

12 **EUROPEAN PATENT APPLICATION**

21 Application number: **88112408.5**

51 Int. Cl.4: **C07D 231/56 , C07F 9/65 ,  
C07D 295/18 , A61K 31/415**

22 Date of filing: **30.07.88**

30 Priority: **07.08.87 US 82760**

43 Date of publication of application:  
**08.02.89 Bulletin 89/06**

64 Designated Contracting States:  
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

71 Applicant: **HOECHST-ROUSSEL  
PHARMACEUTICALS INCORPORATED  
Route 202-206 North  
Somerville New Jersey 08876(US)**

72 Inventor: **Strupczewski, Joseph Thomas  
Stewart Lane 4  
Flemington, N.J. 08822(US)**

74 Representative: **Tergau, Ulrich, Dr.  
HOECHST AKTIENGESELLSCHAFT Zentrale  
Patentabteilung Postfach 80 03 20  
D-6230 Frankfurt am Main 80(DE)**

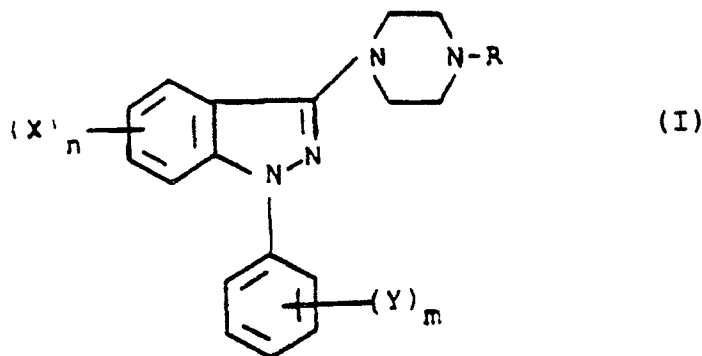
54 **1-Phenyl-3-(1-piperazinyl)-1H-indazoles, a process and intermediates for their preparation, and the use thereof as medicaments.**

57 The present invention relates to novel 1-phenyl-3-(1-piperazinyl)-1H-indazoles and intermediates and a process for the preparation thereof. The compounds according to the invention exhibit analgesic, anti-convulsive and anti-depressant activities, and can therefore be used as medicaments.

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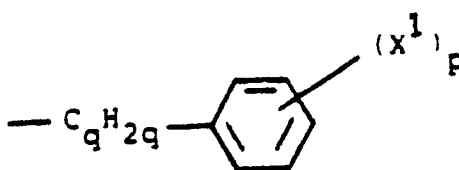
1-Phenyl-3-(1-piperazinyl)-1H-indazoles, a process and intermediates for their preparation, and the use thereof as medicaments

This invention relates to 1-phenyl-3-(1-piperazinyl)-1H-indazoles of the formula I



wherein n is an integer having a value of 0 or 1; m is an integer having a value of 0 to 2, inclusive; X and Y are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, wherein for each value of m, Y may be the same or different; and

20 R is hydrogen, loweralkyl, cycloalkyl, loweralkenyl, hydroxyloweralkyl, diloweralkylaminoloweralkyl, diloweralkylphosphinyloweralkyl, cyano, loweralkoxycarbonyl, loweralkanoyl, aminocarbonyl, loweralkylaminocarbonyl, or a group of the formula

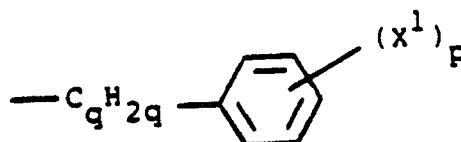


wherein q is an integer having a value of 0 to 5, inclusive, X' is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, and p is an integer having a value of 0 to 5, inclusive, X' is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, and p is an integer having a value of 0 to 2 inclusive, wherein for each value of p, X' may be the same or different; the geometrical isomers, optical antipodes or pharmaceutically acceptable acid addition salts thereof, which are useful for alleviating pain, treating convulsions, and treating depression, alone or in combination with inert adjuvants.

35 Preferred 1-phenyl-3-(1-piperazinyl)-1H-indazoles of this invention are those Formula I compounds wherein R is hydrogen, loweralkyl, cycloalkyl, loweralkenyl, loweralkanoyl, diloweralkylphosphinyl-loweralkyl, aminocarbonyl, loweralkylaminocarbonyl, or diloweralkylaminoloweralkyl. Most preferred 1-phenyl-3-(1-piperazinyl)-1H-indazoles are those Formula I compounds wherein R is hydrogen or loweralkyl.

Subgeneric to the 1-phenyl-3-(1-piperazinyl)-1H-indazoles of this invention are Formula I compounds wherein:

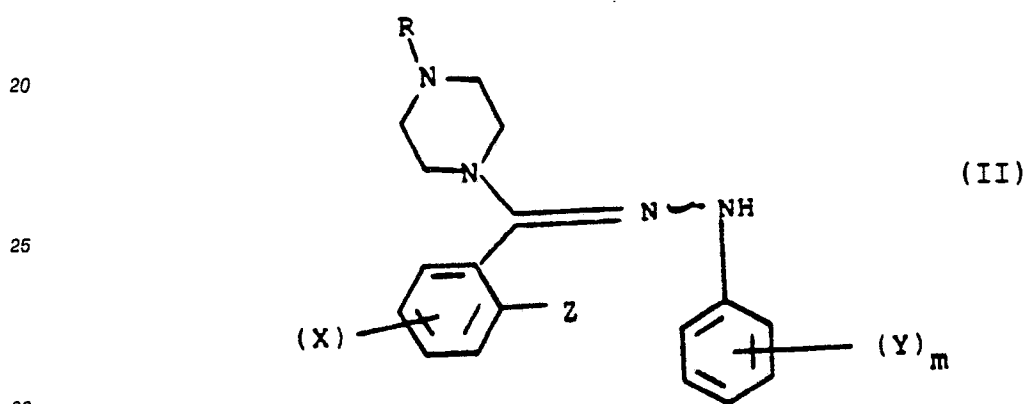
- 45 (a) R is hydrogen, loweralkyl, loweralkenyl, or cycloalkyl; (b) R is



wherein  $q$  is an integer having a value of 0 to 5, inclusive,  $X^1$  is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, and  $p$  is an integer having a value of 0 to 2, inclusive, wherein for each value of  $p$ ,  $X^1$  may be the same or different;

- 5 (c) R is cyano;  
 (d) R is hydroxyalkyl;  
 (e) R is diloweralkylaminoloweralkyl;  
 (f) R is diloweralkylphosphinyloweralkyl;  
 (g) R is loweralkoxycarbonyl;  
 10 (h) R is aminocarbonyl or loweralkylaminocarbonyl;  
 (i) R is loweralkanoyl;  
 (j)  $m$  is 0 or 1;  
 (k) Y is fluorine or chlorine; and  
 (l) Y is trifluoromethyl.

15 In a further embodiment, this invention relates to 1-[(phenylhydrazono) (phenyl)methyl]piperazines of the formula II



wherein R is loweralkyl, loweralkoxycarbonyl, or a group of the formula



wherein

$X^1$  is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl, and  $p$  is an integer having a value of 0 to 2 inclusive, wherein for each value of  $p$ ,  $X^1$  may be the same or different; X and Y are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl;  $n$  is an integer having a value of 0 or 1;  $m$  is an integer having a value of 0 to 2, inclusive; wherein for each value of  $m$ , Y may be the same or different; and Z is fluorine; the geometrical isomers, optical antipodes, or pharmaceutically acceptable acid addition salts thereof.

Subgeneric to the 1-[(phenylhydrazono) (phenyl)methyl]piperazines of Formula II are those compounds wherein R is loweralkyl, loweralkoxycarbonyl, or phenyl.

As used throughout the specification and appended claims, the following definitions shall apply:

"Loweralkyl" - a linear or branched, acyclic hydrocarbon radical containing no unsaturation and having the formula  $-C_xH_{2x+1}$  wherein  $x$  is an integer having a value of 1 to 7 inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 2-pentyl, 3-hexyl, 4-heptyl, and the like. Preferred loweralkyls are those radicals wherein  $x$  has a value of 1 to 3 inclusive, most preferably 1 or 2.

"Loweralkenyl" - a linear or branched, acyclic hydrocarbon radical having one olefinic bond and represented by the formula:  $-C_xH_{2x-1}$ , wherein  $x$  is an integer having a value of 3 to 7 inclusive, such as 2-propenyl, 3-butenyl, 3-pentenyl, 3-hexenyl, 6-heptenyl, and the like. Preferred loweralkenyls are those

radicals wherein x has a value of 3 to 5 inclusive, and, most preferably, is 3.

"Cycloalkyl" - a cyclic hydrocarbon radical of the formula  $-C_xH_{2x-1}$  wherein x has a value of 3 to 7 inclusive, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Preferred cycloalkyls are those radicals wherein x has a value of 3 to 6 inclusive, and, most preferably, is 3.

5 "Loweralkoxy" - an acyclic organic radical of the formula  $-OC_xH_{2x+1}$  wherein x is an integer having a value of 1 to 7 inclusive, such as methoxy, ethoxy, 1- and 2-propoxy, 1,2-dimethylethoxy, 1-butoxy, 1- and 2-pentoxy, 3-hexoxy, 4-heptoxy and the like. Preferred loweralkoxys are those radicals wherein x has a value of 1 to 5 inclusive, most preferably, 1 to 3 inclusive.

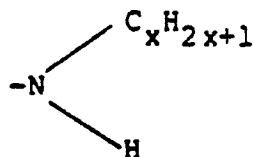
10 "Loweralkylthio" - an acyclic organic radical of the formula  $-SC_xH_{2x+1}$  wherein x is an integer having a value of 1 to 7 inclusive, such as methylthio, ethylthio, 1- and 2-propylthio, 1-butylthio 1- and 2-pentylthio, 3-hexylthio, 4-heptylthio, and the like. Preferred loweralkylthios are those radicals wherein x has a value of 1 to 3 inclusive and, most preferably, is 1 or 2.

15 "Loweralkoxycarbonyl" - an acyclic organic radical of the formula  $-C(O)OC_xH_{2x+1}$  wherein x is an integer having a value from 1 to 5 inclusive, such as methoxycarbonyl, ethoxycarbonyl, 1- and 2-propoxycarbonyl, 1-butoxycarbonyl, 1- and 2-pentoxycarbonyl and the like. Preferred loweralkoxycarbonyls are those radicals wherein x has a value of 1 to 4 inclusive, and most preferably, is 1 or 2.

"Halogen" - a member of the group consisting of fluorine, chlorine, bromine or iodine radicals. Preferred halogens are fluorine or chlorine radicals.

"Loweralkylamino" - an acyclic organic radical of the formula

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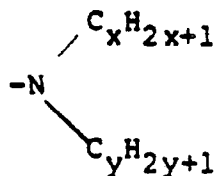
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wherein x is an integer having a value of 1 to 7 inclusive, such as methylamino, ethylamino, 2-propylamino, 1-butylamino, 2-pentylamino, 3-hexylamino, 1-heptylamino, and the like. Preferred loweralkylaminos are those radicals wherein x has a value of 1 to 3 inclusive, and most preferably is 1.

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"Diloweralkylamino" - an acyclic organic radical of the formula

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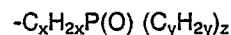


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wherein x and y are independently integers having values of 1 to 7 inclusive, such as dimethylamino, diethylamino, N,N-methylethylamino, N,N-di(2-propyl)amino, N,N-di(1-butyl)amino, N,N-di(2-pentyl)amino, N,N-di(3-hexyl)amino, N,N-di(1-heptyl)amino, and the like. Preferred diloweralkylaminos are those radicals wherein x and y have values of 1 to 3 inclusive, and most preferably, are 1.

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"Diloweralkylphosphinyloweralkyl" - an acyclic organic radical of the formula



wherein x and y are independently integers having values of 1 to 7 inclusive, and z is an integer having a value of 2, wherein for each z, y may be the same or different, such as (dimethyl)phosphinylmethyl, (dimethyl)phosphinylethyl, (diethyl)phosphinylmethyl, di(2-propyl)phosphinylmethyl, di(1-butyl)phosphinylmethyl, di(2-pentyl)phosphinylmethyl, di(3-hexyl)phosphinylethyl, di(1-heptyl)phosphinylethyl, and the like. Preferred diloweralkylphosphinyloweralkyls are those radicals wherein x and y have values of 1 or 2, and most preferably are 1.

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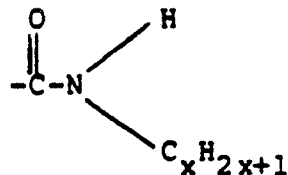
55 "Loweralkanoic acid" - a compound formed by the combination of a carboxyl group with a hydrogen atom or a loweralkyl as previously defined. Examples of loweralkanoic acids are formic, acetic, propionic, 2,2-dimethylacetic, pentanoic, hexanoic, heptanoic, octanoic acid, and the like.

"Loweralkanoyl" - a radical formed by the removal of the hydroxyl function from a loweralkanoic acid.

Exemplary of such radicals are formyl, acetyl, propionyl, 2,2-dimethylacetyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, and the like. Preferred loweralkanoyls are those radicals formed by the removal of the hydroxyl function from alkanic acids having up to 2, most preferably 1, carbon atom(s).

"Aminocarbonyl" - an organic radical of the formula  $-C(O)NH_2$ .

5 "Loweralkylaminocarbonyl" - an organic radical of the formula



15 wherein x is an integer having a value of 1 to 7, inclusive. Preferred loweralkylaminocarbonyls are those radicals wherein x has a value of 1 to 3 inclusive, and most preferably is 1.

To prepare the 1-[(phenylhydrazono)(phenyl)methyl]piperazines of Formula II, a phenylhydrazine 1 is condensed with a 2-fluoro- or 2-chlorobenzoyl halide 2 to form a 2-fluoro- or 2-chlorobenzoic acid hydrazide 3 which is converted to a chlorophenylhydrazone 4 and reacted with a piperazine 5, to form a 1-[(phenylhydrazono)(phenyl)methyl]piperazine 6. See Reaction Scheme A.

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The condensation of a phenylhydrazine 1 with a 2-chloro or 2-fluorobenzoyl halide 2 is accomplished by conventional methods such as are well known in the art. In general, the phenylhydrazine 1 and benzoyl halide 2 are reacted in the presence of a weakly basic organic solvent at a temperature of from about 0 °C to about 20 °C to form a benzoic acid hydrazide 3. Preferred reaction temperatures are subject to variation depending upon the reactivity of the particular starting materials employed. In order to control the rate of reaction between the benzoyl halide 2 and the phenylhydrazine 1, it is recommended that the benzoyl chloride be added to the phenylhydrazine in a dropwise fashion. Among the benzoyl halides there may be mentioned 2-fluorobenzoyl chlorides, 2-chlorobenzoyl chlorides, 2-fluorobenzoyl bromides, and 2-chlorobenzoyl bromides, with 2-fluorobenzoyl chlorides being preferred. Suitable solvents include heterocyclic amines such as pyridine, lutidine, collidine, picoline, and the like. Pyridine is preferred. If desired, the condensation may be conducted in the presence of an inert organic cosolvent such as, a halocarbon, for example, chloroform, methylene chloride, carbon tetrachloride, and the like. The reaction of phenylhydrazine with benzoyl chloride is described for example, in Green, B. et al. *Tetrahedron*, 34, 1633-1639 (1978).

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The chlorination of the benzoic acid hydrazide 3 is well known in the art and is described for example, in Huisgen, R. et al. *Tetrahedron*, 17, 3, 18 (1962). Among the chlorinating agents there may be mentioned phosphorous oxychloride, phosphorous pentachloride, and the like. Phosphorous pentachloride is preferred. Among the solvents suitable for the chlorination reaction are ethereal solvents such as 1,2-dimethoxyethane, bis(2-methoxyethyl) ether, diethyl ether, tetrahydrofuran and the like; inert halocarbons such as chloroform, carbon tetrachloride, methylene chloride, and the like, and mixtures thereof. Diethyl ether is preferred. Recommended temperatures for the reaction of the benzoic acid hydrazide 3 with the chlorinating agent range from about 30 °C to about 100 °C, with temperatures of from about 30 °C to about 65 °C being preferred. Upon completion of the reaction it is generally desirable to treat the reaction medium with an ethereal solution of phenol in order to generate the chlorophenylhydrazone 4 from the phosphorous-containing intermediate.

