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Attorneys For Plaintiffs
AstraZeneca Pharmaceuticals LP and
AstraZeneca UK Limited

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

| | |
|---|---|
| ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED,<br><br>Plaintiffs,<br><br>v.<br><br>ACCORD HEALTHCARE, INC., AND INTAS PHARMACEUTICAL LTD,<br><br>Defendants. | **Civil Action No. _____** |

**COMPLAINT FOR PATENT INFRINGEMENT**

Plaintiffs AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited (collectively, "AstraZeneca"), for their complaint against Defendants Accord Healthcare, Inc., Accord Healthcare Ltd. ("Accord"), and Intas Pharmaceutical Ltd. ("Intas") (collectively "Defendants"), hereby allege as follows:

## THE PARTIES

1. Plaintiff AstraZeneca Pharmaceuticals LP is a limited partnership organized under the laws of Delaware, having its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803.

2. Plaintiff AstraZeneca UK Limited is a company incorporated under the Laws of England and Wales, having a registered office at 15 Stanhope Gate, W1K 1LN, London England.

3. Upon information and belief, Defendant Accord is a corporation organized under the laws of North Carolina, having a place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703 and a former place of business at 8601 Six Forks Road, Suite 400, Raleigh, North Carolina 27615.

4. Upon information and belief, Intas is company organized under the laws of India, having a place of business at Chinubhai Centre off Nehru Bridge Ashram Road, Ahmedabad 380009, Gujarat, India.

5. Upon information and belief, Accord is a wholly-owned subsidiary of Intas.

6. Upon information and belief, the acts of Accord, complained of herein were done at the direction of, with the authorization of, and with the cooperation, participation, assistance of Intas.

## JURISDICTION AND VENUE

7. Upon information and belief, Defendants sell various products and do business throughout the United States, including this District.

8. Defendants manufacture bulk pharmaceuticals and pharmaceutical products that are sold in this District and throughout the United States.

9. This action arises under the Patent Laws of the United States and the Food and Drug Laws of the United States, Titles 35 and 21, United States Code. Jurisdiction is based on 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court under 28 U.S.C. §§ 1391(c), 1391(d), and 1400(b).

10. In its answer to an earlier complaint filed in this Court by AstraZeneca against Accord and Intas involving the same ANDA (Civil Action No. 3:08-cv-04804 (JAP)(TJB)), Defendants, for purposes of that lawsuit, waived their objection to venue and personal jurisdiction in this District.

## CLAIMS FOR RELIEF

### Count 1: Direct Infringement By Accord

11. AstraZeneca realleges paragraphs 1-10 above as if set forth specifically herein.

12. Plaintiff AstraZeneca Pharmaceuticals LP is the holder of New Drug Application ("NDA") No. 22-047, by which the United States Food and Drug Administration ("FDA") first granted approval for 50 mg, 150 mg, 200 mg, 300 mg and 400 mg extended release tablets containing the active ingredient quetiapine (11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo [b,f][1,4] thiazepine) fumarate. The quetiapine fumarate extended release tablets described in NDA No. 22-047 are sold by AstraZeneca in the United States under the trademark SEROQUEL XR®.

13. Plaintiff AstraZeneca Pharmaceuticals LP is the owner of United States Patent No. 4,879,288 (the "'288 patent," a copy of which is attached hereto as Exhibit A),

entitled "Novel Dibenzothiazepine Antipsychotic," which was duly and legally issued by the United States Patent and Trademark Office on November 7, 1989 upon assignment from the inventors Edward J. Warawa and Bernard M. Migler. The '288 patent claims, *inter alia*, quetiapine fumarate, the active ingredient of SEROQUEL XR®, and methods of using that compound.

14. The '288 patent will expire on September 26, 2011.

15. Plaintiff AstraZeneca UK Limited is the owner of United States Patent No. 5,948,437 (the "'437 patent," a copy of which is attached hereto as Exhibit B), entitled "Pharmaceutical Compositions Using Thiazepine," which was duly and legally issued by the United States Patent and Trademark Office on September 7, 1999 upon assignment from the inventors Bhavnish V. Parikh, Robert J. Timko and William J. Addicks. The '437 patent claims, *inter alia*, sustained release formulations of quetiapine fumarate, including SEROQUEL XR® extended release tablets, and processes for preparing and using such formulations.

16. The '437 patent will expire on May 28, 2017.

17. By letter dated September 5, 2008, purporting to be a notice pursuant to 21 U.S.C. § 355 (j)(2)(B) ("First Notice Letter"), Accord notified AstraZeneca that it had submitted to the FDA ANDA No. 90-681 seeking the approval of the FDA to commercially manufacture, use and sell, prior to the expiration of the '288 and '437 patents, quetiapine fumarate extended release tablets in 200, 300, and 400 mg strengths as generic versions of AstraZeneca's SEROQUEL XR® 200, 300, and 400 mg extended release tablets. On October 28, 2008, AstraZeneca filed a complaint against Defendants in this Court for patent infringement based on the ANDA filing described in the First Notice Letter. That suit, Civil Action No. 3:08-cv-04804

(JAP)(TJB) ("the earlier action"), is assigned to the Honorable Joel A. Pisano and Magistrate Tonianne J. Bongiovanni. The present action should be consolidated with the earlier action.

18. By a letter dated January 23, 2009, purporting to be a notice pursuant to 21 U.S.C. § 355 (j)(2)(B) ("Second Notice Letter"), Accord notified AstraZeneca that it had submitted an amendment to its ANDA seeking the approval of the FDA to commercially manufacture, use and sell prior to the expiration of the '288 and '437 patents, quetiapine fumarate extended release tablets in 150 mg strength..

19. In the Second Notice Letter, Accord notified AstraZeneca that, as part of ANDA No. 90-482, it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV") with respect to the '437 patent.

20. In the Second Notice Letter, Accord alleged that claims 3-9, 11 and 12 of the '437 patent will not be infringed by the quetiapine fumarate extended release tablets that are the subject of ANDA No. 90-681. Accord did not allege in the Notice Letter that the quetiapine fumarate extended release tablets that are the subject of ANDA No. 90-681 will not infringe any claim of the '288 patent and claims 1-2, 10, and 13-15 of the '437 patent.

21. Accord also alleged in the Second Notice Letter that claims 1, 2, 10 and 13-15 of the '437 patent are invalid.

22. Accord has infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A) by filing ANDA No. 90-681 seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in the '437 patent, or the use of which is claimed in the '437 patent, prior to the expiration of that patent.

23. The quetiapine fumarate extended release tablets for which Accord seeks approval under ANDA No. 90-681 will infringe one or more claims of the '437 patent under 35 U.S.C. §271(a).

24. The commercial manufacture, use, sale or offer for sale within the United States, or the importation into the United States, of the quetiapine fumarate extended release tablets that are the subject of ANDA No. 90-681 will infringe one or more claims of the '437 patent under 35 U.S.C. § 271(a).

25. AstraZeneca is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 90-482 be a date that is not earlier than the later of May 28, 2017, the expiration date of the '437 patent, or the expiration of any other exclusivity to which AstraZeneca is or becomes entitled.

**Count 2: Direct Infringement By Intas**

26. AstraZeneca realleges paragraphs 1-25 as if set forth specifically herein.

27. Upon information and belief, Intas initiates, directs and controls the activities of Accord with regard to ANDA No. 90-681 and the quetiapine fumarate extended release tablets described therein.

28. Upon information and belief, Intas, through Accord as its agent, initiated, directed and controlled the preparation and filing of ANDA No. 90-681 with the FDA.

29. Upon information and belief, Intas has infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A) by initiating, directing and controlling the preparation and filing of ANDA No. 90-681.

30. Upon information and belief, in the event that the FDA approves ANDA No. 90-681, Intas stands to benefit directly from such approval by being able to commercially

manufacture and distribute the quetiapine fumarate extended release tablets that are the subject of the ANDA.

31. The quetiapine fumarate extended release tablets for which Intas, through Accord as its agent, seeks approval under ANDA No. 90-681 will infringe one or more claims of the ‘437 patent under 35 U.S.C. §271(a).

32. The commercial manufacture, use, sale or offer for sale within the United States, or the importation into the United States, by Intas of the quetiapine fumarate extended release tablets that are the subject of ANDA No. 90-681 will infringe one or more claims of the ‘437 patent under 35 U.S.C. § 271(a).

33. AstraZeneca is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 90-482 be a date that is not earlier than the later of May 28, 2017, the expiration date of the ’437 patent, or the expiration of any other exclusivity to which AstraZeneca is or becomes entitled.

**Count 3: Inducement of Infringement By Intas**

34. AstraZeneca realleges paragraphs 1-33 as if set forth specifically herein.

35. Accord has directly infringed the ‘437 patent under 35 U.S.C. § 271(e)(2)(A) by filing ANDA No. 90-681 seeking FDA approval under 21 U.S.C. § 355(j) to engage in the commercial manufacture, use or sale of a drug claimed in the ‘437 patent, or the use of which is claimed in the ‘437 patent, prior to the expiration of the patent.

36. Upon information and belief, Intas knowingly and intentionally induced and/or aided and abetted Accord in the preparation and filing of ANDA No. 90-681.

37. Upon information and belief, Intas knowingly and intentionally induced and/or aided and abetted Accord in providing information and materials to the FDA in connection with ANDA No. 90-681.

38. Upon information and belief, Intas knowingly and intentionally induced and/or aided and abetted Accord in the development of the quetiapine fumarate extended release tablets that are the subject of ANDA No. 90-681, and that will infringe the '437 patent under 35 U.S.C. § 271(a).

39. Upon information and belief, Intas has, under 35 U.S.C. § 271(b) induced Accord's direct infringement of the '437 patent by knowingly and intentionally inducing and/or aiding and abetting the preparation and filing of ANDA No. 90-681.

**Count 4: Exceptional Case**

40. AstraZeneca realleges paragraphs 1-39 as if set forth specifically herein.

41. Prior to filing ANDA No. 90-681, Defendants were aware of the existence of the '437 patent, and, upon information and belief, were aware that the filing of ANDA No. 90-482, including a Paragraph IV certification with respect to the '437 patent, infringed that patent.

42. The opinions set forth in the Notice Letters that the '437 patent is invalid, and/or not infringed are devoid of an objective, good faith basis in either the facts or the law.

43. This an exceptional one, and AstraZeneca is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) A judgment declaring that the '437 patent remains valid and enforceable, and that the '437 patent has been infringed by Defendants;

(b) A judgment declaring that the effective date of any approval of ANDA No. 90-482 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) be a date which is not earlier than the later of May 28, 2017, the expiration date of the '437 patent, or the expiration of any other exclusivity to which AstraZeneca is or becomes entitled;

(c) A permanent injunction against any infringement of the '437 patent by Defendants, their officers, agents, attorneys, and employees, and those acting in privity or concert with them;

(d) A judgment that this is an exceptional case, and that Plaintiffs are entitled to an award of reasonable attorney fees pursuant to 35 U.S.C. § 285;

(e) To the extent that Defendants have committed any acts with respect to the subject matter claimed in the '437 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), an award of damages for such acts, which this Court should treble pursuant to 35 U.S.C. § 284;

(f) Costs and expenses in this action; and

(g) Such other relief as this Court may deem proper.

Respectfully submitted,

Dated: February 10, 2009

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**CERTIFICATION PURSUANT TO L. CIV. R. 11.2**

Pursuant to Local Civil Rule 11.2, I hereby certify that the matter in controversy is the subject of the following actions:

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES, LTD*, 05-5333 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES, LTD*, 06-1528 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. SANDOZ INC.*, 07-1632 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES, LTD*, 07-3001 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. HANDA PHARMACEUTICALS, LLC and JOHN DOE ENTITY*, 08-3773 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. ACCORD HEALTHCARE, INC., ACCORD HEALTH CARE, INC., ACCORD HEALTHCARE LTD., AND INTAS PHARMACEUTICAL LTD.*, 08-4804 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. HANDA PHARMACEUTICALS, LLC and JOHN DOE ENTITY*, 08-5328 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. HANDA PHARMACEUTICALS, LLC and JOHN DOE ENTITY*, 08-5997 (District of New Jersey)

*ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. BIOVAIL LABORATORIES INTERNATIONAL SRL, BIOVAIL CORPORATION and BTA PHARMACEUTICALS, INC.*, 09-0128 (District of New Jersey)

Dated: February 10, 2009

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# EXHIBIT A

# United States Patent [19]

**Warawa et al.**

[11] **Patent Number: 4,879,288**

[45] **Date of Patent: Nov. 7, 1989**


[54] **NOVEL DIBENZOTHIAZEPINE ANTIPSYCHOTIC**


[75] Inventors: **Edward J. Warawa,** Wilmington, Del.; **Bernard M. Migler,** Cherry Hill, N.J.

