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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The present invention discloses thienopyrimidine derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such thienopyrimidine derivatives are useful in the treatment of diseases associated with inappropriate ErbB family kinase activity.

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CHEMICAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to thienopyrimidine derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such thienopyrimidine derivatives are useful in the treatment of diseases associated with inappropriate ErbB family kinase activity.

BACKGROUND OF THE INVENTION

An important large family of enzymes is the protein kinase enzyme family. Currently, there are about 500 different known protein kinases. Protein kinases serve to catalyze the phosphorylation of an amino acid side chain in various proteins by the transfer of the γ-phosphate of the ATP-Mg^{2+} complex to said amino acid side chain. These enzymes control the majority of the signaling processes inside cells, thereby governing cell function, growth, differentiation and destruction (apoptosis) through reversible phosphorylation of the hydroxyl groups of serine, threonine and tyrosine residues in proteins. Studies have shown that protein kinases are key regulators of many cell functions, including signal transduction, transcriptional regulation, cell motility, and cell division. Several oncogenes have also been shown to encode protein kinases, suggesting that kinases play a role in oncogenesis. These processes are highly regulated, often by complex intermeshed pathways where each kinase will itself be regulated by one or more kinases. Consequently, aberrant or inappropriate protein kinase activity can contribute to the rise of disease states associated with such aberrant kinase activity. Due to their physiological relevance, variety and ubiquitousness, protein kinases have become one of the most important and widely studied family of enzymes in biochemical and medical research.

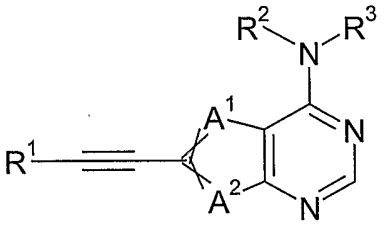
One type of protein kinases is protein tyrosine kinases (PTK). Aberrant PTK activity has been implicated in a variety of disorders including psoriasis, rheumatoid arthritis, bronchitis, as well as cancer. Development of effective treatments for such disorders is a constant and ongoing enterprise in the medical field. The ErbB family

of PTKs, which includes c-ErbB-2, EGFR, and ErbB-4, is one group of PTKs that has attracted interest as a therapeutic target. Currently, of special interest, is the role of ErbB family PTKs in hyperproliferative disorders, particularly human malignancies. Elevated EGFR activity has, for example, been implicated in non-small cell lung, bladder, and head and neck cancers. Furthermore, increased c-ErbB-2 activity has been implicated in breast, ovarian, gastric and pancreatic cancers. Consequently, inhibition of ErbB family PTKs should provide a treatment for disorders characterized by aberrant ErbB family PTK activity. The biological role of ErbB family PTKs and their implication in various disease states is discussed, for instance in U.S. patent 5,773,476; International Patent Application WO 99/35146; M.C. Hung et al, Seminars in Oncology, 26: 4, Suppl. 12 (August) 1999, 51-59; Ullrich et al, Cell, 61: 203-212, April 20, 1990; Modjtahedi et al, Int'l. J. of Oncology, 13: 335-342,1998; and J.R. Woodburn, Pharmacol. Ther., 82: 2-3, 241-250, 1999.

The present inventors have discovered novel thienopyrimidine compounds, which are inhibitors of erbB family kinase activity. Such derivatives are useful in the treatment of disorders associated with inappropriate erbB family kinase activity.

SUMMARY OF THE INVENTION

In a first aspect of the present invention, there is provided a compound of Formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof:
wherein:

one of A^1 and A^2 is S and the other is CH, where ⟋ indicates a single or double bond;

R^1 is the group defined by $-(Z)-(Z^1)_m-(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, $-(CH_2)_qS(O)_2R''$, C_1-C_3 alkyl, $-(CH_2)_qOR''$, -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

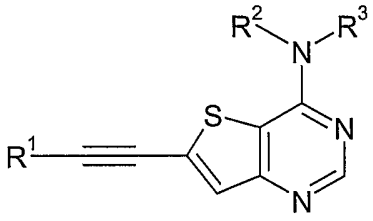
R^3 is the group defined by $-(Q)-(Q^1)_r-(Q^2)$, wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

Q^2 is aralkyl, heteroaryl, or aryl.

In a second aspect of the present invention, there is provided a compound of Formula (I'):



(I')

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

R^1 is the group defined by $-(Z)-(Z^1)_m-(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, $-(CH_2)_qS(O)_2R''$, C_1-C_3 alkyl, $-(CH_2)_qOR''$, -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

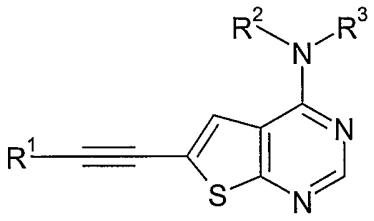
R^3 is the group defined by -(Q)-$(Q^1)_r$-(Q^2), wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

Q^2 is aralkyl, heteroaryl, or aryl.

In a third aspect of the present invention, there is provided a compound of Formula (I''):



(I'')

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

R^1 is the group defined by -(Z)-$(Z^1)_m$-$(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, -$(CH_2)_q$S$(O)_2$R'', C_1-C_3 alkyl, -$(CH_2)_q$OR'', -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

R^3 is the group defined by -(Q)-$(Q^1)_r$-(Q^2), wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

Q^2 is aralkyl, heteroaryl, or aryl.

In a fourth aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a fifth aspect of the present invention, there is provided a method of treating a disorder in a mammal, said disorder being mediated by inappropriate activity of at least one erbB family kinase, comprising: administering to said mammal a therapeutically effective amount of a compound of formula (I) or a salt, solvate or a physiologically functional derivative thereof.

In a sixth aspect of the present invention, there is provided a method of treating a disorder in a mammal, said disorder being mediated by inappropriate activity of at least two erbB family kinases, comprising: administering to said mammal a therapeutically effective amount of a compound of formula (I) or a salt, solvate or a physiologically functional derivative thereof.

In a seventh aspect of the present invention, there is provided a compound of formula (I), or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

In an eighth aspect of the present invention, there is provided the use of a compound of formula (I), or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate activity of at least one erbB family kinase.

In a ninth aspect of the present invention, there is provided the use of a compound of formula (I), or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate activity of at least two erbB family kinases.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein the term "erbB family kinase" includes within its scope EGFR or erbB-1, erbB-2, and erbB-4.

As used herein the term "alkyl" refers to a straight- or branched-chain hydrocarbon radical having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of unsubstituted C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aryl, aryloxy, heteroaryl, heterocyclyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the term "C_1-C_3 alkyl" refers to an alkyl group, as defined above, containing at least 1, and at most 3 carbon atoms respectively. Examples of such branched or straight-chained alkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, and isopropyl.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally

substituted by alkyl, aryl, heteroaryl, heterocyclyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, and C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, and the like.

As used herein, the term "C_1-C_3 alkylene" refers to an alkylene group, as defined above, which contains at least 1, and at most 3, carbon atoms respectively. Examples of "C_1-C_3 alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene, n-propylene, isopropylene, and the like.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo(-Br), and iodo(-I).

As used herein, the term "C_1-C_6 haloalkyl" refers to an alkyl group as defined above containing at least 1, and at most 6 carbon atoms respectively substituted with at least one halo group, halo being as defined herein. Examples of such branched or straight chained haloalkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring containing from 3 to 10 carbon atoms and which optionally includes a C_1-C_3 alkylene linker through which it may be attached. In a like manner the term "C_3-C_7 cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed and which optionally includes a C_1-C_3 alkylene linker through which it may be attached. The C_1-C_3 alkylene group is as defined above. Exemplary "C_3-C_7 cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "C_3-C_7 cycloalkylene" refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered non-aromatic heterocyclic ring, being saturated or having one or more degrees of unsaturation, containing one or more heteroatom substitutions selected from S, S(O), $S(O)_2$, O, or N, optionally substituted with substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halo, aryl, aralkyl, heteroaryl, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuranyl, pyranyl, 1,4-dioxanyl, 1,3-dioxanyl, piperidinyl, piperazinyl, 2,4-piperazinedionyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, tetrahydrothiopyranyl tetrahydrothiophenyl, and the like.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings or fused to one or more cycloalkyl ring(s) to form, for example, anthracene, phenanthrene, napthalene, indan ring systems. Exemplary optional substituents include C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, arylsulfonoamino, alkylcarboxy, alkylcarboxyamide, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamide, carbamoyl optionally substituted by alkyl, aminosulfonyl, ureido, arylurea,

arylthiourea, alkylurea, cycloalkylurea, sulfonylurea, acyl, aroyl, aroylamino, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, heteroaryl, heterocyclyl, aryl, aryloxy, or aralkoxy, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to, indanyl, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, ureido, arylurea, arylthiourea, alkylurea, cycloalkylurea, sulfonylurea, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, C_1-C_6 perfluoroalkyl, heterocyclyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" refers to an aryl or heteroaryl group, as defined herein, attached through a C_1-C_3 alkylene linker, wherein the C_1-C_3 alkylene is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl, and 2-imidazolyl ethyl.

As used herein, the term "heteroaryl" refers to a monocyclic five to seven membered aromatic ring, or to a fused bicyclic or tricyclic aromatic ring system comprising two of such monocyclic five to seven membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen heteroatoms, where N-oxides and sulfur oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino, arylsulfonoamino, alkylcarboxy, alkylcarboxyamide, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamide,

carbamoyl optionally substituted by alkyl, aminosulfonyl, ureido, arylurea, arylthiourea, alkylurea, cycloalkylurea, sulfonylurea, acyl, aroyl, aroylamino, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, heteroaryl, heterocyclyl, aryl, aryloxy, or aralkoxy, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinazolinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of: C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, ureido, arylurea, arylthiourea, alkylurea, cycloalkylurea, sulfonylurea, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halo, C_1-C_6 perfluoroalkyl, heterocyclyl, heterocyclic spiro ring system, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl as defined above and the terms "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" refer to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1, and at most 3 or 6, carbon atoms. Exemplary "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.

As used herein, the term "amino" refers to the group $-NH_2$.

As used herein the term "alkylamino" refers to the group $-NHR_a$ wherein R_a is alkyl as defined above.

As used herein the term "arylamino" refers to the group $-NHR_a$ wherein R_a is aryl as defined above.

As used herein the term "aralkylamino" refers to the group $-NHR_a$ wherein R_a is an aralkyl group as defined above.

As used herein the term "aralkoxy" refers to the group R_bR_aO-, where R_a is alkylene and R_b is aryl or heteroaryl all as defined above.

As used herein the term "aryloxy" refers to the group R_aO-, where R_a is aryl or heteroaryl both as defined above.

As used herein the term "ureido" refers to the group $-NHC(O)NH_2$

As used herein, the term "arylurea" refers to the group $-NHC(O)NHR_aR_b$ wherein R_a is aryl or heteroaryl and R_b is –H, alkyl, or aryl as defined above.

As used herein, the term "arylthiourea" refers to the group $-NHC(S)NHR_a$ wherein R_a is aryl as defined above.

As used herein, the term "alkylurea" refers to the group $-NHC(O)NR_aR_b$ wherein R_a is alkyl and R_b is –H or alkyl as defined above.

As used herein, the term "cycloalkylurea" refers to the group $-NHC(O)NHR_a$ wherein R_a is cycloalkyl as defined above.

As used herein, the term "haloalkoxy" refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkoxy" refers to a haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1, and at most

6, carbon atoms. Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but is not limited to, trifluoromethoxy.

As used herein, the term "alkylsulfanyl" refers to the group R_aS-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfanyl" refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "haloalkylsulfanyl" refers to the group R_aS-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkylsulfanyl" refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)$-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfenyl" refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfonyl" refers to the group $R_aS(O)_2$-, where R_a is alkyl as defined above and the term "C_1-C_6 alkylsulfonyl" refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "alkylsulfonylamino" refers to the group $-NR_bS(O)_2R_a$ wherein R_a is alkyl and R_b is –H or C_1-C_6 alkyl as defined above, and the term "C_1-C_6 alkylsulfonylamino" refers to an alkylsulfonylamino group as defined herein wherein the alkyl moiety contains at least 1, and at most 6, carbon atoms.

As used herein, the term "arylsulfonylamino" refers to the group $-NR_bS(O)_2R_a$ wherein R_a is aryl or heteroaryl and R_b is –H or C_1-C_6 alkyl as defined above.