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Alternatively, the chlorophenylhydrazone 4 can be produced by reacting the benzoic acid 3 with triphenylphosphine and a carbon tetrahalide (e.g. carbon tetrachloride, carbon tetrabromide, and the like, carbon tetrachloride being preferred). The reaction is ordinarily conducted under anhydrous conditions at a temperature of from about 20 °C to about 80 °C, preferably from about 20 °C to about 50 °C in a solvent such as acetonitrile.

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The reaction of a chlorophenylhydrazone 4 with a piperazine 5 to produce a 1-[(phenylhydrazono)-(phenyl)methyl]piperazine 6 is generally conducted neat or in the presence of an aromatic hydrocarbon, a polar aprotic solvent or an ethereal solvent at a temperature of from about 20 °C to about 100 °C. Among the suitable solvents are benzene, toluene, xylene, dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexamethylphosphoramide, diethyl ether, dioxane, 1,2-dimethoxyethane, bis(2-methoxyethyl)ether, tetrahydrofuran and the like, with tetrahydrofuran being preferred. Preferred reaction temperatures are subject to variation depending, in part, upon the solvent employed.

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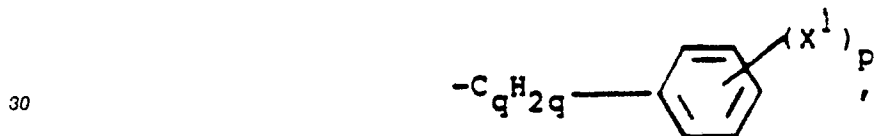
The preparation of the 1-phenyl-3-(1-piperazinyl)-1H-indazoles of this invention is illustrated by Reaction Scheme B.

As illustrated, cyclization of a 1-[(phenylhydrazono)(phenyl)methyl]piperazine 6 wherein R is loweralkyl, loweralkoxycarbonyl or phenyl, yields the corresponding indazole 7.

Cyclization is conventionally carried out by treating the 1-[(phenylhydrazono)(phenyl)methyl]piperazine 6 with an appropriate base such as, for example, an alkali metal hydride, carbonate, or alkoxide. Exemplary  
 5 of the bases suitable for use herein are potassium hydride, sodium hydride, lithium hydride potassium carbonate, potassium t-butoxide, sodium ethoxide, and the like. Potassium t-butoxide and potassium carbonate are preferred. In general, the cyclization reaction is conducted in the presence of a suitable solvent at a temperature of from about 20° C to about 120° C. Included among the suitable solvents are  
 10 ethereal and polar aprotic solvents, ethereal solvents such as, for example, diethyl ether, bis(2-methoxyethyl)ether, tetrahydrofuran, 1,2-dimethoxyethane, dimethylformamide, dimethylacetamide, dimethylsulfoxide and hexamethylphosphoramide. Tetrahydrofuran and dimethylformamide are preferred, with the use of dimethylformamide being recommended when the base is an alkali metal carbonate. Preferred reaction temperatures are subject to variation depending upon factors which include solvent and base selection. For  
 15 example, when the solvent is tetrahydrofuran and the base is potassium t-butoxide, reaction temperatures of from about 20° to about 65° are preferred, whereas, when the solvent is dimethylformamide and the base is potassium carbonate, a reaction temperature of from about 50 to about 120° C is preferred.

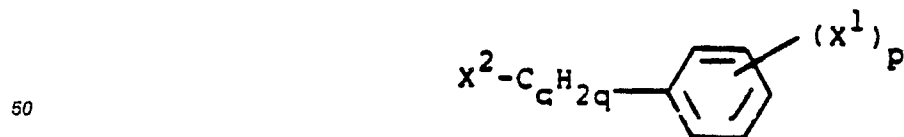
Formula I compounds wherein R is hydrogen 8 may be prepared by the hydrolysis of 1-phenyl-3-(1-piperazinyl)-1H-indazoles 7 wherein R is loweralkoxycarbonyl. The hydrolysis is conveniently performed in an aqueous alkanol in the presence of an appropriate base. Among the suitable alkanols there may be  
 20 mentioned ethanol, 1- and 2-propanol, t-butanol, 2-methoxyethanol, and the like. Ethanol and 2-methoxyethanol are preferred. Appropriate bases include alkali metal hydroxides such as, for example, lithium hydroxide, sodium hydroxide and, most preferably, potassium hydroxide. The hydrolysis is generally conducted at temperatures within a range of from about 70° C to about 125° C.

Alkylation of a Formula I indazole wherein R is hydrogen 8 by treatment with a halide of the Formula  
 25 R<sup>1</sup>X<sup>2</sup> wherein R<sup>1</sup> is loweralkyl, cycloalkyl, loweralkyl, hydroxyl, loweralkyl, loweralkenyl, dialkylphosphinyl, loweralkyl, or



all as previously described, and X<sup>2</sup> is halogen, preferably chlorine or bromine, furnishes a 1-piperazinyl-1H-indazole 9 substituted at the 4-position of the piperazinyl ring by R<sup>1</sup>.

Halides of the formula R<sup>1</sup>X<sup>2</sup> include loweralkylhalides such as, for example, isopropyl bromide, propyl bromide, ethyl chloride, ethyl bromide and the like, ethyl bromide being preferred; cycloalkyl, loweralkyl halides such as for example, (bromomethyl)cyclopropane, (bromomethyl)cyclohexane, (chloromethyl)-  
 40 cyclohexane, (chloromethyl)cyclopropane, and the like, (chloromethyl)cyclopropane being preferred; hydroxyl, loweralkyl halides such as, for example, 3-bromo-1-propanol, 1-bromo-2-propanol, 3-chloro-1-propanol, 1-chloro-2-propanol, 2-chloroethanol, 2-bromoethanol and the like, 2-bromoethanol being preferred; loweralkenyl halides such as, for example, 3-chloro-1-butene, 1-chloro-2-butene, 4-bromo-1-butene, allyl chloride, allyl bromide, and the like, allyl bromide being preferred; dialkylphosphinyl, loweralkyl halides such as, for example, bromomethyl dimethylphosphine oxide, 2-chloroethyl dimethylphosphine oxide, 2-bromoethyl  
 45 dimethylphosphine oxide, chloromethyl dimethylphosphine oxide and the like, chloromethyl dimethylphosphine oxide being preferred; and halides of the formula



wherein q, p, X<sup>1</sup>, and X<sup>2</sup> are as previously defined such as, for example, benzyl chloride, benzyl bromide, (2-chloroethyl)benzene, (2-bromoethyl)benzene, and the like, (2-bromoethyl)benzene being preferred. The  
 55 alkylation reaction is conducted in the presence of an alkali metal carbonate or bicarbonate in a suitable inert organic solvent. Among the alkali metal carbonates and bicarbonates suitable for use in the alkylation reaction there may be mentioned sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, lithium carbonate and the like. Potassium carbonate is preferred. Suitable solvents include polar

aprotic solvents such as, for example, dimethylformamide, dimethylsulfoxide, dimethylacetamide, hexamethylphosphoramide and the like. Dimethylformamide is the solvent of choice for numerous reactions, solvent preference being determined, in part, by the particular halide reacted. The alkylation is generally conducted at a temperature of from about 50 °C to about 100 °C, with temperature ranges of preference being determined in part by the particular halide reacted.

The introduction of cyano functionality to the 4-position of the piperaziny ring of the 1H-indazoles of this invention is accomplished by treating a Formula I indazole wherein R is loweralkyl, preferably methyl, with a cyanogen halide, e.g. cyanogen bromide, under the alkylation conditions previously described to yield a (1H-indazol-3-yl)-1-piperazine carbonitrile. Preferably, the reaction is conducted at a temperature of about 20-25 °C in the presence of potassium carbonate, utilizing dimethylsulfoxide as a solvent.

The introduction of a formyl radical R to the indazoles of this invention is alternatively accomplished by treating a Formula I indazole wherein R is hydrogen with formic acid in the presence of acetic anhydride. The reaction is generally carried out at a temperature of from about 20 °C to about 75 °C, preferably from about 50 °C to about 60 °C in the presence of a suitable solvent. Suitable solvents include ethereal solvents such as, for example, diethyl ether, bis(2-methoxyethyl) ether, and tetrahydrofuran. Tetrahydrofuran is preferred.

Similarly, diloweralkylaminoloweralkyl or loweralkanoyl functionality may be introduced to the 4-position of the piperaziny ring of the 1H-indazoles of the invention by treating a Formula I compound wherein R is hydrogen with an appropriate diloweralkylamino or loweralkanoyl halide (e.g. 2-dimethylaminoethyl chloride, 3-dimethylamino-2-methylpropyl chloride, 2-dimethylaminoisopropyl chloride, acetyl chloride, acetyl bromide, propionyl chloride and the like), under alkylation conditions as previously described.

The 1H-indazoles of this invention can be provided with aminocarbonyl or loweralkylaminocarbonyl functionality at the 4-position of the piperaziny ring thereof by treating a Formula I compound wherein R is hydrogen with a nitro-substituted urea of the formula

$$\text{NO}_2\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}^2$$

wherein R<sup>2</sup> is hydrogen or loweralkyl. The reaction is generally conducted in the presence of a suitable solvent at a temperature of from about 20 °C to about 100 °C, preferably from 80 °C to about 100 °C. Suitable solvents include polar aprotic solvents such as, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide and hexamethylphosphoramide. Dimethylformamide is preferred.

Included among the compounds of this invention are:

- 3-(4-methyl-1-piperaziny)-1-phenyl-1H-indazole;
- 1-phenyl-3-[4-(2-phenylethyl)-1-piperaziny]-1H-indazole;
- 1-phenyl-3-[4-phenylmethyl-1-piperaziny]-1H-indazole;
- 1-phenyl-3-[4-n-propyl-1-piperaziny]-1H-indazole;
- 1-(2-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(3-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(2,4-difluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole;
- 3-(4-methyl-1-piperaziny)-1-[4-(trifluoromethyl)phenyl]-1H-indazole;
- 1-(4-methoxyphenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(4-hydroxyphenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(4-nitrophenyl)-3-(1-piperaziny)-1H-indazole;
- 1-(4-aminophenyl)-3-(1-piperaziny)-1H-indazole;
- 3-[4-(2-hydroxyethyl)-1-piperaziny]-1-phenyl-1H-indazole;
- 6-fluoro-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 6-fluoro-1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 6-fluoro-1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole;
- 6-fluoro-1-(2-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 6-fluoro-1-(2-chlorophenyl)-3-(1-piperaziny)-1H-indazole;
- 6-chloro-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 6-bromo-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 5-fluoro-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 6-methoxy-1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 5-methoxy-1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 5-hydroxy-1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole;
- 5-trifluoromethyl-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 5-nitro-1-phenyl-3-(1-piperaziny)-1H-indazole;
- 5-amino-1-phenyl-3-(1-piperaziny)-1H-indazole;

- 4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile;
- 3-(4-dimethylaminomethyl-1-piperazinyl)-1-phenyl-1H-indazole;
- 3-(4-(2-dimethylamino)ethyl-1-piperazinyl)-1-phenyl-1H-indazole;
- 3-(4-allyl-1-piperazinyl)-1-phenyl-1H-indazole; and
- 5 3-(4-cyclopropylmethyl-1-piperazinyl)-1-phenyl-1H-indazole.

The 1-phenyl-3-(1-substituted and unsubstituted-piperazinyl)-1H-indazoles of this invention are useful as analgetics due to their ability to alleviate pain in mammals. The procedure employed to determine analgetic utility is a modification of the phenyl-p-benzoquinone writhing assay in mice, a standard assay for analgesia (Proc. Soc. Exptl. Bio. Med., 95 729 (1957)]. In the modified procedure phenyl-p-benzoquinone (Eastman, 10 12.5 mg) is dissolved in 5 ml of 95% ethanol and the solution is diluted to a total volume of 100 ml with distilled water. The solution is administered to the subject mice subcutaneously at a dose of 10 ml per kg of body weight. A characteristic "writh", an inward rotation of one or more feet with twisting and turning of the trunk, drawing in of the abdominal wall, lordosis and arching of the back, is produced.

A total of 28 male mice (Charles River, CD-1), weighing 18 to 30 grams, are employed for a time response. The subject animals receive food and water ad libitum. Test compounds are dissolved in distilled water, or suspended in distilled water containing one drop of a suitable surfactant, such as Tween-80. 15

Four groups of five animals (20 animals) are given the test compound subcutaneously at 15, 30, 45 and 60 minutes prior to administration of the phenyl-p-quinone. Four control groups of 2 animals (8 animals) receive an equal volume of the vehicle. After the administration of the phenyl-p-quinone, the mice are placed separately in one liter beakers, and after five minutes, are observed for ten minutes. The number of 20 writhes for each animal is recorded. The following formula is used to compute the percent inhibition;

$$\frac{\bar{x} \text{ Writhes in Control Group} - \bar{x} \text{ Writhes in Drug Group}}{\bar{x} \text{ Writhes in Control Group}} \times 100$$

The time period with the greatest percent of inhibition is considered the peak time. A dose range determination is generally reserved for those compounds which inhibit writhing by greater than 65-70% at the screening dose. 30

A dose range determination is run in the same manner as the time response except 10 animals per group are tested at the peak time of test drug activity. Fifty animals, 4 test drug groups, and a vehicle control are employed. Animals are dosed and tested in a randomized manner. A calculated ED<sub>50</sub>, i.e. the estimated dose at which 50% inhibition of writhing is produced, is determined by a computer linear regression analysis. The calculated subcutaneous (s.c.) dose effecting an approximately 50% inhibition of writhing (ED<sub>50</sub>) in mice produced in this assay is as follow: 35

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COMPOUND	ANALGESIC ACTIVITY (% Inhibition of Writhing) ED (mg/kg)
1-phenyl-3-(1-piperazinyl)-1H-indazole hydrochloride	0.7
1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride	1.6
4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile	65% @ 20mg/kg*
4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carboxylic acid ethyl ester	45% @ 20mg/kg*
3-[4-(dimethylphosphinylmethyl)-1-piperazinyl]-1-phenyl-1H-indazole	66% @ 20mg/kg*
3-(4-allyl-1-piperazinyl)-1-phenyl-1H-indazole hydrochloride	34% @ 20mg/kg*
1-(4-fluorophenyl)-3-(1-piperazinyl)-1H-indazole	50% @ 20mg/kg*
1-(4-fluorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole fumarate	0.8
4-[1-(4-fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester	58% @ 20mg/kg*
3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride	35% @ 20mg/kg*
4-[1-(4-(trifluoromethyl)phenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester	33% @ 20mg/kg*
3-(4-cyclopropylmethyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride	58% @ 20mg/kg*
3-[4-(2-phenylethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride	32% @ 20mg/kg*
3-[4-(2-hydroxyethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole propoxyphene (standard)	62% @ 20mg/kg*
pentazocine (standard)	3.9
	1.3

\* % inhibition of writhing at indicated screening dose, s.c.

Analgesia production is achieved when the 1-phenyl-3-(1-piperaziny)-1H-indazoles of this invention are administered to a subject requiring such treatment as an effective oral, parenteral or intravenous dose of from 1 to 50 mg/kg of body weight per day. 1-phenyl-3-(1-piperaziny)-1H-indazoles which achieve effective analgesia production at doses of about 5 mg/kg of body weight per day are particularly desirable. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and that they do not, to any extent, limit the scope or practice of the invention.

Several of the 1-phenyl-3-(1-piperaziny)-1H-indazoles of this invention are also useful as antidepressants by virtue of their ability to elicit an antidepressant response in mammals. Antidepressant activity is demonstrated in the tetrabenazine induced ptosis assay in mice (International Journal of Neuropharmacology, 8, 72 (1969), a standard assay for antidepressant activity.

In this procedure, male mice (Charles River, CD-1), weighing about 20 to 39 g, are used in test groups of five animals. Test compounds are dissolved, or suspended with 1 drop of Tween-80, in distilled water and administered to the animals in volumes of 10 cc per kg of body weight. Tetrabenazine methanesulfonate (76.78% as the free base) is dissolved in distilled water and the concentration of the solution is adjusted so that the dose, administered intraperitoneally (i.p.) to the animals, is 40 mg of tetrabenazine base per kg of animal body weight.