[73] Assignee: **ICI Americas Inc.,** Wilmington, Del.



[21] Appl. No.: **28,473**

[22] Filed: **Mar. 20, 1987**

[30] **Foreign Application Priority Data**

Mar. 27, 1986 [GB] United Kingdom ..... 8607684

[51] **Int. Cl.**[4] ..... **C07D 417/04;** A61K 31/555

[52] **U.S. Cl.** ..... **514/211;** 540/551

[58] **Field of Search** ..... 540/551; 514/211



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"Piperazinyldibenzazepine", RES. DISCL. 1980, 192, 158–159.

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*Primary Examiner*—Mark L. Berch

*Attorney, Agent, or Firm*—Rosemary M. Miano; Thomas E. Jackson; James T. Jones



[57] **ABSTRACT**

11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4 ]thiazepine is disclosed as a neuroleptic with a much reduced incidence of side effects such as acute dystonia and dyskinesia and tardive diskinesia.


**8 Claims, No Drawings**

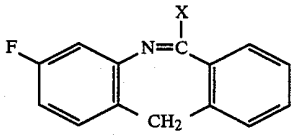
# NOVEL DIBENZOTHIAZEPINE ANTIPSYCHOTIC

## SUMMARY AND BACKGROUND OF THE INVENTION

This invention concerns a novel dibenzothiazepine compound useful for its antidopaminergic activity, for example, as an antipsychotic or neuroleptic.

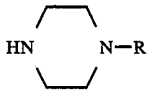
Previous attempts at finding compounds useful in a variety of applications have included U.S. Pat. No. 3,539,573 to Schmutz et al. which discloses selected dibenzothiazepines and dibenzodiazepines as being useful for a variety of medical conditions including as neuroleptic-antidepressants, or neuroleptics. U.S. Pat. No. 3,389,139 to Schmutz et al. teaches compounds based on 6-basic substituted morphanthridines as neuroplegics, neuroleptics and analgesics, with selected compounds being useful for treating psychotic conditions. U.S. Pat. No. 4,097,597 to Horrom et al. discloses dibenzodiazepine derivatives useful as antischizophrenics.

A compound of the following formula I




I

in which X may be as shown in formula Ia




Ia

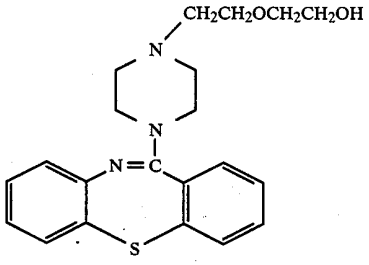
and R may be $(CH_2CH_2O)_2H$, has been Anonymously disclosed in *Res. Discl.* (1980), 192: 158–9.

Compounds used as antipsychotics and neuroleptics have, however, been plagued by the problems of undesired side effects. Such side effects include acute dyskinesias, acute dystonias, motor restlessness, pseudo-Parkinsonism and tardive dyskinesias (TD). Acute syndromes usually have an early onset, for example, 1 to 5 days for acute dystonias and dyskinesias, and may include torsion spasms, muscle spasms and dystonia of the face, neck or back with protrusion of the tongue and tonic spasms of the limbs (dyskinesia). Tardive dyskinesia has a time of maximal risk after months or years of treatment. TD's comprise oral-facial dyskinesia, lingual-facial-buc-cal-cervical dystonias sometimes with involvement of the trunk and extremities. TD's also include repetitive stereotypical movements of the face, tongue and limb such as sucking and smacking of the lips, lateral jaw movements and protrusions of the tongue. When the antipsychotic drug treatment is stopped the symptoms continue, often for months or years. These involuntary movements constitute the most undesirable side effect of antipsychotic drug treatment; for example, the percentage of patients that develop TD has been variously reported to be as high as 20 percent. Thus, there still remains a need for compounds which exhibit antidopaminergic activity without the side effects heretofore experienced with previous compounds.



## DESCRIPTION OF THE INVENTION

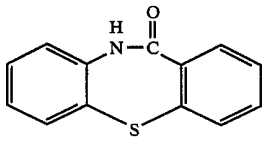
This invention is a compound of formula II:




II

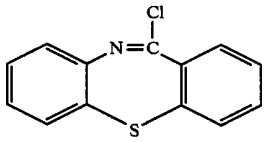
and salts thereof, for example and especially pharmaceutically acceptable salts. Such a compound is useful because of its antidopaminergic activity, for example, as an antipsychotic agent or as a treatment for hyperactivity. Such a compound is of even greater interest in that it may be used as an antipsychotic agent with a substantial reduction in the potential to cause side effects such as acute dystonia, acute dyskinesia, pseudo-Parkinsonism as well as tardive dyskinesia which may result from the use of other antipsychotics or neuroleptics.

The compound of formula II may be made by a variety of methods including taking the lactam of formula III:



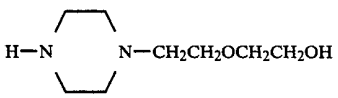

III

which may be prepared by methods well known in the literature, for example, as described by J. Schmutz et al. *Helv. Chim. Acta.*, 48:336 (1965), and treating the lactam of formula III with phosphorous oxychloride ($POCl_3$) to generate the imino chloride of formula IV:




IV

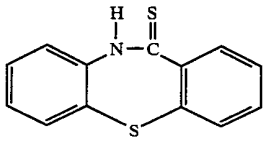
The imino chloride of formula IV may also be generated with other agents such as thionyl chloride or phosphorous pentachloride. The imino chloride is then reacted with 1-hydroxyethoxyethylpiperazine of formula V:




V

to give the compound of formula II.

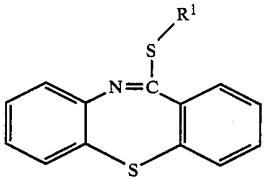
Alternatively, one may convert the lactam of formula III into a thiolactam of formula VI:



VI

by, for example, reacting the lactam of formula III with a polysulfur compound such as phosphorous pentasulfide or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent, obtained from Aldrich).

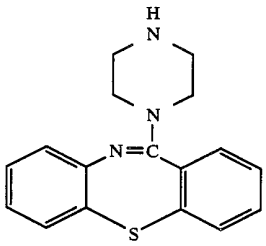
The lactam of formula VI may then be converted into a thioether of formula VII:



VII

where $R^1$ is chosen such that S-$R^1$ is a leaving group, for example, $R^1$ may be (1-3C)alkyl, for example, methyl, by alkylation with an alkyl iodide, for example, methyl iodide. The piperazine of formula V is then reacted with the thioether of formula VII to give the compound of formula II.

A preferred way of making the compound of formula II is as follows. A compound of formula XII:



XII

is reacted with a compound of formula XIII:

$$ZCH_2CH_2OCH_2CH_2OH \qquad XIII$$

(in which Z is an atom or group removable as an anion) and, whereafter, when the compound of formula II is obtained as a base and a salt is required, reacting said compound of formula II obtained in the form of a base with an acid to afford a salt and when the compound of formula II is obtained as a salt and a base is required, neutralizing said compound of formula II obtained in the form of a salt to afford the said base.

A compound of formula XIII is advantageously used in which Z represents a mesyloxy or tosyloxy group, but Z is preferably halogen. Z most preferably represents a chlorine atom.

The reaction is conveniently carried out in the presence of a solvent, preferably a polar organic solvent, more preferably an alcohol, especially a (1-6C)alkanol, for example, methanol, ethanol, propanol, butanol, pentanol, hexanol and isomers thereof especially n-propanol. Other convenient solvents include aprotic solvents such as for example dimethylforamide or N-methyl pyrrolidone. If desired, an appropriate mixture of polar organic and aprotic solvents may be used.

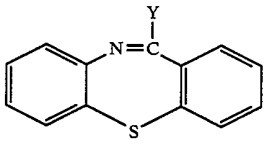
If desired the compound of formula XII may be employed in the form of a salt, but where such a salt is used it is neutralized to afford the corresponding free base prior to reaction with the compound of formula XIII, for example, by in situ neutralization. Such neutralization is advantageously conducted in the presence of a basic substance, preferably an alkali metal carbonate or an alkaline earth metal carbonate, more preferably sodium or potassium carbonate.

Additionally an alkali metal halide, advantageously in a catalytic amount, may optionally be added to the reaction mixture. Sodium iodide is a preferred alkali metal halide. The effect of this addition is to convert Z in formula XIII to a halogen, preferably iodine, whereby the reaction of the compound of formula XII with the compound of formula XIII may be promoted.

The reaction is conveniently performed at ambient temperature or at an elevated temperature, preferably at a temperature between ambient and the reflux temperature of the reaction mixture, more preferably at the reflux temperature, and advantageously the reaction is carried out for an extended period of time, preferably 15 to 30 hours, more preferably about 24 hours.

The salts of the compound of formula II prepared according to the process of the present invention are preferably the pharmaceutically acceptable salts, but other salts may also be prepared. Such other salts may, for example, find use in the preparation of the compound of formula II and the pharmaceutically acceptable salts thereof. Convenient salts may be selected from those pharmaceutically acceptable salts known in the art. These may be obtained, for example, by reacting the compound of formula II with a convenient acid, such as for example, hydrochloric acid, maleic acid, fumaric acid, citric acid, phosphoric acid, methane sulfonic acid, and sulfuric acid. A preferred salt is the hemi-fumarate salt.

The compound of formula XII is preferably prepared by the reaction of an 11-substituted-dibenzo[b,f][1,4]-thiazepine of the formula XIV:

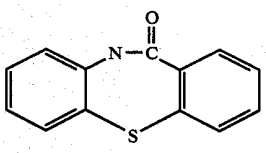


XIV

in which the substituent Y represents an atom (or a group) removable as an anion, with piperazine. A compound of formula XIV may, for example, be used in which Y represents an alkoxy, alkylthio or sulfonate group. Thus, Y may, for example, represent (1-6C)-alkoxy, preferably methoxy or ethoxy, or (1-6C)-alkylthio, preferably methylthio or ethylthio, or Y may represent a tosyloxy group. Preferably Y represents a halogen atom, for example, bromine but especially chlorine. The reaction is conveniently performed at ambient temperature or at an elevated temperature, preferably at a temperature between ambient and the reflux temperature of the reaction mixture, more preferably at the reflux temperature, and advantageously the reaction is carried out in the presence of an inert organic solvent, preferably an aromatic hydrocarbon solvent, such as, for example, xylene or toluene. The reaction is conve-

niently performed for 2 to 15 hours, preferably 3 to 10 hours, more preferably about 5 hours.

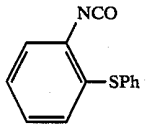
The compounds of formula XIV may, for example, be prepared by methods analogous to those known in the art or, where Y represents halogen, preferably by reacting dibenzo[b,f][1,4]-thiazepine11(10-H)one of formula XV:



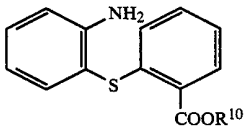
XV

with a halogenating agent, preferably a phosphorous pentahalide or oxyhalide ($POHal_3$). The above halide is selected, for example, from chlorine or bromine, especially chlorine. Where it is desired to prepare a compound of formula XIV in which Y represents a chlorine atom, a preferred halogenating agent is phosphorous oxychloride (POC13) Where it is desired to prepare a compound of formula XIV in which Y represents a bromine atom, a preferred halogenating agent is phosphorous pentabromide. The reaction may advantageously be carried out in the presence of an N,N-disubstituted aniline, preferably N,N-di[1-6C]alkyl) substituted aniline, more preferably an N,N-dimethylaniline. The reaction is advantageously effected at an elevated temperature, preferably at the reflux temperature of the reaction mixture, conveniently for between 3 to 15 hours, preferably 4 to 10 hours, more preferably 6 hours.

