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(54) **METHODE DE TRAITEMENT DE LA DYSCINESIE**
(54) **METHOD FOR TREATING DYSKINESIAS**

(57) La présente invention concerne une méthode de traitement de la dyscinésie, qui comprend l'administration d'une quantité efficace de 2-méthyl-4-(4-méthyl-1-piperazinyl)-10H-thiéno[2,3-b][1,5] benzodiazépine.

(57) The invention provides a method for treating a dyskinesias comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine.

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(54) Title: METHOD FOR TREATING DYSKINESIAS

(57) Abstract

The invention provides a method for treating a dyskinesias comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine.

METHOD FOR TREATING DYSKINESIAS

This invention provides a method for using 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, for the treatment of dyskinesias.

Voluntary movement is the end product of a complex sequence of neural and neuromuscular events. When one or more motor system components are damaged or diseased abnormal movement patterns emerge. Such movement disorders may or may not cause weakness or reflex changes; however, the hallmark characteristic is involuntary movement or paucity. Such movement disorders may result in hyperkinesia or hypokinesia of movement, and with movements of varying frequency, intensity, and amplitude. The causes of such movement disorders include heredity, metabolic derangements, and neurodegenerative diseases. Often such movement disorders can be caused by the use of antipsychotic agents.

Ever since antipsychotics were introduced it has been observed that patients are liable to suffer from drug-induced extrapyramidal symptoms which include drug-induced parkinsonism, acute dystonic reactions, akathisia, tardive dyskinesia and tardive dystonia. The severity of such adverse events, in a considerable number of patients, frequently results in poor compliance or termination of treatment.

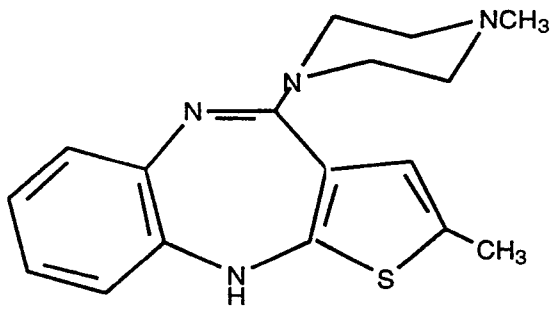
For example, tardive dyskinesia often appears after several months or years of neuroleptic therapy and persists after discontinuation of the drug or drugs. Symptoms may persist indefinitely, though in some cases slow remission is observed over months or years. In general, the likelihood of remission is lower with longer exposure to neuroleptics and with increasing age of the patient. McDowell et al., *Clinical Biology*, Chapter 38, 1988.

It is known that the compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine can

provide antipsychotic activity and is less likely to induce extrapyramidal symptoms. However, Applicant has discovered that surprisingly 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine can be useful for treating both natural and drug-induced dyskinesias. The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine is known and described in U.S. Patent No. 5,229,382, herein incorporated by reference in its entirety.

The presently claimed invention provides a method for treating a dyskinesia comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine compound is of the formula



(I)

or an acid addition salt thereof. The free base of formula (I) is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

Substantially pure Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48

d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_α radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

The term "Form I" shall refer to the polymorph obtainable using the teachings of the '382 patent. x-ray

powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26

2.6007 0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper $K\alpha$ radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

As used herein, the term "dyskinesia" or "dyskinesias" shall include neurological syndromes, natural and drug-induced, consisting of spontaneous and largely uncontrollable movements or paucity of movement. The term shall include both hyperkinesias and hypokinesias. Examples include, but are not limited to, parkinsonism, chorea, athetosis, choreathetosis, tremor, acute dystonic reactions, akathisia, neuroleptic malignant syndrome, tardive dyskinesia and tardive dystonia. It is particularly preferred that the term refers to hyperkinesias. It may be preferred that the term refers to hypokinesias. It is especially preferred that the term shall refer to tardive dyskinesia. It is further preferred that such term shall especially refer to tardive dyskinesia or tardive dystonia. It is preferred that dyskinesia shall include, but is not limited to, parkinsonism, dystonia, tardive dyskinesia, and akathisia.