The test compound is administered intraperitoneally (i.p.) or orally to the subject animals, and the tetrabenazine solution is administered 30 minutes or 60 minutes, respectively, thereafter. Tetrabenazine solution and the solvent used to dissolve, or suspend, the test compounds are administered by the same route and at the same intervals as the test compounds to a control group.

The subject animals are placed in individual plastic containers (10 1/2" x 8" x 6") thirty (i.p.) and sixty minutes (p.o.) after administration of the tetrabenazine solution, and one minute thereafter, the animals are scored for ptosis on the following scale:

Eye Closure	Score
Eyes closed	4
Eyes 3/4 closed	3
Eyes 1/2 closed	2
Eyes 1/4 closed	1
Eyes open	0

The total score for each group of 5 animals will therefore vary from 0 to 20; these scores are used as the indications of the activity of the test compound.

The vehicle-control group score is used as a determinate of the validity of each test. The results are discarded and the test is repeated, if the control score is determined to be less than 17.

A dose range determination is generally reserved for those compounds which inhibit ptosis by greater than about 45-50% at the screening dose.

For calculation of the ED<sub>50</sub>-value of a test compound; i.e., the calculated dose at which the test compound effects a 50% inhibition of tetrabenazine-induced ptosis, four or five doses are administered, and only vehicle-control scores of 17 to 20 are acceptable. A linear-regression analysis is used to estimate ED<sub>50</sub>-values and 95% confidence limits. The intraperitoneal (i.p.) dose effecting a calculated 50% inhibition of ptosis (ED<sub>50</sub>) in mice produced in this assay is as follows:

Table 2

COMPOUND	ANTI-DEPRESSANT ACTIVITY (% Inhibition of Ptois) ED <sub>50</sub> (mg/kg,i.p.)
1-phenyl-3-(1-piperaziny)-1H-indazole hydrochloride	25.4
1-phenyl-3-(4-methyl-1-piperaziny)-1H-indazole hydrochloride	11.1
1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole	17.3
1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole fumarate	65% @ 20 mg/kg*
10 imipramine (standard)	1.3
amitriptyline (standard)	1.5

\* % inhibition of ptois at indicated screening dosage (i.p.)

15 Dosage levels which the 1-phenyl-3-(1-piperaziny)-1H-indazoles of this invention achieve an antidepressant response is subject to variation depending upon the particular compound employed. In general, antidepressant response may be elicited at effect doses ranging from about 0.01 to about 50 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person  
20 administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and they do not, to any extent, limit the scope or practice of the invention.

The compounds of the invention are also useful as anticonvulsants due to their anticonvulsant activity in mammals. Anticonvulsant activity is measured in the male mouse using the supramaximal electroshock  
25 (SES) assay described in Arch. Int. Pharmacodyn. 92: 97-107, 1952. In this procedure groups of animals are used. Drugs are prepared using distilled water and, if insoluble, a surfactant is added. Control animals receive vehicle. Drugs are routinely administered intraperitoneally (i.p.). The dosage volume is 10 ml/kg. A primary screen is given a 30 minute pretreat. The animal's eyes are placed across the output terminals of an A.C. shocker that delivers 206 volts rms for 300 msec. Electrode paste coats the animals eyes at  
30 the point of contact with the terminals. A compound is considered to give protection if the mouse does not exhibit extensor tonus. Protection is expressed as normalized percent inhibition relative to vehicle control.

A time response is carried out using six animals/group. Animals are tested at 30, 60 and 120 minutes post drug. Additional time periods are tested if indicated by previous tests. When the peak activity time has been determined, a dose response is initiated using 10 animals/group at that time period. The ED<sub>50</sub> and  
35 95% confidence interval are calculated by computer probit analysis. The anticonvulsant activity of several of the compounds of this invention is provided in Table 3.

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Table 3

COMPOUND	ANTICONVULSANT ACTIVITY (% Inhibition of Convulsion) ED (mg/kg,i.p.)
1-phenyl-3-(1-piperaziny)-1H-indazole hydrochloride	100% @ 60 mg/kg*
1-phenyl-3-(4-methyl-1-piperaziny)-1H-indazole hydrochloride	14.6
3-[4-(dimethylphosphinylmethyl)-1-piperaziny]-1-phenyl-1H-indazole	24.3
1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole fumarate	12.9
3-(4-methyl-1-piperaziny)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate	27.0
3-(4-ethyl-1-piperaziny)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate	8.2
4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide hemifumarate	38.9
4-[1-(4-fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide	22.7
phenobarbital	8.4

\* % inhibition of convulsions at indicated dosage.

Anticonvulsant activity is achieved when the compounds of this invention are administered to a subject requiring such treatment at an effective oral, parental or intravenous dose of from 1 to 50 mg/kg of body weight per day. A preferred effective dose within this range is from about 5 to 50 mg/kg of body weight per day. A particularly preferred effective amount is about 20 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the compounds of the invention. It is to be further understood that the dosages set forth herein are examples only and that they do not, to any extent, limit the scope or the practice of the invention.

Some compounds within the scope of this invention have greater pharmacological activity in degree or kind than others. For example, the subgeneric group of Formula I compounds wherein R is hydrogen or loweralkyl are more representative of compounds exhibiting analgetic or antidepressant activity. Alternatively, compounds of Formula I wherein R is aminocarbonyl are more representative of compounds exhibiting anticonvulsant activity. These statements of activity are not, however, to be construed as limiting the utility of other compounds defined by Formula I. Further, compounds which are less active, such as those of Formula I wherein R is cyano or alkoxy carbonyl are nevertheless oftentimes desirable as intermediates for the preparation of pharmaceutically more active compounds.

Effective amounts of the present invention may be administered to a subject by any one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The 1-phenyl-3-(1-piperazinyl)-1H-indazoles of this invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience or crystallization, increased solubility and the like.

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

Effective quantities of the compounds of this invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the aforesaid compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 0.5% of active compound, 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 and 300 milligrams of the active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Promogel TM, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit form is a capsule, it may contain, in addition to materials of the preceding 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 and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and nontoxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of this 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 50% of the weight thereof. The amount of active compounds in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 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 benzylalcohol 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 ampules, disposable syringes or multiple dose vials made of glass or plastic.

5 The following Examples are for illustrative purposes only are not to be construed as limiting the invention. All temperatures are given in degrees centigrade ( $^{\circ}$  C).

#### 10 EXAMPLE 1

#### 15 4-(1-Phenyl-1H-indazol-3-yl)-1-piperazine carboxylic acid ethyl ester

#### 20 Step 1

To a stirred solution of 50.0 g of phenylhydrazine in 280 ml of dry pyridine, cooled to about  $5^{\circ}$  was added, dropwise, 80.0 g of *o*-fluorobenzoyl chloride. After coming to ambient temperature, the reaction mixture was stirred for about 2 hours, and then poured into water. The resultant precipitate was recrystallized from toluene to yield 82 g (77.5%) of 2-fluorobenzoic acid, 2-phenylhydrazide.

#### 30 Step 2

A mixture of 5.5 g of 2-fluorobenzoic acid, 2-phenylhydrazide and 20 ml of diethyl ether was refluxed for 1 hour, under nitrogen, and then permitted to stand at ambient temperature for about 20 hours. In the following order, a solution of 5 g of phenol in 5 ml of diethyl ether, 30 ml of methanol, and sufficient water to reach the solution cloud point, were added, dropwise, to the reaction mixture. The mixture was extracted with diethyl ether and the extract washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to an oil. Purification of the oil by means of flash chromatography on silica gel utilizing hexane-ethyl acetate (5%) as the eluent, followed by recrystallization from hexane yielded 1.5 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, phenylhydrazone.

#### 40 Step 3

To 25 ml of stirred, neat ethyl N-piperazinyloxyacetate was added, portionwise, 10.0 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, phenylhydrazone. Upon completion of the addition, the reaction mixture was stirred at  $90^{\circ}$  for five minutes. Dilution of the reaction mixture with water precipitated a gum. The gum was washed with water (2x), and taken up in dichloromethane. The solution was washed with water, brine, dried over anhydrous magnesium sulfate and concentrated to give 17.1 g 4-[(phenylhydrazono)(2-fluorophenyl)methyl]-1-piperazine carboxylic acid ethyl ester.

#### 50 Step 4

55 To a stirred solution, under nitrogen of 16.2 g of 4-[(phenylhydrazono)(2-fluorophenyl)methyl]-1-piperazine carboxylic acid ethyl ester in 150 ml of tetrahydrofuran was added, dropwise, a solution of 6.0 g of potassium *t*-butoxide in 60 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 16 hrs., poured into water, and extracted with dichloromethane. The extract was washed with water,

dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil. The oil was purified on a Water's Model 500 Preparative High Pressure Liquid Chromatograph utilizing two silica gel columns and hexane/ethyl acetate (3:1 by volume) as the eluent. Concentration of the appropriate fractions yielded 5.3 g (51%) of 4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carboxylic acid ethyl ester.

5 Analysis for  $C_{20}H_{22}N_4O_2$ :

Calculated:

68.55%C    6.33%H    15.99%N

Found:

68.11%C    6.28%H    15.93%N

10

## EXAMPLE 2

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### 1-Phenyl-3-(1-piperazinyl)-1H-indazole hydrochloride

20 A stirred solution of 6.4 g of 4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carboxylic acid ethyl ester, 6.1 g of potassium hydroxide in 60 ml of water, and 120 ml of ethanol was refluxed under nitrogen for 32 hours. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with diethyl ether. The extract was washed with water and then with brine, dried over anhydrous magnesium sulfate, and concentrated to give 4.4 g of 1-phenyl-3-(1-piperazinyl)-1H-indazole as a solid. The solid was dissolved in  
25 ethyl acetate/diethyl ether and treated with ethereal hydrogen chloride to precipitate the hydrochloride salt. Recrystallization from methanol/diethyl ether gave 2.5 g (45%) of 1-phenyl-3-(1-piperazinyl)-1H-indazole hydrochloride, mp 265-267°.

Analysis for  $C_{17}H_{18}N_4 \cdot HCl$ :

Calculated:

30 64.86%C    6.08%H    17.80%N

Found:

64.89%C    6.15%H    17.77%N

35

## Example 3

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### 3-(4-Allyl-1-piperazinyl)-1-phenyl-1H-indazole hydrochloride

To a stirred suspension of 5.0 g of 1-phenyl-3-(1-piperazinyl)-1H-indazole and 2.7 g of potassium carbonate in 50 ml of dimethylformamide was added 2.4 g of allyl bromide. The reaction mixture was stirred  
45 at 70° C for 16 hours, poured into water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to yield 3-(4-allyl-1-piperazinyl)-1-phenyl-1H-indazole as an oil. The oil was diluted with diethyl ether and filtered. Treatment of the filtrate with ethereal hydrogen chloride precipitated the hydrochloride salt. Recrystallization from ethanol/diethyl ether gave 2.0 g (21%) of 3-(4-allyl-1-piperazinyl)-1-phenyl-1H-indazole hydrochloride, mp 234-236°.

50 Analysis for  $C_{20}H_{23}N_4 \cdot HCl$ :

Calculated:

67.69%C    6.53%H    15.79%N

Found:

67.33%C    6.56%H    15.98%N

55

## EXAMPLE 4

1-Phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride

5

Step 1

To 20 ml of stirred, neat N-methylpiperazine was added, portionwise, 10.0 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, phenylhydrazine (prepared as in Step 2 of Example 1). Upon completion of the addition, the reaction mixture was allowed to stand at ambient temperature for 30 minutes. The addition of 200 ml of water to the reaction mixture formed a gum. The gum was washed with water (2 x) and taken up in dichloromethane. The solution was washed with water, dried over anhydrous magnesium sulfate and concentrated to give 12.9 g of 1-[(phenylhydrazono)(2-fluorophenyl)methyl]-4-methylpiperazine, as an oil.

15

Step 2

To a stirred solution, under nitrogen of 12.4 g of 1-[(phenylhydrazono)(2-fluorophenyl)methyl]-4-methylpiperazine in 100 ml of a solution of tetrahydrofuran was added dropwise, 5.3 g of potassium t-butoxide in 50 ml of tetrahydrofuran. Following the addition, the reaction mixture was stirred at ambient temperature for 1 hour, poured into water, and extracted with dichloromethane. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was purified on a Water's Model 500 Preparative High Pressure Liquid Chromatograph utilizing two silica gel columns and dichloromethane/methanol (4%) as the eluent. Concentration of the appropriate fractions gave 7.0 g (61%) of 1-phenyl-3-(4-methyl-1-piperazinyl)-1H indazole. Treatment of 3.1 g of the indazole with ethereal hydrogen chloride produced the hydrochloride salt. Recrystallization from ethanol gave 2.8 g of 1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride, mp 244-246°.

30: Analysis for  $C_{15}H_{20}N_4 \cdot HCl$ :

Calculated:

65.74%C    6.44%H    17.04%N

Found:

65.78%C    6.45%H    16.98%N

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EXAMPLE 5

40

1-Phenyl-3-(4-phenyl-1-piperazinyl)-1H-indazole

45

Step 1

To a solution of 6.3 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, phenylhydrazine (prepared as in step 2 of Example 1) in 60 ml of tetrahydrofuran was added 19.0 g of N-phenylpiperazine. The reaction mixture was refluxed for 45 mins, cooled, filtered, and concentrated to yield an oil. The oil was titrated with water, taken up in diethyl ether, washed with water, dried over anhydrous magnesium sulfate and concentrated to give 9.1 g of 1-[(phenylhydrazono)(2-fluorophenyl)methyl]-4-phenylpiperazine.

55



Step 2

To a stirred solution, under nitrogen, of 9.1 g of 1-[(phenylhydrazono)(2-fluorophenyl)methyl]-4-phenyl-  
 5 piperazine in 100 ml of tetrahydrofuran was added, dropwise, a solution of 3.3 g of potassium t-butoxide in  
 35 ml of tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 4 hours and  
 concentrated. The concentrate was diluted with water and extracted with ethyl acetate. The extract was  
 washed with water, dried over anhydrous magnesium sulfate, and concentrated to a solid. The solid was  
 10 flash chromatographed on silica gel utilizing hexane/ethyl acetate (30%) as the eluent. Concentration of the  
 appropriate fractions followed by recrystallization from ethyl acetate/hexane gave 2.1 g (25%) of 1-phenyl-3-  
 (4-phenyl-1-piperazinyl)-1H-indazole, mp 129-130°.

Analysis for  $C_{23}H_{22}N_4$ :

Calculated:

77.93%C    6.26%H    15.81%N

15 Found:

77.91%C    6.04%H    15.76%N

EXAMPLE 6

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1-(2-chlorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride

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Step 1

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To a stirred solution, under nitrogen, of 89.5 g of 2-chlorophenylhydrazine hydrochloride in 600 ml of  
 pyridine, cooled in an ice bath, was added, dropwise, 87.2 g of 2-fluorobenzoyl chloride, such that the  
 reaction temperature did not exceed 15° C. The reaction mixture was stirred at ambient temperature for 16  
 hours and then poured into water. Crystallization of the resultant oil was induced by scratching. Recrystal-  
 35 lization from toluene yielded 65.7 g (60%) of 2-fluorobenzoic acid, 2-(2-chlorophenyl)hydrazide, m.p. 105-  
 107° C.

40 ANALYSIS:

Calculated for  $C_{13}H_{13}ClFN_2O$ :

58.98%C    3.80%H    10.58%N

Found:

45 59.03%C    3.75%H    10.56%N

Step 2

50

A mixture of 5.2 g of 2-fluorobenzoic acid, 2-(2-chlorophenyl)hydrazide, 64.3 g of triphenylphosphine,  
 500 ml of anhydrous acetonitrile and 19.3 ml of carbon tetrachloride was stirred at ambient temperature for  
 16 hours, concentrated in vacuo, and extracted with diethyl ether (4 x 200 ml). The extract was filtered and  
 concentrated to an oil which, was flash chromatographed on silica utilizing hexane/ethyl acetate (25%) as  
 55 the eluent. Concentration of the appropriate fractions yielded 47.5 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, (2-  
 chlorophenyl)hydrazone.

Recrystallization from hexane afforded the analytical sample, m.p. 36-38° C.

