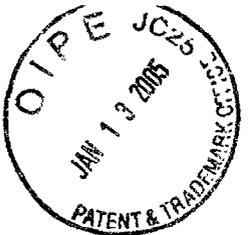


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COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	U.S. Patent No. 5,747,498
Issued:	05 May 1998
To:	Rodney Caughren Schnur and Lee Daniel Arnold
Assignee:	Pfizer Inc.
Title:	Alkynyl and Azido-Substituted 4- Anilinoquinazolines

Mail Stop Patent Ext.
 Commissioner for Patents
 U.S. Patent and Trademark Office
 P.O. Box 1450
 Alexandria, VA 22313-1450

**APPLICATION FOR EXTENSION
 OF PATENT TERM UNDER 35 U.S.C. 156**

Sir:

Applicant, Pfizer, Inc., is a corporation organized and existing under the laws of the state of Delaware, having a place of business at 235 East 42nd Street, New York, New York. Applicant hereby presents this application for extension of the term of U.S. Patent Number 5,747,498 under the authority 35 U.S.C. § 156. A copy of the patent is provided as **Exhibit A**.

Applicant is entitled to apply for this Patent Term Extension of Letters Patent of the United States No. 5,747,498, granted to Rodney Caughren Schnur and Lee Daniel Arnold on May 5, 1998, for "Alkynyl and Azido-Substituted 4-Anilinoquinazolines," because it is the assignee of the entire right, title, and interest in the '498 patent. Pfizer gained rights to the U.S. Patent No. 5,747,498 by an assignment from the inventors recorded in the records of the United States Patent and Trademark Office at Reel 008010, Frame 0503 on May 28, 1996. A copy of the assignment is provided as **Exhibit B**.

Applicant notes that the Abstract of Title for the '498 patent, as rendered on the Office's "Assignments on the Web" website, indicates that Pfizer is the "assignor" and OSI Pharmaceuticals, Inc. ("OSI", formerly known as Oncogene Science, Inc.) is the "assignee" of the patent. A copy of the Abstract is annexed as **Exhibit C**. However, the information set forth in the Abstract is in error.

Pfizer has exclusively licensed the '498 patent to OSI. A copy of the license, dated 23 May 2000, is attached as **Exhibit D**. Applicant and OSI collaborated for several years in the development of TARCEVA™. The collaborative relationship is memorialized in a "Collaboration Research Agreement" recorded in the assignment records of the Patent and Trademark Office at Reel 01073, Frame 0623; Reel 010859, Frame 0249; and Reel 013746, Frame 0394. (It appears that the same document was recorded four times at three locations.) These records are annexed as **Exhibits E, F, and G**. None of these agreements (notwithstanding the use of standard recordation cover sheets that refer to "conveying" and "receiving" parties) effects a conveyance of rights in the '498 patent. Thus, title to the '498 patent remains vested in Pfizer.

Applicant also observes that the license by Pfizer to OSI is a condition of an order by the Federal Trade Commission issued on 27 July 2000. A copy of that order is attached as **Exhibit H**.

Applicant's exclusive licensee, OSI, is the sponsor of New Drug Application ("NDA") No. 21-743 for TARCEVA™ (erlotinib hydrochloride), claimed by U.S. Patent No. 5, 747,498. OSI acts as the agent of the Applicant, Pfizer, for the purpose of this application for patent term extension. Additionally, the undersigned registered practitioner holds a Power of Attorney to represent the applicant, Pfizer, before the U.S. Patent and Trademark Office in connection with the present application for extension of patent term. A copy of the Power of Attorney is attached as **Exhibit I**.

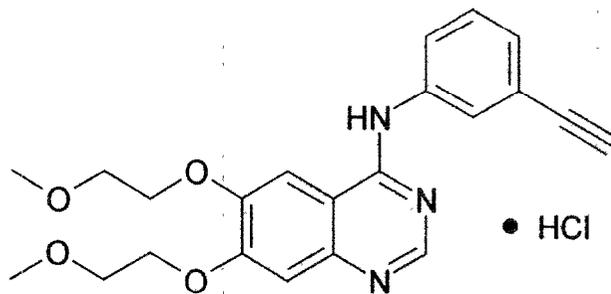
Pfizer is authorized to rely on the activities of the marketing applicant for TARCEVA™ (erlotinib hydrochloride) relating to NDA No. 21-743 with respect to the present application, as established by the letter annexed as **Exhibit J**.

Applicant hereby requests an extension of patent term under U.S.C. 156, as provided by 37 C.F.R. 1.730(c), by providing the following information required under

convenience of the Office, the information is presented in a format that follows the paragraph numbering in 37 C.F.R. 1.740.

