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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CELGENE CORPORATION, NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS PHARMA AG, Plaintiffs, v. SUN PHARMACEUTICAL INDUSTRIES, INC., Defendant.	Civil Action No._____ **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Celgene Corporation ("Celgene"), Novartis Pharmaceuticals Corporation and Novartis AG (together, "Novartis") (collectively, "Plaintiffs"), by their attorneys, for their Complaint against defendant SUN Pharmaceutical Industries, Inc. ("SUN"), allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 271(e)(2). The act of infringement is SUN's filing of Abbreviated New Drug Application No. 20-1231 (the "ANDA") with the United States Food and Drug Administration ("FDA"), by which SUN seeks approval to market a generic version of Novartis' FOCALIN®

drug products prior to the expiration of certain United States patents owned by Celgene and exclusively licensed to Novartis.

THE PARTIES

2. Celgene is a corporation organized under the laws of the State of Delaware, having its principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. Novartis Pharmaceuticals Corporation is a corporation organized under the laws of the State of Delaware, having its principal place of business at One Health Plaza, East Hanover, New Jersey 07936.

4. Novartis Pharma AG is a corporation organized under the laws of Switzerland, having its principal place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

5. SUN is a corporation organized under the laws of the State of Michigan; has a place of business at 270 Prospect Plains Road, Cranbury, New Jersey 08512; owns a facility at 6 Hollywood Court, South Plainfield, New Jersey 07080; and owns a manufacturing facility located at 1 Able Drive, Cranbury, NJ 08512.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

7. This Court has personal jurisdiction over SUN by virtue of SUN's continuous and systematic contacts with New Jersey; its having availed itself of the rights and benefits of New Jersey law; its consent to being sued in New Jersey as evidenced by its registration to do business in New Jersey and its appointment of a registered agent in New Jersey; its regular and established place of business at 270 Prospect Plains Rd., Cranbury, NJ 08512; and its past practice of consenting to personal jurisdiction in this Court in other litigation matters. For example, Sun

consented to jurisdiction in *Astrazeneca AB, et al. v. Sun Pharma Global FZE, et al.*, Civil Action No. 10-1017 (JAP) and *Sepracor Inc. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 09-1302 (DMC).

8. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391 and § 1400(b).

FACTUAL BACKGROUND

9. United States Patent No. 5,908,850 ("the '850 patent"), entitled "Method of Treating Attention Deficit Disorders With D-Threo Methylphenidate," was duly and legally issued to Celgene on June 1, 1999, by the United States Patent and Trademark Office ("PTO"). A copy of the '850 patent is attached hereto as Exhibit A. The '850 patent claims are directed to methods of using dexmethylphenidate hydrochloride to treat Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder.

10. United States Patent No. 6,355,656 ("the '656 patent"), entitled "Phenidate Drug Formulations Having Diminished Abuse Potential," was duly and legally issued to Celgene on March 12, 2002 by the PTO. An *Ex Parte* Reexamination Certificate, which amended certain claims of the '656 patent and added new claims, issued on March 27, 2007, by the PTO. The claims of the '656 patent are directed to, *e.g.*, pharmaceutical dosage forms containing dexmethylphenidate hydrochloride. Copies of the '656 patent and the Ex Parte Reexamination Certificate for the '656 patent are attached hereto as Exhibit B.

11. United States Patent No. 6,528,530 ("the '530 patent"), entitled "Phenidate Drug Formulations Having Diminished Abuse Potential," was duly and legally issued to Celgene on March 4, 2003, by the PTO. The claims of the '530 patent are directed to, *e.g.*, pharmaceutical unit dosages that include pharmaceutical compositions of dexmethylphenidate hydrochloride. A copy of the '530 patent is attached hereto as Exhibit C.

12. Novartis Pharmaceuticals Corporation holds an approved New Drug Application for tablets utilizing as their active pharmaceutical ingredient the hydrochloride salt of *d-threo* methylphenidate, also known as dexmethylphenidate hydrochloride, which it sells as a commercial product under the trade name FOCALIN® in 2.5 mg, 5 mg, and 10 mg dosage strengths. FOCALIN® products are indicated for use in the treatment of Attention Deficit Hyperactivity Disorder.

13. The ’850, ’656, and ’530 patents are listed in the FDA’s publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also known as the “Orange Book,” in conjunction with Novartis’ FOCALIN® products. These patents cover the FOCALIN® products and the use of those products in the treatment of Attention Deficit Hyperactivity Disorder.

14. Celgene is the owner by assignment of all right, title, and interest in the ’850, ’656, and ’530 patents. Celgene has granted to Novartis Pharma AG an exclusive license under the ’850,’656, and ’530 patents in certain fields of use.

ACTS GIVING RISE TO THIS ACTION

15. Plaintiffs received a letter from SUN dated May 24, 2010, notifying them that SUN had filed the ANDA with the FDA, seeking approval to market generic dexmethylphenidate hydrochloride tablets in 2.5 mg, 5 mg, and 10 mg dosage strengths prior to the expiration of the ’850, ’656, and ’530 patents. SUN included in the ANDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Paragraph IV Certification”) that, in SUN’s opinion, all claims of the ’850,’656, and ’530 patents are invalid, unenforceable, or both.

16. Plaintiffs sought access to the ANDA prior to filing this lawsuit, but SUN would not agree to provide it on reasonable terms.

17. On information and belief, SUN's ANDA contains information showing that its proposed generic dexmethylphenidate hydrochloride tablets (a) are bioequivalent to the patented FOCALIN® products, (b) have the same active ingredient as the patented FOCALIN® products, (c) have the same route of administration and strength as the patented FOCALIN® products, and (d) have the same, or substantially the same, dosage form and the same indication and usage as the patented FOCALIN® products.

18. In addition, SUN attached to its May 24, 2010 letter a purportedly "Detailed Statement of Factual and Legal Bases" for its Paragraph IV Certification regarding the '850, '656, and '530 patents. *See* 21 U.S.C. § 335(j)(2)(B)(iv); *see also* 21 C.F.R. §§ 314.95(c)(6)(i)-(ii). With respect to infringement, SUN does not deny that its proposed generic product as described in the ANDA will, if allowed on the market, infringe the claims of the '850 and '530 patents. SUN does present a non-infringement argument relating to the '656 patent, but only as to 5 of the patent's 40 claims. Applicable regulations require an ANDA applicant to set forth in its Paragraph IV Certification notice "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." 21 C.F.R. § 314.95(c)(6). If the applicant contends that the patent will not be infringed by its proposed generic product, its notice must include "[f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed." 21 C.F.R. § 314.95(c)(6)(i). In light of these clear legal requirements, SUN's failure to contest infringement of the '850 and '530 patents, and all but 5 claims of the '656 patent, should be deemed an admission that its proposed generic product is, in fact, infringing.

COUNT I: INFRINGEMENT OF THE '850 PATENT

19. Plaintiffs repeat and reallege the allegations of paragraphs 1-18 as though fully set forth herein.

20. SUN's submission of its ANDA to obtain approval to engage in the commercial manufacture and sale of dexmethylphenidate hydrochloride tablets for use in treatment of Attention Deficit Hyperactivity Disorder, prior to the expiration of the '850 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2).

21. Unless enjoined by this Court, SUN, upon FDA approval of SUN's ANDA, will infringe the '850 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling dexmethylphenidate hydrochloride tablets in the United States for use in treatment of Attention Deficit Hyperactivity Disorder.

22. Plaintiffs will be substantially and irreparably damaged and harmed if SUN's infringement is not enjoined. Plaintiffs do not have an adequate remedy at law.