ANALYSIS:Calculated for  $C_{13}H_9Cl_2N_2$ :

55.14%C    3.20%H    9.90%N

5 Found:

55.05%C    3.10%H    10.17%N

Step 3

10

To a stirred solution, under nitrogen, of 10.0 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, (2-chlorophenyl)-hydrazone was added dropwise, 7.8 g of 1-methylpiperazine. The reaction mixture was stirred at ambient temperature for 2 hrs, cooled, filtered, and concentrated to an oil. Storage at 5° for 16 hrs. solidified the oil.

15 Trituration with hexane gave 9.0 g (74%) of 1-[(2-chlorophenylhydrazone)(2-fluorophenyl)methyl]-4-methylpiperazine. Recrystallization from hexane (2x) afforded the analytical sample, mp 109-111°.

Analysis for  $C_{18}H_{20}ClFN_4$ :

Calculated:

62.33%C    5.81%H    16.15%N

20 Found:

62.15%C    5.78%H    16.27%N

Step 4

25

To a stirred solution, under nitrogen of 9.0 g of 1-[(2-chlorophenyl)hydrazone] (2-fluorophenyl)methyl]-4-methylpiperazine in 90 ml of tetrahydrofuran was added, dropwise a solution of 3.5 g of potassium t-butoxide in 40 ml of tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 2 hours

30 and then concentrated. The concentrate was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to give 8.9 g of 1-(2-chlorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole as an oil. The oil was dissolved in diethyl ether and treated with ethereal hydrogen chloride to precipitate the hydrochloride salt. The salt was recrystallized from ethanol/diethyl ether (3x) to give 6.1 g (64%) of 1-(2-chlorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole

35 hydrochloride, mp 263-265°.

Analysis for  $C_{18}H_{19}ClN_4O$ :

Calculated:

59.50%C    5.55%H    15.42%N

Found:

40 59.52%C    5.51%H    15.31%N

EXAMPLE 7

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1-(2-Chlorophenyl)-3-(1-piperazinyl)-1H-indazole hydrochloride

50

Step 1

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To a stirred solution, under nitrogen, of 30.0 g  $\alpha$ -chloro-2-fluorobenzaldehyde, (2-chlorophenyl)-hydrazone (prepared as in Step 2 of Example 6) in 300 ml of tetrahydrofuran was added, dropwise, a solution of 36.9 g of ethyl N-piperazinyl carboxylate in 50 ml of tetrahydrofuran. The reaction mixture was

stirred at ambient temperature for 16 hours, filtered, and concentrated. The concentrate was diluted with water and then extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to yield 46.8 g of 4-[[2-(chlorophenyl)hydrazono](2-fluorophenyl)methyl]-1-piperazine carboxylic acid ethyl ester as an oil.

5

### Step 2

10 To a stirred solution under nitrogen of 45.2 g of 4-[[2-(chlorophenyl)hydrazono](2-fluorophenyl)methyl]-1-piperazine carboxylic acid ethyl ether in 400 ml of tetrahydrofuran was added, dropwise, a solution of 16.2 g of potassium t-butoxide in 70 ml of tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 16 hours, concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was flash chromatographed on silica gel eluting with 15% hexane-ethyl acetate. Concentration of the appropriate fractions yielded 34 g (80%) of 4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester as an oil.

15

20

### Step 3

A stirred mixture of 28.7 g of 4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester, 450 ml of 2-methoxymethanol, and a solution of 25 g of potassium hydroxide in 250 ml of water, was refluxed for 16 hours, cooled to ambient temperature, concentrated to about one-third of its volume, poured into water, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to yield 1-(2-chlorophenyl)-3-(1-piperazinyl)-1H-indazole as an oil. The oil was dissolved in anhydrous diethyl ether and treated with ethereal hydrogen chloride to precipitate the hydrochloride salt. The salt was recrystallized from acetonitrile to yield 18.8 g (72%) of 1-(2-chlorophenyl)-2-(1-piperazinyl)-1H-indazole hydrochloride. Recrystallization from isopropyl alcohol-diethyl ether afforded the analytical sample, m.p. 197-199°.

30

### 35 ANALYSIS:

Calculated for  $C_{17}H_{17}N_4Cl \cdot HCl$  :

58.46%C    4.51%H    16.04%N

Found:

40 58.54%C    5.01%H    15.95%N

### EXAMPLE 8

45

#### 3-[4-(Dimethylphosphinylmethyl)-1-piperazinyl]-1-phenyl-1H-indazole

50 A stirred mixture of 4.3 g of 1-phenyl-3-(1-piperazinyl)-1H-indazole (prepared as in Example 2), 2.3 g of potassium carbonate, and 2.3 g of chloromethyldimethylphosphine oxide in 75 ml of dimethylformamide was heated at 90°, under nitrogen, for 16 hrs. Additional chloromethyldimethylphosphine oxide (0.6 g) was added, and the reaction mixture heated at 90°C for 24 hrs. The reaction mixture was poured into water and the aqueous solution extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated to an oil. Flash chromatography of the oil on silica gel, eluting with dichloromethane/methanol (10%) followed by concentration of the appropriate fractions and trituration with diethyl ether gave 2.5 g (45%) of 3-[4-dimethylphosphinylmethyl]-1-piperazinyl]-1-phenyl-1H-indazole.

55 Analysis for  $C_{20}H_{25}N_4OP$ :

Calculated:

65.19%C    6.84%H    15.21%N

Found:

65.07%C    6.99%H    15.08%N

5

EXAMPLE 9

10

4-[1-(4-Fluorophenyl)-1H-indazol-3-yl]-1-piperazinecarboxylic acid ethyl ester

15

Step 1

To a stirred mixture of 80.0 g of 4-fluorophenylhydrazine hydrochloride in 500 ml of dry pyridine, under nitrogen and cooled in an ice bath, was added, dropwise, 85.8 g of 2-fluorobenzoyl chloride. Upon completion of the addition, the ice bath was removed and the reaction mixture stirred at ambient temperature for 16 hours. The reaction mixture was poured into water and a precipitate formed. The precipitate was recrystallized from ethanol-water to give 97.1 g (80%) of 2-fluorobenzoic acid, 2-(4-fluorophenyl) hydrazide.

25 Analysis:

Calculated for  $C_{13}H_{10}F_2N_2O$ :

62.90%C    4.06%H    11.29%N

Found:

62.71%C    4.12%H    11.27%N

30

Step 2

To a stirred mixture of 79.5 g of 2-fluorobenzoic acid, 2-(4-fluorophenyl)hydrazide in 350 ml of diethyl ether was added, portionwise, 80.0 g of phosphorous pentachloride. Upon completion of the addition, the reaction mixture was refluxed for 1 hr and then stirred at ambient temperature for 16 hrs. In the following order, a solution of 81.3 g of phenol in 80 ml of diethyl ether, 385 ml of methanol, and sufficient water to reach the solution cloud point, were added, dropwise, to the reaction mixture. Upon standing the reaction mixture separated into two layers. The bottom layer was collected, washed with water, and extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was purified by flash chromatography on silica gel using 5% ethyl acetate-hexane as the eluent. Evaporation of the appropriate fractions gave 61.5 g of -chloro-2-fluorobenzaldehyde, (4-fluorophenyl)hydrazone as an oil. Distillation gave the analytical sample bp 144-155°.

45 Analysis:

Calculated for  $C_{13}H_9ClF_2N_2$ 

58.55%C    3.40%H    10.52%N

Found:

58.44%C    3.52%H    10.44%N

50

Step 3

To a stirred solution, under nitrogen, of 19.3 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, (4-fluorophenyl)hydrazone in 200 ml of tetrahydrofuran was added, dropwise, a solution of 25.2 g of ethyl-1-piperazine carboxylate in 15 ml of tetrahydrofuran. The reaction mixture was stirred at reflux for 45 minutes, cooled and filtered. A solution of 9.7 g of potassium t-butoxide in 110 ml of tetrahydrofuran was added to the

stirred filtrate, under nitrogen. Upon completion of the addition, the filtrate was stirred for 2 hours at ambient temperature, and then concentrated. The residue was diluted with distilled water, and extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to yield 27 g of product as a gum. The gum together with a 1.9 g sample of product from a previous run was purified by flash chromatography on silica gel utilizing 40% ethyl acetate-hexane as the eluent. Concentration of the appropriate fractions gave 8.3 g of 4-[1-(4-fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester. Recrystallization from isopropyl ether gave the analytical sample, mp 109-111°.

Analysis:

Calculated for  $C_{20}H_{25}FN_4O_2$ :

65.20%C    5.75%H    15.21%N

Found:

65.28%C    5.46%H    15.45%N

#### EXAMPLE 10

##### 1-(4-Fluorophenyl)-3-(1-piperaziny)-1H-indazole

A stirred solution of 9.2 g of potassium hydroxide in 90 ml of distilled water, 10.0 g of 4-[1-(4-fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester, and 180 ml of methoxyethanol was refluxed for 16 hours and then poured into water. The aqueous mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to give 6.0 g (75%) of 1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole. Recrystallization from isopropyl ether gave the analytical sample, mp 85-87°.

Analysis for  $C_{17}H_{17}FN_4$ :

Calculated:

68.90%C    5.78%H    18.91%N

Found:

68.82%C    5.85%H    18.77%N

#### EXAMPLE 11

##### 1-(4-Fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole fumarate

To a stirred solution of 8.0 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, (4-fluorophenyl)hydrazone in 90 ml of tetrahydrofuran, was added dropwise, a solution of 6.6 g of N-methylpiperazine in 10 ml of tetrahydrofuran. The reaction mixture was refluxed for 45 minutes, cooled, and filtered. A solution of 4.0 g of potassium tert-butoxide dissolved in 45 ml of tetrahydrofuran was added to the stirred filtrate, under nitrogen. Upon completion of addition, the reaction mixture was stirred at ambient temperature for 16 hours, and then concentrated to an oil. The oil was diluted with distilled water and the aqueous mixture extracted with dichloromethane. The extract was washed with distilled water, dried over anhydrous potassium carbonate and concentrated. The residue, together with 2.1 g of impure product from a previous run, was purified on a Waters Model 500 Preparative High Pressure Liquid Chromatograph utilizing two silica gel columns and dichloromethane-methanol (5%) as the eluent. Concentration of the appropriate fractions gave 3.3 g of 1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole as a solid. The solid was dissolved in 150 ml of acetone and 1.2 g of fumaric acid was added with stirring, to give the fumarate salt. Recrystallization of the salt from methanol-diethyl ether yielded 2.4 g (13%) of 1-(4-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole fumarate, mp 192-194°.

Analysis:

Calculated for  $C_{18}H_{19}FN_4 \cdot C_4H_4O_4$ :  
 61.96%C    5.44%H    13.14%N  
 Found:  
 61.98% C    5.46%H    13.14%N

5

EXAMPLE 12

10

3-(4-ethyl-1-piperaziny)-1-(4-fluorophenyl)-1H-indazole hydrochloride

A mixture of 5.0 g of 1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole, 2.0 g of ethyl bromide, 2.6 g of  
 15 potassium carbonate and 50 ml of dimethylformamide was heated at 50 °C for 16 hours. The mixture was  
 poured into water and the suspension extracted with ethyl acetate. The ethyl acetate extract was washed  
 with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was diluted with  
 anhydrous diethyl ether and treated with ethereal hydrogen chloride. A precipitate was formed and  
 collected. Recrystallized from ethanol-diethyl ether followed by trituration with refluxing isopropanol gave 3.6  
 20 g (59%) of 3-(1-ethyl-4-piperaziny)-1-(4-fluorophenyl)-1H-indazole hydrochloride, mp 251-253 °.

Analysis for  $C_{19}H_{21}FN_4 \cdot HCl$ :

Calculated:

63.24%C    6.15%H    15.53%N

Found:

25 63.21%C    6.10%H    15.49%N

EXAMPLE 13

30

3-(4-Allyl-1-piperaziny)-1-(4-flurophenyl)-1H-indazole hydrobromide

A mixture of 5.0 g of 1-(4-flurophenyl)-3-(1-piperaziny)-1H-indazole, 2.6 g of potassium carbonate, 2.2 g  
 35 of allyl bromide, and 75 ml of dimethylformamide was stirred at 70-75 ° for 16 hours, and then at ambient  
 temperature for 48 hours. The mixture was poured into water and the aqueous mixture was extracted with  
 ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and con-  
 centrated to produce an oil. The oil was dissolved in ethyl acetate and a saturated solution of hydrogen  
 40 bromide in ethyl acetate was added, dropwise, until the solution was acidic. A precipitate was formed and  
 collected. Recrystallization of the precipitate from ethanol gave 2.3 g (33%) fo 3-(4-allyl-1-piperaziny)-1-(4-  
 fluorophenyl)-1H-indazole hydrobromide.

Analysis:

Calculated for  $C_{20}H_{21}FN_4 \cdot HBr$ :

45 57.57%C    5.32%H    13.43%N

Found:

57.43%C    5.46%H    13.31%N

50

EXAMPLE 14

55

3-[4-(Cyclopropyl)methyl-1-piperaziny]-1-(4-fluorophenyl)-1H-indazole hydrochloride

A stirred mixture of 5.0 g of 1-(4-fluorophenyl)-3-(1-piperaziny)-1H-indazole, 1.6 g of sodium bicarbonate, 1.7 g of chloromethylcyclopropane and 60 ml of dimethylformamide was heated at 85-90° for 16  
 5 hours. Additional chloromethylcyclopropane (0.43 g) was added and the reaction mixture heated at 85-90°  
 for 8 hrs. The reaction mixture was then poured into water and the aqueous mixture extracted with ethyl  
 acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to a  
 solid. The solid was purified by flash chromatography on silica gel utilizing ethyl acetate/diethylamine (3%)  
 as the eluent. Concentration of the appropriate fractions gave 3-[4-(cyclopropyl)methyl-1-piperaziny]-1-(4-  
 10 fluorophenyl)-1H-indazole as a solid. The solid was dissolved in anhydrous diethyl ether and treated with  
 ethereal hydrogen chloride to give the hydrochloride salt. The salt was recrystallized from ethanol-diethyl  
 ether (twice) to give 2.6 g (40%) of 3-[4-(cyclopropyl)methyl-1-piperaziny]-1-(4-fluorophenyl)-1H-indazole  
 hydrochloride, mp 213-215°.

## Analysis:

15 Calculated for  $C_{21}H_{23}FN_4 \cdot HCl$ :  
 65.19%C    6.25%H    14.48%N  
 Found:  
 64.95%C    6.54%H    14.51%N

20

EXAMPLE 15

25

3-(4-Methyl-1-piperaziny)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate

30

Step 1

To a stirred solution of 75.0 g of 4-(trifluoromethyl)-phenylhydrazine in 500 ml of dry pyridine, cooled in  
 an ice bath, was added dropwise, under nitrogen, 79.1 g of 2-fluorobenzoyl chloride. Upon completion of  
 35 the addition, the ice bath was removed and the reaction mixture stirred at ambient temperature for 4 hours.  
 The mixture was poured into water and a precipitate formed. Recrystallization of the precipitate from  
 isopropyl alcohol-water gave 108 g (84%) of 2-fluorobenzoic acid, 2-(4-(trifluoromethyl)phenyl)hydrazide as  
 a solid. Subsequent recrystallization from isopropyl alcohol-water gave the analytical sample, mp 163-165°.

40

ANALYSIS:

45 Calculated for  $C_{14}H_{10}F_4N_2O$ :  
 56.38%C    3.38%H    9.40%N  
 Found:  
 56.47%C    3.19%H    9.61%N

50

Step 2

To a stirred suspension of 95.4 g of 2-fluorobenzoic acid, 2-(4-(trifluoromethyl)phenyl)hydrazide, in 400  
 ml of anhydrous diethyl ether was added, portionwise, 80.0 g of phosphorous pentachloride. Upon  
 55 completion of the addition, the reaction mixture was refluxed for 1 hour and then stirred at room  
 temperature for 16 hours. In the following order, a solution of 81.3 g of phenol in 80 ml of diethyl ether, 385  
 ml of methanol and sufficient water to reach the solution cloud point, were added, dropwise, to the reaction  
 mixture. Upon standing, the reaction mixture separated into two layers. The top layer (aqueous) was

extracted with diethyl ether and the extract added to the bottom layer (organic). The combined organic phase was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was purified on a Water's Model 500 High Pressure Liquid Chromatograph using two silica gel columns and 5% ethyl acetate-hexane as the eluent. Concentration of the appropriate fractions gave 79.6 g (78.5%) of  $\alpha$ -chloro-2-fluorobenzaldehyde, [4-(trifluoromethyl)phenyl]hydrazone. Subsequent recrystallization from hexane gave an analytical sample, mp 48-50°.

