

Calculated for $C_{21}H_{26}N_4O_2 \cdot HCl$:	62.60 % C	6.75 % H	3.91 % N
Found:	62.52 % C	6.71 % H	13.84 % N

Example 16

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl heptylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 50 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) portionwise, and the reaction was allowed to proceed for 24 hours. To this mixture was added glacial acetic acid (2.15 ml) followed by a solution of heptylamine (1.45 ml) in tetrahydrofuran which had been treated with 0.56 ml of acetic acid. The reaction mixture was then stirred for 21 hours. The mixture was diluted with water, basified with sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (4.5 g), which was eluted with 5% methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (2.8 g). This material was dissolved in 50 ml of pentane/ether (1:1) and the solution was concentrated to 15 ml, whereupon crystals precipitated out of the solution. These were collected to

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yield a solid (1.0 g), m.p. 83-85°C.

Analysis:

Calculated for $C_{24}H_{32}N_4O_2$:	70.56 % C	7.90 % H	13.72 % N
Found:	70.33 % C	7.69 % H	13.63 % N

Example 17

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl cyclohexylcarbamate hydrochloride

Cyclohexyl isocyanate (1.7 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 2 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 167-169°C. This solid was again eluted through silica with ethyl acetate via HPLC to yield 3.8 g of the product as a solid, m.p. 167-170°C. The product was converted to the hydrochloride salt in methanol/ether to yield 3.9 g of powder, m.p. 219-220°C (dec.).

Analysis:

Calculated for $C_{23}H_{28}N_4O_2 \cdot HCl$:	64.40 % C	6.81 % H	13.06 % N
Found:	64.07 % C	6.77 % H	12.92 % N

Example 18

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl phenylmethylcarbamate

Benzyl isocyanate (2 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3.3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3 g). After stirring twenty hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyll acetate via flash column chromatography to yield 5 g of the product as a solid, m.p. 156-158°C. The product was recrystallized from acetonitrile to yield 3.8 g of crystals, m.p. 162-164°C.

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Analysis:			
Calculated for $C_{24}H_{24}N_4O_2$:	71.98 % C	6.04 % H	13.99 % N
Found:	71.99 % C	6.13 % H	14.03 % N

Example 19

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 4-chlorophenylmethylcarbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by 4-chlorophenylmethylamine (1.5 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.9 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid (3.05 g), m.p. 149-151°C

Analysis:			
Calculated for:	66.29 % C	5.33 % H	12.88 % N
Found:	66.22 % C	5.37 % H	12.81 % N

Example 20

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 2-phenylethylcarbamate hydrochloride

2-Phenylethyl isocyanate (2.1 g) was added to a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (3 g) in 75 mL tetrahydrofuran containing potassium carbonate (milled, 3.5 g). After stirring three hours at ambient temperature, the mixture was filtered and the filtrate was concentrated. The residue was eluted through silica with ethyl acetate via flash column chromatography to yield 4.7 g of the product as a solid. The product was converted

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to the hydrochloride salt in methanol/ether to yield 2.9 g of crystals, m.p. 144-146°C (dec.).

Analysis:

Calculated for $C_{25}H_{26}N_4O_2 \cdot HCl$:	66.58 % C	6.04 % H	12.43 % N
Found:	66.60 % C	5.94 % H	12.38 % N

Example 21

(S)-(-)-1-(Propyl-4-pyridinylamino)-1H-indol-5-yl 1-phenylethylcarbamate

To 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.75 g) in 30 ml of tetrahydrofuran was added potassium carbonate (milled, 0.912 g) followed by (S)-(-)-1-methylbenzyl isocyanate (0.97 g), and the reaction was allowed to proceed for one hour. The reaction mixture was filtered and the filtrate concentrated to yield an oil (3.9 g) which was eluted with 5% methanol in dichloromethane (DCM) on a silica gel column via HPLC. The desired fractions were concentrated to yield a solid 2.6 g, m.p. 78-80°C.

Analysis:

Calculated for $C_{25}H_{26}N_7O_2$:	72.44 % C	6.32 % H	13.52 % N
Found:	72.17 % C	6.34 % H	13.49 % N

Example 22

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl dimethyl carbamate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by dimethylamine (40 wt % in water, 1.44 ml) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl., anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (3.5 g), which was eluted with 5% methanol in dichloromethane on a silica gel column via HPLC.

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The desired fractions were concentrated to yield a solid (2.5 g), m.p. 134-136°C.

Analysis:

Calculated for:	67.43 % C	6.55 % H	16.56 % N
Found:	67.63 % C	6.58 % H	16.58 % N

Example 23

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-piperidin-1-carboxylate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 60 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 4.5 ml of glacial acetic acid was added to the reaction mixture followed by piperidine (0.95 g) in 10 ml of tetrahydrofuran. This mixture was then stirred for 24 hours, quenched with water and basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (4.6 g), which was eluted with 5 % methanol in dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (3.65 g).

