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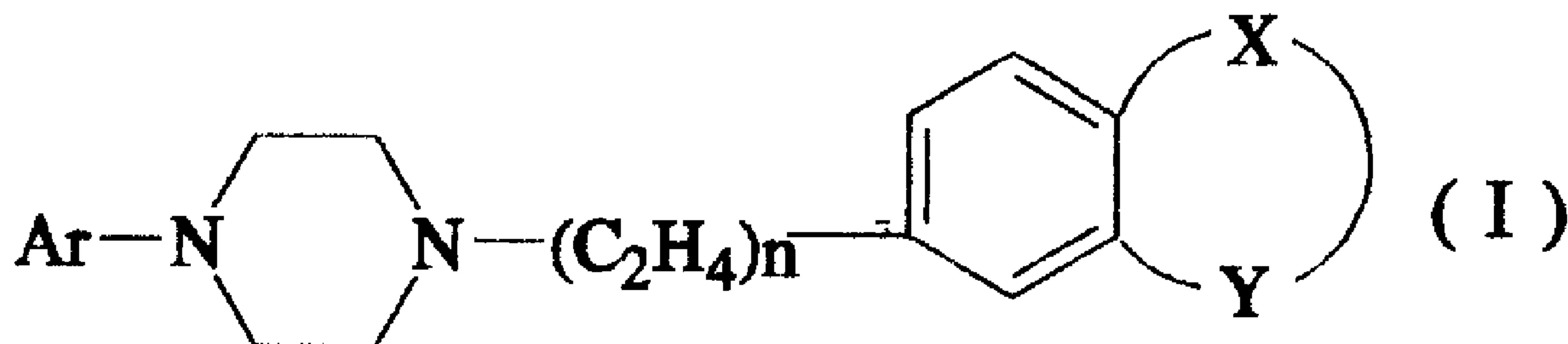
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(54) Titre : METHODE POUR TRAITER LA MALADIE DE GILLES DE LA TOURETTE

(54) Title: METHOD OF TREATING TOURETTE'S SYNDROME

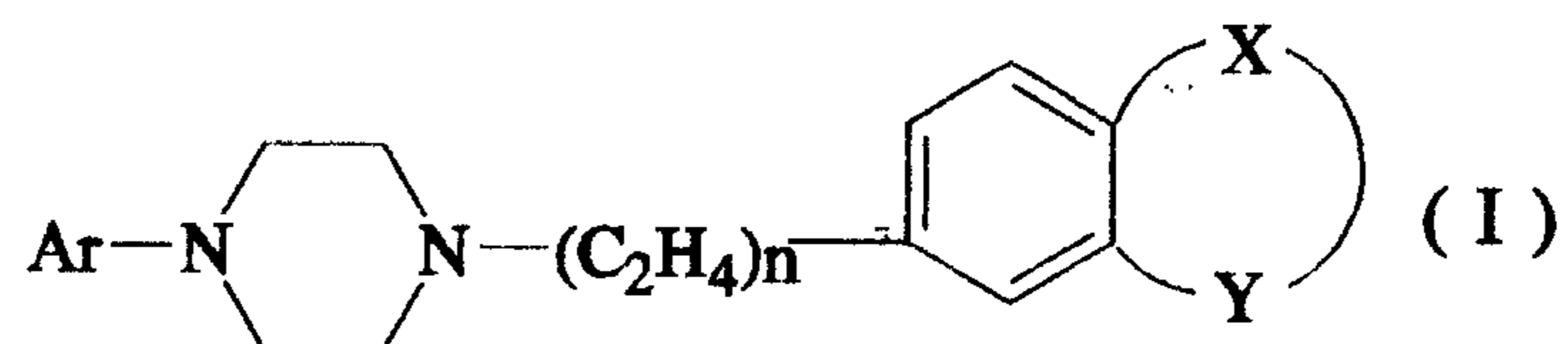


(57) Abrégé/Abstract:

Disclosed is a medicine for treating Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder in a mammal, including a human, comprising an effective amount of a compound of the formula: (see formula I) (wherein Ar is an aromatic radical such as benzoisothiazolyl; n is 1 or 2; X and Y together with the phenyl form quinolyl, benzothiazolyl etc.) or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

Abstract

Disclosed is a medicine for treating Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder in a mammal, including a human, comprising an effective amount of a compound of the formula:



(wherein Ar is an aromatic radical such as benzoisothiazolyl; n is 1 or 2; X and Y together with the phenyl form quinolyl, benzothiazolyl etc.) or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

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METHOD OF TREATING TOURETTE'S SYNDROMEBackground of the Invention

The present invention relates to the use of piperazinyl-heterocyclic compounds of the formula I, as defined below, for the treatment of Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder.

10 Tourette's syndrome is a chronic neuropsychiatric disorder of childhood causes that is characterized by multiple motor and vocal tics, somatosensory urges, and behaviour problems such as attention deficit hyperactivity disorder, learning disabilities, obsessive compulsive disorder, anxiety and depression.

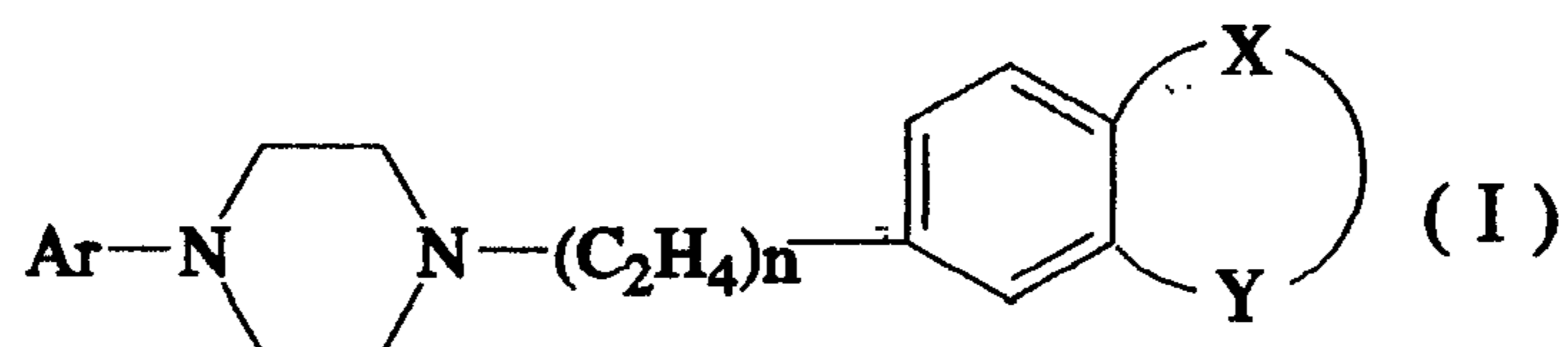
The range of tic symptoms is enormous and includes sudden repetitive movements, gestures and utterances. A typical bout is usually of a brief duration that rarely lasts more than a second. Motor tics vary from abrupt movements (eye blinking, sudden head jerks and shoulder shrugs) to more complex behaviours such as gestures of the hands or face or a
20 slow sustained head tilt. Vocal tics range from simple sniffing to throat clearing to fragments of words or phrases.

The piperazinyl-heterocyclic compounds of formula I of this invention, useful in the treatment of psychotic disorders, are referred to in United States 4,831,031 and 4,883,795 both of which are assigned in common with the present application.