COUNT II: INFRINGEMENT OF THE '656 PATENT

23. Plaintiffs repeat and reallege the allegations of paragraphs 1-18 as though fully set forth herein.

24. SUN's submission of its ANDA to obtain approval to engage in the commercial manufacture, use and sale of dexmethylphenidate hydrochloride tablets, prior to the expiration of the '656 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2).

25. Unless enjoined by this Court, SUN, upon FDA approval of SUN's ANDA, will infringe the '656 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling dexmethylphenidate hydrochloride tablets in the United States.

26. Plaintiffs will be substantially and irreparably damaged and harmed if SUN's infringement is not enjoined. Plaintiffs do not have an adequate remedy at law.

COUNT III: INFRINGEMENT OF THE '530 PATENT

27. Plaintiffs repeat and reallege the allegations of paragraphs 1-18 as though fully set forth herein.

28. SUN's submission of its ANDA to obtain approval to engage in the commercial manufacture, use and sale of dexmethylphenidate hydrochloride tablets, prior to the expiration of the '530 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2).

29. Unless enjoined by this Court, SUN, upon FDA approval of SUN's ANDA, will infringe the '530 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling dexmethylphenidate hydrochloride tablets in the United States.

30. Plaintiffs will be substantially and irreparably damaged and harmed if SUN's infringement is not enjoined. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, plaintiffs pray for the following relief:

(a) a Judgment declaring that the '850 patent, the '656 patent, and the '530 patent remain valid and enforceable and are infringed under 35 U.S.C. § 271(e)(2) by the filing of ANDA No. 20-1231;

(b) an Order declaring that the effective date of any FDA approval of ANDA No. 20-1231 shall be no earlier than the expiration date of Celgene's '850 patent, '656 patent, and '530 patent, and any additional periods of exclusivity, in accordance with 35 U.S.C. § 271(e)(4)(A);

(c) an injunction prohibiting SUN and any of its affiliates, or those working in concert with it, from commercially manufacturing, selling, offering to sell, importing, or using a dexmethylphenidate hydrochloride product covered by the ’850, ’656, or ’530 patents, or otherwise infringing one or more claims of the ’850, ’656, ’530 patents during the life of the patents;

(d) a Judgment declaring that SUN’s generic dexmethylphenidate hydrochloride products as described in ANDA No. 20-1231, if approved by the FDA, would infringe one or more claims of the ’850, ’656, or ’530 patents;

(e) a Judgment declaring that Sun’s commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of generic dexmethylphenidate hydrochloride products as described in ANDA No. 20-1231 would constitute infringement of one or more claims of the ’850 patent, the ’656 patent and/or the ’530 patent;

(f) an injunction prohibiting SUN and any of its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in further acts of infringement of the ’850 patent, the ’656 patent and/or the ’530 patent;

(g) an award of plaintiffs’ costs and attorneys’ fees pursuant to 35 U.S.C. § 271(e)(4) and § 285; and

(h) such other and further relief as this Court may deem just and proper.

Dated: July 1, 2010

Respectfully submitted,

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: July 1, 2010

Respectfully submitted,

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EXHIBIT A

US005908850A

United States Patent [19]

Zeitlin et al.

[11] **Patent Number: 5,908,850**

[45] **Date of Patent: Jun. 1, 1999**

[54] **METHOD OF TREATING ATTENTION DEFICIT DISORDERS WITH D-THREO METHYLPHENIDATE**

[75] Inventors: **Andrew L. Zeitlin**, Millington; **Maghsoud M. Dariani**, Fanwood; **David I. Stirling**, Branchburg, all of N.J.

[73] Assignee: **Celgene Corporation**, Warren, N.J.

[21] Appl. No.: **08/827,230**

[22] Filed: **Apr. 2, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/567,131, Dec. 4, 1995, abandoned.

[51] **Int. Cl.**[6] **A61K 31/445**

[52] **U.S. Cl.** **514/315**

[58] **Field of Search** 514/315

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

[57] **ABSTRACT**

Methods for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS while minimizing drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential by administration of d-threo-methylphenidate or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

METHOD OF TREATING ATTENTION DEFICIT DISORDERS WITH D-THREO METHYLPHENIDATE

This is a continuation of application Ser. No. 08/567,131, filed Dec. 4, 1995, now abandoned, disclosure of which is herein incorporated by reference.

The present invention relates to methods of treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex with decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

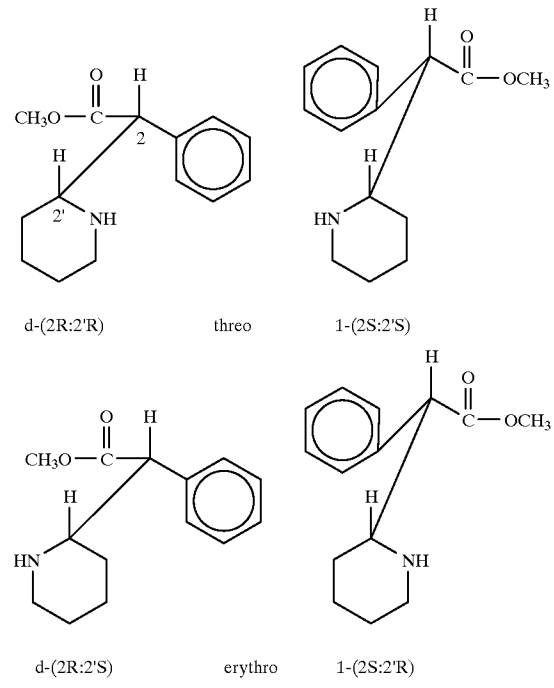
BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed illness in children. Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervous System stimulant with pharmacological activity qualitatively similar to amphetamines, and has been the drug of choice for symptomatic treatment of ADD in children. Greenhill, L., *Child & Adol. Psych. Clin. N.A.,* Vol. 4, Number 1:123–165 (1995). Current administration of racemic methylphenidate, however, results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia et al., *Annals of Neurology,* 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, personality change, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th Int'l. Conf. AIDS,* 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse in AIDS patients.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.,* 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet,* 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.,* 110:286–289 (1989). It is therefore desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

Methylphenidate possesses two centers of chirality and thus can exist as four separate optical isomers. The four isomers of methylphenidate are as follows:



Diastereomers are known in the art to possess differing physical properties, such as melting point and boiling point. For example, while the threo- racemate of methylphenidate produces the desired Central Nervous System action, the erythro- racemate contributes to hypertensive side effects and exhibits lethality in rats.

Additional studies in animals, children and adults have demonstrated pharmacological activity in the d-threo isomer of methylphenidate (2R:2'R) . See Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1987). Although the role of the l-isomer in toxicity or adverse side effects has not been thoroughly examined, the potential for isomer ballast in methylphenidate is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although l-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration, intravenous administration or inhalation results in high l-threo-methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.,* 10:14–21 (1993). Intravenous administration and inhalation are the methods of choice by drug abusers of current methylphenidate formulations. The present invention postulates that the euphoric effect produced by current formulations of methylphenidate is due to the action of l-threo-methylphenidate.

Accordingly, it has been discovered that the use of the d-threo isomer (2R:2'R) of methylphenidate, substantially free of the l-threo isomer produces a methylphenidate medication which retains high activity levels and simultaneously possesses reduced euphoric effect and reduced potential for abuse among patients.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same.

U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and

derivatives thereof (including methylphenidate) into their respective racemates.

Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritaline®) and dextroamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp. Therap.,* 241:300–306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et al., *Clin. Pharmacol. Ther.,* 52:561–568 (1992) studied the administration of dl-threo, d-threo and l-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the l-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., *Intl. J. Psych. Med.,* 25(1):21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS cognitive decline.

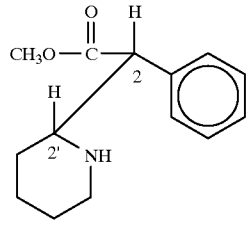
Patrick et al., *Psychopharmacology: The Third Generation of Progress,* Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the l-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

Aoyama et al., *Clin. Pharmacol. Ther.,* 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama et al. describe a correlation between sleep latency in patients and plasma concentration or (+)-threo-methylphenidate.

SUMMARY OF THE INVENTION

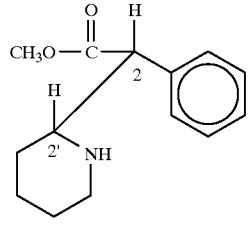
The present invention is based on the discovery that d-threo-methylphenidate (2R:2'R) possesses enhanced therapeutic activity with reduced side effects, and l-threo-methylphenidate produces undesirable side effects, euphoria and drug abuse potential in patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex.

The present invention thus relates to methods of treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse potential through administration of d-threo-methylphenidate (2R:2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the l-threo isomer.

The invention further relates to methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of d-threo-methylphenidate (2R:2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the l-threo isomer.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.,* 25:21–37 (1995). The d-threo isomer use of the present invention thus enables a lowered dosing therapy resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Moreover, administration of the d-threo isomer to patients will result in decreased side effects, reduced euphoric effect, and substantially reduce the potential for abuse of the product.

DETAILED DESCRIPTION OF THE INVENTION

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources.

The d-threo isomer of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped compressed pharmaceutical forms. Isotonic saline solutions containing 20–100 milligrams/milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed must be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 5–50 mg/day, but the actual decision as to dosage must be made by the attending physician.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of d-threo-methylphenidate substantially free of the l-threo isomer.

The invention further provides for treatment of AIDS-related dementia and related cognitive disorders with d-threo-methylphenidate substantially free of the l-threo isomer while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential.

The term, "substantially free of the l-threo-isomer" means that the composition contains at least 90% by weight of d-threo-methylphenidate, and 10% by weight of l-threo-methylphenidate. In the most preferred embodiment, the term "substantially free of the l-threo isomer" means that the composition contains at least 99% by weight of d-threo-methylphenidate and 1% or less of l-threo-methylphenidate.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLE 1

Tablets for chewing, each containing 5 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)	
d-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50° C. and again forced through a sieve of 1.7 mm mesh width. The d-threo-methylphenidate, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 2

Tablets, each containing 10 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)	
d-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 3

Gelatin dry-filled capsules, each containing 20 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 capsules)	
d-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the d-threo-methylphenidate through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 4

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

d-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to 2500 mL.	

The d-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 mL of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare dosage unit forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 milligrams of d-threo-methylphenidate).

What is claimed is:

1. A method of treating at least one of Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder and

providing enhanced therapeutic activity, reduced side effects euphoric effect, or potential for drug abuse as compared to racemic threo methylphenidate, said method comprising administering to a human exhibiting symptoms of such disorder therapeutically effective amounts of D-threo methylphenidate or pharmaceutically acceptable salt thereof, substantially free of L-threo methylphenidate, on a daily basis.

2. The method according to claim **1** wherein the amount administered is 5 mg to 50 mg per day.

3. The method according to claim **1** wherein the amount of d-threo-methylphenidate or a pharmaceutically acceptable salt thereof is greater than 99% by weight.

4. The method according to claim **1** wherein said D-threo methylphenidate is administered together with a pharmaceutically acceptable carrier.

* * * * *

EXHIBIT B

US006355656B1

(12) **United States Patent**
Zeitlin et al.

(10) **Patent No.: US 6,355,656 B1**
(45) **Date of Patent: *Mar. 12, 2002**

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington; **Maghsoud M. Dariani**, Fanwood, both of NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/318,151**

(22) Filed: **May 25, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned, and a continuation-in-part of application No. 08/583,317, filed on Jan. 5, 1996, now Pat. No. 5,733,756.

(51) **Int. Cl.**[7] **A61K 31/445**
(52) **U.S. Cl.** **514/317**
(58) **Field of Search** 514/317

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Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

4 Claims, No Drawings

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PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL

This application is a continuation-in-part of Ser. No. 08/827,230, filed Apr. 2, 1997, now U.S. Pat. No. 5,908,850 which is a continuation-in-part of Ser. No. 08/567,131 filed Dec. 4, 1995, now abandoned and Ser. No. 08/583,317, filed Jan. 5, 1996, now U.S. Pat. No. 5,733,756 both assigned to the assignee hereof. The foregoing applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to phenidate drug compositions for treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex. This invention features such drugs having decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed nervous system illness in children. Patrick et al., J. Phamacol. & Exp. Therap., 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervous System stimulant with pharmacological activity qualitatively similar to amphetamines, and has long been the drug of choice for symptomatic treatment of ADD in children. Greenhill, L., Child & Adol. Psych. Clin. N.A., Vol. 4, Number 1:123–165 (1995).

Current administration of racemic methylphenidate, however, often results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia et al., *Annals of Neurology*, 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th Int'l. Conf. AIDS*, 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry*, 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., Intl. *J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate, a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same. U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and derivatives thereof (including methylphenidate) into their respective racemates. Each of these patents is incorporated herein by reference.

Holmes et al., *J. Clin. Psychiatry*, 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritalin®) and dextroamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp. Therap.*, 241:300306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et: al., *Clin. Pharmacol. Ther.*, 52:561–568 (1992) studied the administration of dl-threo, d-threo and 1-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the 1-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., Intl. *J. Psych. Med.*, 25 (1): 21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS 'cognitive decline.

Patrick et al., Psychopharmacology: The Third Generation of Progress, Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the 1-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

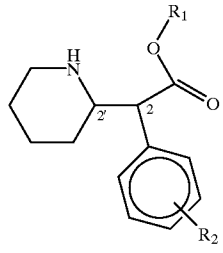
Aoyama et al., *Clin. Pharmacol. Ther.*, 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama at al. describe a correlation between sleep latency in patients and plasma concentration of (+)-threo-methylphenidate.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.*, 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet*, 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.*, 110:286–289 (1989). It is desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

There is a long-felt and very intense need for phenidate drug compositions, especially methyl phenidate, which are less susceptible to unlawful abuse and which exhibit diminished side effects while retaining therapeutic efficacy.

