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(54) Title: 4-ANILIDO SUBSTITUTED QUINAZOLINES AND USE THEREOF AS INHIBITORS OF EPIDERMAL GROWTH FACTOR RECEPTOR KINASES

(57) Abstract: The present invention provides 4-anilido substituted quinazoline compounds which are potent inhibitors of protein tyrosine (PTK) kinase activity, particularly epidermal growth factor receptor (EGFR) kinase activity, and pharmaceutical compositions comprising these compounds. The present invention further provides methods of inhibiting the activity of a protein tyrosine kinase (PTK), for example an EGFR kinase, comprising the step of contacting the PTK with an effective inhibitory amount of any of the quinazoline compounds defined herein. The present invention further provides a method of inhibiting the activity of a protein tyrosine kinase (PTK) in a subject, for example an EGFR kinase, comprising the step of administering to the subject a therapeutically effective amount of any of the quinazoline compounds defined herein. The present invention further provides a method of treating or preventing a protein tyrosine kinase (PTK) related disorder in a subject, for example an EGFR related disorder, comprising the step of administering to the subject a therapeutically effective amount of any of the quinazoline compounds defined herein. The quinazoline compounds are useful in treating a variety of PTK related disorders such as cell proliferative disorders, fibrotic disorders, metabolic disorders and cancer.

4-ANILIDO SUBSTITUTED QUINAZOLINES AND USE THEREOF AS INHIBITORS OF EPIDERMAL GROWTH FACTOR RECEPTOR KINASES

FIELD OF THE INVENTION

[001] The present invention relates to 4-anilido substituted quinazolines which are inhibitors of epidermal growth factor receptor tyrosine kinase (EGF-RTK) activity, their preparation, pharmaceutical compositions containing these compounds, and their use in the treatment of protein kinase related disorders, particularly EGF-RTK related disease states.

BACKGROUND OF THE INVENTION

[002] Protein tyrosine kinases (PTKs) are a family of enzymes, which transfer the γ-phosphate of ATP to the side chain of tyrosine residues on substrate proteins. PTKs are involved in a variety of key cellular processes, including signal transduction and growth regulation. The phosphorylation of substrates by PTKs are key events in cellular signaling.

[003] One class of PTKs is that of the receptor tyrosine kinases (RTKs). These kinases belong to a family of transmembrane proteins and have been implicated in cellular signaling pathways. The predominant biological activity of some receptor tyrosine kinases is the stimulation of cell growth and proliferation, while other receptor tyrosine kinases are involved in arresting growth and promoting differentiation. In some instances, a single tyrosine kinase can inhibit, or stimulate, cell proliferation depending on the cellular environment in which it is expressed. (Schlessinger, J. and Ullrich, A., *Neuron* (1992) 9(3) : 383-391, 1992.) RTKs include the receptors for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin, insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF), and the HER family of transmembrane RTKs, consisting of EGFR (HER1, ErbB1), HER2 (New, ErbB2), HER3 (ErbB3), and HER4 (ErbB4).

[004] Receptor tyrosine kinases are composed of at least three domains: an extracellular glycosylated ligand binding domain for growth factors such as EGF, a transmembrane domain, and a cytoplasmic catalytic domain that can phosphorylate tyrosine residues. Ligand binding to membrane-bound receptors induces the formation of receptor dimers and allosteric changes that activate the intracellular kinase domains and result in the self-phosphorylation (autophosphorylation and/or transphosphorylation) of the receptor on tyrosine residues. Receptor phosphorylation stimulates a physical association of the activated receptor with target molecules. Some of the target molecules are, in turn, phosphorylated, resulting in signal transmission to the cytoplasm. The secondary signal transducer molecules generated by activated receptors result in a signal cascade that regulates cell functions such as cell division or differentiation. Reviews describing intracellular signal transduction include Aaronson, S. A., *Science* (1991), 254:1146-1153; Schlessinger, J. *Trends Biochem. Sci.* (1988) 13:443-447, 1988; and Ullrich, A., and Schlessinger, J., *Cell* (1990) 61:203-212.

[005] Various cell proliferative disorders have been associated with defects in various signaling pathways mediated by PTKs. Enhanced activities of PTKs resulting from overexpression of the normal kinase or due to activating mutations are a hallmark of many diseases involving cellular proliferation, including cancer. Examples of specific receptor tyrosine kinases associated with cell proliferative disorders include, platelet derived growth factor receptor (PDGFr), epidermal growth factor receptor (EGFr), and the related HER2. PTKs are frequently present in common human cancers, such as breast cancer (Sainsbury et al., *Brit. J. Cancer*, 1988, 58, 458; Guerin et al., *Oncogene Res.*, 1988, 3, 21), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., *Oncogene Res.*, 1987, 1, 149), leukemia (Konaka et al., *Cell*, 1984, 37, 1035) and ovarian, bronchial or pancreatic cancer (European Patent Specification No. 0400586). Furthermore, tyrosine kinase activity is rarely detected in normal cells, whereas it is more frequently detectable in malignant cells (Hunter, *Cell*, 1987, 50, 823). It has been shown more recently (U.J. Gullick, *Brit. Med. Bull.*, 1991, 47, 87) that epidermal growth factor receptor which possesses tyrosine kinase activity is overexpressed in many human cancers, such as brain, lung squamous cell, bladder, gastric, breast, head and neck, oesophageal,

gynaecological and thyroid tumors. Moreover, deregulated activity of HER family RTKs is commonly seen in human tumors, and HER family RTKs are oncogenic in many experimental systems (Moasser et al, *Cancer Research*, 2001, 61, 7184-7188).

[006] The involvement of PTKs in cell proliferative disease states identifies them as targets for antiproliferative drugs, particularly for the treatment of cancer. Indeed, numerous PTK blockers have been described and their mechanism of action studied (Levitzki, A.; et al. *Science* (1995), 267, 1782-88; Posner et al. *Mol. Pharmacol.* (1994), 45, 673-683). Recently, Applicants have developed a family of PTK inhibitors, named tyrphostins, designed to mimic the tyrosine substrate (Levitzki et al (1995); Levitzki et al; *Biochem. Pharm.* (1990), 40, 913-920; Levitzki et al. *FASEB J.* (1992), 6, 3275-3282; United States Patent Nos. 5,217,999 and 5,773,476). The pharmacophores of these tyrphostins, and specifically the tyrphostins of the benzylidene malononitrile type, are hydrophilic catechol ring and the more lipophilic substituted cyano-vinyl radical. Kinetic studies have shown that some tyrphostin compounds are pure competitive inhibitors vis-à-vis the tyrosine substrates and non-competitive inhibitors vis-à-vis ATP site (Yaish et al. *Science* (*1988*) 242, 933-935; Gazit et al. *J. Med Chem.* (1989), 32, 2344-2352), while many tyrphostins show competitive inhibition against both the substrate and ATP (Posner et al (1994)).

[007] In a related group of tyrphostins, the hydrophilic catechol ring was exchanged by lipophilic dichloro or dimethoxy phenyl to yield EGFR kinase inhibitors, effective in the low micromolar range (Yoneda et al. *Cancer Res.* (*1991*), 51, 4430-4435).

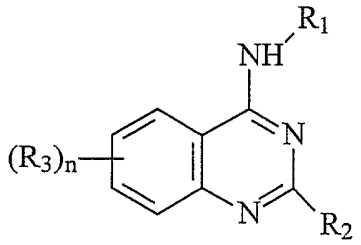
[008] Recently, quinazoline derivatives were reported as potent EGF receptor kinase inhibitors (Barker, A.J. EP 520,722, EP 566,220, AU-A-31010(93); Ward, W.H.J., et al *Biochem. Pharmacol.*, 1994, 48, 659-666 ; Fry, D.W. et al. *Science,* 1994, 265, 1093-1095).

[009] Since PTKs are implicated in various cell proliferative disease states, there is an ongoing need to develop new PTK inhibitors as antiproliferative drugs. Thus there is a need to identify compounds which specifically inhibit tyrosine signal transduction by modulating the activity of RTKs, particularly by modulating the activity of EGF receptor.

SUMMARY OF THE INVENTION

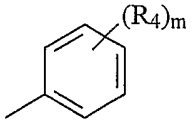
[0010] The present invention provides 4-anilido substituted quinazoline compounds, which are potent inhibitors of protein tyrosine kinases (PTKs), particularly epidermal growth factor receptor (EGFR) kinases. These compounds are useful in treating protein kinase related disease states, particularly EGFR related disease states as defined herein.

[0011] In one embodiment, the present invention provides a compound represented by the structure of formula (I):

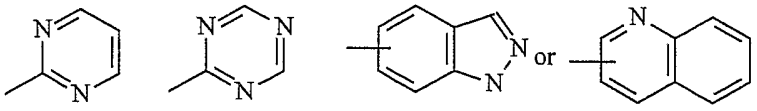


(I)

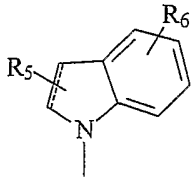
wherein R_1 is an optionally substituted phenyl represented by the structure:



an optionally substituted naphthalene, an optionally substituted cyclohexyl, an optionally substituted heteroaryl represented by the structure:



or R_1 together with the nitrogen to which it is attached is:

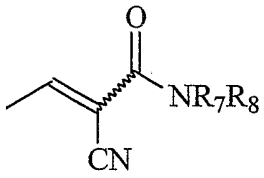


wherein the dotted line represents an optional double bond;

R_2 is H, halogen, phenylamino, or $-SR_7$ wherein R_7 is a heteroaromatic moiety;

R_3 is H, R, OR, NO_2 or NH_2 wherein R is a C_1-C_4 linear or branched chain alkyl;

R_4-R_6 are independently of each other H, halogen, CN, R, NO_2, NH_2, NHR, NR_2, COOH, COOR, CHO, COR, COPh, $CONH_2$, CONHR, $CONR_2$, Ph, OR, OPh, OCH_2Ph, $CH(OR)_2$ wherein R is a C_1-C_4 linear or branched chain alkyl, or R4 is represented by the structure:



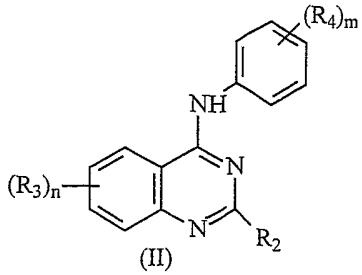
wherein R_7 and R_8 are independently hydrogen or an optionally substituted alkyl, aralkyl or aryl; and

m and n are independently of each other an integer of 1-3;

and pharmaceutically acceptable salts and hydrates thereof;

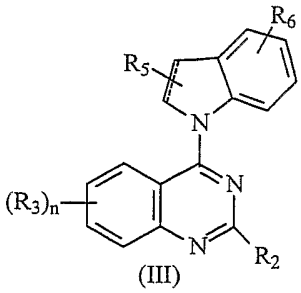
provided that: a) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is H, R or OR, R_4 is not halogen, OR, CN, $CONH_2$, NR_2, CH_3, OH, $COCH_3$ or COOH; b) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is NO_2, R_4 is not halogen or CH_3; c) when R_1 is an optionally substituted phenyl, m is 1, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not CH_3, NH_2, NHR, NR_2, NO_2, CN, OCH_3, halogen or OH; d) when R_1 is an optionally substituted phenyl, m is 1, R_2 is Cl and R_3 is H, R or OR, R_4 is not CH_3, COOH, OCH_3, $CONH_2$ $COCH_3$, OH or halogen; e) when R_1 is an optionally substituted phenyl, m is 2, R_2 is H and R_3 is H, R or OR, R_4 is not 3,4-di-CH_3, 3,4-dihalo, 3-halo-4-CH_3, 3-CH_3-4-halo, 3-halo-5-NH_2 or 3-halo-4-OH; f) when R_1 is an optionally substituted phenyl, m is 2, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3, 3-halo-4-CH_3 or 3-CH_3-4-halo; g) when R_1 is an optionally substituted phenyl, m is 2, R_2 is Cl and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3 or 2-CH_3-4-OCH_3; h) when R_1 is an optionally substituted phenyl, m 3 is, R_2 is H and R_3 is H, R or OR, R_4 is not 3,5-halogen,4-OH; and i) when R_2 is H, R_1 is not 2'-hydroxy-naphthyl.

[0012] In one embodiment, the compound is represented by the structure of formula (II):



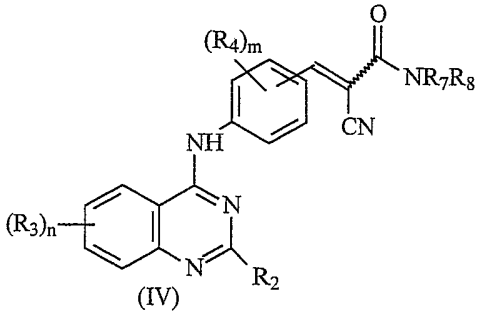
(II)

[0013] In another embodiment, the compound is represented by the structure of formula (III):



(III)

[0014] In another embodiment, the compound is represented by the structure of formula (IV):



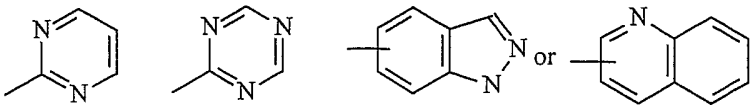
(IV)

[0015] In one embodiment, R_2 is H. In another embodiment, R_2 is Cl. In another embodiment, R_2 is $-SR_7$ wherein R_7 is a heteroaromatic moiety containing at least one sulfur atom and one nitrogen atom. In another embodiment, R_2 is 2-mercaptobenzothiazole.

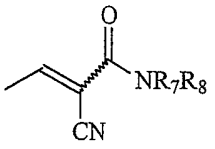
[0016] In one embodiment, R_3 is 6-methyl. In another embodiment, R_3 is 8-methyl. In another embodiment, R_3 is 6,7-dimethoxy. In another embodiment, R_3 is NO_2. In another embodiment, R_3 is NH_2.

[0017] In one embodiment, m is 2. In another embodiment, m is 3. In another embodiment, n is 1. In another embodiment, n is 2.

[0018] In one embodiment, R_1 is an optionally substituted heteroaryl represented by the structure:



[0019] In another embodiment, R_4 is:



[0020] In another embodiment, the compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702);

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897;)

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);
4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);
4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);
4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);
4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);
4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);
4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);
4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004)
4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);
4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);
3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);
N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);
3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);
4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);
4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);
4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);
4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);
4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);
4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);
4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);
4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);
4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and
4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

[0021] In another embodiment, the present invention provides a pharmaceutical composition comprising any of the compounds of formula (I)-(IV) and a pharmaceutically acceptable carrier or excipient.

[0022] In another embodiment, the present invention provides a method of inhibiting the activity of a protein tyrosine kinase (PTK), comprising the step of contacting the PTK with an effective inhibitory amount of any of the compounds of formula (I) – (IV).

[0023] In another embodiment, the present invention provides a method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase, comprising the step of contacting the EGFR kinase with an effective inhibitory amount of any of the compounds of formula (I) – (IV).

[0024] In another embodiment, the present invention provides a method of inhibiting the activity of a protein tyrosine kinase (PTK) in a subject, comprising the step of administering to the subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0025] In another embodiment, the present invention provides a method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase in a subject, comprising the step of administering to the subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0026] In another embodiment, the present invention provides a method of treating or preventing a protein tyrosine kinase (PTK) related disorder in a subject, comprising the step of administering to said subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0027] In another embodiment, the present invention provides a method of treating or preventing an epidermal growth factor receptor (EGFR) kinase related disorder in a subject comprising the step of administering to said subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0028] In another embodiment, the method comprise contacting the PTK or the EGFR kinase with or administering to the subject a compound selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);
2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);
2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);
4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);
4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);
4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);
4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702);
4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);
4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);
2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);
2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);
2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);
2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897;)
4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);
4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);
4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);
4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);
4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);
4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);
4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);
4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);
4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);
4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);
4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);
4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);

4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004)

4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);

4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);

3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);

N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);

3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);

4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);

4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);

4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);

4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);

4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);

4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);

4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);

4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);

4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and

4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

[0029] In one embodiment, the protein tyrosine kinase is a receptor protein tyrosine kinase (RTK). In another embodiment, the receptor protein tyrosine kinase is selected from the group consisting of an epidermal growth factor receptor (EGFR) kinase, a HER receptor kinase, a platelet-derived growth factor receptor (PDGFr) kinase, a fibroblast growth factor receptor (FGF) kinase, a hepatocyte growth factor receptor (HGFr) kinase, an insulin receptor kinase, an insulin-like growth factor-1 receptor (IGF-1r) kinase, a nerve growth factor receptor (NGF) kinase, a vascular endothelial growth factor receptor (VEGFr) kinase, and a macrophage colony stimulating factor receptor (M-CSFr) kinase.

[0030] In one embodiment, the PTK related disorder or the EGFR related disorder is a cell proliferative disorder, a fibrotic disorder, or a metabolic disorder. In another embodiment, the PTK related disorder or the EGFR related disorder is cancer.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

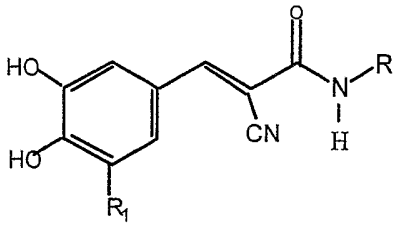
[0031] The present invention provides 4-anilido substituted quinazoline compounds which are potent inhibitors of protein tyrosine (PTK) kinase activity, particularly epidermal growth factor receptor (EGFR) kinase activity, and pharmaceutical compositions comprising these compounds. The present invention further provides methods of inhibiting the activity of a protein tyrosine kinase (PTK), for example an EGFR kinase, comprising the step of contacting the PTK with an effective inhibitory amount of any of the quinazoline compounds defined herein. The present invention further provides a method of inhibiting the activity of a protein tyrosine kinase (PTK) in a subject, for example an EGFR kinase, comprising the step of administering to the subject a therapeutically effective amount of any of the quinazoline compounds defined herein. The present invention further provides a method of treating or preventing a protein tyrosine kinase (PTK) related disorder in a subject, for example an EGFR related disorder, comprising the step of administering to the subject a therapeutically effective amount of any of the quinazoline compounds defined herein. The quinazoline compounds are useful in treating a variety of PTK related disorders, such as cell proliferative disorders, fibrotic disorders, metabolic disorders and cancer.