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Summary of the Invention

The present invention relates to a medicine (i.e. pharmaceutical) for treating Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder in a mammal including a human, comprising, in admixture with a pharmaceutically acceptable carrier or diluent, an effective amount of a compound of the formula:



or a pharmaceutically acceptable acid addition salt thereof, wherein

Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; 6-hydroxy-8-quinolyl; isoquinolyl; quinazolyl; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; idanyl optionally substituted by one or two fluoro; 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;

n is 1 or 2; and

X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl; benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-

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hydroxyindazolyl; indolyl; spiro; oxindolyl optionally substituted by one to three of (C₁-C₃)alkyl, or one of chloro, fluoro or phenyl, the phenyl being optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolinylyl; benzothiazolonyl; benzoimidazolonyl; or benzotriazolyl.

10 The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorders or condition. The term "treatment", as used herein, refers to the act of treating as "treating" is defined immediately above.

A preferred embodiment of this invention relates to the above medicine to be used for treating Tourette's syndrome.

Another preferred embodiment of this invention relates to the above medicine to be used for treating obsessive compulsive disorder.

20 Another preferred embodiment of this invention relates to the above medicine to be used for treating chronic motor tic disorder.

Another preferred embodiment of this invention relates to the above medicine to be the used for treating vocal tic disorder.

Another preferred embodiment of this invention relates to the above medicine wherein X and Y together with

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the phenyl to which they are attached form benzoxazolonyl.

Another preferred embodiment of this invention relates to the above medicine wherein Ar is benzoisothiazolyl and n is 1.

Another preferred embodiment of this invention relates to the above medicine wherein the X and Y, together with the phenyl to which they are attached, form oxindolyl optionally substituted by chloro, fluoro or phenyl.

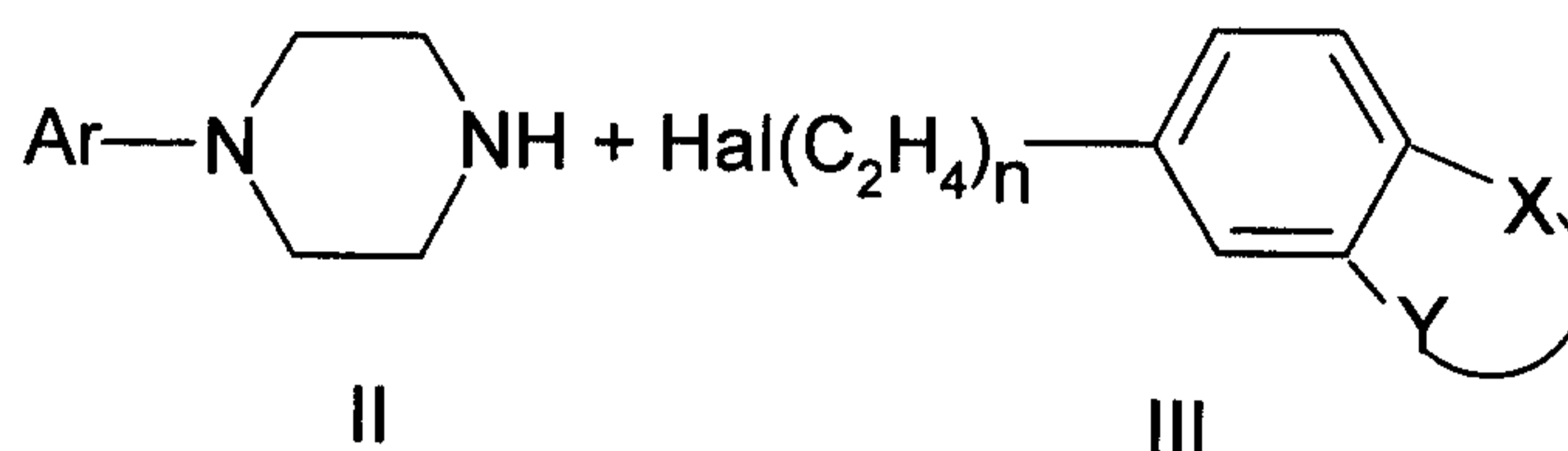
10 Another preferred embodiment of this invention relates to the above medicine wherein Ar is naphthyl and n is 1.

Another aspect of the present invention provides a commercial package comprising the above-described medicine and a written matter which states that the medicine can or should be used for the purpose described in this specification.

Detailed Description of the Invention

20 The piperazinyl-heterocyclic compounds of formula I can be prepared by one or more of the synthetic methods described and referred to in United States Patents 4,831,031 and 4,883,795.

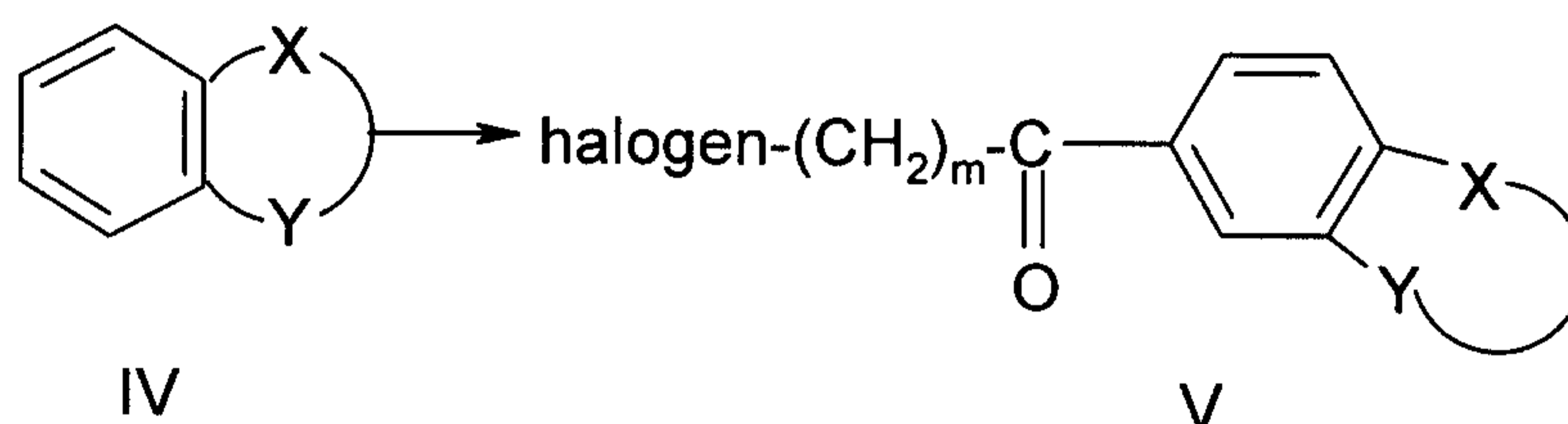
The compounds of formula I may be prepared by reacting piperazines of formula II with compounds of formula III as follows:



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wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is generally conducted in a polar solvent such as a lower alcohol, for instance ethanol, dimethylformamide or methylisobutylketone, and in the presence of a weak base such as a tertiary amine base, for instance triethylamine or diisopropylethylamine. Preferably, the reaction is in the further presence of a catalytic amount of sodium iodide, and a neutralizing agent for hydrochloride such as sodium carbonate. The reaction is preferably conducted at the reflux temperature of the solvent used. The piperazine derivatives of formula II may be prepared by methods known in the art. For instance, preparation may be by reacting an arylhalide of the formula ArHal wherein Ar is as defined above and Hal is fluoro, chloro, bromo or iodo, with piperazine in a hydrocarbon solvent such as toluene at about room temperature to reflux temperature for about half an hour to 24 hours. Alternatively, the compounds of formula II may be prepared by heating an amino-substituted aryl compound of the formula ArNH₂ wherein Ar is as defined above with a secondary amine to allow cyclization to form the piperazine ring attached to the aryl group Ar.

