IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

OSI PHARMACEUTICALS, LLC and GENENTECH, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. _____
APOTEX INC. and APOTEX CORP.,	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs OSI Pharmaceuticals, LLC ("OSI"), and Genentech, Inc. ("Genentech") (collectively, Plaintiffs), by their undersigned attorneys, bring this action against Defendants Apotex Inc., and Apotex Corp., (collectively, "Apotex"), for patent infringement and allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement under the patent laws of the United States, Title 35 of the United States Code, arising from Apotex's filing an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of OSI's Tarceva® prior to the expiration of United States Patent No. 6,900,221 ("the '221 patent") that covers that product and its use.

THE PARTIES

2. Plaintiff OSI is a limited liability company organized and existing under the laws of the State of Delaware, with a principal place of business at 1 Astellas Way, Northbrook, IL 60062.

3. Plaintiff Genentech is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business located at 1 DNA Way, South San Francisco, California 94080-4990.

4. On information and belief, Defendant Apotex Inc. is a corporation existing under the laws of Canada, with its principal place of business at 150 Signet Drive, Toronto, Ontario M9L1T9, Canada.

5. Upon information and belief, acting in concert with Defendant Apotex Corp., Apotex Inc. is in the business of developing, manufacturing, and marketing generic pharmaceutical products that are distributed and sold throughout the United States and in the State of Delaware.

6. On information and belief, Apotex Corp. is a corporation existing under the laws of Delaware, with its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

7. Upon information and belief, acting in concert with Defendant Apotex Inc., Apotex Corp. is in the business of developing, manufacturing, and marketing generic pharmaceutical products that are distributed and sold throughout the United States and in the State of Delaware. Upon information and belief, Apotex Corp. is also the United States agent for Apotex Inc. for purposes including, but not limited to, filing ANDA submissions to and corresponding with FDA.

8. Upon information and belief, Apotex Corp. is a wholly owned affiliate of Apotex Inc. Upon information and belief, Apotex Corp. acts at the direction of, under the control of, and for the direct benefit of Apotex Inc. and is controlled and/or dominated by Apotex Inc.

JURISDICTION AND VENUE

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

10. Venue is proper in this District under 28 U.S.C. § 1391(b), (c), (d), and 28 U.S.C. § 1400(b).

Apotex Inc.

11. On information and belief, this Court has personal jurisdiction over Apotex Inc., which develops, manufactures, seeks regulatory approval for, markets, distributes, and sells generic pharmaceuticals for sale and use throughout the United States, including in the State of Delaware.

12. On information and belief, residents of the State of Delaware purchase pharmaceutical drug products from Apotex Inc. in the State of Delaware.

13. On information and belief, Apotex Inc., itself or through one of its wholly-owned subsidiaries, has authorized distributors in the State of Delaware to distribute Apotex's pharmaceutical drug products throughout the State of Delaware.

14. On information and belief, Apotex Inc.'s submission of ANDA No. 208396, discussed below, indicates its intention to engage in the commercial manufacture, use, sale and/or importation of products that will compete directly with OSI's TARCEVA® product, which is currently being sold throughout the United States, including in Delaware.

15. This Court has personal general jurisdiction over Apotex Inc. by virtue of, *inter alia*, its having conducted business in this District, having availed itself of the rights and benefits of Delaware law, and having engaged in substantial and continuing contacts with Delaware.

Upon information and belief, Apotex Inc. has regular and continuous commercial business dealings with representatives, agents, distributors, and customers located in Delaware.

16. Over the last ten years, Apotex Inc. has been a party to numerous other ANDA-related patent suits in the District of Delaware.

17. In addition, Apotex Inc. has submitted to the jurisdiction of this Court and has previously availed itself of this Court by filing suit in this jurisdiction and/or by asserting civil actions and counterclaims initiated in this jurisdiction. *See, e.g.*, *Apotex, Inc. et al v. Senju Pharmaceutical Co.*, C.A. No. 12-196-SLR (D. Del. Feb. 16, 2012).

18. In the alternative, should Apotex Inc. contest jurisdiction in this forum, this Court has personal jurisdiction over Apotex Inc. under Fed. R. Civ. P. 4(k)(2) because, on information and belief, Apotex Inc. "is not subject to jurisdiction in any state's courts of general jurisdiction," and because "exercising jurisdiction is nevertheless consistent with the United States Constitution and laws" given that Apotex Inc. has filed the ANDA in the United States for a generic product that it intends to market in the United States.

Apotex Corp.

19. This Court has personal jurisdiction over Apotex Corp. by virtue of the fact that, *inter alia*, Apotex Corp. is incorporated under the laws of the state of Delaware.

20. Upon information and belief, Apotex Corp. develops, manufactures, seeks regulatory approval for, markets, distributes, and sells generic pharmaceuticals for sale and use throughout the United States, including in the State of Delaware.

21. This Court has personal specific jurisdiction over Apotex Corp. because Apotex Corp. has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement, including upon information and belief, by acting as

Apotex Inc.'s agent with respect to ANDA filings, such as ANDA No. 208396. In particular, on information and belief, Apotex Corp. collaborated with Apotex Inc. to develop, manufacture, and seek approval for erlotinib hydrochloride tablets 25 mg, 100 mg and 150 mg ("Apotex's Proposed Generic Products"), which will cause tortious injury to Plaintiffs.

THE PATENTS-IN-SUIT

22. On May 31, 2005, the USPTO duly and lawfully issued the '221 patent, entitled "Stable Polymorph on N-(3-Ethynylphenyl)-6, 7-Bis(2MethoxyEthoxy)-4-Quinazolinamine Hydrochloride, Methods of Production, and Pharmaceutical Uses Thereof to inventors Timothy Norris, Jeffrey W. Raggon, Richard D. Connell, James D. Moyer, Michael J. Morin, Shama M. Kajiji, Barbara A. Foster, Karen J. Ferrante, and Sandra L. Silberman. A copy of the '221 patent is attached hereto as Exhibit A.

23. OSI is the owner of the '221 patent and Genentech is a co-exclusive licensee of the '221 patent.

THE TARCEVA® DRUG PRODUCT

24. OSI holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for erlotinib hydrochloride tablets (NDA No. 021743), which it sells under the trade name Tarceva®. The claims of the '221 patents cover, *inter alia*, Tarceva® and its method of use.

25. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '221 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Tarceva®.

ACTS GIVING RISE TO THIS SUIT

26. Pursuant to Section 505 of the FFDCA, Apotex filed an ANDA for erlotinib hydrochloride tablets, seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of erlotinib hydrochloride tablets 25 mg, 100 mg and 150 mg ("Apotex's Proposed Generic Products"), before the patent in suit expires. The Apotex ANDA number is 208396.

27. On information and belief, in connection with the filing of its ANDA as described in the preceding paragraph, Apotex has provided written certifications to the FDA, as called for by Section 505 of the FFDCA, which allege that the claims of the '221 patent are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use or sale of Apotex's Proposed Generic Products.

28. No earlier than July 20, 2015, Apotex sent written notice of its ANDA filing to OSI. The notice alleged that the '221 patent is invalid, unenforceable, and/or will not be infringed by Apotex. Apotex's notice also informed OSI that Apotex seeks approval to market erlotinib hydrochloride tablets 25 mg, 100 mg and 150 mg before the patent in suit expires.

29. This action is being brought pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) within 45 days of OSI's receipt of Apotex's notice.

COUNT 1: APOTEX'S FILING OF THE ANDA INFRINGES THE '221 PATENT

30. Plaintiffs reallege and incorporate by reference the allegations contained in paragraphs 1-29.

31. Apotex's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale or importation of Apotex's Proposed Generic Products,

prior to the expiration of the '221 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

32. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex will infringe the '221 patent by making, using, offering to sell, importing, and selling Apotex's Proposed Generic Products in the United States, and by actively inducing and contributing to infringement by others.

33. There is a justiciable controversy between the parties hereto as to infringement of the '221 patent.

34. Plaintiffs will be substantially and irreparably damaged and harmed if Apotex's infringement of the '221 patent is not enjoined.

35. Plaintiffs do not have an adequate remedy at law.

36. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs OSI and Genentech respectfully request that the Court enter judgment against Apotex and for the following relief:

a. A declaration that, under 35 U.S.C. § 271(e)(2)(A), Apotex infringed the '221 patent by submitting ANDA No. 208396 to the FDA to obtain approval to commercially manufacture, use, offer for sale, sell or import into the United States Apotex's Proposed Generic Products prior to expiration of the '221 patent;

b. A judgment declaring that Apotex's manufacture, sale, offer for sale, marketing and distribution in, or importation into, the United States of the product described in

Apotex's ANDA No. 208396 prior to expiration of the '221 patent will infringe, induce infringement and contribute to the infringement of at least one claim of the '221 patent;

c. A judgment pursuant to 35 U.S.C.§ 271(e)(4)(B) and/or 35 U.S.C. § 283 for a permanent injunction enjoining the Apotex, its officers, agents, servants, employees, and those persons acting in active concert or participation with all or any of them from: (i) manufacturing, using, offering to sell, or selling the Apotex Proposed Generic Products within the United States, or importing the Apotex Proposed Generic Products into the United States, prior to the expiration of the '221 Patent, and (ii) seeking, obtaining or maintaining approval of the Apotex Proposed Generic until expiration of the '221 patent or any later expiration of exclusivity to which Plaintiffs are or become entitled, or such other later time as the Court may determine;

d. A judgment ordering that pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 205943 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the '221 patent or any later expiration of exclusivity to which Plaintiffs are or become entitled;

e. If Apotex manufactures, uses, offers to sell, or sells the Apotex Proposed Generic Products within the United States, or imports the Apotex Proposed Generic Products into the United States, prior to the expiration of the '221 patent, including any extensions, a judgment awarding Plaintiffs monetary relief including damages no less than a reasonable royalty and an accounting together with interest;

f. A declaration that this is an exceptional case action within the meaning of 35 U.S.C. § 285 and that Plaintiffs be awarded their attorneys' fees, costs and expenses incurred in prosecuting this action; and

g. Such other and further relief as the Court deems just and appropriate.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)
Maryellen Noreika (#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
jblumenfeld@mnat.com
mnoreika@mnat.com

Attorneys for Plaintiffs

OF COUNSEL:

Leora Ben-Ami
Peter B. Silverman
KIRKLAND & ELLIS LLP
601 Lexinton Avenue
New York, NY 10022
(212) 446-4000

Amanda Hollis
KIRKLAND & ELLIS LLP
300 N. LaSalle
Chicago, IL 60654
(312) 862-2011

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EXHIBIT A

US006900221B1

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

(10) **Patent No.: US 6,900,221 B1**
(45) **Date of Patent: May 31, 2005**

(54) **STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6, 7-BIS (2METHOXYETHOXY) -4-QUINAZOLINAMINE HYDROCHLORIDE, METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF**

(75) Inventors: **Timothy Norris**, Gales Ferry, CT (US); **Jeffrey W. Raggon**, North Stonington, CT (US); **Richard D. Connell**, East Lyme, CT (US); **James D. Moyer**, East Lyme, CT (US); **Michael J. Morin**, Waterford, CT (US); **Shama M. Kajiji**, Mystic, CT (US); **Barbara A. Foster**, Mystic, CT (US); **Karen J. Ferrante**, East Greenwich, RI (US); **Sandra L. Silberman**, Randolph, NJ (US)

(73) Assignee: **OSI Pharmaceuticals, Inc.**, Melville, NY (US)

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

(21) Appl. No.: **09/711,272**

(22) Filed: **Nov. 9, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/206,420, filed on May 23, 2000, provisional application No. 60/193,191, filed on Mar. 30, 2000, and provisional application No. 60/164,907, filed on Nov. 11, 1999.

