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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED, Plaintiffs, v. SANDOZ INC. Defendant.	Civil Action No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited (collectively, "AstraZeneca"), for their complaint against Defendant Sandoz Inc. ("Sandoz"), hereby allege as follows:

THE PARTIES

1. Plaintiff AstraZeneca Pharmaceuticals LP is a limited partnership organized under the laws of the State 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 Sandoz is a company incorporated under the laws of the State of Colorado, having its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

JURISDICTION AND VENUE

4. 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) and 1400(b).

CLAIM FOR RELIEF: THE '288 PATENT

5. AstraZeneca realleges paragraphs 1-4 above, as if set forth specifically here.

6. Plaintiff AstraZeneca UK Limited is the holder of New Drug Application ("NDA") No. 20-639 by which the United States Food and Drug Administration ("FDA") first

granted approval for 25, 50, 100, 150, 200, 300 and 400 mg tablets containing the active ingredient quetiapine (11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine) fumarate. These tablets, described in NDA No. 20-639, are prescribed and sold in the United States under the trademark SEROQUEL®.

7. AstraZeneca Pharmaceuticals LP is the owner of United States Patent No. 4,879,288 ("the '288 patent," copy attached 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®, and methods of using that compound.

8. The '288 patent received a Patent Term Extension under 35 U.S.C. § 156, thereby extending its term for a period of 1,651 days from March 20, 2007. At present, unless an additional extension is granted, the '288 patent will expire on September 26, 2011.

9. By a letter dated March 22, 2007, purporting to be a notice pursuant to 21 U.S.C. § 355 (j)(2)(B)(ii) (the "First Notice Letter"), Sandoz notified AstraZeneca that it had submitted Abbreviated New Drug Application ("ANDA") No. 78-679 to the FDA under 21 U.S.C. § 355(j), seeking the FDA's approval to commercially manufacture, use and sell quetiapine fumarate tablets in 25 mg strength as a generic version of the SEROQUEL® 25 mg product, prior to the expiration of the '288 patent. The First Notice Letter was addressed to AstraZeneca Pharmaceuticals and LP and AstraZeneca PLC, but not AstraZeneca UK Limited, the holder of NDA No. 20-639. On April 6, 2007, AstraZeneca filed a complaint against Sandoz in this Court for patent infringement based on the ANDA filing described in the First Notice Letter. That suit, Civil Action No. 3:07-cv-01632 (JAP)(TJB) ("the earlier action"), was

assigned to the Honorable Joel A. Pisano and Magistrate Tonianne J. Bongiovanni and consolidated with Civil Action No. 3:05-cv-05333 (JAP)(TJB). On July 9, 2008, a Final Judgment was entered in these actions in favor of AstraZeneca. Sandoz appealed that Final Judgment to the United States Court of Appeals for the Federal Circuit. That appeal is Docket Nos. 08-1480, -1481.

10. By a second letter dated February 18, 2009, purporting to be a notice pursuant to 21 U.S.C. § 355 (j)(2)(B) ("Second Notice Letter," copy attached as Exhibit B), Sandoz notified AstraZeneca that it had submitted an ANDA seeking the approval of the FDA to commercially manufacture, use and sell prior to the expiration of the '288 patent, quetiapine fumarate tablets in 50, 100, 150, 200, 300 and 400 mg strengths as generic versions of the SEROQUEL® 50, 100, 150, 200, 300 and 400 mg products, prior to the expiration of the '288 patent.

11. In its Second Notice Letter, Sandoz notified AstraZeneca that, as part of its ANDA No. 78-679, it had filed a certification of the type described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '288 patent.

12. In its Second Notice Letter, Sandoz alleged that the '288 patent is "unenforceable in view of inequitable conduct committed during the prosecution of the application that matured into the '288 patent." However, Sandoz did not allege in its Second Notice Letter that the quetiapine fumarate tablets that are the subject of its ANDA No. 78-679 will not infringe the '288 patent or that the '288 patent is invalid.