#### 10 ANALYSIS

Calculated for  $C_{14}H_9ClF_4N_2$ :

53.09%C    2.86%H    8.35%N

Found:

15 53.20%C    2.84%H    8.71%N

#### Step 3

20 A solution of 9.5 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, [4-(trifluoromethyl)phenyl]hydrazone and 7.2 g of 1-methylpiperazine in 100 ml of tetrahydrofuran was refluxed for 45 minutes, cooled, filtered, and concentrated to an oil. The oil was diluted with water and the aqueous suspension extracted with diethyl ether, dried over anhydrous magnesium sulfate and concentrated to give 10.9 g of 1-[(4-(trifluoromethyl)phenyl)-hydrazono](2-fluorophenyl)methyl]-4-methylpiperazine.

#### Step 4

30 To a stirred solution of 10.8 g of 1-[(4-(trifluoromethyl)phenyl)hydrazono](2-fluorophenyl)methyl]-4-methylpiperazine, 4.7 g of potassium carbonate, and 110 ml of dimethylformamide was stirred at 120° for 65 hours. The reaction mixture was poured into water and the aqueous mixture extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was purified on a Water's Model 500 High Pressure Liquid Chromatograph utilizing two silica gel columns and ethyl acetate-diethylamine (2%) as the eluent. Concentration of the appropriate fractions gave 5.7 g of 3-(4-methyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole as a solid. The free base was dissolved in diethyl ether and treated with 3.8 g of fumaric acid. The precipitate was recrystallized (2x) from methanol to give 3.3 g (25%) of 3-(4-methyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate, mp 215-217°.

#### ANALYSIS:

45 Calculated for  $C_{19}H_{19}F_3N_4 \cdot C_4H_4O_4$ :

59.98%C    4.86%H    11.76%N

Found:

50 57.95%C    4.90%H    11.83%N

#### EXAMPLE 16

55 4-[1-(4-(Trifluoromethyl)phenyl)-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester



Step 1

To a stirred solution of 25.0 g of  $\alpha$ -chloro-2-fluorobenzaldehyde, [4-(trifluoromethyl)phenyl]hydrazone in  
 5 250 ml of tetrahydrofuran was added dropwise, 10.1 g of ethyl-1-piperazinyloxyacetate. The reaction  
 mixture was refluxed for 45 minutes, cooled and filtered. The filtrate was concentrated in vacuo to an oil,  
 which upon trituration with refluxing hexane, gave 31.9 (92%) of 4-[(4-trifluoromethyl)phenyl]hydrazono) (2-  
 fluorophenyl)methyl]-1-piperazine carboxylic acid ethyl ester as a solid, mp 110-113°.

Recrystallization from isopropyl ether gave the analytical sample, mp 111-113°.

10

ANALYSIS:15 Calculated for  $C_{21}H_{22}F_4N_4O_2$ :

57.52%C    5.06%H    12.78%N

Found:

57.66%C    5.05%H    12.79%N

20

Step 2

A stirred mixture of 27.7 g of 4-[(4-trifluoromethyl)phenyl]hydrazono)(2-fluorophenyl)methyl]-1-piperazine  
 25 carboxylic acid ethyl ester, 10.5 g of potassium carbonate, and 250 ml of dimethylformamide was heated at  
 120° for 64 hours. The reaction mixture was poured into water and the aqueous suspension extracted with  
 ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and con-  
 centrated. The residue was stirred with about 500 ml of hexane for 1 hour, and 21.1 g (80%) of 4-[1-(4-  
 trifluoromethyl)phenyl]-1H-indazol-3-yl]-1-piperazine carboxylic acid ethyl ester collected as a solid, mp  
 30 123-126°. Recrystallization from ethanol/water gave the analytical sample, mp 123-126°.

ANALYSIS:35 Calculated for  $C_{21}H_{21}F_3N_4O_2$ :

60.28%C    5.06%H    13.39%N

Found:

60.21%C    5.08%H    13.45%N

40

EXAMPLE 17

45

3-(1-Piperazinyloxy)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride

A stirred solution of 34.0 g of 4-[1-(4-trifluoromethyl)phenyl]-1H-indazol-3-yl]-1-piperazine carboxylic  
 50 acid ethyl ester, 27.5 g of potassium hydroxide in 275 ml of water, and 550 ml of methoxyethanol was  
 refluxed for 16 hours. The reaction mixture was poured into water and the aqueous suspension extracted  
 with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and  
 concentrated in vacuo to give 28 g of 3-(1-piperazinyloxy)-1-[4-(trifluoromethyl)phenyl]-1H-indazole as a solid. A  
 4.0 g sample of the free base was dissolved in absolute ethanol and treated with ethereal hydrogen chloride  
 55 to precipitate the corresponding hydrochloride salt. Recrystallization from ethanol gave 2.2 g (50%) of 3-(1-  
 piperazinyloxy)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, mp 274-276°.

ANALYSIS:Calculated for  $C_{18}H_{17}F_3N_4 \cdot HCl$ :

56.47%C    4.74%H    14.64%N

5 Found:

56.41%C    4.79%H    14.74%N

EXAMPLE 18

10

3-(4-Ethyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate

15

A mixture of 5.0 g of 3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, 1.7 g of ethyl bromide, 2.2 g of potassium carbonate, and 50 ml of dimethylformamide was stirred at 50-55 °C for 16 hours. The reaction mixture was poured into water and the aqueous mixture extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil which solidified upon standing. The solid was dissolved in diethyl ether and treated with 2.8 g of fumaric acid. The resultant salt was then recrystallized from isopropyl alcohol/diethyl ether (2x) to give 2.6 g (38%) of 3-(4-ethyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole fumarate, mp 194-197 °.

25

ANALYSIS:Calculated for  $C_{20}H_{21}F_3N_4 \cdot C_4H_4O_4$ :

58.77%C    5.14%H    11.42%N

30 Found:

58.60%C    5.20%H    11.37%N

EXAMPLE 19

35

3-[4-(2-hydroxyethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole

40

A stirred mixture of 5.5 g of 3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, 2.3 g of bromoethanol, 2.5 g of potassium carbonate and 60 ml of dimethylformamide was heated, under nitrogen, at 70-75 ° for 16 hours. The reaction mixture was poured into water and the aqueous mixture extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was chromatographed on silica gel utilizing a Waters Model 500 High Pressure Liquid Chromatograph and eluting with dichloromethane/methanol (6%). Evaporation of the appropriate fractions gave an oil which solidified upon standing. Recrystallization of the solid from hexane (2x) gave 2.5 g (40%) of 3-[4-(2-hydroxyethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole, mp 82-84 °.

50

ANALYSIS:55 Calculated for  $C_{20}H_{21}F_3N_4O$ :

61.52%C    5.42%H    14.35%N

Found:

61.40%C    5.35%H    14.32%N

EXAMPLE 20

5

3-[4-(Cyclopropyl)methyl-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole

A stirred mixture of 5.0 g of 3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, 2.2 g of potassium carbonate, and 1.4 g of chloromethylcyclopropane in 50 ml of dimethylformamide was heated at 85-90° for 20 hours. The reaction mixture was poured into water and the aqueous suspension extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was flash chromatographed on silica gel utilizing ethyl acetate as the eluent. Concentration of the appropriate fractions gave 2.7 g (48%) of 3-[4-(cyclopropyl)methyl-1-piperazinyl]-1-[4-trifluoromethyl]phenyl]-1H-indazole, mp 98-100°.

15

ANALYSIS:

20 Calculated for C<sub>22</sub>H<sub>23</sub>N<sub>4</sub>F<sub>3</sub>:  
 65.98%C    5.79%H    13.99%N  
 Found:  
 65.94%C    5.69%H    13.92%N

25

EXAMPLE 21

30

3-[4-(2-Phenylethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride

A stirred mixture of 4.0 g of 3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, 2.4 g of (2-bromoethyl)benzene, 1.8 g of potassium carbonate and 60 ml of dimethylformamide was heated, under nitrogen, at 70-75° for 8 hours, and then stirred at ambient temperature for 8 hours. The reaction mixture was poured into water, and the aqueous mixture extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was chromatographed on a Waters Model High Pressure Liquid Chromatograph utilizing silica columns and eluting with hexane/ethyl acetate (30%). Concentration of the appropriate fractions gave 4.3 g of 3-[4-(2-phenylethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole. The free base was dissolved in diethyl ether and treated with hydrogen chloride to precipitate the corresponding hydrochloride salt. Recrystallization from ethanol/diethyl ether gave 3.1 g of 3-[4-(2-phenylethyl)-1-piperazinyl]-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride, mp 255-257°.

45

ANALYSIS:

50 Calculated for C<sub>26</sub>H<sub>25</sub>F<sub>3</sub>N<sub>4</sub>·HCl:  
 64.12%C    5.38%H    11.51%N  
 Found:  
 63.90%C    5.44%H    11.605N

55

EXAMPLE 22

4-(1-Phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile

To a stirred mixture of 1.5 g of cyanogen bromide 2.0 g of potassium carbonate and 30 ml of dimethylsulfoxide was added, dropwise, a solution of 2.8 g of 1-phenyl-3-(4-methyl-1-piperaziny)-1H-indazole in 30 ml of dimethylsulfoxide. The reaction mixture was stirred at ambient temperature for 1.5 hours and then poured into water. The aqueous mixture was extracted with ethyl acetate, and the extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was purified by flash chromatography on silica gel, utilizing ethyl acetate-hexane (1:1) as the eluent, followed by recrystallization from isopropyl alcohol-water to yield 2.3 g (59%) of 4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile, m.p. 118-120°.

ANALYSIS:

Calculated for  $C_{18}H_{17}N_5$ :

71.26%C    5.65%H    23.09%N

Found:

71.05%C    5.67%H    23.05%N

EXAMPLE 236-Fluoro-1-phenyl-3-(4-methyl-1-piperaziny)-1H-indazole hydrochlorideStep 1

To a stirred mixture, under nitrogen, of 72.3 g of phenylhydrazine hydrochloride in 600 ml of pyridine, cooled in an ice bath, was added, dropwise, 97.1 g of 2,4-difluorobenzoyl chloride, such that the reaction temperature did not exceed 15° C. The reaction mixture was stirred at ambient temperature for about 16 hours. Dilution of the mixture with water formed a precipitate which was collected, dried, and recrystallized from ethyl acetate to yield 98 g (79%) of 2,4-difluorobenzoic acid, 2-phenylhydrazide. Subsequent recrystallization from ethyl acetate afforded the analytical sample, m.p. 171-173° C.

ANALYSIS:

Calculated for  $C_{13}H_{10}F_2N_2O$ :

62.89%C    4.06%H    11.28%N

Found:

62.88%C    3.98%H    11.33%N

Step 2

To a stirred mixture, under nitrogen, of 49.6 g of 2,4-difluorobenzoic acid, 2-phenylhydrazide, 64.3 g of triphenylphosphine, and 500 ml of anhydrous acetonitrile was added 19.3 ml of carbon tetrachloride. The reaction mixture was stirred at ambient temperature for about 16 hours, concentrated, and extracted with

diethyl ether (3x). The diethyl ether extract was filtered and concentrated to a residue which was flash chromatographed on silica gel, eluting first with ethyl acetate-hexane and, in a subsequent run, with ethyl acetate alone. Concentration of the appropriate fractions yielded 47.5 g (89%) of  $\alpha$ -chloro-2,4-difluorobenzaldehyde, phenylhydrazone.

5

### Step 2

To a stirred solution of 17.0 g of  $\alpha$ -chloro-2,4-difluorobenzaldehyde, phenylhydrazone in 150 ml of tetrahydrofuran was added dropwise, 14.1 g of 1-methylpiperazine. The reaction mixture was stirred at ambient temperature for 2 hours, filtered, concentrated in vacuo, diluted with water, and extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to yield 19.1 g of 1-[(phenylhydrazono)(2,4-difluorophenyl)methyl]-4-methylpiperazine.

15

### Step 4

To a stirred solution, under nitrogen, 17.0 g of 1-[(phenylhydrazono)(2,4-difluorophenyl)methyl]-4-methylpiperazine in 200 ml of tetrahydrofuran was added dropwise a solution of 7.1 g of potassium t-butoxide in 75 ml of tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 2 hours, then concentrated, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to yield 6-fluoro-1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole as an oil. The oil was dissolved in ethanol-diethyl ether and treated with ethereal hydrogen chloride to precipitate the hydrochloride salt. Recrystallization from methanol yielded 9.0 (45%) of 6-fluoro-1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride, m.p. 298-300° (dec.).

30

### ANALYSIS:

Calculated for  $C_{18}H_{19}FN_4 \cdot HCl$ :

62.52% C    5.81% H    16.15% N

35 Found:

62.33% C    5.99% H    16.28% N

### EXAMPLE 24

40

#### 1-(2-Fluorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride

45

### Step 1

To a stirred solution, under nitrogen of 35.20 g of 2-fluorophenylhydrazine in 250 ml of dry pyridine, cooled in an ice bath, was added, dropwise, 36.7 ml of 2-fluorobenzoyl chloride. The reaction mixture was stirred at ambient temperature for 21 hours. Upon dilution of the reaction mixture with water a precipitate was formed. Attempts to separate the precipitate by filtration, washing with pyridine, resulted in the formation of an oil. That portion of oil which did not pass into the filtrate was dissolved in dichloromethane and concentrated in vacuo. Upon standing, the filtrate separated into aqueous and organic phases. Treatment of the organic phase with toluene resulted in the formation of a precipitate. Recrystallization of the combined product from toluene yielded 49.18 g of 2-fluorobenzoic acid, 2-(2-fluorophenyl)hydrazide.

50

55

Step 2

To a stirred mixture, under nitrogen, of 3.0 g of 2-fluorobenzoic acid, 2-(2-fluorophenyl)hydrazide, 3.0 g of triphenylphosphine, and 25 ml of acetonitrile was added, dropwise, 1.6 g of carbon tetrachloride. The reaction mixture was stirred for 22 hours at ambient temperature and concentrated to an oil. Flash chromatography on silica gel, eluting with 25% ethyl acetate/hexane afforded  $\alpha$ -chloro-2-fluorobenzaldehyde, (2-fluorophenyl)hydrazone as an oil.

10

ANALYSIS:Calculated for  $C_{13}H_9N_2ClF_2$ :

15 58.54%C 3.41%H 10.51%N

Found:

58.43%C 3.47%H 10.29%N

20

Step 3

To a stirred solution of 20.2 g of  $\alpha$ -chloro-fluorobenzaldehyde, (2-fluorophenyl)hydrazone in 200 ml of tetrahydrofuran was added, dropwise, 16.7 g of N-methylpiperazine. The reaction mixture was stirred at ambient temperature for 16 hours, cooled in an ice bath, and filtered. To the stirred filtrate, under nitrogen, was added, dropwise, a solution of 9.4 g of potassium t-butoxide in 95 ml of tetrahydrofuran. The resulting solution was stirred at ambient temperature for 16 hours and concentrated to a residue, which was then diluted with water and extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated to an oil. The oil was purified on a Water's Model 500 Preparative High Pressure Liquid Chromatograph utilizing two silica gel columns and ethyl acetate/diethylamine (2%) as the eluent to yield 17.9 g (75%) of 1-(2-fluorophenyl)-3-(4-methyl-1-piperaziny)-1H-indazole as an oil. Treatment of a portion of the indazole with ethereal hydrogen chloride produced the corresponding hydrochloride salt. Recrystallization from isopropanol/diethyl ether afforded the analytical sample, m.p. 223-225°.

35

ANALYSIS:40 Calculated for  $C_{18}H_{19}FN_4 \cdot HCl$ :

62.33%C 5.81%H 16.15%N

Found:

62.14%C 5.81%H 16.40%N

45

EXAMPLE 25

50

4-(6-Fluoro-1-phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile

To a stirred mixture of 1.6 g of cyanogen bromide, 2.1 g of potassium carbonate and 30 ml of dimethyl sulfoxide was added, dropwise, a solution of 4.8 g of 6-fluoro-3-(4-methyl-1-piperaziny)-1-phenyl-1H-indazole in 30 ml of dimethyl sulfoxide. The reaction mixture was stirred at ambient temperature for 2 hours and then poured into water. The resulting precipitate was recrystallized from ethanol to yield 2.3 g (48%) of 4-(6-fluoro-1-phenyl-1H-indazol-3-yl)-1-piperazine carbonitrile, m.p. 172-174°.