(51) **Int. Cl.**[7] **C07D 239/94**; A61K 31/517; A61P 35/00

(52) **U.S. Cl.** **514/266.4**; 544/293

(58) **Field of Search** 544/293; 514/266.4

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Primary Examiner—Thomas C. McKenzie
(74) *Attorney, Agent, or Firm*—John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

The present invention relates to a stable crystalline form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph, its production in essentially pure form, and its use. The invention also relates to the pharmaceutical compositions containing the stable polymorph B form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine as hydrochloride, as well other forms of the compound, and to methods of treating hyperproliferative disorders, such as cancer, by administering the compound.

79 Claims, 4 Drawing Sheets

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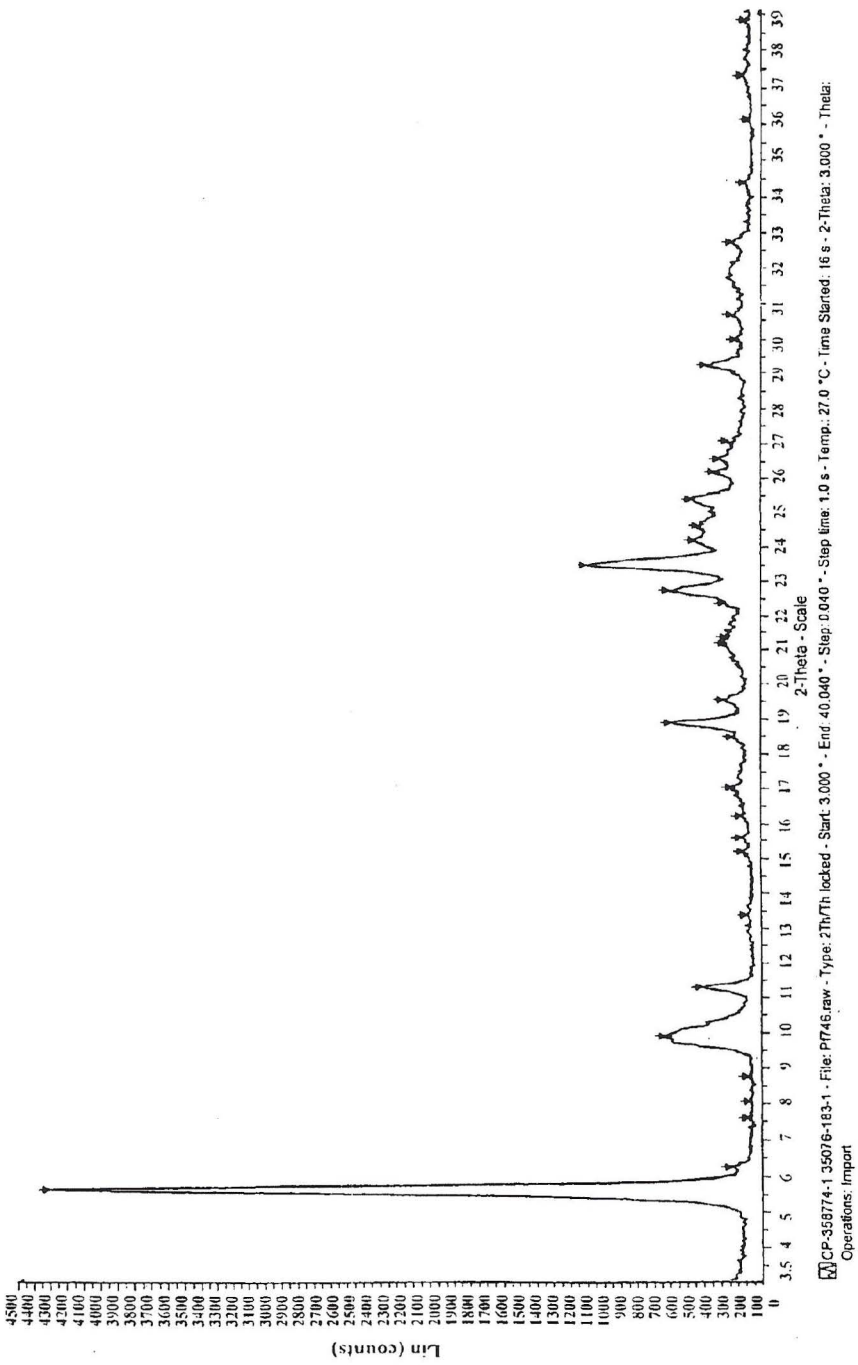
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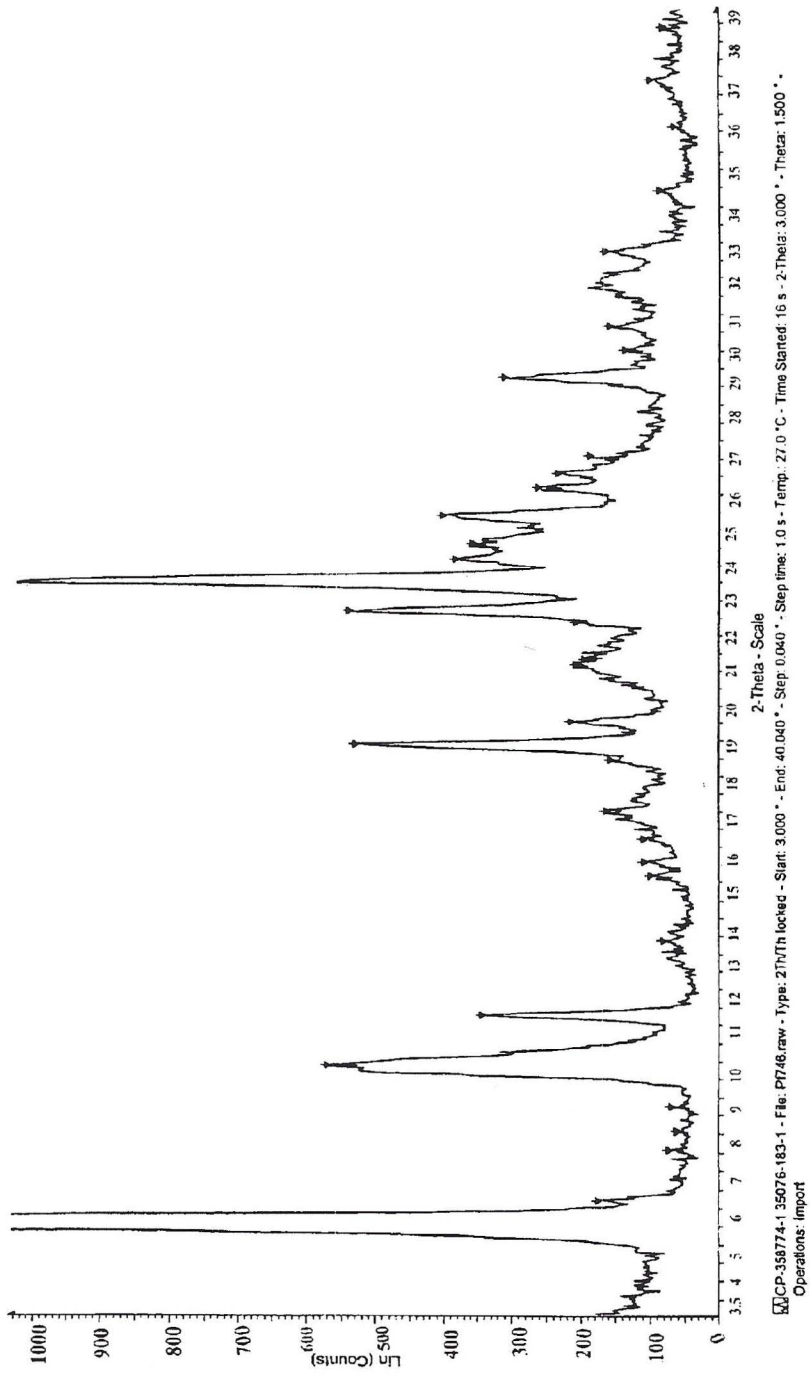
FIGURE 1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3.5 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
2-Theta - Scale
CP-358774-1 35076-183-1 - File: P1748.raw - Type: 2Th/Th locked - Start: 3.000 ° - End: 40.040 ° - Step: 0.040 ° - Step time: 1.0 s - Temp.: 27.0 °C - Time Started: 16 s - 2-Theta: 3.000 ° - Theta: 1.500 ° -
Operations: Import

FIGURE 2

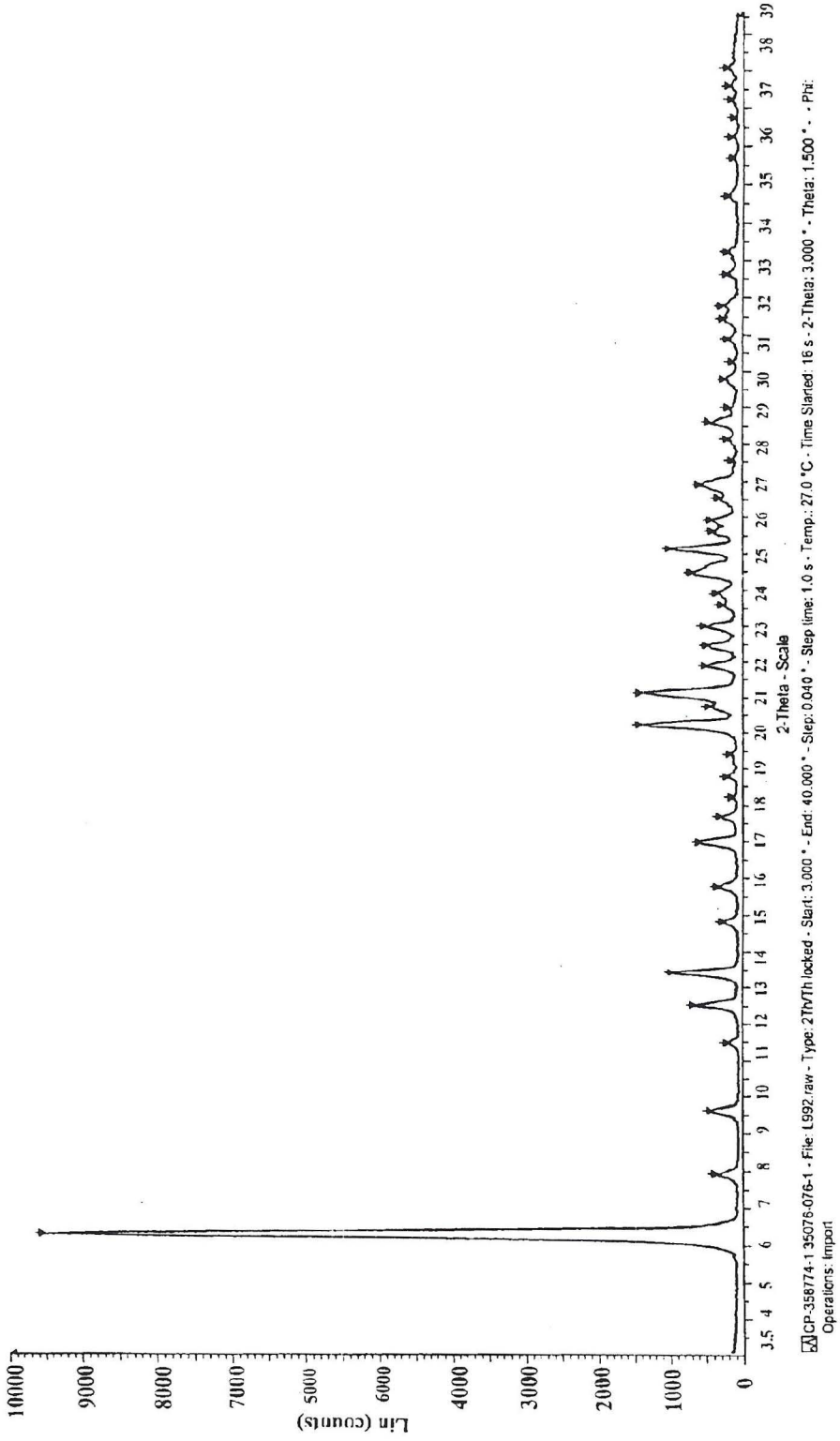

Lin (counts)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3.5 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
2-Theta - Scale
CP-358774-1 35076-076-1 - File: L992.raw - Type: 2Th/Th locked - Start: 3.000 ° - End: 40.000 ° - Step: 0.040 ° - Step time: 1.0 s - Temp.: 27.0 °C - Time Started: 16 s - 2-Theta: 3.000 ° - Theta: 1.500 ° - - Phi:
Operations: Import