The results of pharmacological studies show that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine has muscarinic cholinergic receptor activity. The compound is active at the dopamine D-1 and D-2 receptors as indicated by an IC50 of less than 1 uM in the 3H-SCH233390 (Billard, et al. Life Sciences **35**:1885 (1984)) and the 3H spiperone (Seeman et al Nature **216**:717 (1976)) binding assays respectively. Further, olanzapine is active

at the 5-HT-2 receptor and 5-HT1C receptor. The complex pharmacological profile of the compound provides a medicament which can be useful for the treatment of a dyskinesia.

In vivo animal and clinical observations support that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine has a complex muscarinic receptor subtype profile. For example, rats exposed to an overdose of the compound surprisingly exhibited significant salivation. Further, clinical subjects experienced pupilary constriction rather than the expected pupilary dialation.

Tardive dyskinesia is believed to be caused by post synaptic dopamine receptor hyperactivity in the nigrostriatum. This hypersensitivity can be induced by chronic treatment with neuroleptic drugs. As with other nigrostriatum movement disorders, the balance between acetyl cholinergic and dompaminergic neural systems appears to be disturbed in tardive dyskinesia.

The usefulness of the compound for treating various dyskinesias can be supported by the following studies as described.

I. Effect on Tardive Dyskinesia using rats.

The compound is studied for its ability to reduce oral dyskinesia in fluphenazine treated rats. Fluphenazine is a widely used model for human neuroleptic induced Tardive Dyskinesia. (Waddington et al. *Science* 220: 530-532 (1983). Six adult male rats are maintained for fifteen weeks on ablib food and water with fluphenazine added. The fluphenazine concentration in the water is 30 mg/l for eight weeks and 15 mg/l for the subsequent seven weeks. A control group of rats are maintained under the same conditions; however, the fluphemazine is not added to the water.

Each animal is tested for superfluous oral movement by placing it in a small transparent cage and counting the number of non-directed oral movements for five

minute periods at fifteen minute intervals. After three baseline measurement periods each animal is injected with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine in vehicle or vehicle.

The animals are monitored for oral dyskinesia beginning ten minutes after the injection.

II. Inhibition of Thalamonal-induced rigor in rats.

Rigor is induced in male and female rats (Sprague Dawley strain) by the administration of 7.5 mg/kg of Thalamonal (2.5 mg/ml droperidol and 0.5 mg/ml fentanyl). After 15 minutes each test animal is immobilized in a hammock and bipolar electrode inserted into the calf muscle of one limb. The electromyogram is recorded. Thirty minutes after administration of the Thalamonal, the 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine compound is administered by i.v. injection into the tail vein in increasing doses at 10 minute intervals. Six rats are used per compound and the dose necessary to reduce the intensity of the rigor by 10% and the dose required to completely abolish the rigor are determined by comparison of the integrated electromyograms obtained before and after the administration of the 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine. A placebo control group, wherein the rats are injected with vehicle at 10 minute intervals, is included in the study.

III. Clinical observations.

A double-blind multicenter clinical trial was designed to assess the safety and efficacy of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine in patients wherein one aspect of the study was the effect of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine on patients with and without dyskinesia at study entry. Patients were

randomized to 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine or placebo. The results of the study suggest that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine can be useful for the treatment of dyskinesias.

