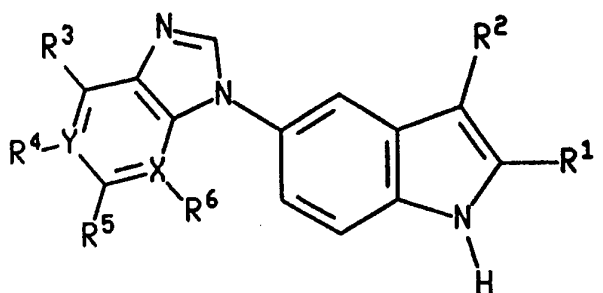




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<p>(54) Title: 5-HETEROARYLINDOLE DERIVATIVES AS BENZODIAZEPINE RECEPTOR SITE AGONISTS AND ANTAGONISTS</p>		
<p>(57) Abstract</p>		
<p>The present invention relates to compounds of formula (I). The present invention also relates to intermediates for the preparation of compounds of formula (I), pharmaceutical compositions and method of use.</p>	 <p style="text-align: right;">(I)</p>	

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-1-

5-HETEROARYLINDOLE DERIVATIVES AS BENZODIAZEPINE RECEPTOR SITE AGONISTS AND ANTAGONISTS

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Background of the Invention

The present invention relates to indole derivatives, intermediates for their preparation, pharmaceutical compositions containing them, and their medicinal use. The active compounds of the present invention are potent agonists and antagonists at the benzodiazepine receptor. Agonists and antagonists of the benzodiazepine receptor are useful in the treatment, prevention and diagnosis of anxiety, memory loss, sleep disorders or seizures. The compounds of the invention are also useful in the treatment of an overdose of benzodiazepine drugs.

The use of benzodiazepine receptor ligands in the treatment of anxiety and other disorders has been discussed in "New Trends in Benzodiazepine Research", 24 Drugs of Today, 649-663 (1988).

European Patent Publication 499,527, which was published on August 19, 1992, refers to β -carboline derivatives which possess an affinity for benzodiazepine receptors and as such are useful agents in the treatment of degenerative central nervous system disorders, such as Alzheimer's disease.

United States Patent 5,243,049, which issued on September 7, 1993, refers to pyrroloquinoline derivatives which are γ -amino butyric acid (GABA) receptor antagonists. These pyrroloquinoline derivatives are claimed to be useful for the treatment of anxiety, sleep disorders, seizures and for enhancing memory.

A series of planar azadiindoles, benzannelated pyridoindoles, and indolopyridoimidazoles have been described as molecular probes that are useful for the definition of the molecular recognition elements of the benzodiazepine receptor in J. Med. Chem., 35, 4105-4117 (1992).

International Patent Application WO 93/23396, published November 25, 1993, refers to fused imidazole and triazole derivatives as 5-HT₁ receptor agonists that are useful for the treatment of migraine and other disorders.

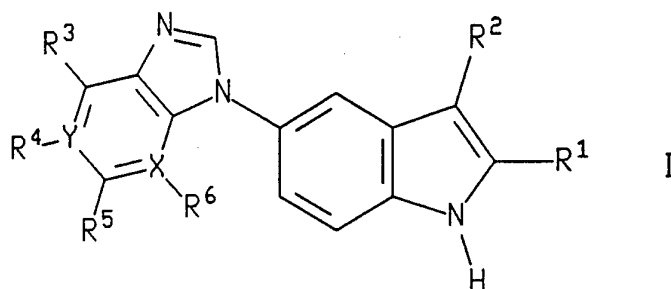
Summary of the Invention

The present invention relates to compounds of the formula

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-2-

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wherein X and Y are independently carbon or nitrogen;

R¹ and R² are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷, -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected, independently, from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected, independently, from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

30 $\begin{matrix} \text{O} & \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel & \parallel \\ -\text{CO}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CNH}_2, & -\text{CNH}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CN-di}(\text{C}_1-\text{C}_5)\text{alkyl}, \text{ and formyl;} \end{matrix}$

wherein said aryl groups and the aryl moieties of said (C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted

-3-

phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, 5 -(C₁-C₃)alkylaryl, -CN, -CHO, CO₂R⁹, -NO₂, -CONR⁹R¹⁰, -(CH₂)_pOH, -(CH₂)_pOR⁹, -(CH₂)_pNR⁹R¹⁰ and halogen (e.g., fluorine, chlorine bromine or iodine); wherein said aryl groups and the aryl moieties of said -(C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen 10 (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

R⁷, R⁸, R⁹, and R¹⁰ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said 15 unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected, independently, from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 20 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected, independently, from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolyl, cinnolinyl 25 and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl, 30

$$\begin{array}{cccc} \text{O} & \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel & \parallel \\ -\text{CO}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CNH}_2, & -\text{CNH}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CN-di}(\text{C}_1-\text{C}_5)\text{alkyl}, \text{ and formyl;} \end{array}$$

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-4-

wherein said aryl groups and the aryl moieties of said $-(C_1-C_3)$ alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from (C_1-C_4) alkyl, halogen (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano,
5 carboxamido, nitro, and (C_1-C_4) alkoxy;

n is 0, 1, 2, or 3;

p is 0, 1, or 2;

and the pharmaceutically accepted salts thereof.

The present invention also relates to the pharmaceutically acceptable acid and
10 base addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate,
15 citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature (e.g., where R^2 contains a carboxylate) are capable of forming base salts with various
20 pharmacologically acceptable cations. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those that form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable alkali metal or alkaline-earth metal cations as sodium, potassium, calcium
25 and magnesium.

Preferred compounds of the invention are compounds of the formula I wherein X is carbon, Y is carbon and R^1 is hydrogen.

Particularly preferred compounds of the invention are compounds of the formula I wherein R^3 , R^5 and R^6 are hydrogen.

30 Specific particularly preferred compounds of the invention are the following:

5-cyano-1-(indol-5-yl)benzimidazole;

5-cyano-1-(3-formylindol-5-yl)benzimidazole;

1-(indol-5-yl)-5-methylbenzimidazole;

- 5-cyano-1-(3-(cyclohexen-1-yl)indol-5-yl)benzimidazole;
1-(3-formylindol-5-yl)-1H-pyrido[4,5-b]imidazole;
1-(3-(cyclohexen-1-yl)indol-5-yl)-5-methylbenzimidazole;
1-(3-cyclohexylindol-5-yl)-5-methylbenzimidazole; and
5 1-(3-benzoylindol-5-yl)-5-methylbenzimidazole;
- and the pharmaceutically acceptable salts of the foregoing compounds.
- Other compounds of formula I include the following:
- 5-ethyl-1-(3-indol-5-yl)benzimidazole;
5-ethyl-1-(3-methylindol-5-yl)benzimidazole;
10 5-ethyl-1-(3-ethylindol-5-yl)benzimidazole;
1-(3-cyclohexylindol-5-yl)-5-ethylbenzimidazole;
5-methyl-1-(3-methylindol-5-yl)benzimidazole;
1-(3-ethylindol-5-yl)-5-methylbenzimidazole;
1-(3-isopropylindol-5-yl)-5-methylbenzimidazole;
15 1-(3-cyclopentylindol-5-yl)-5-methylbenzimidazole;
1-(indol-5-yl)-5-methoxybenzimidazole;
1-(3-methylindol-5-yl)-5-methoxybenzimidazole;
1-(3-ethylindol-5-yl)-5-methoxybenzimidazole;
1-(3-cyclohexylindol-5-yl)-5-methoxybenzimidazole;
20 5-chloro-1-(indol-5-yl)benzimidazole;
5-chloro-1-(3-methylindol-5-yl)benzimidazole;
5-chloro-1-(3-ethylindol-5-yl)benzimidazole;
5-chloro-1-(3-cyclohexylindol-5-yl)benzimidazole;
5-methyl-1-(3-methylindol-5-yl)pyrido[4,5-b]imidazole;
25 1-(3-cyclohexylindol-5-yl)-5-methylpyrido[4,5-b]imidazole;
5-carboxamido-1-(indol-5-yl)benzimidazole;
5-carboxamido-1-(3-methylindol-5-yl)benzimidazole;
5-carboxamido-1-(3-ethylindol-5-yl)benzimidazole;
5-carboxamido-1-(3-cyclohexylindol-5-yl)benzimidazole;
30 5-formyl-1-(indol-5-yl)benzimidazole;
5-formyl-1-(3-methylindol-5-yl)benzimidazole;
5-formyl-1-(3-ethylindol-5-yl)benzimidazole;
5-formyl-1-(3-cyclohexylindol-5-yl)benzimidazole;