13. Sandoz has infringed the '288 patent under 35 U.S.C. § 271(e)(2)(A) by filing its ANDA No.78-679, seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in the '288 patent (or the use of which is claimed in

the ‘288 patent) prior to the expiration of the patent.

14. The quetiapine fumarate tablets for which Sandoz seeks approval in its ANDA No. 78-679 will infringe the ‘288 patent under 35 U.S.C. § 271(a).

15. The commercial manufacture, use, sale or offer for sale within the United States or the importation into the United States, of the quetiapine fumarate tablets for which Sandoz seeks approval in its ANDA No. 78-679 will infringe the ‘288 patent under 35 U.S.C. § 271.

16. 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 Sandoz’s ANDA No. 78-679 be a date that is not earlier than the later of September 26, 2011, the expiration date of the ‘288 patent, or the expiration of any other exclusivity to which AstraZeneca is or becomes entitled.

17. Sandoz was aware of the existence of the ‘288 patent and, upon information and belief, was aware that the filing of its ANDA and certification with respect to the ‘288 patent constituted an act of infringement of that patent.

18. Sandoz’s statement, in its Second Notice Letter, of the factual and legal bases for its opinion regarding the enforceability of the ‘288 patent is devoid of an objective good faith basis in either the facts or the law.

19. In its Second Notice Letter, Sandoz stated as follows:

> “The ‘288 patent is unenforceable in view of inequitable conduct committed during the prosecution of the application that matured into the ‘288 patent. Generally speaking, at the same time as it was mischaracterizing the prior art, the patent applicant was withholding information concerning the true state of the prior art, and thereby procured the ‘288 patent by inequitable conduct. Thus, the ‘288 patent is unenforceable and the Sandoz Product does not infringe any claim of the ‘288 patent. This is illustrated

> by AstraZeneca's predecessor-in-interest's argument to the patent examiner that the prior art references did not disclose that any compound was an atypical antipsychotic. This was not accurate, because the patent on fluperlapine effectively described it as an atypical antipsychotic. According to a published article, the inventors knew that fluperlapine had been reported to be an atypical antipsychotic."

This statement directly contradicts arguments advanced by Sandoz and its co-Defendant-Appellant, Teva, in *AstraZeneca Pharmaceuticals LP v. Teva Pharmaceuticals USA, Inc. et al.*, Docket Nos. 08-1480, -1481.

20. This case is 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 effective date of any approval of Sandoz's ANDA No. 78-679 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 September 26, 2011, the date of expiration or date of the '288 patent, or the expiration of any other exclusivity to which AstraZeneca is or becomes entitled;

(b) A judgment declaring that the '288 patent remains valid, enforceable, and has been infringed by Sandoz;

(c) A permanent injunction against any infringement of the '288 patent by Sandoz, its officers, agents, attorneys, and employees, and/or those acting in privity or concert with Sandoz;

(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 Sandoz has committed any acts with respect to the subject matter claimed in the '288 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 26, 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)

ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED v. ACCORD HEALTHCARE, INC., ACCORD HEALTH CARE, INC., ACCORD HEALTHCARE LTD., AND INTAS PHARMACEUTICAL LTD., 09-0619 (District of New Jersey)

Dated: February 26, 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

[56] **References Cited**

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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

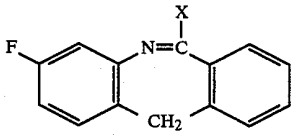
NOVEL DIBENZOTHIAZEPINE ANTIPSYCHOTIC

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.