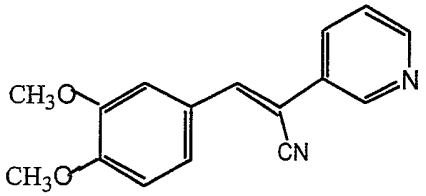
[0032] In another embodiment, the present invention provides method of treating or preventing an epidermal growth factor receptor (EGFR) kinase related disorder in a subject, comprising the step of administering to said subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0033] The present invention provides 4-anilido substituted quinazoline tyrphostins, which are potent inhibitors of epidermal growth factor receptor tyrosine kinase (EGF-RTK) activity. The present invention further provides methods of inhibiting EGF-RTK, comprising administering the quinazoline compounds. The quinazoline compounds are useful in treating or preventing EGF-RTK related diseases states and,

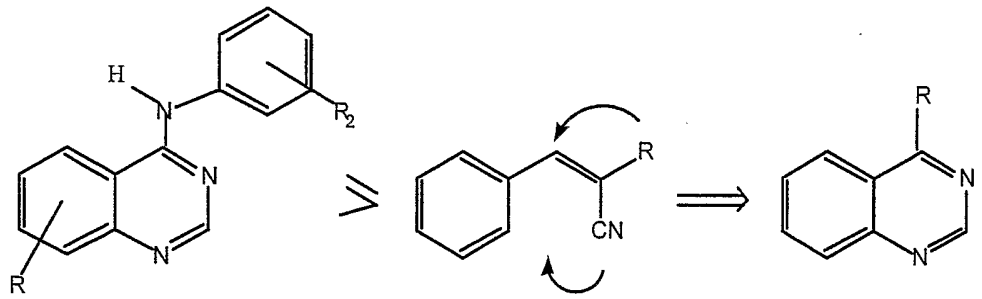
more generally, protein tyrosine kinase (PTK)-related disease states, particularly diseases which are associated with defects in signaling pathways mediated by PTKs.

[0034] As contemplated herein, the quinazoline compounds of the present invention are designed as part of a family of PTK inhibitors – tyrphostins – designed to mimic the tyrosine substrates of PTKs. The pharmacophores of most tyrphostins are a hydrophilic catechol ring and the more lipophillic substituted cyano-vinyl radical.

I 

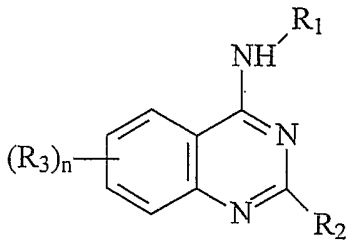
II 

[0035] Quinazolines can be viewed as rigid bicyclic analogs of tyrphostins, in which the cyano vinyl is incorporated into the heterocyclic ring and the α-substituent in I moved to β position (III).

III 

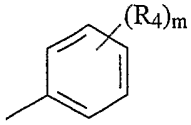
[0036] Applicants have surprisingly found that the novel 4-anilido substituted quinazolines defined herein are potent inhibitors of protein tyrosine kinase activity, particularly EGFR kinase activity.

[0037] The quinazoline compounds provided by the present invention are represented by the general structure of formula (I):

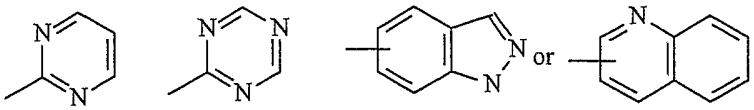


(I)

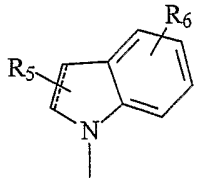
wherein R_1 is an optionally substituted phenyl represented by the structure:



an optionally substituted naphthalene, an optionally substituted cyclohexyl, an optionally substituted heteroaryl represented by the structure:



or R_1 together with the nitrogen to which it is attached is:

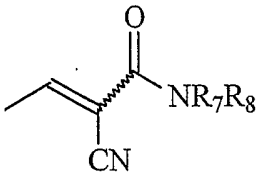


wherein the dotted line represents an optional double bond;

R_2 is H, halogen, phenylamino, or $-SR_7$ wherein R_7 is a heteroaromatic moiety;

R_3 is H, R, OR, NO_2 or NH_2 wherein R is a C_1-C_4 linear or branched chain alkyl;

R_4-R_6 are, independently of each other, H, halogen, CN, R, NO_2, NH_2, NHR, NR_2, COOH, COOR, CHO, COR, COPh, $CONH_2$, CONHR, $CONR_2$, Ph, OR, OPh, OCH_2Ph, $CH(OR)_2$ wherein R is a C_1-C_4 linear or branched chain alkyl, or R4 is represented by the structure:



wherein R_7 and R_8 are independently hydrogen or an optionally substituted alkyl, aralkyl or aryl; and

m and n are, independently of each other, an integer of 1-3;

and pharmaceutically acceptable salts and hydrates thereof;

provided that: a) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is H, R or OR, R_4 is not halogen, OR, CN, $CONH_2$, NR_2, CH_3, OH, $COCH_3$ or COOH; b) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is NO_2, R_4 is not halogen or CH_3; c) when R_1 is an optionally substituted phenyl, m is 1, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not CH_3, NH_2, NHR, NR_2, NO_2, CN, OCH_3,

halogen or OH; d) when R_1 is an optionally substituted phenyl, m is 1, R_2 is Cl and R_3 is H, R or OR, R_4 is not CH_3, COOH, OCH_3, $CONH_2$ $COCH_3$, OH or halogen; e) when R_1 is an optionally substituted phenyl, m is 2, R_2 is H and R_3 is H, R or OR, R_4 is not 3,4-di-CH_3, 3,4-dihalo, 3-halo-4-CH_3, 3-CH_3-4-halo, 3-halo-5-NH_2 or 3-halo-4-OH; f) when R_1 is an optionally substituted phenyl, m is 2, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3, 3-halo-4-CH_3 or 3-CH_3-4-halo; g) when R_1 is an optionally substituted phenyl, m is 2, R_2 is Cl and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3 or 2-CH_3-4-OCH_3; h) when R_1 is an optionally substituted phenyl, m 3 is, R_2 is H and R_3 is H, R or OR, R_4 is not 3,5-halogen,4-OH; and i) when R_2 is H, R_1 is not 2'-hydroxy-naphthyl.

[0038] The following is a list of some of the definitions of the chemical groups used in the present disclosure:

[0039] An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkyl groups. In one embodiment, the alkyl group has 1-12 carbons. In another embodiment, the alkyl group has 1-7 carbons. In another embodiment, the alkyl group has 1-6 carbons. In another embodiment, the alkyl group has 1-4 carbons. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[0040] An "aryl" group refers to an aromatic group having at least one carbocyclic aromatic group or heterocyclic aromatic group (referred to as "heteroaryl" or "heteroaromatic"), which may be unsubstituted or substituted by one or more groups selected from halogen, haloalkyl, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxy or thio or thioalkyl. Nonlimiting examples of carbocyclic aryl rings are phenyl and naphthyl. Nonlimiting examples of heteroaromatic rings are pyranyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyridinyl, furanyl, thiophenyl, thiazolyl, benzothiazolyl, imidazolyl, isoxazolyl, and the like.

[0041] A "hydroxy" group refers to an OH group. An "alkoxy" group refers to an –O-alkyl group wherein alkyl is as defined above. An "aryloxy" group refers to an –O-Ar group wherein Ar is aryl as defined above. A "thio" group refers to an –SH group. An "alkylthio" group refers to an –SR group wherein R is alkyl as defined above. An "arylthio" group refers to an –SAr group wherein Ar is aryl as defined above. A "nitro" group refers to an NO_2 group. A "cyano" or "nitrile" group refers to a –CN group. A "halogen" group refers to an –F, -Cl, -Br, or –I.

[0042] An "amino" group refers to an $-NH_2$ group. An "alkylamino" group refers to an –NHR group wherein R is an alkyl as defined above. A "dialkylamino" group refers to an –NRR' group wherein R and R' are alkyl as defined above. An "arylamino" group refers to an –NHAr group wherein Ar is aryl as defined above. A "diarylamino" group refers to an –NArAr' group wherein Ar and Ar' are aryl as defined above.

[0043] An "amido" group refers to a -C(=O)N- group. A "carboxamido" group refers to a $–CONH_2$ group. An "alkylamido" group refers to a –CONHR group wherein R is alkyl is as defined above. A "dialkylamido" group refers to a –CONRR' group wherein R and R' are alkyl as defined above. An "arylamido" group refers to a –CONHAr group wherein Ar is aryl as defined above. A "diarylamido" group refers to a –CONArAr' group wherein Ar and Ar' are aryl as defined above.

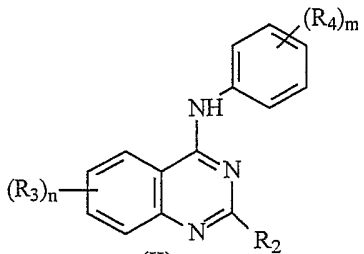
[0044] A "keto" group refers to a COR group or COAr group, wherein R is alkyl as defined above and Ar is aryl as defined above. A "formyl" group refers to a –CHO group.

[0045] An "aralkyl" group refers to an alkyl bound to an aryl, wherein alkyl and aryl are as defined above. An example of an aralkyl group is a benzyl group.

[0046] A "carboxy" group refers to a –COOH group. An alkyl carboxy refers to a –COOR group wherein R is alkyl as defined above. Examples of alkyl carboxy groups are carboxymethyl ($COOCH_3$), carboxyetheyl ($COOCH_2CH_3$) and the like.

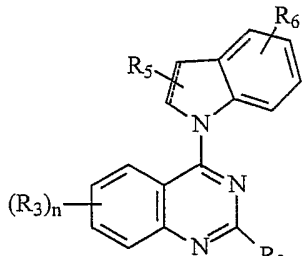
An arylcarboxy refers to a COOR group wherein R is aryl as defined above. An example of an aryl carboxy group is phenyl carboxy (COOPh) and the like.

[0047] In one embodiment, the quinazoline compound which is effective at inhibiting PTK activity is represented by the structure of formula (II):



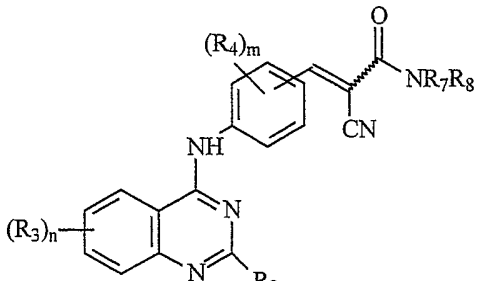
(II)

[0048] In another embodiment, the quinazoline compound which is effective at inhibiting PTK activity is represented by the structure of formula (III):



(III)

[0049] In another embodiment, the quinazoline compound which is effective at inhibiting PTK activity is represented by the structure of formula (IV):

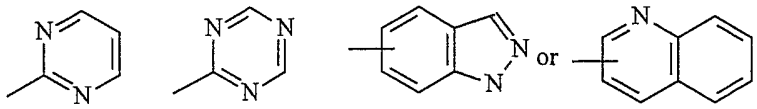


(IV)

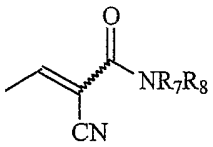
[0050] In one embodiment, R_2 is H. In another embodiment, R_2 is Cl. In another embodiment, R_2 is $-SR_7$ wherein R_7 is a heteroaromatic moiety containing at least one sulfur atom and one nitrogen atom. In another embodiment, R_2 is 2-mercaptobenzothiazole. In another embodiment, R_3 is 6-methyl. In another embodiment, R_3 is 8-methyl. In another embodiment, R_3 is 6,7-dimethoxy. In another embodiment, R_3 is NO_2. In another embodiment, R_3 is NH_2. In another

embodiment, m is 1. In another embodiment, m is 2. In another embodiment, m is 3. In another embodiment, n is 1. In another embodiment, n is 2. In another embodiment, n is 3.

[0051] In another embodiment, R_1 is an optionally substituted heteroaryl represented by the structure:



[0052] In another embodiment, R_4 is:



wherein R_7 and R_8 are independently hydrogen or an optionally substituted alkyl, aralkyl or aryl. In one embodiment, R_7 is hydrogen and R_8 is an optionally substituted alkyl, aralkyl or aryl. In another embodiment, R_7 is an aralkyl. In another embodiment, R_7 is benzyl. In another embodiment, R_7 is cyclohexyl. In another embodiment, R_7 is a substituted cyclohexyl.

[0053] In one embodiment, the quinazoline compound which is effective at inhibiting PTK activity is 2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623). In another embodiment, the quinazoline compound is 2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624). In another embodiment, the quinazoline compound is 2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625). In another embodiment, the quinazoline compound is 4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698). In another embodiment, the quinazoline compound is 4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxy quinazoline (AG 1699). In another embodiment, the quinazoline compound is 4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701). In another embodiment, the quinazoline compound is 4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702). In another embodiment, the

quinazoline compound is 4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxy quinazoline (AG 1813). In another embodiment, the quinazoline compound is 4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814). In another embodiment, the quinazoline compound is 2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827). In another embodiment, the quinazoline compound is 2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885). In another embodiment, the quinazoline compound is 2-(2-mercaptobenzothiazol)-4-(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886). In another embodiment, the quinazoline compound is 2-(2-mercaptobenzothiazol)-4-(3'-chlorophenylamino)-6,7-dimethoxyquinazoline. In another embodiment, the quinazoline compound is(AGL 1897). In another embodiment, the quinazoline compound is 4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924). In another embodiment, the quinazoline compound is 4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925). In another embodiment, the quinazoline compound is 4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927). In another embodiment, the quinazoline compound is 4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929). In another embodiment, the quinazoline compound is 4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930). In another embodiment, the quinazoline compound is 4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931). In another embodiment, the quinazoline compound is 4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932). In another embodiment, the quinazoline compound is 4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933). In another embodiment, the quinazoline compound is 4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980). In another embodiment, the quinazoline compound is 4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981). In another embodiment, the quinazoline compound is 4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002). In another embodiment, the quinazoline compound is 4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003). In another embodiment, the quinazoline compound is 4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004). In another embodiment, the quinazoline compound is 4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064). In another

embodiment, the quinazoline compound is 4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116). In another embodiment, the quinazoline compound is 3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122). In another embodiment, the quinazoline compound is N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123). In another embodiment, the quinazoline compound is 3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124). In another embodiment, the quinazoline compound is 4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxy quinazoline (AGL 2052). In another embodiment, the quinazoline compound is 4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxy quinazoline (AGL 2053). In another embodiment, the quinazoline compound is 4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066). In another embodiment, the quinazoline compound is 4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067). In another embodiment, the quinazoline compound is 4'-(4''-amino)oxyphenyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2373). In another embodiment, the quinazoline compound is 4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377). In another embodiment, the quinazoline compound is 4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398). In another embodiment, the quinazoline compound is 4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250). In another embodiment, the quinazoline compound is 4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402). In another embodiment, the quinazoline compound is 4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

[0054] In another embodiment, the quinazoline compound is 4-(2'-hydroxyphenylamino)-6-methylquinazoline (AG 1541). In another embodiment, the quinazoline compound is 4-(4'-cyanophenylamino)quinazoline (AG 1686). In another embodiment, the quinazoline compound is 4-(2'-cyanophenylamino) quinazoline (AG 1687). In another embodiment, the quinazoline compound is 4-(2'-cyanophenylamino)-6-methylquinazoline (AG 1688). In another embodiment, the quinazoline compound is 4-(3'-chloro-4'-fluoro-phenylamino)-6,7-dimethoxy

quinazoline (AG 1700). In another embodiment, the quinazoline compound is 2,4-bis-(3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1703). In another embodiment, the quinazoline compound is 4-(4'-nitro-phenylamino)-6-methylquinazoline (AG 1707). In another embodiment, the quinazoline compound is 4-(3'-cyano-phenylaminoquinazoline (AGL 1715). In another embodiment, the quinazoline compound is 4-(3'-cyano-phenylamino)-6-methylquinazoline (AGL 1716). In another embodiment, the quinazoline compound is 2-chloro-4-(3-bromophenylamino)-6,7-dimethoxyquinazoline (AGL 1894). In another embodiment, the quinazoline compound is 4-(4'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1923). In another embodiment, the quinazoline compound is 4-(3'-amino-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AGL 2120). In another embodiment, the quinazoline compound is 4-(4'-carboxamido-phenylamino)-6,7-dimethoxyquinazoline (AGL 2353). In another embodiment, the quinazoline compound is 4-(3'-carboxamido-phenylamino)-6,7-dimethoxyquinazoline (AGL 2354). In another embodiment, the quinazoline compound is 4-(4'-hydroxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2355). In another embodiment, the quinazoline compound is 4-(3'-amino-5'-chloro-phenylamino)-6 –methyl quinazoline (AGL 2356). In another embodiment, the quinazoline compound is 4-(3',5'-dichloro-4'-hydroxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2358). In another embodiment, the quinazoline compound is 4-(3',5'-dibromo- 4'-hydroxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2363). In another embodiment, the quinazoline compound is 4-(3'-chloro-4'-hydroxy-phenylamino)-6,7-dimethoxy quinazoline (AGL 2364). In another embodiment, the quinazoline compound is 4-(4'-carboxamido-phenylamino)-6-methylquinazoline (AGL 2396). In another embodiment, the quinazoline compound is 4-(4'-acetyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2399). In another embodiment, the quinazoline compound is 4-(3'-bromo-phenylamino)-6-nitroquinazoline (AGL 2248).