- 1-(indol-5-yl)-5-phenylethylbenzimidazole;
1-(3-methylindol-5-yl)-5-phenylethylbenzimidazole;
1-(3-ethylindol-5-yl)-5-phenylethylbenzimidazole;
1-(3-cyclohexylindol-5-yl)-5-phenylethylbenzimidazole;
5 1-(indol-5-yl)-5-methoxymethylbenzimidazole;
1-(3-methylindol-5-yl)-5-methoxymethylbenzimidazole;
1-(3-ethylindol-5-yl)-5-methoxymethylbenzimidazole;
1-(3-cyclohexylindol-5-yl)-5-methoxymethylbenzimidazole;
5-dimethylaminomethyl-1-(indol-5-yl)benzimidazole;
10 5-dimethylaminomethyl-1-(3-methylindol-5-yl)benzimidazole;
5-dimethylaminomethyl-1-(3-ethylindol-5-yl)benzimidazole; and
5-dimethylaminomethyl-1-(3-cyclohexylindol-5-yl)benzimidazole.

This invention also relates to a method for treating or preventing a condition or disorder selected from anxiety, panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, preferably a human, comprising administering to said mammal requiring such treatment or prevention an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition or disorder.

This invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition selected from anxiety, panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, preferably a human, comprising an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier.

This invention also relates to a method for treating or preventing a condition or disorder arising from an increase or decrease in benzodiazepine receptor neurotransmission in a mammal, preferably a human, comprising administering to said mammal requiring such treatment or prevention an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition or disorder.

This invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition arising from an increase or decrease in benzodiazepine receptor neurotransmission in a mammal, preferably a human,

-7-

comprising an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition or disorder and a pharmaceutically acceptable carrier.

This invention also relates to a method for antagonizing or agonizing the
5 benzodiazepine receptor in a mammal, preferably a human, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition for antagonizing or agonizing the benzodiazepine receptor in a mammal, preferably a human, comprising
10 administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

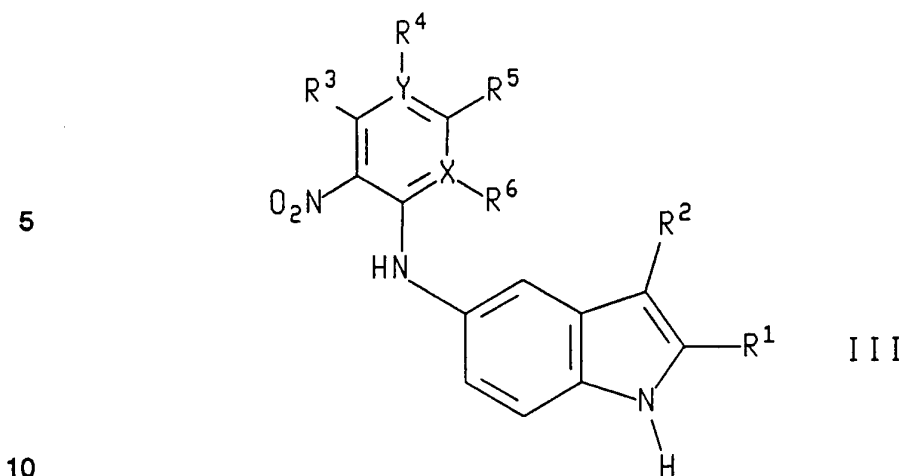
This invention also relates to a method for treating or preventing a condition or disorder selected from anxiety, panic attacks, sleep disorders, seizures, memory loss,
15 convulsions, and drug abuse in a mammal, preferably a human, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition selected from anxiety, panic attacks, sleep disorders,
20 seizures, memory loss, convulsions, and drug abuse in a mammal, preferably a human, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a compound of the formula
25

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-8-



wherein X and Y are independently carbon or nitrogen;

R¹ and R² are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷,
 15 -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle;
 wherein said unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl, 25 thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolyl, cinnolinyl and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from 30 zero to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

-9-

$\begin{array}{cccc} \text{O} & & \text{O} & \text{O} & & \text{O} \\ || & & || & || & & || \\ -\text{CO}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CNH}_2, & -\text{CNH}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CN-di}(\text{C}_1-\text{C}_5)\text{alkyl}, & \text{and formyl}; \end{array}$

- 5 wherein said aryl groups and the aryl moieties of said (C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;
- 10 R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -CN, -CHO, CO₂R⁹, -NO₂, -CONR⁹R¹⁰, -(CH₂)_pOH, -(CH₂)_pOR⁹, -(CH₂)_pNR⁹R¹⁰ and halogen (e.g., fluorine, chlorine bromine or iodine); wherein said aryl groups and the aryl moieties of said -(C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted
- 15 with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;
- R⁷, R⁸, R⁹, and R¹⁰ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-
- 20 unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl,
- 25 pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl,
- 30 indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo,

-10-

chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

5 $\begin{array}{cccc} \text{O} & \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel & \parallel \\ -\text{CO}(\text{C}_1\text{-C}_5)\text{alkyl,} & -\text{CNH}_2, & -\text{CNH}(\text{C}_1\text{-C}_5)\text{alkyl,} & -\text{CN-di}(\text{C}_1\text{-C}_5)\text{alkyl,} \end{array}$ and formyl;

wherein said aryl groups and the aryl moieties of said -(C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted
10 phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen (e.g., fluorine, chlorine bromine or iodine), hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

n is 0, 1, 2, or 3; and

p is 0, 1, or 2.