(1) Identification of the Approved Product [§ 1.740(a)(1)]

The approved product, TARCEVA™, contains as the active ingredient erlotinib having the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine; also known as [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine; also known (by a different numbering system on the quinazoline) as [6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine. The structural formula for erlotinib, present in the approved product as the hydrochloride salt, is:



(2) Federal Statute Governing Regulatory Approval of the Approved Product [§ 1.740(a)(2)]

The approved product TARCEVA™ was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

(3) Date of Approval for Commercial Marketing [§ 1.740(a)(3)]

OSI received permission for commercial marketing or use of TARCEVA™ under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) on 18 November 2004. A copy of the approved label for TARCEVA™ is attached as **Exhibit K**.

(4) Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]

The active ingredient in TARCEVA™ is erlotinib, present in the approved product as erlotinib hydrochloride. Neither erlotinib nor its hydrochloride salt has been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act prior to the approval of NDA 21-743 by the Food and Drug Administration on 18 November 2004.

(5) Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]

This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period, expiring 16 January 2005, pursuant to 37 C.F.R. 1.720(f).

(6) Complete Identification of the Patent for Which Extension Is Being Sought [§ 1.740(a)(6)]

The patent for which extension is being sought is identified as follows:

Inventors: Rodney Caughren Schnur and Lee Daniel Arnold
Patent No.: 5,747,498
Title: Alkynyl and Azido-Substituted 4-Anilinoquinazolines
Issued: 05 May 1998
Expires: 06 June 2015

(7) Copy of the Patent for Which an Extension is Being Sought [§ 1.740(a)(7)]

A copy of U.S. Patent No. 5,747,498, for which an extension is being sought, is attached as **Exhibit A**.

(8) Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]

No disclaimer, certificate of correction or reexamination certificate has issued for U.S. Patent No. 5,747,498. A copy of the most recent maintenance fee statement is attached as **Exhibit L**.

(9) Statement Regarding Patent Claims Relative to Approved Product [§ 1.740(a)(9)]

The statements provided herein are made solely to comply with the requirements of 37 C.F.R. §1.740(a)(9). We note that, as the M.P.E.P. acknowledges, the requirement of 37 C.F.R. §1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

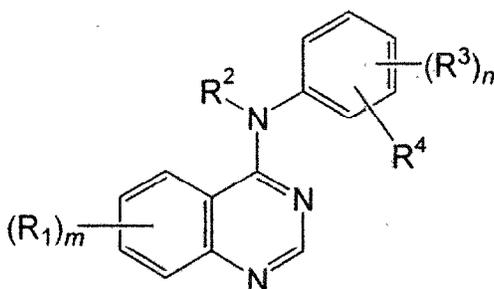
(a) At least the following claims of U.S. Patent No. 5,747,498 cover the approved product, therapeutic methods using the approved product, or methods of manufacturing the approved product. Specifically, the approved product is claimed in Claims 1, 2, 3, 4, 8, 10, 11, 22, and 23; methods of treatment utilizing the approved product are claimed in Claims 12, 13, 14, 27, 28, and 29; and methods of manufacturing the approved product are claimed in Claims 17, 18, 19, 20, and 21.

(b) Pursuant to M.P.E.P. §2573 and 37 C.F.R. §1.740(a)(9), the following explanation is provided which shows how each of the above-listed claims of the patent claim the approved product, or a method of making or using the approved product.

Claim 1 reads as follows:

1. A compound of the formula

I



or a pharmaceutically acceptable salt thereof wherein:

X is halo or hydroxy;

m is 1, 2, or 3;

each R^1 is independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxyamino, carboxy, nitro, guanidino, ureido, cyano, trifluoromethyl, and $-(C_1-C_4 \text{ alkylene})-W$ -(phenyl) wherein W is a single bond, O, S or NH;

or each R^1 is independently selected from R^9 and C_1-C_4 alkyl substituted by cyano, wherein R^9 is selected from the group consisting of R^5 , $-OR^6$, $-NR^6R^6$, $-C(O)R^7$, $-NHOR^5$, $-OC(O)R^6$, cyano, A and $-YR^5$; R^5 is C_1-C_4 alkyl; R^6 is independently hydrogen or R^5 ; R^7 is R^5 , $-OR^6$ or $-NR^6R^6$; A is selected from piperidino, morpholino, pyrrolidino, 4- R^6 -piperazin-1-yl, imidazol-1-yl, 4-pyridon-1-yl, $-(C_1-C_4 \text{ alkylene})(CO_2H)$, phenoxy, phenyl, phenylsulfanyl, C_2-C_4 alkenyl, and $-(C_1-C_4 \text{ alkylene})C(O)NR^6R^6$; and Y is S, SO, or SO_2 ; wherein the alkyl moieties in R^5 , $-OR^6$ and $-NR^6R^6$ are optionally substituted by one to three halo substituents and the alkyl moieties in R^5 , $-OR^6$ and NR^6R^6 are optionally substituted by 1 or 2 R^9