As used herein, the term "alkylcarboxyamide" refers to the group $-NHC(O)R_a$ wherein R_a is alkyl, amino, or amino substituted with alkyl, aryl or heteroaryl as described above.

As used herein the term "alkylcarboxy" refers to the group $-C(O)R_a$ wherein R_a is alkyl as described above.

As used herein, the term "oxo" refers to the group =O.

As used herein, the term "mercapto" refers to the group -SH.

As used herein, the term "carboxy" refers to the group $-C(O)OR_a$, wherein R_a is H or alkyl as defined herein.

As used herein, the term "cyano" refers to the group -CN.

As used herein the term "cyanoalkyl" refers to the group $-R_aCN$ wherein R_a is alkyl as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl, and cyanoisopropyl.

As used herein, the term "aminosulfonyl" refers to the group $-S(O)_2R_aR_b$ wherein R_a and R_b are independently H, C_1-C_6alkyl, aryl, aralkyl, or heteroaryl.

As used herein, the term "carbamoyl" refers to the group $-OC(O)NHR_a$. where R_a is hydrogen or alkyl as defined herein.

As used herein, the term "carboxamide" refers to the group $-C(O)NR_aR_b$ wherein R_a and R_b are independently H, C_1-C_6alkyl, aryl, aralkyl, or heteroaryl.

As used herein, the term "sulfanyl" shall refer to the group -S-.

As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

As used herein, the term "sulfonyl" shall refer to the group $-S(O)_2-$ or $-SO_2-$.

As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyl" refers to the group $R_aC(O)$- , where R_a is aryl as defined herein.

As used herein, the term "aroylamino" refers to the group $R_aC(O)NH$- , where R_a is aryl as defined herein.

As used herein, the term "heteroaroyl" refers to the group $R_aC(O)$- , where R_a is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)$-, where R_a is alkyl as defined herein.

As used herein, the term "acyloxy" refers to the group $R_aC(O)O$- , where R_a is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O$- , where R_a is aryl as defined herein.

As used herein, the term "heteroaroyloxy" refers to the group $R_aC(O)O$- , where R_a is heteroaryl as defined herein.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

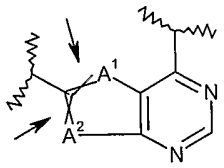
As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. The compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that any tautomers and mixtures of tautomers of the compounds of formula (I) are included within the scope of the compounds of formula (I).

It is to be understood that reference to compounds of formula (I), (I'), or (I") above, following herein, refers to compounds within the scope of formula I, I', or I" as defined above with respect to A^1, A^2, m, n, q, r, R', R", R"', R^1, R^2, R^3, Z, Z^1, Z^2, Q, Q^1, and Q^2 unless specifically limited otherwise.

In one embodiment, A^1 is S and A^2 is CH. In another embodiment, A^1 is CH and A^2 is S.

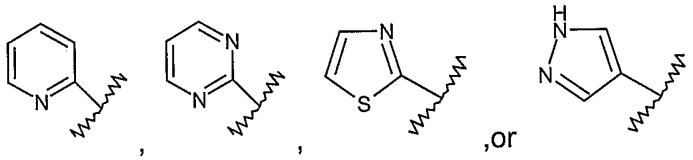
It is understood that the bonds of Formula (I) between A^1 and A^2 each represented by  (see arrows in partial formula (I) following)



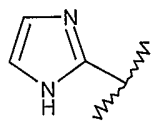
represent either single or double bonds. As is understood by those skilled in the art and specifically illustrated in the working examples following (for instance see Examples 1 and 24) such bonds will each be independently a single or double bond depending on which of A^1 or A^2 is sulfur.

It is also understood that substituent bonding locations having an unfilled valence are indicated by "  ", where it is understood that the unfilled valence is filled by attachment to the remainder of the molecule. The appropriate attachments are further illustrated in the working examples recited below.

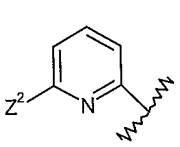
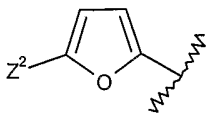
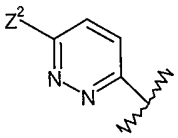
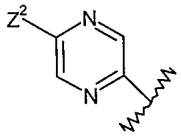
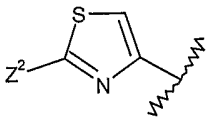
As recited above, R^1 is the group defined by $-(Z)-(Z^1)_m-(Z^2)_n$. In one embodiment, Z is heteroaryl and m and n are each 0. In another embodiment, Z is heteroaryl and m is 0 and n is 0, where the heteroaryl group is selected from



In another embodiment, Z is heteroaryl and m is 0 and n is 0, where the heteroaryl group is

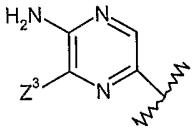


In an alternative embodiment, Z is heteroarylene, m is 0, n is 1, and Z^2 is –C(O)H, -N(H)R' where R' is as defined above. In an alternative embodiment, Z is heteroarylene selected from





or


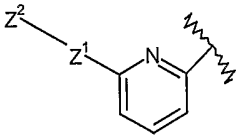
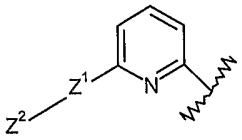
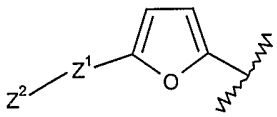
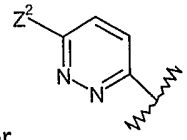
where Z^2 is –C(O)H or -N(H)R' where R' is -H.

In one embodiment, Z is



where Z^3 is $–OCH_3$ or -N(H)R' where R' is -H.

In an another alternative embodiment, Z is heteroarylene, Z^1 is $C(H)_2$ and m is 1, n is 1 and Z^2 is –C(O)H, -N(H)R' where R' is as defined above. In an alternative embodiment, Z is heteroarylene selected from





or

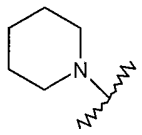
where Z^1 is $C(H)_2$,

Z^2 is -N(H)R' where q is 2 and R' is $–(CH_2)_qS(O)_2CH_3$, or

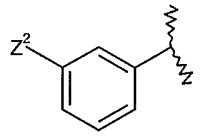
Z^2 is -N(H)R' where q is 2 and R' is $–(CH_2)_qOCH_3$, or

Z^2 is -N(H)R' where R' is C_1-C_3 alkyl, or

Z^2 is heterocyclyl selected from



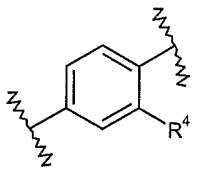
In an alternative embodiment, Z is arylene, m is 0, n is 1, and Z^2 is –C(O)H, -N(H)R' where R' is as defined above. In an alternative embodiment, Z is



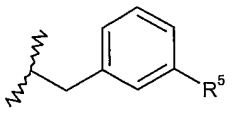
It is also understood that the heteroaryl, heteroarylene, and arylene groups of Z may additionally be optionally substituted as described in the definition for each recited group above. That is, the particular Z group may be optionally substituted as described in the definition of heteroaryl, heteroarylene, and arylene above with at least one additional group other than Z^2 or Z^1-Z^2.

In one embodiment, R^2 is –H. In another embodiment, R^2 is C_1-C_3 alkyl.

As recited above, R^3 is the group defined by -(Q)-$(Q^1)_r$-(Q^2). In one embodiment, Q is arylene, Q^1 is O and r is 1, and Q^2 is aralkyl, aryl, or heteroaryl. In another embodiment, Q is



wherein R^4 is halo, preferably –Cl or -F, Q^1 is O and r is 1, and Q^2 is selected from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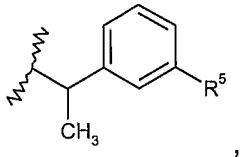
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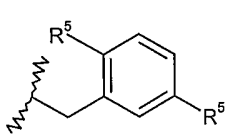
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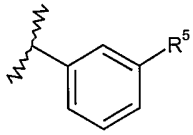
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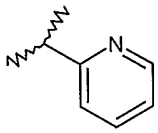
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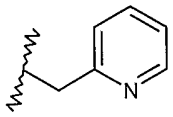
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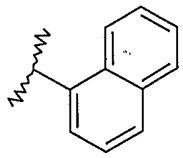
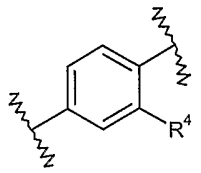
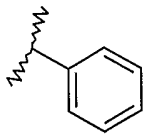

or ,

wherein each R^5 is independently halo, preferably –F, -Cl, or -Br.

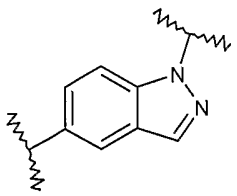
In one embodiment, Q is arylene, Q^1 is S and r is 1, and Q^2 is aryl. In one embodiment, Q is


, .

wherein R^4 is halo, preferably –Cl or -F, Q^1 is S and r is 1, Q^2 is

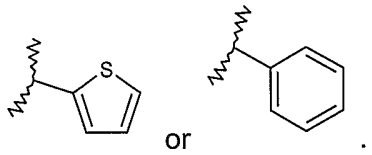

.

In one embodiment, Q is arylene, Q^1 is $S(O)_2$ and r is 1, and Q^2 is aryl or heteroaryl. In one embodiment, Q is



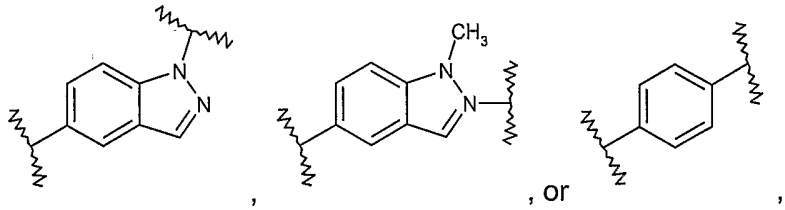
,

Q^1 is $S(O)_2$ and r is 1, and Q^2 is selected from



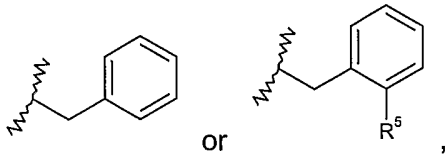
or .

In an alternative embodiment, Q is arylene, r is 0, and Q^2 is aralkyl. In one embodiment, Q is selected from



, , or ,

r is 0, and Q^2 is selected from



or ,

where R^5 is halo, preferably -F.

Specific examples of compounds of the present invention include the following:

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyridin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyrimidin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1,3-thiazol-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde;

6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-({[2-(methylsulfonyl)ethyl]amino}methyl)pyridin-2-yl]ethynyl}thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethynyl}thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({6-[(methylamino)methyl]pyridin-2-yl}ethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[(5-{[(2-methoxyethyl)amino]methyl}-2-furyl)ethynyl]thieno[2,3-d]pyrimidin-4-amine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-2-furaldehyde;

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[4-(phenylsulfonyl)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(4-benzylphenyl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(phenylthio)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indol-5-yl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indazol-5-yl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(6-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(6-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[3,2-d]pyrimidin-4-amine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine;

N-(3-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}phenyl)acetamide;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(1-benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(2,5-difluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-chlorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-[3-chloro-4-(1-naphthyloxy)phenyl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-bromo-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(2-benzyl-1-methyl-1H-benzimidazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(1-benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-[1-(2-fluorobenzyl)-1H-indazol-5-yl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

(R,S)-*N*-{3-chloro-4-[1-(3-fluorophenyl)ethoxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

6-[(2-aminopyrimidin-5-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

N-[3-({4-[(1-benzyl-1H-indazol-5-yl)amino]thieno[3,2-d]pyrimidin-6-yl}ethynyl)phenyl] acetamide; and

6-[(2-amino-1,3-thiazol-4-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[3,2-d]pyrimidin-4-amine;

or a salt, solvate, or physiologically functional derivative thereof.