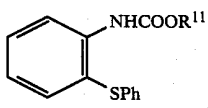
The compound of formula XV may, for example, be prepared according to methods known in the art, for example, by the method disclosed by J. Schmutz et al. *Helv. Chim Acta,* 48: 336 (1965). Preferably the compound of formula XV is prepared by cyclizing a compound selected from compounds of the formulae XVI, XVII, XVIII



XVI



XVII



XVIII

and wherein Ph is phenyl and $OR^{10}$ and $OR^{11}$ represent an atom or group removable as an anion whereby to form a compound of formula XV. The cyclization is advantageously effected under acidic conditions, preferably in the presence of an acid of sulfur or phosphorous, for example, concentrated sulfuric acid or more preferably polyphosphoric acid. The reaction is advantageously carried out at an elevated temperature, preferably at a temperature of from 60 ° **120**°C., especially from 95 ° **105**°C., advantageously for about 4–8 hours, preferably about 6 hours.

In the compounds of formulae XVII and XVIII $R^{10}$ and $R^{11}$ may, for example, represent hydrogen, (1-6-C)alkyl or optionally substituted phenyl. Preferably $R^{10}$ represents methyl or ethyl and $R^{11}$ preferably represents methyl, ethyl or phenyl, but most preferably phenyl.

The compound of formula XVII may, for example, be obtained by the reaction of 2-amino diphenysulfide and phenyl chloroformate.

The new compound of this invention is a central nervous system depressant and may be used as a tranquilizer for the relief of hyperactivity states, for example, in mice, cats, rats, dogs and other mammalian species, and additionally for the management of psychotic states in man, in the same manner as chlorpromazine. For this purpose a compound of formula II, or non-toxic physiologically acceptable acid addition salts thereof, may be administered orally or parenterally in a conventional dosage form such as tablet, pill, capsule, injectable or the like. The dosage in mg/kg of body weight of a compound of the present invention in mammals will vary according to the size of the animal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for a compound of formula II will be at least about 1.0 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 200 mg/kg per day. For humans, a dosage of about 1.0 ° **40** mg/kg per day will be effective, for example, about 50 to 2000 mg/day for an average person weighing 50 kg. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily, and such will depend on the duration and maximum level of activity of a particular compound. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding about 25 to 500 mg per unit of dosage of conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, for example, as described in U.S. Pat. No. 3,755,340. The compound of this invention may contained in or co-administered with one or more known drugs.

No overt toxicity has been observed for this compound at therapeutic doses.

## EXAMPLE 1

### 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperaziny]dibenzo[b,f][1,4]thiazepine (Formula II)

A 2 liter round-bottom flask equipped with a magnetic stirring bar and reflux condenser with a nitrogen inlet was charged with 115.0 grams (g) (0.506 mole) of dibenzo[b,f][1,4]thiazepine-11(10-H)-one (made by the method disclosed by J. Schmutz et al. *Helv. Chim. Acta.,* 48: 336 (1965)), phosphorous oxychloride 700 ml (7.5 moles) and N,N-dimethylaniline 38.0 g (0.313 mole). The grey suspension was heated to gentle refluxing using a heating mantle. After 6 hours of heating, the resulting amber solution was allowed to cool to room temperature (from about 18°–**25**°C.) and was analyzed by thin-layer chromatography (TLC) using silica gel plates, developed with ether-hexane (1:1) and detected with ultraviolet light. Analysis revealed the desired imino chloride, $R_f$=0.70, and an absence of starting lactam.

Excess phosphorous oxychloride, was removed in vacuo using a rotary evaporator. The brown syrupy residue was dissolved in 1500 milliliters (ml) of toluene, treated with 500 ml of an ice-water mixture and stirred for 30 minutes. The toluene layer was separated, washed twice with 200 ml of water and dried with anhydrous magnesium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated in vacuo using a rotary evaporator to give the crude imino chloride as a light yellow solid: 115.15 g (92.6% yield): melting point (mp) 106°–108°.

The above imino chloride, 114.0 g (0.464 mole), and 1000 ml of xylene were placed in a 3 liter 3-necked round bottom flask equipped with a mechanical stirrer, reflux condenser with a nitrogen inlet and a heating mantle. The resulting yellow solution was treated with 161.7 g (0.928 mole) of 1-(2-hydroxyethoxy)ethylpiperazine, rinsing with 200 ml of xylene. This reaction mixture was heated at gentle reflux for 30 hours during which time a brown oil began to separate. The reaction mixture was cooled to room temperature. Thin layer chromatography (TLC) analysis (silica gel, methanol: methylene chloride (1:9), ultraviolet light and iodine detection) indicated complete consumption of the imino chloride and the presence of the desired product with $R_f$=0.5 (approximately). The mixture was treated with 700 ml of 1 Normal (1N) sodium hydroxide and 700 ml of diethyl ether. The layers were separated and the aqueous phase was extracted once with 500 ml of diethyl ether. The combined ether extract was treated with 400 ml of 1N hydrochloric acid. The acidic extract was treated with solid sodium carbonate portionwise to give a brown oil which was extracted four times with 400 ml of methylene chloride. These methylene chloride extracts were combined and dried with anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo using a rotary evaporator to yield the crude product as a viscous amber oil, 194.5 g, which was purified by flash chromatography as follows

The crude product in a minimum of methylene chloride was applied to a 3.5 inch×20 inch column of silica gel packed in methylene chloride. The column was eluted under nitrogen pressure with 4 liter portions each of methylene chloride, and 2%, 4% and 6% methanol:-methylene chloride (2:98: 4:96, 6:94 respectively) while 250 ml fractions were collected. These fractions were monitored by TLC (conditions cited below). The title product began to elute with 4% methanol:methylene chloride (4:96). Combination of the pure fractions and removal of the solvent in vacuo gave the title product 138.7 g (77.7% yield). TLC using silica gel, methanol:-methylene chloride (1:9) with ultraviolet (u.v.) and iodine detection showed a single compound; $R_f$=0.5.

Analysis calculated for: $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.75. Found: C, 65.25; H, 6.52; N, 10.62.

## EXAMPLE 2

### 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperaziny]dibenzo [b,f][1,4]thiazepine, hydrochloride salt

A portion of a product made by the method of Example 1, 10.0 g (26 millimoles (mmol)), was dissolved in 40 ml of ethanol, treated with 30 ml of a saturated ethanolic hydrogen chloride solution and stirred until a turbidity ensued (about 20 minutes). The heterogeneous solution was then added to 500 ml of diethyl ether with stirring. The resulting white crystalline salt was collected by filtration, washed with diethyl ether and dried in vacuo in a drying pistol over refluxing ethanol to give the title compound, 10.7 g, m.p. 218°–219°.

Analysis calculated for: $C_{21}H_{25}N_3O_2S.2HCl$: C, 55.26; H, 5.96; N, 9.20. Found: C, 55.17; H, 6.00; N, 9.07.

## EXAMPLE 3

### 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperaziny]dibenzo [b,f][1,4]thiazepine, maleate

A portion of a product made by the method of Example 1, 3.6 g (9.38 mmol), was dissolved in 25 ml of ethanol and treated with 1.08 g (9.38 mmol) of maleic acid. This mixture was heated with stirring until solution was complete and left to cool to room temperature. Addition of diethyl ether resulted in a precipitate which was collected by filtration, washed with diethyl ether and dried in vacuo in a drying pistol over refluxing ethanol to give the title compound, 4.2 g, m.p. 129°–130°.

Analysis calculated for: $C_{21}H_{25}N_3O_2S.C_4H_4O_4$: C, 60.10; H, 5.85; N, 8.41. Found: C, 60.08: H, 5.85; N, 8.36.

## EXAMPLE 4

### 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperaziny]dibenzo[b,f][1,4]thiazepine, hemifumarate

A portion of a product made by the method of Example 1, 2.1 g (5.47 mmol) was dissolved in 20 ml of ethanol and treated with 0.67 g (5.7 mmol) of fumaric acid. Upon heating, complete solution was effected for a few minutes after which the salt began to crystallize. After one hour at room temperature, the resulting solid was collected by filtration and dried in vacuo in a drying pistol over refluxing ethanol to give the title compound, 2.4 g, m.p. 172°–173°.

Analysis calculated for: $C_{21}H_{25}N_3O_2S.O.5C_4H_4O_4$: C, 62.57; H, 6.16; N, 9.51. Found: C, 62.15; H, 6.19; N, 9.25.

## EXAMPLES 5–8

A number of tests are recognized as showing antidopaminergic activity of a compound and/or as being predictive of antipsychotic activity in mammals. For these tests a compound of formula II in the form of a salt (for example, as described in Example 2) was used. All dosages in the tables are expressed as free base.

## EXAMPLE 5

### Apomorphine-Induced Climbing in Mice

This test has been described by Ther and Schramm [*Arch int. Pharmacodyn.*, 138: 302 (1962); Peuch, Simon and Boissier, *Eur. J. Pharm.*, 50: 291 (1978)]. Mice that are administered an appropriate dose of apomorphine (a dopamine agonist) will climb the walls of a cage or other suitable structure and remain at or near the top for 20–30 minutes. Untreated mice on the other hand will occasionally climb up and then climb down. The exaggerated climbing of apomorphine-treated mice can be antagonized by pretreatment with dopamine blocking agents. The antagonism of apomorphine-induced climbing in mice is therefore an indication of the potential dopamine blocking activity of the agent. Since dopamine blocking agents are typically antipsychotic agents, the test is considered to be evidence for potential antipsychotic activity of the agent. The vehicle itself [hydroxypropylmethylcellulose (HPMC) 0.5% w/v, polyoxyethylene (20) sorbitan monooleate (Tween 80) .1% w/v, and distilled water] or the vehicle with the test compound of the present invention was administered

orally to twenty mice in graded doses. After 30 minutes, apomorphine HCl was administered subcutaneously at 1.25 mg/kg and the mice were placed in cages containing 28 horizontal rungs, upon which the mice could climb. Thirteen minutes later they were scored for climbing. The climbing score was the mean of the highest and lowest rungs on which the mouse climbed during a one-minute time period from 13 ° **14** minutes after apomorphine. The results in 24-hour fasted mice are presented in Table 1. The compound of the present invention antagonized the climbing, a result predictive of antipsychotic activity.

TABLE 1

| Compound Tested | Dosages (mg/kg i.p.) | Mean Climb Score |
|---|---|---|
| Vehicle | — | 24 |
| Formula II (HCl salt) | 10 | 24 |
| Formula II (HCl salt) | 20 | 15 |
| Formula II (HCl salt) | 40 | 2 |
| Formula II (HCl salt) | 80 | 0 |

## EXAMPLE 6

### Antagonism of Apomorphine-Induced Hyperactive in Rats

This test has been described by Swerdlow and Koob [*Pharmacol. Biochem. and Behav.*, 23: 303 (1985)]. Rats that are administered amphetamine at a moderate dose become hyperactivity. The hyperactivity can last for several hours, and can be measured in various ways, for example, by counting the number of times the rat walks from one end of a long alley to the other end. The physiological basis for amphetamine-induced hyperactivity is thought to be the release of excessive amounts of dopamine in the brain. The hyperactivity of anphetamine-treated rats can be antagonized (prevented) by pretreatment with dopamine-blocking agents. The antagonism of amphetamine-induced hyperactivity in rats is, therefore, an indication of the potential dopamine-blocking and potential antipsychotic activity of the agent. The compound of the present invention as the HCl salt or the vehicle (vehicle is defined in Example 5) were administered orally to 20 rats and aaphetamine was then injected intraperitoneally. Activity (walking back and forth in a long alley) was recorded for two hours. The activity scores are presented in Table 2. The compound of the present invention antagonized the hyperactivity, a result predictive of antipsychotic activity.