[0055] The present invention provides compounds and compositions effective at inhibiting protein tyrosine kinases. Thus, in one embodiment, the present invention provides a method of inhibiting the activity of a protein tyrosine kinase (PTK),

comprising the step of contacting the PTK with an effective inhibitory amount of any of the compounds of formula (I) – (IV).

[0056] In another embodiment, the present invention provides a method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase, comprising the step of contacting the EGFR kinase with an effective inhibitory amount of any of the compounds of formula (I) – (IV).

[0057] In another embodiment, the present invention provides a method of inhibiting the activity of a protein tyrosine kinase (PTK) in a subject comprising the step of administering to the subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0058] In another embodiment, the present invention provides a method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase in a subject, comprising the step of administering to the subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0059] In another embodiment, the present invention provides a method of treating or preventing a protein tyrosine kinase (PTK) related disorder in a subject, comprising the step of administering to said subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0060] In another embodiment, the present invention provides method of treating or preventing an epidermal growth factor receptor (EGFR) kinase related disorder in a subject comprising the step of administering to said subject a therapeutically effective amount of any of the compounds of formula (I) – (IV).

[0061] A "protein tyrosine kinase" (PTK) is a protein belonging to a family of enzymes which transfer the γ-phosphate of ATP to the side chain of tyrosine residues on substrate proteins. PTKs are involved in a variety of key cellular processes, including signal transduction and growth regulation. A protein tyrosine kinase, as used herein, refers to a receptor tyrosine kinase (RTK) as well as a cellular tyrosine

kinase (CTK or non-receptor tyrosine kinase). Thus the compounds of the present invention are effective at inhibiting both receptor and non-receptor protein tyrosine kinases.

[0062] A cellular tyrosine kinase (CTK or non-receptor tyrosine kinase) is an intracellular protein which takes part in signal transduction within the cell, including signal transduction to the nucleus. Examples of CTKs are the Src family of oncoproteins. A receptor tyrosine kinases (RTK) is a transmembrane protein which participates in transmembrane signaling pathways. The predominant biological activity of some receptor tyrosine kinases is the stimulation of cell growth and proliferation, while other receptor tyrosine kinases are involved in arresting growth and promoting differentiation. RTKs include the receptors for epidermal growth factor receptor (EGFR), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin, insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF).

[0063] In one embodiment, the protein tyrosine kinase is a receptor protein tyrosine kinase (RTK). In another embodiment, the receptor protein tyrosine kinase is selected from the group consisting of an epidermal growth factor receptor (EGFR) kinase, a HER receptor kinase, a platelet-derived growth factor receptor (PDGFr) kinase, a fibroblast growth factor receptor (FGF) kinase, a hepatocyte growth factor receptor (HGFr) kinase, an insulin receptor kinase, an insulin-like growth factor-1 receptor (IGF-1r) kinase, a nerve growth factor receptor (NGF) kinase, a vascular endothelial growth factor receptor (VEGFr) kinase, and a macrophage colony stimulating factor receptor (M-CSFr) kinase. The compounds and compositions provided herein are useful in the treatment of diseases associated with altered or abnormal activity of protein tyrosine kinases, such as enhanced activity of protein tyrosine kinases.

[0064] The term "protein tyrosine kinase related disorder" as used herein refers to a disorder characterized by abnormal or altered PTK activity. Abnormal or altered activity further refers to either (i) overexpression of PTK in cells which do not

normally express PTKs; (ii) increased PTK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (iii) decreased PTK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of PTKs refers to either amplification of the gene encoding a particular PTK or production of a level of PTK activity which can correlate with a cell proliferation, differentiation and/or growth. Over-activity can also be the result of ligand independent or constitutive activation as a result of mutations such as deletions of a fragment of a PTK responsible for ligand binding.

[0065] Thus, in one embodiment, the present invention is directed to quinazoline compounds-containing preparations which modulate PTK activity signal transduction by affecting the enzymatic activity of the protein tyrosine kinases, thereby interfering with the signal transduction pathways mediated by such proteins.

[0066] Examples of protein tyrosine kinase related disorders are cell proliferative disorders, metabolic disorders and fibrotic disorders.

[0067] Examples of cell proliferative disorders which are mediated by protein tyrosine kinases are cancer, blood vessel proliferative disorders, and mesangia cell proliferative disorders.

[0068] Cancer is a disorder in which a population of cells has become, in varying degrees, unresponsive to the control mechanisms that normally govern proliferation and differentiation. Cancer refers to various types of malignant neoplasms and tumors, including metastasis to different sites. Nonlimiting examples of cancers which can be treated by the quinazoline compounds of formulas I-IV are brain, ovarian, colon, prostate, kidney, bladder, breast, lung, oral and skin cancers which exhibit altered activity of PTK. Specific examples of cancers which the compounds of the present invention are effective at treating or preventing are: adenocarcinoma, adrenal gland tumor, ameloblastoma, anaplastic tumor, anaplastic carcinoma of the thyroid cell, angiofibroma, angioma, angiosarcoma, apudoma, argentaffinoma, arrhenoblastoma, ascites tumor cell, ascitic tumor, astroblastoma, astrocytoma, ataxia-telangiectasia, atrial myxoma, basal cell carcinoma, benign tumor, bone

cancer, bone tumor, brainstem glioma, brain tumor, breast cancer, Burkitt's lymphoma, carcinoma, cerebellar astrocytoma, cervical cancer, cherry angioma, cholangiocarcinoma, a cholangioma, chondroblastoma, chondroma, chondrosarcoma, chorioblastoma, choriocarcinoma, colon cancer, common acute lymphoblastic leukaemia, craniopharyngioma, cystocarcinoma, cystofibroma, cystoma, cytoma, ductal carcinoma in situ, ductal papilloma, dysgerminoma, encephaloma, endometrial carcinoma, endothelioma, ependymoma, epithelioma, erythroleukaemia, Ewing's sarcoma, extra nodal lymphoma, feline sarcoma, fibroadenoma, fibrosarcoma, follicular cancer of the thyroid, ganglioglioma, gastrinoma, glioblastoma multiforme, glioma, gonadoblastoma, haemangioblastoma, haemangioendothelioblastoma, haemangioendothelioma, haemangiopericytoma, haematolymphangioma, haemocytoblastoma, haemocytoma, hairy cell leukaemia, hamartoma, hepatocarcinoma, hepatocellular carcinoma, hepatoma, histoma, Hodgkin's disease, hypernephroma, infiltrating cancer, infiltrating ductal cell carcinoma, insulinoma, juvenile angiofibroma, Kaposi sarcoma, kidney tumour, large cell lymphoma, leukemia, chronic leukemia, acute leukemia, lipoma, liver cancer, liver metastases, Lucke carcinoma, lymphadenoma, lymphangioma, lymphocytic leukaemia, lymphocytic lymphoma, lymphocytoma, lymphoedema, lymphoma, lung cancer, malignant mesothelioma, malignant teratoma, mastocytoma, medulloblastoma, melanoma, meningioma, mesothelioma, metastatic cancer, Morton's neuroma, multiple myeloma, myeloblastoma, myeloid leukemia, myelolipoma, myeloma, myoblastoma, myxoma, nasopharyngeal carcinoma, nephroblastoma, neuroblastoma, neurofibroma, neurofibromatosis, neuroglioma, neuroma, non-Hodgkin's lymphoma, oligodendroglioma, optic glioma, osteochondroma, osteogenic sarcoma, osteosarcoma, ovarian cancer, Paget's disease of the nipple, pancoast tumor, pancreatic cancer, phaeochromocytoma, pheochromocytoma, plasmacytoma, primary brain tumor, progonoma, prolactinoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, rhabdosarcoma, solid tumor, sarcoma, secondary tumor, seminoma, skin cancer, small cell carcinoma, squamous cell carcinoma, strawberry haemangioma, T-cell lymphoma, teratoma, testicular cancer, thymoma, trophoblastic tumor, tumourigenic, vestibular schwannoma, Wilm's tumor, or a combination thereof.

[0069] Blood vessel proliferative disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration, as well as a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis and ocular diseases such as diabetic retinopathy. Other examples are restenosis, retinopathies and atherosclerosis.

[0070] Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathy syndromes, transplant rejection and glomerulopathies. In this regards, PDGFR has been implicated in the maintenance of mesangial cell proliferation.

[0071] Metabolic disorders that are implicated with abnormal PTK activity include psoriasis, diabetes mellitus, wound healing, inflammation and neurodegenerative diseases. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in the Insulin-R and IGF-1R receptor are indicated in type-II diabetes mellitus.

[0072] Fibrotic disorders refer to the abnormal formation of extracellular matrices. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar.

[0073] The term "treating" as used herein refers to abrogating, inhibiting, slowing or reversing the progression of a disease, ameliorating clinical symptoms of a disease or preventing the appearance of clinical symptoms of a disease. The term "preventing" is defined herein as barring a subject from acquiring a disorder or diseases in the first place.

[0074] The term "administering" as used herein refers to a method for bringing a quinazoline compound of the present invention and a target protein tyrosine kinase together in such a manner that the tyrphostin can affect the catalytic activity of the tyrosine kinase directly, i.e. by interacting with the kinase itself, or indirectly, i.e. by interacting with another molecule on which the catalytic activity of the enzyme is dependent. As referred to herein, administration can be accomplished *in vitro*, i.e. in a test tube, or *in vivo*, i.e. in cells or tissues of living organisms, for example humans. In one embodiment, the present invention encompasses administering the compounds of the present invention to a subject.

[0075] The term "contacting" as used herein refers to bringing into contact the protein tyrosine kinase and the compounds defined herein, under *in vivo* conditions or *in vitro* conditions as defined above.

[0076] The term "therapeutically effective amount" refers to the amount of a compound being administered which relieves to some extent one or more of the symptoms of the disorder being treated. Therapeutic effective doses for the quinazoline compounds described herein can be estimated initially from cell culture and/or an animal model. A dose can be formulated in an animal model, and this dose can be used to more precisely determine useful doses in humans.

[0077] The term "effective inhibitory amount" refers to the amount of a compound being administered which inhibits to some extent the protein tyrosine kinase with which it is contacted.

[0078] As contemplated herein, the present invention encompasses the use of quinazoline compounds of formulas I-IV and their isomers, pharmaceutically acceptable salts and hydrates thereof. In addition, the present invention encompasses the use of mixtures of the compounds or their isomers, pharmaceutically acceptable salts and hydrates thereof. An isomer of the compound includes, but is not limited to, optical isomers, structural isomers, conformational isomers and analogs, and the like.

[0079] In one embodiment, this invention encompasses the use of various structural isomers of the quinazoline compounds of the present invention. It will be appreciated by those skilled in the art that the compounds of the present invention may exist as the (Z) or the (E) isomers. The invention encompasses pure (Z)- and (E)- isomers of the compounds defined herein and mixtures thereof.

[0080] The invention includes pharmaceutically acceptable salts of amino-substituted compounds with organic and inorganic acids, for example, citric acid and hydrochloric acid. The invention also includes N-oxides of the amino substituents of the compounds described herein. Pharmaceutically acceptable salts can also be prepared from the phenolic compounds by treatment with inorganic bases, for example, sodium hydroxide. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[0081] For use in medicine, the salts of the compounds will be pharmaceutically acceptable salts. Pharmaceutically acceptable salts include the acid addition salts which are formed by the reaction of free amino groups with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts, which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts formed from free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[0082] This invention further includes derivatives of the quinazoline compounds of any of formulas I-IV. The term "derivative" includes but is not limited to ether derivatives, acid derivatives, amide derivatives, acid derivatives, ester derivatives and the likes. In addition, this invention further includes hydrates of the compounds defined herein. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

[0083] The present invention further provides pharmaceutical compositions comprising any of the compounds represented by formulas I-IV, and a pharmaceutically acceptable carrier or excipient.

[0084] As used herein, "pharmaceutical composition" means therapeutically effective amounts of the compounds of the present invention, together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or Lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCI., acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic acid, hydrogels, etc., or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils).

[0085] Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms, protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intracranially or intratumorally.

[0086] Further, as referred to herein "pharmaceutically acceptable carriers" are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media.

[0087] Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

[0088] Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g. poloxamers or poloxamines) and the compound coupled to antibodies directed against tissue-specific receptors, ligands or antigens or coupled to ligands of tissue-specific receptors.

[0089] Compounds modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene

glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified compounds (Abuchowski et al., 1981; Newmark et al., 1982; and Katre et al., 1987). Such modifications may also increase the compound's solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the compound, and greatly reduce the immunogenicity and reactivity of the compound. As a result, the desired *in vivo* biological activity may be achieved by the administration of such polymer-compound abducts less frequently or in lower doses than with the unmodified compound.

[0090] In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. For example, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984). Preferably, a controlled release device is introduced into a subject in proximity to the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990).

[0091] The pharmaceutical preparation can comprise one or more of the compounds of formulas I-IV alone or can further include a pharmaceutically acceptable carrier, and can be in solid or liquid form such as tablets, powders, capsules, pellets, solutions, suspensions, elixirs, emulsions, gels, creams, or suppositories, including rectal and urethral suppositories. Pharmaceutically acceptable carriers include gums, starches, sugars, cellulosic materials, and mixtures thereof. The pharmaceutical preparation containing the selective androgen receptor modulator can be administered to a subject by, for example, subcutaneous implantation of a pellet; in a further

embodiment, the pellet provides for controlled release of the active compounds of the present invention over a period of time. The preparation can also be administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation, oral administration of a liquid or solid preparation, or by topical application. Administration can also be accomplished by use of a rectal suppository or a urethral suppository.

[0092] The pharmaceutical preparations of the invention can be prepared by known dissolving, mixing, granulating, or tablet-forming processes. For oral administration, the compounds of the present invention or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into a suitable form for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions. Examples of suitable inert vehicles are conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders such as acacia, cornstarch, gelatin, or with disintegrating agents such as cornstarch, potato starch, alginic acid, or with a lubricant such as stearic acid or magnesium stearate.

[0093] Examples of suitable oily vehicles or solvents are vegetable or animal oils such as sunflower oil or fish-liver oil. Preparations can be effected both as dry and as wet granules. For parenteral administration (subcutaneous, intravenous, intraarterial, or intramuscular injection), the compounds of the present invention or their physiologically tolerated derivatives such as salts, hydrates and the like are converted into a solution, suspension, or emulsion, if desired with the substances customary and suitable for this purpose, for example, solubilizers or other auxiliaries. Examples are sterile liquids such as water and oils, with or without the addition of a surfactant, and other pharmaceutically acceptable adjuvants. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, and glycols such as propylene glycols or polyethylene glycols are preferred liquid carriers, particularly for injectable solutions.

[0094] The preparation of pharmaceutical compositions which contain an active component is well understood in the art. Typically, such compositions are prepared as aerosols of the active compound delivered to the nasopharynx or as injectables, either as liquid solutions or suspensions, however, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified. The active therapeutic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof.

[0095] In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents, which enhance the effectiveness of the active ingredient.

[0096] An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts, which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[0097] For topical administration to body surfaces using, for example, creams, gels, drops, and the like, the compounds of the present invention or their physiologically tolerated derivatives such as salts, hydrates, and the like are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[0098] In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein and

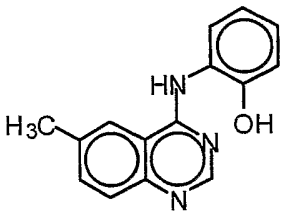
Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

[0099] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXPERIMENTAL DETAILS SECTION

EXAMPLE 1 – PREPARATION OF QUINAZOLINES

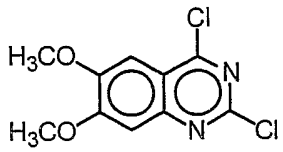
AG 1541 [4-(2'-hydroxyphenylamino)-6-methylquinazoline]



$C_{15}H_{13}N_3O$
Mol. Wt.: 251.29

[00100] 230 mg, 1.3mM, 4-chloro 6-methyl quinazoline (AG 1474) and 145 mg, 1.33 mM, 2-aminophenol in 10 ml ethanol were refluxed for 1 hour. Workup (H_2O, Na_2CO_3, CH_2Cl_2) and trituration with hexane gave 63 mg, 19% yield, light green solid as the free base, mp-270d. NMR DMSO d_6 δ 8.41(1H,S,H_2), 8.27(1H,S,H_5), 7.67(2H,S), 7.54(1H,m), 7.1-6.8(3H,m).

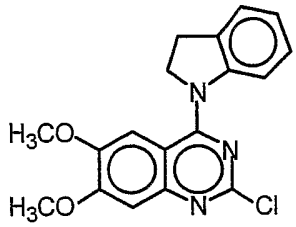
AG 1560 [2,4-dichloro-6,7-dimethoxyquinazoline]



$C_{10}H_8Cl_2N_2O_2$
Mol. Wt.: 259.09

[00101] 8 gr,36 mM, 6,7-dimethoxy 2,4-quinazoline dione, 23 ml ,280 nM $POCl_3$ and 10 ml dimethyl aniline in 40 ml toluene were refluxed for 5 hours. Water and NH_3 were added and the reaction was filtered and washed with EtOAC to give 7g light-green solid, mp-156°. 75% yield. HPLC - 97% pure, Rt=4.87 minutes (RP 18, CH_3CN:H_2O 70:30, UV=254 flow=1.0). NMR $CDCl_3$ δ 7.36(1H,s), 7.28(1H,s), 4,07(3H,s), 4.06(3H,s). NMR DMSO d_6 δ 7.26(1H,s), 6.68 (1H,s), 3.82(3H,s), 3.78(3H,s).