IV. Clinical Study using schizophrenic patients.

A group of schizophrenic patients with diagnosis of tardive dyskinesia of moderate or severe degree are randomized in a double blind clinical trial. Subjects are given a full psychiatric and medical assessment prior to randomization. Each participant is treated with a clinically optimal dose of haloperidol for an initial one to six month stabilization period. Each patient is withdrawn from neuroleptic treatment for four weeks to provide neuroleptic-free assessment of their dyskinetic symptoms. At the conclusion of the first four neuroleptic free (or fixed low-dose) weeks, assessments of the dyskinetic movements are carried out using the Maryland Psychiatric Research Center (MPRC) Involuntary Motor Scale and a videotape of a semistructured motor examination (for later rating independent of clinical information by a single rater). Subjects are then blindly randomized to two different drug groups, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine plus placebo or haloperidol plus benztropine, and stratified by age and severity of dyskinesia.

The dose of neuroleptic drug is ordered by the blind study physician based on clinical psychopathologic symptom response. Patients are treated to optimal clinical response as judged by the blind study physician. Staff, patients, and all raters are blind to the drug group; one nonrating physician and one nurse are nonblind to dispense medication and monitor safety. All subjects are seen weekly for evaluation and medication review.

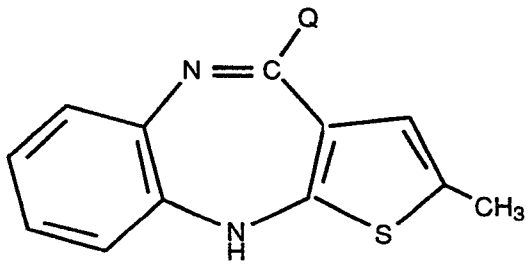
A full outcome assessment is done monthly, which includes ratings with MPRC Involuntary Motor Scale and a

videotaped evaluation session. After 12-treatment months on the blinded medication, each volunteer begins a final four week drug-free assessment period. After the blinded portion of the protocol, each patient is treated with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine at an optimal clinical dose for an additional twelve months during which time the same ratings and rating schedule are continued.

The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can be used for the methods of this invention, both in its free base and acid addition salt forms. The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those of inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or of organic acids, such as organic carboxylic acids, for example glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric or lactic acid, or organic sulfonic acids for example methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, toluene-p-sulfonic or naphthalene-2-sulfonic acid.

The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can be prepared using a process which comprises

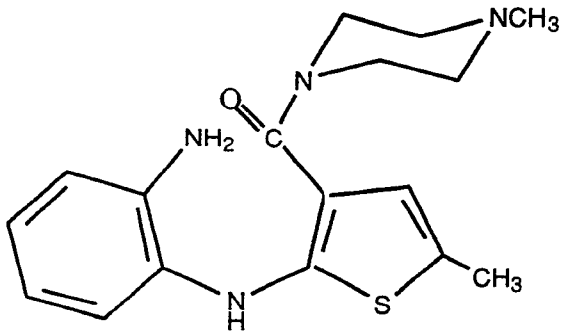
(a) reacting N-methylpiperazine with a compound of the formula



(II)

in which Q is a radical capable of being split off, or

(b) ring-closing a compound of the formula

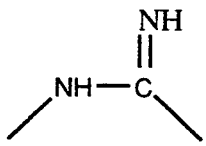


(III)

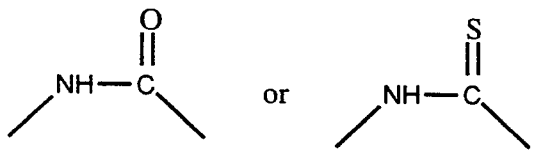
Appropriate reaction conditions and suitable values of Q can readily be chosen for these processes.

In reaction (a)the radical Q can, for example, be an amino group or a mono- or dialkyl-substituted amino group (each alkyl substituent suitably containing 1 to 4 carbon atoms), hydroxyl, thiol, or an alkoxy, alkylthio or alkylsulfonyl group suitably containing 1 to 4 carbon atoms, for example a methoxy or methylthio group, or a halogen atom, especially a chlorine atom. Preferably, Q is amino ($-NH_2$), hydroxyl or thiol, and amino is most preferred. The reaction is preferably carried out at a temperature of from 50°C to 200°C.