TABLE 2

Antagonism of Amphetamine-Induced Hyperactivity in Rats

| Compound Tested | Dosages (mg/kg p.o.) | Activity Score (0–2 Hr) (Mean Number of Crossings of Center Line of Alley) | |
|---|---|---|---|
| Vehicle | | 148 | |
| Formula II (HCl salt) | 10 | 118.3 | $p < .05$ |
| Formula II (HCl salt) | 20 | 92.4 | $p < .0005$ |
| Formula II (HCl salt) | 40 | 64.3 | $p < .0005$ |
| Formula II (HCl salt) | 80 | 39.8 | $p < .0005$ |

## EXAMPLE 7

### Effect of Test Compound on Rat Striatal Levels of Dihydroxyphenylacetic Acid (DOPAC) and Homovanillic Acid (HVA)

Among the various pharmacological effects of antipsychotics, their action as dopamine antagonists in the brain has been extensively investigated. Enhancement of dopamine metabolism (dihydroxyphenylacetic acid and homovanillic acid (DOPAC and HVA)) by antipsychotic agents has been attributed to a blockade of dopamine receptors [A. Carlson and M. Lindquist, *Acta. Pharmac. Tox.*, (1963) 20: 140]. The effects of a compound of the invention on DOPAC and HVA levels in the rat striatum were measured by HPLC using electrochemcial detection according to the method of Saller and Salama [*J. Chromatography*, (1984) 309: 287]. A compound of Formula II (HCl salt) was suspended in the vehicle (as defined in Example 5) and administered intraperitoneally (i.p.) to eight Sprague Dawley rats with the following results.

| Compound Tested | Dosages (mg/kg i.p.) | % Control | |
|---|---|---|---|
| | | DOPAC | HVA |
| Formula II (HCl salt) | 10 | 145 | 140 |
| Formula II (HCl salt) | 20 | 220 | 210 |
| Formula II (HCl salt) | 40 | 300 | 260 |

## EXAMPLE 8

### Conditioned Avoidance in Squirrel Monkeys

The conditioned avoidance test has been described by Herz, A., *Int. Rev. Neurobiol.*, (1960) 2: 229–277. In this test, a warning stimulus is presented for five seconds. The monkeys are trained to press a lever to turn off the warning stimulus thereby avoiding the delivery of electric shocks at 1/sec for 10 seconds that would begin at the end of the warning stimulus. If there is no response during the warning stimulus (no avoidance response) and the shocks begin, a response during the shocks stops the shocks. Trials of this type are repeated every minute for six hours. Antipsychotic drugs produce a marked reduction in responding to the warning stiulus. A compound of the present invention Formula II (HCl salt) was administered orally and the conditioned avoidance test was administered. The vehicle used was that defined in Example 5. The results are presented in Table 3. The compound of the present invention produced a marked reduction of avoidance responses, a result predictive of antipsychotic activity.

TABLE 3

Conditioned Avoidance in Squirrel Monkeys

| Compound Tested | Dosages (mg/kg p.o.) | Number of Monkeys Scoring 75% (Or Less) Avoidance Responses/Number Tested |
|---|---|---|
| Vehicle | — | 0/20 |
| Formula II (HCl salt) | 5 | 0/4 |
| Formula II (HCl salt) | 10 | 15/20 |
| Formula II (HCl salt) | 20 | 19/20 |

## EXAMPLE 9

### Test for Production of Acute Dystonia, Acute Dyskinesia, and Tardive Dyskinesia

One test for predicting whether or not a potential antipsychotic drug will produce involuntary movements of the type described in this application, such as acute dystonia and acute dyskinesia, is in the haloperidol-sensitized and drug-naive cebus monkey. Such tests are described by Barany, Haggstrom and Gunne, *Acta Pharmacol. et Toxicol.*, (1983) 52:86; J. Liebman and R. Neale, *Psychopharmacology*, (1980), 68:25–29; and B. Weiss and S. Santelli, *Science*, (1978), 200:799–801. (Also see a discussion of test results in A. Gunne and S. Barany *Psychopharmacology*, (1979), 63:195–198). Also, antipsychotic drugs that are known to produce tardive dyskinesia in schizophrenic patients produce acute dyskinetic and dystonic reactions in the haloperidol-sensitized cebus monkey. Clozapine, the only antipsychotic drug for which there has been no tardive dyskinesia reported, does not produce a dyskinetic reaction in sensitized cebus monkeys. The compound of Formula II, clozapine, thioridazine or haloperidol were each orally administered to sensitized cebus monkeys. They were then observed in their home cages continuously for eight hours and occurrences of dyskinetic reactions noted. The results are presented in Table 4. The compound of the present invention exhibited markedly fewer dyskinetic and dystonic reactions as compared to the known dyskinetic drugs haloperidol or thioridazine. In addition to producing fewer reactions, the intensity of the reactions produced by the compound of the present invention was less than that of thioridazine or haloperidol. For example, at 20 mg/kg p.o. the compound of the present invention produced reactions in two of thirteen monkeys; however, one of these reactions was extremely weak, lasting only about five minutes. The reaction at 10 mg/kg was also weak, lasting only about twenty seconds. By contrast, the reactions produced by thioridazine or haloperidol typically lasted several hours and were of moderate or high intensity.

TABLE 4

Dyskinetic Reactions in Sensitized Cebus Monkeys

| Compound Tested | Dosages (mg/kg p.o.) | Number of Monkeys with Dyskinetic Reactions/Number Tested |
|---|---|---|
| Haloperidol | 1.0 | 13/13 |
| Thioridazine | 10 | 11/13 |
| Clozapine | 10 | 0/1 |
| Clozapine | 20 | 0/13 |
| Clozapine | 40 | 0/11 |
| Clozapine | 60 | 0/5 |
| Formula II (HCl salt) | 2.5 | 0/13 |
| Formula II (HCl salt) | 5 | 1/13 |
| Formula II (HCl salt) | 10 | 1/13 |
| Formula II (HCl salt) | 20 | 2/13 |
| Formula II (HCl salt) | 40 | 0/4 |

## EXAMPLE 10

(a)

### 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine. (Formula II)

11-Piperazinyldibenzo[b,f][1,4]thiazepine dihydrochloride (25 mmole), sodium carbonate (150 mmole), sodium iodide (1 mmole) and 2-chloroethoxyethanol (27 mmoles) were combined together in n-propanol (60 ml) and N-methyl pyrrolidone (15 ml). The reaction was heated at reflux for 24 hours. Ethyl acetate (75 ml) was added and the reaction washed with water (2×250 ml). The organic phase was dried over magnesium sulfate and the solvent removed in vacuo to give an oil. The oil was dissolved in ethanol and treated with fumaric acid (4 mmole). The product was isolated as the hemi-fumarate salt in 78% yield, melting point (m.p.) 172°–173°.

The thiazepine derivative used as a starting material was prepared as follows:

(b) 11-Piperazinyl-dibenzo[b,f][1,4]thiazepine.

Piperazine (1.7 mole) was dissolved in warm toluene (about 50°C.) (750 ml) and 11-chloro-dibenzo[b,f][1,4]-thiazepine was added. The reaction was heated to reflux and maintained at this temperature for 5 hours. After cooling to ambient temperature the reaction was filtered to remove piperazine hydrochloride, and the organic phase was washed several times with water to remove excess piperazine. The organic phase was dried over magnesium sulfate and after filtration the solvent was removed in vacuo to give the product as an oil. The oil was dissolved in ethanol and treated with a solution of hydrogen chloride in ethanol.

11-Piperazinyl-dibenzo[b,f][1,4]thiazepine was isolated as the dihydrochloride salt in about 88% yield.

(c) 11-Chloro-dibenzo[b,f][1,4]thiazepine

A 2 liter round-bottom flask equipped with a magnetic stirring bar and reflux condenser with a nitrogen inlet was charged with 115.0 g (0.506 mole) of dibenzo[b,f][1,4]thiazepine-11(10-H)one, phosphorous oxychloride 700 ml (7.5 moles) and N,N-dimethylaniline 38.0 g (0.313 mole). The grey suspension was heated to gentle refluxing using a heating mantle. After 6 hours of heating, the resulting amber solution was allowed to cool to room temperature (from about 18°–25°C.) and was analyzed by thin-layer chromatography (TLC) using silica gel plates, developed with ether-hexane (1:1) and detected with ultraviolet light. Analysis revealed the desired imino chloride, $R_f$=0.70, and an absence of starting lactam.

Excess phosphorous oxychloride, was removed in vacuo using a rotary evaporator. The brown syrupy residue was dissolved in 1500 milliliters (ml) of toluene, treated with 500 ml of an ice-water mixture and stirred for 30 minutes. The toluene layer was separated, washed twice with 200 ml of water and dried with anhydrous magnesium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated in vacuo using a rotary evaporator to give the crude imino chloride as a light yellow solid: 115.15 g (92.6% yield): m.p. 106°–108°.

(d) Dibenzo[b,f][1,4]thiazepine-11(10H)one.

Polyphosphoric acid (1.2 mole) was heated at 65° C. and phenyl 2-(phenylthio-phenylcarbamate (0.16 mole) added with stirring. The reaction was heated to 100° C.±5° C. and maintained at this temperature for 6 hours. The reaction was cooled to about 80° C. and water (1.5 liters) was added slowly. After cooling to ambient temperature the product was filtered off as an off-white solid, washed sparingly with acetone and dried. The yield was about 87%.

(e) Phenyl 2-(phenylthio)phenylcarbamate.

2-Amino diphenylsulfide (0.4 mole) was dissolved in toluene (500 ml) and cooled to 5° C. Phenyl chloroformate (0.24 mole) in toluene (50 ml) was added slowly to the stirred solution over 1 hour. When addition was complete a simultaneous addition of phenyl chloroformate (0.24 mole) in toluene (50 ml) and an aqueous solution of sodium hydroxide (0.3 mole) and sodium carbonate (0.35 mole) (200 ml) was started.

After completing the addition, the reaction was stirred for 1 hour. The aqueous phase was discarded and the organic phase was washed with dilute hydrochloric acid. The organic phase was dried over magnesium sulfate. After filtration the toluene was removed in vacuo. Recrystallization of the residue from hexane afforded the urethane in about 90% yield.

## EXAMPLE A

Tablets
Each tablet contains:

| | |
|---|---|
| Compound of formula II | 5 mg |
| Lactose | 88 mg |
| Magnesium stearate | 1 mg |
| Polyvinylpyrrolidone | 2 mg |
| Sodium starch glycolate | 4 mg |

The compound of formula II, lactose, and a portion of the sodium starch glycolate and the polyvinylpyrrolidone are mixed in a suitable mixer and water added until the desired mass for granulation is obtained. The mass obtained may be passed through a suitable size mesh and dried to obtain the optimum moisture content. The remaining sodium starch glycolate and magnesium stearate is then added and the dry granulate is then passed through a further screen before final blending and compression to yield tablets each weighing 100 mg.

## EXAMPLE B

Tablets:
Each tablet contains:

| | |
|---|---|
| Compound of formula II | 250 mg |
| Lactose | 122 mg |
| Magnesium stearate | 4 mg |
| Pregelatinized Starch | 8 mg |
| Sodium starch glycolate | 16 mg |

The tablets are formulated as described in Example A to yield tablets each weighing 600 mg. The pregelatinized starch replaces the polyvinylpyrrolidone.

## EXAMPLE C

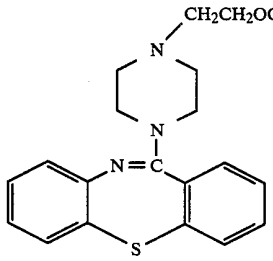
Tablets:
Each tablet contains:

| | |
|---|---|
| Compound of formula II | 100 mg |
| Lactose | 84 mg |
| Stearic Acid | 4 mg |
| Pregelatinized starch | 4 mg |
| Starch (maize) | 8 mg |

The tablets are formulated as described in Example A to yield tablets each weighing 200 mg. The stearic acid pregelatinized starch and starch (maize) replace the magnesium stearate, polyvinylpyrrolidone and sodium starch glycolate.

What is claimed is:

**1.** A compound of formula II




II

and acid addition salts thereof.

**2.** A compound as claimed in claim **1** wherein said acid addition salts are phamaceutically acceptable acid addition salts.

**3.** A compound as claimed in claim **2** wherein said salt is a hemifumarate salt.

**4.** A compound as claimed in claim **2** wherein said salt is a hydrochloride salt.

**5.** A pharmaceutical composition comprising a compound of claim **2** in an amount sufficient to manage a psychotic condition in a living mammal in need of such treatment in association with a non-toxic pharmaceutically acceptable diluent or carrier.

**6.** A pharmaceutical composition comprising a compound of claim **2** in an amount sufficient to reduce hyperactivity in a living mammal in need of such treatment in association with a non-toxic pharmaceutically acceptable diluent or carrier.

**7.** A method of treating psychosis in a living mammal comprising administering to the mammal an effective amount of a composition of claim **2**.