55

ANALYSIS:Calculated for  $C_{18}H_{16}FN_5$ :

67.27%C    5.02%H    21.80%N

5 Found:

67.01%C    4.78%H    21.74%N

EXAMPLE 26

10

4-Formyl-1-(1-phenyl-1H-indazol-3-yl)piperazine

15

To a solution of 3.4 ml of acetic anhydride and 1.5 ml of formic acid heated at 55 ° C for 1.5 hours and then cooled to ambient temperature was added, dropwise, a solution of 5.6 g of 1-phenyl-3-(1-piperazinyl)-1H-indazole in 20 ml of tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated to an oil. Trituration of the oil with refluxing diethyl ether yielded a solid which was

20 recrystallized from isopropanol (3x) to yield 2.6 g (42%) of 4-formyl-1-(1-phenyl-1H-indazol-3-yl)piperazine, m.p. 130-132 ° .

25 ANALYSIS:Calculated for  $C_{18}H_{18}N_4O$ :

70.57%C    5.92%H    18.29%N

Found:

30 70.68%C    5.93%H    18.08%N

EXAMPLE 27

35

4-(1-Phenyl-1H-indazol-3-yl)-1-piperazine carboxamide

40

A mixture of 4.9 g of 1-phenyl-3-(1-piperazinyl)-1H-indazole, 5.1 g of nitrourea, and 80 ml of dimethylformamide was heated on a steam bath for 15 minutes. The reaction mixture was then poured into water and the resulting precipitate was recrystallized from ethyl acetate (2x) to yield 3.1 g (57%) of 4-(1-phenyl-1H-indazol-3-yl)-1-piperazine carboxamide, m.p. 151-153 ° .

45

ANALYSIS:Calculated for  $C_{18}H_{19}N_5O$ :

50 67.27%C    5.96%H    21.79%N

Found:

66.98%C    6.04%H    21.75%N

55

EXAMPLE 28

4-[1-(4-Fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide

A mixture of 5.0 g of 1-(4-fluorophenyl)-3-(1-piperazinyl)-1H-indazole, 5.1 g of nitrourea, and 80 ml of dimethylformamide was heated on a steam bath for 15 minutes. The reaction mixture was then poured into water and the resulting precipitate was recrystallized from ethyl acetate (2x) to yield 2.7 g (47%) of 4-[1-(4-fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide, m.p. 148-158°.

10 ANALYSIS:

Calculated for  $C_{18}F_{18}FN_5O$ :

63.70% C    5.34% H    20.64% N

Found:

15 63.60% C    5.34% H    20.42% N

EXAMPLE 29

20

4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide hemifumarate

25: A mixture of 7.9 g of 1-(2-chlorophenyl)-3-(1-piperazinyl)-1H-indazole, 7.3 g of nitrourea and 100 ml of dimethylformamide was heated on a steam bath for 15 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The concentrate was flash chromatographed on silica gel eluting with chloroform/methanol (5%). Concentration of the appropriate fraction yielded a foam which when stirred overnight afforded 4.0 g of 4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide as a powder. A 3.4 g sample of the free base was dissolved in diethyl ether and treated with 1.1 g of fumaric acid. The resulting salt was recrystallized from ethyl acetate to yield 2.3 g (22%) of 4-[1-(2-chlorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide hemifumarate, m.p. 156-158°.

35

ANALYSIS:

Calculated for  $C_{18}H_{18}ClN_5O \cdot 0.5C_4H_4O_4$ :

40 58.04% C    4.84% H    16.92% N

Found:

59.79% C    4.86% H    16.94% N

45

EXAMPLE 3050 4-[1-(4-Trifluoromethyl)phenyl]-1H-indazol-3-yl]-1-piperazine carboxamide

A mixture of 5.5 g of 3-(1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole, 4.8 g of nitrourea, and 80 ml of dimethylformamide was heated on a steam bath for 15 minutes. The reaction mixture was then poured into water and the resulting precipitate was collected, washed with water, and dried. The precipitate was purified on a Waters Model 500 Preparative High Pressure Liquid Chromatograph (2x) utilizing two

55



silica gel columns and chloroform/methanol (5%) as the eluent. Concentration of the appropriate fractions yielded a solid which was recrystallized from acetonitrile to afford 2.3 g (37%) of 4-[1-(4-trifluoromethyl)-phenyl]-1H-indazol-3-yl]-1-piperazine carboxamide, m.p. 138-140°.

5

ANALYSIS:Calculated for C<sub>19</sub>H<sub>18</sub>F<sub>3</sub>N<sub>5</sub>O:

10 58.60%C    4.66%H    17.99%N

Found:

58.36%C    4.65%H    17.83%N

15

EXAMPLE 3120 4-(6-Fluoro-1-phenyl-1H-indazol-3-yl)-1-piperazine carboxamide

A mixture of 4.5 g of 6-fluoro-1-phenyl-3-(1-piperazinyl)-1H-indazole, 4.3 g of nitrourea, and 75 ml of dimethylformamide was heated on a steam bath for 15 minutes. The reaction mixture was then poured into water and the resulting precipitate was recrystallized twice from toluene (one charcoal treatment) to yield

25 3.5 g (73%) of 4-(6-fluoro-1-phenyl-1H-indazol-3-yl)-1-piperazine carboxamide, m.p. 168-170°.

ANALYSIS:

30

Calculated for C<sub>18</sub>H<sub>18</sub>FN<sub>5</sub>O:

63.70%C    5.34%H    20.64%N

Found:

63.52%C    5.49%H    20.50%N

35

EXAMPLE 32

40

1-(2-Fluorophenyl)-3-(1-piperazinyl)-1H-indazole hydrochloride

A mixture of 4-[1-(2-Fluorophenyl)-1H-indazol-3-yl]-1-piperazine carbonitrile (14.48 g, 0.05 mol) and

45 25% H<sub>2</sub>SO<sub>4</sub> (150 ml) was stirred and refluxed for 18 hours. The solution was cooled in an ice bath and was made basic by the dropwise addition of cold 50% aqueous NaOH. The solid that precipitated was collected and washed with cold H<sub>2</sub>O. The filter cake was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, the CH<sub>2</sub>Cl<sub>2</sub> solution washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and was concentrated to afford 9.0 g of a oil. The oil was dissolved in MeOH-Et<sub>2</sub>O and ethereal HCl was added to precipitate 8.1 g of the HCl salt. A sample (2.7 g) was triturated with boiling50 CH<sub>3</sub>CN cooled and filtered to give 2.4 g of a powder. The salt was then recrystallized from isopropyl alcohol to afford 1.9 g of the HCl salt, m.p. 209-211°. The compound appeared pure by TLC (silica gel: Et<sub>2</sub>NH-EtOAc, 1:1; R<sub>f</sub> = 0.36 (M<sup>+</sup> = 296) were in agreement with the structure.

55

## ANALYSIS:

Calculated for  $C_{17}H_{17}FN_4 \cdot HCl$ :

61.34%C    5.46%H    16.84%N

5 Found:

61.38%C    5.45%H    16.73%N

EXAMPLE 33

10

4-(6-Chloro-1-phenyl-1H-indazol-3-yl)-1-piperazinecarbonitrile

15

To a stirred mixture of 6-Chloro-1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole (35.7 g, 0.11 mol),  $K_2CO_3$  (14.9 g) and DMSO (300 ml) was added, dropwise, BrCN (11.6 g, 0.11 mol) dissolved in DMSO (50 ml). The reaction was stirred at ambient temperature for 2 hours, and then it was poured into  $H_2O$ . The aqueous mixture was extracted with EtOAc; however some of the gummy residue solidified upon contact with the EtOAc, and this was collected. The EtOAc extract was washed ( $H_2O$ ), dried ( $MgSO_4$ ) and the solvent concentrated to afford 19.1 g of a solid. This material was combined with the material isolated by filtration (5.1 g) to afford 24.2 g of the carbonitrile. The compound was treated with refluxing EtOH-MeOH, and after cooling, 19.5 (52%) of solid 166-169° was collected. An analytical sample was obtained by recrystallization of 4.0 g from EtOAc to afford 2.3 g of a solid m.p. 169-171°. The compound appeared pure by TLC (silica gel: EtOAc- $Et_2NH$ , 9:1;  $R_f$  = 0.70, and  $CHCl_3$ -MeOH, (9:1;  $R_f$  = 0.79), and the IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and MS ( $M^+$  = 337) were in agreement with the assigned structure.

## 30 ANALYSIS:

Calculated for  $C_{18}H_{16}ClN_5$ :

63.99%C    4.77%H    20.73%N

Found:

35 63.96%C    4.77%H    20.42%N

EXAMPLE 34

40

6-Chloro-1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole fumarate

To a stirred solution of  $\alpha$ -chloro-4-chloro-2-fluorobenzaldehyde phenylhydrazone (57.5 g, 0.2 mol) in THF (500 ml), under  $N_2$ , was added, dropwise, 1-methylpiperazine (44.4 g, 0.44 mol). The reaction was stirred at ambient temperature for 1 hour, and then it was filtered to remove 1-methylpiperazine hydrochloride. The filtrate was transferred to a reaction vessel equipped with a magnetic stir-bar, and subsequently potassium *t*-butoxide (24.7 g, 0.22 mol) dissolved in THF (250 ml) was added dropwise to the stirred filtrate. The reaction was stirred at ambient temperature for 16 hours, and then it was concentrated to afford a residue. The residue was diluted with  $H_2O$  and the aqueous mixture extracted with  $Et_2O$ . The  $Et_2O$  extract was washed ( $H_2O$ ), dried ( $MgSO_4$ ), and ethereal HCl added until the mixture was acidic. The resultant hydrochloride salt was then collected and dried to afford 41.5 g of the product. Attempts to recrystallize the hydrochloride salt proved difficult; therefore the salt was diluted with  $H_2O$ , stirred and  $NH_4OH$  added until the mixture was basic. The resultant free base was extracted into  $CH_2Cl_2$ , and after washing ( $H_2O$ ) and drying ( $K_2CO_3$ ) and concentrating the extract there remained 38.3 g of the free base as a solid. A portion (5.0 g) of the compound was dissolved in EtOAc (100 ml) and fumaric acid (1.2 g, 1 eq) was added and the mixture was heated at reflux for 5 min. After stirring at ambient temperature for 16 hours, 5.0 g of a

fumarate salt was collected. The salt was recrystallized twice from MeOH (with decolorizing carbon) to yield 2.2 g (43%) of the indazole fumarate, m.p. 193-195°. The compound appeared pure by TLC (silica gel: IPA-CHCl<sub>3</sub>-NH<sub>4</sub>OH, 45:45:1; R<sub>f</sub> = 0.62 and EtOAc-Et<sub>2</sub>NH; 9:1; R<sub>f</sub> = 0.42), and the IR (KBr), NMR (DMSO-d<sub>6</sub>) and MS (M<sup>+</sup> = 326) were in agreement with the structure.

5

## ANALYSIS:

10 Calculated for C<sub>18</sub>H<sub>19</sub>ClN<sub>4</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:  
 59.66%C    5.46%H    12.65%N  
 Found:  
 59.80%C    5.58%H    12.98%N

15

EXAMPLE 35

20

6-Chloro-3-(1-piperazinyl)-1H-indazole Hydrochloride

A stirred mixture of 4-(6-chloro-1-phenyl-1H-indazol-3-yl)-1-piperazinecarbonitrile (9.5 g, 0.028 mol) and 25% aqueous H<sub>2</sub>SO<sub>4</sub> was refluxed for 16 hours. The reaction mixture was cooled in an ice bath, stirred and  
 25 then 50% aqueous NaOH was added dropwise until the mixture was basic. The aqueous mixture was extracted with EtOAc, the extract washed (H<sub>2</sub>O), dried (MgSO<sub>4</sub>) and was concentrated to afford 5.7 g of a solid. A portion (4.1 g) of the solid was dissolved in Et<sub>2</sub>O-EtOH and ethereal HCl was added until the mixture was acidic. The resulting insoluble hydrochloride salt was collected and dried to afford 4.4 g of the product. Recrystallization from EtOH (twice, with one charcoal treatment) yielded 2.4 g (34%) of the  
 30 indazole hydrochloride as a white solid m.p. 271-273°. The compound appeared pure by TLC (silica gel: IPA-CHCl<sub>3</sub>-NH<sub>4</sub>OH, 45:45:1; R<sub>f</sub> = 0.24, and EtOAc-Et<sub>2</sub>NH, 9:1; R<sub>f</sub> = 0.15), and the IR (KBr), NMR (DMSO-d<sub>6</sub>) and MS (M<sup>+</sup> = 312) were in agreement with the assigned structure.

35

## ANALYSIS:

Calculated for C<sub>17</sub>H<sub>17</sub>ClN<sub>4</sub>•HCl:  
 58.47%C    5.20%H    16.05%N  
 40 Found:  
 58.30%C    5.17%H    15.93%N

EXAMPLE 36

45

1-(4-Methylphenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole hydrochloride

50

To a stirred solution, under N<sub>2</sub>, of α-chloro-2-fluorobenzaldehyde(4-methylphenyl)hydrazone (22.1 g, 0.09 mol) in THF (200 ml) was added, dropwise, N-methylpiperazine (27.1 g, 0.27 mol). The solution was allowed to stir at ambient temperature for 3 hours. The solution was cooled in an ice bath for 15 min, and was then filtered and washed with cold THF leaving behind the insoluble N-methyl-piperazine hydrochloride.  
 55 The filtrate was concentrated to afford 38.0 g of 1-[[(-methoxyphenyl)hydrazone](2-fluorophenyl)methyl]-4-methylpiperazine as a liquid.

To a stirred solution of the crude liquid (38.0 g, 0.12 mol) in THF (100 ml) was added, dropwise, potassium tert-butoxide (11.1 g, 0.10 mol) dissolved in the THF (120 ml). The reaction was allowed to stir at

ambient temperature, under N<sub>2</sub>, for 3.5 h. The mixture was concentrated to a liquid, and was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O was washed (H<sub>2</sub>O) dried (MgSO<sub>4</sub>) and was concentrated to afford 24.3 g of a liquid. The liquid was taken up in MeOH-Et<sub>2</sub>O and ethereal HCl was added to precipitate 18.1 g (60%) of the HCl salt. A 4.9 g sample was recrystallized from CH<sub>3</sub>CN yielding 2.2 g m.p. 232-234°. The compound appeared  
 5 pure by TLC [silica gel: Et<sub>2</sub>NH-EtOAc, 1:9, R<sub>f</sub> = 0.53; and CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 8:2, R<sub>f</sub> = 0.61], and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>), and MS (M<sup>+</sup> = 306) were in agreement with the structure.

## 10 ANALYSIS:

Calculated for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>·HCl:

66.55%C    6.77%H    16.34%N

Found:

15 66.16%C    6.78%H    16.22%N

EXAMPLE 37

20

1-(4-Methylphenyl)-3-(1-piperazinyl)-1H-indazole Hydrochloride

25 A mixture of 4-[1-(4-methylphenyl)-1H-indazol-3-yl]-1-piperazine carbonitrile (15.0 g, 0.05 mol) and 25% H<sub>2</sub>SO<sub>4</sub> (150 ml) was stirred and refluxed for 18 hours. The reaction was cooled in an ice bath and made basic by the dropwise addition of 50% NaOH. The aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The CH<sub>2</sub>Cl<sub>2</sub> was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to yield 11.9 g of a oil. The oil was taken up in MeOH-Et<sub>2</sub>O and ethereal HCl was added to precipitate 10.7 g (70%) of the HCl salt. A 3.3 g  
 30 sample was recrystallized twice from MeOH-Et<sub>2</sub>O to afford 2.0 g, m.p. 250-252. The compound appeared pure by TLC (silica gel: EtOH-NH<sub>4</sub>OH, 7:3; R<sub>f</sub> = 0.79, and Et<sub>2</sub>NH-EtOAc, 2:8; R<sub>f</sub> = 0.27) and the IR (KBr), NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>), and MS (M<sup>+</sup> = 292) were in agreement with the structure.