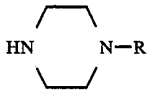
Previous attempts at finding compounds useful in a variety of applications have included U.S. Pat. No. 3,539,573 to Schmutz et al. which discloses selected dibenzothiazepines and dibenzodiazepines as being useful for a variety of medical conditions including as neuroleptic-antidepressants, or neuroleptics. 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



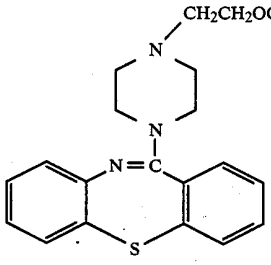
Ia

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

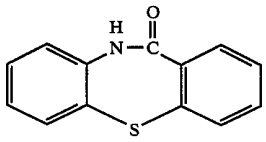
This invention is a compound of formula II:



II

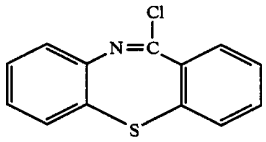
and salts thereof, for example and especially pharmaceutically acceptable salts. Such a compound is useful because of its antidopaminergic activity, for example, as an antipsychotic agent or as a treatment for hyperactivity. Such a compound is of even greater interest in that it may be used as an antipsychotic 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:



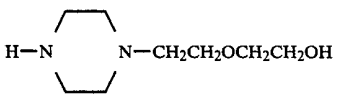
III

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

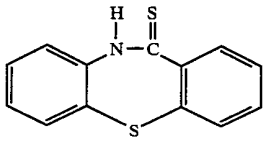
The imino chloride of formula IV may also be generated with other agents such as thionyl chloride or phosphorous pentachloride. The imino chloride is then reacted with 1-hydroxyethoxyethylpiperazine of formula V:



V

to give the compound of formula II.

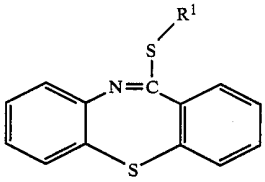
Alternatively, one may convert the lactam of formula III into a thiolactam of formula VI:



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).

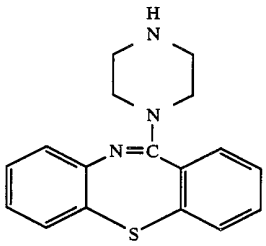
The lactam of formula VI may then be converted into a thioether of formula VII:



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.

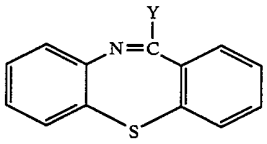
If desired the compound of formula XII may be employed in the form of a salt, but where such a salt is used it is neutralized to afford the corresponding free base prior to reaction with the compound of formula XIII, for example, by in situ neutralization. Such neutralization is advantageously conducted 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:

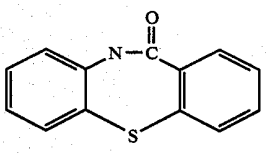


XIV

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.

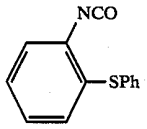
The compounds of formula XIV may, for example, be prepared by methods analogous to those known in the art or, where Y represents halogen, preferably by reacting dibenzo[b,f][1,4]-thiazepine11(10-H)one of formula XV:



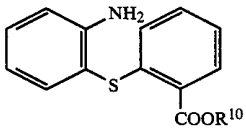
XV

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.

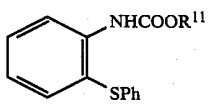
The compound of formula XV may, for example, be prepared according to methods known in the art, for example, by the method disclosed by J. Schmutz et al. *Helv. Chim Acta,* 48: 336 (1965). Preferably the compound of formula XV is prepared by cyclizing a compound selected from compounds of the formulae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

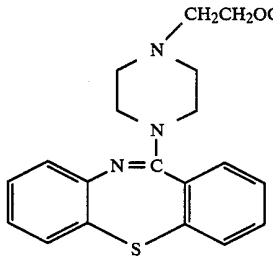
Tablets:
Each tablet contains:

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
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

SANDOZ

Srinivasa S. Rao, Pharm.D.
Director
Regulatory Affairs

Sandoz Inc.
506 Carnegie Centre
Suite 400
Princeton, NJ 08540
Tel: 609-627-8885 (Direct)
Fax: 609-395-2792