Additional examples of compounds of the present invention include the following:

6-[(5-nitro-2-pyridinyl)ethynyl]-*N*-[1-(phenylmethyl)-1*H*-indazol-5-yl]thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-(1*H*-imidazol-2-ylethynyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine;

6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-{1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine; and

N-{3-chloro-4-[(2-pyridinylmethyl)oxy]phenyl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine;

or a salt, solvate, or physiologically functional derivative thereof.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a

substituent in the compound of formula (I). Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

While it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I), or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg

of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy

ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I), and salts, solvates and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula (I) and salts, solvates and physiological functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the human or other animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula (I) for the treatment of neoplastic growth, for example colon or breast carcinoma, will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

The compounds of the present invention and their salts and solvates, and physiologically functional derivatives thereof, may be employed alone or in

combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged as well as combination with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and the use of at least one other cancer treatment method. Preferably, combination therapies according to the present invention comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and at least one other pharmaceutically active agent, preferably an anti-neoplastic agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

The compounds of the Formula (I) or salts, solvates, or physiologically functional derivatives thereof and at least one additional cancer treatment therapy may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination with such other anti-cancer therapies. In one embodiment, the other anti-cancer therapy is at least one additional chemotherapeutic therapy including administration of at least one anti-neoplastic agent. The administration in combination of a compound of formula (I) or salts, solvates, or physiologically functional derivatives thereof with other anti-neoplastic agents may be in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both compounds or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one anti-neoplastic agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Anti-neoplastic agents may induce anti-neoplastic effects in a cell-cycle specific manner, i.e., are phase specific and act at a specific phase of the cell cycle,

or bind DNA and act in a non cell-cycle specific manner, i.e., are non-cell cycle specific and operate by other mechanisms.

Anti-neoplastic agents useful in combination with the compounds and salts, solvates or physiologically functional derivatives thereof of formula I include, but are not limited to, the following:

(1) cell cycle specific anti-neoplastic agents including, but not limited to, diterpenoids such as paclitaxel and its analog docetaxel; vinca alkaloids such as vinblastine, vincristine, vindesine, and vinorelbine; epipodophyllotoxins such as etoposide and teniposide; fluoropyrimidines such as 5-fluorouracil and fluorodeoxyuridine ; antimetabolites such as allopurinol, fludurabine, methotrexate, cladrabine, cytarabine, mercaptopurine and thioguanine; and camptothecins such as 9-amino camptothecin, irinotecan, CPT-11 and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin;

(2) cytotoxic chemotherapeutic agents including, but not limited to, alkylating agents such as melphalan, chlorambucil, cyclophosphamide, mechlorethamine, hexamethylmelamine, busulfan, carmustine, lomustine, and dacarbazine; anti-tumour antibiotics such as doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dacttinomycin and mithramycin; and platinum coordination complexes such as cisplatin, carboplatin, and oxaliplatin; and

(3) other chemotherapeutic agents including, but not limited to, anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene; progestrogens such as megestrol acetate; aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane; antiandrogens such as flutamide, nilutamide, bicalutamide, and cyproterone acetate; LHRH agonists and antagagonists such as goserelin acetate and luprolide, testosterone 5α-dihydroreductase inhibitors such as finasteride; metalloproteinase inhibitors such as marimastat; antiprogestogens; urokinase plasminogen activator receptor function inhibitors; cyclooxygenase type 2 (COX-2) inhibitors such as celecoxib; angiogenic inhibiting agents such as VEGFR inhibitors and TIE-2 inhibitors; growth factor function inhibitors such as inhibitors of the functions of hepatocyte growth factor; platelet derived growth factor receptor (PDGFr), vascular endothelial growth factor receptor (VEGFR) and TIE-2; and other

protein kinase inhibitors such as c-Raf, b-Raf, and cyclin dependent inhibitors such as CDK2 and CDK4 inhibitors.

The compounds of formula (I) and salts, solvates and physiological functional derivatives thereof, are believed to have anticancer activity as a result of inhibition of one or more erbB family protein kinase and its effect on selected cell lines whose growth is dependent on erbB family protein kinase activity.

The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof, or physiologically functional derivatives thereof, for use in medical therapy, and particularly in the treatment of disorders mediated by inappropriate activity of one or more erbB family kinase.

The inappropriate erbB family activity referred to herein is any erbB kinase activity that deviates from the normal erbB family kinase activity expected in a particular mammalian subject. The inappropriate activity may arise from one or more of EGFR (erbB-1), erbB-2, or erbB-4. Inappropriate erbB family kinase activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of erbB family kinase activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase or ligand leading to inappropriate or uncontrolled activation of the receptor. Furthermore, it is also understood that unwanted erbB family kinase activity may reside in an abnormal source, such as a malignancy. That is, the level of erbB family activity does not have to be abnormal to be considered inappropriate, rather the activity derives from an abnormal source.

The present invention is directed to methods of regulating, modulating, or inhibiting one or more erbB family kinase for the prevention and/or treatment of disorders related to unregulated erbB family kinase activity. In particular, the compounds of the present invention can also be used in the treatment of certain forms of cancer. Furthermore, the compounds of the present invention can be used to provide additive or synergistic effects with certain existing cancer chemotherapies and radiation, and/or be used to restore effectiveness of certain existing cancer chemotherapies and radiation.

A further aspect of the invention provides a method of treatment of a mammal suffering from a disorder mediated by inappropriate one or more erbB family kinase activity, including susceptible malignancies, which includes administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or a physiologically functional derivative thereof. In a preferred embodiment, the disorder is cancer.

A further aspect of the invention provides a method of treatment of a mammal suffering from cancer, which includes administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, in the preparation of a medicament for the treatment of a disorder characterized by inappropriate activity of one or more erbB family kinase. In a preferred embodiment, the disorder is cancer.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, in the preparation of a medicament for the treatment of cancer and malignant tumours.

The mammal requiring treatment with a compound of the present invention is typically a human being.

In another embodiment, therapeutically effective amounts of the compounds of formula (I) or salts, solvates or physiologically derived derivatives thereof and agents which inhibit growth factor receptor function may be administered in combination to a mammal for treatment of a disorder mediated by inappropriate activity of one or more erbB family kinase, for instance in the treatment of cancer. Such growth factor receptors include, for example, PDGFR, VEGFR, TIE-2, as well as erbB family kinase inhibitors other than those described herein. Growth factor receptors and agents that inhibit growth factor receptor function are described, for

instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818 and in Shawver et al DDT Vol 2, No. 2 February 1997.

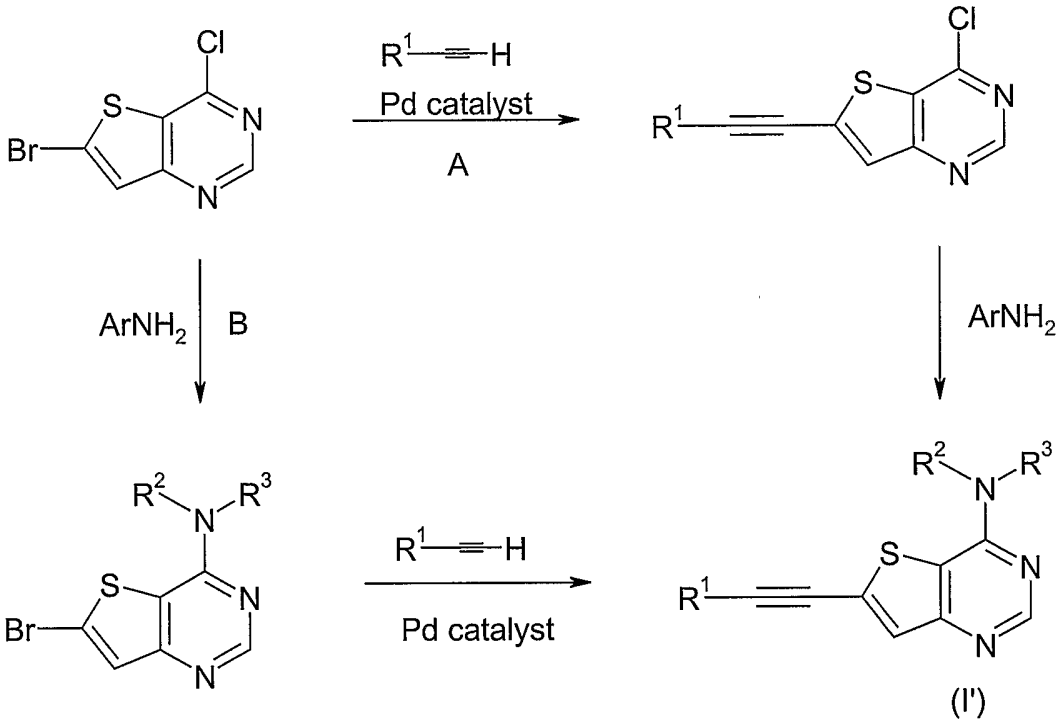
The compounds of the Formula (I) or salts, solvates, or physiologically functional derivatives thereof and the agent for inhibiting growth factor receptor function may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination. The combination may be employed in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both compounds or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the Working Examples.

Compounds of general formula (I), including formulae (I') and (I''), may be prepared by methods known to those of skill in the art. The following synthetic schemes are meant to represent examples only and are not meant to limit the invention in any way. In all of the schemes described below, it is understood that protecting groups may be employed where necessary in accordance with general principles known to those of skill in the art, for example, see T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons. These groups may be removed at a convenient stage of the compound synthesis using methods known to those of skill in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formulae (I), (I'), and (I''). Those of skill in the art will recognize that if a stereocenter exists in compounds of Formulae (I), (I'), and (I'') the present invention is meant to include both enantiomers, mixtures of such enantiomers and the individual enantiomers substantially free of the opposite enantiomer. In addition, when a compound contains more than one stereocenter, one

of skill in the art will recognize that the present invention is meant to include mixtures of diastereomeric compounds, mixtures of enantiomers and the individual enantiomers substantially free of the opposite enantiomer.

Scheme I



The compounds of formula (I"), wherein R^1, R^2 and R^3 are as defined above, may be prepared from the appropriate halogen-substituted thienopyrimidine by the general synthetic routes depicted as A and B shown above in Scheme (I). In step 1 of route A, the halogen-substituted thienopyrimidine is coupled with a terminal acetylenic compound. These reactions are generally performed in the presence of a palladium catalyst, bis(triphenylphosphine)palladium dichloride for example, a copper catalyst, copper(I) iodide for example, a base, triethylamine for example, a solvent, tetrahydrofuran (THF) for example, and at a temperature from 25 °C to 175 °C, preferably 50 °C to 60 °C. The resulting product may then be allowed to react with an arylamine to displace the 6-chloro substituent on the pyrimidine moiety. These displacement reactions are typically performed in a solvent, isopropanol for example, and at a temperature from 25 °C to 175 °C, preferably 50 °C to 80 °C.

Alternatively, the compounds of formula (I') may be prepared by carrying out the displacement and coupling steps described above in reverse order using similar conditions (Route B).

The appropriate halogen-substituted thienopyrimidines are either commercially available or may be prepared using methods known to those of skill in the art. For example, 6-bromo-4-chlorothieno[3,2-d]pyrimidine may be prepared by the procedure described in published PCT application number WO 99/24440.

