



US00RE41065E

(19) **United States**
 (12) **Reissued Patent**
Schnur et al.

(10) **Patent Number:** **US RE41,065 E**
 (45) **Date of Reissued Patent:** **Dec. 29, 2009**

- (54) **ALKYNYL AND AZIDO-SUBSTITUTED 4-ANILINOQUINAZOLINES**
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- (21) Appl. No.: **12/038,530**
- (22) Filed: **Feb. 27, 2008**

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Related U.S. Patent Documents

Reissue of:

- (64) Patent No.: **5,747,498**
 Issued: **May 5, 1998**
 Appl. No.: **08/653,786**
 Filed: **May 28, 1996**

U.S. Applications:

- (63) Continuation-in-part of application No. PCT/IB95/00436, filed on Jun. 6, 1995.

- (51) **Int. Cl.**
C07D 239/94 (2006.01)
C07D 239/70 (2006.01)
A61K 31/517 (2006.01)
A61P 17/06 (2006.01)
A61P 35/00 (2006.01)

- (52) **U.S. Cl.** **514/266.1; 544/293; 544/283**

- (58) **Field of Classification Search** **544/293; 514/266.1**

See application file for complete search history.

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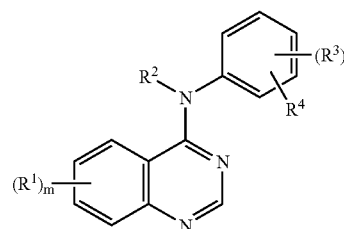
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- (57) **ABSTRACT**

The invention relates to compounds of the formula



and to pharmaceutically acceptable salts thereof, wherein R^1 , R^2 , R^3 , R^4 , n and m are as defined herein. The compounds of formula I are useful in the treatment of hyperproliferative diseases, such as cancer. The invention further relates to processes of making the compounds of formula I and to methods of using such compounds in the treatment of hyperproliferative diseases.

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**ALKYNL AND AZIDO-SUBSTITUTED 4-
ANILINOQUINAZOLINES**

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application is a continuation-in-part of PCT international application number PCT/IB95/00436, filed Jun. 6, 1995, which designates the United States.

BACKGROUND OF THE INVENTION

This invention relates to 4-(substituted phenylamino) quinazoline derivatives which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals.

Many of the current treatment regimes for cancer utilize compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on the rapidly dividing tumor cells can be beneficial. Alternative approaches to anti-cancer agents which act by mechanisms other than the inhibition of DNA synthesis have been explored in order to enhance the selectivity of action against cancer cells.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e. a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins which are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR) which possesses tyrosine kinase activity is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as a selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma which does not express the EGF receptor.

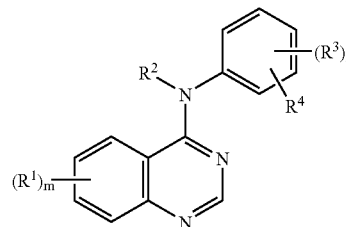
Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. More recently five European patent publications, namely EP 0 566 226 A1, EP 0 602 851 A1, EP 0 635 507 A1, EP 0 635 498 A1 and EP 0 520 722 A1 have disclosed that certain quinazoline derivatives possess anti-cancer properties which result from their tyrosine kinase inhibitory properties. Also PCT publication WO 92/20642 discloses

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Although the anti-cancer compounds described above make a significant contribution to the art there is a continuing search in this field of art for improved anti-cancer pharmaceuticals.

SUMMARY OF THE INVENTION

This invention relates to compounds of the formula



and to pharmaceutically acceptable salts and prodrugs thereof, wherein:

m is 1, 2, or 3;

each R¹ is independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxyamino, carboxy, nitro, guanidino, ureido, cyano, trifluoromethyl, and -(C₁-C₄ alkylene)-W-(phenyl) wherein W is a single bond, O, S or NH;

or each R¹ is independently selected from R⁹ and (C₁-C₄)-alkyl substituted by cyano, wherein R⁹ is selected from the group consisting of R⁵, -OR⁶, -NR⁶R⁶, -C(O)R⁷, -NHOR⁵, -OC(O)R⁶, cyano, A and -YR⁵; R⁵ is C₁-C₄ alkyl; R⁶ is independently hydrogen or R²; R⁷ is R⁵, -OR⁶ or -NR⁶R⁶; A is selected from piperidino, morpholino, pyrrolidino, 4-R⁶-piperazin-1-yl, imidazol-1-yl, 4-pyridon-1-yl, -(C₁-C₄ alkylene)(CO₂H), phenoxy, phenyl, phenylsulfanyl, C₂-C₄ alkenyl, and -(C₁-C₄ alkylene)C(O)NR⁶R⁶; and Y is S, SO, or SO₂; wherein the alkyl moieties in R⁵, -OR⁶ and -NR⁶R⁶ are optionally substituted by one to three substituents independently selected from halo and R⁹, and wherein the alkyl moieties of said optional substituents are optionally substituted by halo or R⁹, with the proviso that two heteroatoms are not attached to the same carbon atom, and with the further proviso that no more than three R⁹ groups may comprise a single R¹ group;