The compounds of formula III may be prepared by known methods. For instance, compounds (III) may be prepared by reacting a halo-acetic acid or halo-butyric acid wherein the halogen substituted is fluoro, chloro, bromo or iodo with a compound of the formula IV as follows:



wherein X and Y are as defined above and m is 1 or 3. The compounds (V) are then reduced, e.g. with triethylsilane and trifluoroacetic acid in a nitrogen atmosphere, to form compounds (III).

When Ar is the oxide or dioxide of benzoisothiazolyl, the corresponding benzoisothiazolyl is oxidized under acid conditions at low temperatures. The acid used is advantageously a mixture of sulphuric acid and nitric acid.

The pharmaceutically acceptable acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base (I) with about one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration and recrystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic,

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5 cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic
such as methanesulfonic, benzenesulfonic, and related acids.

Compounds of formula I, and their pharmaceutically acceptable salt (referred to collectively hereinafter, as "the active compounds of this invention"), can be administered to a human subject either alone, or, preferably, in combination with pharmaceutically-acceptable
10 carriers or diluents, in a pharmaceutical practice. Such compounds can be administered orally or parenterally. Parenteral administration includes especially intravenous and intramuscular administration. Additionally, in a pharmaceutical composition comprising an active compound of this invention, the weight ratio of active ingredient to carrier will normally be in the range from 1:6 to 2:1, and preferably 1:4 to 1:1. However, in any given case, the ratio chosen will depend on
15 such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

For oral use in treating Tourette's syndrome, chronic motor or vocal tic disorder, the active compounds of this invention can be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers
20 which can be used include lactose and corn starch, and lubricating agents, such as magnesium stearate, can be added. For oral administration in capsule form, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For intramuscular and intravenous use, sterile solutions of the
25 active ingredient can be prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

When an active compound of this invention is to be used in a human subject to treat Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder, the
30 daily dosage will normally be determined by the prescribing physician. Moreover, the dosage will vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms. However, in most instances, an effective amount for treating Tourette's syndrome, obsessive compulsive disorder, chronic motor or vocal tic disorder will be a daily dosage in the range from 5 to 500 mg, and preferably 10 mg a day to 80 mg a day, in single or
35 divided doses, orally or parenterally. In some instances it may be necessary to use dosages outside these limits.

The following examples are provided solely for the purpose of further illustration.

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EXAMPLE 16-(2-(4-(1-Naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a 500 ml three-necked round-bottomed flask equipped with mechanical stirrer and nitrogen inlet were added 200 grams of polyphosphoric acid, 13.51 grams (0.1 mole) of benzoxazolone, and 13.89 g (0.1 mole) of bromoacetic acid. The reaction was heated with stirring at 115° C for 2.5 hours and poured into 1 kg ice. The mixture was stirred mechanically for 1 hour to form a purple solid, which was then filtered off and washed with water. The solid was slurried with acetone for 30 minutes, a small amount of purple solid filtered off, and the brown filtrate evaporated. The resulting dark brown gum was slurried with 150 ml ethanol for 30 minutes, and the brown solid filtered off and washed with ethanol. This solid had a m.p. of 192°-194° C.

The solid (6.6 grams, 0.0257 mole) was placed in a 100 ml three-necked round-bottomed flask equipped with magnetic stirrer, dropping funnel, thermometer, and nitrogen inlet and 19.15 ml (0.257 mole) of trifluoroacetic acid added. Triethylsilane (9.44 ml, 0.0591 mole) was added dropwise to the stirring slurry over 30 minutes. The reaction was stirred overnight at room temperature, then poured into 150 grams ice. The mixture was stirred for 15 minutes, and the brown gum filtered off. The gum was dissolved in 100 ml ethyl acetate, and 125 ml cyclohexane added, giving a brown precipitate, which was filtered and washed with cyclohexane. The filtrate was evaporated and the resulting yellow solid slurried with 50 ml isopropyl ether the pale yellow solid was filtered off and dried to give 2.7 g 6-(2-bromoethyl)-benzoxazolone (11% yield for two steps), m.p. 148°-151° C.

B. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and nitrogen inlet were added 0.618 g (2.10 mmol) of N-(1-naphthyl)piperazine 0.472 g (1.95 mmol) of 6-(2-bromoethyl)-benzoxazolone, 0.411 ml (2.92 mmol) of triethylamine, 50 ml ethanol, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml methylene chloride, the pH adjusted with aqueous 1N sodium hydroxide solution, and a little methanol added to facilitate phase separation. The methylene chloride layer was dried over sodium sulfate and evaporated, then chromatographed on silica gel. Fractions containing the product were combined and evaporated, the residue taken up in ethyl acetate, treated with hydrochloride gas, and the resulting hydrochloride salt of the product filtered off to give the white solid title compound, m.p. 282°-285° C., 213 mg (23% yield).

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EXAMPLE 26-(2-(4-(1-Naphthyl)piperazinyl)ethyl)-benzimidazolone

A. To a 500 ml three-necked round-bottomed flask equipped with mechanical stirrer and nitrogen inlet were added 100 grams of polyphosphoric acid, 6.7 grams (0.05 mole) of benzoxazolone, and 6.95 grams (0.05 mole) of bromoacetic acid. The reaction was heated with stirring at 115° C for 1.5 hours and poured into 1 kg ice. The mixture was stirred mechanically for 1 hour to form a gray solid, which was then filtered off and washed with water. The solid was slurried with acetone for 30 minutes, a small amount of purple solid filtered off, and the brown filtrate evaporated. The resulting dark brown gum was taken up in ethyl acetate/water, and the organic layer washed with water and brine, dried, and evaporated to solid, 6.5 grams (51%).

10 NMR (d, DMSO-d₆): 5.05 (s, 2H), 7.4 (m, 1H), 7.7-8.05 (m, 2H).

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The solid (6.0 grams, 0.0235 mole) was placed in a 100 ml three-necked round-bottomed flask equipped with magnetic stirrer, dropping funnel, thermometer, and nitrogen inlet and 18.2 ml (0.235 mole) of trifluoroacetic acid added. Triethylsilane (8.64 ml, 0.0541 mole) was added dropwise to the stirring slurry over 30 minutes. The reaction was stirred overnight at room temperature, then poured into 150 grams ice. The mixture was stirred for 14 minutes, and the pink solid 6-(2-bromoethyl)-benzimidazolone filtered off to give 5.0 grams (42% yield for two steps), m.p. 226°-220° C.

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B. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and nitrogen inlet were added 2.64 grams (12.4 mmol) of N-(1-naphthyl)-piperazine, 3.0 grams (12.4 mmol) of 6-(2-bromoethyl)-benzimidazolone, 1.31 grams (12.4 mmol) sodium carbonate, 50 ml methylisobutylketone, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml ethyl acetate, and the ethyl acetate layer washed with brine, dried over sodium sulfate, and evaporated, then chromatographed on silica gel. Fractions containing the product were combined and evaporated, the residue taken up in tetrahydrofuran, treated with hydrochloric acid gas, and the resulting hydrochloride salt of the product filtered off to give a white solid, m.p. 260°-262° C., 716 mg (14% yield).

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EXAMPLE 36-(2-(4-(8-Quinolyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 0.36 grams (1.5 mmol) of 6-bromoethyl benzoxazolone, 0.32 grams (1.5 mmol) of 8-piperazinyl quinoline, 0.2 grams (1.9 mmol) of sodium carbonate, 50 mg of sodium iodide, and 5 ml of ethanol. The reaction was refluxed for 20 hours, cooled, diluted with water, and the pH adjusted to 4 with 1N Sodium hydroxide, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.3 grams of a yellow oil.