35

## ANALYSIS:

Calculated for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>·HCl:

65.73%C    6.45%H    17.04%N

40 Found:

65.16%C    6.27%H    16.82%N

EXAMPLE 38

45

4-[1-(2-Fluorophenyl)-1H-indazol-3-yl]-1-piperazine carboxamide hemifumarate

50

A solution of 1-(2-fluorophenyl)-3-(1-piperazinyl)-1H-indazole (5.6 g, 0.02 mol), nitrourea (5.1 g, 0.06 mol) and DMF (100 ml) was warmed on a steam bath for 1.5 hours. The reaction mixture was poured into H<sub>2</sub>O and the aqueous mixture was extracted with EtOAc. The EtOAc phase was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to 6.9 g of a oil. The oil was flash chromatographed over silica gel (300 g)  
 55 eluting with 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub>. Concentration of appropriate fractions yielded 4.6 g (65%) of a solid which appeared pure on TLC. A 4.4 g sample was dissolved in EtOAc (60 ml) and fumaric acid (1.1 eq, 1.3 g) was added. The solution was refluxed for 20 minutes and stirred overnight. The precipitate was collected by filtration and washed with EtOAc resulting in 5.1 g of the salt. The salt was recrystallized twice from EtOAc

to afford 2.0 g (25%) of the hemifumarate m.p. 148-150. The compound appeared pure by TLC (silica gel: IPA-CHCl<sub>3</sub>-NH<sub>4</sub>OH, 45:45:1, R<sub>f</sub>=0.53; and CHCl<sub>3</sub>-EtOH, 7:3, R<sub>f</sub>=0.57), and the IR (KBr), NMR (DMSO-d<sub>6</sub>) and MS M<sup>+</sup> = 296) were in agreement with the structure.

6

## ANALYSIS:

Calculated for C<sub>18</sub>H<sub>18</sub>FN<sub>5</sub>O•0.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:

10 60.44%C    5.08%H    17.62%N  
 Found:  
 60.26%C    4.99%H    17.60%N

15

EXAMPLE 3920 1-(4-Methoxyphenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole

To a stirred solution of  $\alpha$ -chloro-2-fluorobenzaldehyde-4-methoxyphenyl hydrazine (48.0 g, 0.17 mol) and THF (300 ml) was added, dropwise, N-methyl-piperazine (2.2 eq, 37.5 g, 0.37 mol). The reaction was allowed to stir under N<sub>2</sub> for 19 hours. The reaction mixture was cooled in an ice bath for ca. 15 minutes, then filtered to remove 1-methylpiperazine hydrochloride. The filtrate was concentrated to 63.7 g of an oil. The oily residue was diluted with H<sub>2</sub>O, and the aqueous mixture was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to afford 53.0 g of 1-[(4-methoxyphenyl)hydrazono]-(2-fluorophenyl)methyl]-4-methylpiperazine as an oil.

To a stirred solution of the crude oil (53.0 g, 0.15 mol) in THF (300 ml) was added, dropwise, KOtBu (18.7 g, 0.17 mol) dissolved in THF (300 ml). The reaction was allowed to stir under N<sub>2</sub> for 17 hours. The reaction mixture was concentrated to an oil and the oil was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The Et<sub>2</sub>O phase was dried with MgSO<sub>4</sub> and concentrated to yield 45.0 g of a liquid. A 5.0 g sample was purified by preparative HPLC (Water's Associates Prep LC/System 500, 2 silica gel columns, eluting with 5% Et<sub>2</sub>NH-EtOAc) to afford 4.0 g of an oil, which was TLC pure. The oil was taken up in anhydrous ether and ethereal HCl was added to precipitate 3.3 g of the HCl salt. The salt was recrystallized from isopropylalcohol (IPA) Et<sub>2</sub>O to afford 2.4 g of crystals, m.p. 229-231.

The compound appeared pure by TLC (silica gel: 10% MeOH-CHCl<sub>3</sub>; R<sub>f</sub>=0.37 and 20% Et<sub>2</sub>NH-EtOAc; R<sub>f</sub>=0.61) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and MS (M<sup>+</sup> = 322) were consistent with the structure.

40

## ANALYSIS:

Calculated for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O•HCl

45 63.58%C    6.47%H    15.67%N  
 Found:  
 63.46%C    6.44%H    15.44%N

50

EXAMPLE 40

55

1-(6-Chloro-1-phenyl-1H-indazol-3-yl)-1-piperazinecarboxamide

A mixture of 6-chloro-1-phenyl-3-(1-piperazinyl)-1H-indazole (5.0 g, 0.016 mol), nitrourea (4.9 g, 0.047 mol) and DMF (75 ml) was heated on a steam bath for 15 min. The reaction was poured into H<sub>2</sub>O, and the solid that precipitated was collected and dried to afford 5.5 g of the urea. Recrystallization from EtOH-H<sub>2</sub>O (charcoal treatment), and then from DMF yielded 2.4 g (42%) of the indazole as a white solid m.p. 194-196°. The compound appeared pure by TLC (silica gel:IPA-CHCl<sub>3</sub>NH<sub>4</sub>OH, 45:45:1; R<sub>f</sub>=0.73, and CHCl<sub>3</sub>-MeOH, 9:1; R<sub>f</sub>=0.35), and the IR (KBr), NMR (DMSO-d<sub>6</sub>) and MS (M<sup>+</sup>=355) were in agreement with the structure.

## ANALYSIS:

Calculated for C<sub>18</sub>H<sub>18</sub>ClN<sub>5</sub>O:  
 60.76%C    5.10%H    19.68%N  
 Found:  
 60.31%C    5.08%H    19.35%N

EXAMPLE 414-[1-(4-Methylphenyl)-1H-indazol-3-yl]-1-piperazinecarboxamide

A solution of 1-(4-methylphenyl)-3-(1-piperazinyl)-1H-indazole (6.5 g, 0.02 mol) nitrourea (5.9 g, 0.06 mol) and DMF (150 ml) was warmed on a steam bath for 1.5 hours. The reaction mixture was poured into H<sub>2</sub>O and the aqueous mixture was extracted with EtOAc. The EtOAc was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to afford 6.8 g of a solid. A 3.8 g sample was purified by preparative HPLC (Water's Associates prep LC/System 500, 2 silica gel columns, eluting 10% Et<sub>2</sub>NH-EtOAc) to afford 3.6 g of a solid. The solid was recrystallized from toluene to afford 2.5 g of the urea, which occluded toluene. A high vacuum pump was used to remove the residual toluene while the compound was heated on a steam bath. The resulting 2.0 g of powder (54%) m.p. 146-148, appeared pure by TLC (silica gel: 20% Et<sub>2</sub>NH-EtOAc; R<sub>f</sub>=0.22, and 20% MeOH-CH<sub>2</sub>Cl<sub>2</sub>; R<sub>f</sub>=0.61) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and MS (M<sup>+</sup>=335) were in agreement with the structure.

## ANALYSIS:

Calculated for C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O:  
 68.03%C    6.32%H    20.88%N  
 Found:  
 68.12%C    6.71%H    20.86%N

EXAMPLE 424-[1-(4-Methoxyphenyl)-1H-indazol-3-yl]-1-piperazinecarboxamide

A solution of 1-(4-methoxyphenyl)-3-(1-piperazinyl)-1H-indazole hydrochloride (5.0 g, 0.01 mol), nitrourea (4.0 g, 0.04 mol) and DMF (200 ml) was warmed on a steam bath for 2 hours. The reaction mixture was poured into H<sub>2</sub>O and the aqueous mixture was extracted with EtOAc. The EtOAc was dried with MgSO<sub>4</sub> and

concentrated to 5.3 g of an oil. Crystallization was achieved with toluene affording 3.3 g (65%) of a powder. The powder was recrystallized again from toluene to afford 3.0 g of the compound m.p. 155-157°. The compound appeared pure by TLC (silica gel: 20% Et<sub>2</sub>NH-EtOAc; R<sub>f</sub>=0.34 and CHCl<sub>3</sub>-MeOH; R<sub>f</sub>=0.39) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and MS (M<sup>+</sup> = 351) were consistent with the assigned structure.

5

## ANALYSIS:

10 Calculated for C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>:  
 64.93%C    6.03%H    19.93%N  
 Found:  
 64.84%C    6.17%H    19.82%N

15

EXAMPLE 43

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1-(4-Methoxyphenyl)-3-(1-piperaziny)-1H-indazole hydrochloride

A mixture of 4-[1-(4-methoxyphenyl)-1H-indazol-3-yl]-1-piperazine carbonitrile (14.0 g, 0.04 mol) and 25% H<sub>2</sub>SO<sub>4</sub> (130 ml) was stirred and refluxed for 3 hours. The reaction mixture was cooled in an ice bath and made basic by the dropwise addition of 50% NaOH. The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to 15.3 g of an oil. The oil was taken up in anhydrous Et<sub>2</sub>O and MeOH, and then ethereal HCl was added to precipitate 12.1 g (88%) of the indazole salt. A 3.5 g sample was recrystallized from EtOH-Et<sub>2</sub>O to afford 2.8 g of the compound m.p. 236-238. The compound appeared pure by TLC (silica gel: 20% Et<sub>2</sub>NH-EtOAc; R<sub>f</sub>=0.33 and CHCl<sub>3</sub>-HOAc-EtOAc (6:3:1); R<sub>f</sub>=0.34) and the IR (CHCl<sub>3</sub>), NMR (DMSO-d<sub>6</sub>) and MS (M<sup>+</sup> = 308) were consistent with the structure.

## 35 ANALYSIS:

Calculated for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O•HCl:  
 62.88%C    6.15%H    16.25%N  
 Found:  
 40 62.67%C    6.17%H    16.17%N

EXAMPLE 44

45

1-(4-Hydroxyphenyl)-3-(4-methyl-1-piperaziny)-1H-indazole

50 A mixture of 1-(4-methoxyphenyl)-3-(4-methyl-1-piperaziny)-1H-indazole (29.0 g, 0.09 mol) and HBr (200 ml) was stirred and refluxed for 2 hours. The mixture was allowed to cool to ambient temperature and H<sub>2</sub>O (700 ml) was added to precipitate a solid, which was collected by filtration. The solid was washed with a dilute NaHCO<sub>3</sub> solution and the resultant powder was collected to afford 24.4 g (70%) of the HBr salt of the compound. The salt was converted to the free base and a 7.5 g sample was purified by preparative HPLC (Water's Associates prep LC/System 500, 2 silica gel columns, eluting with 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) to afford 4.5 g of a solid. The compound was recrystallized twice from EtOAc to afford 2.8 g, m.p. 191-193° of

the compound, which appeared pure by TLC (silica gel: EtOH-NH<sub>4</sub>OH (9:1); R<sub>f</sub>=0.68 and CHCl<sub>3</sub>-MeOH (9:1), R<sub>f</sub>=0.29) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>) and MS (M<sup>+</sup> = 308) were consistent with the structure.

5

## ANALYSIS:

Calculated for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O:

10 70.09%C 6.55%H 18.17%N

Found:

69.98%C 6.51%H 18.17%N

15

EXAMPLE 4520 4-[1-(4-Methoxyphenyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile

To a stirred mixture of BrCN (8.5g, 0.08 mol), K<sub>2</sub>CO<sub>3</sub> (11.2g, 0.08 mol) and DMSO (200 ml) under N<sub>2</sub>, was added, dropwise, 1-(4-methoxyphenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole (25.0g, 0.08 mol) dissolved in DMSO (400 ml). The reaction was allowed to stir at ambient temperature for 18 hours. The reaction was poured into H<sub>2</sub>O and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to 22.0g of a powder (82%). Recrystallization of the compound from IPA gave 17.1g (64%) of crystals. A 2.9g sample was recrystallized again from IPA to afford 2.3g of the compound, mp 118-120°, which appeared pure by TLC (silica gel: 20% Et<sub>2</sub>NH-EtOAc: R<sub>f</sub>=0.67 and 10% MeOH-Toluene; R<sub>f</sub>=0.52) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and MS (M<sup>+</sup> = 333) were in agreement with the structure.

## ANALYSIS:

35

Calculated for C<sub>19</sub>H<sub>19</sub>N<sub>5</sub>O:

68.44%C 5.76%H 21.01%N

Found:

68.13%C 5.74%H 21.03%N

40

EXAMPLE 46

45

1-(2,4-dichlorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole

To a stirred mixture of α-chloro 2 fluorobenzaldehyde-2,4-dichlorophenyl hydrazone (51.0 g, 0.16 mol) and THF (500 ml) under N<sub>2</sub> was added, dropwise, 1-methylpiperazine (35.4 g, 0.35 mol). The reaction was allowed to stir for 16 hours and then was cooled in an ice bath for 30 minutes. The mixture was filtered and washed with cold THF leaving behind the insoluble 1-methylpiperazine hydrochloride. The filtrate was concentrated to afford 72.5 g of 1-[(2,4-dichlorophenyl)hydrazono](2-fluorophenyl)methyl-4-methylpiperazine as an oil.

To a stirred mixture of the crude oil (72.5 g, 0.19 mol) and THF (200 ml) under N<sub>2</sub> was added, dropwise, KotBu (23.5 g, 0.21 mol) dissolved in THF (400 ml). The reaction was allowed to stir for 58 hours. The reaction mixture was concentrated to an oily residue, which was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The Et<sub>2</sub>O extract was washed with H<sub>2</sub>O, dried with MgSO<sub>4</sub> and concentrated to 58.0 g of an oil. A 9.0 g



sample of the oil was flash chromatographed over 500 g silica gel eluting with 20% MeOH-CH<sub>2</sub>Cl<sub>2</sub>. Concentration of appropriate fraction afforded 5.7 g (55%) of an oil. The oil was dissolved in anhydrous Et<sub>2</sub>O and fumaric acid (2.0 g, 1.1 eq) was added. The mixture was stirred overnight and the solid was collected by filtration to afford 4.6 g of the compound. A 3.8 g sample was recrystallized twice from EtOAc to afford 2.2 g of the pure compound, m.p. 150-152°. The compound appeared pure by TLC (silica gel: 20% Et<sub>2</sub>NH-EtOAc; R<sub>f</sub>=0.59 and 9:1 CHCl<sub>3</sub>-MeOH; R<sub>f</sub>=0.40) and the IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>), and MS (M<sup>+</sup> = 360) were in agreement with the structure.

10

## ANALYSIS:

Calculated for C<sub>18</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:

55.35%C    4.65%H    11.74%N

15

Found:

55.12%C    4.67%H    11.41%N

EXAMPLE 47

20

4-[1-(4-Hydroxyphenyl)-1H-indazol-3-yl]-1-piperazinecarboxamide

25

A mixture of 1-(4-hydroxyphenyl)-3-(1-piperazinyl)-1H-indazole (5.9 g, 0.02 mol), nitrourea (5.5 g, 0.06 mol) and DMF (150 ml) was warmed on a steam bath for 2 hours. The reaction mixture was poured into H<sub>2</sub>O (300 ml) and the aqueous mixture was extracted with EtOAc (3X200 ml). The EtOAc phases were combined and washed with brine, dried with MgSO<sub>4</sub> and concentrated to afford 6.5 g of an oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500, 2 silica gel columns, eluting with 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub>) yielding 2.6 g (40%) of a solid. The compound was triturated with hot CH<sub>3</sub>CN then allowed to cool and the resulting solid was collected to afford 2.0 g of the compound, m.p. 203-205°. The compound appeared pure by TLC (silica gel: 9:1 CHCl<sub>3</sub>-MeOH; R<sub>f</sub>=0.11 and IPA-CHCl<sub>3</sub>-NH<sub>4</sub>OH (45:45:1); R<sub>f</sub>=0.49) and the IR (KBr), NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>) and MS (M<sup>+</sup> = 337) were in agreement with the assigned structure.