or each R¹ is independently selected from -NHSO₂R⁵, phthalimido-(C₁-C₄)-alkylsulfonylamino, benzamido, benzenesulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, and R¹⁰-(C₂-C₄)-alkanoylamino wherein R¹⁰ is selected from halo, -OR⁶, C₂-C₄ alkanoyloxy, -C(O)R⁷, and -NR⁶R⁶; and wherein the foregoing R¹ groups are optionally substituted by 1 or 2 substituents independently selected from halo, C₁-C₄ alkyl, cyano, methanesulfonyl and C₁-C₄ alkoxy;

or two R¹ 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;

R² is hydrogen or C₁-C₆ alkyl optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkoxy, -NR⁶R⁶, and -SO₂R⁵;

n is 1 or 2 and each R³ is independently selected from

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groups are optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkoxy, —NR⁶R⁶, and —SO₂R⁵; and,

R⁴ is azido or -(ethynyl)-R¹¹ wherein R¹¹ is hydrogen or C₁-C₆ alkyl optionally substituted by hydroxy, —OR⁶, or —NR⁶R⁶.

Preferred compounds of formula I include those wherein R² is hydrogen and R⁴ is -(ethynyl)-R¹¹.

Other preferred compounds of formula I include those wherein m is 1 or 2;

each R¹ is independently selected from the group consisting of hydrogen, hydroxy, hydroxyamino, carboxy, nitro, carbamoyl, ureido, R⁵ optionally substituted with halo, —OR⁶, carboxy, —C(O)NR⁶R⁶, A or —NR⁶R⁶; —OR⁵ optionally substituted with halo, —OR⁶, —OC(O)R⁶, —NR⁶R⁶, or A; —NR⁶R⁶, —C(O)R⁶, R⁵, —SR⁵, phenyl-(C₂-C₄)-alkoxy, cyano, phenyl; —NHR⁵ optionally substituted with halo or R⁹ wherein said R⁹ is optionally substituted by R⁹; —NHOR⁵, —SR⁵, C₁-C₄ alkylsulfonylamino, phthalimido-(C₁-C₄)-alkylsulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halo-(C₂-C₄)-alkanoylamino, hydroxy-(C₂-C₄)-alkanoylamino, (C₂-C₄)-alkanoyloxy-(C₂-C₄)-alkanoylamino, (C₁-C₄)-alkoxy-(C₂-C₄)-alkanoylamino, (C₁-C₄)-alkoxycarbonyl-(C₂-C₄)-alkanoylamino, carbamoyl-(C₂-C₄)-alkanoylamino, N-(C₁-C₄)-alkylcarbamoyl-(C₂-C₄)-alkanoylamino, N,N-di-[(C₁-C₄)-alkyl]carbamoyl-(C₂-C₄)-alkanoylamino, amino-(C₂-C₄)-alkanoylamino, (C₁-C₄)-alkyl-amino-(C₂-C₄)-alkanoylamino, and di-(C₁-C₄)-alkyl-amino-(C₂-C₄)-alkanoylamino, and wherein said phenyl or phenoxy or anilino substituent in the foregoing R¹ groups is optionally substituted with one or two substituents independently selected from halo, C₁-C₄ alkyl and C₁-C₄ alkoxy;

each R³ is independently selected from hydrogen, methyl, ethyl, amino, halo and hydroxy; and,

R⁴ is ethynyl.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those wherein R² is hydrogen and R⁴ is azido.

Other preferred compounds of formula I include those wherein R³ is halo and R¹ is hydrogen or —OR⁵.

Other preferred compounds of formula I include those wherein R¹ is methoxy.

Specific preferred compounds of formula I include the following:

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

[3-(2'-aminomethyl)-ethynylphenyl]-(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;

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(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-fluorophenyl)-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-(4methylpiperazin-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-methylphenyl)-amine;

[6,7-bis(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynyl-2-methyl-phenyl)-amine;

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