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(54) **BENZOTHIOPHENE ALKANOL PIPERAZINE DERIVATIVES AND THEIR USE AS ANTIDEPRESSANT**

BENZOTHIOPHENALKANOLPIPERAZINDERIVATE UND IHRE VERWENDUNG ALS ANTIDEPRESSIVUM

DÉRIVÉS DE BENZOTHIOPHÈNE ALCANOL PIPÉRAZINE ET LEUR UTILISATION COMME ANTIDÉPRESSEURS

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- **CHEMICAL ABSTRACTS, Columbus, Ohio, US; abstract no. 68: 12797, XP008142514 & SAUTER, FRITZ ET AL.: 'N-Substituted 2-methyl-3-aminoacetylbenzo[b]thiothene and 2-methyl-3-(a -hydroxy-beta-aminoethyl)benzo[b]thiophene.'** **MONATSFESTE FUER CHEMIE vol. 98, no. 5, 1967, pages 2039 - 43**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 2 311 828 B9

Description**FIELD OF INVENTION**

5 **[0001]** The present invention relates to benzothiophene alkanol piperazine derivatives and their use as broad-spectrum antidepressants.

BACKGROUND OF THE INVENTION

10 **[0002]** Depression is a syndrome characterized by significant and lasting low mood, which mainly manifests as affective disorder. The symptoms include low mood, less speech, slow mentality and motion, and even suicide attempt.

[0003] Depression, as a chronic mental disease, has become a major problem which bothers the medical health service in China, due to long treatment course, slow effect onset and higher rate of relapse, disability and suicide. According to "World Health Reports" announced by World Health Organization (WHO), depression has become the
15 fourth largest disease in the world, and depression might become the second largest illness after heart disease by 2020, and thus become a serious problem to human health.

[0004] By now, the action mechanism of antidepressant has not been clearly demonstrated. Drugs having definite effect substantially act on synapses of the nerve ending, and exert their curative effects by adjusting the level of neurotransmitters in synaptic cleft. The biochemistry study on etiology indicated that depression relates mainly to five types
20 of neurotransmitters, i.e., central 5-hydroxytryptamine (5-HT), noradrenaline (NA), dopamine (DA), acetylcholine (Ach), and γ -aminobutyric acid (GABA).

[0005] Antidepressant can be divided into two categories: early non-selective antidepressants and novel selective reuptake inhibitors. Non-selective antidepressants mainly include monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs); selective reuptake inhibitors mainly comprise selective 5-hydroxytryptamine (5-HT) reuptake
25 inhibitors (SSRIs), noradrenaline (NA) reuptake inhibitors (NRIs), noradrenergic and specific 5-HT reuptake inhibitors (NDRIs), 5-HT and NA reuptake inhibitors (SNRIs), 5-HT re-absorption enhancers, and the like.

[0006] There are two trends in the worldwide situation of studies on antidepressant:

One is redevelopment of existing drugs. It includes: 1) further development of new indications of existing drugs, and 2) change of dosage forms of existing drugs.

30 **[0007]** Another is further development of new products, i.e., develop novel antidepressants with better antidepressant effects, faster onset of action and higher safety than existing commercial available drugs by seeking new structural type of compound which acts on a new target or multiple action targets.

[0008] European patent application publication No. EP1008594A1 discloses compounds derived from thiophene and benzothiophene effective for the treatment of anxiety or depression. International patent application publication No. WO
35 0244170 A2 discloses benzothiophene derivatives as serotonin re-uptake inhibitors and showing high affinity to the 5-HT_{1A} receptor for the treatment of neurological disorders.

[0009] Chinese patent application No. 2006100135485 disclosed a benzo[b]thiophene compound modified with substituted phenylpiperazine for the treatment of depression. However, it is hard to be practically applied since no pharmacological data of anti-depression effect in vitro and in vivo was available.

40 **[0010]** Up to date, existing antidepressants still cannot meet the treatment demand. Research on triple selective reuptake inhibitors is continuously drawing attention, and is expected to solve the hysteresis effect of existing antidepressants, and to improve effectiveness and increase safety etc. Triple selective reuptake inhibitors, also known as "broad spectrum" antidepressants, are compounds which are able to simultaneously selectively inhibit three types of monoamine transmitters 5-HT, NA and DA closely related to depression.

45 **[0011]** Studies on 5-HT, NA and DA triple selective reuptake inhibitors developed based on dual reuptake inhibitors have become focus of current antidepressants research, which will have more advantages in onset of action and effectiveness.

[0012] Novel triple selective reuptake inhibitors are now still on clinical research stage. For example, triple selective reuptake inhibitor DOV-216303 developed by DOV Pharmaceutical Inc. is on phase III clinical trial; NS-2359 jointly
50 developed by GlaxoSmithKline and NeuroSearch Inc. is on phase II antidepressant clinical trial now.

[0013] These monoamine transmitter triple selective reuptake inhibitors possess advantages in high effectiveness and fast onset of action and are becoming hot points in the antidepressants field. Research and development of antidepressants is still at its preliminary stage, especially for the research on novel triple routing antidepressants acting on 5-HT, NA and DA, which will further attract increasing attention.

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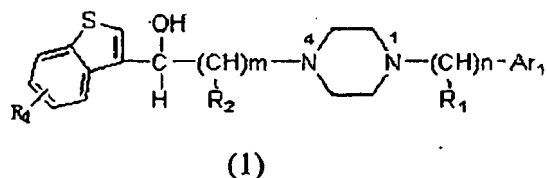
DESCRIPTION OF THE INVENTION

[0014] One of the objects of the present invention is to provide a type of benzothiophene alkanol piperazine derivative,

to overcome the defects of existing antidepressants in prior art, i.e., slow onset, low efficacy, side effects and poor safety etc., and thus meet the requirements of treating depression.

[0015] Another object of the present invention is to provide the use of above mentioned derivative as novel antidepressants.

[0016] The benzothiophene alkanol piperazine derivative mentioned in the present invention is a compound of formula (1)

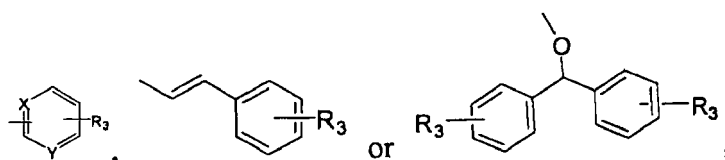


or a pharmaceutically acceptable salt thereof,

wherein the pharmaceutically acceptable salt thereof is a hydrochloride salt, a hydrobromide salt, a sulphate salt, a trifluoro acetate salt or a methanesulfonate salt, preferred pharmaceutically acceptable salt is a hydrochloride salt, a hydrobromide salt, and the pharmaceutically acceptable salt may contain 0.5 to 3 molecules of crystal water;

wherein,

Ar₁ represents:



R₁ and R₂ each independently represents hydrogen; C₁-C₆ alkyl; C₅ or C₆ alicyclic ring; phenyl; or phenyl substituted by C₁-C₆ alkyl, C₁-C₆ alkoxy or halo groups;

R₃ and R₄ each independently represents hydrogen; C₁-C₆ alkyl, phenyl; or phenyl substituted by one to four substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxyl, amino or halo; a 5-member or 6-member ring containing N or O; hydroxyl; C₁-C₆ alkoxy; amino; amino substituted by C₁-C₆ alkyl or C₁-C₆ haloalkyl; halo; carboxylic acid; carboxylic acid ester; nitro or acetonitrile;

X represents C or N;

Y represents C or N;

m is 1, 2 or 3, and

n is 1, 2 or 3.

[0017] Preferred R₃ is hydrogen; C₁-C₂ alkyl; hydroxyl; methoxy; ethoxy; amino; amino substituted by C₁-C₆ alkyl or C₁-C₆ haloalkyl; fluorine atom; phenyl; or phenyl substituted by one to four substituents independently selected from the groups consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxyl, amino and halo; more preferred R₃ is C₁-C₂ alkyl or fluorine atom.

[0018] Asymmetric carbons in the structure of the compound are achiral carbon atoms or chiral carbon atoms with R or S configuration.

[0019] Preferred compound include:

VII-1 N¹-benzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine,

VII-2 N¹-benzhydryl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine,

VII-3 N¹-(p-chlorobenzyl)-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-4 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (threo isomer),

VII-5 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (erythro isomer),

VII-6 N¹-p-aminobenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-7 N¹-p-methoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-8 N¹-p-ethoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-9 N¹-(p-hydroxybenzyl)-N⁴-[1-methyl-2-hydroxy-(benzo[b]thiophene-3-yl)] ethylpiperazine,

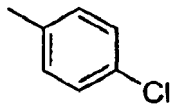
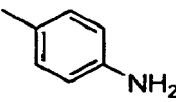
VII-10 N¹-benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,

- VII-11 N¹-cinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-12 N¹- α -phenethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-13 N¹-p-methoxybenzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-14 N¹-benzhydryl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 5 VII-15 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-16 N¹-benzyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-17 N¹-cinnamyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-18 N¹-benzhydryl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 10 VII-19 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-20 N¹-benzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-21 N¹- α -phenethyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-22 N¹-(p-chlorobenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-23 N¹-(p-methoxybenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 15 VII-24 N¹-benzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-25 N¹- α -phenethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-26 N¹-p-nitrobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-27 N¹-p-aminobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-28 N¹-cinnamyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 20 VII-29 N¹-benzhydryl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-30 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-31 N¹-(p-methoxycinnamyl)-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-32 N¹-p-aminocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-33 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 25 VII-34 N¹-(4,4'-dihydroxydiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-35 N¹-p-nitrocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-36 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methylbenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-37 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methoxybenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-38 N¹-benzyl-N⁴-[3-hydroxy-3-(6-aminobenzo[b]thiophene-3-yl)]propylpiperazine,
 30 VII-39 N¹-benzyl-N⁴-[3-hydroxy-3-(6-chlorobenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-40 N¹-benzyl-N⁴-[3-hydroxy-3-(6-methylaminobenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-41 N¹-(β -pyridinemethyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-42 N¹-(4-morpholinebenzyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine, and
 VII-43 N¹-benzyl-N⁴-[2-cyclopentylmethyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine.

[0020] Most preferred benzothiophene alkanol piperazine derivative is VII-10, i.e. N¹-benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine.

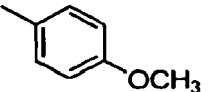
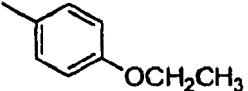
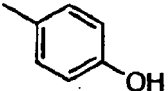
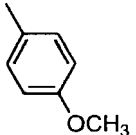
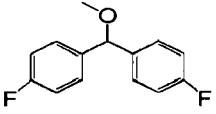
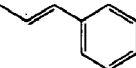
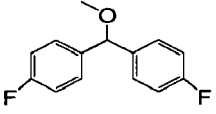
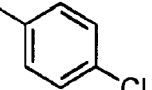
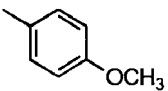
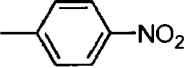
[0021] The structures are shown in Table 1.