When Q is amino, the intermediate of formula (II) may also exist in the imino form:



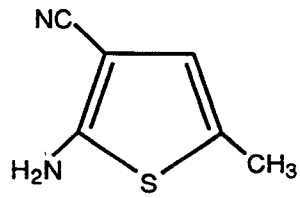
and when Q is hydroxyl or thiol, the intermediates of formula (II) may exist in their amide and thioamide forms:



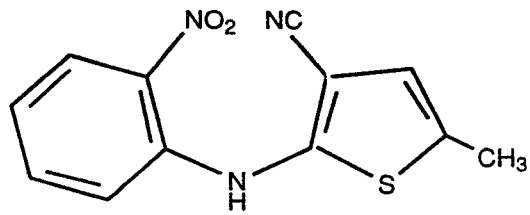
The amidine of formula (II) (Q is $-NH_2$), can be in salt form, for example a salt of a mineral acid such as the

hydrochloride, and can be reacted with N-methylpiperazine in an organic solvent such as anisole, toluene, dimethylformamide or dimethylsulfoxide, preferably at a temperature range of 100 to 150°C.

The amidine is prepared by condensing a thiophene compound of formula



with an ortho-halonitrobenzene, in the presence of a base, for example sodium hydride, in a solvent such as tetrahydrofuran or n-butyl lithium in tetrahydrofuran, or potassium carbonate or lithium hydroxide in dimethylsulfoxide or aqueous sodium hydroxide in dimethylsulfoxide, or with a tetraalkyl-ammonium salt in a two-phase system, to form a nitronitrile of formula:



(IIa)

which can be simultaneously reduced and ring-closed to the amidine of formula (II) employing, for example, stannous chloride and hydrogen chloride in aqueous ethanol or, alternatively by reduction with hydrogen and palladium/carbon or ammonium polysulfide followed by acid-catalyzed ring closure. The intermediate of formula (IIa) may be isolated using ammonium chloride (NH_4Cl) or ammonium acetate (NH_4OAc).

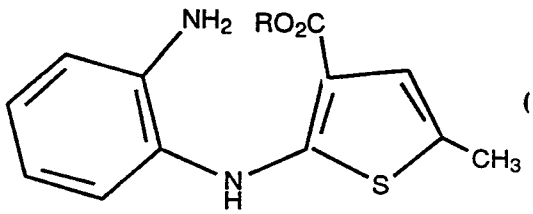
When Q is hydroxyl, reaction (a) is preferably carried out in the presence of titanium tetrachloride which has the ability to react with the N-methylpiperazine to

form a metal amine complex. Other metal chlorides such as those of zirconium, hafnium or vanadium may also be employed. The reaction can be carried out in the presence of an acid binding agent such as a tertiary amine, for example, triethylamine.

Alternatively, the reaction can be carried out using excess of N-methylpiperazine to act as an acid-binding agent. A suitable organic solvent such as toluene or chlorobenzene can be used as a reaction medium, although the use of anisole is particularly desirable, at least as a co-solvent, in view of its ability to form a soluble complex with $TiCl_4$.

If desired, elevated temperatures, for example up to 200°C, can be used to hasten the reaction and a preferred temperature range for carrying out the reaction is from 80°C to 120°C.

The intermediate amide of formula (II) (Q is -OH) can be prepared from the corresponding amidine (Q is $-NH_2$) by alkaline hydrolysis, or can be derived from compounds of formula



(IV)

in which R is an ester group, preferably C_{1-4} alkyl, by ring closure employing, for example, sodium methylsulfinyl methanide in a suitable solvent such as dimethylsulfoxide. Alternatively, the amide can be prepared by ring closure of an amino-acid, employing for example dicyclo-hexylcarbodiimide (DCC) in a suitable solvent such as tetrahydrofuran. The amino-acid can be obtained for example from the above esters by basic hydrolysis using for example sodium hydroxide in ethanol.