FIGURE 3

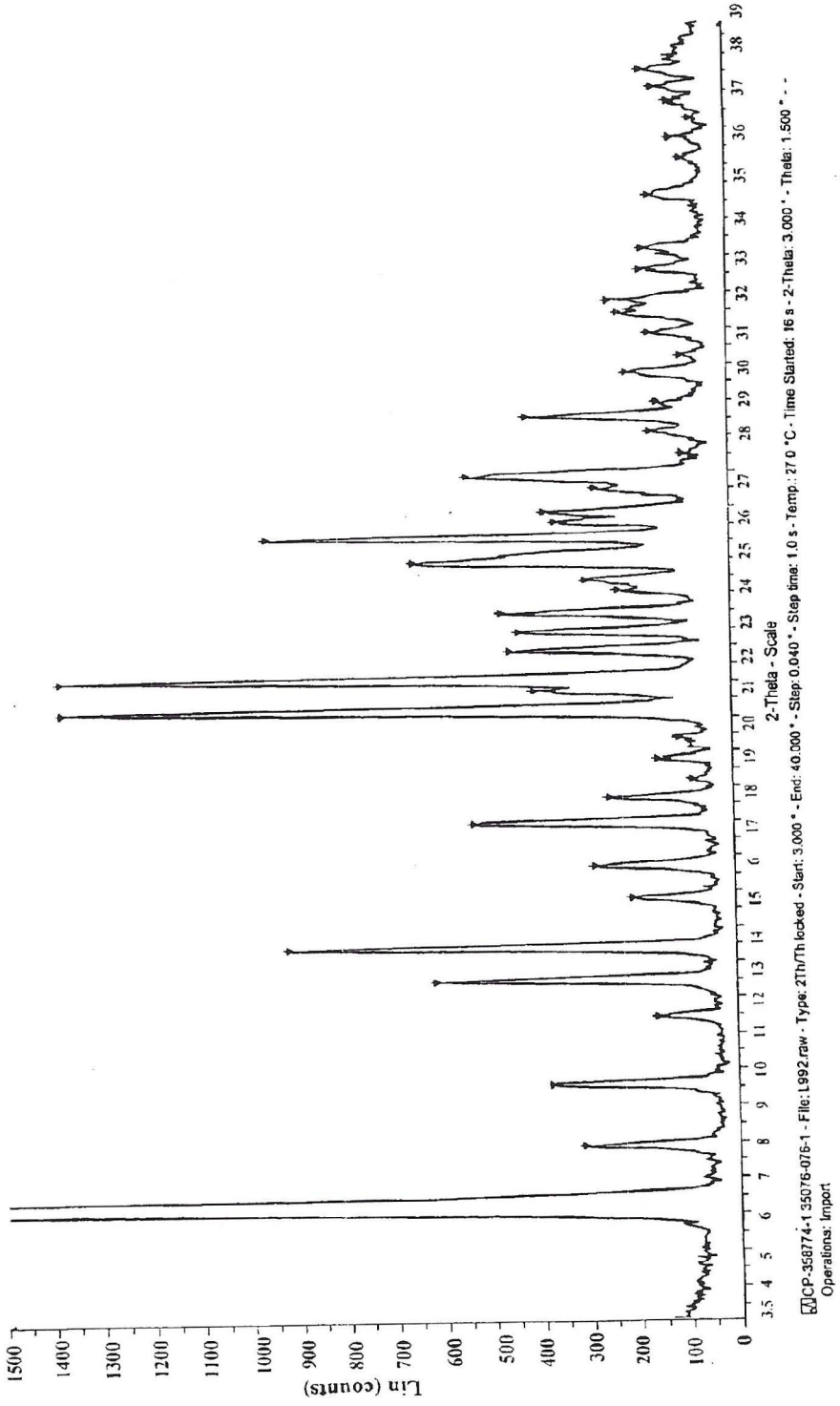

Lin (counts)
2-Theta - Scale
JCP-358774-1 35076-076-1 - File: L992.raw - Type: 2Th/Th locked - Start: 3.000 ° - End: 40.000 ° - Step: 0.040 ° - Step time: 1.0 s - Temp.: 27.0 °C - Time Started: 16 s - 2-Theta: 3.000 ° - Theta: 1.500 ° - -
Operations: Import

FIGURE 4

STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6, 7-BIS (2METHOXYETHOXY) -4-QUINAZOLINAMINE HYDROCHLORIDE, METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

This application claims the benefit of U.S. Provisional Application No. 60/206,420, filed May 23, 2000, U.S. Provisional Application No. 60/193,191, filed Mar. 30, 2000, and U.S. Provisional Application No. 60/164,907, filed Nov. 11, 1999, the contents of which are hereby incorporated by reference.

Throughout this application various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

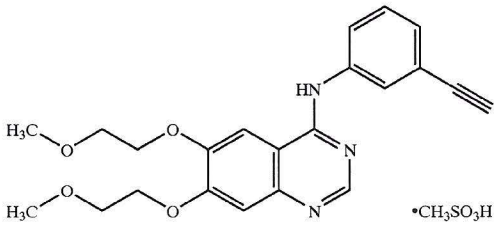
BACKGROUND OF THE INVENTION

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, in either its hydrochloride or mesylate forms, or in an anhydrous and hydrous form, is useful in the treatment of hyperproliferative disorders, such as cancers, in mammals.

U.S. Pat. No. 5,747,498, issued May 5, 1998, which is incorporated herein by reference in its entirety, refers, in Example 20, to [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride, which, the patent discloses, is an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders, such as cancers, in humans.

The mesylate form, described in PCT International Publication No. WO 99/55683 (PCT/IB99/00612, filed Apr. 8, 1999), the entire disclosure of which is incorporated herein by reference, and assigned to a common assignee, and shown in formula 1 below:

1



is useful for the treatment of proliferative disorders, and more preferred with parenteral methods of administration, as compared to the hydrochloride compound, i.e. with greater effectiveness in solution.

The mesylate compounds are more soluble in aqueous compositions than the hydrochloride compound, and thus the mesylate compounds are easily delivered according to parenteral methods of administration. The hydrochloride compound is however preferred with respect to solid administration such as with tablets and oral administration.

SUMMARY OF THE INVENTION

The present invention relates to polymorphs, and methods for the selective production of polymorphs of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, particularly in the stable polymorph form.

The present invention also relates to novel uses of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, in either its hydrochloride or mesylate forms, in an anhydrous or hydrous form, as well as in its various polymorph forms, in the treatment of hyperproliferative disorders, such as cancers, in mammals.

DESCRIPTION OF THE FIGURES

FIG. **1** The X-ray powder diffraction patterns for the hydrochloride polymorph A, the thermodynamically less stable form, over a larger range to show the first peaks.

FIG. **2** The X-ray powder diffraction patterns for the hydrochloride polymorph A, the thermodynamically less stable form, are over a shorter range to show more detail.

FIG. **3** The X-ray powder diffraction patterns for the hydrochloride polymorph B, the thermodynamically more stable form, over a larger range to show the first peaks.

FIG. **4** The X-ray powder diffraction patterns for the hydrochloride polymorph B, the thermodynamically more stable form, over a shorter range to show more detail.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed is a substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91. The polymorph is also characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

Disclosed is a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is substantially free of the polymorph designated the A polymorph. The polymorph is also characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

The polymorph designated the B polymorph may be in substantially pure form, relative to the A polymorph.

Also disclosed is a composition comprising a substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91. The hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine also exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately the values show in Table 3 or in Table 4 below.

And, the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form may characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

Also disclosed is a composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits

an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91 in a weight % of the B polymorph relative to the A polymorph which is at least 70%. This composition may comprise at least 75% polymorph B, by weight; at least 80% polymorph B, by weight; at least 85% polymorph B, by weight; at least 90% polymorph B, by weight; at least 95% polymorph B, by weight; at least 97% polymorph B, by weight; at least 98% polymorph B, by weight; or at least 99% polymorph B, by weight relative to the A polymorph.

Further disclosed is a process for producing the polymorph B of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine by recrystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol and water.

In the process, the recrystallization may comprise the steps of:

a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

b) cooling the solution to between about 65 and 70° C.;

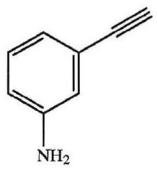
c) clarifying the solution; and

d) precipitating polymorph B by further cooling the clarified solution.

In the process, the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by the steps of:

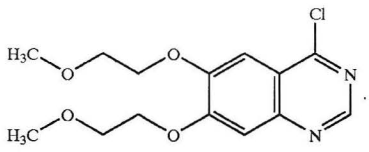
coupling a compound of formula 6

6



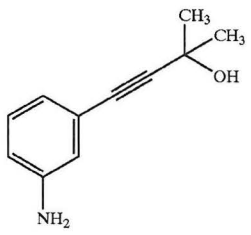
with a compound of formula 4

4



The compound of formula 6 is prepared by reacting a compound of formula formula 5

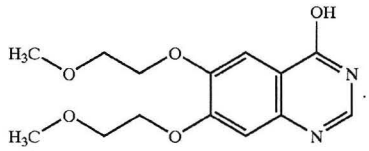
5



in a suspension of metal alkali and solvent and with heating.

The compound of formula 4 is prepared by chlorinating a compound of formula 3

3



Also disclosed is a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which substantially comprises a therapeutically effective amount of the polymorph B and a pharmaceutically acceptable carrier.

The pharmaceutical composition may be adapted for oral administration. It may be in the form of a tablet.

Also disclosed is a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph B.

The method may be for the treatment of a cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.

The method may also be for the treatment of a cancer selected from non-small cell lung cancer (NSCLC), refractory ovarian cancer, head and neck cancer, colorectal cancer and renal cancer.

In the method, the therapeutically effective amount may be from about 0.001 to about 100 mg/kg/day, or from about 1 to about 35 mg/kg/day.

In the method, the therapeutically effective amount may also be from about 1 to about 7000 mg/day; from about 5 to about 2500 mg/day; from about 5 to about 200 mg/day; or from about 25 to about 200 mg/day.

Further disclosed is a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph B in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

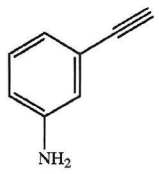
Yet further disclosed is a method of making a composition which composition comprises substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, comprising admixing the crystalline polymorph designated the B polymorph with a carrier.

The carrier may be a pharmaceutically acceptable carrier.

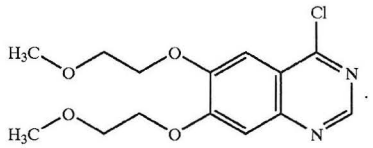
Also disclosed is a method of preparing polymorph B of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride which comprises the step of recrystallizing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.