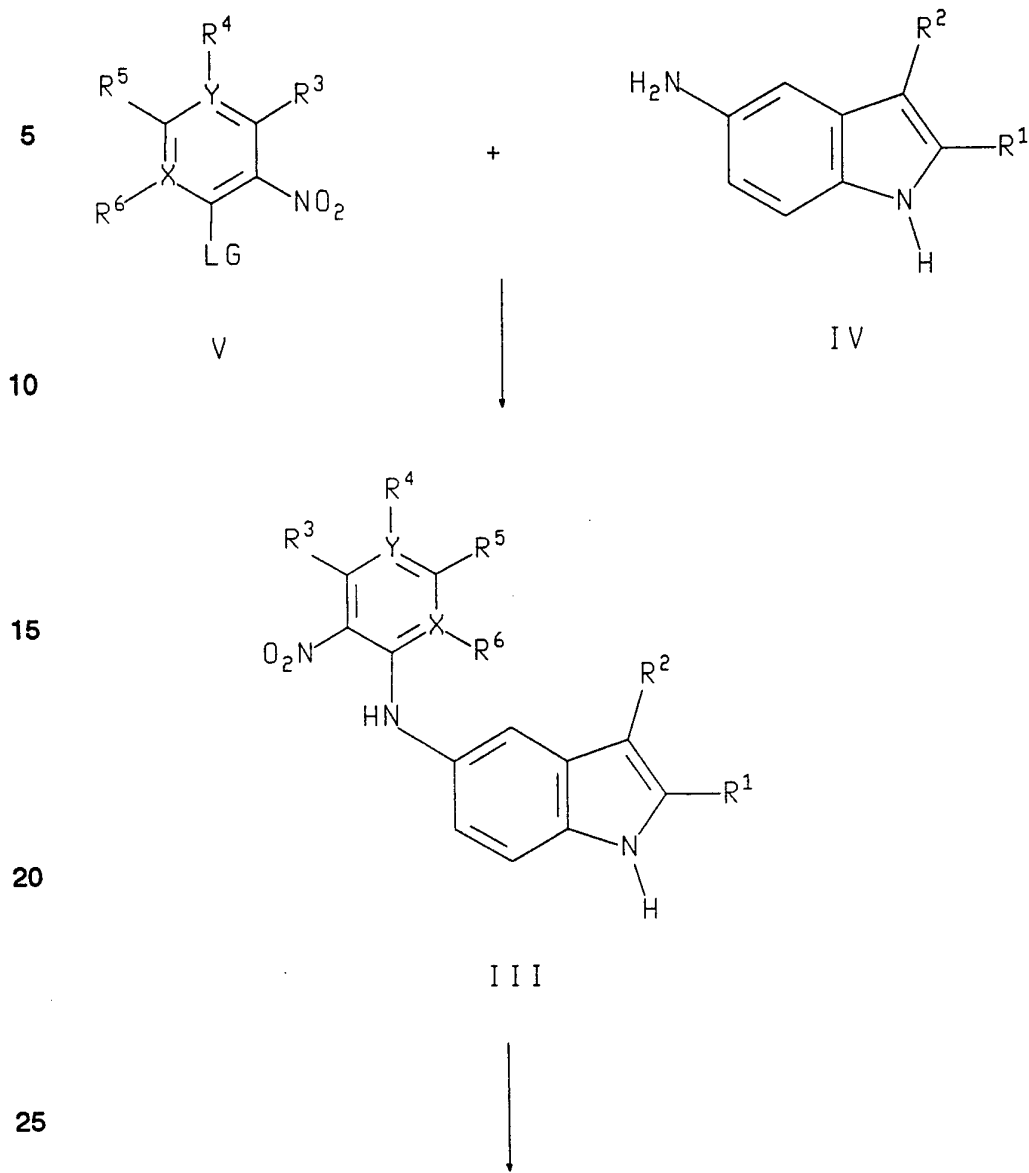
15 The compounds of the formula III are useful as intermediates in preparing the compounds of formula I.

Unless otherwise indicated, the alkyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g. alkoxy), may be linear or branched, and they may also be cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl, or
20 cyclohexyl) or be linear or branched and contain cyclic moieties.

Detailed Description of the Invention

The compounds of formula I can be prepared according to the methods of scheme 1. In the reaction scheme and discussion that follow, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, X and Y, unless otherwise indicated, are as defined above for formula
25 I.

SCHEME 1



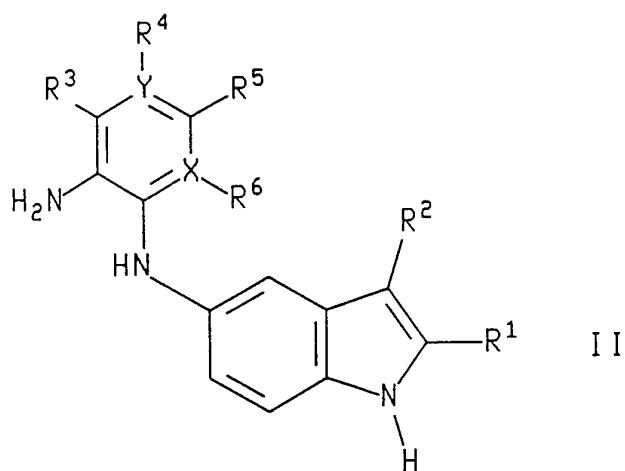
SCHEME 1 (cont.)

III

5



10

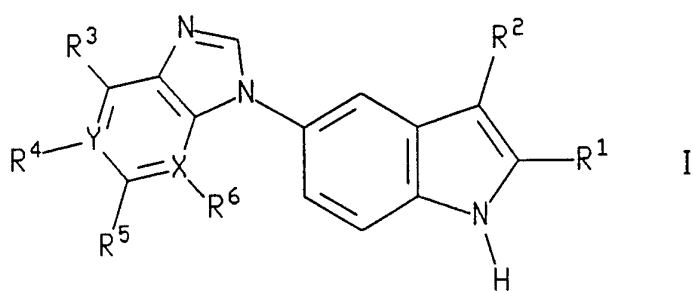


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-13-

Compounds of formula III can be prepared by reacting a compound of formula IV with a compound of formula V, wherein LG is a leaving group such as, for example, fluoro, chloro, bromo, iodo, methylmercapto (SCH₃), methanesulfonyl (SO₂CH₃), thiophenyl (SPh), or phenylsulfonyl (SO₂Ph), under acidic, neutral, or basic conditions
5 in an inert solvent. Basic conditions are preferred. Suitable bases include sodium hydrogen carbonate, sodium carbonate, trialkylamines (including, for example, triethylamine), sodium, and sodium hydride. Triethylamine is the preferred base. Suitable solvents include (C₁-C₄)alcohols, dioxane, diethyl ether, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidine. Ethanol is the preferred
10 solvent. The reaction is usually conducted at a temperature from about 25°C to about 154°C, preferably about 70°C to about 80°C.

Compounds of formula II can be prepared from a reduction of compounds of formula III in an inert solvent. This reduction can be mediated either by transition metals or other metal reducing agents. When a transition metal mediates the reduction,
15 a hydrogen source is also used. Suitable transition metals include palladium on carbon, palladium hydroxide on carbon, and platinum oxide. Palladium on carbon is preferred. Suitable hydrogen sources include hydrogen gas, ammonium formate, and formic acid. Hydrogen gas at a pressure of about one to about three atmospheres is the preferred hydrogen source. Three atmospheres of hydrogen gas is the preferred
20 pressure. Suitable solvents include (C₁-C₄)alcohols, acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidine. Ethanol is the preferred solvent. Other metal reducing agents include iron sulfate (FeSO₄) and zinc (metal)(Zn) in aqueous hydrochloric acid. Of this group, FeSO₄ is preferred. When FeSO₄ is the reducing agent, suitable solvents include aqueous ammonium hydroxide mixed with ethanol and
25 concentrated aqueous hydrochloric acid. Aqueous ammonium hydroxide (mixed with ethanol) is the preferred solvent. All of the above reduction reactions are usually conducted at a temperature of from about 25°C to about 100°C, preferably about 25°C to about 50°C. Compounds of formula II are used directly from the reduction reaction with no purification.

30 Compounds of formula I are prepared from the reaction of a compound of formula II with a formic acid synthon under neutral or acidic conditions in an inert solvent. Formic acid synthon refers to any molecule that is equivalent to formic acid such that it is capable of reacting with a nucleophile to produce a formyl residue.

Suitable formic acid synthons include dimethylformamide dimethylacetal, trimethyl orthoformate, triethyl orthoformate, ethoxymethylenemalononitrile, and diethyl ethoxymethylene malonate. Ethoxymethylenemalononitrile is the preferred formic acid synthon. While neutral conditions are preferred, suitable acid catalysts may accelerate the reaction. Suitable acid catalysts include *p*-toluenesulfonic acid, hydrochloric acid and acetic acid. Suitable solvents include (C₁-C₄)alcohols, dioxane, diethyl ether, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, and N-methylpyrrolidine. 2-Propanol is the preferred solvent. The reaction is usually conducted at a temperature of from about 25°C to about 154°C, preferably about 75°C to about 85°C.