groups, and wherein the alkyl moieties of said optional substituents are optionally substituted by halo or R^9 , with the proviso that two heteroatoms are not attached to the same carbon atom;

or each R^1 is independently selected from $-NHSO_2R^5$, phthalimido-(C_1-C_4)-alkylsulfonylamino, benzamido, benzenesulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, and R^{10} -(C_2-C_4)-alkanylamino wherein R^{10} is selected from halo, $-OR^6$, C_2-C_4 alkanoyloxy, $-C(O)R^7$, and $-NR^6R^6$; and wherein said $-NHSO_2R^5$, phthalimido-(C_1-C_4)-alkylsulfonylamino, benzamido, benzenesulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, and R^{10} -(C_2-C_4)-alkanoylamino R^1 groups are optionally substituted by 1 or 2 substituents independently selected from halo, C_1-C_4 alkyl, cyano, methanesulfonyl and C_1-C_4 alkoxy;

or two R^1 groups are taken together with the carbons to which they are attached to form a 5-8 membered ring that includes 1 or 2 heteroatoms selected from O, S and N;

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by 1 to 3 substituents independently selected from halo, C_1-C_4 alkoxy, $-NR^6R^6$, and $-SO_2R^5$;

n is 1 or 2 and each R^3 is independently selected from hydrogen, halo, hydroxy, C_1-C_6 alkyl, $-NR^6R^6$, and C_1-C_4 alkoxy, wherein the alkyl moieties of said R^3 groups are optionally substituted by 1 to 3 substituents independently selected from halo, C_1-C_4 alkoxy, $-NR^6R^6$, and $-SO_2R$; and,

R^4 is azido or $-(\text{ethynyl})-R^{11}$ wherein R^{11} is hydrogen or C_1-C_6 alkyl optionally substituted by hydroxy, $-OR^6$, or $-NR^6R^6$.

Claim 1 reads on the approved product when the variables in Formula I are defined as follows:

m is 2;

each R^1 is R^9 , wherein R^9 is $-OR^6$, wherein R^6 is R^5 , which is C_{1-4} alkyl (i.e. ethyl) substituted by one R^9 , wherein that R^9 is $-OR^6$, wherein R^6 is R^5 , and that R^5 is C_{1-4} alkyl (i.e. methyl);

n is 1;

R² is hydrogen;

R³ is hydrogen; and

R⁴ is -(ethynyl)-R¹¹, wherein R¹¹ is hydrogen.

Accordingly, Claim 1 reads on the approved product.

Claim 2 reads as follows:

2. The compound according to claim 1 wherein R² is hydrogen and R⁴ is -(ethynyl)-R¹¹.

Claim 2 reads on the approved product when R² is hydrogen and R⁴ is -(ethynyl)-R¹¹, wherein R¹¹ is hydrogen, while the remaining variables are as defined in Claim 1.

Claim 3 reads as follows:

3. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a pharmaceutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

The approved product is approved for use in the treatment of non-small cell lung cancer, which is a hyperproliferative disorder. Further, the approved product is approved as a pharmaceutical composition (i.e. a tablet) containing lactose monohydrate. Pharmaceutically acceptable carriers are defined at column 16, line 21 to include an inert diluent or filler. Lactose monohydrate is an inert diluent or filler within the meaning of the patent. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective.

Claim 3 claims a composition for such cancer treatment comprising a pharmaceutically effective amount of the compound of Claim 1 and a suitable carrier. Thus, Claim 3 reads on the approved product.

Claim 4 reads as follows:

4. The compound of claim 1 wherein each R¹ is independently selected from hydrogen, hydroxy, hydroxyamino, nitro, carbamoyl, ureido, R⁵ optionally substituted with halo, -OR⁶, carboxy, or -C(O)NH₂; -OR⁵ optionally substituted with halo, -OR⁶,

-OC(O)R⁶, -NR⁶R⁶, or A; -NR⁶R⁶, -C(O)NR⁶R⁶, -SR⁵, phenyl-(C₂-C₄)-alkoxy wherein said phenyl moiety is optionally substituted with 1 or 2 substituents independently selected from halo, R⁵ or -OR⁵.

Claim 4 reads on the approved product when R¹ is -OR⁵ (for which R⁵ is C₁-C₄alkyl i.e. ethyl) optionally substituted with -OR⁶ (for which R⁶ is R⁵, which in turn is C₁₋₄alkyl i.e. methyl;

and variables m, n, R², R³ and R⁴ are as defined in Claim 1 in which:

m is 2;

n is 1;

R² is hydrogen;

R³ is hydrogen; and

R⁴ is -(ethynyl)-R¹¹, wherein R¹¹ is hydrogen.

Accordingly, Claim 4 reads on the approved product.