In the method the solvent may further comprises water.

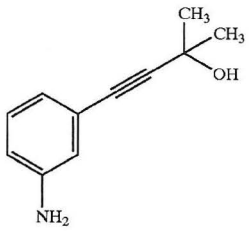
In the method, the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6



with a compound of formula 4

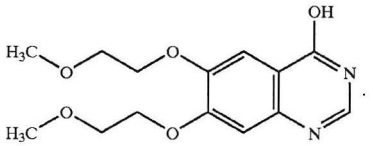


In the method, the compound of formula 6 is prepared by reacting a compound of formula 5



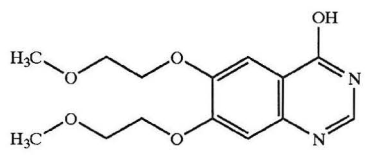
in a suspension of metal alkali and solvent and with heating.

In the method, the compound of formula 4 is prepared by chlorinating a compound of formula 3

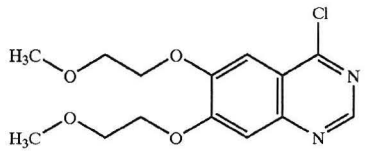


Further disclosed is a method for the production of the polymorph B of claim **1** comprising the steps of:

a) substitution chlorination of starting quinazolinamine compound of formula 3

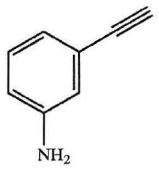


having an hydroxyl group, to provide a compound of formula 4

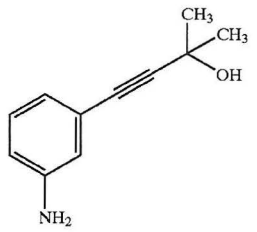


by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide,

b) preparation of a compound of formula 6



in situ from starting material of compound of formula 5



by reaction of the latter in a suspension of metal alkali and solvent and with heating;

c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride;

d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

In this method, the substitution chlorination may be quenched in the presence of aqueous sodium hydroxide; aqueous sodium bicarbonate; aqueous potassium hydroxide; aqueous potassium bicarbonate; aqueous potassium carbonate; aqueous sodium carbonate, or a mixture thereof.

Yet further disclosed is a method for the production of polymorph B of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine by recrystallization comprising the steps of:

a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

b) cooling the solution to between about 65 and 70° C.;

c) clarifying the solution; and

d) precipitating polymorph B by further cooling the clarified solution.

Further disclosed is a composition consisting essentially of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph A,

which is characterized by the following peaks in its X-ray powder diffraction pattern shown in FIG. **1**.

Also disclosed is a composition consisting essentially of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph A, which is characterized by the peaks shown is Table 1 or Table 2 below.

A prodrug of any of the compound herein is also disclosed.

Further disclosed is a method of inducing differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of any of the compounds or compositions disclosed herein.

Also discosed is a method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers and auto immune, neoplastic cutaneous diseases and atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

The treatment may further comprise a palliative or neo-adjuvant/adjuvant monotherapy; or comprises blocking epidermal growth factor receptors (EGFR).

The method of may also be used in the treatment of tumors that express EGFRvIII.

The method may further comprise a combination with any of chemotherapy and immunotherapy; or treatment with either or both anti-EGFR and anti-EGF antibodies; or administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metalloproteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$. (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.

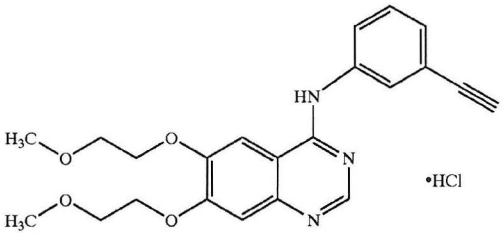
The pharmaceutical compounds used may be radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies, or for the inhibition of tumor growth in humans in a regimen with radiation treatment.

Further disclosed is a method for the chemoprevention of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

Also is a method of inducing differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of the compound of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

It is accordingly an object of the present invention to provide a method for the production of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine in HCl form (Formula 2):

2 (Polymorph form A and B)



making it more suitable for tablet and oral administration and consisting essentially of the stable polymorphic form (polymorph form B) as well as the compound in such polymorph B form and the intermediate polymorph A in essentially pure form.

It is a further object of the present invention to provide such stable polymorph form B in a pharmaceutical orally administered composition.

Stability of the hydrochloride compound is of concern for its use in the treatment of patients since variations will affect effective dosage level and administration. It has been discovered that the hydrochloride of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exists in two polymorph states, polymorph A and B. This contrasts with the mesylate compounds which exist in three polymorph states (mesylate polymorphs A, B and C). Polymorph B of the hydrochloride was found to be the thermodynamically most stable and desirable form and the present invention comprises the polymorph B compound in the substantially pure polymorphic B form and pharmaceutical compositions of the substantially pure form of polymorph B, particularly in tablet form and a method of the selective production of the compound.

The hydrochloride compound disclosed in the U.S. Pat. No. 5,747,498 actually comprised a mixture of the polymorphs A and B, which, because of its partially reduced stability (i.e., from the polymorph A component) was not more preferred for tablet form than the mesylate salt forms.

Specifically, the present invention relates to methods of producing the hydrochloride compound forms of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine and for producing the stable form B in high yield. The mesylate salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine has been discovered to exist in at least three polymorphic forms which have been designated A, B, and C, of increasing stability with different X-ray powder diffraction patterns. The X-ray powder diffraction patterns for the hydrochloride polymorph A (A1 and A2) and B (B1 and B2) forms are shown in FIGS. **1–4** as follows: graphs of FIGS. **1** and **3** are over a larger range to fully show the first peaks for A and B, respectively, and graphs of FIGS. **2** and **4** are over a shorter range to show more overall detail for A and B, respectively.

The data contained in the above X-ray diffraction patterns of FIGS. **1–4** are tabulated in the following Tables 1–4:

TABLE 1

Polymorph A
Anode: Cu - Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 - Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
15.82794	100.0	6.63179	1.7	4.54453	4.8	3.61674	8.2	2.91238	3.5
14.32371	3.9	5.84901	2.1	4.19685	4.7	3.50393	9.3	2.73148	3.7
11.74376	1.5	5.69971	2.3	4.16411	4.4	3.40200	6.0	2.60193	1.8
11.03408	1.2	5.46922	2.4	3.97273	4.7	3.35174	5.3	2.48243	1.3
10.16026	1.4	5.21396	3.6	3.91344	12.4	3.29005	4.2	2.40227	2.2
8.98039	13.1	4.80569	3.5	3.78223	24.2	3.05178	7.1	2.31297	1.7
7.85825	7.8	4.70077	12.2	3.67845	8.8	2.97750	3.0		

TABLE 2

Polymorph A
Anode: Cu - Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 - Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
5.579	100.0	13.340	1.7	19.517	4.8	24.594	8.2	30.673	3.5
6.165	3.9	15.135	2.1	21.152	4.7	25.398	9.3	32.759	3.7
7.522	1.5	15.534	2.3	21.320	4.4	26.173	6.0	34.440	1.8
8.006	1.2	16.193	2.4	22.360	4.7	26.572	5.3	36.154	1.3
8.696	1.4	16.991	3.6	22.703	12.4	27.080	4.2	37.404	2.2
9.841	13.1	18.447	3.5	23.502	24.2	29.240	7.1	38.905	1.7
11.251	7.8	18.862	12.2	24.175	8.8	30.007	3.0		

TABLE 3

Polymorph B
Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 - Coupled: 3.000 to 40.040 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47556	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

TABLE 4

Polymorph B
Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 - Coupled: 3.000 to 40.040 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.914	1.7

It is to be understood that the X-ray powder diffraction pattern is only one of many ways to characterize the arrangement of atoms comprising the compound N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, and that other methods well known in the art, e.g. single crystal X-ray diffraction, may be used to identify in a sample, composition or other preparation the presence of polymorph B of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine.

The present invention relates to a compound which is polymorph B of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91. This invention also relates to a polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately the values shown in Table 4 above.

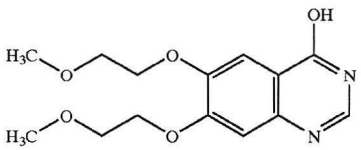
This invention also relates to a compound which is polymorph A of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 5.58, 9.84, 11.25, 18.86, 22.70, 23.50, 24.18, 24.59, 25.40 and 29.24. This invention also relates to a polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately the values shown in Table 2 above.

Method of Production

The polymorph B in substantially pure form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride (compound of formula 1) is prepared, in accordance with the method of the present invention, by the steps of;

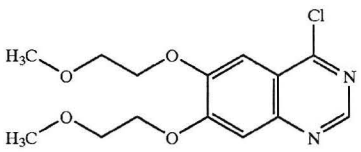
1) substitution chlorination of starting quinazolinamine compound (formula 3):

3



having an hydroxyl group, such as by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride, and dimethylformamide, and finally quenching the reaction with an aqueous solution of sodium hydroxide or sodium bicarbonate. The compound of formula 4:

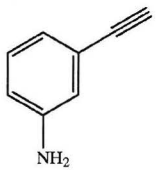
4



is produced in high yield with replacement of the hydroxyl group with chlorine;

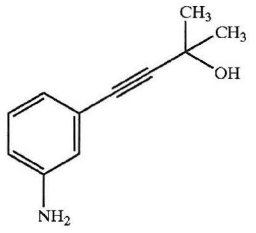
2) preparation of compound of formula 6:

6



from starting material of formula 5:

5



by reaction of the latter in a suspension of NaOH (or KOH, or a combination) in toluene with heating;

3) reaction of the compound of formula 6 with the compound of formula 4 of step 1 wherein the compound of formula 6 replaces the chlorine to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride (compound of formula 2) with a 97% yield.

4) recrystallization of the compound of formula 2 (comprising both polymorph A and polymorph B) into the more stable polymorph B in a solvent comprising alcohol (e.g. 2B-ethanol) and water, generally in high yield, e.g., about 85%.

Accordingly, the present invention relates to a method of preparing polymorph B of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride which comprises recrystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol and water. In one embodiment, the method comprises the steps of heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution; cooling the solution to between about 65 and 70° C.; clarifying the solution; and precipitating polymorph B by further cooling the clarified solution. In an embodiment, the alcohol is ethanol. In a preferred embodiment, the ratio of ethanol to water is about 4:1. It is to be expected that other lower alcohols, e.g., C_1–C_4 alcohols, are also suitable for recrystallization of polymorph B with adjustment of the alcohol to water ratio as needed. In another preferred embodiment, the compound to be recrystallized is present in an amount relative to the total volume of solvent at a weight to volume ratio of about 0.05. In an embodiment, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6 with a compound of formula 4. In another embodiment, the compound of formula 6 is prepared by reacting a compound of formula 5 in a suspension of metal alkali and solvent, with heating.