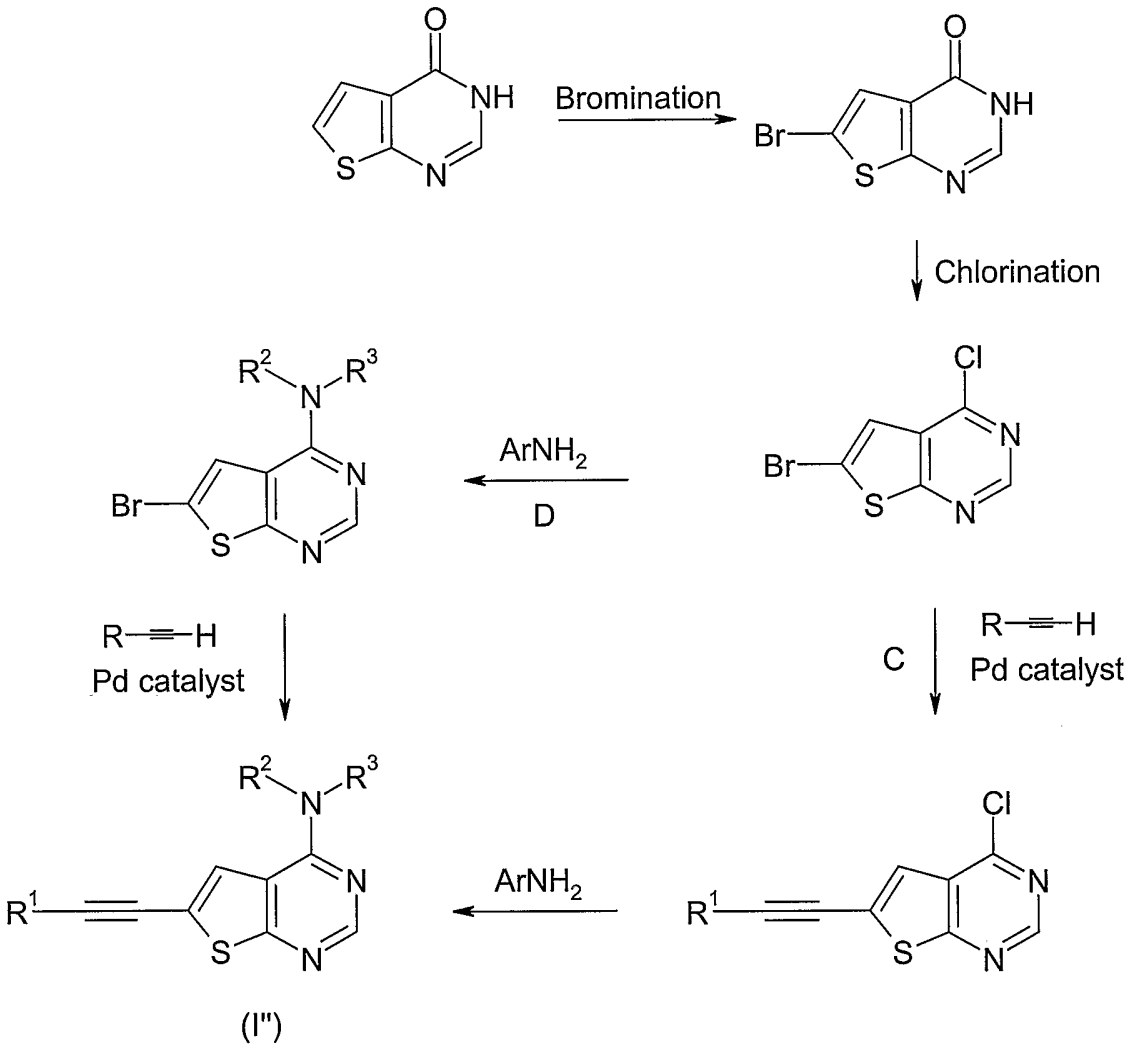
The acetylenyl reagents are either commercially available or can be prepared by methods known to those skilled in the art. For example, see Gilbert et al. (J. Org. Chem., 1982, 47, 1837) and Dinersterin et al. (US Patent 5,409,492).

The arylamines are either commercially available or can be prepared by methods known to those skilled in the art. For example, see the methods described in United States Patents 6,174, 883 and 6,207,669, which are hereby incorporated by reference to the extent they teach the preparation of arylamines useful in the preparation of compounds of the present invention.

The compounds of the general structure (I") wherein R^1, R^2 and R^3 are as defined above may be prepared by the procedure shown below in Scheme (2). In the first step, commercially available (Maybridge Chemical Co.) thieno[2,3-d]pyrimid-4(1H)-one is allowed to react with a brominating agent to afford 6-bromo-thieno[2,3-d]pyrimid-4(1H)-one. These reactions are generally performed in the presence of a brominating reagent such as N-bromosuccinimide (NBS), a solvent, DMF for example, and at a temperature from 25 °C to 175 °C, preferably room temperature.

Next, a substituent capable of acting as a leaving group, chlorine for example, is introduced into the pyrimidine portion of the 6-thienopyrmidine intermediate. The leaving group may be introduced using a reagent capable of reacting selectively with the pyrimidine portion of the molecule, phosphorous oxychloride for example, to afford an appropriately substituted product, These reactions are generally performed at a temperature from 25 °C to 175 °C, preferably 80 °C to 106 °C. For example, 6-bromo-thieno[2,3-d]pyrimid-4(1H)-one was allowed to react with phosphorus oxychloride at 106 °C to afford 6-bromo-4-chlorothieno[2,3-d]pyrimidine.

Scheme 2



The intermediate dihalogenated thieno[2,3-d]pyrimidines can then be converted to compounds of the general structure (I") by the two synthetic routes depicted as C and D in Scheme 2. In the first step of route C, an appropriate dihalogenated thieno[2,3-d]pyrimidine is allowed to react with reagents capable of selectively introducing an acetylenyl group into the 6-position. These reactions are generally performed in the presence of a palladium catalyst, bis(triphenylphosphine)palladium dichloride for example, a copper catalyst, copper(I) iodide for example, a base, triethylamine for example, a solvent, tetrahydrofuran (THF) for example, and at a temperature from 25 °C to 175 °C, preferably 50 °C to 60 °C.

Lastly, the resulting alkyne is allowed to react with an arylamine to displace the 6-chloro substituent on the pyrimidine moiety as described above for step 2 of Scheme 1. These reactions are generally performed in a solvent, isopropanol for example, and at a temperature from 25 °C to 175 °C, preferably 50 °C to 80 °C.

The acetylenyl reagents are either commercially available or can be prepared by methods known to those skilled in the art. For example, see Gilbert et al. (J. Org. Chem., 1982, 47, 1837) and Dinersterin et al., US Patent 5,409,492, which is hereby incorporated by reference to the extent they teach acetylenyl reagents useful in the preparation of compounds of the present invention.

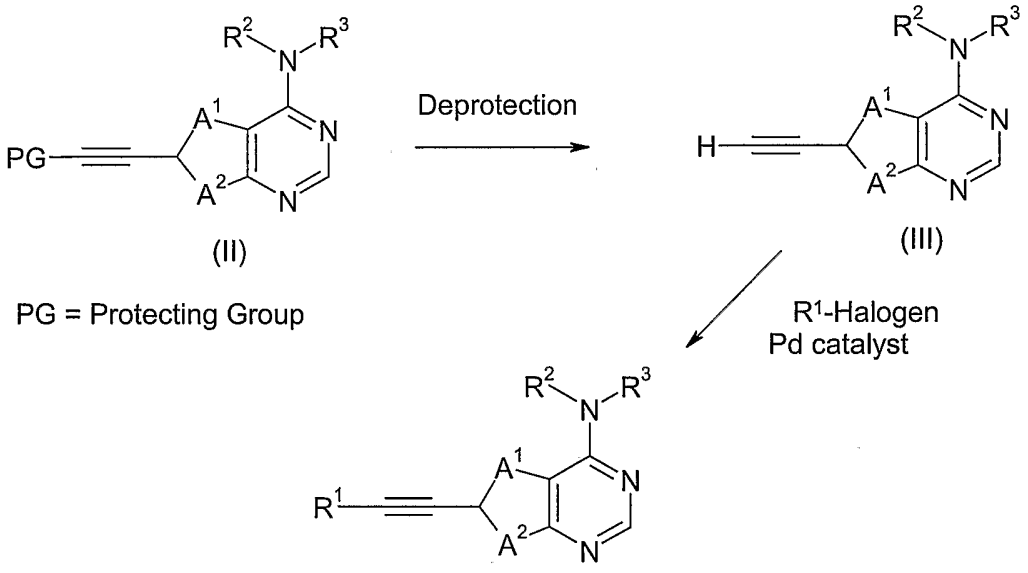
The arylamines are either commercially available or can be prepared by methods known to those skilled in the art. For example, see the methods described in United States Patents 6,174, 883 and 6,207,669, which were incorporated by reference above.

Alternatively, steps C and D in Scheme 2 may be carried out in reverse order using similar conditions as described above to afford the desired products.

Following the steps outlined in Schemes 1 and 2, the R^1 group of compounds of formula (I') and formula (I'') may be further modified to prepare compounds of formula (I), wherein R^1 is heteroaryl which may be optionally substituted as defined above or aryl which may be optionally substituted as defined above. In this process, the acetylenyl reagent employed is a suitably protected acetylene derivative, such as commercially available trimethylsilylacetylene (R_1 = TMS). The coupling of such a suitably protected acetylene derivative would yield compound of formula (II) in Scheme 3. Further elaboration by deprotection, for example by treatment with tetrabutylammonium fluoride, yields compounds of formula (III). Such deprotection reactions are generally performed in a solvent, tetrahydofuran for example, and at a temperature from 0 °C to 100 °C, preferably 0 °C to 25 °C. Compounds of formula (III may be coupled with halogen substituted heteroaryl or aryl compounds to provide the desired heteroaryl derivatives. These reactions are generally performed in the presence of a palladium catalyst, bis(triphenylphosphine)palladium dichloride for example, a copper catalyst, copper(I) iodide for example, a base, triethylamine for example, a solvent, tetrahydrofuran (THF) for example, and at a temperature from 25

°C to 175 °C, preferably 50 °C to 60 °C. The halogen substituted heteroaryl and aryl compounds are either commercially available or can be prepared by methods known to those skilled in the art.

Scheme 3



Compounds of formula (I), wherein R^1 is heteroaryl optionally substituted as defined above or aryl optionally substituted as defined above, may also be prepared from an appropriately substituted 6-halothienopyrimidine derivative, such as those shown in Schemes 1 and 2, by reaction with an appropriately substituted heteroaryl or aryl acetylene derivative, for example, commercially available 3-phenyl-1-propyne. These reactions are generally performed in the presence of a palladium catalyst, bis(triphenylphosphine)palladium dichloride for example, a copper catalyst, copper(I) iodide for example, a base, triethylamine for example, a solvent, tetrahydrofuran (THF) for example, and at a temperature from 25 °C to 175 °C, preferably 50 °C to 60 °C.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data obtained for the compounds exemplified, is consistent with the assigned structure of those compounds.

EXAMPLES

As used herein, the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams); mg (milligrams);
L (liters); mL (milliliters);
µL (microliters); psi (pounds per square inch);
M (molar); mM (millimolar);
i. v. (intravenous); Hz (Hertz);
MHz (megahertz); mol (moles);
mmol (millimoles); rt (room temperature);
min (minutes); h (hours);
mp (melting point); TLC (thin layer chromatography);
T_r (retention time); RP (reverse phase);
MeOH (methanol); i-PrOH (isopropanol);
TEA (triethylamine); TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);
DMSO (dimethylsulfoxide); AcOEt (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea); (CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimide); HOBT (1-hydroxybenzotriazole);
mCPBA (meta-chloroperbenzoic acid; EDC (ethylcarbodiimide hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);

Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);

TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); BSA (bovine serum albumin)
ATP (adenosine triphosphate); HRP (horseradish peroxidase);
DMEM (Dulbecco's modified Eagle medium);
HPLC (high pressure liquid chromatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
TBAF (tetra-n-butylammonium fluoride);
HBTU (O-Benzotriazole-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate).
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
DPPA (diphenylphosphoryl azide);
$fHNO_3$ (fumed HNO_3); and
EDTA (ethylenediaminetetraacetic acid).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

^1H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

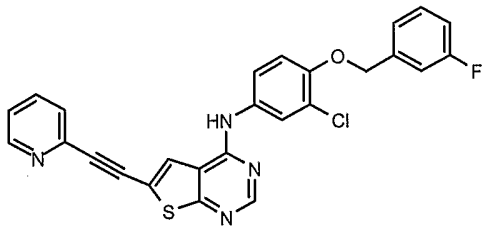
Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102, or a SCIEX-APIiii spectrometer; high resolution MS were obtained using a JOEL SX-102A spectrometer. All mass spectra were taken under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. All reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution or mass spectrometry (electrospray or AP). Flash column chromatography

was performed on silica gel (230-400 mesh, Merck) or using automated silica gel chromatography (Isco, Inc. Sq 16x or 100sg Combiflash).

Reported HPLC retention times (RT) were obtained on a Waters 2795 instrument attached to a Waters 996 diode array detector reading 210-500 nm. The column used was a Synergi Max-RP (50 x 2 mm) model #00B-4337-B0. Solvent gradient was 15% methanol:water to 100% methanol (0.1% formic acid) over 6 min. Flow rate was 0.8 mL/min. Injection volume was 3 microliters.