Table 1

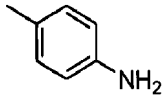
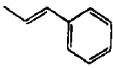
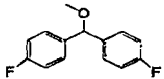
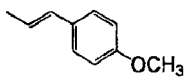
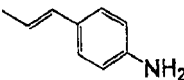
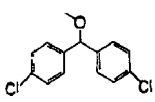
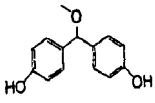
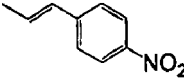

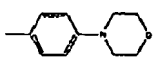

No.	Ar ₁	R ₁	R ₂	R ₄	X	Y	n	m
VII-1	Ph	H	H	H	C	C	1	1
VII-2	Ph	Ph	H	H	C	C	1	1
VII-3		H	H	H	C	C	1	1
VII-4	Ph	H	CH ₃	H	C	C	1	1
VII-5	Ph	H	CH ₃	H	C	C	1	1
VII-6		H	CH ₃	H	C	C	1	1

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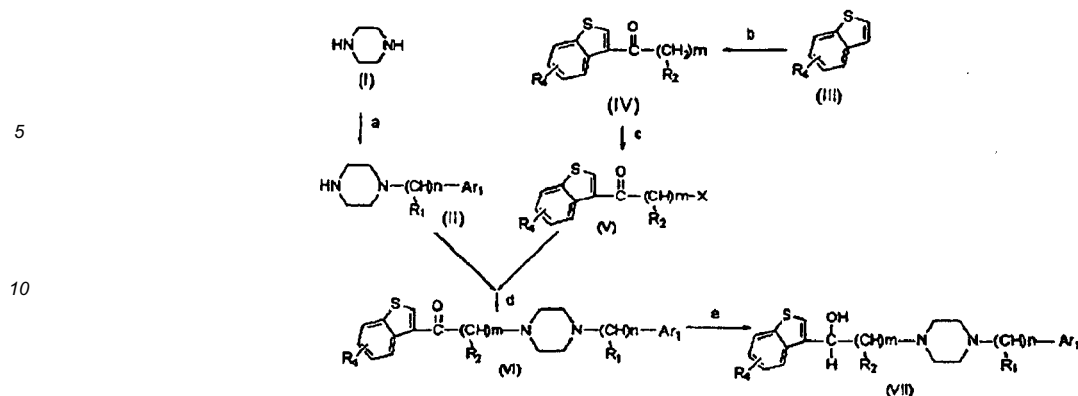
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No.	Ar ₁	R ₁	R ₂	R ₄	X	Y	n	m
VII-7		H	CH ₃	H	C	C	1	1
VII-8		H	CH ₃	H	C	C	1	1
VII-9		H	CH ₃	H	C	C	1	1
VII-10	Ph	H	H	H	C	C	1	2
VII-11	Ph	H	H	H	C	C	1	2
VII-12	Ph	CH ₃	H	H	C	C	1	2
VII-13		H	H	H	C	C	1	2
VII-14	Ph	Ph	H	H	C	C	1	2
VII-15		H	H	H	C	C	2	2
VII-16	Ph	H	CH ₃	H	C	C	1	2
VII-17		H	CH ₃	H	C	C	1	2
VII-18	Ph	Ph	CH ₃	H	C	C	1	2
VII-19		H	CH ₃	H	C	C	2	2
VII-20	Ph	H	C ₄ H ₉	H	C	C	1	1
VII-21	Ph	CH ₃	C ₄ H ₉	H	C	C	1	2
VII-22		H	C ₄ H ₉	H	C	C	1	2
VII-23		H	C ₄ H ₉	H	C	C	1	2
VII-24	Ph	H	H	H	C	C	1	3
VII-25	Ph	CH ₃	H	H	C	C	1	3
VII-26		H	H	H	C	C	1	3

(continued)

No.	Ar ₁	R ₁	R ₂	R ₄	X	Y	n	m
VII-27		H	H	H	C	C	1	3
VII-28		H	H	H	C	C	1	3
VII-29	Ph	Ph	H	H	C	C	1	3
VII-30		H	H	H	C	C	2	3
VII-31		H	H	H	C	C	1	2
VII-32		H	H	H	C	C	1	2
VII-33		H	H	H	C	C	1	2
VII-34		H	H	H	C	C	1	2
VII-35		H	H	H	C	C	1	2
VII-36	Ph	H	H	CH ₃	C	C	1	2
VII-37	Ph	H	H	OCH ₃	C	C	1	2
VII-38	Ph	H	H	NH ₂	C	C	1	2
VII-39	Ph	H	H	Cl	C	C	1	2
VII-40	Ph	H	H	NHCH ₃	C	C	1	2
VII-41		H	CH ₃	H	N	C	1	2
VII-42		H	CH ₃	H	C	C	1	2
VII-43	Ph	H		H	C	C	1	2

[0022] The compounds of the present invention can be synthesized by the following method:



15 [0023] During the above process:

a:



b:



30 c: $\text{CuBr}_2, \text{CHCl}_3, \text{EtOAc};$

d: $\text{K}_2\text{CO}_3, \text{KI}, \text{CH}_3\text{COCH}_3;$

35 e: $\text{NaBH}_4, \text{CH}_3\text{OH};$

[0024] The synthesis of said benzothiophene alkanol piperazine derivatives is started from piperazine (I). Firstly a nucleophilic substitution reaction with a corresponding halogenated arylalkane is performed to obtain N-monoalkylated compound (II). This reaction is carried out in phase transfer catalytic condition, using cetyltrimethylammonium bromide (CTAB) as the phase transfer catalyst, and in a reaction media of benzene/water. N-monoalkylation of piperazine may be carried out under the action of KOH, and the yield may be up to 86%.

[0025] Compound (III) is reacted with corresponding acid chloride to carry out a Friedel-Crafts reaction to obtain benzothiophene alkanone (IV). This reaction is performed in a solvent of chloroform at room temperature, using anhydrous aluminum chloride as catalyst, and the yield is about 60%.

[0026] Compound (IV) is bromized to give halogenated benzothiophene alkanone (V). This reaction is performed under heating to reflux by using CuBr_2 as brominating agent and a mixed solution of chloroform and ethyl acetate as solvent, and the yield is about 75%.

[0027] Compound (II) can be reacted with compound (V) to conduct N⁴-alkylation reaction to give benzothiophene alkanone piperazine compound (VI). The reaction is performed under refluxing for 8-24 hours using $\text{K}_2\text{CO}_3/\text{CH}_3\text{COCH}_3$ as reaction system to give a yield of 80%. Using the above steps, main intermediate (VI) for preparing target compound (VII) can be obtained.

[0028] Compound (VI) is reacted with NaBH_4 in methanol at room temperature for 0.5-2 hours to reduce carbonyl group to obtain corresponding benzothiophene alkanol piperazine compounds (VII). Using the above steps, target compounds VII-1 to VII-43 can be obtained.

[0029] Haloarylalkane, benzothiophene and substituted benzothiophene compounds (III) and alkyl acid chloride compounds in a, b and c are commercial available, the alkyl acid chloride can also be obtained from corresponding alkanolic acid and sulfoxide chloride by conventional synthetic method.

[0030] Said benzothiophene alkanol piperazine derivatives have triple inhibition effect on the reuptake of 5-HT, NA and DA, and can be used to prepare antidepressants.

[0031] The benzothiophene alkanol piperazine derivatives in the present invention may be administrated to patients in need thereof in the form of composition by route of oral administration, injection and the like.

[0032] Said composition includes therapeutically effective amount of said benzothiophene alkanol piperazine derivatives and their pharmaceutical carrier.

[0033] Said carrier is referred to conventional carrier in pharmaceutical field, for example diluents, excipients such as water; adhesive such as cellulose derivatives, gelatin, polyvinylpyrrolidone; fillers such as starch and the like; disintegrating agent such as calcium carbonate, sodium bicarbonate; in addition, other adjuvants such as flavoring agent and sweeteners may be added into the composition.

[0034] For oral administration, it may be formulated into conventional solid preparations such as tablet, powder or capsule; for injection administration, it may be formulated into an injection solution.

[0035] Various preparations of the composition according to the present invention can be prepared using conventional methods in medicine field, wherein the content of active ingredient is 0.1% to 99.5% (by weight).

[0036] The amount administrated in the present invention may vary according to route of administration, age and weight of the patient, type and severity of the disease being treated, and the like, and the daily dose is 5-30 mg/kg body weight (oral) or 1-10 mg/kg body weight (injection). The derivatives of the present invention showed antagonism against depression in animal experiments.

[0037] The inventor discovered that the structures of the compounds of the present invention are **characterized in that** N¹ position of piperazine is connected to a phenyl ring via 1-3 carbon atoms, the structure of which not only differs from the structural types of the compounds reported in the above patent publications, but also has triple inhibition effect on the reuptake of 5-HT, NA, DA and antidepressant activity in vivo. Compared with clinically used antidepressants so far having single or dual action mechanism, e.g. desipramine, fluoxetine, venlafaxine and the like, the said benzothiophene alkanol piperazine derivatives of the present invention may have a broader indication range, faster onset of effect and less toxic and side effects.

Specific Models for Carrying Out the Invention

General method 1: synthesis of N-aralkylpiperazine (II) hydrochloride

[0038] To 18 ml water, piperazine hexahydrate(350mmol, from Shanghai chemical reagent station), solid KOH (100mmol) and CTAB (Hexadecyl Trimethylammonium Bromide, 1mmol) were added, heated to dissolve. 140 ml solution of aralkyl chloride (100mmol, commercial available) in benzene was added dropwise at the temperature of 70°C. After dropping the reactant was refluxed for 3 hours, allowed to stand, and the organic phase was washed with 50ml water and 50ml saturated NaCl solution respectively, dried with MgSO₄ and filtered. The solvent was evaporated to dryness under vacuum, and the concentrate was then dissolved in 50ml absolute alcohol and adjusted to pH of 3 by dropping the solution of HCl/C₂H₅OH. Then a solid precipitated and was filtered and dried. N-aralkyl piperazine hydrochloride was obtained by recrystallization with ethanol. The yield was 75-86%.

General method 2: synthesis of benzothiophene alkanone(IV)

[0039] The alkanoyl chloride compound (28.4mmol) in synthetic route b was dissolved in chloroform (30ml), and AlCl₃(30.8mmol) was added. The reactant was stirred for 1h at room temperature, AlCl₃ dissolved gradually, and the color of the solution became darker to light brown. The temperature was controlled below 10°C. To the mixture 10ml solution of benzothiophene (23.7mmol) in chloroform was added gradually dropwise. After dropping, the reactant was warmed naturally to room temperature and stirred for 1h. The color of the reaction solution became darker to brown. The reaction solution was poured into a mixture of hydrochloric acid (20ml)/crashed ice(50g) under stirring, and the color of organic phase turned lighter to be light yellow to yellow. The organic phase was separated, washed with water (20ml×3) till the aqueous phase to be neutral and dried with anhydrous Na₂SO₄ overnight. The desiccant was filtered, the residue was washed with small amount of chloroform. Then the solvent of the filtrate was evaporated, and light yellow oily substance was obtained. Light yellow oily product was separated by column chromatography (ethyl acetate: petroleum ether=1:400~1:60), allowed to stand and solidified. The yield was 75-85%.