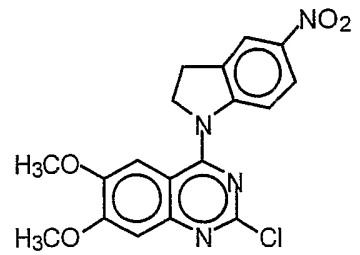
AG 1623 [2-chloro-4-indolyl-6,7-dimethoxyquinazoline]



$C_{18}H_{16}ClN_3O_2$
Mol. Wt.: 341.80

[00102] a. 1.04 gr, 4 mM, 2,4-dichloro quinazoline (AG 1560) and 0.53 gr, 4.5 mM, indoline in 20 ml ethanol were refluxed for 1 hour. Cooling and filtering gave 1.35 gr, 89%, light-yellow solid, as the HCl salt, mp-192°. b. The free base-1.25 gr from a) was treated with 10 ml ammonia in 50 ml water and extracted with ethyl acetate to give 0.86 gr white solid, mp-172°, 77% yield. NMR $CDCl_3$ δ 7.24(1H,s), 7.14(1H,s), 7.30-6.85(4H,m), 4.39(2H,t,J=8.0Hz), 4.03(3H,s,OCH_3), 3.81(3H,s,OCH_3), 3.21(2H,t,J=8.0 Hz).

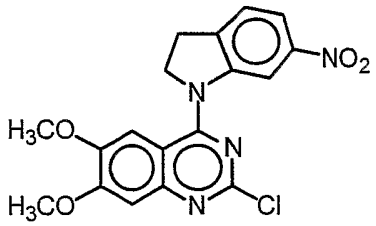
AG 1624 [2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline]



$C_{18}H_{15}ClN_4O_4$
Mol. Wt.: 386.79

[00103] a) 0.4 gr, 1.5 mM, 2,4-dichloro quinazoline (AG 1560) and 0.25 gr, 1.5 mM, 5-nitro indoline in 10 ml ethanol were refluxed for 1 hour. Cooling and filtering gave 0.42 gr, 66%, light-yellow solid, as the HCl salt, mp-250°. b) The free base-0.4 gr from a) was treated with 10 ml ammonia in 50 ml water and extracted with ethyl acetate to give 0.24 gr yellow solid, mp-248°, 66% yield. NMR $CDCl_3$ δ 8.15(1H,m,$H_{4''}$), 8.04(1H,m,$H_{6''}$), 7.30(1H,s,H_8), 6.97(1H,s,H_5), 6.84(1H,s,$H_{7''}$), 4.52(2H,t,J=8.2Hz), 4.06(3H,s,OCH_3), 3.84(3H,s,OCH_3), 3.33 (2H,t,J=8.2 Hz).

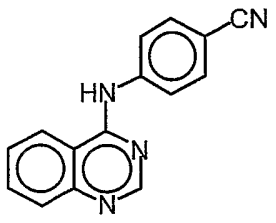
AG 1625 [2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline]



$C_{18}H_{15}ClN_4O_4$
Mol. Wt.: 386.79

[00104] a) 0.4 gr,1.5 mM, 2,4-dichloro quinazoline (AG 1560) and 0.25 gr, 1.5 mM, 6-nitro indoline in 10 ml ethanol were refluxed for 1 hour. Cooling and filtering gave 0.46 gr, 72%, light-yellow solid, as the HCl salt, mp-275°. b) free base-0.32 gr from a) was treated with 10 ml ammonia in 50 ml water and extracted with ethyl acetate to give 0.04 gr yellow solid, mp-264° ,14% yield . NMR $CDCl_3$ δ 7.86(1H,dd,$H_{5''}$), 7.76(1H,d,J=2.0Hz,$H_{7''}$), 7.40(1H,d,J=8.0 Hz,$H_{4''}$), 7.30(1H,s, H_8), 7.04(1H,s,H_5) ,4.52(2H,t,J=8.2Hz), 4.06(3H,s,OCH_3), 3.83(3H,s,OCH_3), 3.33 (2H,t,J=8.2 Hz).

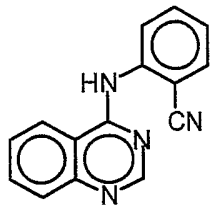
AG 1686 [4-(4'-cyanophenylamino)quinazoline]



$C_{15}H_{10}N_4$
Mol. Wt.: 246.27

[00105] 330 mg, 2mM, 4-chloro quinazoline (AG 1467) and 250 mg, 2.1mM, 4-cyano aniline in 10 ml ethanol were refluxed for 1 hour. Cooling and filtering gave 452 mg, 79%, light-yellow solid, as the HCl salt, mp-275°. NMR DMSO d_6 d 9.04 (1H,S, H_2), 8.16 - 7.85 (8H,m).

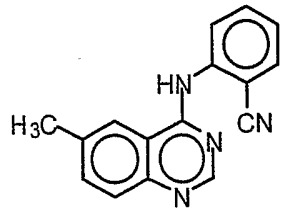
AG 1687 [4-(2'-cyanophenylamino)quinazoline]



$C_{15}H_{10}N_4$
Mol. Wt.: 246.27

[00106] 330 mg, 2mM, 4-chloro quinazoline (AG 1467) and 255 mg, 2.1 mM, 2-cyano aniline in 10 m ethanol were refluxed 1 hour. On cooling no precipitate is formed. The reaction was made basic with aqueous KOH and extracted with CH_2Cl_2. Evaporation and trituration with benzene-hexane gave 56 mg, yellow-green solid, mp-222 as the free base. Yield 11%. NMR $CDCl_3$ d 8.85 (1H,S,H_2), 7.8(6H,m), 6.7 (1H,m), 5.8(1H,mMS - 246(M+, 25%), 238(55), 236(100), 234(99), 118(60), m/e.

AG 1688 [4-(2'-cyanophenylamino)-6-methylquinazoline]

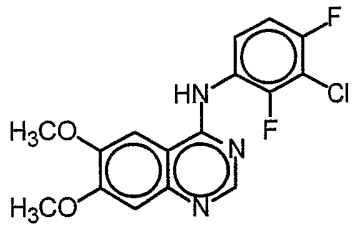


$C_{16}H_{12}N_4$
Mol. Wt.: 260.30

[00107] 307 mg, 1.71 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 216 mg, 1.83 mM, anthranilo nitrile in 10 ml ethanol were refluxed for 1 hour. On cooling no precipitate is formed. The reaction was made basic with aqueous KOH and extracted with CH_2Cl_2. Evaporation and trituration with CCl_4 gave 130 mg,

29% yield, yellow solid, mp-272, as the free base. NMR $CDCl_3$ d 8.70 (1H,S, H_2), 7.90-7.60(6H,m), 7.35(1H,m), 2.50(3H,S). MS - 260 (M^+,18^+), 250(100), 248(65), m/e.

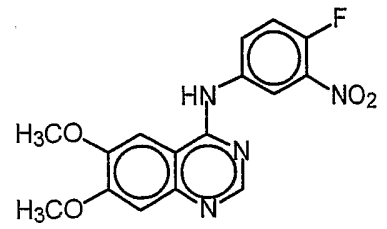
AG 1698 [4-(2',4'-difluoro-3-chloro-phenylamino)-6,7-dimethoxyquinazoline]



$C_{16}H_{12}ClF_2N_3O_2$
Mol. Wt.: 351.74

[00108] 300 mg,1.3 mM, 4-chloro 6,7-dimethoxy quinazoline and 230 mg, 1.4 mM, 2,4-difluoro 3-chloro aniline in 20 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 500 mg white solid, 99% yield, mp-272° as the HCl salt.. NMR DMSO d_6 δ 8.85(1H,s,H_2), 8.39(1H,s), 7.70-7.44(2H,m), 7.40 (1H.s,H_5), 4.01(6H,s,OCH_3). MS-353, 351(M^+,55%,20%), 334,332(M-F,50,17), 333,331(M-HF,40,15), 316(M-Cl, 100%), 158(30) m/e.

AG 1699 [4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline]

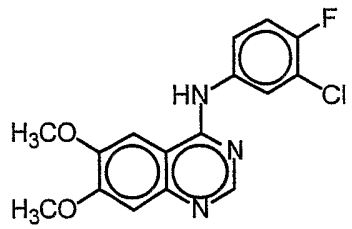


$C_{16}H_{13}FN_4O_4$
Mol. Wt.: 344.30

[00109] 450 mg, 2 mM, 4-chloro 6,7-dimethoxy quinazoline and 320 mg, 2 mM, 3-nitro 4-fluoro aniline in 15 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 710 mg white solid, 94% yield, mp-270° as the HCl salt.. NMR DMSO d_6 δ 8.92(1H,s, H_2),8.64(1H,m), 8.34(1H,m),7.74(1H,m), 7.36(1H.s, H_5),

4.02(3H,s,methoxy), 3.99(3H,s,OCH_3). MS-353, 351(M^+,55%,20%), 334, 332(M-F,50,17), 333, 331(M-HF,40,15), 316(M-Cl, 100%), 158(30) m/e.

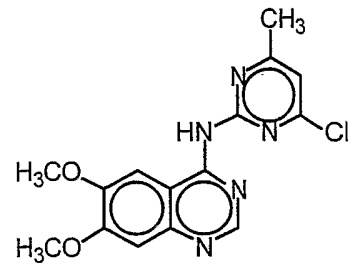
AG 1700 [4-(3'-chloro-4'-fluoro-phenylamino)-6,7-dimethoxyquinazoline]



$C_{16}H_{13}ClFN_3O_2$
Mol. Wt.: 333.75

[00110] 600 mg,2.7 mM, 4-chloro 6,7-dimethoxy quinazoline and 400 mg, 2.8 mM, 3-chloro 4-fluoro aniline in 15 ml ethanol were refluxed 1 hour. Cooling and filtering gave 940 mg white solid, 94% yield, mp-268° as the HCl salt.. NMR DMSOd_6 δ 8.89(1H,s,H_2), 8.31(1H,m), 8.02(1H,m),7.76(1H,m), 7.56(1H,t), 7.33(1H.s,H_5), 4.00(6H,s,OCH_3). MS 335,333(M^+,66%,20%), 334,332(100,40), 316 (15), 149(20) m/e.

AG 1701 [4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline]

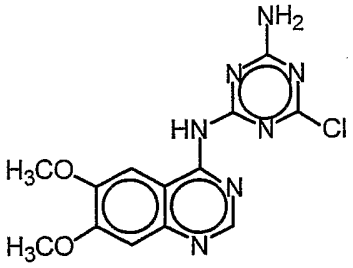


$C_{15}H_{14}ClN_5O_2$
Mol. Wt.: 331.76

[00111] 0.3g, 1.3mM, , 4-chloro 6,7-dimethoxy quinazoline and 0.2g, 1.4mM, 2-amino 3-chloro 6-methyl pyrimidine in 15 ml ethanol were refluxed 1 hour. Cooling and filtering gave 0.4g, 85% yield, white woolly crystals, the HCl salt, mp-

180.NMR DMSO d_6 δ 8.89(1H,S), 7.47(1H,S), 7.41(1H,S), 6.56(1H,S), 4.01(3H,S), 4.0(3H,S), 2.21(3H,S).

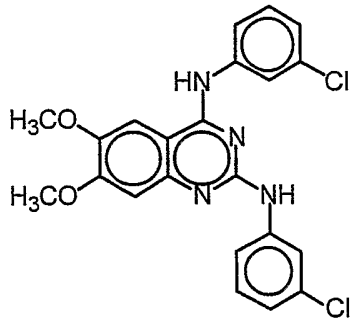
AG 1702 [4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline]



$C_{13}H_{12}ClN_7O_2$
Mol. Wt.: 333.74

[00112] 0.45g, 2.1mM , 4-chloro 6,7-dimethoxy quinazoline and 0.36g, 2.5mM, 2,4-diamino 6-chloro triazine in 10 ml ethanol were refluxed for 1 hour, cooled and filtered to give 0.72g, 92% yield, light-yellow solid, as the HCl salt, mp-200.

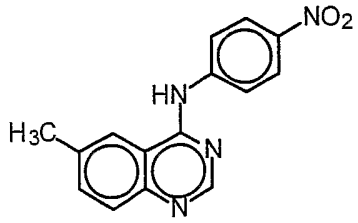
AG 1703 [2,4-bis-(3'-chloro-phenylamino)-6,7-dimethoxyquinazoline]



$C_{22}H_{18}Cl_2N_4O_2$
Mol. Wt.: 441.32

[00113] Obtained in fractions 1-6 of reaction 1690. 37 mg, white solid, mp-98. NMR $CDCl_3$ d 7.85(1H,br.S), 7.72(1H,br.S), 7.6-6.9(8H,m), 3.96(6H,S).

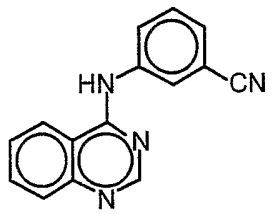
AG 1707 [4-(4'-nitro-phenylamino)-6-methylquinazoline]



$C_{15}H_{12}N_4O_2$
Mol. Wt.: 280.29

[00114] 250 mg, 1.4 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 200 mg , 1.45mM, p-nitro aniline in 10 ml ethanol were refluxed 1.5 hour. Cooling and filtering gave 330 mg, 74% yield, yellow solid, mp-298, as the HCl salt. NMR DMSO d_6 d 9.04 (1H, S, H_2), 8.88(1H, br, S), 8.35, 8.17 (4H,ABq, J_{AB}=9.5 Hz), 7.96(2H,m), 2.58 (3H,S).

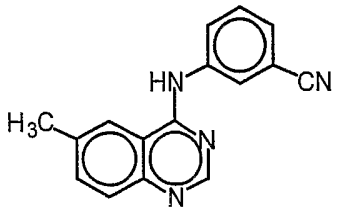
AG 1715 [4-(3'-cyano-phenylaminoquinazoline]



$C_{15}H_{10}N_4$
Mol. Wt.: 246.27

[00115] 305 mg, 1.85mM, 4-chloro quinazoline (AG 1467) and 225 mg, 1.9 mM, m-cyano aniline in 10 ml ethanol were refluxed 0.5 hour, cooled and filtered to give 440 mg, 84% yield, yellow solid, mp-265°, as the HCl salt. NMR DMSO d_6 d 9.02(1H,S,H_2), 8.95(1H, m), 8.32 (1H,br.S), 8.15 - 7.72 (6H,m).

AG 1716 [4-(3'-cyano-phenylamino)-6-methylquinazoline]



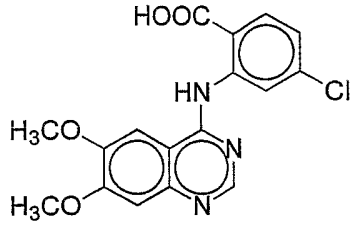
$C_{16}H_{12}N_4$
Mol. Wt.: 260.30

[00116] 324 mg, 1.81 mM, 4-chloro 6-methyl quinazoline (AG 1474) , 4-chloro 6-methyl quinazoline and 220 mg, 1.83 mM, m-cyano aniline in 10 ml ethanol were refluxed for 1 hour. Cooling and filtering gave 450 mg, 80% yield,

light yellow solid, mp-257, as the HCl salt. NMR DMSO d_6 d 9.0 (1H,S, H_2), 8.8(1H,S), 8.33(1H,S), 8.14-7.72 (5H,m), 2.58 (3H,S).

AG 1813

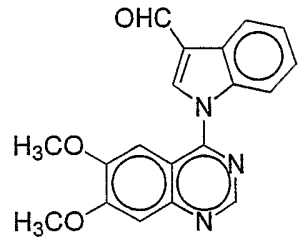
[4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline]



$C_{17}H_{14}ClN_3O_4$
Mol. Wt.: 359.77

[00117] 500 mg, 2.2 mM, 4-chloro 6,7-dimethoxy quinazoline and 400 mg ,2.3 mM, 2-amino 3-chloro benzoic acid in 20 ml ethanol were refluxed 4.5 hours. Cooling and filtering gave 660 mg,76% yield, lemon-yellow solid.

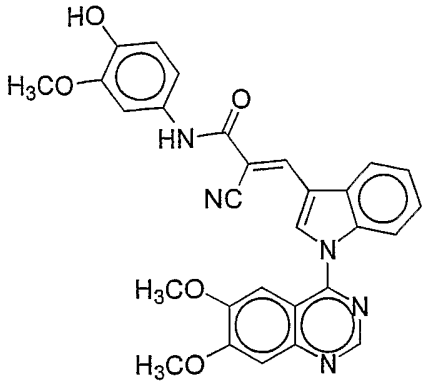
AG 1814 [4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline]



$C_{19}H_{15}N_3O_3$
Mol. Wt.: 333.35

[00118] 500 mg, 2.2 mM, 4-chloro 6,7-dimethoxy quinazoline ,400 mg, 2.8 mM, 3-formyl indole and 0.3 gr crushed KOH in 10 ml DMSO were stirred at ambient temperature. Workup and recrystalization from benzene gave 550 mg,75% yield, white solid. NMR $CDCl_3$ δ 10.21(1H,s,CHO), 9.15(1H,s, H_2), 8.45(1H,d,J=8.0 Hz,$H_{7'}$), 8.30(1H,s,$H_{2'}$),7.49(1H,s, H_8),7.40(3H,m),7.04(1H,s, H_5),4.13,3.80(6H,2 s, OCH_3).