Claim 8 reads as follows:

8. The compound of claim 1 selected from the group consisting of:

(6,7-dimethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;

(6,7-dimethoxyquinazolin-4-yl)-[3-(3'-hydroxypropyn-1-yl)phenyl]-amine;

[3-(2'-(aminomethyl)-ethynyl)phenyl]-(6,7-dimethoxyquinazolin-4-yl)-amine;

(3-ethynylphenyl)-(6-nitroquinazolin-4-yl)-amine;

(6,7-dimethoxyquinazolin-4-yl)-(4-ethynylphenyl)-amine;

(6,7-dimethoxyquinazolin-4-yl)-(3-ethynyl-2-methylphenyl)-amine;

(6-aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine;

(3-ethynylphenyl)-(6-methanesulfonylaminoquinazolin-4-yl)-amine;

(3-ethynylphenyl)-(6,7-methylenedioxyquinazolin-4-yl)-amine;

(6,7-dimethoxyquinazolin-4-yl)-(3-ethynyl-6-methylphenyl)-amine;

(3-ethynylphenyl)-(7-nitroquinazolin-4-yl)-amine;

(3-ethynylphenyl)-[6-(4'-toluenesulfonylamino)quinazolin-4-yl]-amine;

(3-ethynylphenyl)-{6-[2'-phthalimido-eth-1'-yl-sulfonylamino]quinazolin-4-yl}-
amine;

(3-ethynylphenyl)-(6-guanidinoquinazolin-4-yl)-amine;

(7-aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(3-ethynylphenyl)-(7-methoxyquinazolin-4-yl)-amine;
(6-carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(7-carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;
[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine;
(3-azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine;
(3-azido-5-chlorophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine;
(4-azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine;
(3-ethynylphenyl)-(6-methansulfonyl-quinazolin-4-yl)-amine;
(6-ethansulfanyl-quinazolin-4-yl)-(3-ethynylphenyl)-amine
(6,7-dimethoxy-quinazolin-4-yl)-(3-ethynyl-4-fluoro-phenyl)-amine;
(6,7-dimethoxy-quinazolin-4-yl)-[3-(propyn-1'-yl)-phenyl]-amine;
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(5-ethynyl-2-methyl-phenyl)-
amine;
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-4-fluoro-phenyl)-amine;
[6,7-bis-(2-chloro-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
[6-(2-chloro-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-
amine;
[6,7-bis-(2-acetoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
2-[4-(3-ethynyl-phenylamino)-7-(2-hydroxy-ethoxy)-quinazolin-6-yloxy]-ethanol;
[6-(2-acetoxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-
phenyl)-amine;
[7-(2-chloro-ethoxy)-6-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-
amine;
[7-(2-acetoxy-ethoxy)-6-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-
phenyl)-amine;
2-[4-(3-ethynyl-phenylamino)-6-(2-hydroxy-ethoxy)-quinazolin-7-yloxy]-ethanol;
2-[4-(3-ethynyl-phenylamino)-7-(2-methoxy-ethoxy)-quinazolin-6-yloxy]-
ethanol;
2-[4-(3-ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-
ethanol;

[6-(2-acetoxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
(3-ethynyl-phenyl)-{6-(2-methoxy-ethoxy)-7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-quinazolin-4-yl}-amine;
(3-ethynyl-phenyl)-[7-(2-methoxy-ethoxy)-6-(2-morpholin-4-yl)-ethoxy]-quinazolin-4-yl]-amine;
(6,7-diethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(6,7-dibutoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(6,7-diisopropoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(6,7-diethoxyquinazolin-1-yl)-(3-ethynyl-2-methyl-phenyl)-amine;
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynyl-2-methyl-phenyl)-amine;
(3-ethynylphenyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-1-yl]-amine;
[6,7-bis-(2-hydroxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine; and
2-[4-(3-ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethanol.

The nineteenth compound listed in Claim 8 (at column 40, line 1), [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine, is erlotinib. Accordingly, Claim 8 reads on the approved product.

Claim 10 reads as follows:

The compound of claim 1 selected from the group consisting of:

(6,7-diethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(3-ethynylphenyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-1-yl]-amine;
[6,7-bis-(2-hydroxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine;
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine;
(6,7-dimethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(3-ethynylphenyl)-(6-methanesulfonylamino-quinazolin-1-yl)-amine; and,
(6-amino-quinazolin-1-yl)-(3-ethynylphenyl)-amine.

The fourth compound listed in Claim 10 (at column 41, line 44), [6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine, is erlotinib. Accordingly, Claim 10 reads on the approved product.

Claim 11 reads as follows:

11. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

The approved product is approved for use in the treatment of non-small cell lung cancer, which is a hyperproliferative disorder, and is approved as a pharmaceutical composition (i.e. a tablet) containing lactose monohydrate. Pharmaceutically acceptable carriers are defined at column 16, line 21 to include an inert diluent or filler. Lactose monohydrate is an inert diluent or filler within the meaning of the patent. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective.