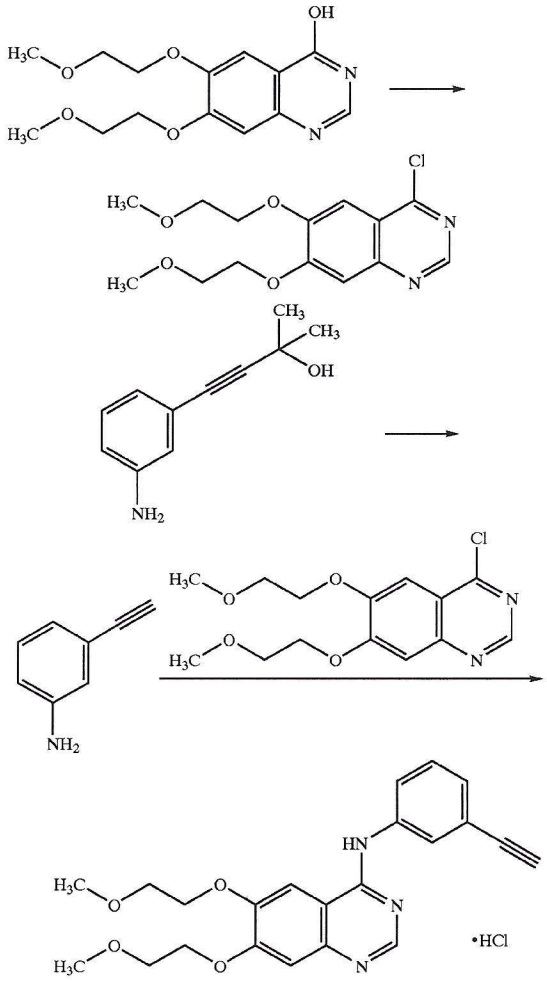
In an embodiment, the compound of formula 4 is prepared by chlorinating a compound of formula 3 by reaction of the latter in a solvent mixture of thionyl chloride, methylene chloride and dimethylformide, and subsequently quenching

the reaction with an aqueous solution of sodium hydroxide. Alternatively, an aqueous solution of sodium bicarbonate can be substituted for the sodium hydroxide solution.

This invention relates to polymorph B of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine prepared by the above methods. In an embodiment, the polymorph B is prepared by using the starting materials described herein. In a preferred embodiment, polymorph B is prepared by reaction of the starting materials described herein with the reagents and conditions according to the methods described herein and in the Examples which follow.

General Synthesis

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride has been found to exist in two distinct anhydrous polymorphic forms A and B. The production method for the various polymorphs is with components separately reacted in accordance with the following scheme:



Uses

As described in the aforementioned U.S. Pat. No. 5,747,498 and PCT International Publication No. WO 99/55683, the compounds made in accordance with the present invention are useful for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of the hydrochloride or mesylate form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and a pharmaceutically acceptable carrier.

The term "compound(s) of the invention" referred to herein is preferably the polymorph B form of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, but is not meant to exclude the mesylate form and its three polymorphs, or polymorph A of the hydrochloride form, or a mixture of polymorphs B and A of the hydrochloride form or other non-crystalline forms of the compound.

The term "treating" as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

"Abnormal cell growth", as used herein, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition), including the abnormal growth of normal cells and the growth of abnormal cells. This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs. Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restenosis. "Abnormal cell growth" as used herein also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzymes farnesyl protein transferase, protein kinases, protein phosphatases, lipid kinases, lipid phosphatases, or activity or trascription factors, or intracellular or cell surface receptor proteins.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is additionally used for the treatment of a variety of additional human tumors containing hyperproliferating cells that are activated by the signal transduction pathways stimulated by EGFR, whether by overexpression (e.g. due to one or more of—altered transcription, altered mRNA degradation or gene amplification) of the EGFR protein itself, another receptor protein with which EGFR can form active heterodimers, or one of the ligands that activate EGFR (e.g. EGF, TGFα, amphiregulin, β-cellulin, heparin-binding EGF, or epiregulin) or a heterodimerizing receptor, or due to a dependence or partial dependence on the activity of a "normal" level of EGFR protein, whether activated by extracellular ligand, intracellular signal transduction pathways and/or genetic alterations or polymorphisms that result in amino acid substitutions that produce increased or ligand-independent activity (e.g. EGFRvIII, Archer G. E. et. al. (1999) Clinical Cancer Research 5:2646–2652). Such tumors, including both benign and malignant, include renal (such as kidney, renal cell carcinoma, or carcinoma of the renal pelvis), liver, kidney, bladder (particularly invasive tumors), breast (including estrogen receptor negative and positive tumors, and progesterone receptor negative and positive tumors), gastric, esophageal (including Barrett's mucosa, squamous cell carcinomas and adenocarcinomas), larynx, ovarian, colorectal (particularly deeply invasive tumors), including anal, prostate, pancreatic, lung (particularly non-small cell lung cancer (NSCLC) adenocarcinomas, large cell tumors and squamous cell carcinomas, but also reactive (squamous metaplasia and inflammatory atypia) as well as precancerous (dysplasia and carcinoma in situ) bronchial lesions associated with both

NSCLC adenocarcinomas and squamous cell carcinomas), gynecological, including vulval, endometrial, uterine (e.g, sarcomas), cervical, vaginal, vulval, and fallopian tube cancers, thyroid, hepatic carcinomas, skin cancers, sarcomas, brain tumors, including glioblastomas (including gliobastoma multiforme), astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas and pituitary adenomas, and various other head and neck tumors (particularly squamous cell carcinomas), and metastases of all of the above.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is also used for the treatment of a variety of additional human hyperplastic conditions containing hyperproliferating cells that are activated by the signal transduction pathways capable of stimulation by EGFR, such as benign hyperplasia of the skin (e.g. psoriasis) or prostate (e.g. BPH), chronic pancreatitis, or reactive hyperplasia of pancreatic ductal epithelium, or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal which composition comprises a therapeutically effective amount of the hydrochloride of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, preferably the polymorph B form, and a pharmaceutically acceptable carrier.

In addition, pharmaceutical compositions including the compounds made in accordance with the present invention provide for the prevention of blastocyte implantation in a mammal, which composition comprises a therapeutically effective amount of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, preferably the polymorph B form, and a pharmaceutically acceptable carrier.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is also used for the treatment of additional disorders in which cells are activated by the signal transduction pathways stimulated by EGFR, whether by overexpression (due to one or more of—altered transcription, altered mRNA degradation or gene amplification) of the EGFR protein itself, another receptor protein with which it can form active heterodimers, or one of the ligands that activate EGFR (e.g. EGF, TGFα, amphiregulin, β-cellulin, heparin-binding EGF, or epiregulin) or a heterodimerizing receptor, or due to a dependence or partial dependence on the activity of a "normal" level of EGFR protein, whether activated by extracellular ligand, intracellular signal transduction pathways and/or genetic alterations or polymorphisms that result in amino acid substitutions that produce increased or ligand-independent activity (e.g. EGFRvIII, Archer G. E. et. al. (1999) Clinical Cancer Research 5:2646–2652). Such disorders may include those of a neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, or blastocoelic nature in which aberrant or 'normal' function, expression, activation or signalling via EGFR may be involved. Such disorders may furthermore involve the modulation by EGF (or other ligands that activate EGFR or heterodimerizing receptors) of adipocyte lipogenesis, bone resorption, hypothalamic CRH release, hepatic fat accumulation, T-cell proliferation, skin tissue proliferation or differentiation, corneal epithelial tissue proliferation or differentiation, macrophage chemotaxis or phagocytosis, astroglial proliferation, wound healing, polycystic kidney disease, lung epithelial proliferation or differentiation (e.g. associated with asthmatic airway remodeling or tissue repair), inflammatory arthritis (e.g. rheumatoid arthritis, systemic lupus erythematosus-associated arthritis, psoriatis arthritis) testicular androgen production, thymic epithelial cell proliferation, uterine epithelial cell proliferation, angiogenesis, cell survival, apoptosis, NFκB activation, vascular smooth muscle cell proliferation, restenosis or lung liquid secretion.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is also used for the treatment of a range of leukemias (chronic and acute) and lymphoid malignancies (e.g. lymphocytic lymphomas), diabetes, diabetic and other retinopathies, such as retinophay or prematurity, age-related macular degeneration, solid tumors of childhood, glioma, hemangiomas, melanomas, including intraocular or uveal melanomas, Kaposi's sarcoma, Hodgkin's disease, epidermoid cancers, cancers of the endocrine system (e.g. parathyroid, adrenal glands), bone small intestine, urethra, penis and ureter, atherosclerosis, skin diseases such as eczema and scleroderma, mycoses fungoides, sarcomas of the soft tissues and neoplasm of the central nervous system (e.g. primary CNS lymphoma, spinal axis tumors, brain stem gliomas, or pituitary adenomas).

The treatment of any of the hyperproliferative or additional disorders described above may be applied as a monotherapy, or may involve in addition to [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, application with one or more additional drugs or treatments (e.g. radiotherapy, chemoradiotherapy) that are anti-hyperproliferative, anti-tumor or antihyperplastic in nature. Such conjoint treatment may be achieved by way of simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment. [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is typically used at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, for any of the above treatments.

Furthermore, the various forms of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine including the mesylate and hydrochloride forms (all polymorph forms) as well as other pharmaceutically acceptable salt forms, and anhydrous and hydrate forms, can be used for treatment, with a therapeutically-effective amount of the aforementioned compounds and a pharmaceutically acceptable carrier, of the specific conditions of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome) and adrenal and skin cancers as well as auto immune and neoplastic cutaneous diseases such as mycoses fungoides, in a mammal, as well as for the chemoprevention of basal or squamous cell carcinomas of the skin, especially in areas exposed to the sun or in persons known to be at high risk for such cancers. In addition, the aforementioned compounds are useful in treatment of atherosclerosis, with epidermal growth factor having been implicated in the hyperproliferation of vascular smooth muscle cells responsible for atherosclerotic plaques (G. E. Peoples et al., Proc. Nat. Acad. Sci. USA 92:6547–6551, 1995).

The compounds of the present invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly in humans. The compounds of the present invention are also inhibitors of angiogenesis and/or vasculogenesis.

The compounds of the present invention may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signalling events related to various protein tyrosine kinases are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, glandular, macrophagal, epithelial, stromal, or blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases are involved. In addition, the compounds of the present invention may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases that are inhibited by the compounds of the present invention.

In addition to direct treatment of the above ailments with the compounds, the utilization and treatment in these and general applications may be as palliative or neo-adjuvant/adjuvant monotherapy, in blocking epidermal growth factor receptors (EGFR) and for use in treatment of tumors that express a variant form of EGFR known as EGFRvIII as described in the scientific literature (e.g., DK Moscatello et al. Cancer Res. 55:5536–5539, 1995), as well as in a combination with chemotherapy and immunotherapy. As described in more detail below, treatment is also possible with both anti-EGFR and anti-EGF antibody combinations or with combination of inhibitors of MMP (matrix-metalloproteinase), other tyrosine kinases including VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$. (cytotoxic T-lymphocyte antigen 4) and erbB2. Further treatments include MAb to VEGFr, and other cancer-related antibodies including rhuMAb-VEGF (Genentech, Phase III), the erbB2 MAb available as Herceptin (Genentech, Phase III), or the avb3 MAb available as Vitaxin (Applied Molecular Evolution/MedImmune, Phase II).

The invention also relates to a pharmaceutical composition and a method of treating any of the mentioned disorders in a mammal which comprises administering to said mammal a therapeutically effective amount of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, preferably in hydrochloride polymorph B form, and a pharmaceutically acceptable carrier.

Combination Therapy

The active compound may be applied as a sole therapy or may involve one or more other materials and treatment agents such as both anti-EGFR and anti-EGF antibody combinations or with combination of inhibitors of MMP (matrix-metallo-proteinase), other tyrosine kinases including VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, as well as MAb to VEGFr, and other cancer-related antibodies including rhuMAb-VEGF, the erbB2 MAb, or avb3.

Thus, the active compound may be applied with one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex® (tamoxifen) or, for example anti-androgens such as Casodex®(4'-cyano-3-(4-fluorophenyl sulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide).