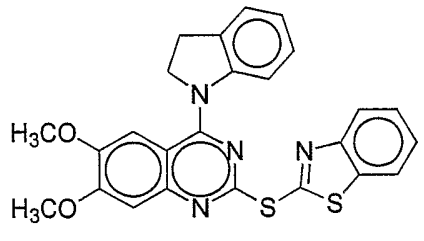
AG 1827 [2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide]



$C_{29}H_{23}N_5O_5$
Mol. Wt.: 521.53

[00119] 50 mg ,0.15 mM, AG 1814 ,33 mg, 0.16 mM, AG 1654 and 8 mg β-alanine in 15 ml ethanol were refluxed for 2.5 hours. Cooling and filtering gave 66 mg, 85% yield, yellow solid, mp-267^0. NMR $CDCl_3$ δ 9.17(1H,s, H_2), 8.88(1H,s,H_2'), 8.86(1H,s,vinyl), 8.0(1H,m·),7.74(2H.m), 7.50(1H,s, H_8), 7.42(2H,m), 7.20(1H,s, H_5), 7.10(1H,m), 6.85(1H.d,J=8.8 Hz), 4.14,3.95, 3.92(9H,3 s,OCH_3).

AGL 1885 [2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline]

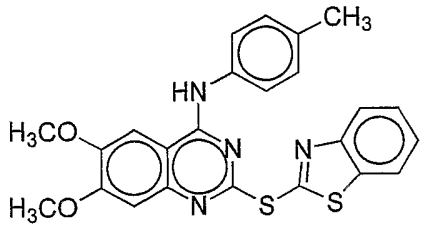


$C_{25}H_{20}N_4O_2S_2$
Mol. Wt.: 472.58

[00120] 135 mg, 0.4 mM, AG 1623 (free base) and 67 mg,0.4 mM, 2-mercapto benzothiazole and 50 mg KOH in 25 ml ethanol were stirred at room temperature 40 hours. Workup gave 85 mg, 45% yield, light-yellow solid, mp-157^0 NMR $CDCl_3$ δ 7.4-6.8(10H,m), 4.02,3.80(6H,2s,OCH_3), 4.38(2H,t,J=6.0 Hz), 3.21(2H,t,J=6.0 Hz).

AGL 1886

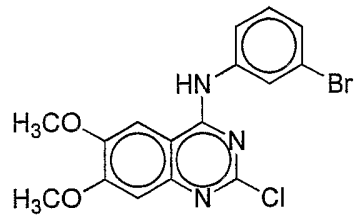
[2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline]



$C_{24}H_{20}N_4O_2S_2$
Mol. Wt.: 460.57

[00121] 29 mg, 0.09 mM, AG 1562 (free base) and 17 mg, 0.1 mM, 2-mercapto benzothiazole and 10 mg KOH in 25 ml ethanol were stirred at room temperature for 50 hours. Workup and trituration with CH_2Cl_2-hexane gave 25 mg, 61% yield, light-yellow solid. NMR $CDCl_3$ δ 7.6-7.1(9H,m), 6.93(1H,s), 3.99, 3.98(6H,2s,OCH_3), 2.36(3H,s, CH_3).

AGL 1894 [2-chloro-4–(3-bromophenylamino)-6,7-dimethoxyquinazoline]

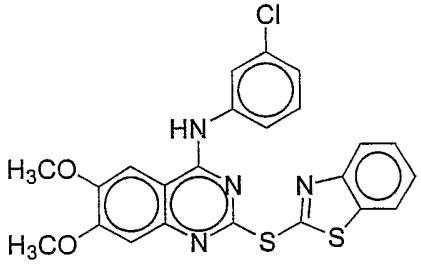


$C_{16}H_{13}BrClN_3O_2$
Mol. Wt.: 394.65

[00122] 1.1 gr, 4.2 mM,AG 1560 (free base) and 0.76, 4.4 mM, 3-bromo aniline in 25 ml ethanol were refluxed 1.5 hours. Workup (EtAc - NH_3) and trituration with benzene-hexane gave 0.61 gr, 37% yield, white solid. NMR $CDCl_3$ δ 7 .74(1H,dt), 7.4(3H,m), 7.20(1H,s), 6.94(1H.s), 4.02, 4.0(6H,2s,OCH_3).

AGL 1897

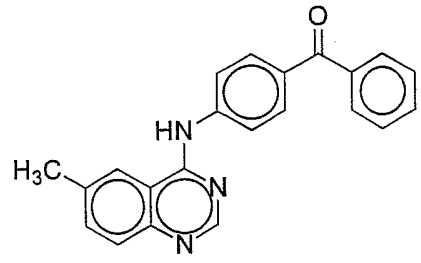
[2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline]



$C_{23}H_{17}ClN_4O_2S_2$
Mol. Wt.: 480.99

[00123] 220 mg, 0.56 mM, AG 1896a (identical to AG 1614) and 100 mg, 0.6 mM, 2-mercapto benzothiazole and 95 mg KOH in 25 ml ethanol were stirred at room temperature for 60 hours. Workup gave 76 mg,28% yield, white solid. NMR $CDCl_3$ δ 7.7-6.9(8H,m),7.22(1H.s),6.95(1H,s), 4.03,4.0(6H,2s,OCH_3).

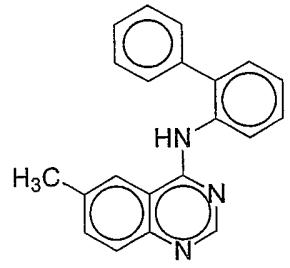
AGL 1923 [4-(4'-phenylcarbonyl-phenylamino)-6-methylquinazoline]



$C_{22}H_{17}N_3O$
Mol. Wt.: 339.40

[00124] 274 mg, 1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 300 mg, 1.5 mM,4-amino benzophenone in 15 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 440 mg,78% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 8.98(1H,s), 8.76(1H,s),8.05-7.50(11H,m), 2.60(3H,s, CH_3).

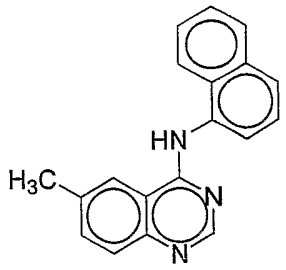
AGL 1924 [4-(2'-phenyl-phenylamino)-6-methylquinazoline]



$C_{21}H_{17}N_3$
Mol. Wt.: 311.39

[00125] 270 mg, 1 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 270 mg, 1.6 mM, 2-amino biphenyl in 15 ml ethanol were refluxed 1.5 hours. Workup (KOH) and trituration with dichloromethane-hexane gave 210 mg,45% yield, pink solid. NMR $CDCl_3$ δ 8.70(1H,m),7.8-6.8(12H.m),2.40(3H.s,CH_3).

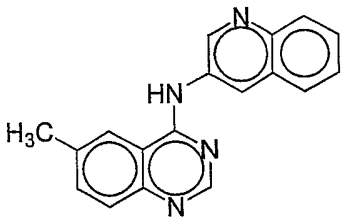
AGL 1925 [4-(1'-naphthylamino)-6-methylquinazoline]



$C_{19}H_{15}N_3$
Mol. Wt.: 285.35

[00126] 270 mg, 1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 230 mg, 1.6 mM,1-amino naphtalene in 15 ml ethanol were refluxed 1.5 hours. Workup (KOH) and trituration with dichloromethane-hexane gave 267 mg, 62% yield. NMR $CDCl_3$ δ 8.64(1H,s), 7.9-7.3(10H,m), 2.60(3H,s,CH_3).

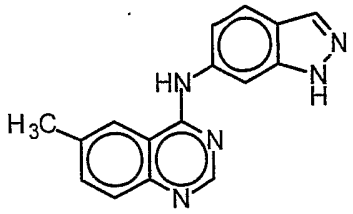
AGL 1927 1924 [4-(3'-quinolyl-amino)-6-methylquinazoline]



$C_{18}H_{14}N_4$
Mol. Wt.: 286.34

[00127] 270 mg, 1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 220 mg,1.6 mM, 3-amino quinoline in 15 ml ethanol were refluxed for 2 hours. Cooling and filtering gave 270 mg, 55% yield light-yellow solid of the HCl salt. NMR DMSO d_6 δ 9.28(1H,d,J=2.4 Hz), 8.96(1H,s), 8.81(1H,br.s), 8.74(1H,d,J=2.0 Hz), 8.07(2H.t,J=5.6 Hz), 7.98(1H,dd,J=8.6,1.4 Hz), 7.92(1H,d,J=8.6 Hz), (7.98 and 7.92 Abq with left wing split), 7.80(1H,m(dtd)), 7.58(1H,m(dtd)), 2.60(3H,s,CH_3).

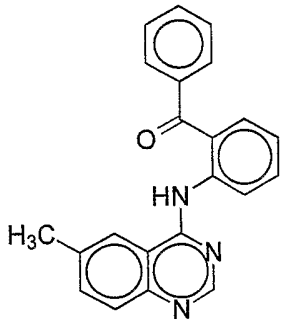
AGL 1929 [4-(6'-indazolyl-amino)-6-methylquinazoline]



$C_{16}H_{13}N_5$
Mol. Wt.: 275.31

[00128] 274 mg,1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 210 mg, 1.6 mM, 6-amino indazole in 15 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 363 mg,77% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 11.8(1H,br.s),9.0(1H,s), 8.90(1H,s), 8.20(1H,s,NH indazole), 8.10-7.92(4H,m), 7.56,7.53(1H,dd,J=8.5, 1.3 Hz(right wing Abq, split)), 2.66(3H, s,CH_3).

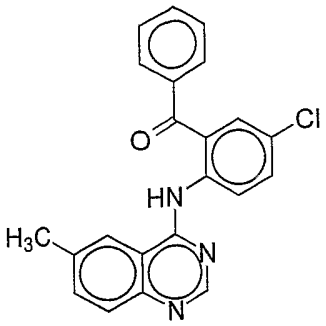
AGL 1930 [4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline]



$C_{22}H_{17}N_3O$
Mol. Wt.: 339.40

[00129] 274 mg,1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 300 mg,1.5 mM, 2-amino benzophenone in 15 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 370 mg,68% yield, light-yellow solid of the HCl salt. NMR DMSO d_6 δ 8.40(1H,d,J=1.3 Hz), 8.22(1H,d,J=8.4 Hz), 8.10(2H,m), 7.92(2H,m), 7.76-7.66(5H,m), 7.28(1H,dd,J=8.2,1.3 Hz (left wing Abq, split)), 7.16(1H,d,J=8.2), 2.66(3H,s,CH_3).

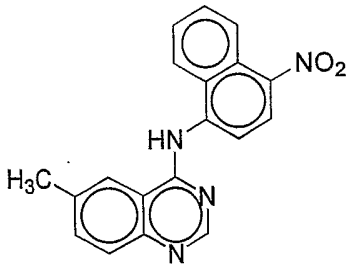
AGL 1931 [4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline]



$C_{22}H_{16}ClN_3O$
Mol. Wt.: 373.84

[00130] 274 mg,1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 300 mg, 1.5 mM 24-amino 4-chloro benzophenone in 15 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 440 mg,78% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 8.38(1H,d,J=0.8 Hz), 8.27(1H,d,J=8.4 Hz), 8.03(1H,dd,J=8.4,1.3 Hz (right wing Abq, split)), 7.99(1H,d,J=1.4 Hz), 7.90(2H,m), 7.76(4H,m), 7.26(1H,dd,J=8.2,1.3 Hz (left wing Abq, split)), 7.10(1H,d,J=8.2), 2.53(3H,s,CH_3).

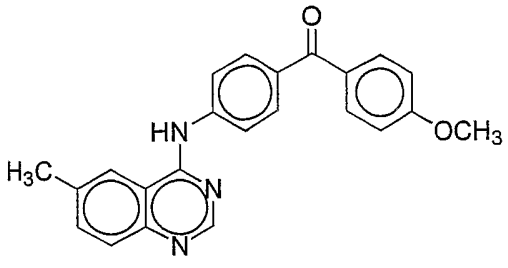
AGL 1932 [4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline]



$C_{19}H_{14}N_4O_2$
Mol. Wt.: 330.35

[00131] 270 mg,1.5 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 370 mg,1.6 mM, 2-amino 4-chloro benzophenone in 15 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 180 mg,29% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 8.98(1H,s), 8.76(1H,s),8.05-7.50(11H,m).

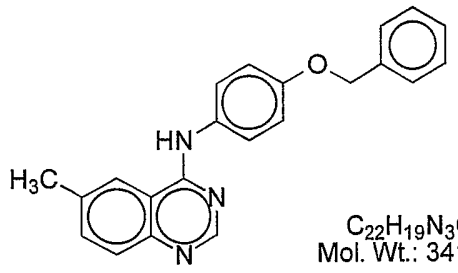
AGL 1933 [4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline]



$C_{23}H_{19}N_3O_2$
Mol. Wt.: 369.42

[00132] 430 mg,2.4 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 600 mg, 2.6 mM,4-amino 4'-methoxy benzophenone (AG 1926) in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 410 mg,42% yield, light-yellow solid, HCl salt. NMR DMSOd_6 δ 8.98(1H,s) ,8.83(1H,s),8.02-7.77(8H,m), 7.12(2H,d,J=8.8 Hz (right wing Abq)), 3.87(3H,s,OCH_3), 2.59(3H,s,CH_3).

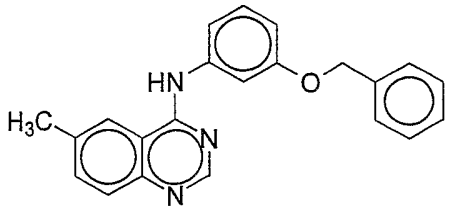
AGL 1980 [4-(4'-benzyloxy-phenylamino)-6-methylquinazoline]



$C_{22}H_{19}N_3O$
Mol. Wt.: 341.41

[00133] 360 mg, 2 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 400 mg, 2 mM,4-phenoxy aniline in 20 ml ethanol were refluxed for 2 hours. Cooling and filtering gave 223 mg, 29% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 8.84(1H,s,H_2), 8.62(1H,d,J=1.4 Hz,H_5), 7.94(1H,dd,J=8.4,1.4 Hz,H_7), 7.82 (1H,d,H_8) ,7.61,7.13(4H,ABq,J=8.5 Hz), 7.40(5H,m),5.17(2H,s), 2.56(3H,s,CH_3). 4-phenoxy aniline-free base NMR Acetone d_6 δ 7.40-7.20(5H,m), 6.76,6.60(4H,ABq,J=8.6 Hz) , 4.98(2H,s).

AGL 1981 [4-(3'-benzyloxy-phenylamino)-6-methylquinazoline]

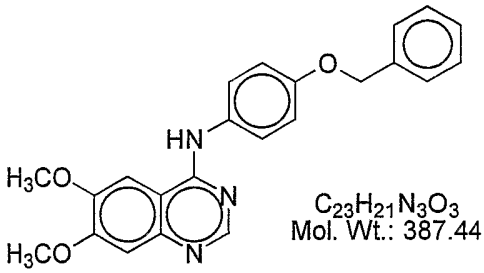


$C_{22}H_{19}N_3O$
Mol. Wt.: 341.41

AG 1981

[00134] 360 mg, 2 mM, 4-chloro 6-methyl quinazoline (AG 1474) and 400 mg, 2 mM,3-phenoxy aniline in 20 ml ethanol were refluxed for 2 hours. Cooling and filtering gave 350 mg,47% yield, light-yellow solid, HCl salt. NMR DMSO d_6 δ 8.89(1H,s,H_2), 8.80(1H,br.s), 8.14(2H,m), 7.40(8H,m), 7.0(1H,m),5.14(2H,s), 2.56(3H,s,CH_3).

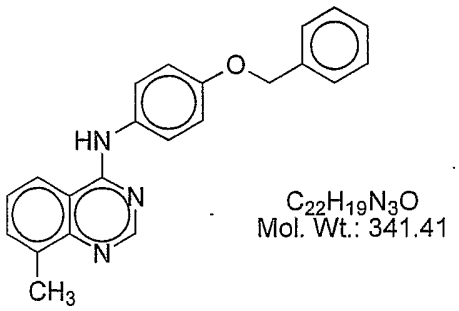
AGL 2002 [4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline]



$C_{23}H_{21}N_3O_3$
Mol. Wt.: 387.44

[00135] 225 mg, 1 mM, 4-chloro 6,7-dimethoxy quinazoline and 210 mg, 1.05 mM, 4-phenoxy aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 380 mg, 90% yield, white solid, HCl salt.

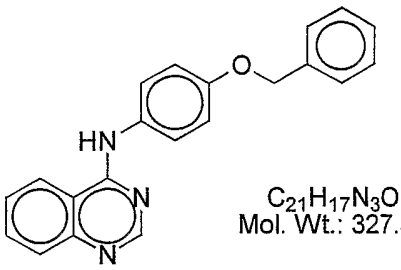
AGL 2003 [4-(4'-benzyloxy-phenylamino)-8-methylquinazoline]



$C_{22}H_{19}N_3O$
Mol. Wt.: 341.41

[00136] 180 mg,1 mM, 4-chloro 8-methyl quinazoline (AG 1473) and 200 mg,1 mM, 4-phenoxy aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 267 mg,73% yield, light-yellow solid, HCl salt.