10 Compounds of formula I wherein R² is hydrogen can be further modified to form additional compounds of formula I wherein R² is as described for formula I using methods known to those skilled in the art. For example, treatment of a compound of formula I wherein R² is hydrogen with a base (preferably an alkyl magnesium halide) in an inert solvent (preferably benzene) at a temperature from about 0°C to about 15 80°C, forms a basic indole salt. The indole salt, so formed, is capable of reacting with electrophiles (i.e., alkyl halides, Michael acceptors, isocyanides, ketone, aldehydes, acid chlorides, anhydrides) at the C3 position of the indole ring, in an inert solvent (preferably benzene) at a temperature from about 0°C to about 80°C leading to compounds of formula I wherein R² is (C₁-C₆)alkyl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷, -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle. Alternatively, a compound of formula I wherein either R¹ or R² is hydrogen can be reacted under neutral or acidic conditions with electrophiles leading to compounds of formula I wherein R¹ or R² may independently 25 be (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷, -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle. The procedures and conditions for carrying out these reactions are known to those skilled in the art, for example, in "Properties and Reactions of Indoles, Isoindoles, and Their Hydrogenated Derivatives," W. A. Reimers, in The Chemistry of Heterocyclic Compounds (A. Weissberger and E. C. Taylor, editors), Vol. 25, Part I (W. J. Houlihan, editor), Wiley-Interscience, New York (1972). pp.70-134, which is hereby 30 incorporated by reference in its entirety.

-15-

Compounds of formula IV and formula V are either commercially available or known to those skilled in the art.

Unless indicated otherwise, the pressure of each of the above reactions is not critical. Generally, the reactions will be conducted at a pressure of about one to about
5 three atmospheres, preferably at ambient pressure (about one atmosphere).

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the
10 reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen
15 mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The compounds of the formula I which are acidic in nature are capable of forming a wide variety of different salts with various inorganic and organic bases.
20 These salts are all prepared by conventional techniques well known to those of ordinary skill in the art. In general, these salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared
25 by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields of the desired final product.

30 The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as "the active compounds of the invention") are useful psychotherapeutics and have high affinity for benzodiazepine receptors in the central nervous system. The active compounds of the invention are agonists, partial

agonists, antagonists, partial antagonists, or reverse antagonists of the benzodiazepine receptor. The active compounds of the invention which are agonists may be used in the treatment of anxiety, and degenerative central nervous system disorders (e.g. Alzheimer's disease). The active compounds of the invention which are antagonists can
5 be used as anti-convulsants or for the treatment of prevention of seizures or memory loss. The active compounds of the invention which are partial or reverse antagonists may also be useful for memory enhancement.

The affinity of these compounds for benzodiazepine receptors may be measured in an in vitro receptor binding assay such as that described by P. Supavilai and M.
10 Karobath in Eur. J. Pharm., Vol. 70, 183 (1981).

An alternate in vitro receptor binding assay may be used in which guinea pig cerebellum can be the receptor source and [³H]flunitrazepam as the radioligand according to the following process. Either of the above two binding assays may be used to distinguish antagonists, agonists, partial or reverse antagonists and partial
15 agonists. The [³H]flunitrazepam assay is summarized below.

Male Hartley guinea pigs may be decapitated and the cerebellums removed by dissection. Each cerebellum may then be homogenized in 50 mMolar TRIS Acetate buffer (tris[hydroxymethyl]aminomethane acetate). The homogenate may then be centrifuged for 10 minutes at 40,000 g.

20 The supernatant may then be decanted and the residual pellet diluted with fresh TRIS Acetate buffer. The pellet may then be resuspended and then centrifuged again for 10 minutes at 40,000 g. The supernatant may then be decanted and the pellet washed one more time using the same procedure just described.

After the last wash cycle, the pellet may be resuspended in 50mM TRIS Acetate
25 buffer. The benzazepine binding of a compound of formula I can be determined by adding to a tube 750 μ l of the tissue suspension prepared according to the above methods with 100 μ l of drug or buffer, 150 μ l of [³H]-flunitrazepam such that the final concentration of the [³H]-flunitrazepam is 1 nM. The tissue, drug and flunitrazepam may then be incubated for 90 minutes at 0°C in the dark.

30 Non-specific binding may be determined by incubating the tissue with flunitrazepam and alprazolam (10 μ M) or chlordiazepoxide (10 μ M).

After 90 minutes, incubation may be terminated by rapid filtration under vacuum through glassfiber filters (eg., Whatman GF/B®) presoaked in 1% polyethyleneimine

(PEI) using a cell harvester. The filter may then be washed three times with ice cold 5mM TRIS Hydrochloride buffer (pH 7.2). The filters may then be placed in a scintillation vial and soaked in 6 mL of scintillation fluid and allowed to sit overnight.

After standing overnight, the vials may then be vortexed and the radioactivity
5 may be quantified by liquid scintillation counting according to methods well known in the art.

Percent inhibition of specific binding may be calculated for each dose of a compound of formula I. An IC_{50} value may then be calculated from the percent inhibition data. Active compounds of the invention are those which have an IC_{50} of less
10 than 250 nM for the benzodiazepine receptor as measured by either of the above procedures.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral
15 (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch,
20 polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for
25 example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g.
30 almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form (e.g., in ampules or in multi-dose containers), with an added preservative. The compositions
5 may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be formulated in powder form for reconstitution with a suitable vehicle, (e.g., sterile pyrogen-free water, before use).

10 The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, (e.g., containing conventional suppository bases such as cocoa butter or other glycerides).

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or
15 suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, (e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver
20 a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Appropriate dosages of the active compounds of the invention for oral,
25 parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above will generally range from about 0.1 mg to about 200 mg of the active ingredient per unit dose. Preferably, the unit dosage will range from about 1 mg to about 100 mg. Administration may be repeated, for example, 1 to 4 times per day. Variations may nevertheless occur depending upon the species of
30 animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger

-19-

doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

Aerosol formulations for treatment of the conditions referred to above (e.g.,
5 migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μ g to 1000 μ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times.

The following Examples illustrate the preparation of the compounds of the
10 present invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent and were obtained on a Bruker 300 MHz instrument. Chromatography refers to column chromatography performed using 32-63 μ m silica gel and executed under nitrogen pressure (flash
15 chromatography) conditions. Room temperature refers to 20-25°C.

Example 1

General Synthesis of 1-Indolyl-1H-benz[b]imidazoles and 1-Indolyl-1H-pyrido[4,5-b]imidazoles

A mixture of a 5-(2-nitroaryl-amino)-1H-indole (2.00 mmol) and 10% Palladium
20 (Pd) on carbon (20% by weight) in absolute ethanol (20 mL) was shaken under a hydrogen atmosphere (3 atm) at room temperature for 8 hours. The resulting reaction mixture was filtered through diatomaceous earth, Celite®, and the filtrate was evaporated under reduced pressure to afford crude 5-(2-aminoaryl-amino)-1H-indole, which was used directly.

25 Alternatively, a mixture of a 5-(2-nitroaryl-amino)-1H-indole (2.00 mmol) and iron sulfate (FeSO₄) (5.5g, 20 mmol, 10 equivalents) in ammonium hydroxide/water/ethanol [1:5:3, respectively, 27 mL total volume] was stirred at room temperature for 24 hours. The resulting reaction mixture was then filtered through diatomaceous earth, Celite®. The ethanol was removed from the filtrate by evaporation under reduced pressure. The
30 remaining aqueous mixture was extracted with methylene chloride (3 x 25 mL), and the organic extracts were combined, dried over magnesium sulfate (MgSO₄), and evaporated under reduced pressure to afford crude 5-(2-aminoaryl-amino)-1H-indole, which was used directly in the next step.