2/18/09

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, Delaware 19803

AstraZeneca PLC
15 Stanhope Gate
W1K 1LN
London, England

Attn: Legal Counsel

Re: **Notice of Certification Under 21 U.S.C. § 355(j)(2)(B) (§ 505(j)(2)(B)) of Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95**
Sandoz, Inc.'s Quetiapine Fumarate Oral Tablets, 50, 100, 150, 200, 300 and 400 mg
Sandoz, Inc.'s ANDA 78-679

Dear Sir or Madam:

Sandoz, Inc. ("Sandoz") of 506 Carnegie Center, Suite 400, Princeton, NJ 08540, U.S.A., hereby gives notice to the NDA holder and/or listed patent owner for the reference listed drug that the FDA has received an Abbreviated New Drug Application ("ANDA") for SEROQUEL® brand quetiapine fumarate, 50, 100, 150, 200, 300 and 400 mg ("the Sandoz Product"), which contains data or information from required bioequivalence and/or bioavailability studies.

The FDA has assigned the Sandoz ANDA the number 78-679.

Sandoz, by submitting its ANDA, seeks to obtain approval to engage in commercial manufacture, use and sale of the Sandoz Product prior to the expiration of the following U.S. Patent ("Listed Patent"), which is/are listed in *Approved Drug Products with Therapeutic Equivalence Evaluation* (the "Orange Book") as having the indicated expiration date:

Patent No.	Patent Owner	Patent Expiry
4,879,288	AstraZeneca Pharmaceuticals LP	Sep 26, 2011

The purpose of this communication is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and/or (ii) (Sections 505(j)(2)(B)(i) and/or (ii) of the Food, Drug and Cosmetics Act) and to inform you that the Sandoz ANDA contains a certification under 21 U.S.C. §355(j)(2)(A)(vii)(IV), which asserts that the claims of the above-listed U.S. Patent(s) are invalid, unenforceable, and/or will not be infringed by the manufacture, use, importation, sale or offer for sale of the Sandoz Product.

A Detailed Statement of the factual and legal basis for Sandoz's opinion that the Listed Patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Sandoz Products is attached hereto.

Offer for Confidential Access

An Offer of Confidential Access to relevant sections of the Sandoz ANDA pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III) is attached hereto.

Anticompetitive Behavior Warning

Please be warned of the following. It is an antitrust violation to assert a patent known not to be infringed. *Loctite v. Ultraseal*, 781 F.2nd 861 (Fed. Cir. 1985). As such, the attached Detailed Statement has outlined in the necessary detail that your patents are not, and cannot be, infringed by the subject matter described in the Sandoz ANDA. As such, your pursuit of an infringement action may be deemed to be an antitrust violation. In addition, it is an antitrust violation to assert a patent known not to be valid. *Handgards v. Ethicon*, 601 F.2nd 986 (9th Cir. 1979). If you launch any patent infringement lawsuit, either now or later, Sandoz may pursue the appropriate remedies against you, including seeking fees, costs, and sanctions for potential violations of Rule 11 (of the Civil Procedure Rules), exceptional case and frivolous suit statutes under the patent laws, and for violations of the antitrust laws, plus any remedy the court deems fit to award.

Reservation of Legal Rights

We reserve the right to allege the same, similar, different or new theories of non-infringement and/or invalidity and nothing in this Notice Letter or Detailed Statement shall be construed as to limit our rights to make any allegation in any subsequent litigation regarding any issue.

Relevant Contact Information

If you have any inquiries concerning this notice or for any service of process or legal information, please contact:

Stephen R. Auten, Esq.
c/o Sandoz Inc.
506 Carnegie Center
Suite 400
Princeton, NJ 08540
(609) 627-8500
(609) 627-8636

Very truly yours,

S. [signature] 2/18/09

Srinivasa S. Rao, Pharm.D.
Director, Regulatory Affairs
Sandoz Inc.