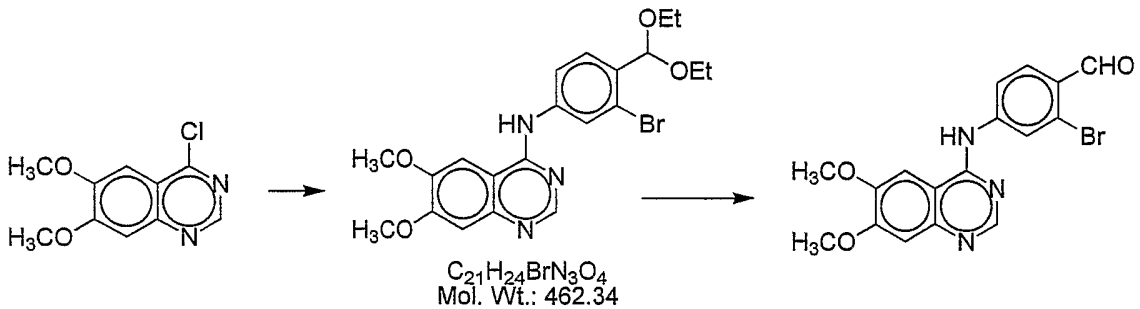
AGL 2004 [4-(4'-benzyloxy-phenylamino)quinazoline]



$C_{21}H_{17}N_3O$
Mol. Wt.: 327.38

[00137] 180 mg, 1.1 mM, 4-chloro quinazoline (AG 1467) and 220 mg, 1.1 mM,4-phenoxy aniline in 20 ml ethanol were refluxed for 2 hours. Evaporation, trituration with little ethanol and filtering gave 200 mg, 52% yield, light-yellow solid, HCl salt.

Synthetic scheme to AG 2064 and AG 2116:

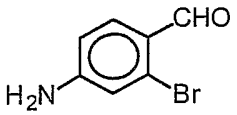


$C_{21}H_{24}BrN_3O_4$
Mol. Wt.: 462.34

AG 2064 **AG 2116**

Scheme 1

Synthesis of 3-bromo 4-formyl aniline-AGL 2054,2073



AG 2054
AG 2073

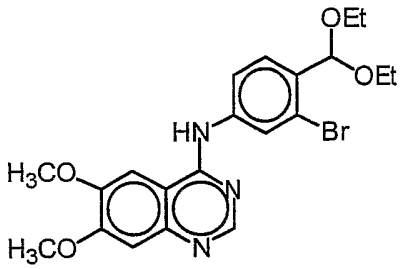
C_7H_6BrNO
Mol. Wt.: 200.03

[00138] To 5.5 gr, 32 mM, 3-bromo aniline in 50 ml DMSO and 4 ml HCl was added 8.1 gr, 60 mM, $CuCl_2$. The black reaction was heated at 100^0 5.5 hours. After neutralizing with sodium carbonate it was extracted with CH_2Cl_2. Chromatography on silica gel and trituration with CH_2Cl_2-hexane gave 1.9 gr, 30% yield, yellow solid, mp-129°. TLC-Rf=0.3 (CH_2Cl_2) violet with ninhydrin. NMR $CDCl_3$ δ 10.1(1H,CHO), 7.75(1H,d,J=8.5 Hz ,H_6), 6.83(1H,d,J=2.2 Hz,H_3), 6.60(1H,dd,J=8.5,2.2 Hz,H_5), 4.20(2H,br.s,NH_2).

[00139] The reaction was done analogous to *B.Liedholm, J.Chem Soc., Perkin Trans.* I, 1992, 2235. The reaction gave variable yields, and is probably sensitive to HCl and DMSO quantities.

AGL 2064

[4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline]

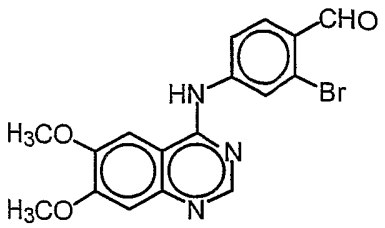


$C_{21}H_{24}BrN_3O_4$
Mol. Wt.: 462.34

[00140] 335 mg,1.5 mM, 4-chloro 6,7-dimethoxy quinazoline and 300 mg, 1.5 mM, 3-bromo 4-formyl aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 450 mg light-yellow solid, 73% yield. NMR $CDCl_3$ δ 8.69(1H,s,H_2), 8.05(1H,s), 7.64(2H,s), 7.26(2H,m), 5.65(1H,s,acetal), 4.03 (3H,s,OCH_3), 4.0(3H,s,OCH_3), 3.65(4H,m), 1.27(6H,t,J=7.0 Hz).

AGL 2116 (see 2085)

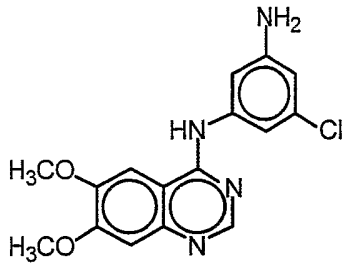
[4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline]



$C_{17}H_{14}BrN_3O_3$
Mol. Wt.: 388.22

[00141] To 200 mg AG 2064 in 5 ml acetonitrile and 10 ml water was added 4 drops HCl. The reaction was refluxed 2 hours. Cooling and filtering gave 130 mg light-yellow solid, 80% yield, mp-222° as the HCl salt. Free base- mp-248° NMR DMSOd6 δ 10.17(1H,CHO), 8.87(1H,s,H_2), 8.42(1H,s), 8.11(2H,m), 7.95(1H,d,J=8.6 Hz), 7.31(1H,s), 4.03(3H,s,OCH_3), 4.0(3H,s,OCH_3).

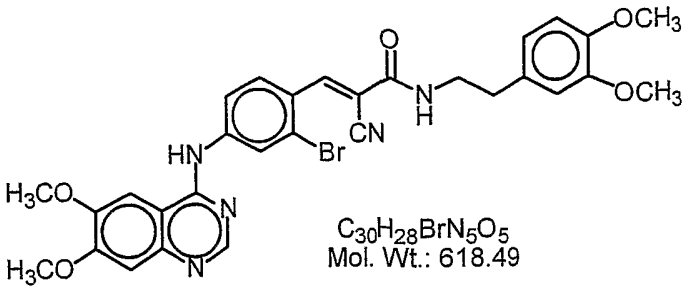
AGL 2120 [4-(3'-amino-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline]



$C_{16}H_{15}ClN_4O_2$
Mol. Wt.: 330.77

[00142] 900 mg, 4 mM, 4-chloro 6,7-dimethoxy quinazoline (A.J. Bridges et al, *J. Med .Chem.*, 39,267(1996)) and 590 mg, 2.6 mM, 5-chloro-1,3-phenylene diamine in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 1.3 gr light-yellow solid, 89% yield, mp-265° as the HCl salt.. NMR DMSO d_6 δ 8.82(1H,s,H_2), 8.30(1H,s,H_8), 7.40(1H,s,H_5), 6.95(1H,br.s), 6.86(1H,br.s), 6.56(1H,br.s), 4.01(3H,s,OCH_3), 3.98(3H,s,OCH_3).

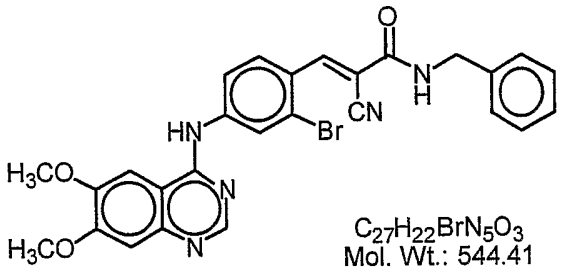
AGL 2122 [3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide]



$C_{30}H_{28}BrN_5O_5$
Mol. Wt.: 618.49

[00143] 250 mg .0.5 mM, AG 2064 was hydrolysed to the aldehyde as described for AG 2116. Then piperidine was added until the reaction became basic and 130 mg, 0.5 mM,AG 480, (ref 10) was added. Reflux for 3 hours, cooling and filtering gave 150 mg, 48% yield, yellow solid, mp-277d NMR DMSO d_6 δ 8.66(1H,s,H_2), 8.48(1H,m), 8.30(1H,s,vinyl), 8.15(2H,m), 7.86(1H,s,H_5), 7.26 (1H,s.H_8), 6.86-6.75(3H,m), 3.99(3H,s,OCH_3), 3.96(3H,s,OCH_3), 3.76(3H,s,OCH_3), 3.72(3H,s,OCH_3), 3.43(2H,q,J=6.4 Hz), 2.77(2H,t,J=6.4 Hz).

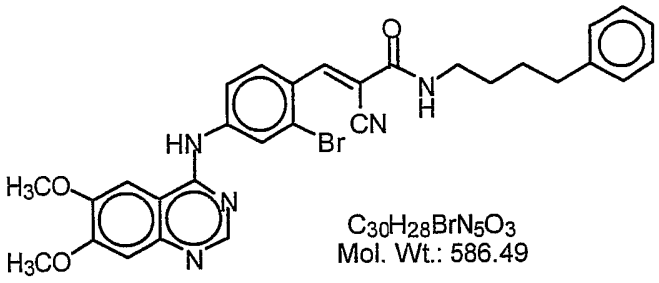
AGL 2123 [N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide]



$C_{27}H_{22}BrN_5O_3$
Mol. Wt.: 544.41

[00144] 150 mg, 0.3 mM, AG 2064 (N-benzyl-3-[2-bromo-quinazoline-4-amine) was hydrolysed to the aldehyde as described for AG 2116. Then piperidine was added until the reaction became basic and 50 mg, 0.3 mM, AG 477 was added. Reflux for 2 hours, cooling and filtering gave 120 mg,74% yield, yellow solid, mp-287°. NMR DMSOd_6 δ 8.64(1H,s,H_2), 8.47(1H,s), 8.38(1H,s,vinyl), 8.18(2H,s), 7.85(1H,s,H_5), 7.35(5H,br.s,Ph), 7.27(1H,s.H_8), 4.45(2H,d,J=6.0 Hz), 3.99 (3H,s,OCH_3),3.96(3H,s,OCH_3).

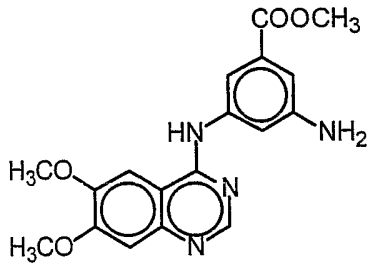
AGL 2124 [3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide]



$C_{30}H_{28}BrN_5O_3$
Mol. Wt.: 586.49

[00145] 150 mg, 0.3 mM, AG 2064 was hydrolysed to the aldehyde as described for AG 2116. Then piperidine was added until the reaction became basic and 70 mg, 0.3 mM, AG 553 was added. Reflux for 2 hours, cooling and filtering gave 115 mg, 66% yield, yellow solid, mp-254°. NMR DMSOd6 δ 8.63(1H,s,H_2), 8.47(1H,m), 8.30(1H,s,vinyl), 8.15(2H,m), 7.85(1H,s,H_5), 7.35-7.15(6H,m with s at 7.26 ppm), 3.99 (3H,s,OCH_3), 3.96(3H,s,OCH_3), 3.3(2H,m), 2.61(2H,t), 1.55(4H,m).

AGL 2052 [4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline]

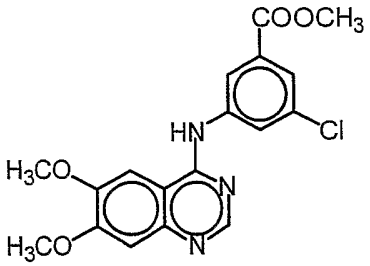


$C_{18}H_{18}N_4O_4$
Mol. Wt.: 354.36

[00146] 670 mg, 3 mM, 4-chloro 6,7-dimethoxy quinazoline (AG 1477), and 500 mg, 3 mM, 5-carbomethoxy-1,3- phenylene diamine (AGR 183), in 20 ml ethanol were refluxed for 2 hours. Cooling and filtering gave 0.49 gr light-yellow solid, 46% yield, mp-130° as the HCl salt. (violet with ninhydrin). NMR $CDCl_3$ δ 8.67(1H,s,H_2),7.73(1H,dt,J=5.5,2.0Hz,$H_{2'}$), 7.43(1H,dt,J=5.5,2.0Hz,$H_{4'}$), 7.26

(1H,s), 7.12(1H,m,$H_{6'}$), 7.02(1H,s), 4.03, 4.01(6H,2s,OCH_3), 3.90(3H,s,methoxy ester). NMR Acetone d_6 δ 8.51(1H,s,H_2), 7.76(1H,s,$H_{5'}$), 7.74(1H,m), 7.55(1H,m), 7.20(1H,s,H_8), 7.08(1H,m), 4.0, 3.96(6H,2s,OCH_3), 3.85(3H, s,methoxy ester).

AGL 2053 [4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline]



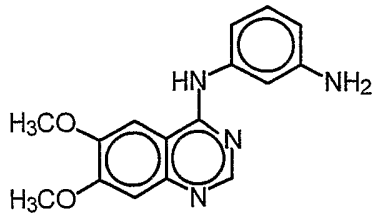
$C_{18}H_{16}ClN_3O_4$
Mol. Wt.: 373.80

[00147] 290 mg,0.8 mM, AG 2052 in 10 ml water and 1 ml HCl was diazotized with 83 mg,1.2 mM, $NaNO_2$ with cooling and the reaction was added into 0.4 gr CuCl in 10 ml water and 2 ml HCl. Slow gas evolution was observed. After 2 hours at room temperature the reaction was worked up (KOH) to give 30 mg, 10% yield, white solid, mp-110°. NMR $CDCl_3$ δ 8.72(1H,s,H_2), 8.36(1H,d,J=7.0 Hz, NH split), 8.05(1H,d,J=7.0 Hz,), 7.75(1H,s),7.28(1H,s), 7.04(1H,s), 4.05, 4.03(6H,2s,OCH_3), 3.94(3H,s,methoxy ester).

AGL 2042

[00148] 45 mg, .2 mM, 4-chloro 6,7-dimethoxy quinazoline, G 1477, and 37 mg, 2 mM, 5-carbomethoxy-3-chloro aniline, AGR 194 (see RAS), in 20 ml ethanol were refluxed 2 hours. Cooling and filtering gave 66 mg white solid, 80% yield, NMR shows 1:1 mixture of SM 1477 : AG 2053.

AGL 2066 [4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline]



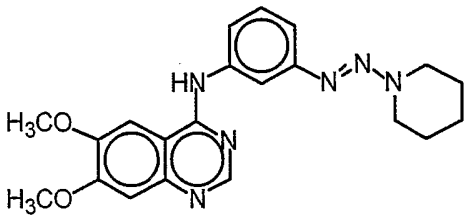
$C_{16}H_{16}N_4O_2$
Mol. Wt.: 296.33

[00149] a) 720 mg, 2 mM, 4-chloro 6,7-dimethoxy quinazoline, AG 1477, and 350 mg, 3.2 mM, 1,3- phenylene diamine in 20 ml ethanol were refluxed 3.5 hours. Workup (KOH) and chromatography gave 0.245 gr light-brown solid, 26% yield, mp-240° NMR $CDCl_3$ δ 8.67(1H,s,H_2), 7.36(1H,s,H_5), 7.26(1H,m, $H_{2'}$), 7.17(1H,t,J=8.0Hz,$H_{5'}$), 7.0(1H,s,H_5), 6.90(1H.dd), 6.50(1H,dd), 4.04, 4.02(6H, 2s,OCH_3).

[00150] 1,3-phenylene diamine- NMR $CDCl_3$ δ 6.97(1H,t,),6.10(2H,m("dd")), 6.0(1H,t).

[00151] b) 930 mg, 4.1 mM, 4-chloro 6,7-dimethoxy quinazoline, AG 1477, and 450 mg, 4.1 mM, 1,3- phenylene diamine in 20 ml ethanol were refluxed 2.5 hours. Cooling and filtering gave 1.27 gr light-yellow solid, 93% yield, mp-262° as the HCl salt. The compound is light sensitive-turns dark yellow after several days as the HCl salt (violet with ninhydrin).

AGL 2067 [4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline]

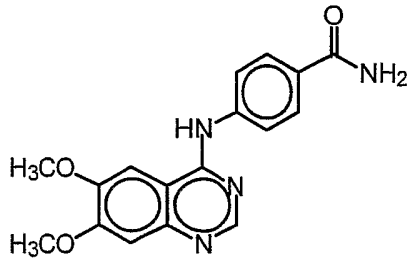


$C_{21}H_{24}N_6O_2$
Mol. Wt.: 392.46

[00152] 570 mg, 1.7 mM, AG 2066, HCl in 10 ml water and 0.5 ml HCl was diazotized with 140 mg, 1.2 mM, $NaNO_2$ in the cold 0.5 hour, and 1 ml piperidine was added. After 20 minutes in the cold and 1 hour at room temperature the solid was filtered, washed with water and dried to give 555 mg, 83% yield, light brown

solid, mp-122° (negative to ninhydrin). NMR $CDCl_3$ δ 8.67(1H,s,H_2), 7.67(1H,s), 7.60(1H,d), 7.38(1H,t,J=8.0 Hz), 7.20(2H,m), 7.02(1H,s), 4.03, 4.02(6H,2s,OCH_3), 1.70(10H,br,s,piperidine ring).

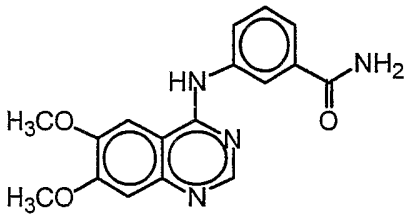
AGL 2353 [4-(4'-carboxamido-phenylamino)-6,7-dimethoxyquinazoline]



$C_{17}H_{16}N_4O_3$
Mol. Wt.: 324.33

[00153] 115 mg, 0.51 mM, 4-chloro 6,7-dimethoxy quinazoline and 70 mg, 0.51 mM, 4-benzamide aniline in 20 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 150 mg white solid, 83% yield, mp-253° as the HCl salt.. NMR DMSO d_6 δ 11.47(1H,br.s), 8.87(1H,s,H_2), 8.36(1H,s,H_5), 8.04(1H,br.s), 8.0, 7.83 (4H,ABq,J_{AB}=8.4 Hz), 7.42(1H,br.s), 7.36(1H,s,H_8), 4.03,4.0 (6H,2s,OCH_3).