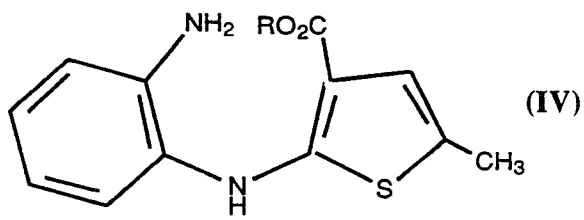
Thioamides of formula (II) (Q is -SH), iminothioethers, iminoethers or iminohalides, or other derivatives containing active Q radicals as specified above, tend to be more reactive towards N-methylpiperazine and can usually be reacted without the necessity for the presence of $TiCl_4$, but otherwise employing the same conditions of temperature and solvent.

The thioamide of formula (II) (Q is -SH) can be prepared by treating a solution of the corresponding amide in an anhydrous basic solvent, such as pyridine, with phosphorous pentasulfide. Similarly, the amide can be converted to the iminothioether, iminoether or iminohalide, or other derivatives containing active Q radicals, by treatment with conventional reagents such as for example in the case of the iminochloride, phosphorous pentachloride.

The intermediate compounds of formula (II) in which Q is a radical capable of being split off, particularly those in which Q is $-NH_2$, -OH or -SH and when Q is $-NH_2$ salts thereof, are novel compounds, and form a further aspect of the present invention.

With regard to reaction (b) above, the compound of formula (III) may be ring-closed by employing, for example, titanium tetrachloride as catalyst and anisole as solvent, and the reaction is preferably carried out at a temperature of 100°C to 250°C, for example from 150°C to 200°C.

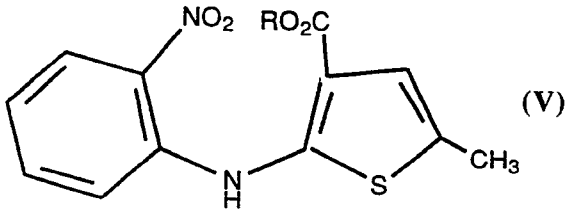
The intermediate compound of formula (III) is preferably prepared <u>in situ</u> without isolation by reacting a compound of formula



(IV)

in which R is an ester group, preferably C_{1-4} alkyl, with N-methylpiperazine, by heating to a temperature of between 30°C and 120°C, for example about 100°C, in a suitable solvent such as for example anisole, and employing $TiCl_4$ as catalyst.

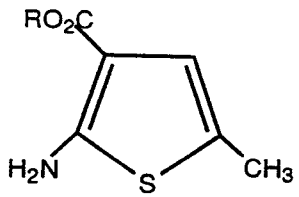
The compound of formula (IV) can be prepared from the corresponding nitro compound of formula



(V)

Such compounds of formula (V) in which R is an ester group, such as for example C_{1-4} alkyl, are novel and form a further aspect of the invention.

If convenient this nitro compound can be converted to the amine of formula (IV) without isolation, before reaction with N-methylpiperazine. Intermediate compounds of formula (V) can be made by condensation of a thiophene of formula



(VI)

with an ortho-halonitrobenzene, preferably ortho fluoro- or chloro- nitrobenzene, in the presence of a base, for example, (a) sodium hydride in a solvent such as for example tetrahydrofuran and at a temperature of from -20°C to 30°C, or (b) anhydrous potassium carbonate or lithium hydroxide in a solvent such as dimethylsulfoxide at a temperature of from 90°C to 120°C. The compound of formula (V) is converted to that of formula (IV) by reduction, for example catalytically, employing hydrogen and

palladium/carbon, or chemically, employing stannous chloride and hydrogen chloride in aqueous ethanol, or ammonium polysulfide, or zinc in aqueous ammonium chloride.

It will be appreciated that the compound of formula (I) may be isolated per se or may be converted to an acid addition salt using conventional methods.