Attachment:

1. Detailed Statement

SANDOZ, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES FOR ITS OPINION THAT U.S. PATENT NO. 4,879,288 IS UNENFORCEABLE, INVALID OR NOT INFRINGED BY THE MANUFACTURE, USE, IMPORTATION, SALE OR OFFER FOR SALE OF THE SANDOZ PRODUCT.

The following constitutes Sandoz's detailed statement of the factual and legal basis for its belief that U.S. Patent No. 4,879,288 is unenforceable, invalid or not infringed by the manufacture, use, sale or offer for sale of Sandoz's quetiapine fumarate oral tablets, 50, 100, 150, 200, 300 and 400 mg (the "Sandoz Product").

Please be advised that Sandoz considers the information in this statement to be confidential, is disclosing this information solely to comply with 21 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.95, and requests that this information be protected from disclosure to third parties by means consistent with its own standards for protecting its own confidential information. THIS CONFIDENTIALITY APPLIES TO THIS STATEMENT, WHICH MAY NOT, AND SHOULD NOT, BE ATTACHED TO ANY COMPLAINT OR OTHER PUBLICLY AVAILABLE DOCUMENT. *See Biovail Labs., Inc. v. Anchen Pharms., Inc.*, 463 F. Supp. 2d 1073, 1083 (C.D. Cal. 2006).

I. THE SANDOZ PRODUCT

The Sandoz Product is quetiapine fumarate oral tablets, 50, 100, 150, 200, 300 and 400 mg.

II. FACTUAL AND LEGAL BASIS FOR UNENFORCEABILITY, NONINFRINGEMENT AND/OR INVALIDITY

A. Inequitable Conduct

Every applicant for patent has a duty of candor to the U.S. Patent and Trademark Office, which duty is enforced by the defense of inequitable conduct that renders all claims unenforceable if the duty has not been upheld. *J.P. Stevens & Co., Inc. v. Lex Tex, Ltd., Inc.*, 747 F.2d 1553 (Fed. Cir. 1984) (en banc). To establish the defense of inequitable conduct, an accused infringer must demonstrate either a material misrepresentation or material omission, made with an intent to deceive the patent examiner. *See, e.g., Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359 (Fed. Cir. 2007).

B. Non-Infringement

The first step in the assessment of patent infringement is to construe the claim terms, which is a matter of law for the court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). Whether a product infringes a claim requires a two-step analysis. First, the claims must be interpreted. Second, the properly-interpreted claims must be compared to the accused product. *Markman*, 570 U.S. at 384-5; *Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558 (Fed. Cir. 1996). To literally infringe a claim, the accused product must practice every limitation in the claim. *Texas Instrum.*, 90 F.3d at 1563.

A product may infringe a patent under the doctrine of equivalents if it contains elements equivalent to each claimed element of the patented invention. Depending upon the facts of a given case, such element-by-element equivalency may be established by proof of insubstantial differences in the role played by elements of the claim and the accused product, or by proof that an accused element performs substantially the same function, in substantially the same way, to produce substantially the same result as the claimed element of the patented invention. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); see also *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605 (1950).

The doctrine of equivalents is also subject to the ancillary doctrine of prosecution history estoppel, which acts to limit infringement by otherwise equivalent products or processes. *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211 (Fed. Cir. 1995).

Furthermore, the doctrine of equivalents is constrained by the prior art. *Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677 (Fed. Cir. 1990). The doctrine does not permit a patent claim to encompass subject matter that could not have been patented. *Id.* at 684. ("[A] patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims."); *see also Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570 (Fed. Cir. 1995) (the doctrine of equivalents does not permit coverage of obvious or "trivial" variations of the prior art).