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5 The oil was dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added, and the mixture concentrated to dryness. The residue was crystallized from isopropanol to give 0.18 grams (32%) of a yellow salt, m.p. 200° NMR (d, CDCl₃): 2.74 (m, 2H), 2.89 (m, 6H), 3.44 (m, 4H), 6.76-7.42 (m, 7H), 8.07 (m, 1H), 8.83 (m, 1H).

EXAMPLE 4

10 6-(2-(4-(6-Quinoly)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 0.36 grams (1.5 mmol) of 6-bromoethylbenzoxazolone, 0.32g (1.5 mmol) of 8-piperazinylquinazoline, 0.85 grams (8.0 mmol) of sodium carbonate, 2 mg of sodium iodide, and 35 ml of ethanol. The reaction was refluxed for 3 days, cooled, diluted with water, and the pH adjusted to 4 with 1N HCl. The aqueous layer was separated, the pH adjusted to 7 with 1N Sodium hydroxide, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 1.3 grams of a yellow oil. The oil was crystallized from chloroform (1.1 g), dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added, and the mixture concentrated to dryness. The residue gave 0.9 grams (58%) of a yellow salt, m.p. 200° C. NMR (d, CDCl₃): 2.72 (m, 6H), 2.86 (m, 2H), 3.83 (m, 4H), 6.9-7.9 (m, 7H), 8.72 (s, 1H).

EXAMPLE 5

35 6-(2-(4-(4-Phthalazinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 1.13 grams (4.7 mmol) of 6-bromoethyl benzoxazolone, 1.0 gram (4.7 mmol) of 4-piperazinyl phthalazine, 0.64 grams (6.0 mmol) of sodium carbonate, and 30 ml of ethanol. The reaction was refluxed for 20 hours, cooled, diluted with water, and the pH adjusted to 4 with 1N HCl. The aqueous layer was separated, the pH adjusted to 7 with 1N Sodium hydroxide, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.5 grams of a red oil. The oil was chromatographed on silica gel using chloroform/methanol as eluent to give 0.2 grams of a pink oil. The oil was dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added and the mixture concentrated to give 0.37 grams (11%) of a yellow salt, m.p. 200° C. NMR (d, CDCl₃): 2.78 (m, 2H), 2.88 (m, 6H), 3.65 (m, 4H), 7.0-8.1 (m, 7H), 9.18 (s, 1H).

EXAMPLE 6

40 6-(2-(4-(4-Methoxy-1-naphthyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 0.24 grams (1.0 mmol) of 6-bromoethylbenzoxazolone, 0.24 grams (1.0 mmol) of 4-methoxy-1-piperazinyl naphthalene, 0.13 grams (1.2 mmol) of sodium carbonate, and 25 ml of ethanol. The reaction was refluxed for 36 hours, cooled, diluted with water, and the product extracted into ethyl

5 acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.49 grams of a yellow oil. The oil was chromatographed on silica gel using chloroform as eluent to give 0.36 grams of yellow crystals. The solid was dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added, and the mixture concentrated to dryness to give 0.26 grams (55%) of white salt crystals, m.p. 200° C. NMR (d, CDCl₃): 2.8-3.2 (m, 12H), 4.01 (s, 3H),
10 6.7-7.6 (m, 7H), 8.26 (m, 2H).

EXAMPLE 7

6-(2-(4-(5-Tetralinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 1.0 gram (3.9 mmol) of 6-bromoethylbenzoxazolone, 0.85 grams (3.9 mmol) of 5-piperazinyltetralin, 0.4 grams (3.9 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml
15 of isopropanol. The reaction was refluxed for 18 hours, cooled, evaporated to dryness, and the residue dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the precipitate which had formed collected by filtration. The precipitate was suspended in ethyl acetate/water, the pH adjusted to 8.5 with 1N Sodium hydroxide, and the ethyl acetate layer
20 separated. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.7 grams of a solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added, and the mixture concentrated to dryness to give 0.70 grams (40%) of a yellow salt, m.p. 200° C. NMR (d, CDCl₃): 1.9 (m, 4H), 2.95 (m, 16H), 6.8-7.2 (m, 6H).

EXAMPLE 8

6-(2-(4-(6-Hydroxy-8-quinolyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 0.84 grams (3.5 mmol) of 6-bromoethylbenzoxazolone, 0.80 grams (3.5 mmol) of 6-hydroxy-8-piperazinyl quinoline, 0.37 grams (3.5 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml of isopropanol. The reaction was refluxed for 18 hours, cooled, evaporated, and the residue
30 dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the phases separated. The aqueous phase was adjusted to pH 8.5 and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.33 grams of a yellow solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with hydrochloric acid gas added, and the mixture concentrated to dryness. The residue was crystallized from isopropanol
35 to give 0.32 grams (20%) of a yellow salt, m.p. 200° C. NMR (d, CDCl₃): 2.8 (m, 8H), 3.4 (m, 4H), 6.7-7.3 (m, 7H), 7.7-7.9 (m, 1H).

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EXAMPLE 96-(2-(4-(1-(6-Fluoro)naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a round-bottomed flask equipped with condenser and nitrogen inlet were added 345 ml (3.68 mol) of fluorebenzene and 48 grams (0.428 mol) of furoic acid. To the stirring suspension was added in portion 120 grams (0.899 mol) of aluminum chloride. The reaction was then stirred at 95° C. for 16 hours and then quenched by addition to ice/water/1N HCl. After stirring 1 hour, the aqueous layer was decanted off, and benzene and a saturated aqueous solution of sodium bicarbonate added. After stirring 1 hour, the layers were separated, the aqueous layer washed with benzene, acidified, and extracted into ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate, and evaporated to a solid. The solid was triturated with isopropyl ether to give 5.0 grams (6.1%) of white solid 6-fluoro-1-naphthoic acid, NMR (d, DMSO-d₆): 7.0-8.0 (m, 5H), 8.6 (m, 1H).

B. To a 125 ml round-bottomed flask equipped with condenser, addition funnel, and nitrogen inlet were added 5.0 grams (26.3 mmol) of 6-fluoro-1-naphthoic acid and 50 ml acetone. To the stirring suspension were added dropwise 6.25 ml (28.9 mmol) of diphenyl phosphoryl azide and 4 ml (28.9 mmol) of triethylamine. The reaction was refluxed 1 hour, poured into water/ethyl acetate, and filtered. The filtrate was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was further treated with hydrochloric acid to form the hydrochloride salt and then liberated with sodium hydroxide to afford the free base 6-fluoro-1-amino-naphthalene as an oil, 1.0 gram (24%).

C. To a 125 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 1.0 gram (6.21 mmol) of 6-fluoro-1-amino naphthalene, 1.8 grams (7.76 mmol) of N-benzyl bis(2-chloroethyl)amine hydrochloride, 3.3 ml (19.2 mmol) of diisopropylethylamine, and 50 ml isopropanol. The reaction was refluxed 24 hours, cooled, and evaporated to an oil. The oil was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using methylene chloride as eluent to afford 1.5 grams (75.5%) of an oil, 1-benzyl-4-(6-fluoronaphthyl)-piperazine.

D. To a 125 ml round-bottomed flask equipped with nitrogen inlet were added 1.5 grams (4.69 mmol) of 1-benzyl-4-(6-fluoronaphthyl)-piperazine, 1.2 ml (31.3 mmol) of formic acid, 3.0 grams 5% palladium on carbon, 50 ml ethanol. The reaction was stirred at room temperature for 16 hours, the catalyst filtered under N₂, and the solvent evaporated. The oil, N-(1-(6-fluoro)naphthyl)-piperazine (0.420 grams, 39%), was used directly in the following step.

E. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and nitrogen inlet were added 0.420 grams (1.83 mmol) of N-(1-naphthyl)piperazine, 0.440 grams (1.83 mmol) of 6-(2-bromoethyl)-benzoxazolone, 194 mg (1.83 mmol) of sodium carbonate, 50 ml methylisobutylketone, and a catalytic amount of sodium iodide. The reaction was refluxed for 3

5 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml ethyl acetate, the pH adjusted with aqueous 1N Sodium hydroxide solution, the layers separated, and the ethyl acetate layer washed with water and brine. The ethyl acetate layer was dried over sodium sulphate and evaporated, then chromatographed on silica gel. Fractions containing the product were combined and evaporated, the residue taken up in ether/methylene chloride, treated with hydrochloric acid gas, and the resulting hydrochloride salt of the product filtered off to give a white solid, m.p. 295°-300° C., 214 mg (22% yield).

EXAMPLE 10

6-(4-(4-(1-Naphthyl)piperazinyl)butyl)-benzoxazolone

A. To a 500 ml round-bottomed flask equipped with mechanical stirrer and nitrogen inlet were added 200 grams polyphosphoric acid, 16.7 grams (0.1 mol) 4-bromobutyric acid, and 13.51 grams (0.1 mol) benzoxazolone. The reaction was heated at 115° C. for 1 hour and 60° C. for 1.5 hours. It was then poured onto ice, stirred for 45 minutes and the solid filtered and washed with water. The solid was suspended in acetone, stirred for 20 minutes, filtered, washed with petroleum ether, and dried to give 12.3 grams (43%) of white solid 6-(4-bromobutyryl)-benzoxazolone NMR (d, DMSO-d₆): 1.77 (quin, 2H), 3.00 (t, 2H), 3.45 (t, 2H), 7.0-7.8 (m, 3H).

B. To a 100 ml three-necked round-bottomed flask equipped with dropping funnel, thermometer, and nitrogen inlet were added 10 grams (0.035 mol) 6-(4-bromobutyryl)-benzoxazolone and 26.08 ml (0.35 mol) trifluoroacetic acid. To the stirring suspension was added dropwise 12.93 ml (0.080 mol) triethylsilane, and the reaction stirred at room temperature for 16 hours. The reaction was then poured into water, and the resulting white solid filtered and washed with water. It was then suspended in isopropyl ether, stirred, and filtered to afford white solid 6-(4-trifluoroacetoxybutyl)-benzoxazolone, m.p. 100°-103° C., 10.47 grams (98.7%).

C. To a 250 ml round-bottomed flask equipped with nitrogen inlet were added 5.0 grams (0.0164 mol) 6-(trifluoroacetoxybutyl)-benzoxazolone, 100 ml methanol, and 1 gram sodium carbonate. The reaction was stirred at room temperature for 1 hour, evaporated, and the residue taken up in methylene chloride/methanol, washed with aqueous HCl, dried over sodium sulfate, and evaporated to white solid 6-(4-chlorobutyl)-benzoxazolone, m.p. 130°-133° C., 2.57 grams (75.7%).

E. To a 100 ml round-bottom flask equipped with condenser and nitrogen inlet were added 0.658 grams (3.10 mmol) of 6-(4-chlorobutyl)-benzoxazolone, 0.7 grams (3.10 mmol) of N-(1-naphthyl)piperazine, 0.328 grams sodium carbonate, 2 mg sodium iodide, and 50 ml isopropanol. The reaction was refluxed for 3 days, evaporated, taken up in methylene chloride, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate as eluent, and the product dissolved in

5 acetone, precipitated with ethereal HCl, and the white solid filtered, washed with acetone, and dried to afford 6.76 grams (46.0%) of a white solid, m.p. 231°-233° C.

EXAMPLE 11

6-(2-(4-(3-(N-(3-Trifluoromethyl)phenyl)indazolyl)-piperazinyl)ethyl)benzoxazolone

To a 125 ml round-bottomed flask equipped with condenser were added 1.0 gram (2.89
10 mmol) of N-(3-tri-fluoromethylphenyl)indazolyl)piperazine, 0.70 grams (2.89 mol) of 6-(2-bromoethyl)benzoxazolone, 0.31 grams (2.89 mmol) of sodium carbonate, and 50 ml of methyl isobutyl ketone, and the mixture refluxed 18 hours. The reaction was cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was isolated, washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to an oil.
15 The oil was chromatographed on silica gel using ethyl acetate/methylene chloride as eluent, and the product fractions collection and dissolved in ether, precipitated with hydrochloride gas, and the solid collected to give the hydrochloride salt of the title compound, m.p. 280°-282° C., 0.75 grams (47%).

EXAMPLE 12

5-(2-(4-(1-Naphthyl)piperazinyl)ethyl)oxindole

20 A. To a 250 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 30.7 grams (230 mmol) aluminum chloride, 150 ml carbon disulfide, and 3.8 ml (48 mmol) chloroacetyl chloride. To the stirring mixture was added 5.0 grams (37 mmol) of oxindole portionwise over 15 minutes. The reaction was stirred a further 10 minutes, then refluxed 2
25 hours. The reaction was cooled, added to ice, stirred thoroughly, and the beige precipitate filtered, washed with water, and dried to afford 7.67 grams (97%) of 5-chloroacetyl-oxindole. NMR (d, DMSO-d₆): 3.40 (s, 2H), 5.05 (s, 2H), 6.8-7.9 (m, 3H).

B. To a 100 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 5.0 grams (23.9 mmol) of 5-chloroacetyl oxindole and 18.5 ml trifluoroacetic acid. To the
30 stirring solution was added 8.77 ml (54.9 mmol) of triethylsilane while cooling to prevent exotherm, and the reaction stirred 16 hours at room temperature. The reaction was then poured into ice water, stirred and the beige solid filtered, washed with water and hexane, and dried to give 5-(2-chloroethyl)oxindole, m.p. 168°-170° C., 3.0 grams (64%).

C. To a 50 ml round bottomed flask equipped with condenser and nitrogen inlet were
35 added 370 mg (1.69 mmol) 5-(2-chloroethyl)oxindole, 400 mg (1.69 mmol) N-(1-naphthyl)piperazine hydrochloride, 200 mg (1.69 mmol) sodium carbonate, 2 mg sodium iodide, and 50 ml methylisobutylketone. The reaction was refluxed 24 hours, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel with ethyl acetate, and
40 the product fractions collected and evaporated to give a foam. The foam was dissolved in ether,

5 treated with hydrochloric acid gas, and the precipitate collected, washed with ether, and dried to afford a white solid, m.p. 303°-305° C., 603 mg (84%).

EXAMPLE 13

6-(2-(4-(4-(2-,1,3-Benzothiadiazolyl)piperazinyl)ethyl)-benzoxazolone

A. To a 125 ml round-bottomed flask equipped with condenser and nitrogen inlet were
10 added 2.0 grams (13.2 mmol) 4-amino-2,1,3-benzothiadiazole, 2.54 grams (13.2 mmol)
mechlorethamine hydrochloride, 4.19 grams (39.6 mmol) sodium carbonate, 2 mg sodium iodide,
and 50 ml ethanol. The reaction was refluxed 2 days, cooled, and evaporated. The residue was
taken up in methylene chloride, washed in water, dried over sodium sulfate, and evaporated. The
residue was chromatographed on silica gel using ethyl acetate/methanol as eluent, and the
15 product fractions collected and evaporated to an oil of 4-(2,1,3-benzothiadiazolyl)-N-
methylpiperazine, 628 mg (20%). NMR (d, CDCl₃): 2.5 (s, 3H), 2.8 (m, 4H), 3.6 (m, 4H), 6.8 (m,
1H), 7.5 (m, 2H).