**8.** A method of treating hyperactivity in a living mammal comprising administering to the mammal an effective amount of a composition of claim **2**.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 4,879,288 PAGE 1 of 2

DATED : NOVEMBER 7, 1989

INVENTOR(S) : WARAWA, 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, line, 53 "facial-buc-cal-cervical" should read --facial-buccal-cervical--.

Column 3, line, 68 "dimethylforamide" should read --dimethylformamide--.

Column 6, line, 9 "formula XVII" should read --formula XVIII--.

Column 6, line, 10 "diphenysulfide" should read --diphenylsulfide--.

Column 6, line, 33 "1.0 ° 40" should read --1.0 to 40--.

Column 6, line, 51 "-1-piperaziny]" should read ---1-piperazinyl]--.

Column 7, line, 59 "-1-piperaziny]" should read ---1-piperazinyl]--.

Column 8, line, 6 "-1-piperaziny]" should read ---1-piperazinyl]--.

# UNITED STATES PATENT AND TRADEMARK OFFICE
# CERTIFICATE OF CORRECTION

PATENT NO. : 4,879,288

DATED : NOVEMBER 7, 1989

INVENTOR(S) : WARAWA, 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 8, line, 22 "-1-piperaziny]" should read ---1-piperazinyl]--.

Column 9, line, 9 "13 ° 14" should read --13 to 14--.

Column 9, line, 26 "Hyperactive" should read --Hyperactivity--.

Column 9, line, 32 "become hyperactivity." should read --become hyperactive.--.

Column 9, line, 48 "aaphetamine" should read --amphetamine--.

Column 10, line, 48 "stiulus" should read --stimulus--.

Column 12, line, 6 "(4 mmole)." should read --(14 mmole).--.

Signed and Sealed this

Twenty-fifth Day of January, 1994

*Attest:*

BRUCE LEHMAN

*Attesting Officer*

*Commissioner of Patents and Trademarks*

# EXHIBIT B

US005948437A

# United States Patent [19]

**Parikh et al.**

[11] **Patent Number: 5,948,437**

[45] **Date of Patent: Sep. 7, 1999**

[54] **PHARMACEUTICAL COMPOSITIONS USING THIAZEPINE**

[75] Inventors: **Bhavnish Vinod Parikh**, Hockessin, Del.; **Robert Joseph Timko**, West Chester, Pa.; **William Joseph Addicks**, Morgantown, W. Va.

[73] Assignee: **Zeneca Limited**, United Kingdom

[21] Appl. No.: **08/864,306**

[22] Filed: **May 28, 1997**

**Related U.S. Application Data**

[60] Provisional application No. 60/018,816, May 31, 1996.

[51] **Int. Cl.**[6] ..... **A61K 9/20**

[52] **U.S. Cl.** ..... **424/464**; 424/470; 424/458; 514/211

[58] **Field of Search** ..... 424/464, 401; 514/211; 540/551

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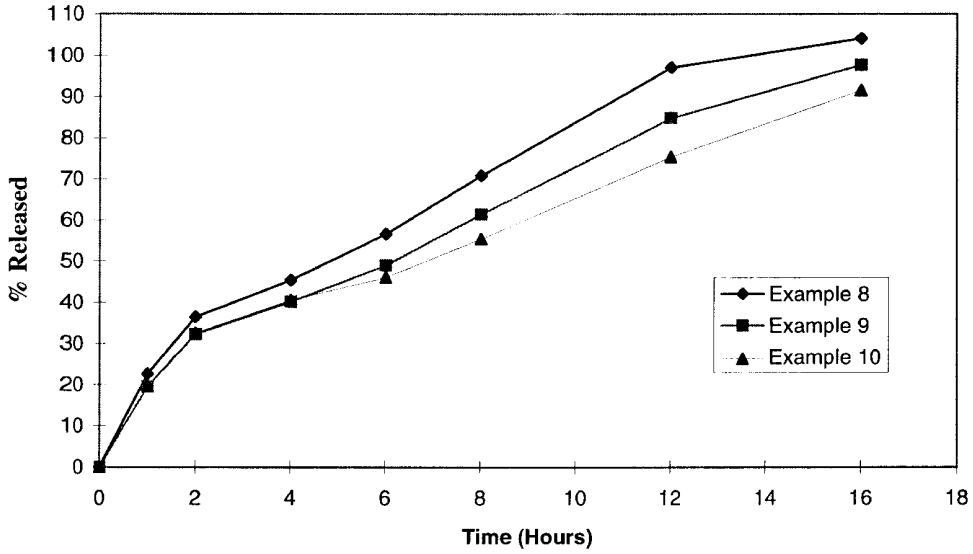
| WO 92/10169 | 6/1992 | WIPO . |

*Primary Examiner*—Thurman K. Page
*Assistant Examiner*—William E. Benston, Jr.

[57] **ABSTRACT**

The invention relates to sustained release formulations comprising 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo[b,f] [1,4]thiazepine or a pharmaceutically acceptable salt thereof, to methods of treating psychotic states and hyperactivity utilizing the sustained release formulations and to a process for preparing the sustained release formulations.

**15 Claims, 2 Drawing Sheets**



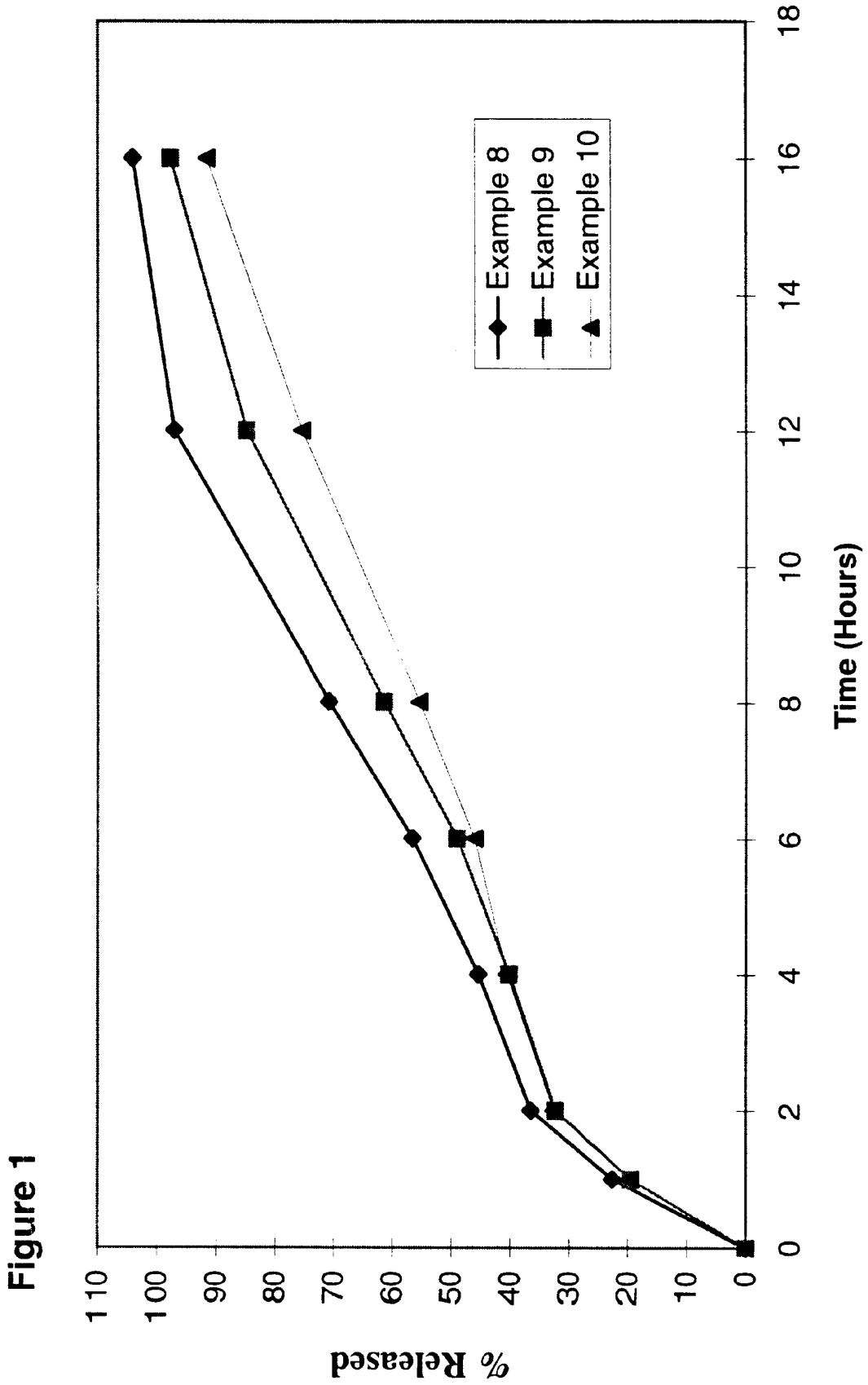
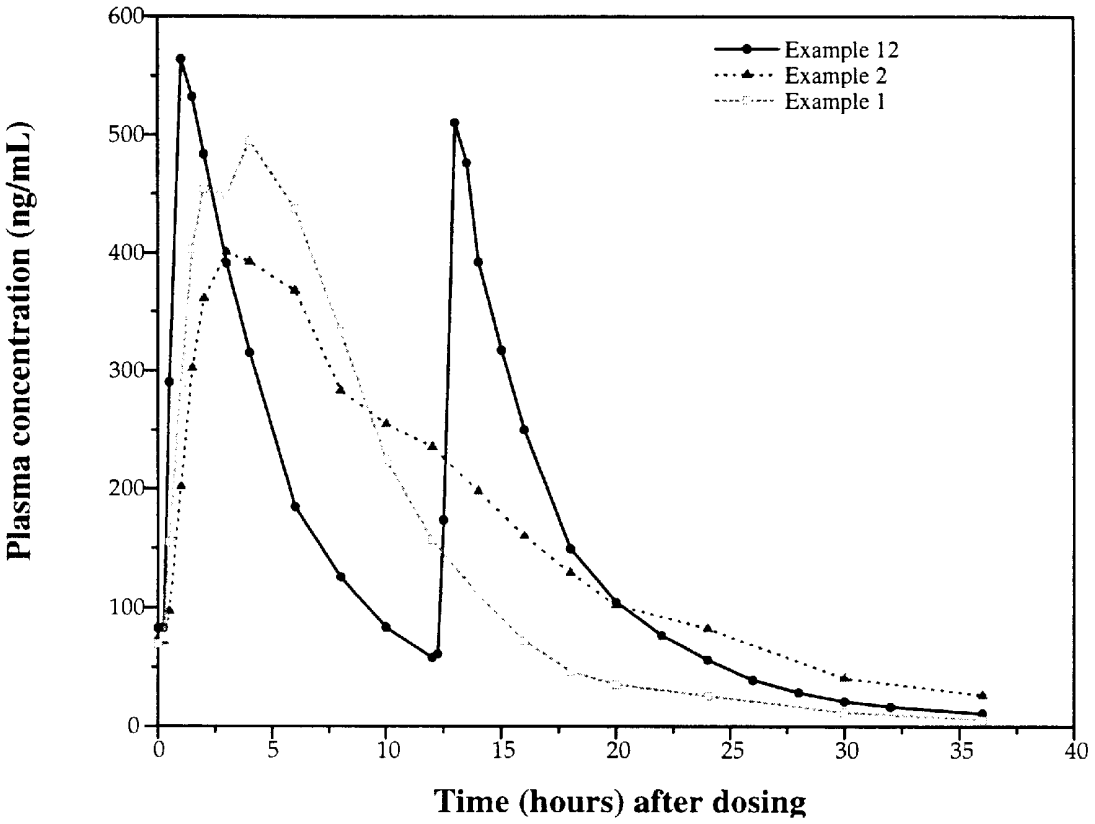

Example 8
Example 9
Example 10
% Released
0
10
20
30
40
50
60
70
80
90
100
110
Time (Hours)
0
2
4
6
8
10
12
14
16
18

Figure 1

**Figure 2**


Example 12
Example 2
Example 1
Plasma concentration (ng/mL)
600
500
400
300
200
100
0
0
5
10
15
20
25
30
35
40
Time (hours) after dosing

# PHARMACEUTICAL COMPOSITIONS USING THIAZEPINE

This application claims the benefit of U.S. Provisional Application No. 60/018,816, filed on May 31, 1996.

The present invention relates to a pharmaceutical composition and more particularly to a sustained release pharmaceutical composition comprising 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4] thiazepine or a pharmaceutically acceptable salt thereof.