C. Invalidity

A patent is presumed valid. 35 U.S.C. § 282. This presumption places the burden of persuasion on the party challenging validity. *Smithkline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 885 (Fed. Cir. 1988). "[T]he presumption is one of law, not fact, and does not constitute 'evidence' to be weighed against a challenger's evidence." *Avia Group Int'l, Inc. v. L.A. Gear Calif., Inc.*, 853 F2d 1557, 1562 (Fed. Cir. 1988). The burden is "especially difficult" when the party asserting invalidity relies only upon prior art that was considered by the PTO. *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990). "Where the PTO has considered a piece of prior art, and issued a patent notwithstanding that prior art, a court owes some deference to the PTO's decision." *Minnesota Mining and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1572 (Fed. Cir. 1992) (citation omitted). Even in such a case, the presumption can be overcome if the party challenging validity establishes invalidity by clear and convincing evidence. *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1096 (Fed. Cir. 1985).

i. Anticipation

Invalidity of a patent claim may be established under the legal doctrine of anticipation. 35 U.S.C. § 102. A determination that a claimed invention is anticipated requires a showing that each feature (element) of a claim is found, either expressly or under principles of inherency, in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device, product, or method. *Electro Med. Sys. S.A. v. Cooper Life,* 34 F.3d 1048 (Fed. Cir. 1994); *Minnesota Mining & Mfg. Co.*, 976 F.2d 1at 1565. A feature is inherent in a prior art reference when it naturally (and always) occurs as a consequence of following the teachings of the reference. *Schering Corp. v. Geneva Pharms. Inc.,* 339 F.3d 1373 (Fed. Cir.

2003). Additional references may be relied upon to explain terminology in the anticipating reference (*In re Baxter Travenol Labs.*, 952 F.2d 388 (Fed. Cir. 1991)), to show that the anticipating reference is enabling (*In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985)), or to show that a characteristic not disclosed expressly in the reference is nonetheless inherent. *Schering Corp.*, 339 F.3d at 1379.

ii. Obviousness

A patent is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The following inquiries are pertinent to resolving this issue: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the difference between the prior art and the claims at issue. *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 17 (1966). Obviousness is not determined in hindsight in view of the invention in question. Instead, prior art is considered by the hypothetical artisan at a time just before the invention was made. *Al-Site Corp. v. VSI Int'l*, 174 F.3d 1308, 132 (Fed. Cir. 1999).

A reference must be considered for all that is taught—disclosures that diverge and teach away from the invention as well as disclosures that point toward and teach the invention. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). A reference teaches away if it would have led a person skilled in the art in a direction different from that taken by the inventor. *Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 885 (Fed. Cir. 1998). "The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by" the inventor. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). It is impermissible to select only those portions of a reference that support a given position and exclude other parts necessary to the full appreciation of what the reference fairly teaches. *Bausch & Lomb, Inc. v. Barnes-Hind*, 796 F.2d 443, 448 (Fed. Cir. 1986).

The United States Supreme Court has clarified certain aspects of the obviousness analysis, particularly with respect to the Federal Circuit's requirement that there be a "teaching suggestion, or motivation" to combine the teachings of two or more separate references. In *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007), the Court expressly rejected a rigid requirement for a motivation to combine, stating:

> [t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.

KSR, 127 S.Ct. at 1741. The Court further stated:

> [i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee

> controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under §103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

KSR, 127 S.Ct. at 1741-42. Instructing that the obviousness analysis should not be limited by looking only at the problem that the patentee was trying to solve, the Court stated:

> [t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR, 127 S.Ct. at 1742. The Court noted that in some instances, the fact that it may have been "obvious to try" to make a claimed invention may be dispositive:

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

Id.

When examining the obviousness of a compound and/or a method of using that compound, structural similarity alone may be sufficient to give rise to an expectation that two compounds with similar structures will have similar properties. *In re Merck*, 800 F.2d 1091 (Fed. Cir. 1986), (citing *In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979)). Structural similarity between a claimed compound and prior art compounds creates a *prima facie* case of obviousness. *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990). The burden then falls on an applicant to rebut that *prima facie* case. *Id.* at 693. A rebuttal or counter-argument can consist of test data showing that the claimed compounds possess unexpectedly improved properties from the prior art compounds. All evidence of the properties of the claimed and prior art compounds must be considered in determining the ultimate question of patentability.