-20-

The 5-(2-aminoaryl-amino)-1H-indole was then combined with either dimethylformamide dimethylacetal (10 mL), triethyl orthoformate/formic acid (5 mL/5 mL), or ethoxymethylene-malononitrile (0.49 g, 4.01 mmol, 2.0 equivalents) in 2-propanol (10 mL) and heated at reflux under nitrogen for 1 to 24 hours, depending on the substrate. When dimethylformamide dimethylacetal was used, the reaction solvent is changed to toluene after 1 hour, a catalytic amount (5 mg) of *p*-toluenesulfonic acid was added, and the reaction solution was heated at reflux under nitrogen for 12-24 hours depending on the substrate. The resultant reaction solution was then evaporated under reduced pressure, and the residue was triturated or column chromatographed using silica gel (approximately 50 g) and an appropriate solvent system to afford the appropriate 1-indolyl-1H-benz[b]imidazole or 1-indolyl-1H-pyrido[4,5-b]imidazole.

Following this procedure the following compounds were prepared.

A. 5-Cyano-1-(indol-5-yl)benzimidazole

5-(4-Cyano-2-nitrophenyl-amino)-1H-indole (0.56 g, 2.0 mmoles) was reduced by catalytic hydrogenation, to form 5-(4-cyano-2-aminophenyl-amino)-1H-indole (0.50 g, 2.0 mmole). The 5-(4-cyano-2-aminophenyl-amino)-1H-indole was cyclized using ethoxymethylenemalononitrile (0.49 g, 2.0 mmoles) in propanol, and the cyclization reaction was heated for 24 hours. Column chromatography using ethyl acetate/hexanes [1:1] afforded the title compound (94%) as a yellow solid. Mp, 263.0-264.0° C; ¹³C NMR (DMSO-d₆) δ 147.2, 143.5, 137.5, 135.8, 128.5, 128.1, 127.3, 127.0, 125.3, 120.2, 118.2, 116.7, 113.1, 112.6, 104.8, 102.2; HRMS calculated for C₁₆H₁₀N₄ 258.0904, found 258.0904. Analytical calculated for C₁₆H₁₀N₄: C, 74.40; H, 3.90; N, 21.69. Found: C, 74.20; H, 3.92; N, 21.69.

B. 1-(indol-5-yl)-5-methylbenzimidazole

5-(4-Methyl-2-nitrophenyl-amino)-1H-indole (0.47 g, 2.0 mmoles) was reduced by catalytic hydrogenation to form 5-(4-methyl-2-aminophenyl-amino)-1H-indole (0.41 g, 2.0 mmoles). The 5-(4-methyl-2-aminophenyl-amino)-1H-indole was cyclized with ethoxymethylenemalononitrile (0.49 g, 2.0 mmole) in propanol, while being heated for 14 hours. Column chromatography using 10% ethyl acetate in methylene chloride afforded the title compound (81%) as a yellow solid. Mp, 215.0-216.0°C; R_f = 0.3 in 10% ethyl acetate in methylene chloride; ¹H NMR (DMSO-d₆) δ 11.43 (br s, NH), 8.42 (s, 1H), 7.76 (d, *J*=1.4 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 7.56 (d, *J*=0.5 Hz, 1H), 7.52 (t, *J*=2.6 Hz, 1H), 7.42 (d, *J*=8.3 Hz, 1H), 7.30 (dd, *J*=8.5 and 1.7 Hz, 1H), 7.12 (br d,

-21-

$J=8.3$ Hz, 1H), 6.56 (dd, $J=2.7$ and 0.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 156.5, 144.3, 143.8, 137.2, 134.0, 130.0, 129.1, 128.0, 126.4, 119.7, 119.0, 117.3, 113.4, 111.7, 103.0, 21.6; FAB LRMS (m/z, relative intensity) 249 (23), 248 ($[\text{MH}]^+$, 100); HRMS calculated for $\text{C}_{16}\text{H}_{13}\text{N}_3$ 247.1107, found 247.1092.

5

Example 25-Cyano-1-(3-formylindol-5-yl)benzimidazole

Phosphorus oxychloride (0.54 mL, 5.81 mmol, 1.5 eq) was added to dimethylformamide (10 mL) at room temperature, and to this solution was added 5-cyano-1-(indol-5-yl)benzimidazole (1.00 g, 3.87 mmol). The resulting reaction solution
10 was heated at 40°C under nitrogen for 2 hours. An aqueous solution of 10% sodium hydroxide (10 mL) was then added, followed by enough solid sodium hydroxide to adjust the pH to above 13. This mixture was heated at reflux under nitrogen for 1 hour, cooled, and the precipitated solid was filtered to afford the title compound (1.00 g, 90%) as an off-white solid. Mp, greater than 200°C; IR (KBr) 2225, 1675 cm^{-1} ; ^1H NMR
15 (DMSO- d_6) δ 10.00 (s, 1H), 8.82 (s, 1H), 8.49 (s, 1H), 8.38 (d, $J=0.7$ Hz, 1H), 8.26 (d, $J=2.0$ Hz, 1H), 7.78 (d, $J=8.6$ Hz, 1H), 7.73 (dd, $J=8.5$ and 1.4 Hz, 1H), 7.67 (d, $J=8.4$ Hz, 1H), 7.54 (dd, $J=8.6$ and 2.2 Hz, 1H); LRMS (m/z, relative intensity) 287 (18), 286 (M^+ , 100), 258 (18), 230 (11). HRMS calculated for $\text{C}_{17}\text{H}_{10}\text{N}_4\text{O}$: 286.0853. Found: 286.0870.

20

Example 35-Cyano-1-(3-(cyclohexen-1-yl)indol-5-yl)benzimidazole

A solution of sodium methoxide (0.25 g, 4.6 mmol, 3 equivalents), 5-cyano-1-(indol-5-yl)benzimidazole (0.40 g, 1.54 mmol), and cyclohexanone (0.175 mL, 1.69 mmol, 1.1 equivalents) in N,N-dimethylformamide (8 mL) was heated at 130°C under
25 nitrogen for 12 hours. The solvent was removed by evaporation under reduced pressure, and the residue was partitioned between ethyl acetate (25 mL) and water (25 mL). The organic layer was separated, dried (MgSO_4), and evaporated under reduced pressure. Column chromatography of the residue (0.16 g) using silica gel (approximately 5 g) and elution with ethyl acetate/hexanes [1:1] afforded the title
30 compound (19%) as a pale yellow solid. $R_f = 0.3$ in ethyl acetate/hexanes [1:1]; ^1H NMR (CDCl_3) δ 10.35 (br s, 1H), 8.18 (s, 1H), 8.05 (s, 1H), 7.80 (s, 1H), 7.45-7.43 (m, 3H), 7.21 (s, 1H), 7.07 (dd, $J=8.5$ and 1.9 Hz, 1H), 6.04 (br m, 1H), 2.32 (br m, 2H), 2.08 (br m, 2H), 1.72-1.60 (m, 2H), 1.60-1.50 (m, 2H); ^{13}C NMR (CDCl_3) δ 145.7, 142.4,

-22-

137.5, 136.7, 130.9, 126.8, 125.7, 124.8, 123.8, 123.6, 122.5, 119.5, 119.2, 118.2, 117.2, 112.7, 112.1, 105.6, 28.4, 25.5, 22.9, 22.2.