In a further embodiment, the compounds of the invention may be administered in conjunction with an anti-angiogenesis agent(s) such as a MMP-2 (matrix-metalloproteinase-2) inhibitor(s), a MMP-9 (matrix-metalloproteinase-9) inhibitor(s), and/or COX-II (cyclooxygenase II) inhibitor(s) in the methods of treatment an compositions described herein. For the combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the chemotherapeutic or other agent useful for inhibiting abnormal cell growth (e.g., other antiproliferative agent, anti-angiogenic, signal transduction inhibitor or immune-system enhancer) can be determined by those of ordinary skill in the art, based on the effective amounts for the compound described herein and those known or described for the chemotherapeutic or other agent. The formulations and routes of administration for such therapies and compositions can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic or other agent in combination therewith.

The invention also relates to production of compounds used in a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, bioloical response modifiers, anti-hormones, and anti-androgens.

The compounds are also useful as radiation sensitizers for cancer treatment and may be combined with anti-hormonal therapies. Parameters of adjuvant radiation therapies are for example contained in PCT/US99/10741, as published on 25 Nov. 1999, in International Publication No. WO 99/60023, the disclosure of which is included herein by reference thereto. With such mode of treatment for example, for inhibiting tumor growth, a radiation dosage of 1–100 Gy is utilized preferably in conjunction with at least 50 mg of the pharmaceutical compound, in a preferred dosage regimen of at least five days a week for about two to ten weeks.

Thus, this invention further relates to a method for inhibiting abnormal cell growth in a mammal which method comprises administering to the mammal an amount of the compound of the invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with radiation therapy, wherein the amount of the compound, salt, solvate or prodrug is in combination with the radiation therapy effective in inhibiting abnormal cell growth in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with the compound of the invention in the methods and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172

(published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain patent application number 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

(R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[(4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

(R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts and solvates of said compounds.

Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

The compound of the present invention can also be used with signal transduction inhibitors, such as other agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and other molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors, such as VEGF receptors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as other organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTINT™ (Genentech, Inc. of South San Francisco, Calif., USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published Jul. 27, 1995), WO 98/14451 (published Apr. 9, 1998), WO 98/02434 (published Jan. 22, 1998), and other compounds described in U.S. Pat. No. 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, N.Y., USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, N.J., USA), and OLX-103 (Merck & Co. of Whitehouse Station, N.J., USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Mass.). These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, Calif., USA), can also be combined with the compound of the present invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published Aug. 17, 1995), WO 99/61422 (published Dec. 2, 1999), U.S. Pat. No. 5,834,504 (issued Nov. 10, 1998), WO 98/50356 (published Nov. 12, 1998), U.S. Pat. No. 5,883,113 (issued Mar. 16, 1999), U.S. Pat. No. 5,886,020 (issued Mar. 23, 1999), U.S. Pat. No. 5,792,783 (issued Aug. 11, 1998), WO 99/10349 (published Mar. 4, 1999), WO 97/32856 (published Sep. 12, 1997), WO 97/22596 (published Jun. 26, 1997), WO 98/54093 (published Dec. 3, 1998), WO 98/02438 (published Jan. 22, 1998), WO 99/16755 (published Apr. 8, 1999), and WO 98/02437 (published Jan. 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Wash., USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, Calif.; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colo.) and Chiron (Emeryville, Calif.). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Tex., USA) and 2B-1 (Chiron), can furthermore be combined with the compound of the invention, for example those indicated in WO 98/02434 (published Jan. 22, 1998), WO 99/35146 (published Jul. 15, 1999), WO 99/35132 (published Jul. 15, 1999), WO 98/02437 (published Jan. 22, 1998), WO 97/13760 (published Apr. 17, 1997), WO 95/19970 (published Jul. 27, 1995), U.S. Pat. No. 5,587,458 (issued Dec. 24, 1996), and U.S. Pat. No. 5,877,305 (issued Mar. 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in U.S. Provisional

Application No. 60/117,341, filed Jan. 27, 1999, and in U.S. Provisional Application No. 60/117,346, filed Jan. 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compound of the present invention in accordance with the present invention.

The compound of the invention can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as farnesyl protein transferase inhibitors. Specific CTLA4 antibodies that can be used in the present invention include those described in U.S. Provisional Application 60/113,647 (filed Dec. 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

It is expected that the compound of the invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells.

Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of the compound of the invention, pharmaceutically acceptable salt or solvate thereof, or prodrug thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, solvate, or prodrug in this method can be determined according to the means for ascertaining effective amounts of the compound of the invention described herein.

The subject invention also includes isotopically-labelled compounds, which compounds are identical to the above recited compound of the invention, but for the fact that one or more atoms thereof are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the compound of the invention include isotopes of hydrogen, carbon, nitrogen and oxygen, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O and ^{17}O, respectively. Compounds of the present invention, and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the Methods and/or the examples below, nd substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent, using methods ell known in the art. Accordingly, reference to the compound of the invention for use in the therapeutic methods and pharmaceutical compositions described herein also encompasses isotopically-labelled forms of the compound.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is typically used at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, for any of the above treatments.

Patients that can be treated with the compound of the invention, alone or in combination, include, for example, patients that have been diagnosed as having psoriasis, BPH, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphona, spinal axis tumors, brain stem gliomas or pituitary adenomas).

Activity

The in vitro activity of the compounds of the present invention in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response, e.g., cancer) may be determined by the following procedure.

The activity of the compounds of the present invention, in vitro, can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., Lys_3—Gastrin or polyGluTyr (4:1) random copolymer (I. Posner et al., *J. Biol. Chem.* 267 (29), 20638–47 (1992)) on tyrosine by epidermal growth factor receptor kinase by a test compound relative to a control.

Affinity purified, soluble human EGF receptor (96 ng) is obtained according to the procedure in G. N. Gill, W. Weber, *Methods in Enzymology* 146, 82–88 (1987) from A431 cells (American Type Culture Collection, Rockville, Md.) and preincubated in a microfuge tube with EGF (2 μg/ml) in phosphorylation buffer+vanadate (PBV: 50 mM HEPES, pH 7.4; 125 mM NaCl; 24 mM $MgCl_2$; 100 μM sodium orthovanadate), in a total volume of 10 μl, for 20–30 minutes at room temperature. The test compound, dissolved in dimethylsulfoxide (DMSO), is diluted in PBV, and 10 μl is mixed with the EGF receptor/EGF mix, and incubated for 10–30 minutes at 30° C. The phosphorylation reaction is initiated by addition of 20 μl ^{33}P-ATP/substrate mix (120 μM Lys_3-Gastrin (sequence in single letter code for amino acids, KKKGPWLEEEEEAYGWLDF), 50 mM Hepes pH 7.4, 40 μM ATP, 2 pCi γ-[^{33}P]-ATP) to the EGFr/EGF mix and incubated for 20 minutes at room temperature. The reaction is stopped by addition of 10 μl stop solution (0.5 M EDTA, pH 8; 2 mM ATP) and 6 μl 2N HCl. The tubes are centrifuged at 14,000 RPM, 4° C., for 10 minutes. 35 μl of supernatant from each tube is pipetted onto a 2.5 cm circle of Whatman P81 paper, bulk washed four times in 5% acetic acid, 1 liter per wash, and then air dried. This results in the binding of substrate to the paper with loss of free ATP on washing. The [^{33}P] incorporated is measured by liquid

scintillation counting. Incorporation in the absence of substrate (e.g., lys_3-gastrin) is subtracted from all values as a background and percent inhibition is calculated relative to controls without test compound present. Such assays, carried out with a range of doses of test compounds, allow the determination of an approximate IC_{50} value for the in vitro inhibition of EGFR kinase activity.

Other methods for determining the activity of the compounds of the present invention are described in U.S. Pat. No. 5,747,498, the disclosure of which is incorporated herein.

Pharmaceutical Compositions

The pharmaceutical composition may, for example and most preferably, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, and suspension. Less preferred (with the mesylate form being the preferred form) are compositons for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof. Additionally, it is also possible to administer the compound of the invention topically and this may be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The compound of the invention may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal species and the disease or disorder being treated. The compound may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The compound may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. As an alternative, the compound may be administered with the animal feedstuff, and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Administration and Dosage

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods preferably include oral routes such as in the form of tablets, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration. While parenteral administration is usually preferred, oral administration is preferred for the hydrochloride B polymorph.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration and the judgement of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, is also useful for the treatment of patients (as measured, for example, by increased survival times) by using combination therapies, for example in NSCLC (IIIb/V), as a 1^{st} line therapy with carboplatin/paclitaxel or gemcitabine/cisplatin, in NSCLC (IIIb/V), as a 2^{nd} line therapy with taxotere, and in head and neck cancers, as a 2nd line therapy with methotrexate for patients refractory to 0.5FU/cisplatin.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, is also useful for the treatment of patients with additional conditions, including pancreatic cancer, with or without gemcitabine co-treatment, as first line therapy, for renal cancer, gastric cancer, prostate cancer, colorectal cancer (e.g. as a 2nd line therapy for patients who have failed 5FU/LCV/Irinotecan therapy), and also for hepatocellular, bladder, brain, ovarian, breast, and cervical cancers. For such treatments, in advanced disease patients with refractory disease, treatment effectiveness is readily monitored by an increased response rate, an increased time to progression or an increase in survival time.

[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride, preferably the stable polymorph B form, is typically used at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, for any of the above treatments.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. This invention will be better understood from the Experimental Details

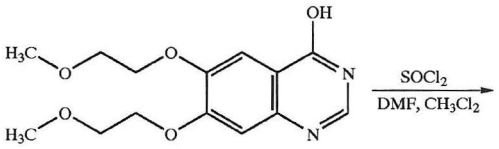
which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

Example 1

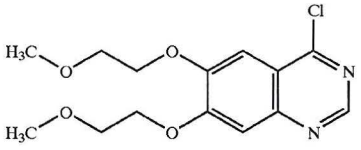
Preparation of Compound of Formula 4

Reaction:



MW = 294.31

3



MW = 312.75

4

The following materials were used in the synthesis of the compound of formula 4:

Materials	Quantity	Units	Equivalents/ Volumes
Compound of formula 3	88.0	kg	1 equivalent
Thionyl chloride	89.0	kg	2.5 equivalents
Dimethylformamide	11	kg	0.5 equivalent
methylene chloride	880.0	L	10 L/kg
50% sodium hydroxide solution	as required	L	1 equivalent
Heptane	880.0	L	10 L/kg

The following procedure is exemplary of the procedure to follow in the synthesis of the formula 4 compound:

88.0 kg of the compound of formula 3, 880.0 L methylene chloride, and 11.0 kg of dimethylformamide were charged to a clean, dry, glass-lined vessel under nitrogen atmosphere. 89 Kg of thionyl chloride were added to the mix while it is maintained at a temperature of a less than 30° C. during the charge. The contents of the reaction vessel were then heated for a minimum of five hours at reflux temperature before sampling for reaction completion and the pH is adjusted to be maintained between 7.0 to 8.0, by using 50% NaOH, as required and the temperature of the reaction mixture is maintained at less than 25° C. The biphasic mixture is stirred for fifteen to twenty minutes and allowed to settle for a minimum of thirty minutes. The layers were separated and the organic layer was concentrated to ⅓ of its volume by removing methylene chloride. 880 L heptane was added with continued distillation of the remaining methylene chloride until the distillate reaches a temperature between 65 and 68° C. The mixture was then cooled to between 10 to 15° C. over 5 hours and granulated for a minimum of 1 hour with the solids being isolated by filtration and washed with 220 L heptane. The solids (formula 4 compound) were dried in a vacuum drier at 45 to 50° C.

Example 2

Alternative Preparation of Compound of Formula 4

In the reaction shown in Example 1, sodium bicarbonate may successfully be used instead of sodium hydroxide as shown in this Example.