Claim 11 claims a composition for such cancer treatment comprising a therapeutically-effective amount of the compound of Claim 1 and a suitable carrier. Thus, Claim 11 reads on the approved product.

Claim 12 reads as follows:

12. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

The approved product is approved for use in the treatment of non-small cell lung cancer, which is a hyperproliferative disorder, in mammalian patients. Claim 12 claims such treatment comprising administering a therapeutically-effective amount of the compound of claim 1. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective. Thus, Claim 12 reads on an approved method of use of the approved product.

Claim 13 reads as follows:

13. The method of claim 12 wherein said hyperproliferative disorder is cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer. Claim 13 claims such treatment of cancer comprising administering a therapeutically-effective amount of the compound of Claim 1. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective. Thus, Claim 13 reads on an approved method of use of the approved product.

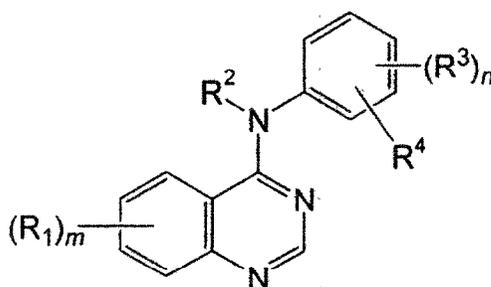
Claim 14 reads as follows:

14. The method of claim 13 wherein said cancer is brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, gynecological or thyroid cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer. Claim 14 claims such treatment of lung cancer comprising administering a therapeutically-effective amount of the compound of claim 1. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective. Thus, Claim 14 reads on an approved method of use of the approved product.

Claim 17 reads as follows:

17. A process for preparing a compound of the formula



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

m is 1, 2, or 3;

each R^1 is independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxyamino, carboxy, nitro, guanidino, ureido, cyano, trifluoromethyl, and $-(C_1-C_4 \text{ alkylene})-W$ -(phenyl) wherein W is a single bond, O, S or NH;

or each R^1 is independently selected from R^9 and (C_1-C_4) alkyl substituted by cyano, wherein R^9 is selected from the group consisting of R^5 , $-OR^6$, $-NR^6R^6$, $-C(O)R^7$, $-NHOR^5$, $-OC(O)R^6$, cyano, A and $-YR^5$; R^5 is C_1-C_4 alkyl; R^6 is independently hydrogen or R^5 ; R^7 is R^5 , $-OR^6$ or $-NR^6R^6$; A is selected from piperidino, morpholino, pyrrolidino, 4- R^6 -piperazin-1-yl, imidazol-1-yl, 4-pyridon-1-yl, $-(C_1-C_4 \text{ alkylene})(CO_2H)$, phenoxy, phenyl, phenylsulfanyl, C_2-C_4 alkenyl, and $-(C_1-C_4 \text{ alkylene})C(O)NR^6R^6$; and Y is S, SO, or SO_2 ; wherein the alkyl moieties in R^5 , $-OR^6$ and $-NR^6R^6$ are optionally substituted by one to three substituents independently selected from halo and R^9 , and wherein the alkyl moieties of said optional substituents are optionally substituted by halo or R^9 , with the proviso that two heteroatoms are not attached to the same carbon atom, and with the further proviso that no more than three R^9 groups may comprise a single R^1 group;

or each R^1 is independently selected from $-NHSO_2R^5$, phthalimido- (C_1-C_4) -alkylsulfonylamino, benzamido, benzenesulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, and R^{10} - (C_2-C_4) -alkanyl amino wherein R^{10} is selected from halo, $-OR^6$, C_2-C_4 alkanoyloxy, $-C(O)R^7$, and $-NR^6R^6$; and wherein the foregoing R^1 groups are optionally substituted by 1 or 2 substituents independently selected from halo, C_1-C_4 alkyl, cyano, methanesulfonyl and C_1-C_4 alkoxy;

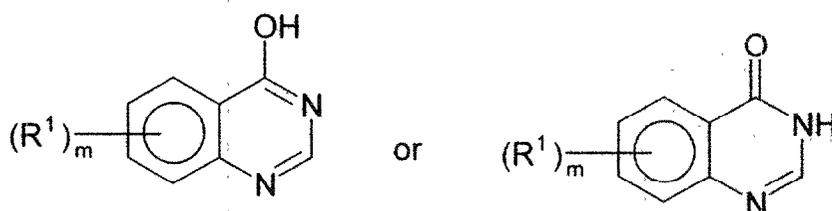
or two R^1 groups are taken together with the carbons to which they are attached to form a 5-8 membered ring that includes 1 or 2 heteroatoms selected from O, S and N;