Analysis:

Calculated for $C_{22}H_{26}N_4O_2$:	69.81%C	6.92%H	14.80%N
Found:	69.45%C	6.94%H	14.68%N

Example 24

1-(Propyl-4-pyridinylamino)-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolin-1-carboxylate

To a solution of 1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.5 g) in 40 ml of tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.83 g) and this mixture was stirred for 24 hours. Then 3.5 ml of glacial acetic acid was added to the reaction mixture. Then 1,2,3,4-tetrahydroisoquinoline (1.49 g) in 10 ml of tetrahydrofuran which had been acidified with 0.60 ml of glacial acetic acid was added to the

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reaction mixture dropwise. This was stirred for 24 hours and then the reaction mixture was quenched with water, basified with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried (sat. NaCl, anhy. $MgSO_4$). After filtration, the solvent was evaporated to yield an oil (5.6 g) which was eluted with 5 % methanol/dichloromethane on a silica gel column via HPLC. The desired fractions were concentrated to yield an oil (4.2 g). This material was dissolved in pentane/ether (1 : 1), whereupon a solid precipitated out of the solution. This material was collected to yield a solid, 2.6 g, m.p. 141 - 143 °C.

Analysis:

Calculated for $C_{26}H_{26}N_4O_2$:	73.21%C	6.15%H	13.14%N
Found:	73.12%C	6.22%H	12.95%N

Example 25

1-(3-Fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole

To 250 ml 1-methyl-2-pyrrolidinone was added 5-phenylmethoxy-1H-indol-1-amine (27.3 g), and the mixture was heated to 80 °C. Then, 4-chloro-3-fluoropyridine hydrochloride (22 g) was added, and the mixture was heated at 80 °C for two hours. After cooling, the mixture was poured into 1 liter of ice-water, stirred for five minutes, and adjusted to pH 9 with milled K_2CO_3. The product was extracted with ethyl acetate (3X). The organic layer was washed with water (2X) and dried (saturated NaCl, anhydrous $MgSO_4$). After filtration, the filtrate was concentrated to give an oil, 46 g of which was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 1) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on cooling, 32.2 g, m.p. 140°C. A sample of this material was recrystallized from ether, m.p. 157 - 159 °C.

Analysis:

Calculated for $C_{20}H_{16}FN_3O$:	72.06%C	4.84%H	12.60%N
Found:	71.98%C	4.90%H	12.51%N

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Example 26

1-[(3-Fluoro-4-pyridinyl)propylamino]-5-phenylmethoxy-1H-indole hydrochloride

To 100 ml of dry DMF (dimethylformamide) was added 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (20.0 g), and the solution was cooled to 0°C. To this was added potassium t-butoxide (6.7 g), and the mixture was stirred at 0°C for ten minutes, and thereafter a solution of n-propylbromide (5.5 ml) in 10 ml dry DMF was added. After stirring at 0 °C for thirty minutes and then at ambient temperature for two hours, the mixture was poured into 500 ml cold water, stirred for five minutes and extracted with ethyl acetate (3X). The organic layer was washed successively with water (2X) and saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to give an oil, 23 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 2) via HPLC. The desired fractions were combined and concentrated to give an oil, 19.3 g. A 2.0 g sample of this oil was dissolved in 50 ml methanol, and the solution was acidified to pH 1 with ethereal HCl and diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g, m.p. 200 °C (dec.).

Analysis:

Calculated for $C_{23}H_{22}FN_3O/HCl$:	67.06%C	5.63%H	10.20%N
Found:	66.74%C	5.55%H	10.05%N

Example 27

1-(3-Fluoro-4-pyridinylamino)-1H-indol-5-ol

In a 500 ml Parr hydrogenation bottle, 10 % Pd/C (1.0 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-(3-fluoro-4-pyridinylamino)-5-phenylmethoxy-1H-indole (5.0 g) in 200 ml ethanol. The mixture was shaken at 50°C under 50 psi hydrogen gas for two hours. After cooling, the mixture was filtered, and the filtrate was concentrated to give an oil (5.0 g) which was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 1) via HPLC. The desired

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fractions were combined and concentrated to give a crystalline solid, 3.5 g, m.p. 70 - 73 °C.

Analysis:

Calculated for $C_{13}H_{10}FN_3O$:	64.19%C	4.14%H	17.28%N
Found:	64.06%C	4.30%H	16.93%N

Example 28

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol-hydrochloride

In a 500 ml Parr hydrogenation bottle, 10 % Pd/C (1.5 g) was suspended in 50 ml ethanol, and to this was added a solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]-5-phenylmethoxy-1H-indole (15.0 g) in 200 ml ethanol. The mixture was shaken under 34.5 x 10^4 Pa (50 psi) hydrogen gas for three hours at 50 °C. Upon cooling, the mixture was filtered, and the filtrate was concentrated to give a solid, 11.4 g. This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 3) via HPLC, and the desired fractions were concentrated to give a solid, 8.5 g, m.p. 90 - 95 °C. A 2.0 g sample of this material was dissolved in 50 ml methanol, the pH was adjusted to 1 with ethereal HCl, and the solution was diluted with 200 ml ether. The resultant precipitate was collected and dried to give 2.1 g of the product, m.p. 218 °C (dec.).