General method 3: synthesis of bromobenzothiophene alkanone(V)

[0040] The benzothiophene alkanone (21mmol) was dissolved in ethyl acetate(50ml) and chloroform(50ml), then CuBr₂(40.2mmol) was added, the reaction was performed under refluxing for 3 hours. CuBr produced was filtered out. The filtrate was washed with water (20ml×3), dried with anhydrous Na₂SO₄ overnight. The desiccant was filtered, the residue was washed with a small amount of ethyl acetate. The solvent of the filtrate was evaporated. Light yellow crystalline solid was obtained by recrystallization with ethanol. The yield was about 75%.

General method 4: synthesis of N¹-aralkyl-N⁴-benzothiophene formyl alkyl piperazine(VI) hydrochloride

[0041] N-aralkyl piperazine(II) hydrochloride(10mmol), bromobenzothiophene alkanone (V) (12mmol), potassium iodide (1mmol) and anhydrous K₂CO₃(35mmol) were placed into acetone (50ml) to react under stirring at 50°C for 8h. After filtered, the solvent was evaporated to dryness under vacuum. 50ml of water was added, the reactant was extracted with EtOAc (100ml×3). The ester layers were pooled and washed with 20ml water and 30ml saturated NaCl solution successively, dried with MgSO₄. After filtration, the solvent was evaporated. The concentrate was dissolved by adding 30ml of ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH (5N). The precipitated solid was filtered and recrystallized in ethanol/water or methanol to give a hydrochloride salt of compound (VI).

General method 5: synthesis of N¹-aralkyl-N⁴-benzothiophene alkanol piperazine (VII) hydrochloride

[0042] N¹-aralkyl-N⁴-benzothiophene formyl alkyl piperazine hydrochloride (VI) (3.5mmol) was placed into 60ml of methanol, and NaBH₄(14mmol) was added in portions. The reactant was stirred for 1h at the room temperature. After removing methanol by vacuum evaporation, 20ml of water was added and the reaction was extracted with EtOAc (40ml×3). The ester layers were pooled and washed with 20ml of saturated NaCl solution, then dried with MgSO₄. After filtration and the solvent was removed by vacuum evaporation, the residue was dissolved in 20ml ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH. A solid was precipitated and filtered. The hydrochloride salt of product (VII) was obtained by recrystallization with ethanol/water. If the product was a mixture of threo-form and erythro-form isomer, the corresponding threo-form and erythro-form of the compounds could be obtained by separation through neutral alumina column.

Example 1

VII-1 N¹-benzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine hydrochloride

[0043] 4.2g of N¹-phenyl-N⁴-(2-carbonyl-2-(benzo[b]thiophene-3-yl)]ethylpiperazine hydrochloride (12mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(2-chloroacetyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.2g of product was obtained in a yield of 75.7%. m.p.=267.8-269.4°C(dec).

[0044] MS(m/z): 353.2[M+1]⁺.

[0045] ¹HNMR(DMSO) : 7.81(d, J=7.6Hz, 1H, Ar-H), 7.70(dd, J=1.6, 6.8Hz, 1H, Ar-H), 7.28-7.32(m, 4H, Ar-H), 7.24-7.28(m, 3H, Ar-H), 7.22(s, 1H, thiophene), 4.60(d, J=10Hz, 1H, >CH-OH), 3.54(m, 2H, -CH₂-Ph), 2.75-2.78(m, 2H, CH₂), 2.52-2.74(m, 8H, piperazine).

Example 2

VII-2 N¹-benzhydryl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine hydrochloride

[0046] 3.8g of N¹-benzhydryl-N⁴-[2-carbonyl-2-(benzo[b]thiophene-3-yl)]ethylpiperazine hydrochloride (9mmol) was synthesized using N¹-benzhydrylpiperazine (20mmol) and 3-(2-chloroacetyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.1g of product was obtained in a yield of 80.5%. m.p.=278.0-279.8°C(dec).

[0047] MS(m/z): 429.1 [M+1]⁺.

[0048] ¹HNMR(DMSO) : 7.78-7.87(m, 4H, Ar-H), 7.28-7.45(m, 10H, Ar-H), 7.22(s, 1H, thiophene), 4.60(d, J=10Hz, 1H, -CH-OH), 5.07(m, 1H, -CH-Ph₂), 2.75-2.78(m, 2H, CH₂), 2.50-3.50(m, 8H, piperazine).

Example 3

VII-3 N¹-p-chlorobenzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine hydrochloride

[0049] 5.0g of N¹-(p-chlorobenzyl-N⁴-[2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (13mmol) was synthesized using N¹-p-chlorobenzylpiperazine (20mmol) and 3-(2-chloroacetyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.6g of product was obtained. m.p.=250.1-252.3°C(dec).

[0050] MS(m/z): 388.12[M+1]⁺.

[0051] ¹HNMR(DMSO) : 7.78-7.87(m, 4H, Ar-H), 7.28-7.45(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(d, J=10Hz, 1H, -CH-OH), 5.07(m, 2H, -CH₂-Ph), 2.75-2.78(m, 2H, CH₂), 2.50-3.50(m, 8H, piperazine).

Example 4

VII-4 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (threo isomer)

5 **[0052]** 4.37g of N¹-phenyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (10mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 1.2g of product was obtained by separation via column chromatography. m.p=268.0-270.4°C(dec).

[0053] MS(m/z): 367.2[M+1]⁺.

10 **[0054]** ¹HNMR(DMSO) : 7.28-7.81(m, 5H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(m, J=10Hz, 1H, CH-OH), 3.54(m, 2H, CH₂-Ph), 2.75-2.78(m, 1H, CH-CH₃), 2.52-2.74(m, 8H, piperazine), 0.93(d, 3H, CH-CH₃).

Example 5

15 VII-5 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (erythro isomer)

[0055] 4.37g of N¹-phenyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (10mmol) was synthesized using N¹-benzyl piperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 1.95 g of product was obtained by separation via column chromatography, m.p=220.7-222.0°C(dec).

[0056] MS(m/z): 367.1[M+1]⁺.

[0057] ¹HNMR(DMSO) : 7.28-7.79(m, 5H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.17(s, 1H, thiophene), 5.14(m, 1H, CH-OH), 3.53(m, 2H, CH₂-Ph), 2.82-2.86(m, 1H, CH-CH₃), 2.52-2.74(m, 8H, piperazine), 1.08(d, 3H, CH-CH₃).

Example 6

25 VII-6 N¹-p-aminobenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride

[0058] 4.2g of N¹-p-aminophenyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (11mmol) was synthesized using N¹-p-aminobenzyl piperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.2 g of product was obtained in a yield of 76.2%. m.p=255.7-257.4°C(dec).

[0059] MS(m/z): 382.2[M+1]⁺.

30 **[0060]** ¹HNMR(DMSO) : 7.28-7.81(m, 4H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(m, J=10Hz, 1H, CH-OH), 4.0(m, 2H, NH₂), 3.54(m, 2H, CH₂-Ph), 2.75-2.78(m, 1H, CH-CH₃), 2.52-2.74(m, 8H, piperazine), 0.93(d, 3H, CH-CH₃).

Example 7

40 VII-7 N¹-p-methoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride

[0061] 5.1 g of N¹-(p-methoxy)benzyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (13mmol) was synthesized using N¹-p-methoxy-benzylpiperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.7 g of product was obtained. m.p=262.0-264.4°C(dec).

[0062] MS(m/z): 397.1[M+1]⁺.

45 **[0063]** ¹HNMR(DMSO) : 7.28-7.81(m, 4H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(m, J=10Hz, 1H, CH-OH), 3.54(m, 2H, CH₂-Ph), 3.37(s, 3H, O-CH₃), 2.75-2.78(m, 1H, CH-CH₃), 2.52-2.74(m, 8H, piperazine), 0.93(d, 3H, CH-CH₃).

Example 8

VII-8 N¹-p-ethoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride

55 **[0064]** 4.37 g of N¹-p-ethoxybenzyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (10mmol) was synthesized using N¹-p-ethoxy-benzyl piperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 1.2 g of product was obtained in a yield of 27.3%. m.p=268.0-270.4°C(dec).

[0065] MS(m/z): 411.2[M+1]⁺.

[0066] ¹HNMR(DMSO) : 7.28-7.81(m, 4H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(m, J=10Hz, 1H, -CH-OH), 3.54(m, 2H, -CH₂-Ph), 3.37(m, 3H, O-CH₃), 2.75-2.78(m, 1H, -CH-CH₃), 2.52-2.74(m, 8H, piperazine), 2.49(m, 2H, CH₂CH₃), 1.24(m, 3H, CH₂CH₃), 0.93(d, 3H, CH-CH₃).

5

Example 9

VII-9 N¹-p-hydroxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride

10 [0067] 4.2 g of N¹-p-hydroxybenzyl-N⁴-[1-methyl-2-carbonyl-2-(benzo[b]thiophene-3-yl)] ethylpiperazine hydrochloride (11mmol) was synthesized using N¹-p-hydroxybenzylpiperazine (20mmol) and 3-(2-bromopropionyl)-benzo[b] thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.7 g of product was obtained. m.p=256.4-258.3°C(dec).

[0068] MS(m/z): 383.2[M+1]⁺.

15 [0069] ¹HNMR(DMSO) : 7.28-7.81(m, 4H, Ar-H), 7.24-7.28(m, 4H, Ar-H), 7.22(s, 1H, thiophene), 4.60(m, J=10Hz, 1H, -CH-OH), 3.54(m, 2H, -CH₂-Ph), 2.75-2.78(m, 1H, -CH-CH₃), 2.52-2.74(m, 8H, piperazine), 0.93(d, 3H, CH-CH₃).

Example 10

20 VII-10 N¹-benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride

[0070] 4.37 g of N¹-benzyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride (10mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.95 g of product was obtained in a yield of 90%. m.p=257.5-259.0°C(dec).

25

[0071] MS(m/z): 367.1[M+1]⁺.

[0072] ¹HNMR(DMSO) : 7.65-7.90(m,4H,Ar-H), 7.46(s,1H,thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29 (m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.58-3.51 (m,8H, piperazine), 2.24-2.56(m,2H,-CH₂CH₂N).

30

Example 11

VII-11 N¹-cinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride

35 [0073] 4.63 g of N¹-cinnamyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride (10mmol) was synthesized using N¹-cinnamylpiperazine(20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.35 g of product was obtained in a yield of 93%. m.p=191.5-192.4°C(dec).

[0074] MS(m/z): 393.1[M+1]⁺.

40 [0075] ¹HNMR(DMSO) :7.65-7.90(m,4H,Ar-H),7.46(s,1H,thiophene), 7.43-7.45(m, 5H, Ar-H), 6.15-6.33(m, 2H, N-CH=CH-Ph), 5.26-5.29(m, 1H, CH₂CHOH), 3.73-3.74(m, 2H, N-CH₂-CH=),3.51(m, 2H, -CHOHCH₂-),2.58-3.51(m,8H, piperazine), 2.24-2.56 (m, 2H, -CH₂CH₂N).