Materials	Quantity	Units	Equivalents/ Volumes
Compound of formula 3	30.0	kg	1 equivalent
Thionyl chloride	36.4	kg	3 equivalents
Dimethylformamide	3.75	kg	0.5 equivalent
methylene chloride	300	L	10 L/kg
50% sodium hydroxide solution	as required	L	
Heptane	375	L	12.5 L/kg
Heptane (wash)	90	L	3 L/kg
Sodium Bicarbonate	64.2	Kg	7.5 equivalents

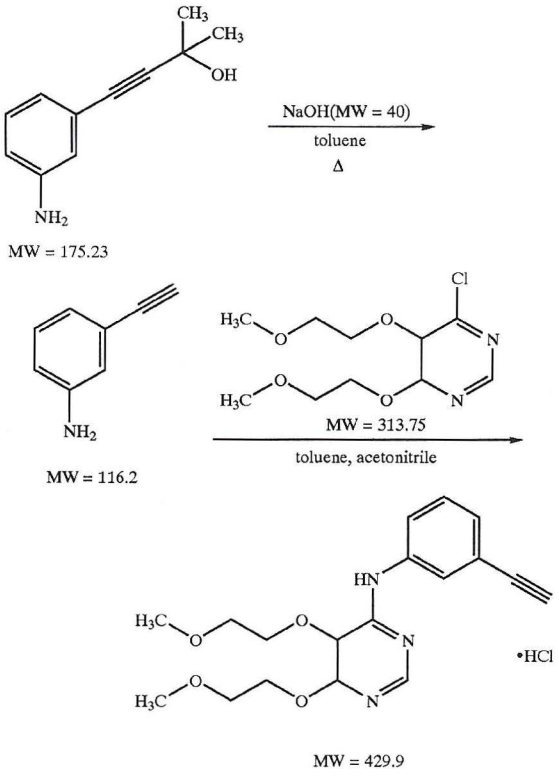
30.0 kg of the compound of formula 3, 300.0 L methylene chloride, and 3.75 kg of dimethylformamide were charged to a clean, dry, glass-lined vessel under a nitrogen atmosphere. 36.4 kg of thionyl chloride was added to the mix while it was maintained at a temperature of less than 30° C. during the charge. The contents of the reaction vessel were then heated at reflux temperature for 13 h before sampling for reaction completion. The reaction mixture was cooled to 20–25° C. and added slowly to a stirred solution of sodium bicarbonate 64.2 kg and water 274 L cooled to 4° C. so that the temperature was maintained at less than 10° C. The final pH of the mixture was adjusted to within the range 7.0 to 8.0 by using 50% sodium hydroxide solution as required. The biphasic mixture was stirred for fifteen to twenty minutes and allowed to settle for a minimum of thirty minutes at 10–20° C. The layers were separated and the organic layer was concentrated to ⅓ of its volume by removing methylene chloride. 375 L of heptane was added with continued distillation of the remaining methylene chloride until the distillate reached a temperature between 65 and 68° C. The mixture was then cooled to 0 to 5° C. over 4 hour and granulated for a minimum of 1 hour with the solids being isolated by filtration and washed with 90 L heptane.

The solids (formula 4 compound) were dried in a vacuum drier at 45 to 50° C.

Example 3

Preparation of Compound of Formulas 6 and 2 (Step 2)

Reaction:



The following materials were used in the synthesis of the compound of formula 6, as intermediate, and the compound of formula 2:

Materials	Quantity	Units	Equivalents/Volumes
Compound of formula 5	61.1	kg	1.2 equivalents
Toluene	489	L	8 L/kg (WRT to formula 5 c'mpd)
Sodium hydroxide pellets	4.5	kg	0.16 equivalents
Filteraid	0.5	kg	0.017 kg/kg (WRT to c'mpd 5)
Compound of formula 4	90.8	kg	1.0 equivalent
Acetonitrile	732	L	12 L/kg (WRT to c'mpd 5)

Example 4

Preparation of Compound of Formula 2

The following procedure is exemplary of the procedure to follow in the synthesis of the formula 2 compound and intermediate compound of formula 6:

61.1 kg of formula 5 compound, 4.5 kg sodium hydroxide pellets and 489 L toluene were charged to a clean, dry, reaction vessel under nitrogen atmosphere and the reaction temperature is adjusted to between 105 to 108° C. Acetone to was removed over four hours by atmospheric distillation while toluene is added to maintain a minimum volume of 6 L of solvent per kg of formula 5 compound. The reaction mixture was then heated at reflux temperature, returning distillates to pot, until the reaction was complete. The mixture was then cooled to between 20 to 25° C., at which time a slurry of 40.0 L toluene and 0.5 kg filteraid was charged to the reaction mixture and the mixture was agitated for ten to fifteen minutes. The resultant material was filtered to remove filteraid, and the cake is washed with 30 L toluene (compound of formula 6).

The filtrate (compound of formula 6) was placed in a clean, dry reaction vessel under nitrogen atmosphere, and 90.8 kg of the compound of formula 4 was charged into the reaction vessel together with 732 L acetonitrile. The reaction vessel was heated to reflux temperature and well agitated. Agitator speed was lowered when heavy solids appear. When the reaction was complete, the contents of reaction vessel were cooled to between 19 to 25° C. over three to four hours and the contents were agitated for at least one hour at a temperature between 20 and 25° C. The solids (compound of formula 2, polymorph A form, or mixture of polymorph A and B) were then isolated by filtration and the filter cake was washed with two portions of 50 L acetonitrile and dried under vacuum at a temperature between 40 and 45° C.

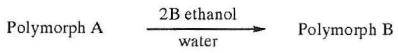
It has been discovered that the production of the A polymorph is favored by the reduction of the amount of acetonitrile relative to toluene, and particularly favored if isopropanol is used in place of acetonitrile. However, the use of isopropanol or other alcohols as cosolvents is disfavored because of the propensity to form an ether linkage between the alcoholic oxygen and the 4-carbon of the quinazoline, instead of the desired ethynyl phenyl amino moiety.

It has been further discovered that adjusting the pH of the reaction to between pH 1 and pH 7, preferably between pH 2 and pH 5, more preferably between pH 2.5 and pH 4, most preferably pH 3, will improve the rate of the reaction.

Example 5

Recrystallization of Compound of Formula 2 (Which may be in Polymorph A Form or a Mixture of Polymorphs A and B) to Polymorph B (Step 3)

Reaction:



The following materials were used in the conversion of polymorph A (or mixtures of polymorphs A and B) to polymorph B of the compound of formula 2:

Materials	Quantity	Units	Equivalents/Volumes
Polymorph A (formula 2)	117.6	kg	1 equivalent
2B-ethanol	1881.6	L	16 L/kg
Water	470.4	L	4 L/kg

The following procedure is exemplary of procedures used to convert polymorph A (or mixtures of polymorphs A and B) into the more thermodynamically stable polymorph B of the compound of formula 2:

117.6 kg of the polymorph A (or mixtures of polymorphs A and B) were charged to a clean, dry, reaction vessel together 1881.6 L 2B-ethanol and 470.4 L water under a nitrogen atmosphere. The temperature was adjusted to reflux (~80° C.) and the mixture was agitated until the solids dissolve. The solution was cooled to between 65 and 70° C. and clarified by filtration. With low speed agitation, the solution was further cooled to between 50 and 60° C. over a minimum time of 2 hours and the precipitate was granulated for 2 hours at this temperature. The mixture was further cooled to between 0 and 5° C. over a minimum time of 4 hours and granulated for a minimum of 2 hours at this temperature. The solids (polymorph B) were isolated by filtration and washed with at least 100 L 2B-ethanol. The solids were determined to be crystalline polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride substantially free of the polymorph A from. The solids obtained by this method are substantially homogeneous polymorph B form crystals relative to the polymorph A form. The method allows for production of polymorph B in an amount at least 70% by weight, at least 80% by weight, at least 90% by weight, at least 95% by weight, and at least 98% by weight relative to the weight of the polymorph A. It is to be understood that the methods described herein are only exemplary and are not intended to exclude variations in the above parameters which allow the production of polymorph B in varying granulations and yields, according to the desired storage, handling and manufacturing applications of the compound. The solids were vacuum dried at a temperature below 50° C. and the resultant product was milled to provide the polymorph B in usable form.

Example 6

Clinical Studies Utilizing Treatment with the Stable Polymorph B Form of [6,7-bis(2-methoxyethoxy) quinazolin-4-yl]-(3-ethynylphenyl)-amine Hydrochloride

The stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride is a potent, selective and orally active inhibitor of the epidermal growth factor receptor (EFGR) protein-tyrosine kinase, an oncogene that has been associated with the aberrant growth that is characteristic of cancer cells. This compound is being evaluated in clinical trials in normal healthy volunteers and in cancer patients in order to assess its safety profile and effectiveness.

Phase I Clinical Studies

Phase I clinical studies of the stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride have been effectively completed in volunteers, initially, and subsequently in cancer patients, at single doses ranging from 25–200 mg/day or 100–1600 mg/week. Data from these studies revealed no adverse events that were greater than moderate in severity for a dose of 150 mg/day. In a daily dosing regimen study the dose limiting toxicity at 200 mg/day was diarrhea. This observed side effect was effectively controlled at the 150 mg daily dose level using Loperamide (Imodium®). The second adverse event observed in these studies, and most significant toxicity at 150 mg daily, was a monomorphic acneiform rash analogous to that reported for other EGFR inhibitor agents in clinical trials. This rash had an "above-waist" distribution including face, scalp, neck, arms, chest and back. The rash has a unique histopathology of PMN infiltration with mild epidermal hyperproliferation. It is not consistent with drug hypersensitivity nor does it appear to be a "named" dermatological condition. This rash has not been a significant impediment to patients staying on the Phase II trials. The stable polymorph B form of [6,7-bis(2-methoxyethoxy) quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride has been tested in a total of 290 patients in Phase I and ongoing Phase II studies and demonstrates a well tolerated safety profile. Furthermore, preliminary evidence of effectiveness was observed in Phase I studies. For example, in one Phase I study of 28 patients, 8 patients remain alive over a year after inception of treatment and 12 patients remained alive from 9–22 months.

In order to establish a suitable safety profile, the stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride is also used at doses of 1–7000 mg/day, preferably 5–2500 mg/day, most preferably 5–200 mg/day, in Phase I clinical combination studies with one or more additional drugs or treatments, preferably selected from one of the following group—Taxol, Gemcitabine, Taxotere, Capcitabine, 5FU, Cisplatin, Temozolomide, radiation treatment, and chemoradiation treatment.

Phase II and Phase III Clinical Studies

Three Phase II single agent studies of the stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride in refractory non-small cell lung cancer, advanced head and neck cancer and refractory ovarian cancer, at a 150 mg daily dose were initiated.

Indications of single agent anti-tumor activity for the stable polymorph B form of [6,7-bis(2-methoxyethoxy) quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride was seen in patients with advanced cancers in several different tumor types. For example, initial findings indicate that the stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride is a well-tolerated oral medication that is active as a monotherapy when administered to patients with advanced head and neck cancer. In preliminary results 3 patients had objective partial responses, while another 9 patients showed evidence of a stabilization of their disease status. The acneiform rash, which is apparently characteristic of all the anti-EGFR inhibitors undergoing clinical testing, was reported in approximately 70% of the first group of patients in this study.