Analysis:

Calculated for $C_{16}H_{16}FN_3O\backslash HCl$:	59.72%C	5.33%H	13.06%N
Found:	59.30%C	5.36%H	12.62%N

Example 29

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl methylcarbamate

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.5 g) in 50 ml THF was added potassium carbonate (1.2 g), followed by methyl isocyanate (0.53 ml). After stirring at ambient temperature for three hours, the mixture was filtered, and the filtrate was concentrated to give a solid, 3.0 g, m.p. 165 - 166 °C.

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This material was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 1) via HPLC. The desired fractions were combined and concentrated to give a solid, 2.7 g, m.p. 177 - 178 °C.

Analysis:

Calculated for $C_{18}H_{19}FN_4O_2$:	63.14%C	5.59%H	16.37%N
Found:	63.27%C	5.68%H	16.23%N

Example 30

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-butylcarbamate hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 50 ml tetrahydrofuran was added milled K_2CO_3 (1.1 g), followed by butyl isocyanate (0.9 ml). After stirring at ambient temperature for four hours, the mixture was filtered, and the filtrate was concentrated to give an oil, 5 g. This oil was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 4) via HPLC. The desired fractions were combined and concentrated to give an oil, which solidified on standing, 2.7 g, m.p. 95 - 98 °C. This solid was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.9 g of a solid, m.p. 140 °C (dec.). This material was recrystallized from ethyl acetate/ether (1 : 10) to give the product as crystals, 2.4 g, m.p. 142 °C (dec.).

Analysis:

Calculated for $C_{21}H_{25}FN_4O_2$/HCl:	59.92%C	6.23%H	13.31%N
Found:	60.31%C	6.26%H	13.31%N

Example 31

1-[(3-Fluoro-4-pyridinyl)propylamino]-1H-indol-5-yl-heptylcarbamate-hydrochloride

To a solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-1H-indol-5-ol (2.2 g) in 65 ml tetrahydrofuran was added 1,1'-carbonyldiimidazole (1.5 g), and the mixture was stirred at ambient temperature for four hours. The mixture was cooled with an ice bath, and thereafter glacial acetic acid (2.0 ml) was added, followed by a solution of

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heptylamine (2 ml) and acetic acid in tetrahydrofuran (20 ml). After stirring at ambient temperature for twenty hours, the mixture was poured into 200 ml water, the pH adjusted to 8 with $NaHCO_3$ solution, and the product was extracted with ethyl acetate. The organic layer was washed successively with water and saturated NaCl solution, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to give an oil, 4.2 g, which was eluted on a silica gel column with ethyl acetate/dichloromethane (1 : 3) via HPLC. The desired fractions were combined and concentrated to give an oil, 2.6 g. This oil was dissolved in ether, the pH was adjusted to 1 with ethereal HCl, and the resultant precipitate was collected and dried to give 2.5 g of solid, m.p. 140 °C (dec.). This material was recrystallized from ethyl acetate/ether (1 : 4) to give crystals, 2.3 g, m.p., 246 °C (dec.).

Analysis:

Calculated for $C_{24}H_{31}FN_4O_2$/HCl:	62.26%C	6.97%H	12.10%N
Found:	62.62%C	7.08%H	12.06%N

Example 32

3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine

p-Benzyloxyphenylhydrazine hydrochloride was prepared by the method of Mentzer, et al., [C.A. 48:33412]. Thus, p-benzyloxyaniline hydrochloride (72.6 g) was diazotized with conc. HCl (174 ml) and sodium nitrite (23.2 g) in water (40 ml) at 0°C. A solution of stannous chloride (169.3 g) in conc. HCl (435 ml) was added rapidly and the reaction mixture stirred for two hours. The solid product was filtered and washed with absolute ethanol, then partially dissolved in boiling methanol/ ethanol (1 : 1) and filtered hot, yielding 52.5 g of p-benzyloxyphenylhydrazine hydrochloride. The conversion of the above compound to 3-methyl-5-benzyloxy-indole was conducted according to the method of Keglevic, et al. [C.A. 56:4710h]. Thus, the above hydrazine hydrochloride (34.0 g) was dissolved in 25 % aqueous HOAc (1.4 L) at 80 °C. Propionaldehyde diethyl acetal (22.1 ml) was then added and the reaction mixture stirred for 0.75 hour. Upon cooling to room temperature, ether was added to the reaction mixture and the layers were separated. The aqueous phase was extracted with ether (2x). The combined organics were washed

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with 5 % aqueous NaOH until the aqueous extract was basic to litmus. The organic phase was then washed with brine and dried (K_2CO_3). Filtration and concentration afforded 29.0 g of 3-methyl-5-benzyloxyindole. 3-Methyl-5-(phenylmethoxy)-1H-indol-1-amine was prepared using the procedure of Somei, et al., [Tetrahedron Lett. No. 5, pp. 461 - 462, 1974]. Thus, to a solution of the above product (17.3 g) in dry DMF (260 ml) maintained at 0 °C was added milled potassium hydroxide (20.5 g) under nitrogen. Hydroxylamine-O-sulfonic acid (10.7 g) was added portionwise (10 % wt.) every ten minutes. After stirring for 1 hour at room temperature, water and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with brine and dried (K_2CO_3). Filtration and concentration gave the crude product. Purification via preparative HPLC (silica gel, DCM) afforded 6.0 g of the desired product as a solid which was recrystallized from ether, m.p. 104 - 106°C.