Example 4

1-(3-Formylindol-5-yl)-1H-pyrido[4,5-b]imidazole

5 A mixture of 5-(3-nitropyrid-2-ylamino)-1H-indole (5.50 g, 21.63 mmol) and 10% palladium on carbon (1.00 g) in absolute ethanol (75 mL) was shaken under a hydrogen atmosphere (3 atm) for 5 hours. The resulting mixture was filtered through Celite®, and the filtrate was evaporated under reduced pressure. The residue (4.95 g) was dissolved in dimethylformamide dimethylacetal (25 mL), and the resulting solution
10 was heated at reflux under nitrogen for 12 hours. The resulting reaction solution was evaporated under reduced pressure, and the residue was suspended in a solution of 10% aqueous sodium hydroxide and ethanol (5:1, respectively, 75 mL). The resulting mixture was heated at reflux under nitrogen for 3 hours. The pH of this mixture was adjusted to pH 7 with concentrated hydrochloric acid (HCl) followed by a saturated
15 solution of sodium hydrogen carbonate. The resulting aqueous mixture was extracted with ethyl acetate (3 times 75 mL). The organic extracts were combined, dried (MgSO₄), and evaporated under reduced pressure. The residue was adhered to silica gel (approximately 10 g) using methanol, and this mixture was placed on top of a silica gel plug (200 g). A solution of 5% methanol in ethyl acetate 5 Liters (L) was passed
20 through this silica gel filter. The last 3L of solvent was evaporated under reduced pressure. Trituration of the residue in hot ethyl acetate afforded the title compound (1.54 g, 29%) as an off-white powder. Mp, >280°C; R_f = 0.2 in ethyl acetate; ¹H NMR (DMSO-d₆) δ 12.45 (br s, NH), 9.99 (s, 1H), 8.86 (s, 1H), 8.51 (d, J=1.8 Hz, 1H), 8.45 (s, 1H), 8.43 (dd, J=4.7 and 1.5 Hz, 1H), 8.22 (dd, J=8.0 and 1.5 Hz, 1H), 7.73 (d, J=8.7 Hz, 1H), 7.69 (dd, J=8.7 and 1.9 Hz, 1H), 7.39 (dd, J=8.0 and 4.7 Hz, 1H);
25 LRMS (m/z, relative intensity) 263 (19), 262 (M⁺, 100), 234 (57), 233 (37), 206 (17). Analytical calculated for C₁₅H₁₀N₄O · 0.25 H₂O: C, 67.54; H, 3.97; N, 21.00. Found: C, 67.82; H, 3.99; N, 20.68.

Example 5

1-(3-(Cyclohexen-1-yl)indol-5-yl)-5-methylbenzimidazole

30 To a stirred solution of sodium (0.325 g, 14.2 mmol, 7.0 equivalents) in absolute methanol (10 mL) was added 1-(indol-5-yl)-5-methylbenzimidazole (0.500 g, 2.02 mmol) and cyclohexanone (0.84 mL, 8.08 mmol, 4.0 equivalents), and the resulting reaction

-23-

solution was heated at reflux under nitrogen for 12 hours. The resulting mixture was evaporated under reduced pressure, and the residue was column chromatographed using silica gel (approximately 25 g) and eluted with 20% ethyl acetate in methylene chloride to afford the title compound (0.160 g, 0.49 mmol, 24%) as a pale yellow foam.

5 Mp, 101.0-102.0°C; R_f = 0.75 in 5% MeOH in methylene chloride; $^1\text{H NMR}$ (CD_3OD) d 8.25 (s, 1H), 7.88 (s, 1H), 7.53-7.50 (m, 2H), 7.35-7.33 (m, 2H), 7.21 (br d, $J=8.5$ Hz, 1H), 7.12 (d, $J=8.2$ Hz, 1H), 6.14 (br m, 1H), 4.90 (s, 1 exchangeable H), 2.46 (s, 3H), 2.19 (br m, 2H), 1.86-1.75 (m, 2H), 1.75-1.63 (m, 2H); IR (KBr) 2929, 2859, 1615, 1579, 1494, 1447 cm^{-1} .

10

Example 6

1-(3-Cyclohexylindol-5-yl)-5-methylbenzimidazole

A mixture of 1-(3-(cyclohexen-1-yl)indol-5-yl)-5-methylbenzimidazole (0.110 g, 0.34 mmol), 10% Pd on carbon (0.027 g), and absolute ethanol (2 mL) was shaken under an atmosphere of hydrogen (3 atm) for 72 hours. The resulting reaction mixture
15 was filtered through Celite®, and the filtrate was evaporated under reduced pressure to afford the title compound (0.090 g, 80%) as a dark brown foam. Mp, decomposes 120°C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$) d 11.5 (br s, NH), 8.41 (s, 1H), 7.73 (s, 1H), 7.56-7.52 (m, 2H), 7.39 (d, $J=8.4$ Hz, 1H), 7.27-7.24 (m, 2H), 7.13 (d, $J=8.0$ Hz, 1H), 2.88-2.75 (m, 1H), 2.45 (s, 3H), 2.10-1.60 (m, 10 H); IR (KBr) 2924, 2851, 1612, 1580, 1492, 1447
20 cm^{-1} ; FAB LRMS (m/z , relative intensity) 331 (25), 330 ($[\text{MH}]^+$, 100). HRMS calculated for $\text{C}_{22}\text{H}_{23}\text{N}_3$: 329.1887. Found: 329.1874.

Example 7

1-(3-Benzoylindol-5-yl)-5-methylbenzimidazole

To a stirred solution of 1-(indol-5-yl)-5-methylbenzimidazole (1.00 g, 4.04 mmol,
25 2.0 equivalents) in anhydrous benzene (10 mL) at 0°C under nitrogen was added a solution of ethyl magnesium bromide in ether (3.0 M, 1.33 mL, 4.00 mmol, 2.0 equivalents) dropwise, and the resulting reaction solution was stirred at 0°C under nitrogen for 30 minutes. Then, benzoyl chloride (0.23 mL, 1.98 mmol) was added dropwise rapidly to the reaction solution, and the resulting mixture was stirred at room
30 temperature under nitrogen for 30 min. A saturated solution of sodium hydrogen carbonate (25 mL) was then added to the reaction mixture, and the resulting aqueous mixture was extracted with ethyl acetate (2 x 25 mL). The extracts were combined, dried (MgSO_4), and evaporated under reduced pressure. The residue (2.1 g) was

-24-

column chromatographed using silica gel (approximately 100 g) and eluted with ethyl acetate/hexanes (1:1) to afford the title compound (0.045 g, 0.13 mmol, 6%) as a white foam. $R_f = 0.65$ in ethyl acetate/hexanes (1:1); $^1\text{H NMR}$ (CD_3OD) δ 8.05-7.95 (m, 3H), 7.81 (d, $J=6.8$ Hz, 1H), 7.71 (d, $J=8.5$ Hz, 1H), 7.61-7.39 (m, 7H), 7.18 (d, $J=8.4$ Hz, 1H), 2.48 (s, 3H); FAB LRMS (m/z , relative intensity) 352 ($[\text{MH}]^+$, 78%), 248 ($[\text{MH}]^+$ -Ph(CO), 100).

Example 8

General Synthesis of 5-(2-Nitroaryl-amino)-1H-indoles

A solution of the 5-amino-1H-indole (2.00 mmol), a 2-nitrohaloarene (3.00 mmol, 1.5 eq), and a base (3.00 mmol) in an appropriate inert solvent (10 mL) was heated at reflux under nitrogen for 1 to 24 hours, depending on the substrate. The solvents were evaporated under reduced pressure, and the residue was column chromatographed using silica gel (approximately 50 g) and eluted with an appropriate solvent system to afford the 5-(2-nitroaryl-amino)-1H-indole derivative. In some cases recrystallization of the solid obtained from chromatography was performed to obtain analytically pure samples of the appropriate 5-(2-nitroaryl-amino)-1H-indole.