B. To a 25 ml round-bottomed flask equipped with condenser and nitrogen inlet were
added 620 mg (2.64 mmol) of 4-(2,1,3-benzothiadiazolyl)-N-methylpiperazine, 0.224 ml (2.64
20 mmol) vinyl chloroformate, and 15 ml dichloroethane. The reaction was refluxed 16 hours,
cooled, and evaporated. The residue was chromatographed on silica gel using methylene
chloride/ethyl acetate as eluent, and the product fractions collected to give yellow solid 4-(2,1,3-
benzothiadiazolyl)-N-vinyloxycarbonylpiperazine, 530 mg (69%). NMR (d, CDCl₃): 3.6 (m, 4H),
3.8 (m, 4H). 4.4-5.0 (m, 2H), 6.6-7.6 (m, 4H).

25 C. To a 50 ml round-bottomed flask equipped with condenser and nitrogen inlet were
added 530 mg (1.83 mmol) 4-(2,1,3-benzothiadiazolyl)-N-vinyloxycarbonylpiperazine and 25 ml
ethanol, and the suspension saturated with hydrochloric acid gas. The reaction was refluxed
2.75 hours, cooled and evaporated. The residue was triturated with acetone to give a yellow
solid N-(2,1,3-benzothiadiazolyl)-piperazine, m.p. 240°-244°C., 365 mg (62%).

30 D. To a 125 ml round-bottomed flask equipped with condenser and nitrogen inlet were
added 365 mg (1.13 mmol) N-(2,1,3-benzothiadiazolyl)-piperazine, 275 mg (1.13 mmol) 6-(2-
bromoethyl)benzoxazolone, 359 mg (3.39 mmol) sodium carbonate, 2 mg sodium iodide and 40
ml ethanol. The reaction was heated at reflux for 2 days, cooled and evaporated. The residue
was taken up in methylene chloride, washed with water, dried over sodium sulfate, and
35 evaporated. The residue was chromatographed on silica gel using ethyl acetate/methanol as
eluent and the product fractions collected, dissolved in methylene chloride/methanol, precipitated
by addition of an ethereal solution of HCl, and the solid filtered, washed with ether, and dried to
give 228 mg (45%), m.p. 166°-170° C.

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EXAMPLE 146-(2-(4-(1-Naphthyl)-piperazinyl)ethyl)benzothiazolone

To a 100 ml round-bottomed flask with condenser and nitrogen inlet were added 1.0 gram (3.88 mmol) of 6-(2-bromoethyl)benzothiazolone, 822 mg (3.88 mmol) N-(1-naphthyl)piperazine, 410 mg (3.88 mmol) sodium carbonate, and 50 ml methylisobutylketone. The reaction was refluxed for 24 hours, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated. The resulting solid was treated with hot ethyl acetate to afford a white solid, m.p. 198°-220°C., 540 mg (36%).

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EXAMPLE 156-(2-(4-(3-benzisothiazolyl)piperazinyl)ethyl)benzoxazolone

To a 125 ml round-bottomed flask equipped with condenser were added 4.82 grams (0.022 mol) of N-(3-benzisothiazolyl)piperazine (prepared according to the procedure given in U.S. Pat. No. 4,411,901), 5.32 grams (0.022 mol) of 6-(2-bromo)ethylbenzoxazolone, 2.33 grams (0.022 mol) of sodium carbonate, and 50 ml of methyl isobutyl ketone. The mixture was refluxed for 18 hours. The reaction was cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was isolated, washed with water and saturated aqueous sodium chloride solution dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using ethyl acetate as eluent, and the product fractions collected and triturated with methylene chloride/isopropyl ether to give a white solid, m.p. 185°-187°C. NMR (CDCl₃): 1.7 (bs, 1H), 2.8 (m, 8H), 3.6 (m, 4H), 6.9-8.0 (m, 7H).

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EXAMPLE 165-(2-(4-(1,2-benzisothiazol-3-yl)-piperazinyl)ethyl)oxindole

To a 125 ml round-bottom flask equipped with nitrogen inlet and condenser were added 0.62 grams (3.20 mmol) 5-(2-chloroethyl)-oxindole, 0.70 grams (3.20 mmol) sodium carbonate, 2 mg sodium iodide, and 30 ml methylisobutyl ketone. The reaction was refluxed 40 hours, cooled, filtered, and evaporated. The residue was chromatographed on silica gel, eluting the byproducts with ethyl acetate (1 1) and the product with 4% methanol in ethyl acetate (1.5 1). The product fractions (R_f = 0.2 in 5% methanol in ethyl acetate) were evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid was filtered and washed with ether, dried, and washed with acetone. The latter was done by slurrying the solid acetone and filtering. The title compound was obtained as a high melting, non-hygroscopic solid product, m.p. 288°-288.5° C., 0.78 (59%).

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In a manner analogous to that for preparing 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-oxindole, the following compounds were made:

- 5 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-ethyloxindole hydrochloride, 25%, m.p. 278°-279° C.;
- 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-methyloxindole hydrochloride hemihydrate, 42%, m.p. 283°-285° C.; MS(%): 392(1), 232(100), 177(31); Anal. for $C_{22}H_{24}N_4OS.HCl.\frac{1}{2}H_2O$: C 60.33, H 5.98, N 12.79. Found: C 60.37, H 5.84, N 12.77;
- 10 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-(3-chlorophenyl)oxindole hydrochloride hydrate, 8%, m.p. 221°-223° C.; MS(%): 488(1), 256(4), 232(100), 177(15); Anal. for $C_{27}H_{25}ClN_4OS.HCl.H_2O$: C 59.67, H 5.19, N 10.31. Found: C 59.95, H 5.01, N 10.14;
- 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-3,3-dimethyloxindole hydrochloride hemihydrate, 40%, m.p. 289°-291° C.; MS(%): 406(1), 232(100), 177(42); Anal. for $C_{23}H_{26}N_4OS.HCl.\frac{1}{2}H_2O$: C 61.11, H 6.24, N 12.39. Found: C 61.44, H 6.22, N 12.01;
- 15 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1,3-dimethyloxindole, 76%, m.p. 256° C.;
- 5'-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-spiro[cyclopentane-1,3'-indoline]-2'-one hydrochloride hemihydrate, 50%, m.p. 291°-293° C. (dec.); MS(%): 432(1), 232(100), 200(11), 177(36); Anal. for $C_{25}H_{28}N_4OS.HCl.\frac{1}{2}H_2O$: C 62.81, H 6.33, N 11.72. Found: C 63.01, H 6.32, N 11.34;
- 20 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1,3,3-trimethyloxindole hydrochloride hemihydrate, 63%, m.p. 225°-257° C.; MS(%): 420(1), 232(100), 177(37); Anal. for $C_{24}H_{28}N_4OS.HCl.\frac{1}{2}H_2O$: C 61.85, H 6.49, N 12.02. Found: C 61.97, H 6.34, N 11.93;
- 25 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ether)-6-fluorooxindole hydrochloride hydrate, 18%, m.p. 291°-293° C.; MS(%): 396(1), 232(100), 177(53); Anal. for $C_{21}H_{21}FOS.HCl.\frac{1}{2}H_2O$: C 55.93, H 5.36, N 12.42. Found: C 56.39, H 5.30, N 12.19;
- 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-7-fluorooxindole hydrochloride, 9%, m.p. 253° C.;
- 30 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-chlorooxindole hydrochloride, 20%, m.p. >300° C.; MS(%): 488(1), 256(4), 232(100), 177(15); Analysis for $C_{21}H_{21}ClN_4OS.HCl.\frac{1}{2}H_2O$: C 52.50, H 4.71, N 11.39. Found: C 52.83, H 4.93, N 11.42;
- 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-fluoro-3,3-dimethyloxindole hydrochloride, 35%, m.p. 284°-286° C.; Anal. for $C_{23}H_{25}FN_4OS.HCl.H_2O$: C 57.67, H 5.89, N 11.70. Found: C 58.03, H 5.79, N 11.77;
- 35 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)oxindole hemihydrate, 26%, m.p. 131°-135° C.; MS(%): 406(2), 270(8), 243(65), 232(23), 177(45), 163(100); Anal. for $C_{23}H_{26}N_4OS.\frac{1}{2}H_2O$: C 66.48, H 6.55, N 13.48. Found: C 66.83, H 6.30, N 13.08;