Analysis:

Calculated for $C_{16}H_{16}N_2O$:	76.16%C	6.39%H	11.10%N
Found:	75.86%C	6.37%H	10.87%N

Example 33

3-Methyl-5-(phenylmethoxy)-1-(4-pyridinylamino)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (6.31 g) and 1-methyl-2-pyrrolidinone (109 ml) was added 4-chloropyridine hydrochloride (3.94 g). The resulting mixture was heated at 80 °C for 4 - 5 hours. Another batch of reaction was also carried out with the amine (2.94 g) and 4-chloropyridine hydrochloride (1.84 g) in nmp (50 ml) at 80 °C for 4 hours. The above reaction mixtures were poured together into dilute aqueous sodium bicarbonate and extracted with EtOAc (4x) and ether (1x). The combined organic layers were washed with water and brine followed by drying (K_2CO_3). Filtration, concentration and purification via flash column chromatography (silica gel, 2% Et_3N/ether/0 - 5 % MeOH) afforded 7.55 g of the desired product. Recrystallization from EtOAc gave a solid, m.p. 167.5 - 169.5°C.

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Analysis:			
Calculated for $C_{21}H_{19}N_3O$:	76.57%C	5.81%H	12.76%N
Found:	76.73%C	6.05%H	12.76%N

Example 34

3-Methyl-1-(4-pyridinylamino)-1H-indol-5-ol

3-Methyl-5-phenylmethoxy-1-(4-pyridinylamino)-1H-indole (2.20 g) was subjected to hydrogenolysis in absolute ethanol (80 ml) with 10 % Pd-C (0.26 g) at 34.5 x 10^4 Pa (50 psig) hydrogen at 50 °C for 2 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. Concentration and recrystallization from methanol afforded 0.50 g of highly crystalline product, m.p. 239 - 241 °C (dec.).

Analysis:			
Calculated for $C_{14}H_{13}N_3O$:	70.28%C	5.48%H	17.56%N
Found:	69.95%C	5.46%H	17.41%N

Example 35

3-Methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole hemifumarate

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1- (4-pyridinylamino)-1H-indole (7.78 g) and dimethylformamide (150 ml) maintained at 0 °C under nitrogen with stirring, was added sodium hydride (0.64 g, 97 % purity). The resulting mixture was stirred at 0 °C for an additional 15 minutes at which time propyl bromide (2.25 ml) was added dropwise and the ice bath was removed. Stirring was continued at room temperature for 2 - 3 hours until complete reaction was observed by TLC (silica gel, ether). The reaction mixture was poured into water and the product extracted with EtOAc (3x) and ether (1x). The combined organic layers were washed successively with water (2x) and brine (2x), dried (K_2CO_3) and decolorized with activated carbon. Filtration and concentration gave the desired product (7.65 g) as an oil. The hemifumarate was prepared with 1.0 eq. fumaric acid in abs. ethanol. A

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highly crystalline solid resulted, m.p. 165.5 - 167°C.

Analysis:

Calculated for $C_{24}H_{25}N_3O/0.5\ C_4H_4O_4$:	72.70%C	6.35%H	9.78%N
Found:	72.66%C	6.55%H	9.73%N

Example 36

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol hemioxalate

The benzyl group of 3-methyl-5-(phenylmethoxy)-1-(propyl-4-pyridinylamino)-1H-indole (7.80 g) was cleaved in a Parr hydrogenation apparatus in abs. EtOH (275 ml) over 10 % Pd-C (0.80 g) at 34.5 x 10^4 Pa (50 psig) and 50°C for 2 - 3 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with methanol. The combined filtrate was concentrated and the product purified via flash column chromatography (silica gel, 2 % Et_3N/ether) affording 5.80 g of the product as an oil. Dissolving in absolute ethanol followed by addition of 1.0 eq of anhydrous oxalic acid (in abs. EtOH) resulted in formation of a solid, the hemioxalate, m.p. 235 - 237 °C.

Analysis:

Calculated for $C_{17}H_{19}N_3O/0.5\ C_2H_2O_4$:	66.23%C	6.19%H	12.88%N
Found:	65.91%C	6.33%H	12.58%N

Example 37

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-methylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.06 g) and tetrahydrofuran (49 ml) was added milled K_2CO_3 (1.06 g) followed by dropwise addition of methyl isocyanate (0.48 ml) at room temperature under nitrogen. Stirring was continued for 2.3 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2 % Et_3N/EtOAc) afforded 2.30 g of the desired carbamate as an oil. The product

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was crystallized from ether, m.p. 147 - 149 °C.

Analysis:

Calculated for $C_{19}H_{22}N_4O_2$:	67.44%C	6.55%H	16.56%N
Found:	67.49%C	6.68%H	16.53%N

Example 38

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-butylcarbamate

To a stirred solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.11 g) and tetrahydrofuran (50 ml) was added milled K_2CO_3 (1.09 g), followed by dropwise addition of butyl isocyanate (0.93 ml) at room temperature under nitrogen. Stirring was continued for 2.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 2 % Et_3N/EtOAc) afforded 2.65 g of the desired carbamate as an oil. This oil was dissolved in a small amount of EtOAc and diluted with ether, whereupon the product crystallized as a white powder, m.p. 120 - 122 °C.