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by 1 to 3 substituents independently selected from halo, C_1-C_4 alkoxy, $-NR^6R^6$, and $-SO_2R^5$;

n is 1 or 2 and each R³ is independently selected from hydrogen, halo, hydroxy, C₁-C₆alkyl, -NR⁶R⁶, and C₁-C₄alkoxy, wherein the alkyl moieties of said R³ groups are optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄alkoxy, -NR⁶R⁶, and -SO₂R; and, R⁴ is azido or -(ethynyl)-R¹¹ wherein R¹¹ is hydrogen or C₁-C₆alkyl optionally substituted by hydroxy, -OR⁶, or -NR⁶R⁶;

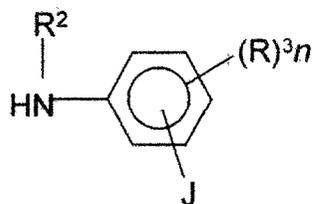
which comprises

a) treating a compound of the formula



wherein R¹ and m are as defined above, with CCl₄ and (C₆-C₁₀aryl)₃P, optionally supported on an inert polymer, wherein the aryl moieties of said (C₆-C₁₀aryl)₃P are optionally substituted by C₁-C₆alkyl; and

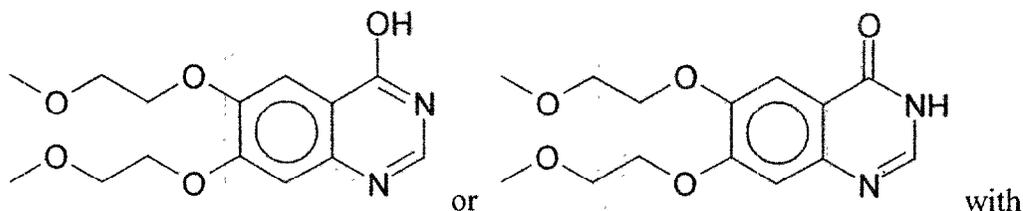
b) treating the product of step a) with a compound of the formula¹



wherein R², R³ and n are as defined above, and J is Y or R⁴, wherein R⁴ is as defined above and wherein Y is NH₂, Br, I or trifluoromethanesulfonyloxy, with the proviso that when J is Y then the product of step b) must further be treated with an alkyne where Y is Br, I or trifluoromethanesulfonyloxy, or an azide where Y is NH₂.

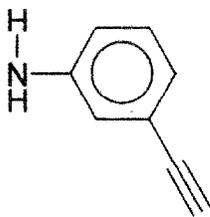
¹ The formula is reproduced as it appears in the patent. However, the patent reflects a typographical error: the "R group" substituent of the phenyl ring should be represented as -(R³)_n, rather than -(R)³. Pfizer intends to file a request for a Certificate of Correction to rectify this error.

The approved product may be produced by a process which includes treating



CCl_4 and $(\text{C}_6\text{-C}_{10}\text{aryl})_3\text{P}$, and

treating the product with



Claim 17 reads on a method of manufacturing the approved product when m is 2; R^1 is R^9 , in which R^9 is $-\text{OR}^6$, in which R^6 is R^5 , which is C_{1-4} alkyl (i.e. ethyl) substituted by one R^9 , in which this R^9 is $-\text{OR}^6$, in which this R^6 is R^5 , which is C_{1-4} alkyl (i.e. methyl); n is 1; R^2 is hydrogen; R^3 is hydrogen; and R^4 is $-(\text{ethynyl})-\text{R}^{11}$, in which R^{11} is hydrogen.

Claim 18 reads as follows:

18. The process of claim 17 wherein each aryl group is selected from phenyl, naphth-1-yl and naphth-2-yl.

Claim 18 provides that each aryl group may be phenyl such that reactant $(\text{C}_6\text{-C}_{10}\text{aryl})_3\text{P}$ is $\text{P}(\text{Ph})_3$ in a method of manufacturing a compound of Formula I or a pharmaceutically acceptable salt. Accordingly, when the variables of Formula I are as defined in Claim 17, Claim 18 reads on a method of manufacturing the approved product.

Claim 19 reads as follows:

19. The process of claim 17 wherein each Ar in $(\text{C}_6\text{-C}_{10}\text{aryl})_3\text{P}$ is phenyl.

Claim 19 provides that each aryl group is phenyl such that reactant $(\text{C}_6\text{-C}_{10}\text{aryl})_3\text{P}$ is $\text{P}(\text{Ph})_3$ in a method of manufacturing a compound of Formula I or a pharmaceutically acceptable salt. Accordingly, when the variables of Formula I are as defined in Claim 17, Claim 19 reads on a method of manufacturing of the approved product.

Claim 20 reads as follows:

20. The process of claim 17 wherein said $(C_6-C_{10}aryl)_3P$ is supported on an inert polymer.

Claim 20 provides that reactant $(C_6-C_{10}aryl)_3P$ is supported on an inert polymer in a method of manufacturing a compound of Formula I or a pharmaceutically acceptable salt. Accordingly, when the variables of Formula I are as defined in Claim 17, Claim 20 reads on a method of manufacturing of the approved product.