35

## ANALYSIS:

40

Calculated for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>:

64.07%C    5.69%H    20.76%N

Found:

63.79%C    5.72%H    20.65%N

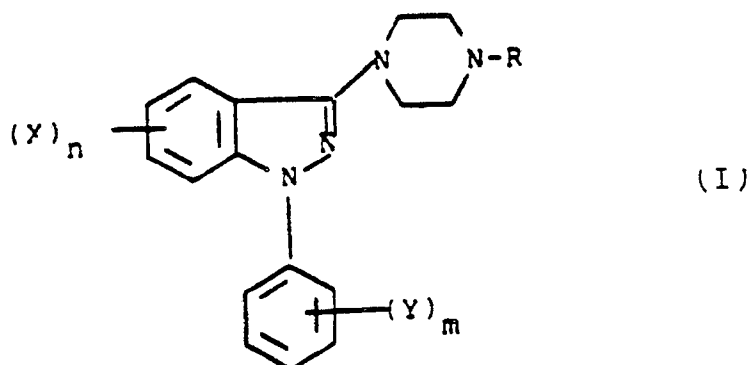
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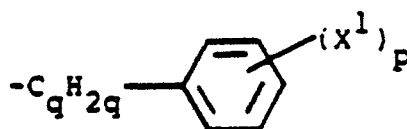
## Claims

1. A compound of the formula I



wherein n is an integer having a value of 0 or 1; m is an integer having a value of 0 to 2 inclusive; X and Y are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, wherein for each value of m, Y may be the same or different; and R is hydrogen, loweralkyl, cycloalkyl, loweralkyl, loweralkenyl, hydroxy, loweralkyl, diloweralkylaminoloweralkyl, diloweralkylphosphinyl, loweralkyl, cyano, loweralkylcarbonyl, loweralkanoyl, aminocarbonyl, loweralkylaminocarbonyl, or a group of the formula

20



wherein q is an integer having a value of 0 to 5, inclusive, X' is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, and p is an integer having a value of 0 to 2 inclusive, wherein for each value of p, X' may be the same or different; the geometrical isomers, optical antipodes or pharmaceutically acceptable acid addition salts thereof.

35

2. A compound according to claim 1 wherein n is 0, m is 0 or 1, Y is halogen or trifluoromethyl and R is hydrogen, loweralkyl, cycloalkyl, loweralkyl, loweralkenyl, loweralkanoyl, aminocarbonyl, loweralkylaminoloweralkyl, diloweralkylaminoloweralkyl or diloweralkylphosphinyl, loweralkyl.

3. A compound according to claim 2 wherein R is hydrogen, loweralkyl, or cycloalkyl, loweralkyl.

4. The compound of claim 3 which is 1-phenyl-3-(1-piperazinyl)-1H-indazole, or a pharmaceutically acceptable acid addition salt thereof.

40

5. The compound according to claim 3 which is 1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole or a pharmaceutically acceptable acid addition salt thereof.

6. The compound according to claim 3 which is 1-(4-fluorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole or a pharmaceutically acceptable acid addition salt thereof.

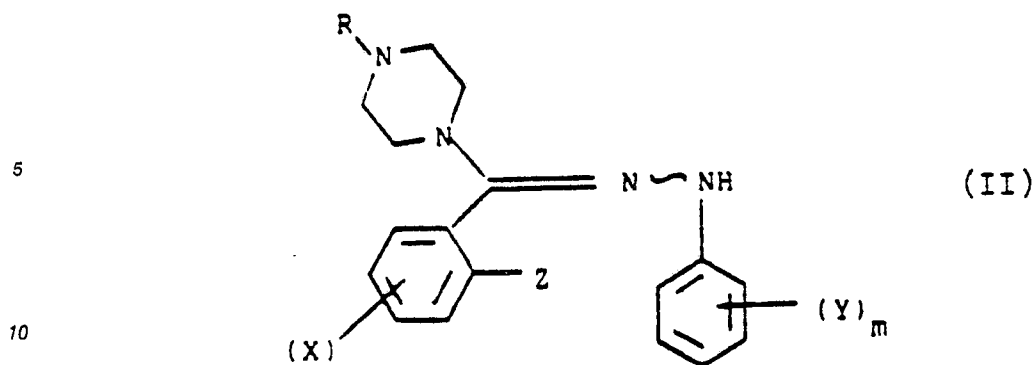
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7. The compound according to claim 2 which is 3-[4-(dimethylphosphinylmethyl)-1-piperazinyl]-1-phenyl-1H-indazole or a pharmaceutically acceptable acid addition salt thereof.

8. The compound according to claim 3 which is 3-(4-ethyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole or a pharmaceutically acceptable acid addition salt thereof.

9. A compound of the formula II

50



15 wherein R is loweralkyl, loweralkoxycarbonyl or a group of the formula



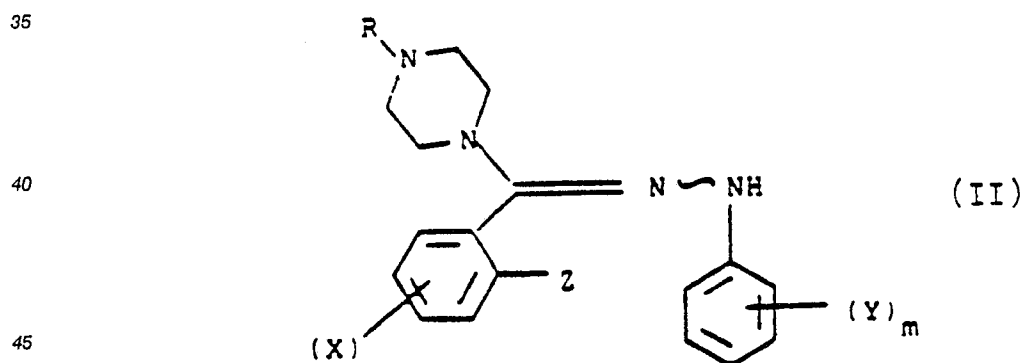
25 wherein X<sup>1</sup> is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl, and p is an integer having a value of 0 to 2 inclusive, wherein for each value of p, X<sup>1</sup> may be the same or different; X and Y are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl, n is an integer having a value of 0 or 1; m is an integer having a value of 0 to 2 inclusive; wherein for each value of m, Y may be the same or different; and Z is fluorine or chlorine; the geometrical isomers, optical antipodes, or pharmaceutically acceptable acid addition salts thereof.

30 10. A pharmaceutical composition which comprises as the action ingredient a compound as defined in claim 1 in association with a pharmaceutically suitable carrier therefor.

11. Use of a compound as defined in claim 1 for the preparation of a medicament having analgesic, anti-convulsant and/or antidepressant activity.

12. A process for the preparation of a compound as defined in claim 1, which comprises

a) treating a compound of the formula II



50 wherein X, Y, m and n are as defined in claim 9, R is loweralkyl, loweralkoxycarbonyl or phenyl and Z is fluorine or chlorine, with an inorganic base in the presence of an inert organic solvent,

b) optionally hydrolyzing a compound of the formula I, wherein R is loweralkoxycarbonyl to afford a compound of the formula I, where R is hydrogen,

55 c) optionally treating a compound of the formula I where R is hydrogen, with a halide of the formula R<sup>1</sup>X<sup>2</sup> wherein R<sup>1</sup> is loweralkyl, cycloalkyl, loweralkyl, hydroxyl, loweralkenyl, diloweralkylphosphinyl, loweralkyl, diloweralkylamino, loweralkanoyl, cyano or a radical of the formula wherein q, p, and X<sup>1</sup> are as previously described, and X<sup>2</sup> is halogen, to afford a compound of the formula I where R has the meaning of R<sup>1</sup> as previously defined,

d) optionally treating a compound of the formula I wherein R is hydrogen, with formic acid in the presence of acetic anhydride to afford a compound of the formula I where R is the formyl group,

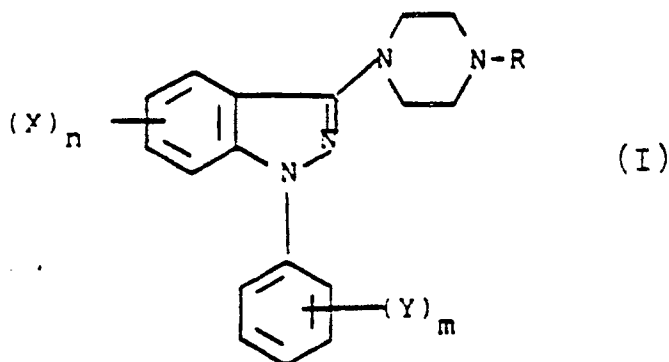
e) optionally treating a compound of the formula I wherein R is hydrogen with a nitro-substituted urea of the formula

$\text{NO}_2\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}^2$  wherein  $\text{R}^2$  is hydrogen or loweralkyl, to afford a compound of the formula I wherein R is aminocarbonyl or loweralkylaminocarbonyl,

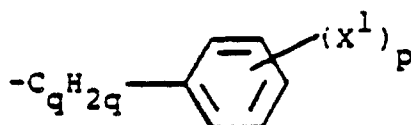
f) and optionally preparing in a routine manner known in the art a pharmaceutically acceptable acid addition salt thereof.

Claims for the following Contracting States: ES, GR

1. A process for the preparation of a compound of the formula I

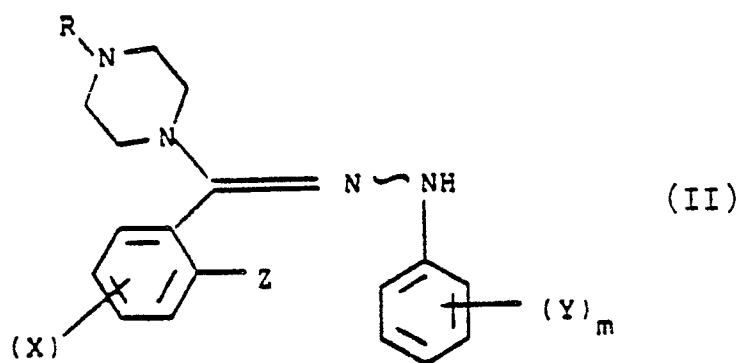


wherein n is an integer having a value of 0 or 1; m is an integer having a value of 0 to 2 inclusive; X and Y are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, wherein for each value of m, Y may be the same or different; and R is hydrogen, loweralkyl, cycloalkyl, loweralkenyl, hydroxyloweralkyl, diloweralkylaminoloweralkyl, diloweralkylphosphinyloweralkyl, cyano, loweralkylcarbonyl, loweralkanoyl, aminocarbonyl, loweralkylaminocarbonyl, or a group of the formula



wherein q is an integer having a value of 0 to 5, inclusive,  $\text{X}'$  is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, loweralkylamino, amino, nitro, cyano, mercapto, hydroxy, or trifluoromethyl, and p is an integer having a value of 0 to 2 inclusive, wherein for each value of p,  $\text{X}'$  may be the same or different; the geometrical isomers, optical antipodes or pharmaceutically acceptable acid addition salts thereof, which comprises

a) treating a compound of the formula II



wherein X, Y, m and n are as defined in above, R is loweralkyl, loweralkoxycarbonyl or phenyl and Z is fluorine or chlorine, with an inorganic base in the presence of an inert organic solvent.

b) optionally hydrolyzing a compound of the formula I, wherein R is loweralkoxycarbonyl to afford a compound of the formula I, where R is hydrogen,

5 c) optionally treating a compound of the formula I where R is hydrogen, with a halide of the formula  $R^1X^2$  wherein  $R^1$  is loweralkyl, cycloalkyl, loweralkyl, hydroxyl, loweralkenyl, diloweralkylphosphinyl, loweralkyl, diloweralkylamino, loweralkanoyl, cyano or a radical of the formula



15 wherein q, p, and  $X^1$  are as previously described, and  $X^2$  is halogen, to afford a compound of the formula I where R has the meaning of  $R^1$  as previously defined,

d) optionally treating a compound of the formula I wherein R is hydrogen, with formic acid in the presence of acetic anhydride to afford a compound of the formula I where R is the formyl group,

20 e) optionally treating a compound of the formula I wherein R is hydrogen with a nitro-substituted urea of the formula

$NO_2NH-C(=O)-NHR^2$  wherein  $R^2$  is hydrogen or loweralkyl to afford a compound of the formula I wherein R is aminocarbonyl or loweralkylaminocarbonyl,

25 f) and optionally preparing in a routine manner known in the art a pharmaceutically acceptable acid addition salt thereof.

2. A process according to claim 1 wherein n is 0, m is 0 or 1, Y is halogen or trifluoromethyl and R is hydrogen, loweralkyl, cycloalkyl, loweralkyl, loweralkenyl, loweralkanoyl, aminocarbonyl, loweralkylaminocarbonyl, diloweralkylaminocarbonyl or diloweralkylphosphinyl.

3. A process according to claim 2 where R is hydrogen, loweralkyl or cycloalkyl.

30 4. A process according to claim 3 wherein 1-phenyl-3-(1-piperazinyl)-1H-indazole or a pharmaceutically acceptable acid addition salt thereof is prepared.

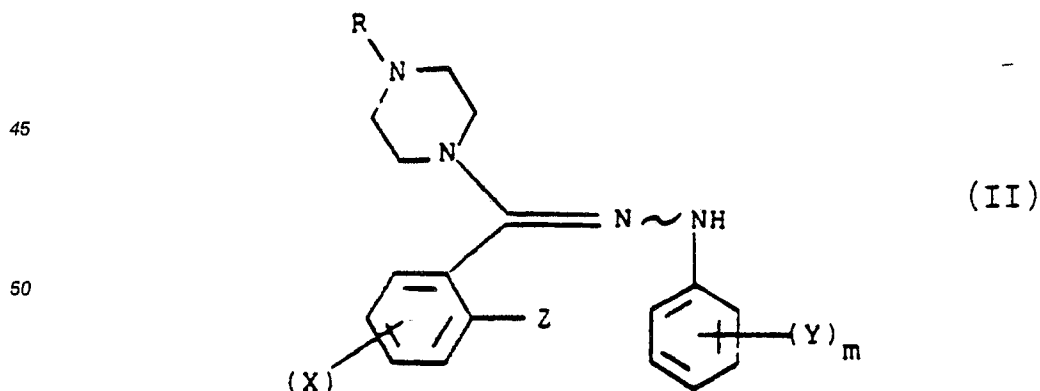
5. The process according to claim 3 wherein 1-phenyl-3-(4-methyl-1-piperazinyl)-1H-indazole or a pharmaceutically acceptable acid addition salt thereof is prepared.

35 6. The process according to claim 3 wherein 1-(4-fluorophenyl)-3-(4-methyl-1-piperazinyl)-1H-indazole or a pharmaceutically acceptable acid addition salt thereof is prepared.

7. The process according to claim 2 wherein 3-[4-(dimethylphosphinylmethyl)-1-piperazinyl]-1-phenyl-1H-indazole or a pharmaceutically acceptable acid addition salt thereof is prepared.

8. The process according to claim 3 wherein 3-(4-ethyl-1-piperazinyl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole or a pharmaceutically acceptable acid addition salt thereof is prepared.

40 9. A process for the preparation of a compound of the formula II



55 wherein R is loweralkyl, loweralkoxycarbonyl or a group of the formula

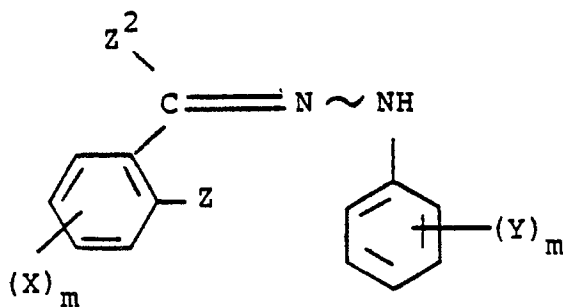


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wherein  $X^1$  is halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl, and  $p$  is an integer having a value of 0 to 2 inclusive, wherein for each value of  $p$ ,  $X^1$  may be the same or different;  $X$  and  $Y$  are independently halogen, loweralkyl, loweralkoxy, loweralkylthio, diloweralkylamino, nitro, cyano, or trifluoromethyl,  $n$  is an integer having a value of 0 or 1;  $m$  is an integer having a value of 0 to 2 inclusive; wherein for each value of  $m$ ,  $Y$  may be the same or different; and  $Z$  is fluorine or chlorine; the geometrical isomers, optical antipodes, or pharmaceutically acceptable acid addition salts thereof, which comprises reacting a compound of the formula 4

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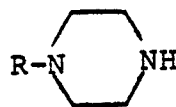


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wherein  $X$ ,  $Y$ ,  $n$  and  $m$  are as previously defined,  $Z$  is fluorine or chlorine and  $Z^2$  is chlorine, with a compound of the formula

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where  $R$  is as previously defined.

10. Use of a compound as defined in claim 1 for the preparation of a medicament having analgesic, anti-convulsant and/or anti-depressant activity.

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