Analysis:

Calculated for $C_{22}H_{28}N_4O_2$:	69.45%C	7.42%H	14.72%N
Found:	69.67%C	7.44%H	14.68%N

Example 39

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-heptylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (2.23 g) and tetrahydrofuran (53 ml) was added 1,1'-carbonyldiimidazole (2.57 g) at room temperature with stirring under nitrogen. Stirring was continued for 96 hours, at which time acetic acid (1.54 ml) was added. To the resulting reaction mixture was added a solution consisting of heptyl amine (1.76 ml), acetic acid (0.71 ml) and THF (5 ml). After stirring for 24 hours, an additional solution of heptyl amine (1.17 ml), acetic acid (0.48 ml) and THF (5 ml) was added and stirring continued for 3 hours.

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The reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2 Et_3N/ether) afforded 1.60 g of the desired carbamate after recrystallization from ether/pentane, m.p. 102 - 104 °C.

Analysis:

Calculated for $C_{25}H_{34}N_4O_2$:	71.06%C	8.11%H	13.26%N
Found:	71.10%C	8.08%H	13.25%N

Example 40

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl-phenylmethylcarbamate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.80 g) and tetrahydrofuran (43 ml) were added with stirring at room temperature milled potassium carbonate (0.93 g) and benzyl isocyanate (0.87 ml). Stirring was continued under nitrogen for 16 hours. The mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration followed by purification via flash column chromatography (silica gel, 2 % Et_3N/EtOAc) afforded 2.28 g of the desired carbamate. Recrystallization from ether gave a highly crystalline solid, m.p. 149 - 151 °C.

Analysis:

Calculated for $C_{25}H_{26}N_4O_2$:	72.44%C	6.32%H	13.52%N
Found:	72.39%C	6.73%H	13.92%N

Example 41

3-Methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-yl, 1,2,3,4-tetrahydro-2-isoquinolin-1-carboxylate

To a solution consisting of 3-methyl-1-(propyl-4-pyridinylamino)-1H-indol-5-ol (1.67 g) and tetrahydrofuran (40 ml) was added 1,1'-carbonyldiimidazole (1.92 g) at

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room temperature with stirring under nitrogen. Stirring was continued for 48 hours, at which time acetic acid (1.6 ml) was added. To the resulting reaction mixture was added a solution consisting of 1,2,3,4-tetrahydroisoquinoline (1.6 ml), acetic acid (0.76 ml) and THF (10 ml). After stirring for 16 hours, the reaction mixture was poured into a dilute aqueous sodium bicarbonate solution and the product extracted with ether (3x). The combined organic layer was washed with brine and dried ($MgSO_4$). Filtration, concentration and purification via flash column chromatography (silica gel, 2 % Et_3N/ether) gave 2.41 g of the desired carbamate as a foam. The compound formed a white powder in ether/pentane, m.p. 160 - 162°C.

Analysis:

Calculated for $C_{27}H_{28}N_4O_2$:	73.61%C	6.41%H	12.72%N
Found:	73.57%C	6.38%H	12.61%N

Example 42

1-[(3-Fluoro-4-pyridinyl)amino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 3-methyl-5-(phenylmethoxy)-1H-indol-1-amine (4.81 g) and 1-methyl-2-pyrrolidinone (83 ml) was added 4-chloro-3-fluoro pyridine hydrochloride (3.20 g). The resulting mixture was heated at 80 °C for 2 hours. Upon cooling to room temperature, dilute aqueous sodium bicarbonate and ethyl acetate were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed successively with water (2x) and brine (1x), and thereafter dried ($MgSO_4$). Filtration and concentration gave the crude product. Purification via flash column chromatography (silica gel, 50 % ethyl acetate/dichloromethane) afforded 4.0 g of the desired product as a solid, m.p. 210 - 213 °C.

Example 43

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-5-(phenyl-

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methoxy)-1H-indole (3.76 g) and dimethylformamide (108 ml), cooled to 0°C under nitrogen with stirring, was added sodium hydride (0.29 g). The resulting mixture was stirred at 0°C for an additional 15 minutes, at which time 1-bromopropane (1.03 ml) was added dropwise and the ice bath removed. Stirring was continued at room temperature overnight, at which time the reaction appeared complete by TLC (silica gel, 50% ether/hexane). The reaction mixture was poured into water and the product extracted with EtOAc (3x). The combined organic layers were washed with brine and dried ($MgSO_4$). Filtration and concentration gave the crude product as an oil. Purification via preparative HPLC (silica gel, 30% EtOAc/hexane) afforded 2.80 g of the desired product as a solid which was recrystallized from ether, m.p. 94-96°C.

