# METHOD FOR TREATING AUTISM

This invention provides a method for using 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, (hereinafter referred as "olanzapine"), for the treatment of autism and mental retardation.

Autism and mental retardation are seriously incapacitating conditions for which there has been little available treatment. The patient suffering from autism has gross and sustained impaired reciprocal social interaction. Impairment in communication is marked and sustained as well. The autistic patient suffers from restricted repetitive and stereotyped patterns of behavior, interests, and activies which are non-functional and/or abnormal in either intensity or focus. Further, the juvenile patient younger than three years old displays delays in at least one of the following areas: social interaction, language as used in social communication, or symbolic or imaginative play.

The patient suffering from mental retardation has subaverage general intellectual functioning.

Both mental retardation and autism can be debilitating conditions which may require institutionalization, if severe.

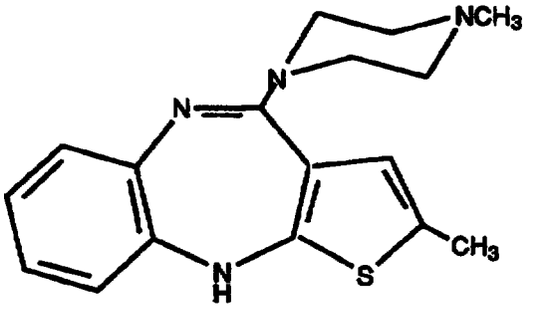
It is known that olanzapine can provide antipsychotic activity and is currently undergoing investigation for this purpose. Olanzapine is a known compound and described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety. However, olanzapine was not known to be useful for the treatment of autism and mental retardation. Applicants have discovered that olanzapine can be useful for the treatment of autism and/or mental retardation. Olanzapine could address a long felt need for treatments which provide a favorable safety profile and effectively

provide relief for the patient suffering from autism and/or mental retardation.

The presently claimed invention provides a method for treating autistic disorder, comprising administering an effective amount of olanzapine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

The presently claimed invention further provides a method for treating mental retardation, comprising administering an effective amount of olanzapine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

Olanzapine is of the formula




(I)

or an acid addition salt thereof.

It is especially preferred that olanzapine will be the 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
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 |
| 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.

It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

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 polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

| d |
|---|
| 9.9463 |
| 8.5579 |
| 8.2445 |
| 6.8862 |
| 6.3787 |
| 6.2439 |
| 5.5895 |
| 5.3055 |
| 4.9815 |
| 4.8333 |
| 4.7255 |
| 4.6286 |
| 4.533 |
| 4.4624 |
| 4.2915 |
| 4.2346 |
| 4.0855 |
| 3.8254 |
| 3.7489 |
| 3.6983 |
| 3.5817 |
| 3.5064 |
| 3.3392 |

3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

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

| d | $I/I_1$ |
|---|---|
| 9.9463 | 100.00 |
| 8.5579 | 15.18 |
| 8.2445 | 1.96 |
| 6.8862 | 14.73 |
| 6.3787 | 4.25 |
| 6.2439 | 5.21 |
| 5.5895 | 1.10 |
| 5.3055 | 0.95 |
| 4.9815 | 6.14 |
| 4.8333 | 68.37 |
| 4.7255 | 21.88 |
| 4.6286 | 3.82 |
| 4.533 | 17.83 |
| 4.4624 | 5.02 |
| 4.2915 | 9.19 |
| 4.2346 | 18.88 |
| 4.0855 | 17.29 |
| 3.8254 | 6.49 |
| 3.7489 | 10.64 |
| 3.6983 | 14.65 |

| | |
|---|---|
| 3.5817 | 3.04 |
| 3.5064 | 9.23 |
| 3.3392 | 4.67 |
| 3.2806 | 1.96 |
| 3.2138 | 2.52 |
| 3.1118 | 4.81 |
| 3.0507 | 1.96 |
| 2.948 | 2.40 |
| 2.8172 | 2.89 |
| 2.7589 | 2.27 |
| 2.6597 | 1.86 |
| 2.6336 | 1.10 |
| 2.5956 | 1.73 |

The x-ray powder diffraction patterns herein were obtained with a copper $K\alpha$ of wavelength $\lambda$ = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "$I/I_1$".

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 "autistic disorder" shall refer to a condition characterized as an Autistic Disorder, in the DSM-IV-R as catagory 299.**. Thus, including but not limited to 299.00, 299.80, and 299.10. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). It is especially preferred to treat Autistic Disorder catagory 299.00 using olanzapine. Accordingly, the term "mental retardation" shall refer to the condition characterized as such in the DSM-IV-R as catagories 317.**, 318.**, and 319. Thus, including but not limited to 317,

318.0, 318.1, 318.2 and 319. It is especially preferred to treat catagory 318.* using olanzapine.

The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

The results of pharmacological studies show that olanzapine 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 autism and/or mental retardation.