Example 12

45

VII-12 N¹-α-phenethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride

[0076] 4.50 g of N¹-α-phenethyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-α-phenethylpiperazine (20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.0 g of product was obtained in a yield of 76.7%. m.p=189.1-192.2°C(dec).

50

[0077] MS(m/z): 381.1[M+1]⁺.

[0078] ¹HNMR(DMSO) : 7.65-7.94(m,4H,Ar-H),7.43-7.48(m,5H,Ar-H), 5.21(m, 1H, CH-CH₃), 4.36-4.37(m, 1H, CH-OH), 3.50-3.60(m, -CH₂-CH₂-N), 3.20-3.50(m, 8H, piperazine), 2.56-2.58 (m, 2H, -CH₂-CH₂-N), 1.83(d, 3H, CH-CH₃).

55

Example 13

VII-13 N¹-p-methoxybenzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

5 **[0079]** 4.92g of N¹-p-methoxybenzyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-p-methoxybenzyl piperazine (20mmol) and 3-(3-chlorpropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.30g of product was obtained in a yield of 87.4%. m.p.=240.0-242.0°C(dec).

[0080] MS(m/z): 420.9[M+1]⁺.

10 **[0081]** ¹HNMR(DMSO): 7.29-7.92(d, 4H, Ar-H), 7.47(s, 1H, thiophene), 7.00-7.21(m, 4H, Ar-H), 5.30-5.80(1H, -CHOH), 5.15(d, 1H, CH-OH), 3.73 (O-CH₃), 3.59(m, 2H, -CH₂-CH₂-N), 3.22-3.37(m, 8H, piperazine), 2.30-2.43(m, 2H, CHOH-CH₂).

Example 14

VII-14 N¹-benzhydryl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride

15 **[0082]** 5.13 g of N¹-benzhydryl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-benzhydryl piperazine(20mmol) and 3-(3-chlorpropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 2.95g of product was obtained in a yield of 57.5%. m.p.=119.2-121.0°C(dec).

[0083] MS(m/z): 443.1[M+1]⁺.

20 **[0084]** ¹HNMR(DMSO):7.78-7.87(m, 6H, Ar-H), 7.28-7.45(m, 9H, Ar-H), 5.36-5.40(m, 1H, CH₂CHOH), 5.07(s, 1H, -CH-Ph₂),4.28-4.29(m, 2H, -CH₂-CH₂-N), 2.50-3.50(m, 8H, piperazine), 2.34(m, 2H, -CHOH-CH₂-).

Example 15

VII-15 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b] thiophene-3-yl)]propylpiperazine hydrochloride

30 **[0085]** 5.93g of N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-carbonyl-3-(benzo[b] thiophene-3-yl)]propylpiperazine hydrochloride (10mmol) was synthesized using N¹-(4,4'-difluorodiphenylmethoxy)ethylpiperazine (20mmol) and 3-(3-chlorpropionyl) -benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.93g of product was obtained in a yield of 82.8%. m.p.=155.3-158.0°C(dec).

35 **[0086]** MS(m/z): 523.1[M+1]⁺.

[0087] ¹HNMR(DMSO): 7.84-7.92(m, 4H, Ar-H), 7.48(s, 1H, thiophene), 7.32-7.39(m, 8H, Ar-H), 5.49(m, 1H, O-CH-Ph₂), 5.25(d, 1H, CH-OH), 3.76(m, 2H, -CH₂-CH₂-O), 3.27(m, 8H, piperazine), 3.12(br, 2H, -CH₂-CH₂-N), 2.80(br, 2H, N-CH₂-CH₂-), 2.36-2.40(m, 2H, CHOH-CH₂-).

Example 16

VII-16 N¹-benzyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

45 **[0088]** 4.9g of N¹-benzyl-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (13mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(2-methyl-3-chlorpropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.2g of product was obtained. m.p.=155.3-158.0°C(dec).

[0089] MS(m/z): 381.1[M+1]⁺.

50 **[0090]** ¹HNMR(DMSO): 7.65-7.90(m,4H,Ar-H),7.46(s,1H,thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, -CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine),2.24-2.56(m,2H,-CHCH₂N),0.93 (d,3H,CH-CH₃).

Example 17

VII-17 N¹-cinnamyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

55 **[0091]** 4.8g of N¹-cinnamyl-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (12mmol) was synthesized using N¹-cinnamyl piperazine (16.2mmol) and 3-(2-methyl-3-chlorpropionyl)-benzo[b]thi-

ophene (20mmol) according to general method 4, then the reduction of carbonyl was performed in general method 5. 4.3g of product was obtained. m.p=157.2-158.9°C(dec).

[0092] MS(m/z): 407.1[M+1]⁺.

[0093] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H), 6.15-6.33(m, 2H, N-CH-CH-Ph), 5.26-5.29(m, 1H, -CHOH), 3.73-3.74(m, 2H, N-CH₂-CH=), 3.51(m, 1H, -CHOHCH-), 2.58-3.51(m, 8H, piperazine), 2.24-2.56 (m, 2H, -CHCH₂N), 0.93(d, 3H, CH-CH₃).

Example 18

VII-18 N¹-benzhydryl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0094] 4.5g of N¹-benzhydryl-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-benzhydrylpiperazine (16.2mmol) and 3-(2-methyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.9g of product was obtained in a yield of 86.6%. m.p=159.3-161.0°C(dec).

[0095] MS(m/z): 457.1[M+1]⁺.

[0096] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 10H, Ar-H), 5.26-5.29(m, 1H, -CHOH), 4.28(s, 1H, N-CH-Ph₂), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 0.93(d, 3H, CH-CH₃).

Example 19

VII-19 N¹-(4,4-difluorodiphenylmethoxy)ethyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0097] 5.9g of N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (11mmol) was synthesized using N¹-(4,4'-difluorodiphenylmethoxy)ethylpiperazine (16.2mmol) and 3-(2-methyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.8g of product was obtained in a yield of 81.4%. m.p=154.3-155.0°C(dec).

[0098] MS(m/z): 537.1[M+1]⁺.

[0099] ¹HNMR(DMSO): 7.84-7.92(m, 4H, Ar-H), 7.48(s, 1H, thiophene), 7.32-7.39(m, 8H, Ar-H), 5.49(m, 1H, O-CH-Ph₂), 5.25(d, 1H, CH-OH), 3.76(m, 2H, -CH₂-CH₂:O), 3.27(m, 8H, piperazine), 3.12(m, 2H, -CH-CH₂-N), 2.80(m, 2H, N-CH₂-CH₂-), 2.36-2.40(m, 1H, CHOH-CH-), 0.93(d, 3H, CH-CH₃).

Example 20

VII-20 N¹-benzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0100] 5.5g of N¹-benzyl-N⁴-[2-butyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (13mmol) was synthesized using N¹-benzylpiperazine (16.2mmol) and 3-(2-butyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.9g of product was obtained in a yield of 89.1%. m.p=156.3-158.0°C(dec).

[0101] MS(m/z): 423.1[M+1]⁺.

[0102] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, -CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 1.25-1.29(m, 6H, CH₂-CH₂-CH₂-CH₃), 0.96 (3H, CH₂CH₂-CH₃).

Example 21

VII-21 N¹-α-phenethyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0103] 5.6g of N¹-phenethyl-N⁴-[2-butyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (13mmol) was synthesized using N¹-α-phenethyl piperazine (16.2mmol) and 3-(2-butyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.9g of product was obtained in a yield of 87.5%. m.p=165.3-168.0°C(dec).

[0104] MS(m/z): 437.1[M+1]⁺.

[0105] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H),

5.26-5.29(m,1H,-CHOH), 4.28(d,1H,N-CH-Ph), 3.51(m, 1H,-CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 1.25-1.29(m, 6H, CH₂-CH₂-CH₂-CH₃), 0.96(3H,CH₂CH₂-CH₃), 1.34(m,3H,CHCH₃).

Example 22

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VII-22 N¹-p-chlorobenzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0106] 5.5g of N¹(p-chlorobenzyl)-N⁴-[2-butyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride (12mmol) was synthesized using N¹-p-chlorobenzyl piperazine(16.2mmol) and 3-(2-butyl-3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.7g of product is obtained in a yield of 85.4%. m.p= 153.6-156.0°C(dec).

[0107] MS(m/z): 458.1 [M+1]⁺.

[0108] ¹HNMR(DMSO):7.65-7.90(m,4H,Ar-H), 7.46(s,1H,thiophene), 7.43-7.45(m, 4H, Ar-H), 5.26-5.29(m, 1H,-CHOH), 4.28(s,2H,N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 1.25-1.29(m, 6H, CH₂-CH₂-CH₂-CH₃), 0.96(3H,CH₂CH₂-CH₃).

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Example 23

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VII-23 N¹-p-methoxybenzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride

[0109] 5.9g of N¹-p-methoxybenzyl-N⁴-[2-butyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride (13mmol) was synthesized using N¹-p-methoxybenzylpiperazine(16.2mmol) and 3-(2-butyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 5.2g of product was obtained in a yield of 88.1%. m.p=159.7-162.0°C(dec).

[0110] MS(m/z): 453.2[M+1]⁺.

[0111] ¹HNMR(DMSO):7.65-7.90(m,4H,Ar-H), 7.46(s,1H,thiophene), 7.43-7.45(m, 4H, Ar-H), 5.26-5.29(m, 1H,-CHOH), 4.28(s,2H,N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 1.25-1.29(m, 6H, CH₂-CH₂-CH₂-CH₃), 0.96(3H,CH₂CH₂-CH₃), 3.73(s,3H,-OCH₃).

Example 24

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VII-24 N¹-benzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

[0112] 4.9g of N¹-benzyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (13mmol) was synthesized using N¹-benzylpiperazine(16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.3g of product was obtained in a yield of 87.8%. m.p=153.3-155.7°C(dec).

[0113] MS(m/z): 381.1[M+1]⁺.

[0114] ¹HNMR(DMSO):7.65-7.90(d,4H,Ar-H), 7.46(s,1H,thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.24-3.51 (m, 10H, piperazine), 1.28-1.32(m,4H,CH₂-CH₂CH₂).

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Example 25

VII-25 N¹-α-phenethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

[0115] 5.9g of N¹-α-phenethyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (15mmol) was synthesized using N¹-α-phenethylpiperazine(16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 5.2g of product was obtained in a yield of 88.1%. m.p=155.3-158.0°C(dec).

[0116] MS(m/z): 395.1[M+1]⁺.

[0117] ¹HNMR(DMSO): 7.65-7.94(m,4H,Ar-H),7.73(s, 1H, thiophene), 7.43-7.48(m, 5H, Ar-H),5.21(m, 1H, CH-CH₃), 4.36-4.37(m, 1H, CH-OH), 3.50-3.60(m, -CH₂-CH₂-N), 3.20-3.50 (m, 8H, piperazine), 2.56-2.58(m, 2H, -CH₂-CH₂-N), 1.83(d, J=6.4, 3H, >CH-CH₃), 1.31(2H,CH-CH₂-CH₂).