Analysis:

Calculated for $C_{24}H_{24}FN_3O$:	74.01%C	6.21%H	10.79%N
Found:	73.58%C	6.09%H	10.56%N

Example 44

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol

The benzyl group of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-5-(phenylmethoxy)-1H-indole (15.82 g) was cleaved in a Parr hydrogenation apparatus in absolute ethanol (200 ml) over 10% Pd-C (1.58 g) at $34.5x10^4$ Pa (50 psig) and 50°C for 7.5 hours. The catalyst was removed by filtration through a pad of celite and the solids washed with absolute ethanol. The combined filtrate was concentrated and the product purified via preparative HPLC (silica gel, 3:1 dichloromethane/EtOAc) affording 5.0 g of the desired product as an oil. Addition of EtOAc solidified the product which was recrystallized from EtOAc to give a solid, m.p. 157-160°C.

Analysis:

Calculated for $C_{17}H_{18}FN_3O$:	68.21%C	6.06%H	14.04%N
Found:	67.81%C	6.09%H	13.73%N

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Example 45

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl methylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of methyl isocyanate (0.46 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, 50% EtOAc/dichloromethane) afforded 2.35 g of the desired carbamate as a solid. The product was recrystallized from ether, m.p. 163-164°C.

Analysis:

Calculated for $C_{19}H_{21}FN_4O_2$:	64.03%C	5.94%H	15.72%N
Found:	63.84%C	6.10%H	15.55%N

Example 46

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl butylcarbamate

To a stirred solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.10 g) and tetrahydrofuran (47 ml) was added milled K_2CO_3 (1.02 g) followed by dropwise addition of butyl isocyanate (0.87 ml) at room temperature under nitrogen. Stirring was continued for 15 hours, at which time the reaction mixture was filtered through a pad of celite and the solids washed with EtOAc. Concentration afforded the crude product. Purification via flash column chromatography (silica gel, ether) afforded 2.3 g of the desired product as an oil. The product was crystallized from ether/pentane, m.p. 83-84°C.

Analysis:

Calculated for $C_{22}H_{27}FN_4O_2$:	66.31%C	6.83%H	14.06%N
Found:	65.99%C	6.83%H	13.88%N

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Example 47

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl heptylcarbamate

To a solution consisting of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.54 g) and anhydrous tetrahydrofuran (57 ml) was added carbonyl diimidazole (2.75 g) under nitrogen with stirring. The resulting reaction mixture was stirred at room temperature for two days, at which time acetic acid (1.65 ml) was added followed by a solution of heptylamine (1.89 ml) in tetrahydrofuran (5 ml) and acetic acid (0.76 ml). After stirring for 24 hours, an additional equivalent of heptylamine (1.26 ml) in tetrahydrofuran (5 ml) and acetic acid (0.52 ml) was added. After an additional 24 hours the reaction was complete and the reaction mixture was poured into $NaHCO_3$ (aq.) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq.) and brine. Drying (Na_2SO_4), filtration and concentration gave a crude product. Purification via flash column chromatography (silica gel, 30% EtOAc/hexane) afforded 3.38 g of the desired product as an oil. Addition of ether and pentane solidified the product. The solid was filtered and washed with pentane, m.p. 90-93°C.

Analysis:

Calculated for $C_{25}H_{33}FN_4O_2$:	68.16%C	7.55%H	12.72%N
Found:	67.87%C	7.35%H	12.60%N

Example 48

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl phenylmethylcarbamate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)-propylamino]- 3-methyl-1H-indol-5-ol (2.66 g) in tetrahydrofuran (59 ml) was added milled potassium carbonate (1.29 g) followed by dropwise addition of benzyl isocyanate (1.21 ml) at room temperature under nitrogen. Stirring was continued for 17.0 hours at which time the reaction mixture was filtered through a pad of celite and the solids washed with ethyl acetate. Concentration afforded a crude product. Purification via flash column

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chromatography (silica gel, ether) afforded 3.34 g of the desired carbamate as a foam. This foam was dissolved in ether and the product crystallized as a solid. The solid was recrystallized from ether, m.p. 143-144°C.

Analysis:

Calculated for $C_{25}H_{25}FN_4O_2$:	69.42%C	5.83%H	12.96%N
Found:	69.44%C	5.83%H	12.84%N

Example 49

1-[(3-Fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-yl-1,2,3,4-tetrahydro-2-isoquinolin-1-carboxylate

To a stirred solution of 1-[(3-fluoro-4-pyridinyl)propylamino]-3-methyl-1H-indol-5-ol (2.51 g) in anhydrous tetrahydrofuran (56 ml) was added 1,1'-carbonyl diimidazole (2.72 g) at room temperature under nitrogen. After 24 hours the reaction appeared complete by TLC (silica gel, 60% EtOAc/hexane) and acetic acid (1.60 ml) was added to the reaction mixture followed by the dropwise addition of a solution of 1,2,3,4-tetrahydroisoquinoline (1.58 ml) in tetrahydrofuran (5.0 ml) and acetic acid (0.75 ml). After 72 hours, the reaction was not complete by TLC (60% EtOAc/dichloromethane) and an additional equivalent of 1,2,3,4-tetrahydroisoquinoline (1.05 ml) was added as a tetrahydrofuran (5.0 ml) and acetic acid (0.51 ml) solution. After 1.5 hours the reaction appeared complete and the mixture was poured into $NaHCO_3$ (aq) and ether. The layers were separated and the aqueous phase was extracted with ether (3x). The combined organic layers were washed successively with $NaHCO_3$ (aq) and brine, and dried (Na_2SO_4). The organic phase was filtered and concentrated to give a crude product. Purification via flash column chromatography (silica gel., 30% EtOAc/dichloromethane) afforded 2.70 g of the desired product as an oil which solidified on standing. Recrystallization from ether (2x) gave a solid which was filtered and washed with ether, m.p. 157-160°C.