The usefulness of the compound for treating a Autistic Disorder and/or Mental Retardation can be supported by the following studies as described.

I. Clinical observations.

A double-blind multicenter clinical trial was designed to assess the safety and efficacy of olanzapine. Patients were randomized to olanzapine or placebo. The results of the study suggest that olanzapine can be useful for the treatment of Autism.

Further, results of the study suggest that olanzapine can be useful for the treatment of Mental Retardation.

Olanzapine 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 Autistic Disorder, a dose range of from 1 to 30 mg, preferably 2.5 to 30 mg per day is suitable. For the treatment of Mental Retardation, a dose range of from about 1 to about 30 mg per day is preferred. Radiolabelled olanzapine, 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 30 mg or 1 to 10 mg of olanzapine 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.

Olanzapine 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 olanzapine, 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.

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 30 mg, more usually 1 to 30 mg, of the active ingredient.

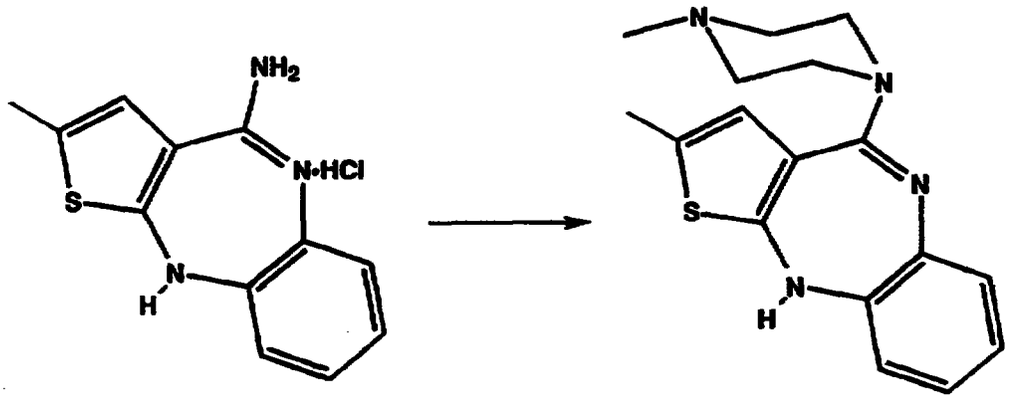
The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. Olanzapine can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. Further, the following preparations illustrate a method for preparing of the especially preferred Form II olanzapine polymorph.

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%

**Preparation 2**

Form II olanzapine polymorph

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 ≥ 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 olanzapine (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.

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We Claim:

1. A method for treating Autistic Disorder comprising administering to a mammal in need of such treatment, an effective amount olanzapine, or a pharmaceutically acceptable salt or solvate thereof.

2. A method of **Claim 1** wherein the Autistic Disorder is classified as a DSM-IV-R catagory selected from the group consisting of 299.0, 299.80, and 299.10.

3. A method of **Claim 2** wherein the Autistic Disorder is classified as DSM-IV-R catagory 299.0.

4. A method of **Claim 1** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar 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 |
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3.0638
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5. A method of **Claim 2** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

| d |
|---|
| 10.2689 |
| 8.577 |
| 7.4721 |
| 7.125 |
| 6.1459 |
| 6.071 |
| 5.4849 |
| 5.2181 |
| 5.1251 |
| 4.9874 |
| 4.7665 |
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| 3.0848 |
| 3.0638 |
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| 2.8739 |
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6. A method of **Claim 1** wherein the effective amount is from about 1 mg to about 25 mg per day.

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7. A method of **Claim 4** wherein the effective amount is from about 1 mg to about 30 mg per day.

8. A method for treating Mental Retardation comprising administering to a mammal in need of such treatment, an effective amount olanzapine, or a pharmaceutically acceptable salt or solvate thereof.

9. A method of **Claim 8** wherein the Mental Retardation is classified as a DSM-IV-R catagory selected from the group consisting of 317, 318.0, 318.1, 318.2, and 319.

10. A method of **Claim 9** wherein the Mental Retardation is selected from the group consisting of 318.0, 318.1, and 318.2.

11. A method of **Claim 8** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

| d |
|---|
| 10.2689 |
| 8.577 |
| 7.4721 |
| 7.125 |
| 6.1459 |
| 6.071 |
| 5.4849 |
| 5.2181 |
| 5.1251 |
| 4.9874 |
| 4.7665 |
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12. A method of **Claim 8** wherein the effective amount is from about 1 mg to about 25 mg per day.

13. A method of **Claim 11** wherein the effective amount is from about 1 mg to about 30 mg per day.

14. A use of olanzapine or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for therapeutic use in the treatment of Autistic Disorder.

15. A use of olanzapine or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for therapeutic use in the treatment of Mental Retardation.

16. A use as claimed by any one of Claims 14 or 15 wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

| d |
|---|
| 10.2689 |
| 8.577 |
| 7.4721 |
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