Example 1

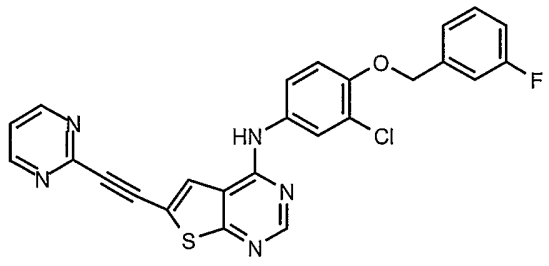
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyridin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine



N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[2,3-d]pyrimidin-4-amine (100 mg, 0.244 mmol, prepared from 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine, trimethylsilyl acetylene, dichlorobis(triphenylphosphine)palladium (II), Cu(I) and triethylamine according to standard methods), 2-iodopyridine (55 μL, 108 mg, 0.528 mmol), triethylamine (61 μL, 0.44 mmol), CuI (11 mg, 0.058 mmol), and dichlorobis(triphenylphosphine)palladium (II) (8.2 mg, 0.012 mmol) were placed in a N_2-flushed reaction vessel and THF (1.5 mL) was added. The resulting mixture was heated at 40 °C for 1-5 h until no starting material was observed by TLC. The mixture was concentrated, dissolved in 5:1 $CHCl_3$/MeOH and filtered. The filtrate was absorbed onto silica gel and purified by silica gel chromatography eluting with hexanes/ethyl acetate to afford, after concentration of the relevant fractions 75.3 mg of the title compound as a light yellow powder, mp 180 °C. HRMS: 486.0796 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 5.23 (s, 2H), 7.16 (t, 1H, J = 9.2 Hz), 7.26 (d, 1H, J = 7.7 Hz), 7.30-7.32 (m, 2H), 7.42-7.47 (m, 1H), 7.65 (dd, 1H, J = 8.9, 2.5 Hz), 7.71 (d, 1H, J = 7.7 Hz), 7.88 (t, 1H, J = 7.7 Hz), 8.01 (d, 1H, J = 2.4 Hz), 8.21 (s, 1H), 8.54 (s, 1H), 8.64 (d, 1H, J = 4.3 Hz), 9.78 (s, 1H).

Example 2

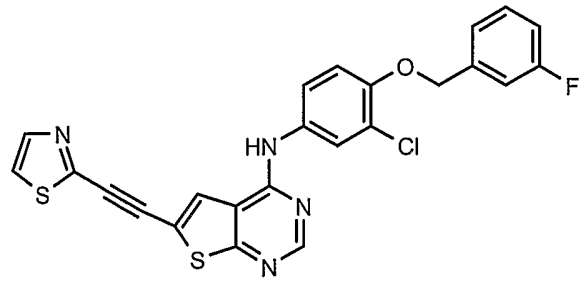
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyrimidin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine



The procedure of example 1 was followed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[2,3-d]pyrimidin-4-amine (88 mg, 0.215 mmol), 2-bromopyrimidine (42 mg, 0.264 mmol), triethylamine (55 μL, 0.40 mmol), Cu(I)I (4.5 mg, 0.024 mmol), dichlorobis(triphenylphosphine)palladium (II) (6.6 mg, 0.009 mmol) in THF (1.5 mL). Workup and silica gel chromatography afforded 59.7 mg of the title compound as a light yellow powder, mp 225 °C. HRMS: 488.0742 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.23 (s, 2H), 7.17 (t, 1H, J = 8.4 Hz), 7.26 (d, 1H, J = 9.2 Hz), 7.30-7.32 (m, 2H), 7.42-7.48 (m, 1H), 7.55 (t, 1H, J = 4.5 Hz), 7.64 (dd, 1H, J = 8.8, 2.5 Hz), 8.00 (d, 1H, J = 2.6 Hz), 8.30 (s, 1H), 8.56 (s, 1H), 8.87 (s, 1H), 8.88 (s, 1H), 9.82 (s, 1H).

Example 3

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1,3-thiazol-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine

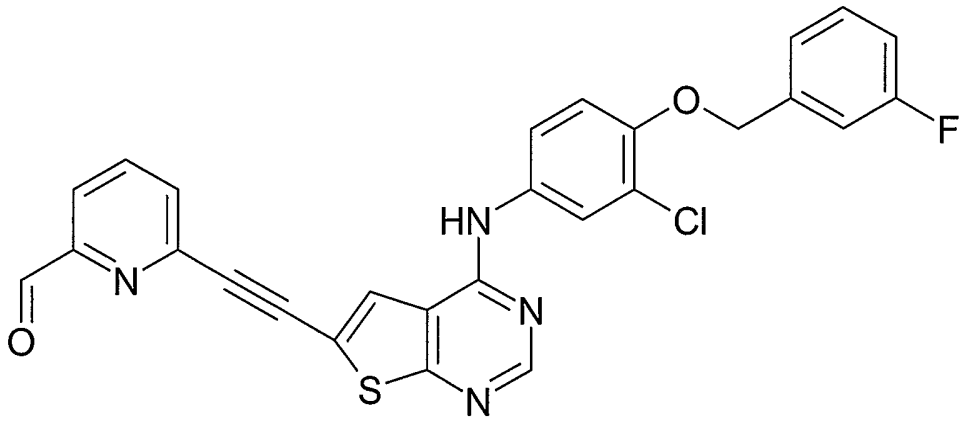


The general procedure of example 1 was followed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[2,3-d]pyrimidin-4-amine (101.4 mg, 0.247 mmol), 2-bromothiazole (48 μL, 87.4 mg, 0.528 mmol), triethylamine (61 μL, 0.44 mmol), Cu(I)I (8.6 mg, 0.045 mmol), dichlorobis(triphenylphosphine)palladium (II) (8.2 mg, 0.012 mmol) in THF (1.5 mL). Workup and silica gel chromatography supplied 13.1 mg of the title compound as a dark yellow powder, mp 204 °C. HRMS:

493.0341 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 5.23 (s, 2H), 7.16 (t, 1H, J = 8.8 Hz), 7.26 (d, 1H, J = 9.7 Hz), 7.30-7.31 (m, 2H), 7.42-7.48 (m, 1H), 7.64 (dd, 1H, J = 9.0, 2.4 Hz), 8.00-8.03 (m, 3H), 8.27 (s, 1H), 8.56 (s, 1H), 9.81 (s, 1H).

Example 4

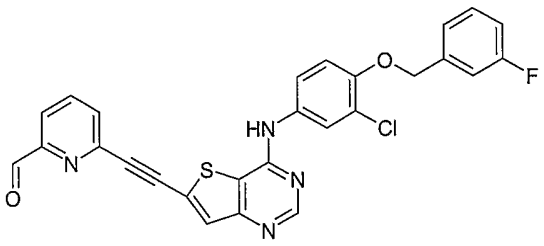
6-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde



The general procedure of example 1 was followed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[2,3-d]pyrimidin-4-amine (166.4 mg, 0.406 mmol), 2-bromo-6-pyridine carboxaldehyde (108 mg, 0.581 mmol), triethylamine (104 μL, 0.748 mmol), Cu(I)I (8 mg, 0.042 mmol), $(PPh_3)_2PdCl_2$ (15 mg, 0.021 mmol) in THF (2.0 mL). Workup and silica gel chromatography supplied 112.6 mg of the title compound as a bright yellow powder. Electrospray MS: 513 (ES-). ^1H NMR (400 MHz, DMSO-d_6) δ 5.23 (s, 2H), 7.16 (t, 1H, J = 8.4 Hz), 7.26 (m, 2H), 7.44 (m, 1H), 7.42-7.48 (m, 1H), 7.64 (dd, 1H, J = 9.0, 2.4 Hz), 7.95 (d, 1H, 7 = 7.7), 7.99-8.01 (m, 2H), 8.12 (t, 1H, J = 7.9), 8.27 (s, 1H), 8.55 (s, 1H), 9.80 (s, 1H), 9.96 (s, 1H).

Example 5

6-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde



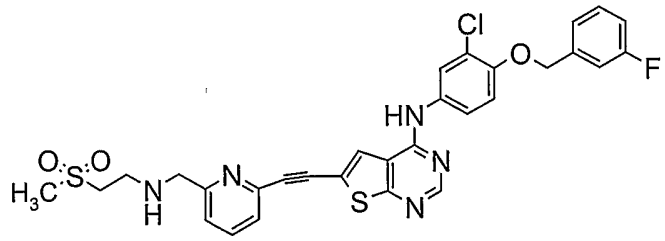
The general procedure of example 1 was followed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine (301 mg, 0.734 mmol), 2-bromo-6-pyridine carboxaldehyde (195 mg, 1.05 mmol), triethylamine (188 μL, 1.35 mmol), Cu(I)I (11.4 mg, 0.06 mmol), $(PPh_3)_2PdCl_2$, (35 mg, 0.05 mmol) in THF (3.0 mL). Workup and silica gel chromatography supplied 121.4 mg of the title compound as a bright yellow powder. MS: 513 (AP-). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.23 (s, 2H), 6.85 (s, 1H), 7.0-7.07 (m, 2H), 7.62 (d, 1H, J = 2.4), 7.69 (s, 1H), 7.80 (dd, 1H, J = 7.4, 1.5), 7.92-7.99 (m, 2H, 8.69 (s, 1H), 10.09 (s, 1H).

Assay Found: C 62.98; H 3.27; N 10.68;

$C_{27}H_{16}Cl_1F_1N_4O_2S_1$ requires C 62.97; H 3.13; N 10.88.

Example 6

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-({[2-(methylsulfonyl)ethyl] amino}methyl)pyridin-2-yl]ethynyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride

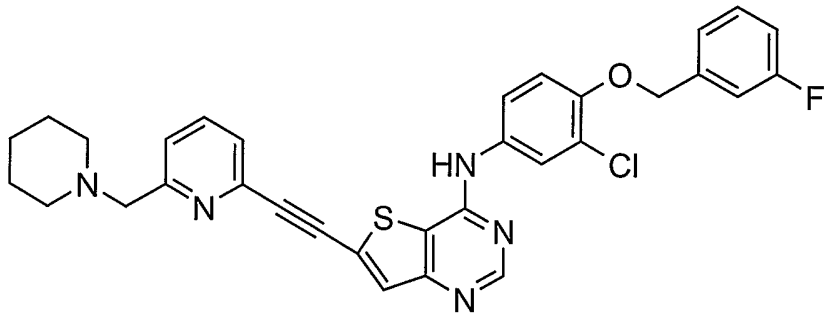


A solution of 6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde (24.6 mg, 0.0485 mmol) in N,N-DMF (2.0 mL) and MeOH (1.0 mL) was treated with 2-(methylsulfonyl)ethanamine (30 mg, 0.243 mmol) followed by sodium cyanoborohydride (11.5 mg, 0.183 mmol). The mixture was stirred under N_2 for 16 h and concentrated with a rotary evaporator. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give a residue that was purified by silica gel chromatography, eluting with MeOH in $CHCl_3$ (0% to 5% gradient) to afford the free base (15.2 mg). This material was dissolved in 1:1 1 N aq. HCl/CH_3CN and lyophilized to afford 12.1 mg of the title compound as a reddish solid, mp 170 °C.

HRMS: 621.1071 $(MH)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 3.13 (s, 3H), 3.47 (m, 2H), 3.63 (t, 2H), J = 6.8, 4.43 (s, 2H), 5.23 (s, 2H), 7.16 (t, 1H< J = 8.6, 7.23-7.31 (m, 3H), 7.45 (m, 1H), 7.56 (d, 1H, J = 8.0, 7.76 (s, 1H, 7.78 (s, 1H), 7.98 (t, 1H< J = 7.7), 8.09 (s, 1H), 8.55 (s, 1H, 8.55 (s, 1H), 8.58 (s, 1H), 9.62 (s, 3H), 10.41 (s, 1H).