It is desirable in the treatment of a number of diseases, both therapeutically and prophylactically, to provide the active pharmaceutical ingredient in a sustained release form. Desirably the sustained release provides a generally uniform and constant rate of release over an extended period of time which achieves a stable and desired blood (plasma) level of the active ingredient without the need for frequent administration of the medicament.

While there are numerous sustained release formulations known in the art which utilize gelling agents, such as hydroxypropyl methylcelluloses, it has been found to be difficult to formulate sustained release formulations of soluble medicaments and gelling agents, such as hydroxypropyl methylcellulose, for several reasons. First of all, active ingredients which are soluble in water tend to generate a sustained release product which is susceptible to a phenomenon known as dose dumping. That is, release of the active ingredient is delayed for a time but once release begins to occur the rate of release is very high. Moreover, fluctuations tend to occur in the plasma concentrations of the active ingredient which increases the likelihood of toxicity. Further, some degree of diurnal variation in plasma concentration of the active ingredient has also been observed. Finally, it has been found to be difficult to achieve the desired dissolution profiles or to control the rate of release of the soluble medicament.

Accordingly, a need exists for sustained release formulations of soluble medicaments, such as, 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4] thiazepine or a pharmaceutically acceptable salt, which overcome, or at least alleviate, one or more of the above described difficulties and which further provide the advantageous property of allowing the active medicament to be administered less frequently, e.g. once a day, while achieving blood (plasma) levels similar to those attained by administering smaller doses of the medicament more frequently, e.g. two or more times daily.

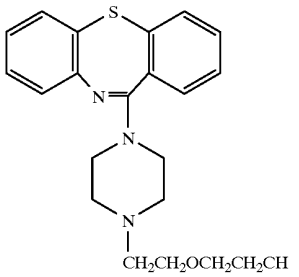
FIG. **1** shows the release (dissolution) profiles of the sustained release formulations of Examples 8, 9 and 10 which are obtained by immersing a suitable tablet in 750 mL of 0.1 N HCl for 2 hours at 37° C. and a speed of 100 rpm and then adding 250 mL of 0.2 M sodium phosphate buffer to the dissolution media to afford a pH of 6.2.

FIG. **2** shows the plasma concentration versus time profiles of the active ingredient for the sustained release formulations of examples 1 and 2 and the immediate release formulation of example 12.

The compound, 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine (see Formula I below), and its pharmaceutically acceptable salts exhibit useful antidopaminergic activity and may be used, for



I




example, as an antipsychotic agent (for example, for the management of the manifestations of psychotic disorders) or as a treatment for hyperactivity. It is a compound of particular interest since it may be used as an antipsychotic agent with a substantial reduction in the potential to cause side effects such as acute dystonia, acute dyskinesia, pseudo-Parkinsonism and tardive dyskinesia which side-effects may result from the use of other antipsychotics or neuroleptics.

The preparation, physical properties and beneficial pharmacological properties of 11 -[4-[2-(2- hydroxyethoxy) ethyl]-1 -piperazinyl]dibenzo[b,f][1,4]-thiazepine, and its pharmaceutically acceptable salts are described in published European Patents EP 240,228 and 282,236 as well as in U.S. Pat. No. 4,879,288, the entire contents of which are herein incorporated by reference.

According to the present invention there is provided a sustained release formulation comprising a gelling agent, preferably hydroxypropyl methylcellulose, and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4] thiazepine, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients. Preferably, the sustained release formulation comprises a hydrophilic matrix comprising a gelling agent, preferably hydroxypropyl methylcellulose, and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1piperazinyv]dibenzo-[b,f][1,4] thiazepine, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients.

The term gelling agent as used herein means any substance, particularly a hydrophilic substance, which forms a gel when in contact with water and thus includes such substances as hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl ethylcellulose, methylcellulose, ethylcellulose, carboxyethylcellulose, carboxymethyl hydroxyethylcellulose, carbomer, sodium carboxymethylcellulose, polyvinylpyrrolidone, and the like, or mixtures thereof. The gelling agent is preferably hydroxypropyl methylcellulose.

The amount of gelling agent, preferably hydroxypropyl methylcellulose, is preferably selected such that the active ingredient is released from the formulation, in a controlled fashion, over a period of 4 hours or longer, preferably over a period of 8 hours or longer and in particular over a period of between 8 and 24 hours, that is so that at least 60% of the active ingredient has been released at the end of this period.

The gelling agent, preferably hydroxypropyl methylcellulose, is conveniently present in about 5 to 50% (by weight), more conveniently about 5 to 40%, most conveniently about 8 to 35% and in particular about 10 to 35%. It is generally preferred that the gelling agent, preferably hydroxypropyl methylcellulose, is present in about 10 to 30%, more preferably about 15 to 30%.

The hydroxypropyl methylcellulose may contain more than one grade of polymer and is commercially available under several trademarks, e.g. METHOCEL® E, F, J and K from the Dow Chemical Company, U.S.A. and METALOSE™ SH from Shin-Etsu, Ltd., Japan. The various grades available under a given trademark represent differences in methoxy and hydroxypropoxy content as well as in viscosity. The methoxy content ranges from 16.5 to 30% by weight, the hydroxypropoxy content ranges from 4 to 32% by weight and the viscosities of a 2% aqueous solution at 20° C. range from 3 cps to 100,000 cps. For example, the hydroxypropyl methylcellulose preferably comprises (a) a polymer with a viscosity of about 40 to 60 cps (in particular about 50 cps), a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight; or (b) a polymer with a viscosity of about 3,500 to 5,600 cps (in particular about 4,000 cps), a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight; or (c) a polymer with a viscosity of about 80 to 120 cps (in particular about 100 cps), a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight; or (d) a polymer with a viscosity of about 3500 to 5600 cps (in particular about 4,000 cps), a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof. More preferably, the hydroxypropyl methylcellulose is selected from the group consisting of (a)–(d) or mixtures thereof as described above with the proviso that if the formulation contains a hydroxypropyl methylcellulose described under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

In one embodiment the hydroxypropyl methylcellulose comprises 8 to 12% of a polymer having a viscosity of about 4,000 cps, and preferably about 5 to 10%. In a further embodiment hydroxypropyl methylcellulose comprises 10 to 35% of a polymer having a viscosity of about 50 cps, and preferably about 10 to 15%.

In a specific embodiment the hydroxypropyl methylcellulose comprises 15% of a polymer having a viscosity of about 50 cps, and optionally about 5% of a hydroxypropyl methylcellulose polymer having a viscosity of about 4,000 cps.

In particular the 11-[4-[2-(2-hydroxyethoxy)-ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine, or pharmaceutically acceptable salt thereof (preferably the hemifumarate salt),. is present in about 10 to 90% by weight, preferably about 20 to 80% by weight, more preferably about 35 to 65% by weight, most preferably about 40 to 60% by weight and especially about 43.2 to 57.6% by weight.

The formulation will, in general, contain one or more excipients. Such excipients will include diluents such as lactose, microcrystalline cellulose, dextrose, mannitol, sucrose, sorbitol, gelatin, acacia, dicalcium phosphate, tricalcium phosphate, monocalcium phosphate, sodium phosphate, sodium carbonate and the like, preferably lactose and microcrystalline cellulose; lubricants such as stearic acid, zinc, calcium or magnesium stearate and the like, preferably magnesium stearate; binders such as sucrose, polyethylene glycol, povidone (polyvinylpyrrolidone), corn or maize starch, pregelatinized starch and the like, preferably povidone (polyvinylpyrrolidone); colorants such as ferric oxides, FD & C dyes, lakes and the like; flavoring agents; and pH modifiers which include suitable organic acids or alkali metal (e.g. lithium, sodium or potassium) salts thereof, such as benzoic acid, citric acid, tartaric acid, succinic acid, adipic acid and the like or the corresponding alkali metal salts thereof, preferably the alkali metal salts of such acids and in particular the sodium salt of citric acid (i.e. sodium citrate). The excipient(s) will, in general, be present in about 10 to 90% by weight, preferably about 20 to 80% by weight, more preferably about 20 to 45% by weight, most preferably about 20 to 40% by weight and especially about 22.4 to 36.8% by weight. The formulation preferably may contain one or more pharmaceutically acceptable excipients selected from the group consisting of microcrystalline cellulose, lactose, magnesium stearate, sodium citrate and povidone. In particular, the formulation may contain one or more of (a) microcrystalline cellulose, preferably in the amount of about 4 to 20% by weight, (b) lactose, preferably in the amount of about 5 to 20% by weight, (c) magnesium stearate, preferably in the amount of about 1 to 3% by weight, (d) about 10 to 30% by weight, preferably about 12.5 to 25% and in particular about 12.5% by weight of sodium citrate, and (e) about 1 to 15% by weight, preferably about 4 to 6% by weight and in particular about 5% by weight of povidone (polyvinylpyrrolidone).

According to the present invention there is also provided a sustained release formulation comprising a gelling agent, preferably hydroxypropyl methylcellulose, and 11-[-4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients wherein one of the excipients is a pH modifier.

According to the present invention there is also provided a sustained release formulation comprising 11 -[4-[2-(2-hydroxyethoxy)ethyl]- 1 -piperazinyl] dibenzo-[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, as active ingredient and 5 to 40% of hydroxypropyl methylcellulose, together with one or more pharmaceutically acceptable excipients.

According to the present invention there is also provided a sustained release formulation comprising about 35 to 65% of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, as active ingredient and about 5 to 40% by weight of hydroxypropyl methylcellulose, together with one or more pharmaceutically acceptable excipients.

According to the present invention there is also provided a sustained release formulation comprising about 35 to 65% of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, as active ingredient and about 15 to 30% of hydroxypropyl methylcellulose, together with about 20 to 45% of one or more pharmaceutically acceptable excipients.

According to the present invention there is also provided a sustained release formulation comprising about 35 to 65% of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1 **1**-piperazinyl]-dibenzo[b,f][1,4]thiazepine as active ingredient, or a pharmaceutically acceptable salt thereof, about 5 to 40% by weight of hydroxypropyl methylcellulose, about 4 to 12% microcrystalline cellulose, about 8 to 20% lactose and the remainder being one or more further pharmaceutically acceptable excipients. Such further excipients may include components which act as a lubricant (for example, magnesium stearate) during the manufacture of the formulation or dosage form.

According to the present invention there is also provided a sustained release formulation comprising about 5 to 40% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content

of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof; about 35 to 65% by weight of 11-[4[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl) -dibenzo[b,f][1,4] thiazepine or a pharmaceutically acceptable salt thereof; and about 20 to 45% by weight of one or more pharmaceutically acceptable excipients; with the proviso that if the formulation contains a hydroxypropyl methylcellulose described under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

Other formulations within the ambit of this latter group are those comprising about 8 to 35% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40–60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight or mixtures thereof; about 35 to 65% by weight of 11-[4-[2-(2-hydroxyethoxy) ethyl]1-piperazinyl]dibenzo[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof; and about 20 to 45% by weight of one or more pharmaceutically acceptable excipients.

Still other formulations within the ambit of this latter group are those comprising about 10 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a)–(d) or mixtures thereof as described above; about 40 to 60% by weight of 11 -[4-[2-(2-hydroxyethoxy)ethyl]-1 -piperazinyl]dibenzo[b,f] [1,4]thiazepine or a pharmaceutically acceptable salt thereof; and about 20 to 40% by weight of one or more pharmaceutically acceptable excipients.

Preferred formulations within this latter group are those comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a)–(d) or mixtures thereof as described above; about 43.2 to 57.6% by weight of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo [b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof; and about 22.4 to 36.8% by weight of one or more pharmaceutically acceptable excipients.

Particularly preferred formulations within this latter group are those comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a)–(d) or mixtures thereof as described above; about 43.2 to 57.6% by weight of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f]-[1,4]thiazepine or a pharmaceutically acceptable salt thereof; and about 22.4 to 36.8% by weight of one or more pharmaceutically acceptable excipients selected from the group consisting of (a) about 4 to 12% by weight of microcrystalline cellulose, (b) about 5 to 20% by weight of lactose, (c) about 1 to 3% by weight of magnesium stearate, (d) about 10 to 30% by weight of sodium citrate and (e) about 1 to 15% by weight of povidone (polyvinylpyrrolidone).