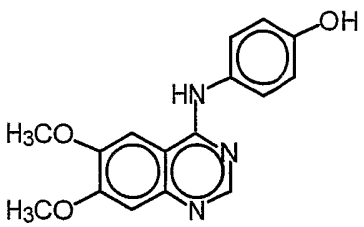
AGL 2354 [4-(3'-carboxamido-phenylamino)-6,7-dimethoxyquinazoline]



$C_{17}H_{16}N_4O_3$
Mol. Wt.: 324.33

[00154] 115 mg, 0.51 mM, 4-chloro 6,7-dimethoxy quinazoline and 70 mg, 0.51 mM, 3-benzamide aniline in 20 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 152 mg white solid, 84% yield, mp-261° as the HCl salt. NMR DMSO d_6 δ 8.85(1H,s,H_2), 8.22(1H,s,H_5), 8.15(1H,br.s), 8.07(1H,br.s), 7.90-7.50(4H,m),7.33(1H,s,H_8), 4.02,4.01(6H,2s,OCH_3).

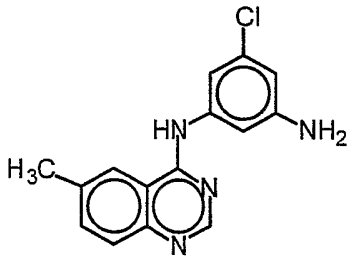
AGL 2355 [4-(4'-hydroxy-phenylamino)-6,7-dimethoxyquinazoline]



$C_{16}H_{15}N_3O_3$
Mol. Wt.: 297.31

[00155] 115 mg,0.51 mM, 4-chloro 6,7-dimethoxy quinazoline and 60 mg, 0.55 mM, 4-hydroxy aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 163 mg light-yellow solid, 97% yield, mp-256° as the HCl salt. NMR DMSO d_6 δ 11.18(1H,br.s), 9.70(1H,br.s), 8.74(1H,s,H_2), 8.21(1H,s,H_5), 7.42, 6.85 (4H,ABq,J_{AB}=8.8 Hz), 7.32(1H,s,H_8), 3.99,3.97 (6H,2s,OCH_3).

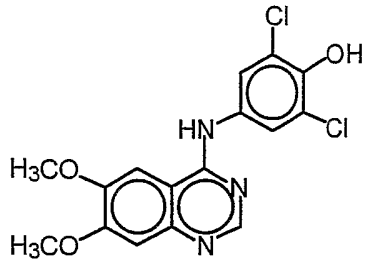
AGL 2356 [4-(3'-amino-5'-chloro-phenylamino)-6 -methylquinazoline]



$C_{15}H_{13}ClN_4$
Mol. Wt.: 284.74

[00156] 300 mg, 1.66 mM, 4-chloro 6-methyl quinazoline and 200 mg, 1.4 mM, 3-amino 5-chloro aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 190 mg light-yellow solid, 42% yield, mp-259° as the HCl salt.

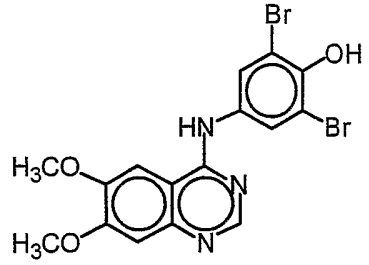
AGL 2358 [4-(3',5'-dichloro- 4'-hydroxy-phenylamino)- 6,7-dimethoxyquinazoline]



$C_{16}H_{13}Cl_2N_3O_3$
Mol. Wt.: 366.20

[00157] 170 mg,0.75 mM, 4-chloro 6,7-dimethoxy quinazoline and 140 mg, 0.78 mM, 4-hydroxy 3,5-dichloro aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 270 mg light-yellow solid, 89% yield, mp-283d° as the HCl salt. NMR DMSO d_6 δ 11.30(1H,br.s), 10.40(1H,br.s), 8.88(1H,s,H_2), 8.26(1H,s,H_5), 7.81(2H,s), 7.31(1H,s,H_8), 4.01,4.0(6H,2s,OCH_3).

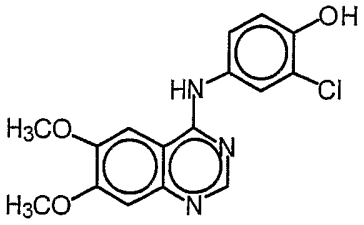
AGL 2363 [4-(3',5'-dibromo- 4'-hydroxy-phenylamino)- 6,7-dimethoxyquinazoline]



$C_{16}H_{13}Br_2N_3O_3$
Mol. Wt.: 455.10

[00158] 85 mg, 0.38 mM, 4-chloro 6,7-dimethoxy quinazoline and 105 mg, 0.39 mM, 4-hydroxy 3,5-dibromo aniline in 20 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 180 mg light grey-white solid, 96% yield, mp-320d° as the HCl salt. NMR DMSO d_6 δ 11.40(1H,br.s), 10.20(1H,br.s), 8.90(1H,s,H_2), 8.30(1H,s,H_5), 8.0(2H,s),7.33(1H,s,H_8), 4.02,4.0(6H,2s,OCH_3).

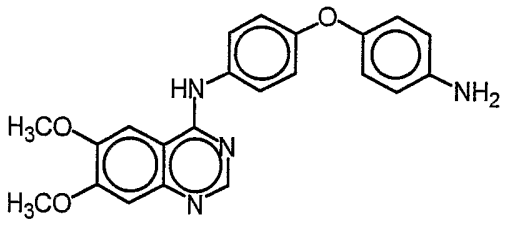
AGL 2364 [4-(3'-chloro- 4'-hydroxy-phenylamino)- 6,7-dimethoxyquinazoline]



$C_{16}H_{14}ClN_3O_3$
Mol. Wt.: 331.75

[00159] 85 mg, 0.38 mM, 4-chloro 6,7-dimethoxy quinazoline and 60 mg, 0.42 mM, 3-chloro 4-hydroxy aniline in 20 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 120 mg light-yellow solid, 85% yield, mp-196° as the HCl salt. NMR DMSO d_6 δ 11.2(1H,br.s), 10.5(1H,br.s), 8.81(1H,s,H_2), 8.24(1H,s,H_5), 7.71(1H,s,H_8), 7.44(1H,dt,$H_{6''}$,J=8.0,2.0Hz), 7.31(1H,d,$H_{2''}$, J=2.0Hz), 7.08(1H,dd,$H_{5''}$), 3.99(6H,s,OCH_3).

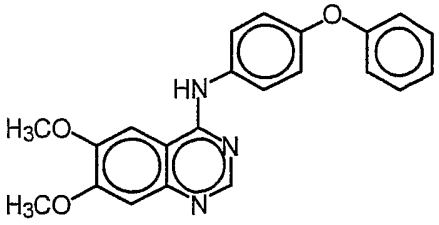
AGL 2373 [4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline]



$C_{22}H_{20}N_4O_3$
Mol. Wt.: 388.42

[00160] 120 mg, 0.53 mM, 4-chloro 6,7-dimethoxy quinazoline and 220 mg, 1.1 mM, 4,4'-oxy-dianiline and 6 drops dimethyl aniline in 20 ml ethanol were refluxed for 2 hours. Cooling and filtering gave 130 mg light-yellow solid, 63% yield, mp-242° as the free base. NMR DMSO d_6 δ 8.68(1H,s,H_2), 8.17(1H,s), 7.62,6.98 (4H,ABq,J_{AB}=8.4 Hz), 7.28(1H.s,H_5), 6.90,6.80 (4H,ABq, J_{AB}=8.4 Hz), 3.99,3.97 (6H,2s,OCH_3).

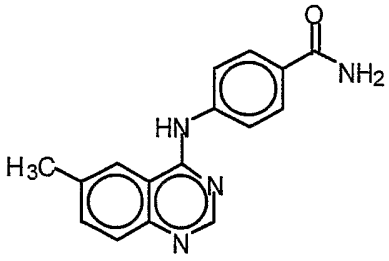
AGL 2377 [4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline]



$C_{22}H_{19}N_3O_3$
Mol. Wt.: 373.40

[00161] 110 mg,0.49 mM, 4-chloro 6,7-dimethoxy quinazoline and 100 mg, 0.54 mM, 4-phenoxy aniline and 3 drops dimethyl aniline in 20 ml ethanol were refluxed 2 hours. Cooling and filtering gave 155 mg light-yellow solid, 84% yield, mp-254° as the free base. MR DMSO d_6 δ 8.81(1H,s,H_2), 8.34(1H,s), .72,7.08 (4H,ABq,J_{AB}=8.4 Hz), 7.36(1H.s,H_5), .40,7.10 (5H,m), 4.01,3.99 (6H,2s,OCH_3).

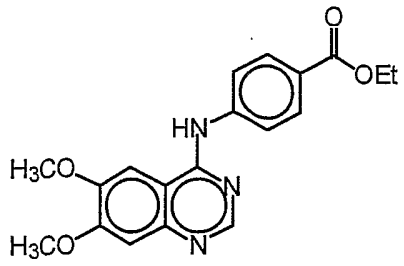
AGL 2396 [4-(4'-carboxamido-phenylamino)-6-methylquinazoline]



$C_{16}H_{14}N_4O$
Mol. Wt.: 278.31

[00162] 0.9 gr, mM, 4-chloro 6-methyl quinazoline and 0.7 gr , 5.1 mM, 4-benzamide aniline and 30 ml ethanol were refluxed 1 hours. Cooling and filtering gave 1.1 gr light-yellow solid, 70% yield, mp-272° as the HCl salt.

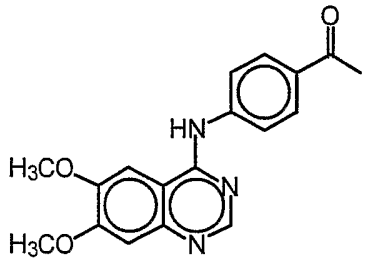
AGL 2398 [4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline]



$C_{19}H_{19}N_3O_4$
Mol. Wt.: 353.37

[00163] 80 mg,0.35 mM, 4-chloro 6,7-dimethoxy quinazoline and 60 mg, 0.36 mM, 4-ethyl amino benzoate and 15 ml ethanol were refluxed 1 hours. Cooling and filtering gave 105 mg light-yellow solid, 77% yield, mp-251° as the HCl salt. NMR DMSO d_6 δ 11.44(1H,br,s), 8.90(1H,s,H_2), 8.36(1H,s), 8.06,7.95 (4H,ABq,J_{AB}=8.4Hz), 7.38(1H.s,H_5), 4.05, 4.01(6H,2s,OCH_3), 4.35(2H,q), 1.35(3H,t). MS-353 (M^+,100%), 324(M-Et,60%), 308(M-OEt,60%), 208(M-COOEt,23), 264(20) m/e.

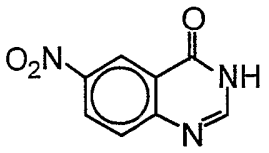
AGL 2399 [4-(4'-acetyl-phenylamino)-6,7-dimethoxyquinazoline]



$C_{18}H_{17}N_3O_3$
Mol. Wt.: 323.35

[00164] 113 mg,0.5 mM, 4-chloro 6,7-dimethoxy quinazoline and 70 mg, 0.52 mM, 4'-amino acetophenone in 10 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 105 mg light-yellow solid, 58% yield, mp-246° as the HCl salt. NMR DMSO d_6 δ 11.44(1H,br.s), 8.90(1H,s,H_2), 8.36(1H,s), 8.06, 7.95 (4H,ABq,J_{AB}=8.4 Hz), 7.38(1H.s,H_5), 4.05,4.01(6H,2s,OCH_3), 2.61(3H,s).

AGL 2246, 2078

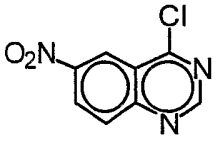


$C_8H_5N_3O_3$
Exact Mass: 191.03
Mol. Wt.: 191.14

[00165] **A. 2246**- 5 gr 5-nitro anthranilic acid and 15 ml formamide were heated at 180^0 1.5 hours. Water was added to the cooled solution and the solid filtered, washed with water and dried to give 4.1 gr, 79% yield, light-yellow solid. NMR DMSO d_6 δ 8.80(1H,d,J=2.6 Hz, H_5), 8.54(1H,dd,J=9.0,2.6 Hz, H_7), 8.32(1H,s,H_2),7.86(1H,d,J=9.0 Hz, H_8).

[00166] **B. 2078** - 11 gr, 75 mM, AG 1463, 40 ml H_2SO_4 and 18 gr,180 mM, KNO_3 were stirred 18 hours at room temperature (with addition of KNO_3 the suspension clarifies). wWter and KOH were added and the solid filtered to give 14 gr ,98% yield, light-yellow solid, mp-303°. NMR DMSOd_6 δ 12.75(1H,br,s), 8.80(1H,d,J=2.6Hz,H_8), 8.54(1H,dd,J=9.0,2.6Hz,H_6), 8.32(1H,s,H_2), 7.86(1H,d,J= 9.0 Hz, H_5).

AGL 2247,2392,2403



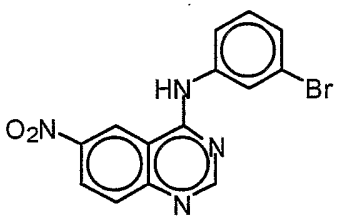
$C_8H_4ClN_3O_2$
Exact Mass: 209.00
Mol. Wt.: 209.59

[00167] **A. 2247**- 4.8 gr, 25 mM, AG 2246, 5 ml, 25 mM, $POCl_3$ and 5 ml, 41 mM, dimethyl aniline in 50 ml toluene were refluxed 3 hours. Water and NH_3 were added and the reaction extracted with ethyl acetate. Chromatography gave 0.7 gr, 13% yield, light yellow-orange solid, mp-110°. NMR DMSOd_6 δ 9.25(1H,s,H_2), 9.21(1H,d,J=2.6 Hz,H_5),8.74(1H,dd,J=9.2,2.6 Hz,H_7),8.27(1H,d,J=9.2 Hz, H_8). When the chlorination was done without dimethyl aniline, only SM was recovered.

[00168] **B. 2392-** 6 gr, 31 mM (4gr 2246 and 2 gr 2078), 3.8 ml, 40 mM, $POCl_3$ and 4 ml, 32 mM, dimethyl aniline in 50 ml toluene were refluxed 2 hours. Water and were was added and the reaction extracted with ethyl acetate. Chromatography gave 0.17 gr, 3% yield, light yellow-orange solid, mp-110°.

[00169] **C. 2403-** 7.5 gr, 2078, 40 ml thionyl chloride and 15 drops DMF were refluxed 2.5 hours. The reaction was poured onto ice and KOH to neutralization added**[?]**. The light-yellow solid was filtered and dried to yield 7.7 gr, 93%, identical to AGL 2392.

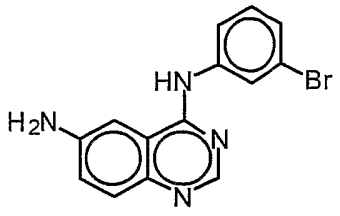
AGL 2248 [4-(3'-bromo-phenylamino)-6-nitroquinazoline]



$C_{14}H_9BrN_4O_2$
Mol. Wt.: 345.15

[00170] 0.7 gr, 3.3 mM, AG 2247 and 0.58 gr, 3.4 mM 3-bromo aniline in 30 ml ethanol were refluxed 1.5 hours. Cooling and filtering gave 1.06 gr, 84% yield, light-pink solid, mp-260°. NMR DMSOd6 δ 9.87(1H,d, J=2.6 Hz,H_5), 9.02(1H,s,H_2), 8.76(1H,dd,J=8.8,2.6 Hz,H_7), 8.15(1H,d,J=8.8 Hz, H_8), 8.08(1H,narr.m),7.82(1H,spl.d),7.51(2H,m). MA m/e (CI)- 346,344(M^+,40,35%), 316,314(M-NO,45,43), 300, 298(M-nitro,7,6), 265(M-Br,25),237(100%). The free base-sample was treated with ammonia-dichloromethane to give light-yellow solid, mp-252d°. NMR $CDCl_3$ δ 8.92(1H,d,J=2.6 Hz,H_5), 8.91(1H,s,H_2), 8.60(1H,dd, J=8.8,2.6Hz,H_7), 8.13(1H,t),8.05(1H,d,J=8.8 Hz, H_8), 7.7(1H,m), 7.30(2H,m).

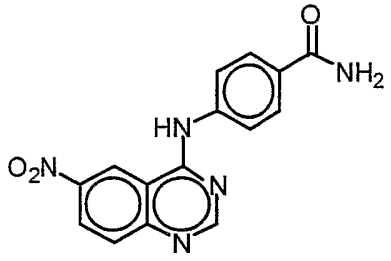
AGL 2250 [4-(3'-bromo-phenylamino)-6-aminoquinazoline]



$C_{14}H_{11}BrN_4$
Mol. Wt.: 315.17

[00171] 0.5 gr AG 2248 in 20 ml ethanol was hydrogenated in PAAR with 10% Pd/C for 4 hours. Filtering and evaporating gave 183 mg,55% yield, yellow-orange solid, mp-233d°. NMR $CDCl_3$ δ 8.56(1H,s,H_2), 7.77(3H,m), 7.43(2H,m), 7.10(2H,m). MA m/e (CI)- 316(M^+,8%),265(25),237(M-Br,100%). Molecular ion very weak.