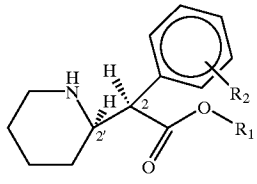
SUMMARY OF INVENTION

Phenidate drugs in accordance with this invention have the structure:

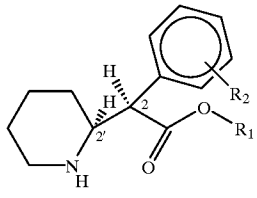


where R_1 is C_1–C_4 alkyl and R_2 is either C_1–C_4 alkyl or hydrogen. Of this family of drugs, methylphenidate, where R_1 is methyl and R_2 is hydrogen, is the most well known, having long been prescribed under the trade mark Ritalin®. Phenidate drugs are α-aryl-α-piperidyl-2-acetic acids and comprise two centers of asymmetry, existing as four separate optical isomers as follows:

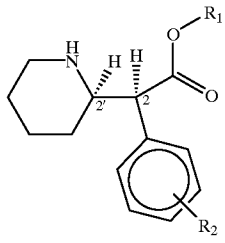
2R, 2′R; D-THREO



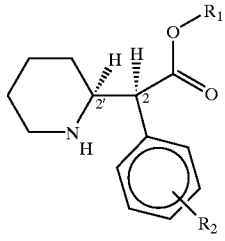
2R, 2′S; D-ERYTHRO



2S, 2′R; L-ERYTHRO



2S, 2′S; L-THREO



It is known that certain physiological properties of methylphenidate and other phenidate drugs are dependent upon stereochemistry. Thus, while the threo racemate of methylphenidate is understood to produce the desired central nervous system action, the erythro racemate is thought to contribute to hypertensive side effects.

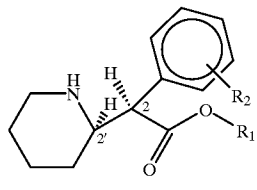
It is now believed, however, that another stereochemical distinction also applies. Studies in animals, children and adults have demonstrated pharmacological activity in the D-threo isomer of methylphenidate (2R,2'R). See Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152–158 (1987). The role of the L-threo isomer in toxicity or adverse side effects has not been examined heretofore although the potential for isomer ballast in methylphenidate and other phenidate drugs is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although L-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration by extensive first pass metabolism, intravenous administration or inhalation results in high L-threo methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.*, 10:14–21 (1993). Intravenous administration and inhalation are methods of choice by drug abusers of current, racemic methylphenidate formulations. It is now believed that the euphoric effect produced by current formulations of methylphenidate is due to the action of L-threo-methylphenidate, rather than the pharmaceutically efficacious D-threo compound.

Accordingly, it has now been discovered that the incorporation into pharmaceutical formulations of the D-threo isomer (2R,2'R) of a phenidate drug, especially methylphenidate, with the substantial exclusion of the other three isomers of the phenidate, especially the L-threo isomer, produces a phenidate medication dosage form which retains high pharmaceutical efficacy levels upon administration to patients, while simultaneously possessing fewer or reduced side-effects, reduced euphoric effect and reduced potential for abuse.

Patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex are benefitted by receiving phenidate drug, especially the preferred methylphenidate, in a dosage form which substantially excludes three of the four stereoisomers, D erythro, Lerythro, and L-threo. Stated alternatively, such dosage forms comprise D-threo phenidate in the substantial absence of L-threo and both erythro stereoisomers.

The present invention also provides dosage forms of phenidate drugs for treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse. This is accomplished by formulating dosage forms for administration to patients comprising D-threo-phenidate or a pharmaceutically acceptable salt thereof, substantially free of the L-threo isomer and both erythro isomers. The invention further provides methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential comprising administering D-threo-phenidate (2R, 2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the other three stereoisomeric forms of the drug.

In accordance with the invention, R_1 is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl. It is preferred that R_1 be methyl. R_2 may be hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl and may appear either ortho, meta or para to the acetic acid moiety.

Additional substitutients may also appear in the phenidate drug molecule, either in the aryl ring, in the pipiridine heterocycle of in the ester function, however, extensive substitution is not preferred.

Salts of phenidates, such as the conventional hydrochloride salts, are also within the spirit of the invention and all such salts are specifically contemplated hereby.

Preferably, R_1 is methyl and R_2 is hydrogen such that the phenidate drug is methylphenidate.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.*, 25:21–37 (1995). The exclusive D-threo isomer formulations of the present invention enable a lowered dosing therapy with avoidance of the administration of the stereoisomer believed to be responsible for adverse side effects and abuse potential resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources. Moreover, the D-threo- isomer of methylphenidate and other phenidate drugs can be prepared in accordance with Ser. No. 08/583,317 filed Jan. 5, 1996, which application forms a parent to this application and has been incorporated herein by reference. Examples forming part of this application set forth certain preferred synthetic routes to the phenidate compounds useful in the practice of this invention. Persons of ordinary skill will be able to modify such procedures to prepare the lower alkyl substituted phenyl derivatives and lower alkyl esters contemplated herein without undue experimentation. Thus, preparation of ethyl, propyl, isopropyl etc. esters is a simple matter in view of the synthetic schemes set forth. Likewise, substituting the phenyl ring with one or more alkyl or other substituients may also be accomplished.

The dosage forms of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and other conventional, pharmaceutical forms. Isotonic saline solutions, conveniently containing about 1–40 milligrams of drug per milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes. Rectal administration can conveniently be effected through the use of suppositories such as can easily be formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed should be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 1–50 mg/day, but the actual decision as to dosage will depend upon the exact phenidate drug being employed and will be made by the attending physician as a matter of routine. Such physician can, however, determine an appropriate regime employing well-known medical considerations. Such persons will appreciate that the overall dosage amount will be significantly smaller than that used with the corresponding racemic drug, since the undesired enantiomers are not included in the present dosage forms.

Accordingly, a pharmaceutically effective amount of a phenidate drug in accordance with this invention will be understood by persons of ordinary skill in the art to be that amount of the selected D-threo phenidate which, upon administration to a patient, would result in a sensible and therapeutically useful effect.

When phenidates other than methylphenidate are to be administered, it will be appreciated that the effective amount of drug will likely be different than for methylphenidate. Determination of such amount, however, is well within the routine skill of the practitioner. In accordance with preferred embodiments, from 1 to about 50 mg will be administered to patients, with from about 2 to about 20 mg per day being still more preferred. In still more preferred embodiments, patients will receive from about 2½ to about 12 mg per day.

It is desirable to provide unit dosage forms for administration of compounds of the invention comprising from about 1 to about 50 mg of drug, with amounts of from about 2 to about 20 and particularly from about 2½ to about 12 mg being still more preferred. Oral administration is the protocol of choice, however other routes of administration, such as intravenous, intraperitoneal, rectal and the like may also be employed in formulating the unit dosage forms of this invention. Carriers, diluents and excipients are conventionally employed in formulating unit dosage forms and the same are selected as a matter of routine depending upon the selected route of administration. For oral administration, formulation into tablets using tabletting excipients are conveniently employed, although capsular and other oral forms are also useful.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of D-threo-methylphenidate substantially free of the L-threo and other isomers. The invention gives rise to methods of treatment of AIDS related dementia and related cognitive disorders with D-threo-methylphenidate substantially free of the remaining isomers.

The term, "substantially free as it applies to a stereoisomer in accordance with a composition of this invention means that the composition contains no more than 10% by weight of the isomer in question. It is preferred that such composition have less than about 2% of the unwanted isomers and even more preferred that less than 1% be present. When applied to a plurality of stereoisomers, then all of the isomers, taken together, comprise no more than 10% by weight of the composition and preferrably less than 2%. It is preferred that compositions characterized as being "substantially free" of all stereoisomers but the D-threo isomer comprise no more than about 5% of other isomers. It is still more preferred that no more than 1% of the undesired isomers be present.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLES

A suitable salt medium for the microbiological transformations described in the following examples has been denominated "media A" and has the following composition:

$MgSO_4$	1.00 g/L
$CaCl_2$	0.021 g/L
$ZnSO_4.7H_2O$	0.20 mg/L
$MnSO_4.4H2O$	0.10 mg/L
H_3BO_3	0.02 mg/L
$CUSO_4.5H2O$	0.10 mg/L
$CoCL_2.6H_2O$	0.05 mg/L
$NiCl_2.6H2O$	0.01 mg/L
$FeSO_4$	1.50 mg/L
$NaMoO_4$	2.00 mg/L
Fe EDTA	5.00 mg/L
KH_2PO_4	20.00 mg/L
NaOH	to pH 7

Example 1

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one

Preparation of Biocatalyst

Lactamase is obtained from Pseudomonas cepacia grown on 1–2% penicillin as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 2 g/l of penicillin is inoculated with *Pseudomonas cepacia*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 2 g/l penicillin. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic (+/−)trans-7-phenyl-1-azabicyclo (4,2,0)octan-8-one (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract of lactamase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 3 hours under these conditions. A lactamase with opposite stereoselectivity obtained from a microorganism such as Rhodococcus rhodochrous can be used to resolve (+/−)trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one to L-ritalinic acid and the D-trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one. This lactam is then hydrolyzed to the D-ritalinic acid by conventional means.