Example 7

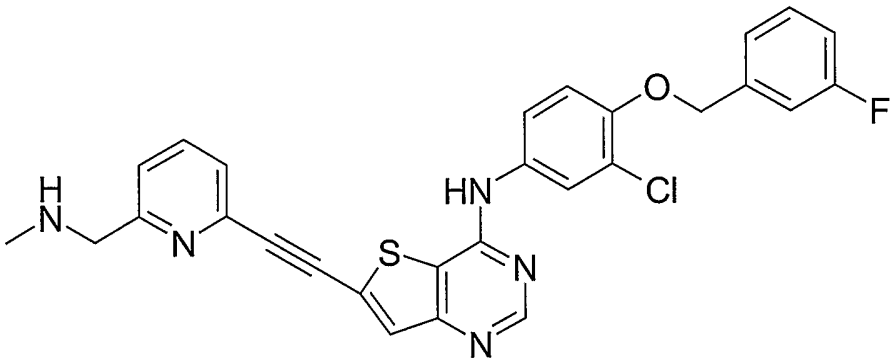
N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethynyl}thieno[3,2-d]pyrimidin-4-amine



To a solution of piperidine (23 μL, 0.23 mmol) and acetic acid (2 μL) in CH_2Cl_2 (4.0 mL) was added a slurry of 6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde (61 mg, 0.118 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred at ambient temperature for 1 h, then sodium triacetoxyborhydride (62 mg, 0.293 mmol) was added. The mixture was stirred for 3 h, then partitioned between saturated aq. $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give 73 mg of crude product. Silica gel chromatography (10:1: 0.1 ethyl acetate/methanol/triethylamine eluant) gave 30.5 mg of title compound was obtained as a bright yellow solid. Electrospray MS 582.0 (ES-). HRMS (M+H)+ 584.1677. ^1H NMR (400 MHz, DMSO-d_6) δ 1.45 (m, 2H), 1.59 (m, 4H), 2.44 (m, 4H), 3.65 (s, 2H), 5.22 (s, 2H), 6.86 (s, 1H), 6.99 (d, 1H, J = 8.8), 7.04 (m, 1H), 7.22 (m, 2H), 7.37 (m, 2H), 7.46 (d, 1H, J = 7.5), 7.53 (d, 1H< J = 7.9), 7.62 (m, 2H), 7.69 (t, 1H< J = 7.7), 8.67 (s, 1H).

Example 8

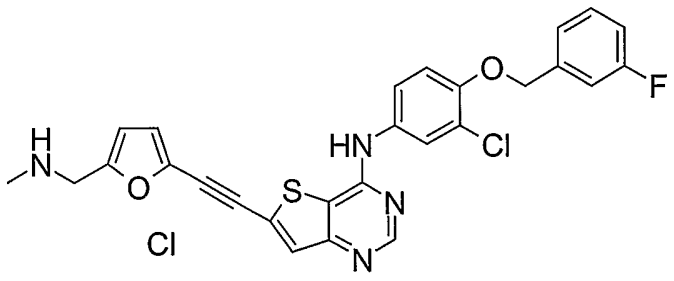
N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({6-[(methylamino)methyl]pyridin-2-yl}ethynyl)thieno[3,2-d]pyrimidin-4-amine



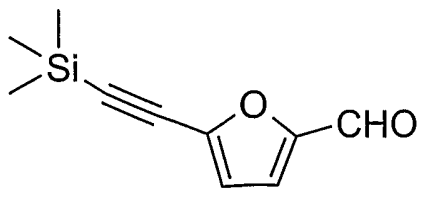
A procedure similar to the foregoing procedure was followed using 6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde (55.9 mg, 0.109 mmol), methylamine hydrochloride (15.7 mg, 0.235 mmol), triethylamine (30.4 mL, 0.218 mmol) and sodium triacetoxyborohydride (60 mg, 0.283 mmol) to yield, after chromatography 35.4 mg of the title compound as a bright yellow solid. Electrospray MS 529.9 (ES+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H), 3.90 (s, 2H), 5.22 (s, 2H), 6.99-7.04 (m, 2H), 7.23-7.28 (m, 2H), 7.36-7.39 (m, 2H), 7.47 (d, 1H, J = 7.7), 7.63 (m, 2H), 7.70 (t, 1H, J = 7.7), 8.67 (s, 1H).

Example 9

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride

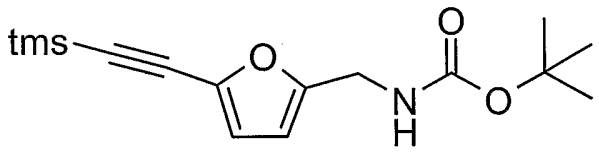


Step A - 5-[(Trimethylsilyl)ethynyl]-2-furaldehyde



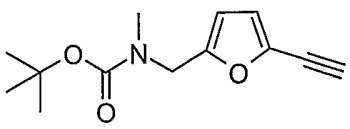
A dried, N_2-flushed flask equipped with a stirring bar was charged with 5-bromo-2-furaldehyde (4.0 g, 22.9 mmol), Cu(I)I (100 mg, 0.52 mmol), $(PPh_3)_2PdCl_2$ (405 mg, 0.58 mmol), THF (50 mL), and triethylamine (100 mg, 0.52 mmol), followed by trimethylsilylacetylene (3.78 mL, 25.2 mmol). The stirred mixture was heated to 40 °C under N_2. A solid formed that was collected by suction filtration, washed with 2:1 hexanes/ethyl acetate and dried en vacuo to give 3.9 g of the crude product. Purification by silica gel chromatography (15:1 hexanes/ethyl acetate eluant) provided 2.50 g of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 9H), 6.69 (d, 1H, J = 3.6), 7.18 (d, 1H, J = 3.6), 9.59 (s, 1H).

Step B - tert-Butyl {5-[(trimethylsilyl)ethynyl]-2-furyl}methylcarbamate



5-[(Trimethylsilyl)ethynyl]-2-furaldehyde (0.6 g, 3.12 mmol), methylamine hydrochloride (675 mg, 10 mmol) and MeOH (20 mL) were combined and to the mixture was added sodium cyanoborohydride (316 mg, 5.0 mmol). The mixture was stirred for 5 h, stripped with a rotary evaporator and partitioned between $CHCl_3$ and $NaHCO_3$. The organic layer was dried, filtered and concentrated to give the free base as an oil. This material was taken up in CH_2Cl_2 (10 mL) and di-tert-butyl dicarbonate (764 mg, 3.5 mmol) was added. The mixture was stirred for 2 days, then concentrated and purified by flash chromatography (10:1 H/EA eluant) to give 284 mg of the title compound as a colorless oil. ^{1}H NMR (400 MHz, CDCl3): δ 0.23 (s, 9H), 1.44 (s, 9H), 2.87 (s, 3H), 4.3 (s, 2H), 6.1 (bs, 1H), 6.52 (d, 1H, J = 3.1).

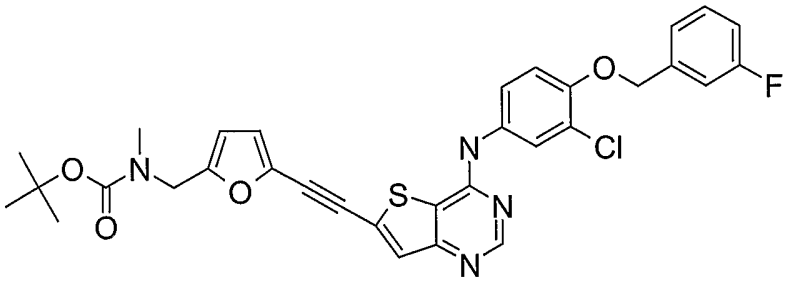
Step C - tert-Butyl (5-ethynyl-2-furyl)methyl(methyl)carbamate



A solution of tert-butyl {5-[(trimethylsilyl)ethynyl]-2-furyl}methylcarbamate (284.2 mg, 0.92 mmol) in THF (10 mL) at $^-$10 °C was treated with 1.0 M TBAF in THF (1.02 mL) and the mixture was stirred for 15 min. The mixture was partitioned

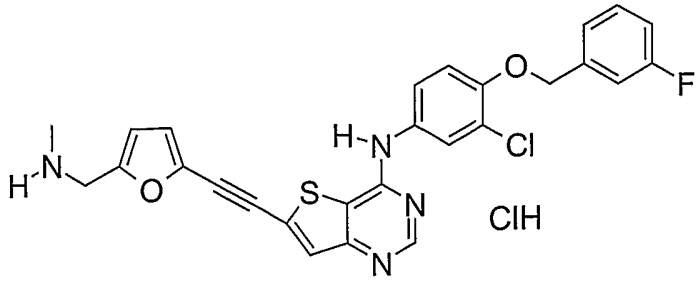
between sat. aq. $NaHCO_3$ and 1:1 hexanes/ethyl acetate. The organic layer was dried, filtered and concentrated to give 190 mg of the title compound as a brown solid. Electrospray MS 305.8 (ES+).

Step D - tert-butyl (5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl} amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-2-furyl)methyl(methyl)carbamate



A reaction tube under N_2 was charged with 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine hydrochloride (230 mg, 0.459 mmol), Cu(I)I (3.3 mg, 0.017 mmol), Pd $(PPh_3)_2Cl_2$ (20 mg, 0.028 mmol), THF (2.5 mL), and triethylamine (197 μL) in that order. A solution of tert-butyl {5-[(trimethylsilyl)ethynyl]-2-furyl}methylcarbamate (113.4 mg, 0.482 mmol) in THF (1.0 mL) was added dropwise and the mixture was heated at 34 °C for 20 h. The mixture was cooled to room temperature and partitioned between sat. aq. $NaHCO_3$ and 5:1 $CHCl_3$/i-PrOH. The organic layer was separated, dried, and concentrated to give 394 mg of crude product. Purification by silica gel chromatography (2:1 to 1:1 hexanes: ethyl acetate eluant) gave 68.4 mg of the title compound as a yellow solid, mp 153 °C. ^{1}H NMR (400 MHz, CDCl3) δ 1.48 (s, 9H), 2.92 (s, 3H), 4.40 (s, 2H), 5.22 (s, 2H), 6.27 (s, 1H), 6.75 (d, 1H, J = 3.4), 6.93 (s, 1H), 7.00 (d, 1H, J = 8.8), 7.05 (m, 1H), 7.25 (m, 1H), 7.35-7.43 (m, 2H), 7.54 (s, 1H), 7.63 (d, 1H), J = 2.2), 8.68 (s, 1H).

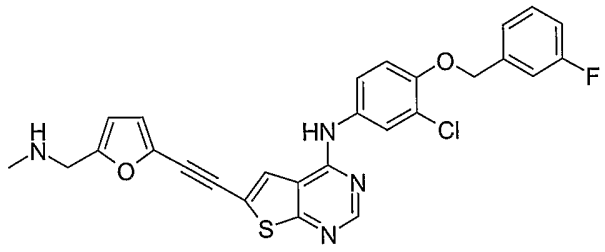
Step E - N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



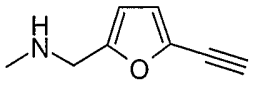
A flask was charged with tert-butyl (5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-2-furyl)methyl(methyl)carbamate (59.2 mg, 0.096 mmol), and 4 N HCl/dioxane (2.5 mL). A thick preciptate formed. After 1 h the mixture was diluted with diethyl ether and the precipitate was collected by suction filtration and dried en vacuo to give 54.4 mg of the title compound as a yellow solid. Electrospray MS 519.0 (ES+). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (t, 3H, J = 5.5), 4.25 (t, 2H, J = 5.4), 5.25 (s, 2H), 6.80 (d, 1H, J = 3.5), 7.13-7.18 (m, 2H), 7.25-7.31 (m, 3H), 7.41-7.47 (m, 1H), 7.60 (dd, 1H, J = 9.0, 2.6), 7.82 (s, 1H), 7.89 (d, 1H, J = 2.4), 8.70 (s, 1H), 9.26 (s, 2H), 10.58 (s, 1H).

Example 10

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[2,3-d]pyrimidin-4-amine



Step A - 1-(5-Ethynyl-2-furyl)-N-methylmethanamine



5-[(Trimethylsilyl)ethynyl]-2-furaldehyde (151 mg, 0.79 mmol), methylamine hydrochloride (485 mg, 7.2 mmol) and MeOH (10 mL) were combined and to the mixture was added sodium cyanoborohydride (61 mg, 0.97 mmol). The mixture was stirred for 4 h, and treated with K_2CO_3 (1.5 g). The mixture was stirred for 36 h, filtered and concentrated. The residue was partitioned between $CHCl_3$ and sat. aq. $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give the title compound as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.41 (s, 1H), 3.73 (s, 2H), 6.19 (d, 1H), J = 3.2), 6.60 (d, 1H), J = 3.2).