The compound has an IC_{50} of less than 1 mM in the ^{3}H-QNB binding assay described by Yamamura, HI and Snyder, SH in Proc.Nat.Acad.Sci. USA 71 1725 (1974) indicating that it has muscarinic-cholinergic activity.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine compound is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. For treatment of a dyskinesia, a dose range of from 1 to 30 mg, preferably 1 to 20 mg per day is suitable. Radiolabelled 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine, can be detected in the saliva and thus the compound can potentially be monitored in patients to assess compliance.

A preferred formulation of the invention is a solid oral formulation comprising from about 1 to about 20 mg or 1 to 10 mg of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine as an effective amount of the active ingredient.

Most preferably, the solid oral formulation is contained in packaging materials which protect the formulation from moisture and light. For example, suitable packaging materials include amber colored high density polyethylene bottles, amber colored glass bottles, and other containers made of a material which inhibits the passage of light. Most preferably, the packaging will include a desiccant pack. The container may be sealed with an aluminum

foil blister to provide the desired protection and maintain product stability.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine compound will normally be administered orally or by injection and, for this purpose, it is usually employed in the form of a pharmaceutical composition.

Accordingly, pharmaceutical compositions comprising 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, as active ingredient associated with a pharmaceutically acceptable carrier may be prepared. In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. The active ingredient can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxy-benzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. For example, one such preferred quick release formulation is described in U.S. Patent Nos. 5,079,018, 5,039,540, 4,305,502, 4,758,598, and 4,371,516, hereby incorporated by reference. Such formulation most preferably comprises 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, water, hydrolyzed gelatin, and mannitol.

Depending on the method of administration, the compositions for the treatment of central nervous system conditions may be formulated as tablets, capsules, injection solutions for parenteral use, gel or suspension for transdermal delivery, suspensions or elixirs for oral use or suppositories. Preferably the compositions are formulated in a unit dosage form, each dosage containing from 0.25 to 100 mg, more usually 1 to 30 mg, of the active ingredient. When a sustained release formulation is desired, the unit dosage form may contain from 0.25 to 200 mg of the active ingredient. A preferred formulation of the invention is a capsule or tablet comprising 0.25 to 75 mg or 1 to 30 mg of active ingredient together with a pharmaceutically acceptable carrier therefor. A further preferred formulation is an injection which in unit dosage form comprises 0.25 to 30 mg or 1 to 30 mg of active ingredient together with a pharmaceutically acceptable diluent therefor.

The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine compound can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. It is most desirable to prepare a rapidly dissolving formulation comprising 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine. Such 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine may be prepared using the techniques described herein by the Preparation section herein *infra*.

As used herein mixing steps may be accomplished using common agitation methods such as stirring, shaking, and the like. As used herein the phrase "producing crystalline product from the mixture" shall refer to crystallization from the stated mixture of compound and solvent. Further, the artisan recognizes that crystallization processes may include

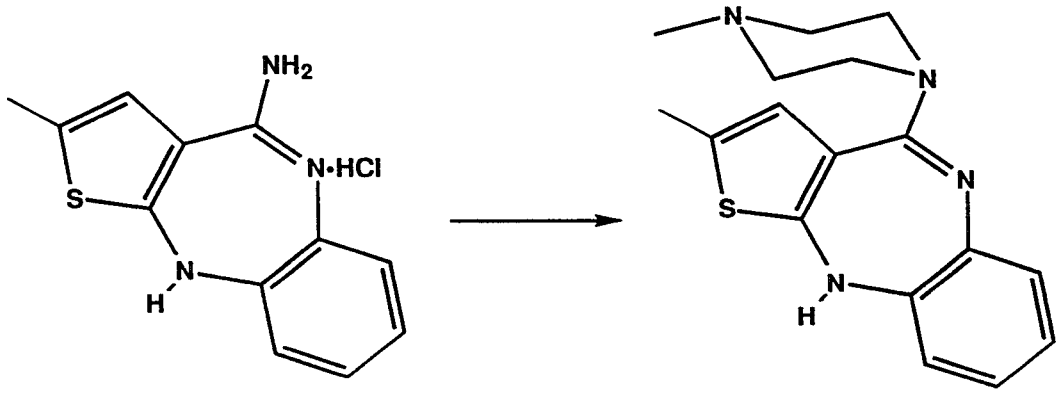
seeding, chilling, scratching the glass of the reaction vessel, and other such common techniques.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes
Intermediate 1 : 75 g
N-Methylpiperazine (reagent) : 6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until ≤ 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The