5 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)-7-fluorooxindole hydrate, 7%, m.p. 126°-129° C.; MS(%): 424(3); Anal. for $C_{23}H_{25}FN_4OS \cdot H_2O$: C 57.67, H 5.89, N 11.70. Found: C 57.96, H 5.62, N 11.47;

10 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)-1-ethyloxindole hemihydrate, 25%, m.p. 126°-128° C.; MS(%): 434(2), 298(10), 271(55), 232(34), 177(53), 163(100); Anal. for $C_{25}H_{30}N_4OS \cdot \frac{1}{2}H_2O$: C 67.69, H 7.04, N 12.63. Found: C 67.94, H 6.73, N 12.21;

5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-1-ethyloxindole hydrochloride hydrate, 21%, m.p. >300° C.; MS(%): 399(1), 225(96), 182(30), 70(100); Anal. for $C_{26}H_{29}N_3O \cdot HCl \cdot H_2O$: C 68.78, H 7.10, N 9.26. Found: C 69.09, H 6.72, N 9.20;

15 5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-6-fluorooxindole hydrochloride, 23%, m.p. 289°-291° C.; MS(%): 389(1), 232(3), 225(100), 182(32), 70(84); Anal. for $C_{24}H_{24}FN_3O \cdot HCl \cdot \frac{1}{2}CH_2Cl_2$: C 62.82, H 5.60, N 8.97. Found: C 62.42, H 5.82, N 8.77;

5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-7-fluorooxindole hydrochloride, 22%, m.p. 308° C.(dec.); MS(%): 389(1), 225(100); Anal. for $C_{24}H_{24}FN_3O \cdot HCl \cdot CH_2Cl_2$: C 58.78, H 5.93, N 8.23. Found: C 58.82, H 5.80, N 8.27;

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EXAMPLE 176-(4-(2-(3-Benzisothiazolyl)piperazinyl)ethyl)phenyl)benzothiazolone

To a 100 ml round-bottomed flask equipped with condenser and nitrogen inlet were added 1.03 grams (4 mmol) 6-(2-bromoethyl)-benzothiazolone, 0.88 grams (4 mmol) N-benzisothiazolylpiperazine, 0.84 grams (8 mmol) sodium carbonate, 2 mg sodium iodide, and 40 ml methylisobutyl ketone. The reaction was refluxed 36 hours, cooled, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel using ethyl acetate as eluent to afford an oil, which was taken up in methylene chloride and precipitated by addition of ether saturated with HCl. The solid was filtered, washed with ether, dried briefly, washed with a minimal amount of acetone and dried to afford a white solid, m.p. 288°-290° C., 1.44 grams 30 (76.7%).

EXAMPLE A

A. Following the general procedure for the preparation of 5-(chloroacetyl)oxindole in Example 12A, the following intermediates were prepared from the appropriate oxindoles:

35 5-(chloroacetyl)-1-ethyl-oxindole (81%, m.p. 157°-159° C., NMR($CDCl_3$): 1.30(t,3H), 3.60(s,2H), 3.85(q,2H), 4.70(s,2H), 6.85-8.15(m,2H);

5-(chloroacetyl)-1-methyloxindole($C_{11}H_{10}ClNO_2$, 92%, m.p. 201°-202°C.;

40 1-(3-chlorophenyl)-5(chloroacetyl)oxindole, 98% m.p. 143°-145° C., NMR(DMSO- d_6): 3.85(br s,2H), 5.10(s,2H), 6.8(d,1H), 7.4-7.6(m,4H), 7.9 (s+d,2H); MS(%): 319(17), 270(100), 179(46), 178(38);

- 5 1,3-dimethyl-5-(chloroacetyl)oxindole, 97% m.p. 206° - 207° C.
 5-(chloroacetyl)-spirocyclopentane[1,3']-indol-2-one, 99%, m.p. 203° -204° C.(dec.);
 NMR(DMSO-d₆): 2.0(br s,8H), 4.95(s,2H), 6.9(d,1H), 7.8(d+s,2H), 10.6(br s, 1H);
 5-(chloroacetyl)-1,3,3-trimethyloxindole, 82%, m.p. 182° -185° C., NMR(CDCl₃):
 1.45(s,6H), 3.25(s,3H), 4.65(s,2H), 6.9(d,1H), 7.9(s,1H), 8.0(d,1H);
- 10 6-fluoro-5-(chloroacetyl)oxindole, 96%, m.p. 178° -180° C.; NMR(DMSO-d₆): 3.5(s,2H),
 4.8(d,2H), 6.7-7.2(m,2H), 7.8(d,1H);
 7-fluoro-5-(chloroacetyl)oxindole, 91%, m.p. 194° -196° C., NMR(DMSO-d₆): 3.68(s,2H),
 5.13(s,2H) 7.65-7.9(dd,2H);
 6-chloro-5-(chloroacetyl)oxindole, 99%, m.p. 206° -207° C.;
- 15 5-(chloroacetyl)-3,3-dimethyl-6-fluorooxindole, 89%, m.p. 185° - 188° C.;
 5-(γ-chlorobutyryl)oxindole, 84%, oil, MS(%): 239, 237(55);
 1-ethyl-5-(γ-chlorobutyryl)oxindole, 99%, oil, NMR(CDCl₃): 1.2(t,3H), 1.5-2.7(m,5H), 3.0-
 3.2(m,2H), 3.5-4.0(m,3H), 6.8-7.0(d,1H), 7.9(s,1H), 7.95(d,1H), and
 5-(γ-chlorobutyryl)-7-fluorooxindole, 53%, m.p. 156° - 160° C.
- 20 EXAMPLE B
 By the same procedure as that used to prepare 5-(2-chloroethyl)oxindole in Example 12B,
 the following were prepared:
 5-(2-chloroethyl)-1-ethyloxindole, 93%, m.p. 120° - 122° C.; NMR (CDCl₃): 1.30(t,2H),
 3.55(s,2H), 3.65-4.0(m,4H), 6.8-7.3(m,3H);
- 25 5-(2-chloroethyl)-1-methyloxindole, 99%, m.p. 127° - 130° C.; NMR (CDCl₃): 3.1(t,2H),
 3.2(s,2H), 3.5(s,2H), 3.75(t,2H), 6.8(d,1H), 7.15(s,1H), 7.3(d,1H);
 5-(2-chloroethyl)-1-(3-chlorophenyl)oxindole, 83%, m.p. 75° - 76° C.;
- 5-(2-chloroethyl)-1,3-dimethyloxindole, 58%, m.p. 73° - 75° C., NMR CDCl₃): 1.45-
 1.55(d,3H), 3.03-3.2(t,2H), 3.25(s,3H), 3.30-3.60(q,1H), 3.65-3.90(t,2H), 6.85-6.90(d,1H),
 30 7.15(s,1H), 7.15-7.30(d,1H);
 5'-(2-chloroethyl)-spiro[cyclopentane-1,3'-indoline]-2'-one, 92%, m.p. 140° -142° C.;
 NMR(DMSO-d₆): 2.8(br s,8H), 2.90(t,2H), 3.7(t,2H), 6.6-7.1(m,3H), 10.2(br s,1H);
 5-(2-chloroethyl)-,3,3-trimethyloxindole, 83%, oil;
- 5-(2-chloroethyl)-6-fluorooxindole 62%, m.p. 188° -190° C.; NMR(DMSO-d₆) 3.05(t,2H),
 35 3.5(2,2H), 3.85(t,2H), 6.6-7.3(m,2H);
 5-(2-chloroethyl)-7-fluorooxindole, 79%, m.p. 176° -179° C.; MS(%); 213(50), 180(20),
 164(100), 136(76);
 5-(2-chloroethyl)-6-chlorooxindole, 94%, m.p. 210° -211° C.;
- 5-(2-chloroethyl)-3,3-dimethyl-6-fluorooxindole (C₁₂H₁₃ClFNO, 84%, m.p. 195° -196° C.,
 40 NMR(DMSO-d₆): 1.3(s,6H), 3.05(t,2H), 3.7(t,2H), 6.65(d,1H), 7.1(d,1H), 10.1(br s,1H);