Following this procedure the following compounds were prepared.

A. 5-(4-Cyano-2-nitrophenyl-amino)-1H-indole

5-Aminoindole (0.264 g, 2.00 mmoles) and 4-chloro-3-nitrobenzotrile (0.444 g, 3.00 mmoles) were combined with triethylamine (0.42 ml, 3.01 mmoles) in absolute ethanol and the reaction was heated at reflux under nitrogen for 3 hours. After evaporation of the solvent, the residue was chromatographed using ether/hexanes [1:1] to afford the title compound (79%) as a red amorphous solid. Mp, decomposes 134°C ; $^{13}\text{C NMR}$ ($\text{DMSO}-d_6$) δ 146.9, 137.3, 134.8, 131.9, 131.3, 128.9, 128.3, 126.9, 119.8, 118.2, 117.9, 117.2, 112.5, 101.5, 97.4; LRMS (m/z , relative intensity) 278 (M^+ , 100), 261 (31), 244 (73), 231 (78). HRMS calculated for $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}_2$: 278.0802. Found: 278.0808. Analytical calculated for $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}_2$: C, 64.74; H, 3.62; N, 20.13. Found: 64.84; H, 3.57; N, 20.13.

B. 5-(4-Methyl-2-nitrophenyl-amino)-1H-indole

5-Aminoindole (0.264 g, 2.00 mmoles) and 4-fluoro-3-nitrotoluene (0.465 g, 3.00 mmoles) were combined with triethylamine (0.42 ml, 3.01 mmoles) in which 4-fluoro-3-nitrotoluene was the only solvent and the reaction was heated at 225°C under nitrogen for 18 hours. Chromatography using ether/hexanes [1:1] afforded the title compound

-25-

(90%) as a red amorphous solid. Mp, decomposes 94°C; R_f = 0.55 in ethyl acetate/hexanes [1:1]; ^{13}C NMR (CDCl_3) δ 143.4, 137.3, 134.2, 131.8, 131.1, 128.7, 126.1, 125.6, 120.8, 117.9, 116.2, 112.1, 102.8, 20.1; LRMS (m/z, relative intensity) 267 (M^+ , 45), 250 (5), 233 (20), 220 (13). HRMS calculated for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: 267.1005.

5 Found: 267.0993.

C. 5-(3-Nitropyrid-2-ylamino)-1H-indole

5-Aminoindole (0.264 g, 2.00 mmoles) and 2-chloro-3-nitropyridine (0.476 g, 3.00 mmoles) were combined with triethylamine (0.42 ml, 3.01 mmoles) in absolute ethanol. The reaction was heated at room temperature under nitrogen for 72 hours.

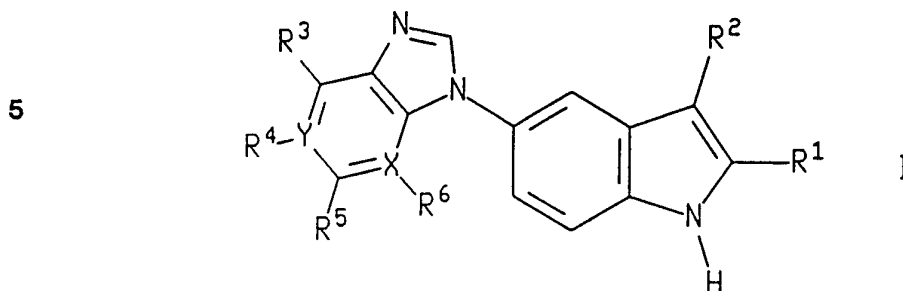
10 The resulting reaction mixture was filtered to afford the title compound (69%) as a dark red solid. Mp, 162.0-163.5°C; R_f = 0.6 in diethyl ether; ^{13}C NMR (DMSO-d_6) δ 155.6, 150.5, 135.5, 133.5, 129.7, 127.9, 127.6, 125.9, 118.5, 115.0, 113.4, 111.2, 101.2. Analytical calculated for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$: C, 61.41; H, 3.96; N, 22.04. Found: 61.22; H, 3.80; N, 22.08.

15

-26-

CLAIMS

1. A compound of the formula



- 10 wherein X and Y are independently carbon or nitrogen;

R¹ and R² are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷, -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle;

- 15 wherein said unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 20 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused 25 heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

30 $\begin{array}{cccc} \text{O} & \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel & \parallel \\ -\text{CO}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CNH}_2, & -\text{CNH}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CN-di}(\text{C}_1-\text{C}_5)\text{alkyl}, \text{ and formyl;} \end{array}$

-27-

wherein said aryl groups and the aryl moieties of said (C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

5 R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -CN, -CHO, CO₂R⁹, -NO₂, -CONR⁹R¹⁰, -(CH₂)_pOH, -(CH₂)_pOR⁹, -(CH₂)_pNR⁹R¹⁰ and halogen; wherein said aryl groups and the aryl moieties of said -(C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents
10 independently selected from (C₁-C₄)alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

 R⁷, R⁸, R⁹, and R¹⁰ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said
15 unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl,
20 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolyl, cinnolyl
25 and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo, chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-
30 C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

-28-

$\begin{array}{cccc} \text{O} & & \text{O} & \text{O} & \text{O} \\ || & & || & || & || \\ -\text{CO}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CNH}_2, & -\text{CNH}(\text{C}_1-\text{C}_5)\text{alkyl}, & -\text{CN-di}(\text{C}_1-\text{C}_5)\text{alkyl}, & \text{and formyl;} \end{array}$

- 5 wherein said aryl groups and the aryl moieties of said $-(\text{C}_1-\text{C}_3)\text{alkylaryl}$ groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from $(\text{C}_1-\text{C}_4)\text{alkyl}$, halogen, hydroxy, cyano, carboxamido, nitro, and $(\text{C}_1-\text{C}_4)\text{alkoxy}$;
- n is 0, 1, 2, or 3; and
- 10 p is 0, 1, or 2;
- and the pharmaceutically accepted salts thereof.
2. A compound according to claim 1, wherein X is carbon; Y is carbon and R_1 is hydrogen.
3. A compound according to claim 1, said compound being selected from:
- 15 5-cyano-1-(indol-5-yl)benzimidazole;
- 5-cyano-1-(3-formylindol-5-yl)benzimidazole;
- 1-(indol-5-yl)-5-methylbenzimidazole;
- 5-cyano-1-(3-(cyclohexen-1-yl)indol-5-yl)benzimidazole;
- 1-(3-formylindol-5-yl)-1H-pyrido[4,5-b]imidazole;
- 20 1-(3-(cyclohexen-1-yl)indol-5-yl)-5-methylbenzimidazole;
- 1-(3-cyclohexylindol-5-yl)-5-methylbenzimidazole; and
- 1-(3-benzoylindol-5-yl)-5-methylbenzimidazole;
- and the pharmaceutically acceptable salts thereof.
4. A method for treating or preventing a condition selected from anxiety,
- 25 panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, comprising administering to said mammal requiring such treatment or prevention an amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof, effective in treating or preventing such condition or disorder.
5. A pharmaceutical composition for treating or preventing a condition or
- 30 disorder selected from anxiety, panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, comprising an amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof, effective in treating or preventing such condition or disorder and a pharmaceutically acceptable carrier.