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Example 26

VII-26 N¹-p-nitrobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

5 [0118] 5.3g of N¹-p-nitrobenzyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (12mmol) was synthesized using N¹-p-nitrobenzylpiperazine(16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.8g of product was obtained. m.p=168.4-171.0°C(dec).

[0119] MS(m/z): 442.1[M+1]⁺.

10 [0120] ¹HNMR(DMSO):7.65-7.90(d, 4H, Ar-H),7.46(s, 1H, thiophene),7.33-7.35(m, 4H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.24-3.51(m, 10H, piperazine), 1.28-1.32 (m,4H,CH₂-CH₂-CH₂).

Example 27

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VII-27 N¹-p-aminobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

[0121] 5.5g of N¹-p-aminobenzyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (14mmol) was synthesized using N¹-p-aminobenzylpiperazine (16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.7g of product was obtained. m.p=158.0-161.1°C(dec).

[0122] MS(m/z): 396.1[M+1]⁺.

20 [0123] HNMR(DMSO):7.65-7.90 (d, 4H, Ar-H),7.46(s, 1H, thiophene),7.48-7.5 5(m, 4H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 3.00(m, 2H, NH₂), 2.24-3.51 (m, 10H, piperazine),1.28-1.32(m, 4H, CH₂-CH₂-CH₂).

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Example 28

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VII-28 N¹-cinnamyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

[0124] 5.7g of N¹-cinnamyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (14mmol) was synthesized using N¹-cinnamylpiperazine(16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 5.0g of product was obtained in a yield of 87.8%. m.p=145.5-148.20(dec).

35 [0125] MS(m/z): 407.1[M+1]⁺.

[0126] ¹HNMR(DMSO):7.65-7.90(d,4H,Ar-H),7.46(s,1H,thiophene),7.43-7.45(m, 5H, Ar-H), 6.15-6.33(m,2H,-CH=CH-Ph),5.26-5.29(m, 1H, CH₂CHOH), 3.73-3.74(m, 2H, N-CH₂-CH=), 3.51 (m, 2H, -CHOHCH₂-), 2.24-3.51(m, 10H, piperazine), 1.28-1.32 (m,4H,CH₂-CH₂-CH₂).

Example 29

VII-29 N¹-benzhydryl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

45 [0127] 5.5g of N¹-benzhydryl-N⁴-[4-carbonyl-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride (12mmol) was synthesized using N¹-benzhydrylpiperazine(16.2mmol) and 3-(4-chlorobutyryl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.8g of product was obtained in a yield of 87.3%. m.p=165.9-168.30(dec).

[0128] MS(m/z): 457.1[M+1]⁺.

50 [0129] ¹HNMR(DMSO): 7.78-7.87 (m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.28-7.45(m, 10H, Ar-H), 5.36-5.40(m, 1H, CH₂CHOH), 5.07(m, 1H, -CH-Ph₂), 4.28-4.29(m, 2H, -CH₂-CH₂-N-), 2.50-3.50(m, 8H, piperazine), 2.34(m, 2H, -CHOH-CH₂-), 1.30(2H,CH₂-CH₂-CH₂).

Example 30

55 VII-30 N¹-(4,4 -difluorodiphenylmethoxy)ethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine hydrochloride

[0130] 6.4g of N¹-(4,4 -difluorodiphenylmethoxy)ethyl-N⁴-[4-carbonyl-4-(benzo[b]thiophene -3-yl)]butylpiperazine hydrochloride (12mmol) was synthesized using N¹-4,4'-difluorodiphenylmethoxy)ethylpiperazine (16.2mmol) and 3-(4-

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chlorbutyryl)-benzo [b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 5.3g of product was obtained in a yield of 82.8%. m.p=157.3-159.7□(dec).

[0131] MS(m/z): 537.1[M+1]⁺.

[0132] ¹HNMR(DMSO): 7.68-7.84(d,4H,Ar-H),7.48(s,1H,thiophene),7.32-7.39(m,8H, Ar-H), 5.49(m,1H,O-CH-Ph₂), 5.25(d,1H,CH-OH), 3.76(m, 2H, -CH₂-CH₂=O), 3.27(m, 8H, piperazine), 3.12(m, 2H, -CH₂-CH₂-N), 2.80(m, 2H, N-CH₂-CH₂-), 2.36-2.40(m, 2H, CHOH-CH₂-), 1.29(2H,CH₂-CH₂-CH₂).

Example 31

VII-31 N¹-p-methoxycinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0133] 4.20 g of N¹-p-methoxycinnamyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-p-methoxycinnamyl piperazine(20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.87g of product was obtained in a yield of 92%. m.p=256.5-258.0□(dec).

[0134] MS(m/z): 367.1[M+1]⁺.

[0135] ¹HNMR(DMSO): 7.65-7.90 (m, 4H, Ar-H),7.46(s, 1H, thiophene),7.43-7.45(m, 4H, Ar-H), 6.32-6.39(m, 2H,-CH=CH-), 5.26-5.29(m, 1H, CH₂CHOH), 3.73-3.74(m, 2H, N-CH₂-CH=), 3.51(m, 2H, -CHOHCH₂-), 3.0(s, 1H, OCH₃), 2.58-3.51(m, 8H, piperazine), 2.24-2.56 (m, 2H, -CH₂CH₂N).

Example 32

VII-32 N¹-p-aminocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0136] 4.03g of N¹-p-aminocinnamyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-p-aminocinnamyl piperazine(20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.60g of product was obtained in a yield of 88%. m.p=252.5-255.0.0□(dec).

[0137] MS(m/z): 408.1[M+1]⁺.

[0138] ¹HNMR(DMSO):7.65-7.90(m,4H,Ar-H),7.46(s,1H,thiophene),7.43-7.45(m,4H, Ar-H), 6.32-6.39(m, 2H,-CH=CH-), 5.26-5.29(m, 1H, CH₂CHOH), 4.0(s,2H,NH₂), 3.73-3.74 (m,2H,N-CH₂-CH=), 3.51(m,2H,-CHOHCH₂-), 2.58-3.51(m,8H,piperazine), 2.24-2.56 (m,2H,-CH₂CH₂N).

Example 33

VII-33 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene -3-yl)]propylpiperazine hydrochloride

[0139] 5.01g of N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-carbonyl-3-(benzo[b] thiophene-3-yl)]propylpiperazine hydrochloride (9mmol) was synthesized using N¹-(4,4'-difluorodiphenylmethoxy)ethylpiperazine (20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.15g of product was obtained in a yield of 83%. m.p=267.5-269.0□(dec).

[0140] MS(m/z): 556.1[M+1]⁺.

[0141] ¹HNMR(DMSO) : 7.84-7.92(m, 4H, Ar-H), 7.48(s, 1H, thiophene), 7.32-7.39(m, 8H, Ar-H),5.49(s, 1H, O-CH-Ph₂), 5.25(d, 1H, CH-OH), 3.76(m, 2H, -CH₂-CH₂-O), 3.27(m, 8H, piperazine), 3.12(m, 2H, -CH₂-CH₂-N), 2.80(br, 2H, N-CH₂-CH₂-), 2.36-2.40(m, 2H, CHOH-CH₂-).

Example 34

VII-34 N¹-(4,4'-dihydroxydiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b] thiophene-3-yl)]propylpiperazine hydrochloride

[0142] 4.17g of N¹-(4,4'-dihydroxydiphenylmethoxy)ethyl-N⁴-[3-carbonyl-3-(benzo[b] thiophene-3-yl)]propylpiperazine hydrochloride (8mmol) was synthesized using N¹-(4,4'-dihydroxydiphenylmethoxy)ethylpiperazine (20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.45g of product was obtained in a yield of 83%. m.p=275.5-277.00(dec).

[0143] MS(m/z): 519.1[M+1]⁺.

[0144] ¹HNMR(DMSO) : 7.84-7.92(m, 4H, Ar-H), 7.48(s, 1H, thiophene), 7.36-7.45(m, 8H, Ar-H), 5.49(s, 1H, O-CH-Ph₂), 5.25(d, 1H, CH-OH), 3.76(m, 2H, -CH₂-CH₂-O), 3.27(m, 8H, piperazine), 3.12(m, 2H, -CH₂-CH₂-N), 2.80(br,

2H, N-CH₂-CH₂-), 2.36-2.40(m, 2H, CHOH-CH₂-).

Example 35

5 VII-35 N¹-p-nitrocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0145] 3.90g of N¹-p-nitrocinnamyl-N⁴-[3-carbonyl-3-(benzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (9mmol) was synthesized using N¹-p-nitrocinnamyl piperazine (20mmol) and 3-(3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.42g of product was obtained in a yield of 87%. m.p=240.5-242.0□(dec).

[0146] MS(m/z): 438.1[M+1]⁺.

[0147] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m 4H, Ar-H), 6.32-6.39(m, 2H, -CH=CH-), 5.26-5.29(m, 1H, CH₂CHOH), 3.73-3.74(m, 2H, N-CH₂-CH=), 3.51(m, 2H, -CHOHCH₂-), 2.58-3.51(m, 8H, piperazine), 2.24-2.56(m, 2H, -CH₂CH₂N).

Example 36

VII-36 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methylbenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

20 [0148] 3.03g of N¹-benzyl-N⁴-[3-carbonyl-3-(5-methylbenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (8mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(3-chloropropionyl)-5-methylbenzo[b]thiophene(20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 2.65g of product was obtained in a yield of 87%. m.p=252.5-254.0□(dec).

[0149] MS(m/z): 381.1[M+1]⁺.

25 [0150] ¹HNMR(DMSO): 7.65-7.90(m, 3H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.35(m, 3H, CH₃), 2.58-3.51(m, 8H, piperazine), 2.24-2.56(m, 2H, -CH₂CH₂N).

Example 37

30 VII-37 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methoxybenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0151] 3.87g of N¹-benzyl-N⁴-[3-carbonyl-3-(5-methoxybenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(3-chloropropionyl)-5-methoxybenzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.35g of product was obtained in a yield of 86%. m.p=252.5-255.0□(dec).

[0152] MS(m/z): 397.1[M+1]⁺.

35 [0153] ¹HNMR(DMSO):7.65-7.90(m,3H,Ar-H),7.46(s,1H,thiophene),7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.35(m,3H,-OCH₃), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.58-3.51(m,8H,piperazine),2.24-2.56(m,2H,-CH₂CH₂N).

Example 38

45 VII-38 N¹-benzyl-N⁴-[3-hydroxy-3-(6-aminobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0154] 3.42g of N¹-benzyl-N⁴-[3-carbonyl-3-(6-aminobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (9mmol) was synthesized using N¹-benzyl piperazine(20mmol) and 3-(3-chloropropionyl)-6-aminobenzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.02g of product was obtained in a yield of 88%. m.p=242.5-245.0□(dec). ,

50 [0155] MS(m/z): 382.1[M+1]⁺.