Claim 21 reads as follows:

21. The process of claim 20 wherein said inert polymer is a divinylbenzene-cross-linked polymer of styrene is phenyl.

Claim 21 provides that reactant $(C_6-C_{10}aryl)_3P$ is supported on an inert polymer, divinylbenzene-cross-linked polymer of styrene, in a method of manufacturing a compound of Formula I or a pharmaceutically acceptable salt. Accordingly, when the variables of Formula I are as defined in Claim 17, Claim 21 reads on a method of manufacturing of the approved product.

Claim 22 reads as follows:

22. The composition of claim 3 wherein said hyperproliferative disorder is cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer, which is a hyperproliferative disorder. As evidenced by the approval of the product, the FDA has determined that the dosages provided by the approved product formulations are effective. Claim 22 claims a composition for such cancer treatment comprising a pharmaceutically effective amount of the compound of Claim 1. Thus, Claim 22 reads on the approved product.

Claim 23 reads as follows:

The composition of claim 22 wherein said cancer is selected from the group consisting of renal, liver, kidney, colorectal, brain, lung, skin, bladder, gastric, pancreatic, breast, head, neck, oesophageal, vulval, gynecological, and thyroid cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer. Claim 23 claims a composition for such lung cancer treatment comprising a pharmaceutically effective amount of the compound of Claim 1. Thus, Claim 23 reads on the approved product.

Claim 27 reads as follows:

27. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a pharmaceutically effective amount of the compound of claim 1.

The approved product is approved for use in the treatment of non-small cell lung cancer, which is a hyperproliferative disorder, in mammalian patients. Thus, Claim 27 reads on an approved method of use of the approved product.

Claim 28 reads as follows:

28. The method of claim 27 wherein said hyperproliferative disorder is cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer. Thus, Claim 28 reads on an approved method of use of the approved product.

Claim 29 reads as follows:

29. The method of claim 28 wherein said cancer is selected from the group consisting of renal, liver, kidney, colorectal, brain, lung, skin, bladder, gastric, pancreatic, breast, head, neck, oesophageal, vulval, gynecological, and thyroid cancer.

The approved product is approved for use in the treatment of non-small cell lung cancer. Thus, Claim 29 reads on an approved method of use of the approved product.

(10) Relevant Dates Under 35 U.S.C. §156 for Determination of Applicable Regulatory Review Period [§1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and human Services to determine the applicable review period are as follows:

(a) *Patent Issue Date*

U.S. Patent No. 5,747,498 issued on 5 May 1998.

(b) *IND Effective Date [35 U.S.C. §156(g)(1)(B)(i); 37 C.F.R. §1.740(a)(10)(i)(A)]*

Investigational New Drug Application (IND 53,728) was submitted on 15 July 1997 and the IND was effective on 10 October 1997.

(c) *NDA submission Date [35 U.S.C. §156(g)(1)(B)(i); 37 C.F.R. §1.740(a)(10)(i)(B)]*

New Drug Application (NDA 21-743) was submitted on 20 January 2004 as part of a rolling NDA submission procedure.

(d) *NDA Issue Date [35 U.S.C. §156(g)(1)(B)(ii); 37 C.F.R. §1.740(a)(10)(i)(C)]*

New Drug Application (NDA 21-743) was approved on 18 November 2004.

(11) Summary of Significant Events During Regulatory Review Period
[§ 1.740(a)(11)]

A brief description of the significant activities undertaken during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached as **Exhibit M**. The owner of the '498 patent, Pfizer, is entitled to rely upon the activities of the NDA sponsor, OSI, for the purpose of the present application under 35 U.S.C. § 156, as evidenced by the letter annexed as Exhibit J. See M.P.E.P. § 2752.

(12) Statement Concerning Eligibility for and Duration of Extension Sought
Under §156 [§ 1.740(a)(12)]

(12)(A) Applicant is of the opinion that U.S. Patent No. 5,747,498 is eligible for an extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension as follows:

- a) 35 U.S.C. 156(a): U.S. Patent No. 5,747,498 claims a product, a method of using a product, or a method of manufacturing a product.
- b) 35 U.S.C. 156(a)(1): The term of U.S. Patent No. 5,747,498 has not expired before submission of this application.
- c) 35 U.S.C. 156(a)(2): The term of U.S. Patent No. 5,747,498 has never been extended under this provision of the law.
- d) 35 U.S.C. 156(a)(3): The application is submitted by an agent of the patent owner of record in accordance with the requirements of 35 U.S.C. 156(d) and the rules of the U.S. Patent and Trademark Office.
- e) 35 U.S.C. 156(a)(4): The product TARCEVA™ has been subjected to a regulatory review period before its commercial marketing or use.
- f) 35 U.S.C. 156(a)(5)(A): The commercial marketing or use of the product, TARCEVA™, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal

Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred.

g) 35 U.S.C. 156(c)(4): No other patent has been extended for the same regulatory review period for the product, TARCEVA™.