6. A method for treating or preventing a condition or disorder arising from an increase or decrease in benzodiazepine receptor neurotransmission in a mammal, comprising administering to said mammal requiring such treatment or prevention an amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof, effective in treating or preventing such condition or disorder.

7. A pharmaceutical composition for treating or preventing a condition or disorder arising from an increase or decrease in benzodiazepine receptor neurotransmission in a mammal, comprising an amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof, effective in treating or preventing such a condition or disorder and a pharmaceutically acceptable carrier.

8. A method of antagonizing or agonizing the benzodiazepine receptor in a mammal, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof.

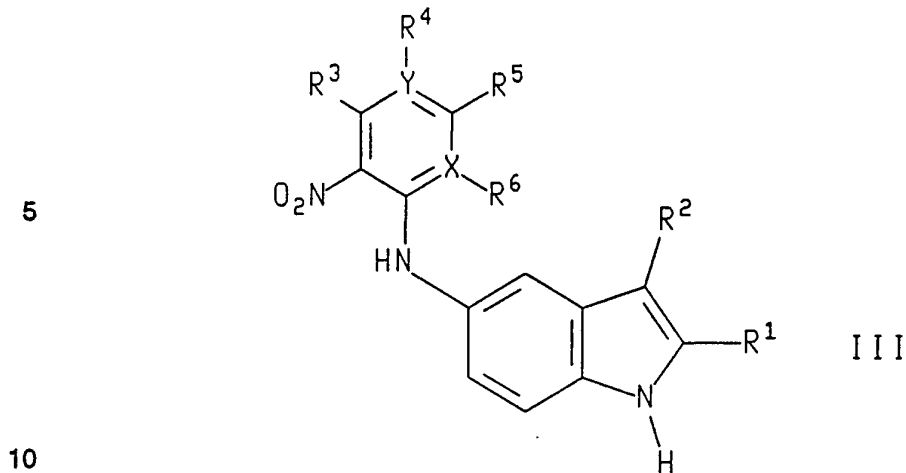
9. A pharmaceutical composition for antagonizing or agonizing the benzodiazepine receptor in a mammal, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof and a pharmaceutically acceptable carrier.

10. A method for treating or preventing a condition or disorder selected from anxiety, panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof.

11. A pharmaceutical composition for treating or preventing a disorder or condition selected from anxiety, panic attacks, sleep disorders, seizures, memory loss, convulsions, and drug abuse in a mammal, comprising administering to said mammal a benzodiazepine receptor antagonizing or agonizing amount of a compound according to claim 1, or the pharmaceutically accepted salts thereof and a pharmaceutically acceptable carrier.

12. A compound of the formula

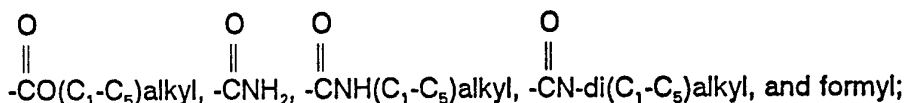
-30-



wherein X and Y are independently carbon or nitrogen;

R¹ and R² are independently selected from hydrogen, (C₁-C₆)alkyl, aryl, -(C₁-C₃)alkylaryl, -(CH₂)_n-(C₄-C₇)cycloalkyl, -(CH₂)_nCHO, -(CH₂)_nCO₂R⁷,
 15 -(CH₂)_nCONR⁷R⁸, 3-succinamido, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl,
 25 thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxaliny, quinazolinyl, cinnolinyl and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused heterocycle may optionally be substituted on one or more ring carbon atoms with from zero to three substituents, said substituents being independently selected from bromo,
 30 chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,

-31-

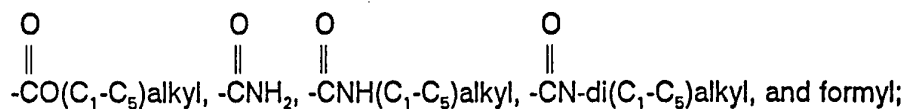


5 wherein said aryl groups and the aryl moieties of said (C₁-C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from (C₁-C₄)alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and (C₁-C₄)alkoxy;

R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl,
 10 -(C₁-C₃)alkylaryl, -CN, -CHO, CO₂R⁹, -NO₂, -CONR⁹R¹⁰, -(CH₂)_pOH, -(CH₂)_pOR⁹,
 -(CH₂)_pNR⁹R¹⁰ and halogen; wherein said aryl groups and the aryl moieties of said -(C₁-
 C₃)alkylaryl groups are independently selected from phenyl and substituted phenyl,
 wherein said substituted phenyl may be substituted with from one to three substituents
 independently selected from (C₁-C₄)alkyl, halogen, hydroxy, cyano, carboxamido, nitro,
 15 and (C₁-C₄)alkoxy;

R⁷, R⁸, R⁹, and R¹⁰ are independently selected from hydrogen, (C₁-C₆)alkyl, aryl,
 -(C₁-C₃)alkylaryl, unsaturated heterocycle, benzo-fused heterocycle, -(C₁-C₃)alkyl-
 unsaturated heterocycle, and -(C₁-C₃)alkyl-benzo-fused heterocycle; wherein said
 unsaturated heterocycle and unsaturated heterocycle moiety of said -(C₁-C₃)alkyl-
 20 unsaturated heterocycle are selected independently from pyrrolyl, furyl, thienyl, oxazolyl,
 isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-
 oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl,
 pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl,
 1,2,5-oxathiazinyl, and 1,2,6-oxathiazinyl; wherein said benzo-fused heterocycle and the
 25 benzo-fused heterocyclic moiety of said -(C₁-C₃)alkyl-benzo-fused heterocycle are
 selected independently from benzoxazolyl, benzothiazolyl, benzimidazolyl,
 thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl,
 indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxaliny, quinazoliny, cinnolinyl
 and benzoxazinyl; wherein each of said unsaturated heterocycle, benzo-fused
 30 heterocycle, -(C₁-C₃)alkyl-unsaturated heterocycle and -(C₁-C₃)alkyl-benzo-fused
 heterocycle may optionally be substituted on one or more ring carbon atoms with from
 zero to three substituents, said substituents being independently selected from bromo,
 chloro, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₅)alkylthio, (C₁-C₅)alkylamino, (C₁-
 C₄)alkylsulfonyl, (C₁-C₅)dialkylamino, hydroxy, amino, nitro, cyano, trifluoromethyl,
 35

-32-



- 5 wherein said aryl groups and the aryl moieties of said $-(\text{C}_1\text{-C}_3)\text{arylaryl}$ groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with from one to three substituents independently selected from $(\text{C}_1\text{-C}_4)\text{alkyl}$, halogen, hydroxy, cyano, carboxamido, nitro, and $(\text{C}_1\text{-C}_4)\text{alkoxy}$;
- n is 0, 1, 2, or 3; and
- 10 p is 0, 1, or 2.
13. A compound according to claim 12 wherein X is carbon; Y is carbon and R_1 is hydrogen.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/IB 94/00407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/04 A61K31/395 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 066 654 (A.H. ROBINS COMPANY, INC.) 19 November 1991 * column 1-2 *	1,7
A	WO,A,93 23396 (MERCK SHARP & DOHME LTD.) 25 November 1993 see claims	1
P,X	WO,A,94 10171 (PFIZER INC.) 11 May 1994 * claims ; page 8, formula III, page 11, formula VIII *	1,7,12, 13

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document but published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
O document referring to an oral disclosure, use, exhibition or other means	*&* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 10 January 1995	Date of mailing of the international search report 20. 01 95
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Van Bijlen, H
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 94/00407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 4,6,8 and 10 are directed to a method of treatment of

(diagnostic method practised on) the human/animal body, the search has been
carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/IB 94/00407

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