Step B - N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino) methyl]-2-furyl}ethynyl)thieno[2,3-d]pyrimidin-4-amine

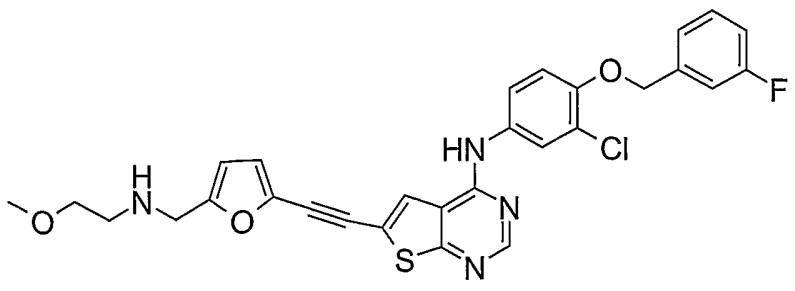
A procedure similar to that of example 1 was employed using 1-(5-ethynyl-2-furyl)-N-methylmethanamine(35.2 mg, 0.26 mmol) N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride (122 mg, 0.245 mmol), $Pd(PPh_3)_2Cl_2$ (10 mg, 0.014 mmol), Et_3N (119 μL, 0.85 mmol), THF (1.0 mL), Cu(I)I (2.0 mg, 0.01 mmol)) afforded 35.0 mg of the title compound as a yellow solid, mp 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.44 (s, 3H), 3.76 (s, 2H), 5.14 (s, 2H), 6.25 (d, 1H, J = 3.3), 6.67 (d, 1H, J = 3.3), 6.94-7.01 (m, 2H), 7.21-7.25 (m, 2H), 7.30-7.42 (m, 2H), 7.72 (d, 1H, J = 2.6), 8.56 (s, 1H).

Assay Found: C 61.50; H 3.97; N 10.25;

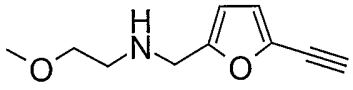
$C_{27}H_{20}Cl_1F_1N_4O_2S_1 \cdot 0.5H_20$ requires C 61.42; H 4.01; N 10.61.

Example 11

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[(5-{[(2-methoxyethyl)amino]methyl}-2-furyl)ethynyl]thieno[2,3-d]pyrimidin-4-amine

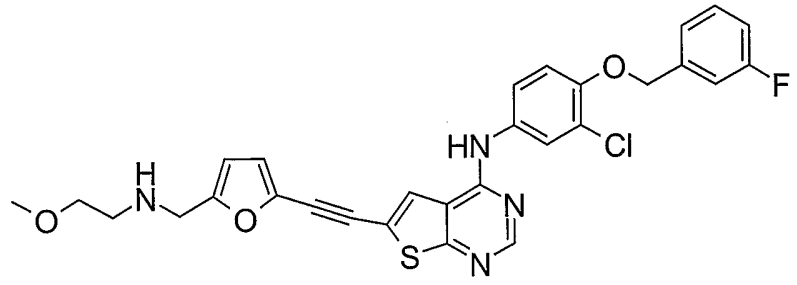


Step A - N-[(5-Ethynyl-2-furyl)methyl]-2-methoxyethanamine



A solution of 5-[(trimethylsilyl)ethynyl]-2-furaldehyde (201 mg, 1.05 mmol) and 2-methoxyethylamine (181 μL, 2.08 mmol) were stirred in CH_2Cl_2 and acetic acid (1 drop) was added. The mixture was allowed to stir for 20 min and sodium triacetoxy borohydride (580 mg, 2.64 mmol) was added. The mixture was allowed to stir for 16 h, then partitioned between sat. aq. $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried, filtered and concentrated to give the silyl acetylene product. This material was dissolved in methanol (4 mL) and stirred with 188 mg K_2CO_3 for 20 h. The mixture was concentrated with a rotary evaporator to leave a material that was filtered and concentrated to give 85.5 mg of the title compound as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (t, 2H, J = 4.8), 3.33 (s, 3H), 3.37 (s, 1H), t, 2H, J = 4.8, s, 2H), d, 1H, J = 3.2, 6.56 (d, 1H, J = 3.2.

Step B - N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[(5-{[(2-methoxyethyl) amino]methyl}-2-furyl)ethynyl]thieno[2,3-d]pyrimidin-4-amine



A procedure similar to that of example 1 using N-[(5-ethynyl-2-furyl)methyl]-2-methoxyethanamine (81.2 mg, 0.472 mmol), N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride (217 mg, 0.433 mmol), $Pd(PPh_3)_2Cl_2$ (16.5 mg, 0.024 mmol), Et_3N (197 □L, 1.42 mmol), THF (2.0 mL), Cu(I)I (2.6 mg, 0.014 mmol) and THF (2.0 mL) afforded 103.1 mg of the title compound as a yellow solid, mp 127 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.64 (bs, 2H), 3.21 (s, 3H), 3.35 (t, 2H, J = 5.6), 3.71 (bs, 2H), 5.22 (s, 2H), 6.40 (d, 1H, J = 3.6, 6.96 (d, 1H, J = 3.6), 7.15 (t, 1H, J = 6.4), 7.24-7.31 (m, 3H), 7.41-7.47 (m, 1H),

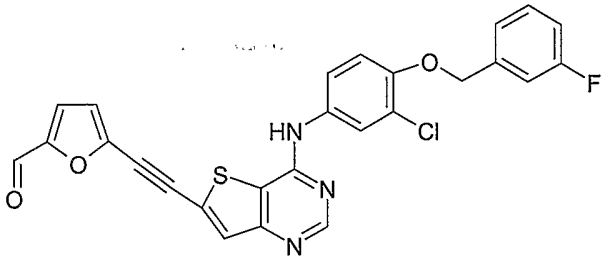
7.62 (dd, 1H, J = 8.8, 2.4), 7.98 (d, 1H, J = 2.4, 8.10 (s, 1H), 8.52 (s, 1H), 9.73 (s, 1H). HRMS (M+H)+ 563.1320.

Assay Found: C 61.62; H 4.39; N 9.75;

$C_{29}H_{24}Cl_1F_1N_4O_3S_1$ requires C 61.86; H 4.30; N 9.95.

Example 12

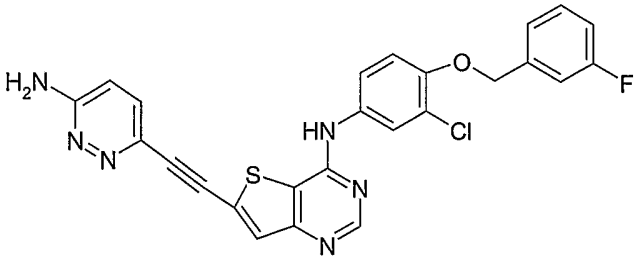
5-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-2-furaldehyde



A procedure similar to that of example 1 was employed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine and 5-bromo-2-furaldehyde to give 31 mg of the title compound as a yellow solid. Electrospray MS 504.3 (ES+). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.26 (s, 2H), 7.18 (t, 1H, J=8.6Hz), 7.25-7.36 (m, 4H), 7.43-7.51 (m,1H), 7.62 (dd,1H, J=2.5,9.0 Hz), 7.68 (d,1H,J=3.8Hz), 7.93 (d, 1H, 2.5Hz), 7.95 (s, 1H), 8.62 (s, 1H), 9.65 (s, 1H), 9.89 (s, 1H).

Example 13

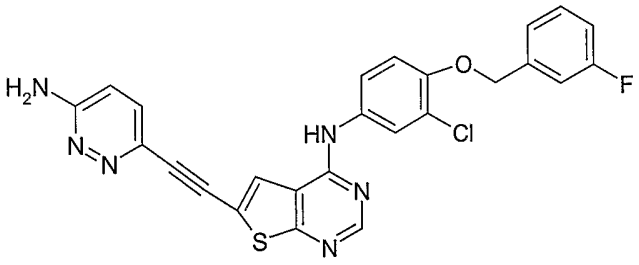
6-[(6-Aminopyridazin-3-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine



A procedure similar to that of example 1 was employed using N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine and 6-iodopyridazin-3-amine (prepared according to the method of Bert U. W. Maes Tetrahedron 56 (2000) 1777-1781) to give 106 mg of the title compound. HRMS: (M+H)+ 503.0852. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.27 (s, 2H), 6.80 (d, 1H, 9Hz), 7.01 (s, 2H), 7.19-7.48 (m, 4H), 7.54-7.61 (m, 3H), 7.79 (s, 1H), 7.97 (d, 1H, 2.5Hz), 8.61 (s, 1H), 9.82 (s, 1H).

Example 14

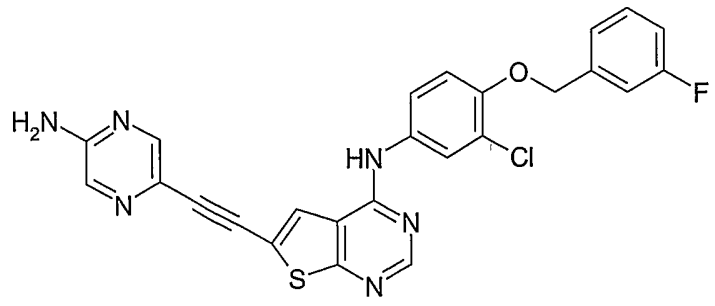
6-[(6-Aminopyridazin-3-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine



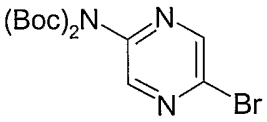
A procedure similar to that of the foregoing example was employed using 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride and 6-iodopyridazin-3-amine to give 31 mg of the title compound as an orange solid. HRMS: (M+H)+ 503.0869. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.28 (s, 2H), 6.83 (d, 1H), 6.99 (s, 2H), 7.22 (t, 1H, J=8.6Hz), 7.30-7.37 (m, 3H), 7.47-7.57 (m, 2H), 7.70 (dd, 1H, J=2.5, 9 Hz), 8.06 (d, 1H, J=2.7Hz), 8.19 (s, 1H), 8.59 (s, 1H), 9.8 (s, 1H).

Example 15

6-[(5-Aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine

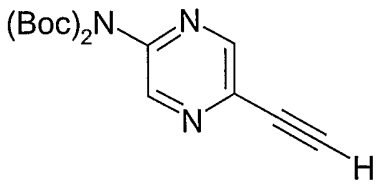


Step A - Di-(tert-butyl) 5-bromopyrazin-2-ylimidodicarbonate



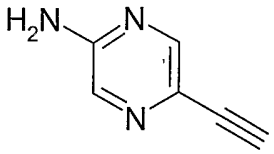
A solution of 2-amino-5-bromopyrazine (1.0g, 5.75 mmol), 4-dimethylaminopyridine (37 mg, 0.30 mmol) and di-tertbutyldicarbonate (2.5g, 11.4 mmol) were stirred in CH_2Cl_2 at room temperature overnight. The crude material was absorbed on celite and purified by silica gel chromatography (hexane:ethyl acetate) on silica gel column to yield 1.4 g of the title compound as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 18H), 8.68 (d, 1H, J=1.1 Hz), 8.82 (d, 1H, J=1.2 Hz)

Step B - Di(tert-butyl) 5-ethynylpyrazin-2-ylimidodicarbonate



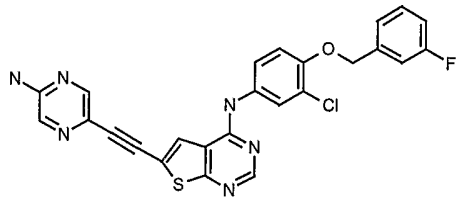
A reaction tube under N_2 was charged with di(tert-butyl) 5-bromopyrazin-2-ylimidodicarbonate (200mg, 0.53mmol), Cu(I) (3 mg, 0.016 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol), THF (3 mL), and triethylamine (163 μL, 1.17mmol) in that order. Trimethylsilylacetylene (90 μL, 0.64 mmol) in THF (1.0 mL) was added dropwise and the mixture was heated at 40 °C for 1.5h. The mixture was cooled to room temperature and allowed to sit overnight. The cooled reaction mixture was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The organic layer was separated, dried, and concentrated to give 252 mg of crude product. Purification by silica gel chromatography (97:3 to 8:2 hexanes: ethyl acetate eluent) gave 166 mg of the TMA intermediate as a white solid. The solid was dissolved in CH_2Cl_2 and cooled to 0°C. The solution was treated with a 1.0 molar solution of TBAF (1.1 mL, 1.1 mmoL) in THF for 3 h, then partitioned between EtOAc and water. The organic layer was separated and dried over Na_2SO_4. The mixture was filtered and concentrated and the residue was purified by silica gel chromatography (eluting with 97:3 to 8:2 hexanes:EtOAc) to yield 100 mg of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.73 (s, 1H), 8.74 (d, 1H, J=1.1 Hz), 8.79 (d, 1H, J=1.1 Hz).