(12)(B): The length of extension of the patent term of U.S. Patent 5,747,498 claimed by applicant is **1261 days**. The length of the extension was determined pursuant to 37 CFR 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on 10 October 1997 and ended on 18 November 2004 which is a total of 2596 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(1)(B)(i) began on 10 October 1997 and ended on 20 January 2004, which is 2293 days; and

(ii) The period of review under 35 U.S.C. 156(g)(1)(B)(ii) began on 20 January 2004 and ended on 18 November 2004, which is 303 days;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph 12(B)(a) above (2596 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (05 May 1998) which is 207 days, and

(ii) The number of days during which applicant did not act with due diligence which is 0 days, and

(iii) One-half of (2293 minus 207 days), which is 1043 days;

(iv) The regulatory review period is calculated by subtracting the number of days determined in sub-paragraph 12(B)(b)(i)-(iii) from the entire regulatory review period as determined in sub-paragraph 12(B)(a) (which is 2596 days - 207 - 1043 days) which equals 1346 days.

(c) The number of days as determined in sub-paragraph 12(B)(b)(iv) (1346 days) when added to the term of the patent (06 June 2015) would result in the date 11 February 2019;

(d) Fourteen (14) years, when added to the date of NDA approval (18 November 2004) would result in the date 18 November 2018.

(e) The earlier date as determined in sub-paragraphs 12(B)(c) and 12(B)(d) is 18 November 2018.

(f) Since the original patent was issued after 24 September 1984, five (5) years when added to the expiration date of the patent (06 June 2015) would result in the date 06 June 2020.

(g) The earlier date as determined in sub-paragraph 12(B)(e) and 12(B)(f) is 18 November 2018, which is 1261 days extension from the expiration date of the patent.

(13) Statement Pursuant to 37 C.F.R. [§ 1.740(a)(13)]

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. § 1.765.

(14) Applicable Fee [§ 1.740(a)(14)]

The prescribed fee for receiving and acting upon this application is to be charged to Deposit Account **50-2783** as authorized in the attached letter, which is submitted in triplicate.

(15) Name and Address for Correspondence [§ 1.740(a)(14)]

Correspondence related to this application for extension of the patent term of U.S.

Patent No. 5,747,498 should be addressed to:

Shu M. Lee (Reg. No. 41,147)
OSI Pharmaceuticals Inc.
58 South Service Road, Suite 110
Melville, NY 11747

Tel. (631) 962-2056 or (516) 924-4035
Fax (631) 752-3880

(16) Additional Copies of the Application for Extension [§ 1.740(b)]

This application for extension of the patent term of U.S. Patent No. 5,747,498 is being submitted as one original and TWO additional copies thereof. Applicant hereby certifies that each copy submitted herein is a true copy.

Transmitted herewith IN THREE COPIES total is the application for extension of patent term of U.S. Patent No. 5,747,498 under 35 U.S.C. 156. Please charge \$1,120.00 in accordance with 37 CFR 1.20(j)(1) to OSI Pharmaceuticals, Inc. Deposit Account No. 50-2783. The undersigned has authority to request that the Office charge this account for this application.

Respectfully submitted,



Matthew J. Golden
Registration No. 35,161
Mintz, Levin, Cohn, Ferris, Glovsky and
Popeo, P.C.
Attorney for Applicant
Telephone No. (212) 692-6818

Date: Jan 13, 2005

Index of Attachments

- Exhibit A: Copy of U.S. Patent No. 5,747,498
- Exhibit B: Assignment from inventors to Pfizer Inc.
- Exhibit C: Abstract of Title from USPTO Database for U.S. Patent No. 4,747,498
- Exhibit D: Exclusive License Agreement between OSI and Pfizer
- Exhibit E: Collaboration Research Agreement between OSI and Pfizer recorded at Reel 010703, Frame 0623
- Exhibit F: Collaboration Research Agreement between OSI and Pfizer recorded at Reel 010859, Frame 0250
- Exhibit G: Collaboration Research Agreement between OSI and Pfizer recorded at Reel 013746, Frame 0442
- Exhibit H: Order from the Federal Trade Commission issued 27 July 2000
- Exhibit I: Authorization of Agent/Power of Attorney for U.S. Patent No. 5,747,498
- Exhibit J: Letter from OSI authorizing Pfizer's reliance on the activities of OSI before the Food and Drug Administration for obtaining an extension of patent term
- Exhibit K: Approved label for TARCEVA™
- Exhibit L: Maintenance Fee Statement for U.S. Patent No. 5,747,498
- Exhibit M: Brief Description of Significant Activities During Applicable Regulatory Review Period