In the above-described formulations the 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]-thiazepine is preferably in the form of a hemifumarate salt which form has an equilibrium solubility in water at 20° C. of 3.29 mg/mL.

Formulations of particular interest include those described in the accompanying Examples and so formulations substantially as defined in the accompanying Examples are provided as a further feature of the present invention.

As mentioned above, the compound 11-[4-[2-(2-hydroxyethoxy)ethyl]-l-piperazinyl]dibenzo[b,f]]1,4]-thiazepine, and its pharmaceutically acceptable salts, exhibit useful antidopaminergic activity and may be used, for example, as an antipsychotic agent (for example, for the management of the manifestations of psychotic disorders) or as a treatment for hyperactivity. Thus, the present invention also provides a method of treating psychotic states, for example psychosis, in a warm-blooded animal, such as man, which comprises administering an effective amount of the formulation of the present invention to said warm-blooded animal.

The present invention also provides a method of treating hyperactivity in a warm-blooded animal which comprises administering to said warm-blooded animal an effective amount of a formulation of the present invention.

The formulations of the present invention may be prepared by conventional technology well known to those skilled in the art such as wet granulation, direct compression, dry compaction (slugging) and the like. Thus, for example, the active ingredient 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f]-[1,4] thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent, preferably hydroxypropyl methylcellulose, and other excipients are mixed together to form the sustained release formulations of the present invention. Preferably the active ingredient 11-[4-[2-(2-hydroxyethoxy) ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent, preferably hydroxypropyl methylcellulose, and other excipients are mixed together to form a mixture suitable for compressing into tablets, which mixture is then compressed to form tablets or is filled into capsules.

The mixing process is preferably carried out by mixing the components, wet granulating the mixed components, drying the mixture, milling the dried mixture, blending the mixture with a lubricant such as magnesium stearate and compressing the blended mixture to form tablets or filling the blended mixture into capsules.

A preferred process for preparing the formulations of the invention comprises the following steps:

(a) mixing 11-[4-[2-(2-hydroxyethoxy)ethyl]1-piperazinyl]dibenzo[b,f][1,4]-thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent, preferably hydroxypropyl methylcellulose, and other excipients;

(b) wet granulating the mixed components;

(c) drying the mixture;

(d) milling the dried mixture;

(e) blending the mixture with a lubricant such as magnesium stearate; and

(f) compressing the blended mixture to form tablets.

The dosage forms may be coated with one or more coatings as is well known in the art such as, for example, shellac, zein, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, polymethacrylates, polyvinyl acetate phthalate, cellulose acetate phthalate, triacetin, dibutyl sebacate, a mixture of polyethylene glycol, titanium dioxide and hydroxypropyl methylcellulose, and the like.

The sustained release properties of the formulation of the present invention may be demonstrated by monitoring the dissolution of the active ingredient. The dissolution of the active ingredient may be monitored using standard procedures well known to those skilled in the art (e.g. the dissolution test procedures, such as the Rotating Basket Method (Apparatus I) or Paddle Method (Apparatus II), disclosed in the U.S. Pharmacopeia (USP)). Such procedures include those in which the formulation is immersed in an aqueous medium such as water or hydrochloric acid and aliquots of the medium are withdrawn at various time points over a period of 24 hours. The aliquots are analyzed using high pressure liquid chromatography (HPLC) with UV detection to determine the concentration of dissolved active ingredient using standard methodology. In a particular example a tablet is immersed in about 900 mL of water and the dissolution profile determined. In another particular example, the dissolution profile is determined by the Rotating Basket method by immersing a tablet in 750 mL of 0.lN HCl for 2 hours at a speed of 100 rpm and then adding 250 mL of 0.2 M phosphate buffer to the dissolution media to afford a pH of 6.2.

The formulation preferably releases the active ingredient in a controlled manner over a period of up to about 8 hours or longer. For example, the formulation described in Example 2 below released about 90% of the active ingredient over 16 hours, and the formulation described in Example 1 released about 90% of the active ingredient over a period of 8 hours.

The plasma concentration versus time profiles of the active ingredient illustrated in FIG. **2** were obtained utilizing the following procedure. Thirty-two patients were assigned to either Group A or Group B with 16 patients in each group. After a 2-day drug-free period (days 1 and 2), all patients were given oral doses of the immediate release formulation of example 12 twice daily for a 9-day period (days 3 through 11) with fixed step-wise increases in dose from 25 to 200 mg. Starting on day 12, patients began a randomized treatment sequence within their respective groups (Group A or B). Group A patients followed a treatment sequence that included one of each of the following formulations of the active ingredient administered according to the sequence randomized: two 100 mg tablets of the immediate release formulation of example 12 while fasting administered every 12 hours (Treatment 1), one 400 mg tablet of the formulation of example 2 while fasting (Treatment 2) and one 400 mg tablet of the formulation of example 2 with a meal (Treatment 3). Group B patients were randomized to a treatment sequence that included one of each of the following formulations of the active ingredient administered according to the sequence randomized: two 100 mg tablets of the immediate release formulation of example 12 while fasting administered every 12 hours (Treatment 1), one 400 mg tablet of the formulation of example 1 while fasting (Treatment 4) and one 400 mg tablet of the formulation of example 1 with a meal (Treatment 5). On days 12, 16 and 20 patients received trial treatment according to their assigned treatment sequences. On the evenings of days 13 and 17, patients received 200 mg doses of the immediate release formulation of example 12 and on days 14, 15, 18 and 19 the patients received 200 mg dose of the immediate release formulation of example 12 twice daily. Blood samples were taken from each subject on days 3, 10, 11, 14, 15, 18 and 19 before the morning dose. On days, 12, 16 and 20 blood samples were taken from each subject immediately before dose administration and at specified time intervals from immediately after dose administration to 36 hours after dose administration. The concentration of the active ingredient in the blood samples was quantified using liquid-liquid extraction and high performance liquid chromatography with ultraviolet absorbance detection. The plasma concentration of the active ingredient over time profiles for the formulations of examples 1 (n=11), 2(n=10) and 12(n=10 for Group A and 12 for Group B) are illustrated in FIG. **2** and Table A summarizes the mean area under the curve (AUC) values for a 24 hour dosing interval and the mean maximum blood concentration ($C_{max}$) values for each of the examples.

TABLE A

| | Group A | | Group B | |
|---|---|---|---|---|
| Example No. | $AUC_{0-24}$ | $C_{max}$ | $AUC_{0-24}$ | $C_{max}$ |
| 1 | — | — | 4886 | 565 |
| 2 | 5609 | 433 | — | — |
| 12 | 5347 | 703 | 4818 | 563 |

The dose of the compound of the present invention which is administered will necessarily be varied according to principles well known in the art taking account of the route of administration, the duration of treatment, the severity of the psychotic condition, the size and age of the patient, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus readily be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf. In general, the compound will be administered to a warm blooded animal (such as man) so that an effective dose is received, generally a daily dose in the range of about 0.01 to about 40 mg/kg body weight. For example, when administered orally, it is generally administered in the range of about 0.1 to about 40 mg/kg body weight. Preferably, the compound of the present invention is administered in about a 25, 50, 200, 300 or 400 mg strength.

The formulation of the present invention will, in general, be in the form of a unit dosage form, and, in particular, the formulation will be in the form of a tablet.

It will be apparent to those skilled in the art that the formulation can be co-administered with other therapeutic or prophylactic agents and/or medicaments that are not medically incompatible therewith. The formulation of the present invention does not, in general, show any indication of overt toxicity in laboratory test animals at several multiples of the minimum effective dose of the active ingredient.

The invention is further illustrated by the following non-limiting Examples in which temperatures are expressed in degrees Celsius. The compound 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f]]1,4]-thiazepine, and its pharmaceutically acceptable salts, may be prepared as described in published European Patents EP 240,228 or 282,236 as well as in U.S. Pat. No. 4,879,288, the entire contents of which are herein incorporated by reference.

## EXAMPLE 1

The following process was used to prepare tablets having the composition defined in Table 1.

11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo-[b,f]]1,4]thiazepine hemifumurate (3453.8g), lactose (1144.7g), microcrystalline cellulose (381.5g) and METHOCEL® E50LV (900 g) were blended in a planetary mixer for approximately 3 minutes.

The mixture was wet granulated in a planetary mixer using purified water. The wet mass was dried in a fluidized bed drier at about 65° C. until the loss on drying was less than about 3% as measured by a moisture balance.

The dried granulation was milled using a hammer type or similar mill operating at fast speed, knives forward with suitable screen (e.g. 20 to 40 mesh).

Magnesium stearate was passed through an appropriate screen (e.g. 20 to 40 mesh).

The dry granulated material was blended for approximately 3 minutes in a conventional blender (for example, Patterson-Kelley Twin Shell) with the screened magnesium stearate.

The blended mixture was compressed into tablets using a conventional rotary tablet press (for example, Kilian LX-21).

TABLE 1

| | mg/Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 460.51 | 57.6 |
| Lactose NF | 152.62 | 19.1 |
| Microcrystalline Cellulose NF | 50.87 | 6.3 |
| METHOCEL ® E50LV Premium (b) | 120.00 | 15.0 |
| Purified water (c) | q.s | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f]][1,4]thiazepine hemifumarate
(b) METHOCEL ® E50LV Premium is hydroxypropyl methylcellulose with a viscosity of 40–60 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP. Note that the particular METHOCEL ® E50LV Premium utilized in this example had a viscosity of 48 cps, a methoxy content of 28.9% by weight and a hydroxypropoxy content ofless than 9.0% by weight (i.e. 8.0%).
(c) Added but not retained.

The plasma concentration over time profile of the active ingredient for the formulation of Example 1 is shown in FIG. **2**.

## EXAMPLE 2

The procedure described in Example 1 was repeated using METHOCEL® E50LV and METHOCEL® E4M in place of METHOCEL® E50LV to afford tablets of the following composition.

TABLE 2

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 460.51 | 57.6 |
| Lactose NF | 81.74 | 10.2 |
| Microcrystalline Cellulose NF | 81.75 | 10.2 |
| METHOCEL ® E50LV Premium (b) | 120.00 | 15.0 |
| METHOCEL ® E4M Premium CR (d) | 40.00 | 5.0 |
| Purified water (c) | q.s | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate
(b) METHOCEL ® E50LV Premium is hydroxypropyl methylcellulose with a viscosity of 40–60 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP. Note that the particular METHOCEL ® E50LV Premium utilized in this example had a viscosity of 48 cps, a methoxy content of 28.9% by weight and a hydroxypropoxy content ofless than 9.0% by weight (i.e. 8.0%).
(c) Added but not retained.
(d) METHOCEL ® E4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications from HPMC 2910 USP. Note that the particular METHOCEL ® E4M Premium CR utilized in this example had a viscosity of 4364 cps, a methoxy content of 28.5% by weight and a hydroxypropoxy-content of 7.8% by weight.

The plasma concentration over time profile of the active ingredient for the formulation of Example 2 is shown in FIG. **2**.

## EXAMPLE 3

Following a procedure similar to that described in Example 1, tablets of the following composition can be prepared.

TABLE 3

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Lactose NF | 49.31 | 6.2 |
| Microcrystalline Cellulose NF | 49.31 | 6.2 |
| Sodium citrate | 100.00 | 12.5 |
| METHOCEL ® K100LV Premium CR (b) | 200.00 | 25.0 |
| METHOCEL ® K4M Premium CR (c) | 40.00 | 5.0 |
| Purified water (d) | q.s | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo[b,f][1,4]thiazepine hemifumarate
(b) METHOCEL ® K100LV Premium CR is hydroxypropyl methylcellulose with a viscosity of 80 to 120 cps, a methoxy content of 19 to 24% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2208 USP. Note that the particular METHOCEL ® K100LV Premium CR utilized in this example must have a hydroxypropoxy content of less than 9.0% by weight.
(c) METHOCEL ® K4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 19 to 24% by weight and a hydroxypropoxy content of 7 to 12% be weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specification of HPMC 2208 USP.
(d) Added but not retained

## EXAMPLE 4

Following a procedure similar to that described in Example 1, tablets of the following composition can be prepared.