product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Form II

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency $\geq$ 97%, total related substances < 0.5% and an isolated yield of > 73%.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

EXAMPLE 2

The process substantially as described above in Example 1 was repeated using the following ingredients to provide pharmaceutically elegant tablet formulations containing 1, 2.5, 5, 7.5, and 10 mg 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, respectively, per tablet:

1 mg 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine per tablet:

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	1.0
Other Ingredients	
Lactose	67.43
Hydroxypropyl Cellulose	3.40
Crospovidone	4.25
Microcrystalline Cellulose	8.50
Magnesium Stearate	0.42
Subcoating	
Hydroxypropyl Methylcellulose	1.70
Coating	
Color Mixture White	3.47
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 2.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	2.5
Other Ingredients	
Lactose	102.15
Hydroxypropyl Cellulose	5.20
Crospovidone	6.50
Microcrystalline Cellulose	13.00
Magnesium Stearate	0.65
Subcoating	
Hydroxypropyl Methylcellulose	2.60

Coating	
Color Mixture White	5.30
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 5.0 mg Tablets

Names of Ingredients	**Quantity (mg/tablet)**
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	5.00
Other Ingredients	
Lactose	156.00
Hydroxypropyl Cellulose	8.00
Crospovidone	10.00
Microcrystalline Cellulose	20.00
Magnesium Stearate	1.00
Subcoating	
Hydroxypropyl Methylcellulose	4.00
Coating	
Color Mixture White	8.16
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 7.5 mg Tablets

Names of Ingredients	**Quantity (mg/tablet)**
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	7.50
Other Ingredients	
Lactose	234.00

Hydroxypropyl Cellulose	12.00
Crospovidone	15.00
Microcrystalline Cellulose	30.00
Magnesium Stearate	1.50
Subcoating	
Hydroxypropyl Methylcellulose	6.00
Coating	
Color Mixture White	12.24
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 10.0 mg Tablets

Names of Ingredients	**Quantity (mg/tablet)**
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	10.00
Other Ingredients	
Lactose	312.00
Hydroxypropyl Cellulose	16.00
Crospovidone	20.00
Microcrystalline Cellulose	40.00
Magnesium Stearate	2.00
Subcoating	
Hydroxypropyl Methylcellulose	8.00
Coating	
Color Mixture White	16.32
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

EXAMPLE 4

Pulvule Formulation

A pulvule formulation is prepared by blending the active with silicone starch, and filling it into hard gelatin capsules.

	Per 300 mg capsule
Compound of the invention	30.0 mg
Silicone	2.9 mg
Starch flowable	267.1 mg

EXAMPLE 5

Tablet Formulation

A tablet formulation is made by granulating the active with appropriate diluent, lubricant, disintegrant and binder and compressing

Compound of the invention	10.0 mg
Magnesium stearate	0.9 mg
Microcrystalline cellulose	75.0 mg
Povidone	15.0 mg
Starch, directly compressible	204.1 mg

EXAMPLE 6

Aqueous Injection Formulation

An aqueous injection of active is prepared as a freeze-dried plug, for reconstitution in a suitable, sterile diluent before use (to a total volume of 10 ml).