The "discovery," however, that the claimed compound possesses a property not disclosed in the prior art does not by itself defeat a *prima facie* case. *In re Dillon*, 919 F.2d at 693. *See also, In re Merck*, 800 F.2d at 1099, where the Federal Circuit stated:

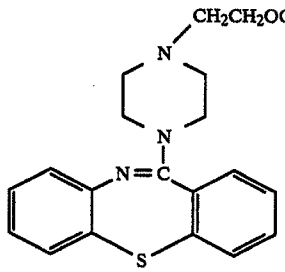
> [t]he core of it is that, while there are some differences in degree between the properties of amitrptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable

> degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the *prima facie* case.

Evidence of secondary considerations, if present, must be considered in determining obviousness, but there must be a nexus between such evidence and the merits of the claimed invention. *Graham*, 383 U.S. at 17. The existence of such evidence, however, does not control the obviousness determination. *Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). Examples of secondary considerations are commercial success, copying, prior failure of others, licenses under the patent, a long-standing need for the invention, unexpected results, skepticism by others in the art, and contemporaneous development by others. *Graham*, 383 U.S. at 17-18; *DMI, Inc.*, 802 F.2d at 425. Commercial success is not a relevant factor in determining obviousness where others were legally barred from practicing the invention. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

III. U.S. PATENT NO. 4,879,288

The '288 patent, entitled "Novel Dibenzothiazepine Antipsychotic", issued November 7, 1989. The '288 patent issued from U.S. Application Serial No. 07/028,473, filed March 20, 1987, and claims the benefit of Great Britain Application Serial No. 8607684, filed March 27, 1986. The '288 patent has 8 claims, one of which is an independent claim. Independent claim 1 reads as follows:

> 1. A compound of formula II
>
> 
>
>
> and acid additional salts thereof.

Dependent claims 2-4 add various limitations on the type of salt. Specifically, claim 4 limits the salt to a hydrochloride salt. Dependent claims 5-8 add various limitations to the use of the compound in claim 1. Specifically, claim 6 limits the use of the compound in claim 1 to managing a psychotic condition. Claim 8 limits the use of the compound in claim 1 to treating hyperactivity.

According to the specification of the '288 patent, compounds used as antipsychotic agents and neuroleptics had been plagued by the problems of undesired side effects, which include acute dyskinesias, acute dystonias, motor restlessness, pseudo-Parkinsonism, and tardive dyskinesias. Col. 1, lines 10-22. To overcome these problems, the patent discloses the compound of formula II (quetiapine) that is useful as an antipsychotic agent with substantial reduction in side effects in humans. Col. 2, lines 18-27.

Example 9 describes a test for predicting whether a potential psychotic drug will produce dyskinetic side effects in humans. Col. 11, lines 1-59. The claimed compound, clozapine, thioridazine, and haloperidol were tested. The known dyskinetic drugs, haloperidol and thioridazine, produced a dyskinetic reaction lasting several hours and were of moderate to high intensity. The claimed compound "exhibited markedly fewer dyskinetic and dystonic reactions" compared with the haloperidol and thioridazine. Col. 11, lines 27-30. In addition to causing fewer reactions, the intensity of the reactions produced by the claimed compound was also less. Clozapine did not produce any dyskinetic reaction.

B. The '288 Patent's Prosecution History

As originally filed, U.S. Application Serial No. 07/028,473 had 10 claims. The Examiner required a restriction and a provisional election was made, narrowing the claims to 8. In an Office Action mailed April 15, 1988, the Examiner rejected claims 1-8 under 35 U.S.C. § 103 as unpatentable over U.S. Patent No. 3,539,573 ("Schmutz") in view of U.S. Pat. No. 3,459,745 ("Fouche II") and others. According to the Examiner the Schmutz reference taught compounds of "virtually identical structure" to the compound of the claimed invention, the only difference being a side chain. Secondary references such as Fouche II taught the interchangeability of the side chain disclosed in Schmutz for the side chain of the claimed compound. The Examiner stated that applicants have "simply made a modification known in 5 other tricyclic ring systems and done it on a 6^{th}." One skilled in the art would have realized that this is a conventional modification, and when the modification was made to the compounds of Schmutz, the claimed compound would result.