Trans-7-phenyl-i-azabicyclo(4,2,0)-octan-8-one may be prepared by the method of Corey, Mol, or Earle (Corey et al., *J. Amer. Chem. Soc.*, 87:2518 (1965); Earle et al., *J. Chem. Soc. C.*, 2093 (1969);Moll F. *Naturforsch., Teil B*, 21:297 (1966).

Isolation of D-lactam.

The reaction mixture prepared above is extracted with methylene chloride and the organic layer is dried with $MgSO_4$. The organic layer is then filtered and concentrated by rotary evaporation at 30° with reduced pressure, to yield an oil product. The oil product may be further purified by column chromatography.

Example 2

Preparation of D-threo-2-(piperid-2-yl)-2-phenylacetic acid from threo-2-(piperid-2-yl)-2-phenyl-2-acetamide

Preparation of Amidase

Amidase is obtained from Acinetobacter baumanni grown on 30 mM 2-cyanobutane as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with Acinetobacter baumanni. After the mixture in incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetamide (0.5 g) prepared by, e.g. the method of Hartmann, U.S. Pat. No. 2,507,631, is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of amidase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions. An amidase with opposite stereoselectivity obtained from a microorganism such as Rhodococcus rhodochrous can be used to resolve DL-threo-2-(piperid-2-yl)-2-phenyl-acetamide to L-ritalinic acid and the D-threo-2-(piperid-2-yl)-2-phenyl-acetamide. This amide is then hydrolyzed to the D-ritalinic acid by conventional means.

Example 3

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one.

Racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one (0.5 g) is added to a mixture of 20 ml 50 mM phosphate buffer pH 7.5 and 1 ml of Pseudomonas putida cell extract. The reaction is maintained at 30° C. until the enantiomeric excess as determined by chiral chromatography is no less than 98% D-ritalinic acid, generally about 24 hours under these conditions. Alternatively, a cell extract containing an amidase of opposite stereoselectivity may be used to effect a resolution of racemic trans-7-phenyl-1-aza-bicyclo(4,2,0)-octan-8-one where L-ritalinic acid is produced and the D-lactam is isolated as the product.

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer dried with $MgSO_4$. The organic layer is then filtered and concentration by rotary evaporation at 30° with reduced pressure, to yield an oil. The oil product may be further purified by column chromatography.

Example 4

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from threo-2-(piperid-2-yl)-2-phenyl-acetonitrile

Nitrile hydratase and amidase are obtained from Alcaligenes faecalis grown on 30 mM 2-cyanobutane or 2-phenylacetonitrile as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with Alcaligenes faecalis.

After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane or 2-phenylacetonitrile. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetonitrile (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of Alcaligenes faecalis with nitrile hydratase and amidase activity. The reaction is maintained at 30° C. until the enantiomer excess

as-determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions.

Example 5

The use of an esterase/lipase for the stereoselective enrichment of DL-threo-α-phenyl-α-piperidyl-acetic acid methyl ester

A microbial source of a stereoselective esterase or lipase may be obtained from commercial sources such as Novo Nordisk's "Humicola lipolase" or an ATCC Pseudomonas strain 31809 or 31808. Esterase/lipase is obtained from Pseudomonas sp. ATCC strain 31809 grown on 1% olive oil in media A supplemented with 8 g/l nutrient broth. Fifty ml of media A containing the 1% olive oil and 8 g/l nutrient broth is inoculated with Pseudomonas sp. ATCC strain 31809. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of media with 1% olive oil supplemented with 8 g/l nutrient broth. After 24 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer, pH 7.5 and again concentrated to a paste. Cells are ruptured as above.

DL-threo-α-phenyl-α-piperidylacetic acid methyl ester (0.5 g) prepared by the method of Hartmann is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract. The reaction is maintained at 30° C. until the enantiomeric excess, as determined by chiral chromatography, is no less than 98% D-threo-methylphenidate, generally in about 25 hours under these conditions.

PREPARATION OF EXEMPLARY DOSAGE FORMS

Example 6

Tablets for chewing, each containing 5 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 tablets)

D-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

The solid ingredients are each forced through a 0.25 mm mesh sieve. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a 2 mm mesh sieve, dried at 50° C. and forced through a 1.7 mm mesh sieve. The D-threo-methylphenidate, glycine and saccharin are carefully mixed, the granulated mannitol and lactose, stearic acid and talc added and the whole mixed thoroughly. The mass is compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking groove on the one side.

Example 7

Tablets, each containing 10 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 tablets)

D-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a 0.6 mm mesh sieve. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh and compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 8

Gelatin dry-filled capsules, each containing 20 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 capsules)

D-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the D-threo-methylphenidate through a 0.2 mm mesh sieve and the two components intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a 0.9 mm mesh sieve and the whole again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a 0.8 mm mesh sieve and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into gelatin dry-fill capsules.

Example 9

A 0.2% injectable or infusible solution can be prepared, in the following exemplary manner:

D-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to	2500 ml.

The D-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 ml of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare unit dosage forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules such that each contains, respectively 2.0 or 5.0 milligrams of D-threo-methylphenidate.

What is claimed is:

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of D-threo-methylphenidate or a

pharmaceutically acceptable salt thereof said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

2. The unit dosage of claim **1** comprising from about 2 to about 20 milligrams of D-threo-methylphenidate.

3. The unit dosage of claim **1** comprising from about 2½ to about 12 milligrams of D-threo-methylphenidate.

4. The unit dosage of claim **1** in a form suitable for oral administration.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,355,656 B1
DATED : March 12, 2002
INVENTOR(S) : Andrew L. Zeitlin et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Lines 7 and 8, delete "and Ser. No. 08/583,317, filed, Jan. 5, 1996, now U.S. Pat. No. 5,733,756 both".
Line 9, "application are" and insert therefor -- application is --.

Column 5,
Line 3, delete "of in" and insert therefor -- or in --.

Column 6,
Line 44, after "free", insert quotation marks -- " --.

Signed and Sealed this

Twenty-ninth Day of July, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006355656C1

(12) EX PARTE REEXAMINATION CERTIFICATE (5729th)

United States Patent
Zeitlin et al.

(10) **Number: US 6,355,656 C1**
(45) **Certificate Issued: *Mar. 27, 2007**

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

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Reexamination Request:
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Patent No.: **6,355,656**
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Appl. No.: **09/318,151**
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(*) Notice: This patent is subject to a terminal disclaimer.

Certificate of Correction issued Jul. 29, 2003.

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/317**
(58) **Field of Classification Search** 514/317
See application file for complete search history.