[0156] ¹HNMR(DMSO): 7.65-7.90(m, 3H, Ar-H),7.46(s, 1H, thiophene),7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 4.02(m,2H,-NH₂), 3.51(m, 2H, -CHOHCH₂-), 2.58-3.51(m, 8H, piperazine), 2.24-2.56(m, 2H, -CH₂CH₂N).

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Example 39

VII-39 N¹-benzyl-N⁴-[3-hydroxy-3-(6-chlorobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

5 [0157] 3.21g of N¹-benzyl-N⁴-[3-carbonyl-3-(6-chlorobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (8mmol) was synthesized using N¹-benzyl piperazine(20mmol) and 3-(3-chloropropionyl)-6-chlorobenzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.01g of product was obtained in a yield of 93%. m.p=251.5-253.0□(dec).

[0158] MS(m/z): 402.1[M+1]⁺.

10 [0159] ¹HNMR(DMSO): 7.69-7.95(m, 3H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 2H, -CHOHCH₂-), 2.58-3.51(m, 8H, piperazine), 2.24-2.56(m, 2H, -CH₂CH₂N).

Example 40

15 VII-40 N¹-benzyl-N⁴-[3-hydroxy-3-(6-methylaminobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride

[0160] 3.87g of N¹-benzyl-N⁴-[3-carbonyl-3-(6-methylaminobenzo[b]thiophene-3-yl)]propyl piperazine hydrochloride (10mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(3-chloropropionyl)-6-methylaminobenzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 3.35g of product was obtained in a yield of 86%. m.p=252.5-255.0□(dec).

[0161] MS(m/z): 396.1[M+1]⁺.

20 [0162] ¹HNMR(DMSO): 7.69-7.95 (m, 3H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 5H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 4.0(m, 1H, NH), 3.51 (m, 2H, -CHOHCH₂-), 2.98-3.51(m, 8H, piperazine), 2.78(m, 3H, CH₃NH) 2.24-2.56 (m, 2H, -CH₂CH₂N).

Example 41

30 VII-41 N¹-(β-pyridinemethyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride

[0163] 4.9g of N¹-(β-pyridinemethyl)-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride (13mmol) was synthesized using N¹-(β-pyridinemethyl)piperazine (20mmol) and 3-(2-methyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.2g of product was obtained. m.p=157.3-159.0□(dec).

35 [0164] MS(m/z): 382.1[M+1]⁺.

[0165] ¹HNMR(DMSO): 7.65-7.90(m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 4H, Ar-H), 5.26-5.29(m, 1H, -CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.58-3.51 (m, 8H, piperazine), 2.24-2.56(m, 2H, -CHCH₂N), 0.93(d, 3H, CH-CH₃).

Example 42

40 VII-42 N¹-(4-morpholinebenzyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride

[0166] 5.2g of N¹-(4-morpholinebenzyl)-N⁴-[2-methyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)]propylpiperazine hydrochloride (12mmol) was synthesized using N¹-(4-morpholinebenzyl)piperazine (20mmol) and 3-(2-methyl-3-chloropropionyl)-benzo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.5g of product was obtained. m.p=151.3-153.0□(dec).

[0167] MS(m/z): 466.6[M+1]⁺.

50 [0168] ¹HNMR(DMSO) : 7.65-7.90 (m, 4H, Ar-H), 7.46(s, 1H, thiophene), 7.43-7.45(m, 4H, Ar-H), 5.26-5.29(m, 1H, CH₂CHOH), 4.28(s, 2H, N-CH₂-Ph), 3.51(m, 1H, -CHOHCH-), 2.65-3.51(10H, piperazine, -CH₂-N, Comb), 1.85-2.55(m, 8H, morphrine-H), 1.06(d, 3H, CH₃).

Example 43

55 VII-43 N¹-benzyl-N⁴-[2-cyclopentylmethyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride

[0169] 5.2g of N¹-benzyl-N⁴-[2-cyclopentylmethyl-3-carbonyl-3-(benzo[b]thiophene-3-yl)] propylpiperazine hydrochloride (12mmol) was synthesized using N¹-benzylpiperazine (20mmol) and 3-(2-cyclopentylmethyl-3-chloropropionyl)-ben-

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zo[b]thiophene (20mmol) according to general method 4, then the reduction of carbonyl was performed according to general method 5. 4.8g of product was obtained. m.p=159.3-161.0°C(dec).

[0170] MS(m/z): 435.1[M+1]⁺.

[0171] ¹HNMR(DMSO) :7.65-7.90(m,4H,Ar-H),7.46(s,1H,thiophene),7.43-7.45(m, 5H, Ar-H), 5.26-5.29 (m,1H,-CHOH), 4.28(s,2H,N-CH₂-Ph), 3.51(m,1H,-CHOHCH-), 2.58-3.51 (m,8H,piperazine), 2.24-2.56(m,2H,-CHCH₂N), 1.49-1.65(m,9H,Ar-H).

Example 44

[0172]

Tablet :	derivatives of Example 1-43	10mg
	sucrose	150m
	corn starch	38mg
	calcium stearate	2mg

[0173] Preparation: The active ingredient was mixed with sucrose and corn starch, then the mixture was wetted by adding water, stirred evenly, dried and then crushed and screened, then calcium stearate was added. The mixture obtained was stirred evenly and then pressed into tablets. The weight per tablet was 200mg containing 10mg of active ingredient.

Example 45

[0174]

Injection:	derivatives of Example 1-43	20mg
	water for injection	80mg

[0175] Preparation: The active ingredient was mixed evenly with water for injection and filtered, then the mixture obtained was subpacked into ampoules under sterile conditions. The weight per ampoule was 10mg containing 2mg of active ingredient.

Example 46

[0176] Pharmacological experimental studies on the *in vivo* and *in vitro* antidepressant effect of the compounds.

1. Inhibition effect of the compounds on the uptake of 5-HT, NA and DA by brain synaptosomes

[0177] Study on the reuptake of monoamine neurotransmitters by brain synaptosomes was performed, which is currently one of the important means adopted in the worldwide in pharmacological studies of central nervous. This method can not only be used to study the mechanism of drug's action, but also be used for screening new drugs acting by this mechanism. In this experiment, studies on the inhibition effect of the compounds of the present invention on the reuptake of 5-HT, NA and DA by brain synaptosomes was performed, using the method as mentioned above with Venlafaxine (an effective dual inhibitor on the reuptake of 5-HT and NA) and DOV 21947 (a triple inhibitor on the reuptake of 5-HT, NA and DA) as the positive controls. The method was as follows:

1.1 Preparation of rat brain synaptosomes

[0178] Male SD rats were sacrificed by cervical dislocation and then the brains thereof were taken out rapidly by decollation and placed on ice. Brain tissues related (for [³H]5-HT and [³H]NA reuptake experiment, prefrontal cortex was taken; for [³H]DA reuptake experiment, corpus striatum was taken) were separated and weighed. 10 times (V/W) of 0.32mo1/L ice-cold sucrose solution was added and was homogenized electrically with glass-teflon. The homogenate was centrifugated at 4°C at 1000g×10min. Then the supernatant was taken and centrifugated at 4°C at 17000g×20min. The precipitation was suspended in 30 volume of KRH Buffer(125mM NaCl, 4.8mM KCl, 1.2mM CaCl₂, 1.2mM MgSO₄, 1.0mM KH₂PO₄, 22mM NaHCO₃, 25mM HEPES, 10mM Glucose, 10 mM Pargyline, 0.2mg/ml Ascorbic Acid) and then was preserved in an ice bath for use. (for NA reuptake experiment, the cortex needed was suspended in 20 volume of

KRH Buffer)

1.2 [³H]5-HT/NA/DA reuptake experiments

[0179] According to the reference, stocked solution of the tested substance was thawed immediately before use and was diluted with KBH Buffer to 100 μ mol/L. 50 μ l thereof was added into 500 μ l total reaction system, and the final concentration was 10 μ mol/L. Then 50 μ l suspended synaptic membrane was added and mixed evenly, incubated in water bath for 30min at 37 \square . Then 10nmol/L [³H] 5-HT (50nmol/L [³H]DA or 60nmol/L [³H]NA) was added. After incubated for 10min, the reaction system was immediately taken out and the reaction was stopped by adding 2ml of ice-cold 150mmol/L Tris-HCl buffer solution. The samples were collected on the circular fiberglass membrane by vacuum filtration, and the membrane was washed 3 times with 3ml of ice-cold Tris-HCl buffer solution. The membrane was removed, baked for 15min in a far-infrared oven and placed into an EP tube. 1.5ml scintillation fluid was added and was tested by liquid scintillation counter overnight. For the solvent control total connecting tube and the non-specific connecting tube, no tested substance was added; for the total connecting tube, 50 μ l solvent was added; for the non-specific connecting tube in the [³H]5-HT reuptake experiment, 600 μ mol/L Cocaine was added; for the non-specific connecting tube in the [³H]NA reuptake experiment, 100 μ mol/L DOV 21947 was added; for the non-specific connecting tube in the [³H]DA reuptake experiment, 600 μ mol/L Cocaine was added.

[0180] 1.3 Results: At the same concentration condition(the control drugs and the tested substances were all 0.1mmol/L), with Venlafaxine (an antidepressant already saled in the market) and DOV 21947(a new compound at phase II clinical trial) being as positive controls, the results determined of the inhibition rates for the reuptake of 5-HT, NA and DA were shown in table 2.

Table 2 Inhibition effect of the compounds on the uptake of 5-HT, NA and DA by brain synaptosomes

compounds	inhibition effect on the uptake of 5-HT	inhibition effect on the uptake of NA	inhibition effect on the uptake of DA
VII-4	40.2 \pm 11.0*#	60.1 \pm 4.1	14.5 \pm 10.0*#
VII-5	73.6 \pm 8.7*#	26.2 \pm 5.2*#	11.4 \pm 11.5*#
VII-10	95.6 \pm 2.5*#	77.4 \pm 13.8	78.0 \pm 8.0*#
VII-11	101.2 \pm 1.3	49.7 \pm 13.8	97.9 \pm 1.1*#
VII-12	103.6 \pm 0.5*	50.8 \pm 2.7	98.0 \pm 1.5*#
VII-14	77.8 \pm 5.8*#	44.9 \pm 17.6	87.3 \pm 4.3*#
VII-15	101.6 \pm 1.2	53.5 \pm 8.6	102.2 \pm 1.3*
Venlafaxine	106.9 \pm 1.7	46.4 \pm 4.6	48.6 \pm 4.1
DOV 21947	108.6 \pm 3.8	61.9 \pm 6.0	104.1 \pm 4.2*

*compared with Venlafaxine, p<0.05; # compared with DOV 21047, p<0.05

[0181] At the concentration of 10 μ mol/L, the five compounds, i.e., VII-10, VII-11, VII-12, VII-14 and VII-15 had stronger inhibition activity on the reuptake of 5-HT, NA and DA. They showed similar potency to those of Venlafaxine and DOV 21947.