TABLE 4

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Lactose NF | 89.31 | 11.1 |
| Microcrystalline Cellulose NF | 89.31 | 11.1 |
| Sodium citrate | 100.00 | 12.5 |
| METHOCEL ® K100LV Premium CR (b) | 120.0 | 15.0 |
| METHOCEL ® E4M Premium CR (c) | 40.00 | 5.0 |
| Purified water (d) | q.s. | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo[b,f][1,4]thiazepine hemifumarate
(b) METHOCEL ® K100LV Premium CR is hydroxypropyl methylcellulose with a viscosity of 80 to 120 cps, a methoxy content of 19 to 24% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2208 USP. Note that the particular METHOCEL ® K100LV Premium CR utilized in this example must have a hydroxypropoxy content of less than 9.0% by weight.
(c) METHOCEL ® E4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from the Dow Chemical Company, Michigan, USA. This product meets the specification of HPMC 2910 USP.
(d) Added but not retained

## EXAMPLE 5

Following a procedure similar to that described in Example 1, tablets of the following composition can be prepared.

TABLE 5

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Lactose NF | 69.31 | 8.7 |
| Microcrystalline Cellulose NF | 69.31 | 8.7 |
| Sodium citrate | 100.00 | 12.5 |
| METHOCEL ® K100LV Premium CR (b) | 200.00 | 25.0 |
| Purified water (d) | q.s. | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate
(b) METHOCEL ® K100LV Premium CR is hydroxypropyl methylcellulose with a viscosity of 80 to 120 cps, a methoxy content of 19 to 24% by weight and a hydropropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2208 USP. Note that the particular METHOCEL ® K100LV Premium CR utilized in this example must have a hydroxypropoxy content of less than 9.0% by weight.
(c) Added but not retained.

## EXAMPLE 6

Following a procedure similar to that described in Example 1, tablets of the following composition can be prepared.

TABLE 6

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Povidone USP (b) | 40.00 | 5.0 |
| Microcrystalline Cellulose NF | 38.62 | 4.8 |
| Sodium citrate | 200.00 | 25.0 |
| METHOCEL ® E50LV Premium (c) | 80.00 | 10.0 |
| METHOCEL ® E4M Premium CR (d) | 80.00 | 10.0 |

TABLE 6-continued

| | mg\Tablet | % of Tablet |
|---|---|---|
| Purified water (e) | q.s | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate
(b) The reagent is a polyvinylpyrrolidone polymer having a K-value of 29–32 which may be obtained from ISP Technologies Inc., Wayne, New Jersey, USA, under the trademark PLASDONE ® K-29/32. This product meets the specifications for Povidone USP.
(c) METHOCEL ® E50LV Premium is hydroxypropyl methylcellulose with a viscosity of 40–60 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP. Note that the particular METHOCEL ® E50LV Premium utilized in this example must have a hydroxypropoxy content of less than 9.0% by weight.
(d) METHOCEL ® E4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP.
(e) Added but not retained

## EXAMPLE 7

Following a procedure similar to that described in Example 1, tablets of the following composition can be prepared.

TABLE 7

| | mg\Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Povidone USP (b) | 40.00 | 5.0 |
| Microcrystalline Cellulose NF | 38.62 | 4.8 |
| Sodium citrate | 200.00 | 25.0 |
| METHOCEL ® E50LV Premium (c) | 80.00 | 10.0 |
| METHOCEL ® E4M Premium CR (d) | 80.00 | 10.0 |
| Purified water (e) | q.s | — |
| Magnesium stearate NF | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate.
(b) This reagent is a polyvinylpyrrolidone polymer having a K-value of 90 which may be octained from ISP Technologies Inc., Wayne, New Jersey, USA, inder the trademark PLASDONE ® K-90. This product meets the specifications for Povidone USP.
(c) METHOCEL ® E50LV Premium is hydroxypropyl methylcellulose with a viscosity of 40–60 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP. Note that the particular METHOCEL ® E50LV Premium utilized in this example must have a hydroxypropoxy content of less than 9.0% by weight.
(d) METHOCEL ® E4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP.
(e) Added but not retained.

Following a procedure similar to that described in Example 1, tablets of the following compositions were prepared:

TABLE 8

| | Example 8 | | Example 9 | | Example 10 | |
|---|---|---|---|---|---|---|
| | mg/ tablet | % of tablet | mg/ tablet | % of tablet | mg/ tablet | % of tablet |
| Active Ingredient (a) | 345.38 | 43.2 | 345.38 | 43.2 | 345.38 | 43.2 |
| Lactose NF | 109.31 | 13.7 | 69.31 | 8.7 | 49.31 | 6.2 |
| Microcrystalline Cellulose NF | 109.31 | 13.7 | 69.31 | 8.7 | 49.31 | 6.2 |
| Sodium citrate | 100.00 | 12.5 | 100.00 | 12.5 | 100.00 | 12.5 |
| METHOCEL ® K100LV Premium CR (b) | 120.00 | 15.0 | 200.00 | 25.0 | 200.00 | 25.0 |
| METHOCEL ® K4M Premium CR (c) | — | — | — | — | 40.00 | 5.0 |
| Purified water (d) | q.s. | — | q.s. | — | q.s. | — |
| Magnesium stearate NF | 16.00 | 2.0 | 16.00 | 2.0 | 16.00 | 2.0 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate
(b) METHOCEL ® K100LV Premium CR is hydroxypropyl methylcellulose with a viscosity of 80 to 120 cps, a methoxy content of 19 to 24% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2208 USP. Note that the particular METHOCEL ® K100LV Premium CR utilized in this example had a viscosity of 90 cps, a methoxy content of 22.7% by weight and a hydroxypropoxy contentof 8.5% by weight.
(c) METHOCEL ® K4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 19 to 24% by weight and a hydroxypropoxy content of 7 to 12% by weight, which may be obtained from the Dow Chemical Company, Michigan, USA. This product meets the specification of HPMC 2208 USP. Note that the particular METHOCEL ® K4M Premium CR utilized in this example had a viscosity of 4105 cps, a methoxy content of 22.3% by weight and a hydroxypropoxy content of 9.7% by weight.
(d) Added but not retained.

The release dissolution profile of the formulations of Examples 8, 9 and 10 are shown in FIG. **1**.

## EXAMPLE 11

Following a procedure similar to that described in Example 1, tablets of the following composition were prepared:

| | mg/Tablet | % of Tablet |
|---|---|---|
| Active ingredient (a) | 345.38 | 43.2 |
| Povidone USP (b) | 80.00 | 10.00 |
| Sodium citrate USP | 100.00 | 12.5 |
| Microcrystalline cellulose NF | 138.62 | 17.3 |
| METHOCEL ® E4M Premium CR (c) | 120.00 | 15.0 |
| Purified water (d) | q.s. | — |
| Magnesium Stearate NF | 16.0 | 2.0 |

(a) The active ingredient is 11-[4-[2(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine hemifumarate
(b) This reagent is a polyvinylpyrrolidone polymer having a K-value of 90 which may be obtained from ISP Technologies Inc., Wayne, New Jersey, USA, under the trademark PLASDONE ® K-90. This product meets the specifications for Povidone USP.
(c) METHOCEL ® E4M Premium CR is hydroxypropyl methylcellulose with a viscosity of 3,500 to 5,600 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight which may be obtained from The Dow Chemical Company, Michigan, USA. This product meets the specifications for HPMC 2910 USP. Note that the particular METHOCEL ® E4M Premium CR utilized in this example had a viscosity of 4364 cps, a methoxy content of 28.5% by weight and a hydroxypropoxy-content of 7.8% by weight.
(d) Added by not retained.

## EXAMPLE 12

| | Mg/Tablet |
|---|---|
| CORE | |
| Active ingredient (a) | 115.13 |
| Povidone USP (b) | 8.33 |
| Dicalcium phosphate dihydrate USP | 10.00 |
| Microcrystalline cellulose NF | 32.88 |
| Sodium starch glycolate NF | 8.33 |
| Lactose NF | 22.33 |
| Magnesium stearate NF | 3.00 |
| Purified water (c) | q.s. |
| COATING | |
| Hydroxypropyl methylcellulose 2910 USP (d) | 5.00 |
| Polyethylene glycol 400 NF | 1.00 |
| Yellow ferric oxide NF | 0.15 |
| Titanium dioxide USP | 1.85 |

(a) The active ingredient is 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo[b,f][1,4]thiazepine hemifumarate.
(b) This reagent is a polyvinylpyrrolidone polymer having a K-value of 29–32 which may be obtained from ISP Technologies Inc., Wayne, New Jersey, USA, under the trademark PLASDONE ® K-29/32. This product meets the specification for Povidone USP.
(c) Added but not retained.
(d) The hydroxypropyl methylcellulose utilized in this example was PHARMACOAT ® 606 which may be obtained from Shin-Etsu, Ltd., Japan and has a viscosity in the range of 4.5 to 8.0 cps, a methoxy content of 28 to 30% by weight and a hydroxypropoxy content of 7 to 12% by weight.

The above described immediate release composition was prepared by the following process: The active ingredient, povidone, dicalcium phosphate dihydrate, and portions of the microcrystalline cellulose and sodium starch glycolate were mixed in a mixer-granulator (for example, a Littleford MGT) for approximately 5 minutes. Purified water was added while mixing until a suitable mass was obtained. The wet granules were passed through a cone mill fitted with an appropriate screen (e.g. 6.35 mm) and then were dried in a fluidized bed dryer set at an inlet temperature of approximately 65° C. to a loss on drying level of less than 2.5% w/w. The dried granules were then passed through a suitable mill fitted with an appropriate screen (e.g. #20 mesh in a hammer mill). The granulation was combined in a blender (e.g. V-blender) with lactose and the remainder of the microcrystalline cellulose and sodium starch glycolate and was blended for approximately 5 minutes. The magnesium stearate was passed through a suitable mill fitted with an appropriate screen (e.g. 40 mesh) and then was added to the dry granulated material and blended for approximately 3 minutes. The blended mixture was then compressed into tablets using conventional rotary compression equipment. The tablets were then film coated using conventional drum coating equipment with an aqueous suspension of the film coating constituents (i.e. hydroxypropyl methylcellulose, polyethylene glycol 400, yellow ferric oxide and titanium dioxide) at an inlet temperature of approximately 80° C.

What Is Claimed Is:

**1**. A sustained release formulation comprising a gelling agent and 11 -[4-[2-(2-hydroxyethoxy)ethyl]- 1 -piperazinyl]dibenzo-[b,f] [1,4]thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients.

**2**. A sustained release formulation according to claim **1** wherein the gelling agent is hydroxypropyl methylcellulose.

**3**. A sustained release formulation according to claim **2** comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by

weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof; with the proviso that if the formulation contains a hydroxypropyl methylcellulose described under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

**4**. A sustained release formulation according to claim **3** comprising about 5 to 40% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a)–(d) or mixtures thereof.

**5**. A sustained release formulation according to claim **4** comprising about 8 to 35% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a)–(d) or mixtures thereof.

**6**. A formulation according to claim **5** comprising about 10 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a)–(d) or mixtures thereof.

**7**. A formulation according to claim **6** comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a)–(d) or mixtures thereof.

**8**. A formulation according to claim **7** wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of microcrystalline cellulose, lactose, magnesium stearate, sodium citrate and povidone.

**9**. A formulation according to claim **8** wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of (a) about 4 to 20% by weight of microcrystalline cellulose, (b) about 5 to 20% by weight of lactose, (c) about I to 3% by weight of magnesium stearate, (d) about 10 to 30% by weight of sodium citrate and (e) about 1 to 15% by weight of povidone.

**10**. A formulation according to claim **1** wherein 11 -[4-[2-(2hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4] thiazepine is in the form of a hemifumarate salt.

**11**. A formulation according to claim **1** wherein one of the one or more pharmaceutically acceptable excipients is a pH modifier.

**12**. A formulation according to claim **11** wherein the pH modifier is sodium citrate.

**13**. A method of treating psychotic states or hyperactivity in a warm-blooded animal which comprises administering to said warm-blooded animal an effective amount of a formulation according to anyone of claims **1**–**12**.

**14**. A process for preparing a formulation according to anyone of claims **1** or **2** which comprises mixing 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[[b,f][1,4] thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent and other excipients.

**15**. A process for preparing a formulation according to anyone of claims **1** or **2** which comprises:

(a) mixing 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent and other excipients;

(b) wet granulating the mixed components;

(c) drying the mixture;

(d) milling the dried mixture;

(e) blending the mixture with a lubricant; and

(f) compressing the blended mixture to form tablets.

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