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5 5-(4-chlorobutyl)oxindole, 40%, oil, NMR(CDCl₃): 1.6-2.0(m,4H), 2.6(m,2H), 3.6(m,4H), 6.8-7.15(m,3H), 9.05(br s,1H);

 5-(4-chlorobutyl)-ethyloxindole, 48%, oil, NMR(CDCl₃): 1.25(t,3H), 1.5-1.95(m,4H), 2.6(m,2H), 3.5(s,2H), 3.55(t,2H), 3.75(q,2H), 6.7-7.2(m,3H); and

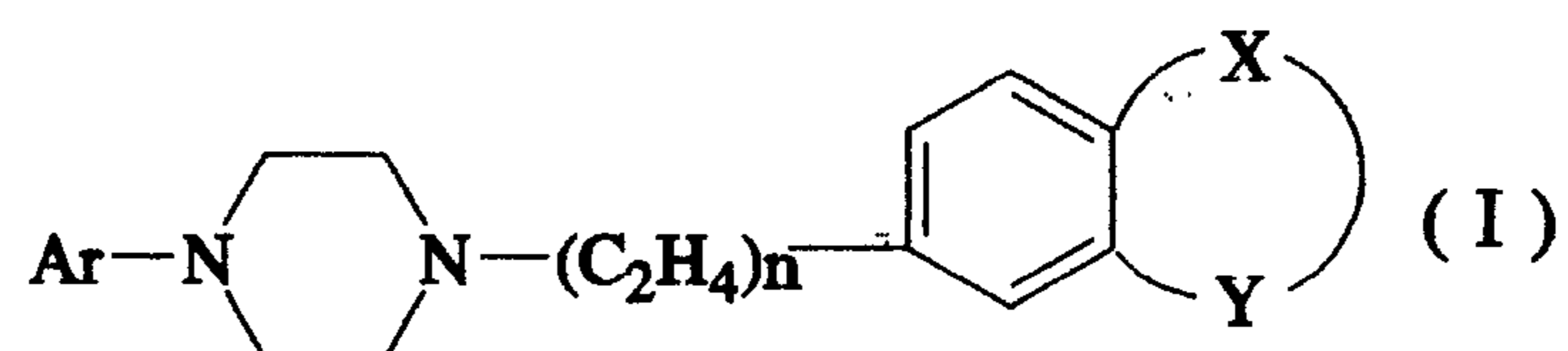
 5-(4-chlorobutyl)-7-fluorooxindole, 71%, m.p. 168° -173° C.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A medicine for treating Tourette's syndrome, obsessive compulsive disorder or chronic motor or vocal tic disorder in a mammal, which comprises:

(A) an effective amount of a compound of the formula:



(wherein:

Ar is (1) benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; (2) naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; (3) quinolyl; (4) 6-hydroxy-8-quinolyl; (5) isoquinolyl; (6) quinazolyl; (7) benzothiazolyl; (8) benzothiadiazolyl; (9) benzotriazolyl; (10) benzoxazolyl; (11) benzoxazolonyl; (12) indolyl; (13) indanyl optionally substituted by one or two fluoro; (14) indazolyl optionally substituted by 1-trifluoromethylphenyl or (15) phthalazinyl;

n is 1 or 2; and

X and Y together with the phenyl to which they are attached form (1) quinolyl; (2) 2-hydroxyquinolyl; (3) benzothiazolyl; (4) 2-aminobenzothiazolyl; (5)

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benzothiazolyl; (6) indazolyl; (7) 2-hydroxyindazolyl; (8) indolyl; (9) oxindolyl optionally substituted by one to three of (C₁-C₃)alkyl or one of chloro, fluoro or phenyl, the phenyl being optionally substituted by one chloro or fluoro; (10) benzoxazolyl; (11) 2-aminobenzoxazolyl; (12) benzoxazolonyl; (13) 2-aminobenzoxazolinylyl; (14) benzothiazolonyl; (15) benzoimidazolonyl; or (16) benzotriazolyl),

or a pharmaceutically acceptable acid addition salt thereof, and

(B) a pharmaceutically acceptable carrier or diluent.

2. A medicine according to claim 1, for treating Tourette's syndrome.
3. A medicine according to claim 1, for treating obsessive compulsive disorder.
4. A medicine according to claim 1, for treating chronic motor tic disorder.
5. A medicine according to claim 1, for treating vocal tic disorder.
6. A medicine according to any one of claims 1 to 5, wherein X and Y together with the phenyl to which they are attached form benzoxazolonyl.

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7. A medicine according to claim 2, wherein Ar is benzoisothiazolyl and n is 1.
8. A medicine according to any one of claims 1 to 5, wherein X and Y together with the phenyl to which they are attached form oxindolyl optionally substituted by chloro, fluoro or phenyl.
9. A medicine according to any one of claims 1 to 5, wherein Ar is naphthyl and n is 1.
10. A medicine according to any one of claims 1 to 9 with a daily dosage of the compound of the formula (I) or salt for a human subject in the range of 5 to 500 mg.
11. A medicine according to any one of claims 1 to 9 with a daily dosage of the compound of the formula (I) or salt for a human subject in the range of 10 to 80 mg.
12. A commercial package comprising the medicine according to claim 1 or any one of claims 6 to 11 and a written matter which states that the medicine can or should be used for treating Tourette's syndrome, obsessive compulsive disorder or chronic motor or vocal tic disorder in a human.
13. A commercial package according to claim 12, wherein the written matter states that the medicine can or should be

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used for treating Tourette's syndrome.

14. A commercial package according to claim 12, wherein the written matter states that the medicine can or should be used for treating obsessive compulsive disorder.

15. A commercial package according to claim 12, wherein the written matter states that the medicine can or should be used for treating chronic motor tic disorder.

16. A commercial package according to claim 12, wherein the written matter states that the medicine can or should be used for treating vocal tic disorder.

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PATENT AGENTS