2. Results of *in vivo* antidepression of compound VII-10

[0182] A preliminary study was carried out on the *in vivo* antidepression effect of compound VII-10 using the Forced Swimming Test in Learned Helplessness Experiment, with Venlafaxine as the positive control. The results were shown in table 3:

Table 3 Results of forced swimming test of preferred compounds

compounds	dosage (mg/kg)	immobility time (s)
CMC-Na	20ml/kg	138 \pm 30.1
	18.24	80.8 \pm 46.8*
Venlafaxine	9.12	77.4 \pm 47.2**

(continued)

compounds	dosage (mg/kg)	immobility time (s)
	4.56	57.1±37.8**
VII-10	25.4	84±48.9**
	12.7	87.5±35.7
	6.35	90.7±46.3

*compared with positive group, $p < 0.5$, significant difference exists;

** compared with positive group, $p < 0.05$, extremely significant difference exists.

[0183] In the forced swimming test, VII-10 was able to significantly reduce the immobility time in swimming due to despair in the water. The efficacy ($84 \pm 48.9s$) at the dose of 25.4mg/kg was similar to that of positive control Venlafaxine ($80.8 \pm 46.8s$) at the same molar quantities, i.e., 18.24mg/kg, which showed extremely significant difference from the blank group. It suggests that VII-10 had a much stronger *in vivo* antidepressant activity and the potency was similar to Venlafaxine.

3. Acute toxicity

[0184] Initial screening was performed by the method reported in "Modern Pharmacological Experiments Methods" edited by Zhang Juntian. The LD_{50} for mice single-fed was 1.1g/kg of compound VII-10, which was obtained via statistics of Bliss.

4. Bacterial reverse mutation test for VII-10.

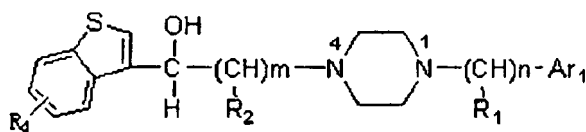
[0185] Bacterium: histidine auxotrophic mutant strains of Salmonella TA₉₇, TA₉₈, TA₁₀₀ and TA₁₀₂

[0186] Experimental method: the method reported in the literature: Maron DM et al: (1983) *Mutat Res.* 113, 173-216.

[0187] Results: The experiment included two parts: -S₉ and +S₉. TA₉₈ in -S₉ test system and TA₉₇ in +S₉ test system both showed bacteriostatic effect at 5000μg per culture dish. The other dosages had no bacteriostatic effect for all the strains, with a well growing background. For all the dosages tested, both in -S₉ and +S₉ test systems, no significant increase of number of reverse mutation colonies was found. Ames test result was negative.

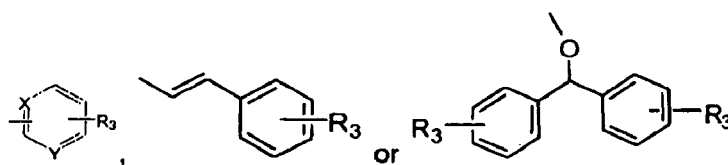
Claims

1. A benzothiophene alkanol piperazine derivative, characterized in that said benzothiophene alkanol piperazine derivative is a compound of formula (1)



or a pharmaceutically acceptable salt thereof,
wherein,

Ar₁ represents:



R₁ and R₂ each independently represent hydrogen; C₁-C₆ alkyl; C₅ or C₆ alicyclic ring; phenyl; or phenyl

substituted by C₁-C₆ alkyl, C₁-C₆ alkoxy or halo groups;

R₃ and R₄ each independently represent hydrogen; C₁-C₆ alkyl; phenyl; or phenyl substituted by one to four substituents independently selected from the groups consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxyl, amino or halo; a 5-member or 6-member ring containing N or O; hydroxyl; C₁-C₆ alkoxy; amino; amino substituted by

C₁-C₆ alkyl or C₁-C₆ haloalkyl; halo; carboxylic acid; carboxylic acid ester; nitro or acetonitrile;

X represents C or N;

Y represents C or N;

m is 1, 2 or 3, and

n is 1, 2 or 3.

2. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, R₃ is hydrogen; C₁-C₂ alkyl; hydroxyl; methoxy; ethoxy; amino; amino substituted by C₁-C₆ alkyl or C₁-C₆ haloalkyl; fluorine atom; phenyl; or phenyl substituted by one to four substituents independently selected from the groups consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxyl, amino and halo.
3. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, R₃ is C₁-C₂ alkyl or fluorine atom.
4. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, asymmetric carbons in the structure of the compound are achiral carbon atoms or chiral carbon atoms with R or S configuration.
5. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, the pharmaceutically acceptable salt is a hydrochloride salt, a hydrobromide salt, a sulphate salt, a trifluoroacetate salt or a methanesulphonate salt.
6. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, the pharmaceutically acceptable salt contains 0.5 to 3 molecules of crystal water.
7. The benzothiophene alkanol piperazine derivative according to claim 1, **characterized in that**, it is selected from:

VII-1 N¹-benzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine,

VII-2 N¹-benzhydryl-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine,

VII-3 N¹-(p-chlorobenzyl)-N⁴-[2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-4 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (threo isomer),

VII-5 N¹-benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)]ethylpiperazine (erythro isomer),

VII-6 N¹-p-aminobenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-7 N¹-p-methoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-8 N¹-p-ethoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-9 N¹-(p-hydroxybenzyl)-N⁴-[1-methyl-2-hydroxy-(benzo[b]thiophene-3-yl)] ethylpiperazine,

VII-10 N¹-benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,

VII-11 N¹-cinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,

VII-12 N¹-α-phenethyl -N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,

VII-13 N¹-p-methoxybenzyl)-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-14 N¹-benzhydryl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,

VII-15 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b] thiophene-3-yl)] propylpiperazine,

VII-16 N¹-benzyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-17 N¹-cinnamyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-18 N¹-benzhydryl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-19 N¹-(4,4'-difluorodiphenylmethoxy)ethyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b] thiophene-3-yl)] propylpiperazine,

VII-20 N¹-benzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-21 N¹-α-phenethyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-22 N¹-(p-chlorobenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-23 N¹-(p-methoxybenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)] propylpiperazine,

VII-24 N¹-benzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,

VII-25 N¹-α-phenethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,

VII-26 N¹-p-nitrobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,

VII-27 N¹-p-aminobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)] butylpiperazine,

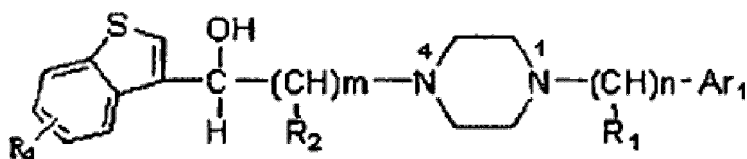
VII-28 N¹-cinnamyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-29 N¹-benzhydryl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-30 N¹-(4,4-difluorodiphenylmethoxy)ethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophene-3-yl)]butylpiperazine,
 VII-31 N¹-(p-methoxycinnamyl)-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-32 N¹-p-aminocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-33 N¹-(4,4-difluorodiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-34 N¹-(4,4-dihydroxydiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-35 N¹-p-nitrocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-36 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methylbenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-37 N¹-benzyl-N⁴-[3-hydroxy-3-(5-methoxybenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-38 N¹-benzyl-N⁴-[3-hydroxy-3-(6-aminobenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-39 N¹-benzyl-N⁴-[3-hydroxy-3-(6-chlorobenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-40 N¹-benzyl-N⁴-[3-hydroxy-3-(6-methylaminobenzo[b]thiophene-3-yl)]propylpiperazine,
 VII-41 N¹-(β-pyridinemethyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine,
 VII-42 N¹-(4-morpholinebenzyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine, and
 VII-43 N¹-benzyl-N⁴-[2-cyclopentylmethyl-3-hydroxy-3-(benzo[b]thiophene-3-yl)]propylpiperazine.

8. A pharmaceutical composition for antidepressant, **characterized in that**, said pharmaceutical composition comprises therapeutically effective amount of benzothiophene alkanol piperazine derivative according to any one of claims 1-7, together with a pharmaceutically acceptable carrier.

9. The benzothiophene alkanol piperazine derivative according to any one of claims 1-7 for use as an antidepressant.

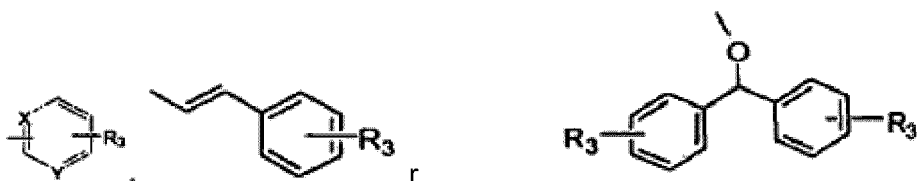
Patentansprüche

1. Benzothiophenalkanolpiperazinderivat, **dadurch gekennzeichnet, dass** das Benzothiophenalkanolpiperazinderivat eine Verbindung der Formel (1) ist



oder ein pharmazeutisch akzeptables Salz davon,
 worin

Ar₁ bedeutet:



R₁ und R₂ jeweils unabhängig voneinander bedeuten: Wasserstoff; C₁-C₆-Alkyl; C₅- oder C₆-alicyclischer Ring; Phenyl; oder durch C₁-C₆-Alkyl-, C₁-C₆-Alkoxy- oder Halogengruppen substituiertes Phenyl;
 R₃ und R₄ jeweils unabhängig voneinander bedeuten: Wasserstoff; C₁-C₆-Alkyl; Phenyl; oder substituiertes Phenyl mit ein bis vier Substituenten, die unabhängig ausgewählt sind aus der Gruppe bestehend aus C₁-C₆-Alkyl, C₁-C₆-Alkoxy, Hydroxyl, Amin oder Halogen; ein N oder O enthaltender 5-gliedriger oder 6-gliedriger Ring; Hydroxyl; C₁-C₆-Alkoxy; Amin; durch C₁-C₆-Alkyl oder C₁-C₆-Halogenalkyl substituiertes Amin; Halogen; Carboxylsäure; Carboxylsäureester; Nitro oder Acetonitril;
 X C oder N bedeutet;
 Y C oder N bedeutet;

m 1, 2 oder 3 ist, und

n 1, 2 oder 3 ist.