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Primary Examiner—Dwayne C. Jones

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

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EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim **1** is determined to be patentable as amended.

Claims **2**, **3** and **4**, dependent on an amended claim, are determined to be patentable.

New claims **5**–**40** are added and determined to be patentable.

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof *mixed with a pharmaceutically acceptable carrier, diluent or excipient,* said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

5. The pharmaceutical unit dosage of claim 1 wherein said excipient is a tableting excipient.

6. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of mannitol, lactose, talc, glycine, stearic acid and saccharin.

7. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of lactose, corn starch, polyethylene glycol, talc and magnesium stearate.

8. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of microcrystalline cellulose, sodium lauryl sulfate and magnesium stearate.

9. The pharmaceutical unit dosage of claim 1 that comprises a pharmaceutically acceptable salt of D-threo-methylphenidate.

10. The pharmaceutical unit dosage of claim 9 that comprises a hydrochloride salt of D-threo-methylphenidate.

11. The pharmaceutical unit dosage of claim 4 that is a solid oral dosage form.

12. The pharmaceutical unit dosage of claim 11 that is a tablet.

13. The pharmaceutical unit dosage of claim 4 that is a capsule.

14. The pharmaceutical unit dosage of claim 4 that is a dragee.

15. The pharmaceutical unit dosage of claim 1 that is suitable for parenteral administration.

16. The pharmaceutical unit dosage of claim 1 that is suitable for transdermal administration.

17. The pharmaceutical unit dosage of claim 16 that is a transdermal patch.

18. A pharmaceutical unit dosage comprising 1 milligram of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

19. The pharmaceutical unit dosage of claim 18 that is a tablet.

20. The pharmaceutical unit dosage of claim 19 that comprises a hydrochloride salt of D-threo-methylphenidate.

21. A pharmaceutical unit dosage comprising 2 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

22. The pharmaceutical unit dosage of claim 21 that is a tablet.

23. The pharmaceutical unit dosage of claim 22 that comprises a hydrochloride salt of D-threo-methylphenidate.

24. A pharmaceutical unit dosage comprising 2½ milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

25. The pharmaceutical unit dosage of claim 24 that is a tablet.

26. The pharmaceutical unit dosage of claim 25 that comprises a hydrochloride salt of D-threo-methylphenidate.

27. A tablet comprising 5 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

28. The tablet of claim 27 that comprises a hydrochloride salt of D-threo-methylphenidate.

29. A pharmaceutical unit dosage comprising 10 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

30. The pharmaceutical unit dosage of claim 29 that is a tablet.

31. The pharmaceutical unit dosage of claim 30 that comprises a hydrochloride salt of D-threo-methylphenidate.

32. A pharmaceutical unit dosage comprising 12 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically

acceptable carrier, diluent or excipient, said dosage having less that 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

33. The pharmaceutical unit dosage of claim 32 that is a tablet.

34. The pharmaceutical unit dosage of claim 33 that comprises a hydrochloride salt of D-threo-methylphenidate.

35. A pharmaceutical unit dosage comprising 20 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

36. The pharmaceutical unit dosage of claim 35 that is a tablet.

37. The pharmaceutical unit dosage of claim 36 that comprises a hydrochloride salt of D-threo-methylphenidate.

38. A pharmaceutical unit dosage comprising 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

39. The pharmaceutical unit dosage of claim 38 that is a tablet.

40. The pharmaceutical unit dosage of claim 39 that comprises a hydrochloride salt of D-threo-methylphenidate.

* * * * *

EXHIBIT C

US006528530B2

(12) **United States Patent**
Zeitlin et al.

(10) **Patent No.: US 6,528,530 B2**
(45) **Date of Patent: *Mar. 4, 2003**

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/955,556**

(22) Filed: **Sep. 18, 2001**

(65) **Prior Publication Data**

US 2002/0035126 A1 Mar. 21, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/318,151, filed on May 25, 1999, now Pat. No. 6,355,656, which is a continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/445**
(52) **U.S. Cl.** **514/317**
(58) **Field of Search** 514/317

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(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

4 Claims, No Drawings

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PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL

This application is a continuation of U.S. application Ser. No. 09/318,151 filed May 25, 1999, now U.S. Pat. No. 6,355,656 which is a CIP of U.S. application Ser. No. 08/827,230 filed Apr. 2, 1997, now U.S. Pat. No. 5,908,850, which is a continuation of U.S. application Ser. No. 08/567, 131 filed Dec. 4, 1995, now abandoned the contents of which are incorporated herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to phenidate drug compositions for treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex. This invention features such drugs having decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed nervous system illness in children. Patrick et al., J. Phamacol. & Exp. Therap., 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervcus System stimulant with pharmacological activity qualitatively similar to amphetamines, and has long been the drug of choice for symptomatic treatment of ADD in children. Graenhill, L., Child & Adol. Psych. Clin. N.A., Vol. 4, Number 1:123–165 (1995).

Current administration of racemic methylphenidate, however, often results in notable aide effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia at al., *Annals of Neurology,* 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th int'l. Conf. AIDS,* 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., Intl. *J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate, a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same. U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and derivatives thereof (including methylphenidate) into their respective racemates. Each of these patents is incorporated herein by reference.

Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritalin®) and dexamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp Therap.,* 241:300306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et: al., *Clin. Pharmacol. Ther.,* 52:561–568 (1992) studied the administration of dl-threo, d-threo and 1-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the 1-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., Intl. *J. Psych. Med.,* 25 (1) :21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS' cognitive decline.

Patrick et al., Psychopharmacology: The Third Generation of Progress, Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the 1-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

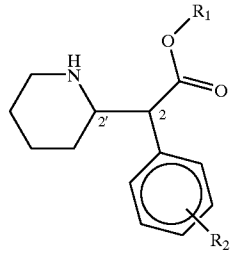
Aoyama et al., *Clin. Pharmacol. Ther.,* 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama et al. describe a correlation between sleep latency in patients and plasma concentration of (+)-threo-methylphenidate.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.,* 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet,* 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.,* 110:286–289 (1989). It is desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

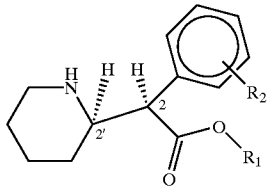
There is a long-felt and very intense need for phenidate drug compositions, especially methyl phenidate, which are less susceptible to unlawful abuse and which exhibit diminished side effects while retaining therapeutic efficacy.

SUMMARY OF INVENTION

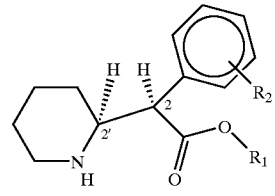
Phenidate drugs in accordance with this invention have the structure:



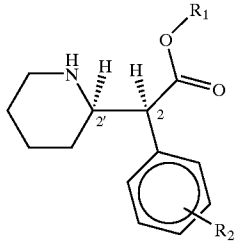
where R_1 is C_1–C_4 alkyl and R_2 is either C_1–C_4 alkyl or hydrogen. Of this family of drugs, methylphenidate, where R_1 is methyl and R_2 is hydrogen, is the most well known, having long been prescribed under the trade mark Ritalin®. Phenidate drugs are α-aryl-α-piperidyl-2-acetic acids and comprise two centers of asymmetry, existing as four separate optical isomers as follows:



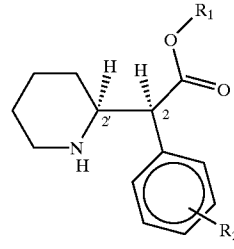
2R,2′R; D-THREO



2R,2′S; D-ERYTHRO



2S,2′R; L-ERYTHRO



2S,2′S; L-THREO

It is known that certain physiological properties of methylphenidate and other phenidate drugs are dependent upon stereochemistry. Thus, while the threo racemate of methylphenidate is understood to produce the desired central nervous system action, the erythro racemate is thought to contribute to hypertensive side effects.