Claims 1-8 were also rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,097,597 ("Horrom") in view of Schmutz, among others. In Horrom, the closest prior art was example 1, which differed from the claimed compound in that it was a diazepine rather than a thiazepine. But secondary references taught the precise equivalence. The Examiner also made rejections on other prior art.

In an Amendment dated October 17, 1988, applicants argued that the claimed compound was an "atypical antipsychotic," i.e., 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. Schmutz and Fouche II were characterized as describing only tests of "typical" antipsychotic activity. Moreover, the atypical properties of the prior art compound, clozapine, were described as having been discovered only in clinical testing. The use of clozapine, a clinically effective atypical antipsychotic, was further described as having been severely limited due to an associated, sometimes fatal side effect, agranulocytosis. Therefore, with these and other arguments, the applicants argued that the discovery of an "atypical antipsychotic" was not obvious in view of the prior art.

In a final Office Action mailed December 2, 1988, the Examiner again rejected pending claims 1-8 as being obvious over Horrom in view of references such as Schmutz. Claims 1-8 were also rejected under 35 U.S.C. § 103 over Schmutz in view of Fouche II, among other

references. The Examiner emphasized that *prima facie* obviousness had clearly been demonstrated. Only very small differences separated the claims from prior art compounds exemplified in Schmutz and Horrom. The Examiner stated that once a *prima facie* case of obviousness had been made, it must be overcome by a side-by-side comparison with the closest art compound(s).

In response to this final rejection, the applicant provided test data on two compounds exemplified in Schmutz and on the compound described in Example 1 of Horrom. The test data showed that the claimed compound was active and exhibited a substantially reduced probability for inducing dyskinesias in humans, unlike the prior art compounds. Applicants concurrently filed a Notice of Appeal that was received by the USPTO on May 4, 1989. A telephone interview occurred on May 12, 1989. On May 22, 1989, a Notice of Allowance was mailed. Neither the telephonic interview summary nor the Notice of Allowance provided any reasons for the allowance.

C. The '288 Patent Is Unenforceable

The '288 patent is unenforceable in view of inequitable conduct committed during the prosecution of the application that matured into the '288 patent. Generally speaking, at the same time as it was mischaracterizing the prior art, the patent applicant was withholding information concerning the true state of the prior art, and thereby procured the '288 patent by inequitable conduct. Thus, the '288 patent is unenforceable and the Sandoz Product does not infringe any claim of the '288 patent. This is illustrated by AstraZeneca's predecessor-in-interest's argument to the patent examiner that the prior art references did not disclose that any compound was an atypical antipsychotic. This was not accurate, because the patent on fluperlapine effectively described it as an atypical antipsychotic. According to a published article, the inventors knew that fluperlapine had been reported to be an atypical antipsychotic.

Furthermore, AstraZeneca is aware of the basis for Sandoz' belief that the '288 patent is unenforceable, because it has been detailed in briefs served by Sandoz on AstraZeneca in a case now pending before the U.S. Court of Appeals for the Federal Circuit. This case bears the caption *AstraZeneca Pharmaceuticals LP et al. v. Teva Pharmaceuticals USA, Inc. et al.*, Docket Nos. 2008-1480, -1481.

SUMMARY

For the reasons stated above, all of the claims of U.S. Patent No. 4,879,288 are unenforceable against the manufacture, use, or sale of the Sandoz Product.

S. Rao 2/18/09

Srinivasa S. Rao, Pharm.D.
Director, Regulatory Affairs
Sandoz Inc.