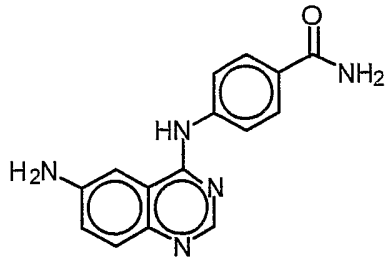
AGL 2402 [4-(4'-carboxamido-phenylamino)-6-nitroquinazoline]



$C_{15}H_{11}N_5O_3$
Mol. Wt.: 309.28

[00172] 1.6 gr, 7.6 mM, 4-chloro 6-nitro quinazoline and 1 gr,7.9 mM, 4-benzamide aniline in 30 ml ethanol were refluxed for 1.5 hours. Cooling and filtering gave 1.6 gr light-yellow solid, 60% yield, mp-333° as the HCl salt. NMR DMSO d_6 δ 9.84(1H,d,J=2 Hz,H_5), 8.97(1H,s,H_2), 8.73(1H,dd,J=9.2,2.0 Hz,H_7), 8.09(1H,d,J=9.2 Hz,H_8), 8.02, 7.90(4H,ABq,J_{AB}=8.4 Hz), 7.40(2H,br,s).

AGL 2404 [4-(4'-carboxamido-phenylamino)-6-aminoquinazoline]



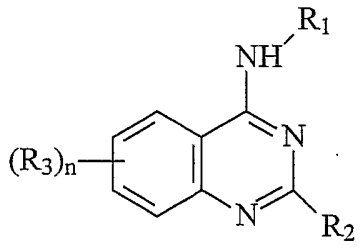
$C_{15}H_{13}N_5O$
Mol. Wt.: 279.30

[00173] To 500 mg, 1.45 mM, AGL 2402 in 30 ml ethanol and 10 ml water was added 0.4 ml hydrazine hydrate and about 100 mg Ra-Ni alloy in water. The reaction was refluxed 1 hour. Cooling, filtering, adding water and filtering again gave 350 mg light-yellow solid, 84% yield, mp-292d° as the free base. NMR DMSO d_6 δ 9.53(1H,s), 8.39(1H,s,H_2), 8.02,7.97(4H,ABq,J_{AB}=8.4 Hz), 7.56(1H.d,J=9.0 Hz,H_8), 7.37(1H,s,NH), 7.28(1H,d,J=2.0 Hz,H_5), 7.24(1H,d,J=2.0 Hz,H_7), 5.64(2H,s,NH).

[00174] It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described herein above. Rather, the scope of the invention is defined by the claims which follow:

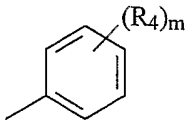
What we claim is:

1. A compound represented by the structure of formula (I):

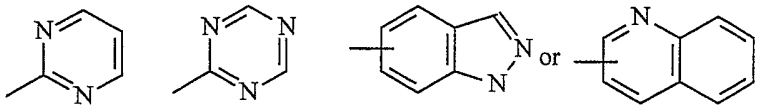


(I)

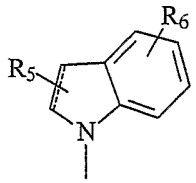
wherein R_1 is an optionally substituted phenyl represented by the structure:



an optionally substituted naphthalene, an optionally substituted cyclohexyl, an optionally substituted heteroaryl represented by the structure:



or R_1 together with the nitrogen to which it is attached is:

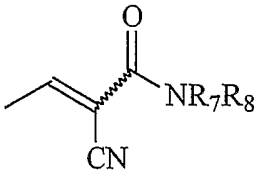


wherein the dotted line represents an optional double bond;

R_2 is H, halogen, phenylamino, or $-SR_7$ wherein R_7 is a heteroaromatic moiety;

R_3 is H, R, OR, NO_2 or NH_2 wherein R is a C_1-C_4 linear or branched chain alkyl;

R_4-R_6 are independently of each other H, halogen, CN, R, NO_2, NH_2, NHR, NR_2, COOH, COOR, CHO, COR, COPh, $CONH_2$, CONHR, $CONR_2$, Ph, OR, OPh, OCH_2Ph, $CH(OR)_2$ wherein R is a C_1-C_4 linear or branched chain alkyl, or R4 is represented by the structure:



wherein R_7 and R_8 are independently hydrogen or an optionally substituted alkyl, aralkyl or aryl; and

m and n are, independently of each other, an integer of 1-3;

and pharmaceutically acceptable salts and hydrates thereof;

provided that:

a) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is H, R or OR, R_4 is not halogen, OR, CN, $CONH_2$, NR_2, CH_3, OH, $COCH_3$ or COOH;

b) when R_1 is an optionally substituted phenyl, m is 1, R_2 is H and R_3 is NO_2, R_4 is not halogen or CH_3;

c) when R_1 is an optionally substituted phenyl, m is 1, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not CH_3, NH_2, NHR, NR_2, NO_2, CN, OCH_3, halogen or OH;

d) when R_1 is an optionally substituted phenyl, m is 1, R_2 is Cl and R_3 is H, R or OR, R_4 is not CH_3, COOH, OCH_3, $CONH_2$ $COCH_3$, OH or halogen;

e) when R_1 is an optionally substituted phenyl, m is 2, R_2 is H and R_3 is H, R or OR, R_4 is not 3,4-di-CH_3, 3,4-dihalo, 3-halo-4-CH_3, 3-CH_3-4-halo, 3-halo-5-NH_2 or 3-halo-4-OH;

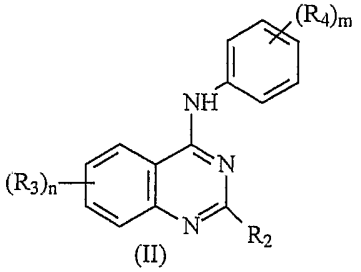
f) when R_1 is an optionally substituted phenyl, m is 2, R_2 is phenylamino and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3, 3-halo-4-CH_3 or 3-CH_3-4-halo;

g) when R_1 is an optionally substituted phenyl, m is 2, R_2 is Cl and R_3 is H, R or OR, R_4 is not 3,4-di-OCH_3 or 2-CH_3-4-OCH_3;

h) when R_1 is an optionally substituted phenyl, m 3 is, R_2 is H and R_3 is H, R or OR, R_4 is not 3,5-halogen,4-OH; and

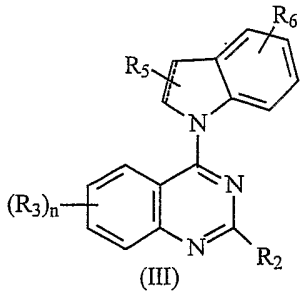
i) when R_2 is H, R1 is not 2'-hydroxy-naphthyl.

2. A compound according to claim 1, represented by the structure of formula (II):



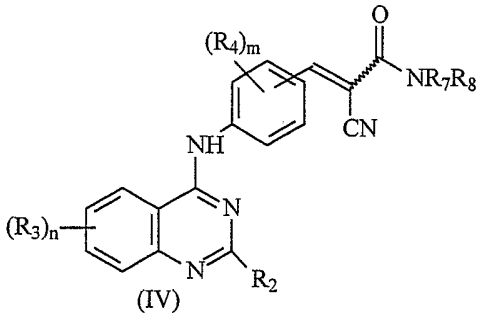
(II)

3. A compound according to claim 1, represented by the structure of formula (III):



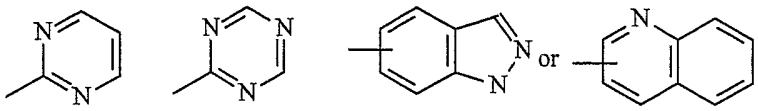
(III)

4. A compound according to claim 1, represented by the structure of formula (IV).



(IV)

5. A compound according to claim 1, wherein R_1 is an optionally substituted heteroaryl represented by the structure:



6. A compound according to claim 1, wherein R_2 is H.

7. A compound according to claim 1, wherein R_2 is Cl.

8. A compound according to claim 1, wherein R_2 is $-SR_7$ wherein R_7 is a heteroaromatic moiety containing at least one sulfur atom and one nitrogen atom.

9. A compound according to claim 1, wherein R_2 is 2-mercaptobenzothiazole.

10. A compound according to claim 1, wherein R_3 is 6-methyl.

11. A compound according to claim 1, wherein R_3 is 8-methyl.

12. A compound according to claim 1, wherein R_3 is 6,7-dimethoxy.

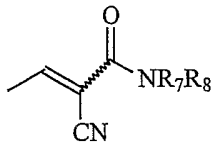
13. A compound according to claim 1, wherein R_3 is NO_2.

14. A compound according to claim 1, wherein R_3 is NH_2.

15. A compound according to claim 1, wherein m is 2 or 3.

16. A compound according to claim 1, wherein n is 1 or 2.

17. A compound according to claim 1, wherein R_4 is:



18. A compound according to claim 1, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702);

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897;)

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);

4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);
4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);
4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);
4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);
4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004)
4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);
4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);
3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);
N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);
3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);
4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);
4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);
4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);
4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);
4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);
4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);
4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);
4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);
4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and
4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

19. A pharmaceutical composition comprising the compound according to claim 1; and a pharmaceutically acceptable carrier or excipient.
20. A pharmaceutical composition comprising the compound according to claim 2; and a pharmaceutically acceptable carrier or excipient.
21. A pharmaceutical composition comprising the compound according to claim 3; and a pharmaceutically acceptable carrier or excipient.

22. A pharmaceutical composition comprising the compound according to claim 4; and a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition comprising any of the compounds according to claim 18; and a pharmaceutically acceptable carrier or excipient.

24. A method of inhibiting the activity of a protein tyrosine kinase (PTK), comprising the step of contacting said PTK with an effective inhibitory amount of a compound according to claim 1.

25. The method according to claim 24, wherein said protein tyrosine kinase is a receptor protein tyrosine kinase (RTK).

26. The method according to claim 25, wherein said receptor protein tyrosine kinase is selected from the group consisting of an epidermal growth factor receptor (EGFR) kinase, a HER receptor kinase, a platelet-derived growth factor receptor (PDGFr) kinase, a fibroblast growth factor receptor (FGF) kinase, a hepatocyte growth factor receptor (HGFr) kinase, an insulin receptor kinase, an insulin-like growth factor-1 receptor (IGF-1r) kinase, a nerve growth factor receptor (NGF) kinase, a vascular endothelial growth factor receptor (VEGFr) kinase, and a macrophage colony stimulating factor receptor (M-CSFr) kinase.

27. The method according to claim 24, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);

4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);

4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);

4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);

4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);

4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);

4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);

4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);

3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);

N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);

3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);

4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);

4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);

4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);

4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);

4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);

4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);

4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);
4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);
4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and
4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

28. A method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase, comprising the step of contacting said EGFR kinase with an effective inhibitory amount of a compound according to claim 1.

29. The method according to claim 28, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);
2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);
2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);
4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);
4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);
4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);
4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)
4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);
4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);
2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);
2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);
2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);
2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);
4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);
4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);
4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);
4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);
4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);
4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);
4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);

4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);

4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);

4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);

4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);

4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);

4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);

3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);

N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);

3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);

4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);

4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);

4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);

4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);

4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);

4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);

4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);

4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);

4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and

4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

30. A method of inhibiting the activity of a protein tyrosine kinase (PTK) in a subject comprising the step of administering to said subject a therapeutically effective amount of a compound according to claim 1.

31. The method according to claim 30, wherein said protein tyrosine kinase is a receptor protein tyrosine kinase (RTK).

32. The method according to claim 31, wherein said receptor protein tyrosine kinase is selected from the group consisting of an epidermal growth factor receptor (EGFR) kinase, a HER receptor kinase, a platelet-derived growth factor receptor (PDGFr) kinase, a fibroblast growth factor receptor (FGF) kinase, a hepatocyte growth factor receptor (HGFr) kinase, an insulin receptor kinase, an insulin-like growth factor-1 receptor (IGF-1r) kinase, a nerve growth factor receptor (NGF) kinase, a vascular endothelial growth factor receptor (VEGFr) kinase, and a macrophage colony stimulating factor receptor (M-CSFr) kinase.

33. The method according to claim 30, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);
4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);
4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);
4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);
4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);
4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);
4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);
4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);
4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);
4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);
3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);
N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);
3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);
4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);
4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);
4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);
4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);
4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);
4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);
4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);
4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);
4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and
4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

34. A method of inhibiting the activity of an epidermal growth factor receptor (EGFR) kinase in a subject, comprising the step of administering to said subject a therapeutically effective amount of a compound according to claim 1.

35. The method according to claim 34, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);

4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);

4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);

4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);

4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);
4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);
4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);
4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);
3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);
N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);
3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);
4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);
4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);
4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);
4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);
4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);
4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);
4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);
4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);
4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and
4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

36. A method of treating or preventing a protein tyrosine kinase (PTK) related disorder in a subject, comprising the step of administering to said subject a therapeutically effective amount of a compound according to claim 1.

37. The method according to claim 36, wherein said protein tyrosine kinase is a receptor protein tyrosine kinase (RTK).

38. The method according to claim 37, wherein said receptor protein tyrosine kinase is selected from the group consisting of a platelet-derived growth factor receptor (PDGFr) kinase, a fibroblast growth factor receptor (FGF) kinase, a hepatocyte growth factor receptor (HGFr) kinase, an insulin receptor kinase, an insulin-like

growth factor-1 receptor (IGF-1r) kinase, a nerve growth factor receptor (NGF) kinase, a vascular endothelial growth factor receptor (VEGFr) kinase, and a macrophage colony stimulating factor receptor (M-CSFr) kinase.

39. The method according to claim 36, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);

4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);

4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);

4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);

4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);

4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);

4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);

4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);

3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);

N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);

3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);

4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);

4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);

4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);

4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);

4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);

4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);

4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);

4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);

4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and

4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

40. The method according to claim 36, wherein the PTK related disorder is a cell proliferative disorder, a fibrotic disorder, or a metabolic disorder.

41. The method according to claim 36, wherein the PTK related disorder is cancer.

42. A method of treating or preventing an epidermal growth factor receptor (EGFR) kinase related disorder in a subject comprising the step of administering to said subject a therapeutically effective amount of a compound according to claim 1.

43. The method according to claim 42, wherein said compound is selected from the group consisting of:

2-chloro-4-indolyl-6,7-dimethoxyquinazoline (AG 1623);

2-chloro-4-(5'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1624);

2-chloro-4-(6'-NO_2-indolyl)-6,7-dimethoxyquinazoline (AG 1625);

4-(2',4'-difluoro-3'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1698);

4-(4'-fluoro-3'-nitro-phenylamino)-6,7-dimethoxyquinazoline (AG 1699);

4-(3'-chloro-6'methyl-pyrimidine-amino)-6,7-dimethoxyquinazoline (AG 1701);

4-(2',4'-diamino-6'-chloro-triazine-amino)-6,7-dimethoxyquinazoline (AG 1702)

4-(2'-carboxy-5'-chloro-phenylamino)-6,7-dimethoxyquinazoline (AG 1813);

4-(3'-formyl-indolyl)-6,7-dimethoxyquinazoline (AG 1814);

2-cyano-N-(3,4-dimethoxyphenyl)-3-[1-(6,7-dimethoxy-quinazoline-4-yl)-1H-indol-3-yl)-acrylamide (AG 1827);

2-(2-mercaptobenzothiazol)-4 -indolyl-6,7-dimethoxyquinazoline (AGL 1885);

2-(2-mercaptobenzothiazol)-4–(4'-methylphenylamino)-6,7-dimethoxyquinazoline (AGL 1886);

2-(2-mercaptobenzothiazol)-4–(3'-chlorophenylamino)-6,7-dimethoxyquinazoline (AGL 1897);

4-(2'-phenyl-phenylamino)-6-methylquinazoline (AGL 1924);

4-(1'-naphthylamino)-6-methylquinazoline (AGL 1925);

4-(3'-quinolyl-amino)-6-methylquinazoline (AGL 1927);

4-(6'-indazolyl-amino)-6-methylquinazoline (AGL 1929);

4-(2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1930);

4-(4'-chloro-2'-phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1931);

4-(1'-(4'-nitro)naphthylamino)-6-methylquinazoline (AGL 1932);

4-(4'-(4''-methoxy)phenylcarbonyl-phenylamino)-6-methylquinazoline (AGL 1933);

4-(4'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1980);

4-(3'-benzyloxy-phenylamino)-6-methylquinazoline (AGL 1981);

4-(4'-benzyloxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2002);

4-(4'-benzyloxy-phenylamino)-8-methylquinazoline (AGL 2003);

4-(4'-benzyloxy-phenylamino)quinazoline (AGL 2004);

4-(3'-bromo-4'-diethoxymethyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2064);

4-(3'-bromo-4'-formyl-phenylamino)-6,7-dimethoxyquinazoline (AGL 2116);

3-[2-bromo-4-(6,7-dimethoxy-quinazoline-4-amino)-phenyl)-2-cyano-N-[2-(3,4-dimethoxy-phenylethyl]-acrylamide (AGL 2122);

N-benzyl-3-[2-bromo-4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-2-cyano-acrylamide (AGL 2123);

3-[2-bromo-4-(6,7-dimethoxyquinazoline-4-ylamino)-phenyl]-2-cyano-N-(4-phenylbutyl)-acrylamide (AGL 2124);

4-(3'-amino-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2052);

4-(3'-chloro-5'-carbomethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2053);

4-(3'-amino-phenylamino)-6,7-dimethoxyquinazoline (AGL 2066);

4-(3'-(1-piperidineazo)-phenylamino)-6,7-dimethoxyquinazoline (AGL 2067);

4'-(4''-amino)oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2373);

4'-oxyphenyl-phenylamino)- 6,7-dimethoxyquinazoline (AGL 2377);

4-(4'-carboethoxy-phenylamino)-6,7-dimethoxyquinazoline (AGL 2398);

4-(3'-bromo-phenylamino)-6-aminoquinazoline (AGL 2250);

4-(4'-carboxamido-phenylamino)-6-nitroquinazoline (AGL 2402); and

4-(4'-carboxamido-phenylamino)-6-aminoquinazoline (AGL 2404).

44. The method according to claim 42, wherein the EGFR related disorder is a cell proliferative disorder, a fibrotic disorder, or a metabolic disorder.

45. The method according to claim 42, wherein the EGFR related disorder is cancer.