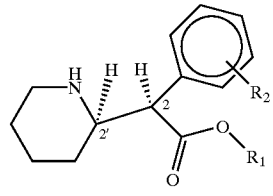
It is now believed, however, that another stereochemical distinction also applies. Studies in animals, children and adults have demonstrated pharmacological activity in the D-threo isomer of methylphenidate (2R,2′R). See Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1987). The role of the L-threo isomer in toxicity or adverse side effects has not been examined heretofore although the potential for isomer ballast in methylphenidate and other phenidate drugs is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although L-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration by extensive first pass metabolism, intravenous administration or inhalation results in high L-threo methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.,* 10:14–21 (1993). Intravenous administration and inhalation are methods of choice by drug abusers of current, racemic methylphenidate formulations. It is now believed that the euphoric effect produced by current formulations of methylphenidate is due to the action of L-threo-methylphenidate, rather than the pharmaceutically efficacious D-threo compound.

Accordingly, it has now been discovered that the incorporation into pharmaceutical formulations of the D-threo isomer (2R,2′R) of a phenidate drug, especially methylphenidate, with the substantial exclusion of the other three isomers of the phenidate, especially the L-threo isomer, produces a phenidate medication dosage form which retains high pharmaceutical efficacy levels upon administration to patients, while simultaneously possessing fewer or reduced side-effects, reduced euphoric effect and reduced potential for abuse.

Patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex are benefitted by receiving phenidate drug, especially the preferred methylphenidate, in a dosage form which substantially excludes three of the four stereoisomers, D erythro, Lerythro, and L-threo. Stated alternatively, such dosage forms comprise D-threo phenidate in the substantial absence of L-threo and both erythro stereoisomers.

The present invention also provides dosage forms of phenidate drugs for treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse. This is accomplished by formulating dosage forms for administration to patients comprising D-threo-phenidate or a pharmaceutically acceptable salt thereof, substantially free of the L-threo isomer and both erythro isomers. The invention further provides methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential comprising administering D-threo-phenidate (2R, 2′R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the other three stereoisomeric forms of the drug.

In accordance with the invention, R_1 is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl. It is preferred that R_1 be methyl. R_2 may be hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl and may appear either ortho, meta or para to the acetic acid moiety. Additional substitutients may also appear in the phenidate drug molecule, either in the aryl ring, in the pipiridine heterocycle of in the ester function, however, extensive substitution is not preferred.

Salts of phenidates, such as the conventional hydrochloride salts, are also within the spirit of the invention and all such salts are specifically contemplated hereby.

Preferably, R_1 is methyl and R_2 is hydrogen such that the phenidate drug is methylphenidate.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.,* 25:21–37 (1995). The exclusive D-threo isomer formulations of the present invention enable a lowered dosing therapy with avoidance of the administration of the stereoisomer

believed to be responsible for adverse side effects and abuse potential resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources. Moreover, the D-threo-isomer of methylphenidate and other phenidate drugs can be prepared in accordance with Ser. No. 08/583,317 filed Jan. 5, 1996, which application forms a parent to this application and has been incorporated herein by reference. Examples forming part of this application set forth certain preferred synthetic routes to the phenidate compounds useful in the practice of this invention. Persons of ordinary skill will be able to modify such procedures to prepare the lower alkyl substituted phenyl derivatives and lower alkyl esters contemplated herein without undue experimentation. Thus, preparation of ethyl, propyl, isopropyl etc. esters is a simple matter in view of the synthetic schemes set forth. Likewise, substituting the phenyl ring with one or more alkyl or other substituents may also be accomplished.

The dosage forms of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and other conventional, pharmaceutical forms. Isotonic saline solutions, conveniently containing about 1–40 milligrams of drug per milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes. Rectal administration can conveniently be effected through the use of suppositories such as can easily be formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed should be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 1–50 mg/day, but the actual decision as to dosage will depend upon the exact phenidate drug being employed and will be made by the attending physician as a matter of routine. Such physician can, however, determine an appropriate regime employing well-known medical considerations. Such persons will appreciate that the overall dosage amount will be significantly smaller than that used with the corresponding racemic drug, since the undesired enantiomers are not included in the present dosage forms.

Accordingly, a pharmaceutically effective amount of a phenidate drug in accordance with this invention will be understood by persons of ordinary skill in the art to be that amount of the selected D-threo phenidate which, upon administration to a patient, would result in a sensible and therapeutically useful effect.

When phenidates other than methylphenidate are to be administered, it will be appreciated that the effective amount of drug will likely be different than for methylphenidate. Determination of such amount, however, is well within the routine skill of the practitioner. In accordance with preferred embodiments, from 1 to about 50 mg will be administered to patients, with from about 2 to about 20 mg per day being still more preferred. In still more preferred embodiments, patients will receive from about 2½ to about 12 mg per day.

It is desirable to provide unit dosage forms for administration of compounds of the invention comprising from about 1 to about 50 mg of drug, with amounts of from about 2 to about 20 and particularly from about 2½ to about 12 mg being still more preferred. Oral administration is the protocol of choice, however other routes of administration, such as intravenous, intraperitoneal, rectal and the like may also be employed in formulating the unit dosage forms of this invention. Carriers, diluents and excipients are conventionally employed in formulating unit dosage forms and the same are selected as a matter of routine depending upon the selected route of administration. For oral administration, formulation into tablets using tabletting excipients are conveniently employed, although capsular and other oral forms are also useful.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of D-threo-methylphenidate substantially free of the L-threo and other isomers. The invention gives rise to methods of treatment of AIDS related dementia and related cognitive disorders with D-threo-methylphenidate substantially free of the remaining isomers.

The term, "substantially free as it applies to a stereoisomer in accordance with a composition of this invention means that the composition contains no more than 10% by weight of the isomer in question. It is preferred that such composition have less than about 2% of the unwanted isomers and even more preferred that less than 1% be present. When applied to a plurality of stereoisomers, then all of the isomers, taken together, comprise no more than 10% by weight of the composition and preferrably less than 2%. It is preferred that compositions characterized as being "substantially free" of all stereoisomers but the D-threo isomer comprise no more than about 5% of other isomers. It is still more preferred that no more than 1% of the undesired isomers be present.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLES

A suitable salt medium for the microbiological transformations described in the following examples has been denominated "media A" and has the following composition:

$MgSO_4$	1.00 g/L
$CaCl_2$	0.021 g/L
$ZnSO_4.7H_2O$	0.20 mg/L
$MnSO_4.4H_2O$	0.10 mg/L
H_3BO_3	0.02 mg/L
$CUSO_4.5H_2O$	0.10 mg/L
$CoCL_2.6H_2O$	0.05 mg/L
$NiCl_2.6H_2O$	0.01 mg/L
$FeSO_4$	1.50 mg/L
$NaMoO_4$	2.00 mg/L
Fe EDTA	5.00 mg/L
KH_2PO_4	20.00 mg/L
NaOH	to pH 7

Example 1

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

Preparation of Biocatalyst

Lactamase is obtained from *Pseudomonas cepacia* grown on 1–2% penicillin as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 2 g/l of penicillin is inoculated with *Pseudomonas cepacia*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 2 g/l penicillin. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic (+/−-)trans-7-phenyl-1-azabicyclo(4,2,0)octan-8-one (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract of lactamase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 3 hours under these conditions. A lactamase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve (+/−)trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one to L-ritalinic acid and the D-trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one. This lactam is then hydrolyzed to the D-ritalinic acid by conventional means.

Trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one may be prepared by the method of Corey, Mol, or Earle (Corey et al., *J. Amer. Chem. Soc.,* 87:2518 (1965); Earle et al., *J. Chem. Soc. C.,* 2093 (1969); Moll F. *Naturforsch*., Teil B, 21:297 (1996).

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer is dried with $MgSO_4$. The organic layer is then filtered and concentrated by rotary evaporation at 30° with reduced pressure, to yield an oil product. The oil product may be further purified by column chromatography.

Example 2

Preparation of D-threo-2-(piperid-2-yl)-2-phenylacetic acid from threo-2-(piperid-2-yl)-2-phenyl-2-acetamide

Preparation of Amidase

Amidase is obtained from *Acinetobacter baumanni* grown on 30 mM 2-cyanobutane as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Acinetobacter baumanni*. After the mixture in incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetamide (0.5 g) prepared by, e.g. the method of Hartmann, U.S. Pat. No. 2,507,631, is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of amidase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions. An amidase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve DL-threo-2-(piperid-2-yl)-2-phenyl-acetamide to L-ritalinic acid and the D-threo-2-(piperid-2-yl)-2-phenyl-acetamide. This amide is then hydrolyzed to the D-ritalinic acid by conventional means.

Example 3

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

Racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one (0.5 g) is added to a mixture of 20 ml 50 mM phosphate buffer pH 7.5 and 1 ml of *Pseudomonas putida* cell extract. The reaction is maintained at 30° C. until the enantiomeric excess as determined by chiral chromatography is no less than 98% D-ritalinic acid, generally about 24 hours under these conditions. Alternatively, a cell extract containing an amidase of opposite stereoselectivity may be used to effect a resolution of racemic trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one where L-ritalinic acid is produced and the D-lactamis isolated as the product.

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer dried with $MgSO_4$. The organic layer is then filtered and concentration by rotary evaporation at 30° with reduced pressure, to yield an oil. The oil product may be further purified by column chromatography.

Example 4

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from threo-2-(piperid-2-yl)-2-phenyl-acetonitrile

Nitrile hydratase and amidase are obtained from *Alcaligenes faecalis* grown on 30 mM 2-cyanobutane or 2-phenylacetonitrile as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Alcaligenes faecalis*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane or 2-phenylacetonitrile. After 40 hours of incubation at 30° C., the cells are concentrated a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetonitrile (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of *Alcaligenes faecalis* with nitrile hydratase and amidase activity. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions.

Example 5

The Use of an Esterase/lipase for the Stereoselective Enrichment of DL-threo-α-phenyl-α-piperidyl-acetic acid methyl ester

A microbial source of a stereoselective esterase or lipase may be obtained from commercial sources such as Novo Nordisk's "Humicola lipolase" or an ATCC Pseudomonas strain 31809 or 31808. Esterase/lipase is obtained from Pseudomonas sp. ATCC strain 31809 grown on 1% olive oil in media A supplemented with 8 g/l nutrient broth. Fifty ml of media A containing the 1% olive oil and 8 g/l nutrient broth is inoculated with Pseudomonas sp. ATCC strain 31809. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of media with 1% olive oil supplemented with 8 g/l nutrient broth. After 24 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer, pH 7.5 and again concentrated to a paste. Cells are ruptured as above.

DL-threo-α-phenyl-α-piperidylacetic acid methyl ester (0.5 g) prepared by the method of Hartmann is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH and 1 ml cell extract. The reaction is maintained at 30° C. until the enantiomeric excess, as determined by chiral chromatography, is no less than 98% D-threo-methylphenidate, generally in about 25 hours under these conditions.

Preparation of Exemplary Dosage Forms

Example 6

Tablets for chewing, each containing 5 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)

D-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

The solid ingredients are each forced through a 0.25 mm mesh sieve. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a 2 mm mesh sieve, dried at 50° C. and forced through a 1.7 mm mesh sieve. The D-threo-methylphenidate, glycine and saccharin are carefully mixed, the granulated mannitol and lactose, stearic acid and talc added and the whole mixed thoroughly. The mass is compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking groove on the one side.

Example 7

Tablets, each containing 10 milligrams of D-threo-methylphenidate, can be prepared in the following manner: composition (for 1000 tablets)

D-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a 0.6 mm mesh sieve. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh and compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 8

Gelatin dry-filled capsules, each containing 20 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 capsules)

D-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the D-threo-methylphenidate through a 0.2 mm mesh sieve and the two components intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a 0.9 mm mesh sieve and the whole again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a 0.8 mm mesh sieve and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into gelatin dry-fill capsules.

Example 9

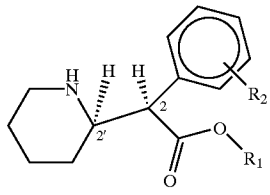
A 0.2% injectable or infusible solution can be prepared, in the following exemplary manner:

D-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to 2500 ml.	

The D-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 ml of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare unit dosage forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules such that each contains, respectively 2.0 or 5.0 milligrams of D-threo-methylphenidate.

What is claimed is:

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein R_1 is C_1–C_4 alkyl, and R_2 is hydrogen or C_1–C_4 alkyl, in a pharmaceutically acceptable carrier or diluent, said dosage form having less than 10% by weight of other stereoisomers of the compound or salt.

2. The unit dosage of claim **1** comprising from about 2 to about 20 milligrams of said compound.

3. The unit dosage of claim **1** comprising from about 2½ to about 12 milligrams of said compound.

4. The unit dosage of claim **1** in a form suitable for oral administration.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,528,530 B2
DATED : March 4, 2003
INVENTOR(S) : Andrew L. Zeitlin and Maghsoud M. Dariani

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], **References Cited**, OTHER PUBLICATIONS, "Patrick et al.," reference, delete "thre-o-Methylphenidate", and insert -- threo-Methylphenidate", --;
"Srinivas et al.," reference, delete "dl-th-reo-Methylphenidate" and insert -- dl-threo-Methylphenidate --;

Column 1,
Line 29, delete "Nervcus" and insert -- Nervous --;
Line 32, delete "Graenhill," and insert -- Greenhill, --;

Column 4,
Line 16, delete "Lerythro," and insert -- L erythro, --;

Column 5,
Line 21, delete "substituients" and insert -- substituents --;

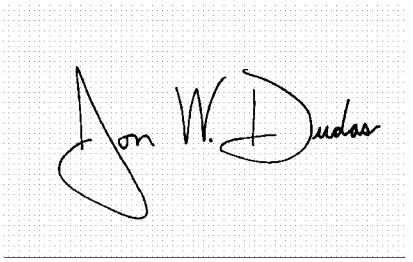
Column 7,
Line 20, delete "(+/– -)" and insert -- (+/-) --;

Column 8,
Line 29, delete "D-lactamis" and insert -- D-lactam is --;
Line 52, after "concentrated" insert -- to --;

Column 9,
Lines 26-27, delete "buffer pH and 1 ml" and insert -- buffer pH 7 and 1 ml --.

Signed and Sealed this

Twenty-eighth Day of September, 2004



JON W. DUDAS
Director of the United States Patent and Trademark Office