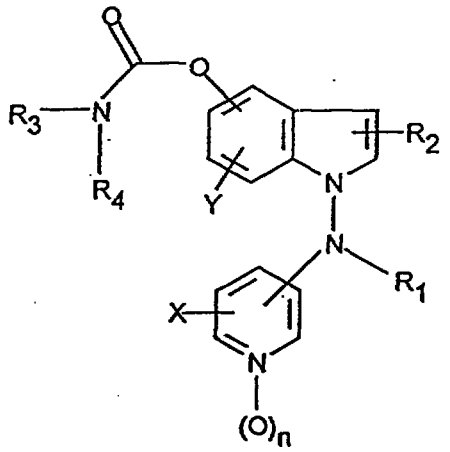
Analysis:

Calculated for $C_{27}H_{27}FN_4O_2$:	70.72%C	5.94%H	12.22%N
Found:	70.93%C	5.85%H	12.11%N

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Claims:

1. A compound of the formula I a,



(Ia)

wherein

n is 0 or 1;

X is hydrogen, halogen, nitro, amino,
trifluoromethyl, (C_1-C_8)alkyl, or (C_1-C_8)alkoxy;

Y is hydrogen, halogen, nitro, amino,
trifluoromethyl, (C_1-C_8)alkyl, or (C_1-C_8)alkoxy;

R_1 is hydrogen, (C_1-C_8)alkyl, phenyl(C_1-C_8)alkyl,
up to C_8 alkenyl, up to C_8 alkynyl, (C_1-C_8)alkanoyl,
phenyl(C_1-C_8)-alkanoyl, heteroaryl(C_1-C_8)alkyl or
heteroaryl(C_1-C_8)alkanoyl, where phenyl is optionally substituted with 1 or 2 substituents selected from: (C_1-C_8)alkyl, (C_1-C_8)-alkoxy, halogen or trifluoromethyl, and heteroaryl is furanyl, thienyl, pyrrolyl or pyridinyl;

R_2 is hydrogen, (C_1-C_8)alkyl, formyl or cyano;

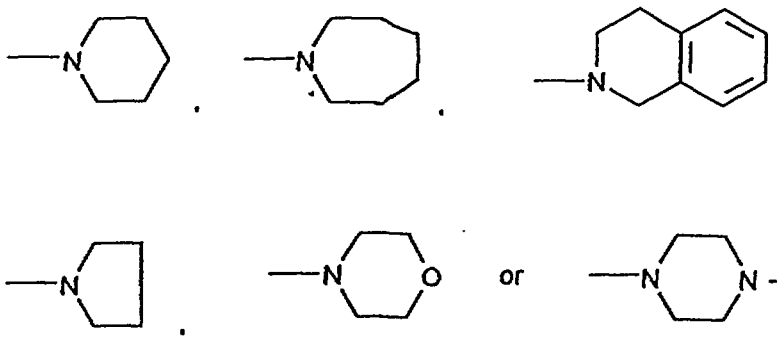
R_3 is hydrogen or (C_1-C_8)-alkyl;

R_4 is (C_1-C_8)alkyl, phenyl(C_1-C_8)-alkyl, cyclo(C_3-C_7)-alkyl or phenyl, where phenyl in each case is optionally substituted with 1 or 2 substituents selected from: (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, halogen or trifluoromethyl or $_{R4}$ is a heteroaryl selected from: furanyl, thienyl, pyrrolyl and pyridinyl;

or alternatively, $-NR_3R_4$ taken together constitutes

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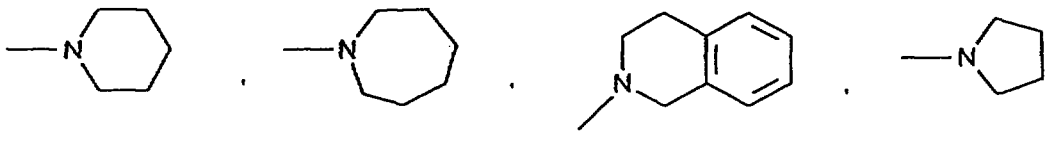


R_5 being hydrogen, $(C_1$-$C_8)$-alkyl, phenyl, phenyl$(C_1$-$C_8)$alkyl, heteroaryl or heteroaryl$(C_1$-$C_8)$alkyl where phenyl in each case is optionally substituted with 1 or 2 substituents selected from: $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, halogen or trifluoromethyl, and heteroaryl in each case is furanyl, thienyl, pyrrolyl or pyridinyl, and all optical and geometrical stereoisomers and racemic mixtures thereof and the pharmaceutically acceptable acid addition salts thereof.

2. A compound as defined in claim 1, wherein
n is 0,
X is hydrogen or halogen and Y is hydrogen.

3. A compound of the formula Ia as defined in claim 2, wherein R_1 and R_2 are each independently H or $(C_1$-$C_8)$-alkyl.