The early data emerging from the 48 patient Phase II study in refractory non-small cell lung cancer (NSCLC) patients also indicates the effectiveness of treatment with the stable polymorph B form of [6,7-bis(2-methoxyethoxy) quinazolin-4-yl]-(3-ethynylphenyl)-amine hydrochloride as a single agent anti-tumor drug for NSCLC. Of the first 19 evaluable patients in the study, 5 had objective partial responses, while another 4 patients showed evidence of a stabilization of their disease status. Partial responses were observed in two patients who had been treated previously with two and three different chemotherapy regimens. Thus it appears that the stable polymorph B form of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine

hydrochloride is a well tolerated, oral medication which is active in non-small cell lung cancer.

Qualification criteria for the open label, single agent study required the patients to have failed platinum-based chemotherapy and to have tumors that are histopathologically confirmed to be EGFR positive. The primary endpoint in the study is response rate with stable disease and time-to-progression amongst the secondary end-points.

Evidence of anti-tumor activity can also be seen in the patients with ovarian cancer in the on-going Phase II study. In preliminary results 2 patients had objective partial responses, while another 4 patients showed evidence of a stabilization of their disease status. Documented evidence of anti-tumor activity was also seen in other EGFR positive tumor types, including colorectal and renal cell carcinoma, from Phase I studies in cancer patients with multiple tumor types.

What is claimed is:

1. A homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-Quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14, and 26.91.

2. The polymorph of claim **1**, characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

3. A crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph.

4. The polymorph of claim **3**, characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

5. A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier, wherein the composition is free of the A polymorph.

6. The composition of claim **5**, wherein the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

7. The composition of claim **5**, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

8. A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim **3** and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is free of the A polymorph.

9. The pharmaceutical composition of claim **8**, wherein said composition is adapted for oral administration.

10. The pharmaceutical composition of claim **9**, wherein the pharmaceutical composition is in the form of a tablet.

11. The pharmaceutical composition of claim **8**, wherein the therapeutically effective amount is from 1 to 7000 mg.

12. The pharmaceutical composition of claim **11**, wherein the therapeutically effective amount is from 5 to 2500 mg.

13. The pharmaceutical composition of claim **12**, wherein the therapeutically effective amount is from 100 to 1600 mg.

14. The pharmaceutical composition of claim **11**, wherein the therapeutically effective amount is from 5 to 200 mg.

15. The pharmaceutical composition of claim **14**, wherein the therapeutically effective amount is from 25 to 200 mg.

16. A composition consisting of a homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu—Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)

Range #1—Coupled 3.000 to 40.040 StepSize: 0.040 StepTime 1.00

Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.63967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
6.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

or,

Polymorph B

Anode: Cu—Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)

Range# 1—Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00

Soothing Width: 0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.6
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.8	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

and at least one carrier.

17. A method of treating abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim **3**, wherein the abnormal cell growth is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

18. The method of claim **17**, wherein the abnormal cell growth is brain, squamous cell, bladder, gastric, pancreatic, hepatic glioblastoma multiforme breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer.

19. The method of claim **17**, wherein the abnormal cell growth is non-small call lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

20. The method of claim **17**, wherein the therapeutically effective amount in from about 0.001 to about 100 mg/kg/day.

21. The method of claim **17**, wherein the therapeutically effective amount is from about 1 to about 35 mg/kg/day.

22. The method of claim **17**, wherein the therapeutically effective amount is from about 1 to about 7000 mg/day.

23. The method of claim **22**, wherein the therapeutically effective amount is from about 5 to about 2500 mg/day.

24. The method of claim **23**, wherein the therapeutically effective amount is from about 5 to about 200 mg/day.

25. The method of claim **24**, wherein the therapeutically effective amount is from about 25 to about 200 mg/day.

26. A method for the treatment of abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim **3** in combination with an anti-tumor agent selected from the group consisting of a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

27. The method of claim **18**, wherein the abnormal cell growth is pancreatic cancer.

28. The method of claim **18**, wherein the abnormal cell growth is colorectal cancer.

29. The method of claim **18**, wherein the abnormal cell growth is prostate cancer.

30. The method of claim **18**, wherein the abnormal cell growth is breast cancer.

31. The method of claim **18**, wherein the abnormal cell growth is esophageal cancer.

32. The method of claim **18**, wherein the abnormal cell growth is ovarian cancer.

33. The method of claim **18**, wherein the abnormal cell growth is glioblastoma multiforme.

34. The method of claim **18**, wherein the abnormal cell growth is hepatic cancer.

35. The method of claim **18**, wherein the abnormal cell growth is renal cancer.

36. The method of claim **18**, wherein the abnormal cell growth is gastric cancer.

37. The method of claim **18**, wherein the abnormal cell growth is bladder cancer.

38. The method of claim **19**, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC).

39. The method of claim **19**, wherein the abnormal cell growth is head and neck cancer.

40. The method of claim **17**, wherein the therapeutically effective amount is from 100 to 1600 mg/week.

41. The method of claim 17, wherein the therapeutically effective amount of the polymorph is administered weekly.

42. A method of inhibiting the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier, so as to thereby inhibit the development of basal or squamous cell carcinoma of the skin.

43. A method of treating a subject with a tumor by inducing differentiation of tumor cells expressing an epidermal growth factor receptor (EGFR) in the tumor comprising contacting the cells with an effective amount of the compound of claim 3, or a composition of claim 5 so as to thereby treat the subject, wherein the tumor is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HFV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.

45. The method of claim 44, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.

46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

47. The method of claim 44, for use in treatment of tumors that express EGFRvIII.

48. The method of claim 44, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.

49. The method of claim 44, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.

50. The method of claim 44, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.

51. The method of claim 44, wherein the pharmaceutical composition is used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.

52. The method of claim 44, wherein the pharmaceutical composition is used fox the inhibition of tumor growth in humans in a regimen with radiation treatment.

53. The method of claim 44 for the treatment of non-small cell lung cancer (NSCLC).

54. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers, or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms,

wherein the treatment further comprises,

a) treatment with either or both anti-EGFR and anti-EGF antibodies,

b) administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelia growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab, or

c) radiation treatment.

55. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal cancers, or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, and a pharmaceutically acceptable carrier.

56. The method of claim 55, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.

57. The method of claim 55, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

58. The method of claim 55, for use in treatment of tumors that express EGFRvIII.

59. The method of claim 55, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.

60. The method of claim 55, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.

61. The method of claim 55, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 MAb.

62. The method of claim 55, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.

63. The method of claim 55, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.

64. The method of claim 55 for the treatment of glioma.

65. The method of claim 55 for the treatment of melanoma.

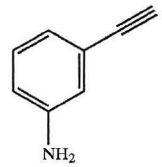
66. A process for preparing a crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-

quinazolinamine hydrochloride designated the B polymorph, which is free of the A polymorph, which comprises the step of recrystallizing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.

67. The process of claim **66**, wherein the solvent further comprises water.

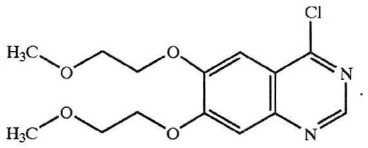
68. The process of claim **66**, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6

6



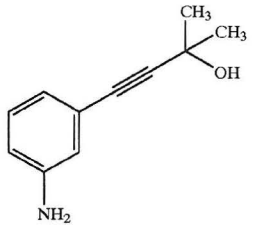
with a compound of formula 4

4



69. The process of claim **68**, wherein said compound of formula 6 is prepared by heating a compound of formula 5

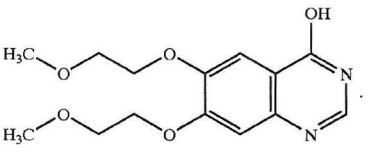
5



in a suspension of metal alkali and solvent.

70. The process of claim **68**, wherein said compound of formula 4 is prepared by chlorinating a compound of formula 3

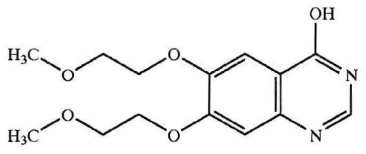
3



71. A process for the production of the polymorph B of claim **1** comprising the steps of:

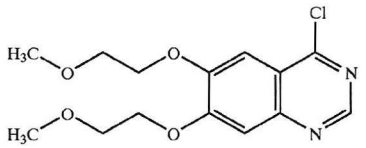
a) substitution chlorination of a compound of formula 3

3



having an hydroxyl group, to provide a compound of formula 4

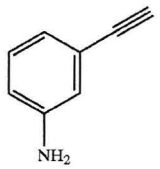
4



by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

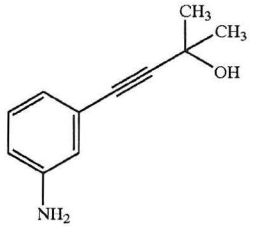
b) preparation of a compound of formula 6

6



in situ from starting material of compound of formula 5

5



by heating the compound of formula 5 in a suspension of metal alkali and solvent;

c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-mothoxyethoxy)-4-quinazolinamine hydrochloride; and

d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

72. The process of claim **71**, wherein the substitution chlorination is quenched in the presence of aqueous sodium hydroxide.

73. The process of claim **71**, wherein the substitution chlorination is quenched in the presence of aqueous sodium bicarbonate.

74. The process of claim **71**, wherein the substitution chlorination is quenched in the presence of aqueous potassium hydroxide, aqueous potassium bicarbonate, aqueous potassium carbonate, aqueous sodium carbonate, or a mixture thereof.

75. A process of making a composition which composition comprises a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, comprising admixing the crystalline-polymorph with a carrier.

76. The process of claim **75**, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in FIG. **3**.

77. The process of claim **75**, wherein the carrier is a pharmaceutically acceptable carrier.

78. A process for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:

a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

b) cooling the solution to between about 65 and 70° C.;

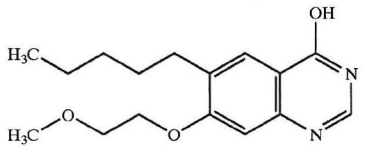
c) clarifying the solution; and

d) precipitating polymorph B by further cooling the clarified solution.

79. A process for the production of the polymorph B of claim **3** comprising the steps of:

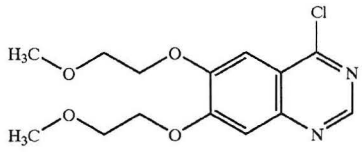
a) substitution chlorination of a compound of formula 3

3



having an hydroxyl group, to provide a compound of formula 4

4

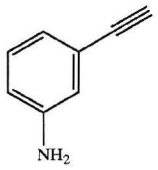


by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

b) quenching the substitution chlorination in the presence of aqulous sodium bicarbonate;

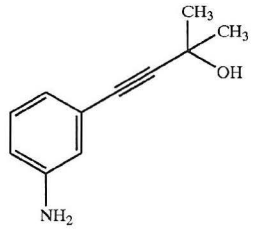
c) preparation of a compound of formula 6

6



in situ from starting material of compound of formula 5

5



by heating the compound of formula 5 in a suspension of metal alkali and solvent;

d) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; and

e) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

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CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
OSI PHARMACEUTICALS, LLC and GENENTECH, INC.

DEFENDANTS
APOTEX INC. and APOTEX CORP.

(b) County of Residence of First Listed Plaintiff
(EXCEPT IN U.S. PLAINTIFF CASES)

County of Residence of First Listed Defendant
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Jack B. Blumenfeld 302-658-9200
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street; P.O. Box 1347; Wilmington, DE 19899

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 271
Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER RULE 23, F.R.Cv.P. **DEMAND $** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY *(See instructions):* JUDGE Robinson DOCKET NUMBER 09-185 (Consolidated)

DATE 09/02/2015 SIGNATURE OF ATTORNEY OF RECORD /s/ Jack B. Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) **Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) **County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) **Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; **NOTE: federal question actions take precedence over diversity cases.**)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerk(s) in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. **Origin.** Place an "X" in one of the six boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.