Compound of the invention is contacted with Mannitol N Hydrochloric acid and/or N sodium hydroxide to adjust pH to 5-5.5.

Compound of the invention	20.0 mg

Mannitol	20.0 mg
N Hydrochloric acid and/or N sodium hydroxide to adjust pH to 5-5.5.	

EXAMPLE 7

Controlled Release IM Formulation

A controlled release injection for intramuscular injection is formed from a sterile suspension of micronised active in an oleaginous vehicle.

Compound of the invention	50.0 mg
Aluminium stearate	0.04 mg
Sesame oil	2 ml

EXAMPLE 8

Capsule Formulation

A formulation is prepared by blending the active with silicone starch and starch, and filling it into hard gelatine capsules.

	Per 300 mg capsule
Compound of the invention	2.5 mg
Starch flowable with 0.96% silicone 220	222.5 mg
Starch flowable	75.0 mg

Example 9

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine Granules

The granules were produced by blending the mannitol and Hydroxymethyl propyl cellulose in a high shear mixer; granulating with the aqueous suspension of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and polysorbate 20; wet sized and subsequently dried in a fluid bed dryer. These are dry sized and reblended prior to packaging.

1a. 250mg Sachets

INGREDIENT	MG/SACHET
Active	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	2.50
Other Ingredients	
Mannitol	234.97
Hydroxypropyl methyl cellulose 3cps	12.50
Polysorbate 20	0.028

1b. 750mg Sachets

INGREDIENT	MG/SACHET
Active	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	7.50
Other Ingredients	
Mannitol	704.93
Hydroxypropyl methyl cellulose 3cps	37.49
Polysorbate 20	0.08

1c. 1000mg Sachets

INGREDIENT	MG/SACHET
Active	

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine	10.0
Other Ingredients	
Mannitol	939.90
Hydroxypropyl methyl cellulose 3cps	49.99
Polysorbate 20	0.11

Such granules are most preferably contacted with an acidic medium if a suspension or solution is desired.

We Claim:

1. A method for treating a dyskinesia comprising administering to a mammal in need of such treatment, an effective amount 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, or a pharmaceutically acceptable salt thereof.

2. A method of **Claim 1** wherein the dyskinesia is a hyperkinesia.

3. A method of **Claim 1** wherein 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine is substantially pure Form II 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine having a typical X-ray powder diffraction pattern substantially as follows, using a Sieman's D5000 diffractometer wherein d represents the interplaner spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516

d
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

4. A method of **Claim 3** wherein the dyskinesia is tardive dyskinesia.

5. A method of **Claim 1** wherein the effective amount is from about 1 mg to about 20 mg per day.

6. A method of **Claim 2** wherein the dyskinesia is a chorea.

7. A method of **Claim 2** wherein the dyskinesia is a athetosis.

8. A method of **Claim 1** wherein the dyskinesia is drug-induced.

9. A method of **Claim 1** wherein the dyskinesia is naturally occurring.

10. A method of **Claim 2** wherein the dyskinesia is dystonia.

11. A method of **Claim 1** wherein the dyskinesia is parkinsonism.

12. A method of **Claim 2** wherein the dyskinesia is tremor.

13. A method of **Claim 1** wherein the dyskinesia is a neurological syndrome consisting of spontaneous and substantially uncontrollable movements or paucity of movement.

14. A method of **Claim 13** wherein the dyskinesia is neuroleptic malignant syndrome.

15. A method of **Claim 2** wherein the dyskinesia is choreathetosis.

16. A method of **Claim 2** wherein the dyskinesia is selected from the group consisting of parkinsonism, dystonia, and tardive dyskinesia.

17. A method of **Claim 2** wherein the dyskinesia is selected from the group consisting of tardive dystonia and tardive dyskinesia.

18. A method of **Claim 2** wherein the dyskinesia is hemiballismus.

19. A method of **Claim 2** wherein the dyskinesia is akathisia.