4. A compound of the formula Ia as defined in claim 3 wherein R_3 is hydrogen, R_4 is $(C_1$-$C_8)$-alkyl, phenyl-$(C_1$-$C_8)$-alkyl, where phenyl is optionally substituted as indicated in claim 1, cyclo-$(C_3$-$C_7)$-alkyl or alternatively -NR_3R_4 taken together constitutes



5. A compound as defined in claim 1, which is 1-(propyl-4-pyridinylamino)-1H-indol-5-yl methylcarbamate.

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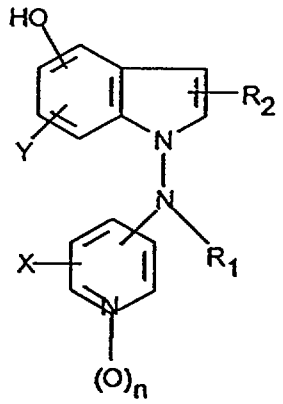
6. A compound as defined in claim 1, which is (S)-(-)-1-(propyl-4-pyridinyl-amino)-1H-indol-5-yl 1-phenylethylcarbamate.

7. A pharmaceutical composition which comprises a compound as defined in any one of the preceding claims as the active ingredient and a suitable carrier therefor.

8. Use of a compound as defined in any one of the preceding claims for the preparation of a medicament having the activity of alleviating a memory dysfunction characterized by a cholinergic deficit.

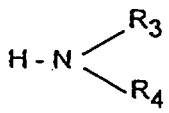
9. A process for the preparation of a compound of the formula Ia, as defined in any one of claims 1 to 6 which comprises

a) reacting a compound of the formula XV



(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with 1,1'-carbonyldiimidazol to afford an intermediate which is treated with an amine of the formula

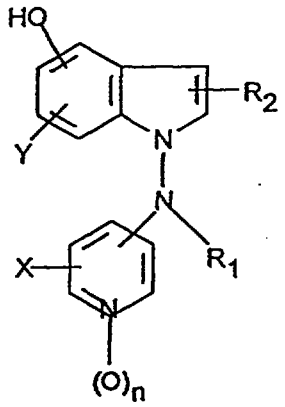


wherein R_3 and R_4 are defined as in claim 1, or

b) reacting a compound of the formula XV

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(XV)

wherein X, Y, R_1, R_2 and n are defined as in claim 1 with an isocyanate of the formula

$$R_4 - NCO$$

wherein R_4 is defined as above, to afford a compound of the formula Ia, where X, Y, R_1, R_2, R_4 and n are as defined above and R_3 is hydrogen.

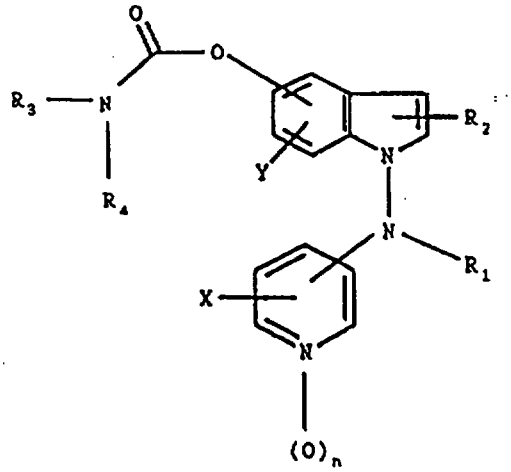
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ABSTRACT

1-(Substituted pyridinylamino)-1H-indol-5-yl substituted carbamates, a process and Intermediates for their preparation and their use as medicaments.

There are disclosed various compounds of the formula below,



where

n is 0 or 1;

X is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

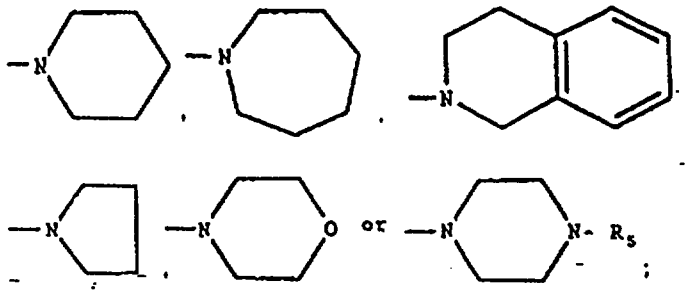
Y is hydrogen, halogen, nitro, amino, trifluoromethyl, loweralkyl, or loweralkoxy;

R_1 is hydrogen, loweralkyl, aryllowerallkyl, loweralkenyl, loweralkynyl, loweralkanoyl, aryllowerallkanoyl, heteroaryllooweralkyl or heteroaryllowerallkanoyl;

R_2 is hydrogen, loweralkyl, formyl or cyano;

R_3 is hydrogen or loweralkyl;

R_4 is loweralkyl, aryllowerallkyl, cycloalkyl, aryl or heteroaryl;
or alternatively, $-NR_3R_4$ token together constitutes



R_5 being hydrogen, loweralkyl, aryl, aryllowerallkyl, heteroaryl or heteroaryllowerallkyl, which compounds are useful for the treatment of various memory dysfunctions characterized by a cholinergic deficit such as Alzheimer's disease.