- 5 2. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass** R₃ bedeutet: Wasserstoff; C₁-C₂-Alkyl; Hydroxyl; Methoxy; Ethoxy; Amin; durch C₁-C₆-Alkyl oder C₁-C₆-Halogenalkyl substituiertes Amin; Fluoratom; Phenyl; oder substituiertes Phenyl mit ein bis vier Substituenten, die unabhängig ausgewählt sind aus der Gruppe bestehend aus C₁-C₆-Alkyl, C₁-C₆-Alkoxy, Hydroxyl, Amin und Halogen.
- 10 3. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass** R₃ ein C₁-C₂-Alkyl oder Fluoratom ist.
- 15 4. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass** asymmetrische Kohlenstoffatome in der Verbindungsstruktur achirale Kohlenstoffatome oder chirale Kohlenstoffatome mit R- oder S-Konfiguration sind.
- 20 5. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass** das pharmazeutisch akzeptable Salz ein Hydrochloridsalz, ein Hydrobromidsalz, ein Sulfatsalz, ein Trifluoracetatsalz oder ein Methansulfonatsalz ist.
- 25 6. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass** das pharmazeutisch akzeptable Salz 0,5 bis 3 Moleküle Kristallwasser enthält.
- 30 7. Benzothiophenalkanolpiperazinderivat nach Anspruch 1, **dadurch gekennzeichnet, dass**, es ausgewählt ist aus:
- 35 VII-1 N¹-Benzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-2 N¹-Benzhydryl-N⁴-[2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-3 N¹-(p-Chlorobenzyl)-N⁴-[2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-4 N¹-Benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin (threo-Isomer).
 VII-5 N¹-Benzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin (erythro-Isomer),
 30 VII-6 N¹-p-Aminobenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-7 N¹-p-Methoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-8 N¹-p-Ethoxybenzyl-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-9 N¹-(p-Hydroxybenzyl)-N⁴-[1-methyl-2-hydroxy-2-(benzo[b]thiophen-3-yl)]ethylpiperazin,
 VII-10 N¹-Benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 35 VII-11 N¹-Cinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-12 N¹-α-Phenethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-13 N¹-p-Methoxybenzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-14 N¹-Benzhydryl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-15 N¹-(4,4'-Difluordiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 40 VII-16 N¹-Benzyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-17 N¹-Cinnamyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-18 N¹-Benzhydryl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-19 N¹-(4,4'-Difluordiphenylmethoxy)ethyl-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 45 VII-20 N¹-Benzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-21 N¹-α-Phenethyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-22 N¹-(p-Chlorobenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-23 N¹-(p-Methoxybenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 50 VII-24 N¹-Benzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 VII-25 N¹-α-Phenethyl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 VII-26 N¹-p-Nitrobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 VII-27 N¹-p-Aminobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 VII-28 N¹-Cinnamyl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 VII-29 N¹-Benzhydryl-N⁴-[4-hydroxy-4-(benzo[b]thiophen-3-yl)]butylpiperazin,
 55 VII-30 N¹-(4,4'-Difluordiphenylmethoxy)ethyl-N⁴-(4-hydroxy-4-(benzo[b]thiophen-3-yl))-butylpiperazin,
 VII-31 N¹-(p-Methoxycinnamyl)-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-32 N¹-p-Aminocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-33 N¹-(4,4'-Difluordiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,

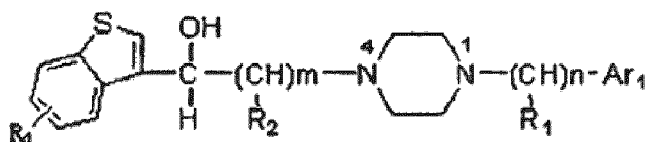
VII-34 N¹-(4,4'-Dihydroxydiphenylmethoxy)ethyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-35 N¹-p-Nitrocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-36 N¹-Benzyl-N⁴-[3-hydroxy-3-(5-methylbenzo[b]thiophen-3-yl)]propylpiperazin,
 VII-37 N¹-Benzyl-N⁴-[3-hydroxy-3-(5-methoxybenzo[b]thiophen-3-yl)]propylpiperazin,
 VII-38 N¹-Benzyl-N⁴-[3-hydroxy-3-(6-aminobenzo[b]thiophen-3-yl)]propylpiperazin,
 VII-39 N¹-Benzyl-N⁴-[3-hydroxy-3-(6-chlorobenzo[b]thiophen-3-yl)]propylpiperazin,
 VII-40 N¹-Benzyl-N⁴-[3-hydroxy-3-(6-methylaminobenzo[b]thiophen-3-yl)]propylpiperazin,
 VII-41 N¹-(β-Pyridinmethyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin,
 VII-42 N¹-(4-Morpholinobenzyl)-N⁴-[2-methyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazine, und
 VII-43 N¹-Benzyl-N⁴-[2-cyclopentylmethyl-3-hydroxy-3-(benzo[b]thiophen-3-yl)]propylpiperazin.

8. Pharmazeutische Zusammensetzung zur Antidepression, **dadurch gekennzeichnet, dass** die genannte pharmazeutische Zusammensetzung eine therapeutisch wirksame Menge eines Benzothiophenalkanolpiperazinderivates nach einem der Ansprüche 1-7 zusammen mit einem pharmazeutisch akzeptablen Träger umfasst.

9. Benzothiophenalkanolpiperazinderivat nach einem der Ansprüche 1-7 zur Verwendung als ein Antidepressivum.

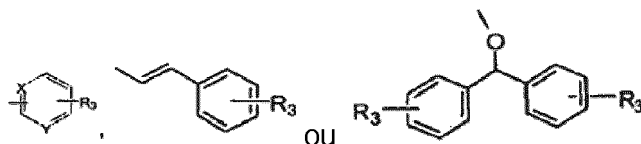
Revendications

1. Dérivé de benzothiophène-alcanol-pipérazine, **caractérisé en ce que** ledit dérivé de benzothiophène-alcanol-pipérazine est un composé de formule (1)



ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel

Ar₁ représente :



R₁ et R₂ représentent chacun indépendamment hydrogène ; alkyle en C₁-C₆; cycle alicyclique en C₅ ou C₆ ; phényle ; ou phényle substitué par des groupes alkyle en C₁-C₆, alcoxy en C₁-C₆ ou halogéno ;

R₃ et R₄ représentent chacun indépendamment hydrogène ; alkyle en C₁-C₆ ; phényle ; ou phényle substitué par un à quatre substituants indépendamment choisis dans le groupe constitué d'alkyle en C₁-C₆, alcoxy en C₁-C₆, hydroxyle, amino ou halogéno ; un cycle de 5 chaînons ou 6 chaînons contenant N ou O ; hydroxyle ; alcoxy en C₁-C₆ ; amino ; amino substitué par alkyle en C₁-C₆ ou halogénoalkyle en C₁-C₆ halogéno ; acide carboxylique ; ester d'acide carboxylique ; nitro ou acétonitrile ;

X représente C ou N ;

Y représente C ou N ;

m est 1,2 ou 3, et

n est 1, 2 ou 3.

2. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce que**, R₃ est hydrogène ; alkyle en C₁-C₂ ; hydroxyle ; méthoxy ; éthoxy ; amino ; amino substitué par alkyle en C₁-C₆ ou halogénoalkyle en C₁-C₆ ; un atome de fluor ; phényle ; ou phényle substitué par un à quatre substituants indépendamment choisis dans le groupe constitué d'alkyle en C₁-C₆, alcoxy en C₁-C₆, hydroxyle, amino et halogéno.

3. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce que**, R₃ est alkyle en C₁-C₂ ou un atome de fluor.

4. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce que** les carbones asymétriques dans la structure du composé sont des atomes de carbone achiraux ou des atomes de carbone chiraux ayant une configuration R ou S.
5. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce que**, le sel pharmaceutiquement acceptable est un sel de chlorhydrate, un sel de bromhydrate, un sel de sulfate, un sel de trifluoroacétate ou un sel de méthanesulfonate.
6. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce que**, le sel pharmaceutiquement acceptable contient de 0,5 à 3 molécules d'eau cristalline.
7. Dérivé de benzothiophène-alcanol-pipérazine selon la revendication 1, **caractérisé en ce qu'il est choisi parmi** :
- VII-1 N¹-benzyl-N⁴-[2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-2 N¹-benzhydryl-N⁴-[2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-3 N¹-(p-chlorobenzyl)-N⁴-[2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-4 N¹-benzyl-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine (isomère thréo),
 VII-5 N¹-benzyl-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine (isomère érythro),
 VII-6 N¹-p-aminobenzyl-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-7 N¹-p-méthoxybenzyl-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-8 N¹-p-éthoxybenzyl-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-9 N¹-(p-hydroxybenzyl)-N⁴-[1-méthyl-2-hydroxy-2-(benzo[b]thiophène-3-yl)]éthylpipérazine,
 VII-10 N¹-benzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-11 N¹-cinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-12 N¹-α-phénéthyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-13 N¹-p-méthoxybenzyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-14 N¹-benzhydryl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-15 N¹-(4,4'-difluorodiphénylméthoxy)éthyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-16 N¹-benzyl-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-17 N¹-cinnamyl-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-18 N¹-benzhydryl-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-19 N¹-(4,4'-difluorodiphénylméthoxy)éthyl-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-20 N¹-benzyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-21 N¹-α-phénéthyl-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-22 N¹-(p-chlorobenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-23 N¹-(p-méthoxybenzyl)-N⁴-[2-butyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-24 N¹-benzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-25 N¹-α-phénéthyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-26 N¹-p-nitrobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-27 N¹-p-aminobenzyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-28 N¹-cinnamyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-29 N¹-benzhydryl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-30 N¹-(4,4'-difluorodiphénylméthoxy)éthyl-N⁴-[4-hydroxy-4-(benzo[b]thiophène-3-yl)]butylpipérazine,
 VII-31 N¹-(p-méthoxycinnamyl)-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-32 N¹-p-aminocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-33 N¹-(4,4'-difluorodiphénylméthoxy)éthyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-34 N¹-(4,4'-dihydroxydiphénylméthoxy)éthyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-35 N¹-p-nitrocinnamyl-N⁴-[3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-36 N¹-benzyl-N⁴-[3-hydroxy-3-(5-méthylbenzo[b]thiophène-3-yl)]propylpipérazine,
 VII-37 N¹-benzyl-N⁴-[3-hydroxy-3-(5-méthoxybenzo[b]thiophène-3-yl)]propylpipérazine,
 VII-38 N¹-benzyl-N⁴-[3-hydroxy-3-(6-aminobenzo[b]thiophène-3-yl)]propylpipérazine,
 VII-39 N¹-benzyl-N⁴-[3-hydroxy-3-(6-chlorobenzo[b]thiophène-3-yl)]propylpipérazine,
 VII-40 N¹-benzyl-N⁴-[3-hydroxy-3-(6-méthylaminobenzo[b]thiophène-3-yl)]propylpipérazine,
 VII-41 N¹-(β-pyridineméthyl)-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine,
 VII-42 N¹-(4-morpholinebenzyl)-N⁴-[2-méthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine, et
 VII-43 N¹-benzyl-N⁴-[2-cyclopentylméthyl-3-hydroxy-3-(benzo[b]thiophène-3-yl)]propylpipérazine.

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8. Composition pharmaceutique pour traitement antidépresseur, **caractérisée en ce que** ladite composition pharmaceutique comprend une quantité thérapeutiquement efficace de dérivé de benzothiophène-alcanol-pipérazine selon l'une quelconque des revendications 1 à 7, conjointement avec un véhicule pharmaceutiquement acceptable.

5 9. Dérivé de benzothiophène-alcanol-pipérazine selon l'une quelconque des revendications 1 à 7 pour utilisation en tant qu'antidépresseur.

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REFERENCES CITED IN THE DESCRIPTION

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