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(54) **ALKYNL AND AZIDO-SUBSTITUTED 4-ANILINOQUINAZOLINES**

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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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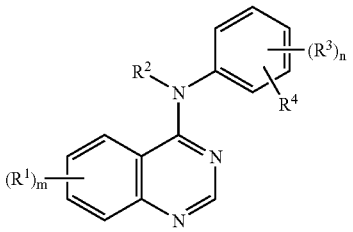
(57) **ABSTRACT**

The invention relates to compounds of the formula

I



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.

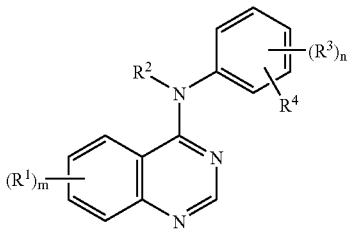
Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. More recently five European patent publications, namely EP 0 566 226 A1, EP 0 602 851 A1, EP 0 635 507 A1, EP 0 635 498 A1 and EP 0 520 722 A1 have disclosed that certain quinazoline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

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

I



and to pharmaceutically acceptable salts and prodrugs 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 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 alkylene)(CO_2H), phenoxy, phenyl, phenylsulfanyl, C_2–C_4 alkenyl, and -(C_1–C_4 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)-alkanoylamino 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 R^3 is independently selected from

groups are optionally substituted by 1 to 3 substituents independently selected from halo, C_1–C_4 alkoxy, —NR^6R^6, and —SO_2R^5; and,

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

Preferred compounds of formula I include those wherein R^2 is hydrogen and R^4 is -(ethynyl)-R^{11}.

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

each R^1 is independently selected from the group consisting of hydrogen, hydroxy, hydroxyamino, carboxy, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, —OR^6, carboxy, —$C(O)NR^6R^6$, A or —NR^6R^6; —OR^5 optionally substituted with halo, —OR^6, —$OC(O)R^6$, —NR^6R^6, or A; —NR^6R^6, —$C(O)R^6$ R^5, —SR^5, phenyl-(C_2–C_4)-alkoxy, cyano, phenyl; —NHR^5 optionally substituted with halo or R^9 wherein said R^9 is optionally substituted by R^9; —$NHOR^5$, —SR^5, C_1–C_4 alkylsulfonylamino, phthalimido-(C_1–C_4)-alkylsulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halo-(C_2–C_4)-alkanoylamino, hydroxy-(C_2–C_4)-alkanoylamino, (C_2–C_4)-alkanoyloxy-(C_2–C_4)-alkanoylamino, (C_1–C_4)-alkoxy-(C_2–C_4)-alkanoylamino, (C_1–C_4)-alkoxycarbonyl-(C_2–C_4)-alkanoylamino, carbamoyl-(C_2–C_4)-alkanoylamino, N-(C_1–C_4)-alkylcarbamoyl-(C_2–C_4)-alkanoylamino, N,N-di-[(C_1–C_4)-alkyl]carbamoyl-(C_2–C_4)-alkanoylamino, amino-(C_2–C_4)-alkanoylamino, (C_1–C_4)-alkyl-amino-(C_2–C_4)-alkanoylamino, and di-(C_1–C_4)-alkyl-amino-(C_2–C_4)-alkanoylamino, and wherein said phenyl or phenoxy or anilino substituent in the foregoing R^1 groups is optionally substituted with one or two substituents independently selected from halo, C_1–C_4 alkyl and C_1–C_4 alkoxy;

each R^3 is independently selected from hydrogen, methyl, ethyl, amino, halo and hydroxy; and,

R^4 is ethynyl.

Other preferred compounds of formula I include those wherein each R^1 is independently selected from hydrogen, hydroxy, hydroxyamino, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, —OR^6, carboxy, or —$C(O)NH_2$; —OR^5 optionally substituted with halo, —OR^6, —$OC(O)R^6$, —NR^6R^6, or A; —NR^6R^6, —$C(O)NR^6R^6$, —SR^5, phenyl-(C_2–C_4)-alkoxy wherein said phenyl moiety is optionally substituted with 1 or 2 substituents independently selected from halo, R^5 or —OR^5.

Other preferred compounds of formula I include those wherein R^2 is hydrogen and R^4 is azido.

Other preferred compounds of formula I include those wherein R^3 is halo and R^1 is hydrogen or —OR^5.

Other preferred compounds of formula I include those wherein R^1 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)-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)-(6,7-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-(4methyl-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;

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