Step C - 5-Ethynylpyrazin-2-amine



A solution of di(tert-butyl) 5-ethynylpyrazin-2-ylimidodicarbonate (350 mg) and trifluroacetic acid (1.0 mL, 12.98 mmoL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1h. Additional CH_2Cl_2 (40 mL) was added and the reaction mixture was adjusted to pH=7 with saturated aqueous NaHCO3. The organic layer was dried over Na_2SO_4, filtered and concentrated to yield 165 mg of a light brown solid that was purified by silica gel chromatography (8:2 to 6:4 hexanes: EtOAc) to obtain 90 mg of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.02 (s, 1H), 6.89 (broad s, 2H), 7.82 (d, 1H, J=1.3 Hz), 8.05 (d, 1H, J=1.1 Hz).

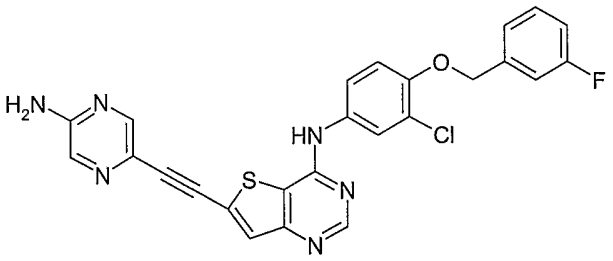
Step D - 6-[(5-Aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[2,3-d]pyrimidin-4-amine



A procedure similar to example 1 using 5-ethynylpyrazin-2-amine and 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine provided 1.55 g of the title compound as light orange solid. HRMS: (M+H)+ 503.0869. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 3H), 7.10 (s, 1H), 7.17-7.21 (m, 1H), 7.27-7.34 (m, 3H), 7.45-7.50 (m, 1H), 7.67 (dd, 1H, J=9, 2.4 Hz), 7.87 (s, 1H), 8.03 (d, 1H, 2.2 Hz), 8.09 (s, 1H), 8.23 (s, 1H), 8.54 (s, 1H), 9.73 (s, 1H).

Example 16

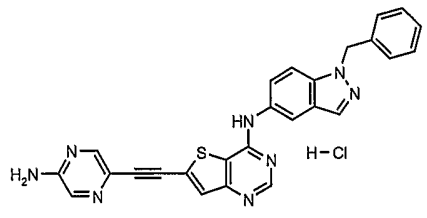
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine



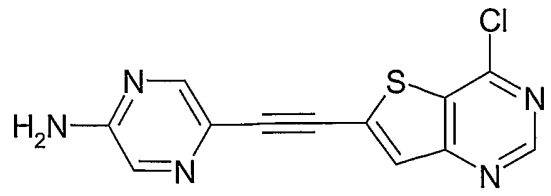
A procedure similar to the foregoing example using using 5-ethynylpyrazin-2-amine (94 mg, 0.78 mmol), 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine hydrochloride (390 mg, 0.716 mmol), Cu(I)I (4.2 mg, 0.02 mmol), $Pd(PPh_3)_2Cl_2$ (29 mg, 0.04 mmol) was employed to afford, after purification of the crude product, 193.5 mg of the title compound as a yellow solid. HRMS: (M+H)+ 503.0843. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.21 (s, 2H), 7.15 (s, 2H), 7.17-7.34 (m, 4H), 7.45-7.50 (m, 1H), 7.62 (dd, 1H, J=9, 2.2 Hz), 7.71 (s, 1H), 7.92 (s, 1H), 8.25 (s, 1H), 8.60 (s, 1H), 9.79 (s, 1H).

Example 17

6-[(5-aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



Step A - 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine



Nitrogen was bubbled through a solution of 6-bromo-4-chlorothieno[3,2-d]pyrimidine (4.70 g, 18.8 mmol), 5-ethynylpyrazin-2-amine (2.47 g, 20.7 mmol), $Pd(PPh_3)_2Cl_2$ (0.860 g, 1.20 mmol), and Cu(I)I (0.125 g, 0.660 mmol) in 100 mL THF for 5 minutes. Triethylamine (8.60 mL, 62.0 mmol) was added and the reaction mixture was heated to 50 °C for 1 hour, then cooled to room temperature and filtered through Celite. Silica gel was added to the filtrate and the solvent was removed in vacuo. The resulting solid was loaded on to a column of silica gel and eluted with 0 – 20% MeOH: CH_2Cl_2 gradient to give a yellow solid, which was triturated with warm THF to the title compound (2.88 g). ^{1}H NMR (400 MHz, DMSO) δ 7.24 (s, 2H), 7.92 (s, 1H), 8.01 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H).

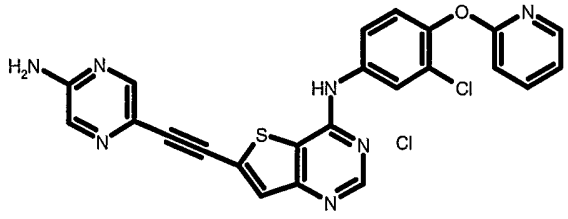
Step B - 6-[(5-aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine hydrochloride

5-[(4-Chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine (75 mg, 0.26 mmol) was combined with 1-benzyl-1H-indazol-5-amine (58 mg, 0.26 mmol) and 1 drop of conc. HCl in isopropyl alcohol. The suspension was heated to 60 °C for 15 h. The resulting orange suspension was filtered and washed with cold isopropyl alcohol. Filtration yielded 103 mg (77%) of an orange powder. MS (ESI): (M+H)+ = 475. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.69 (s, 2H), 7.25-7.11 (m, 5H), 7.35-7.26 (m, 2H), 7.35-7.26 (m, 2H), 7.55 (dd, 1H), 7.68 (s, 1H), 7.73 (m, 1H), 7.81-10.76 (br s, 1H), 7.90 (s, 1H), 8.04 (s, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 8.72 (m, 1H).

The following Examples 18-23 were prepared similar to the procedure of Example 17 from the indicated starting materials and were characterized as the indicated product.

Example 18

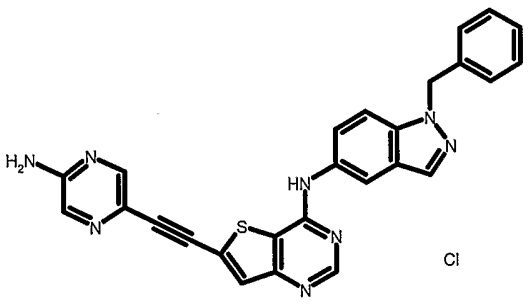
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(pyridin-2-yloxy)aniline and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 19

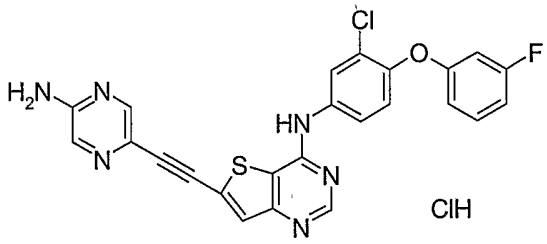
6-[(5-aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 1-benzyl-1H-indazol-5-amine and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 20

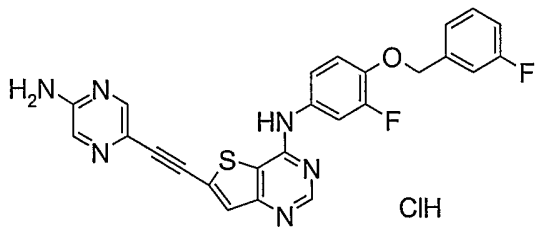
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(3-fluorophenoxy)aniline and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 21

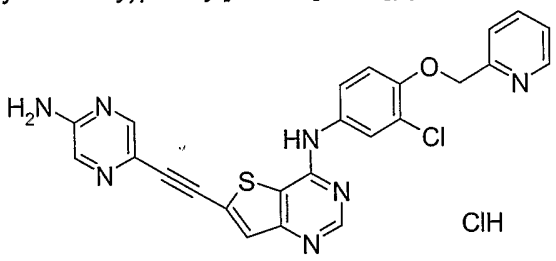
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-fluoro-4-[(3-fluorobenzyl)oxy]aniline and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 22

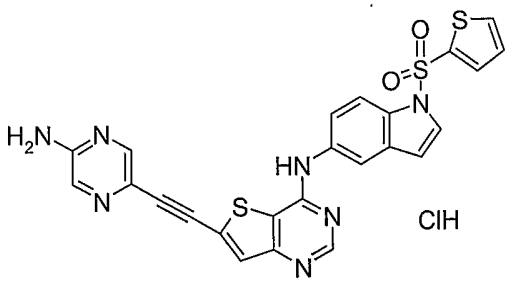
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(pyridin-2-ylmethoxy)aniline and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 23

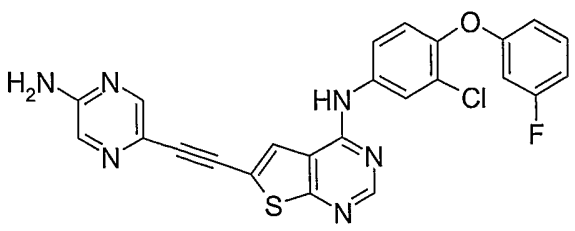
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[3,2-d]pyrimidin-4-amine hydrochloride



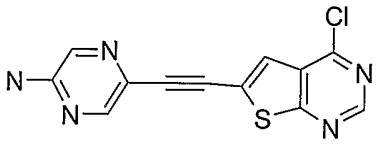
The title product was prepared from 1-(thien-2-ylsulfonyl)-1H-indol-5-amine and 5-[(4-chlorothieno[3,2-d]pyrimidin-6-yl)ethynyl]pyrazin-2-amine.

Example 24

6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine



Step A - 5-[(4-Chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine



To an N_2-flushed flask was added 6-bromo-4-chlorothieno[2,3-d]pyrimidine (3.6 g, 14 mmol), THF (100 mL) Cu(I)I (0.11 g, 0.57 mmol), $PdCl_2(PPh_3)_2$ (0.81g, 1.15mmol) and triethylamine (8 mL, 60mmol). 5-Ethynyl-2-pyrazinamine dissolved in THF (60 mL) was then added to the reaction dropwise over 15 min. The reaction was then heated at 80 °C for 3 h. The reaction was cooled to room temperature, concentrated with a rotary evaporator and purified by chromatography using CH_2Cl_2 and EtOAc to afford 2.02 g of the title compound. ^1H NMR (300MHz, DMSO-d_6): δ. 8.99 (s, 1H); 8.25 (s, 1H); 7.92 (s, 1H); 7.85 (s, 1H); 7.18 (s, 2H).

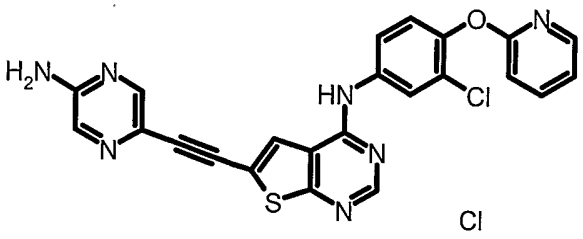
Step B - 6-[(5-aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl] thieno[2,3-d]pyrimidin-4-amine

The procedure followed was similar to that used to prepare Example 17, Step B, except 3-chloro-4-(3-fluorophenoxy)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine were utilized to supply the title compound.

The following Examples 25-34 were prepared similar to the procedure of Example 24 from the indicated starting materials and were characterized as the indicated product.

Example 25

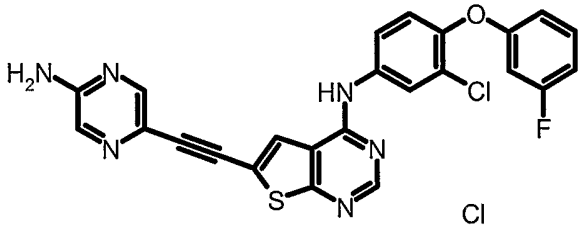
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(pyridin-2-yloxy)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 26

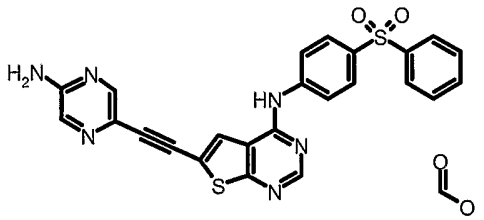
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(3-fluorophenoxy)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 27

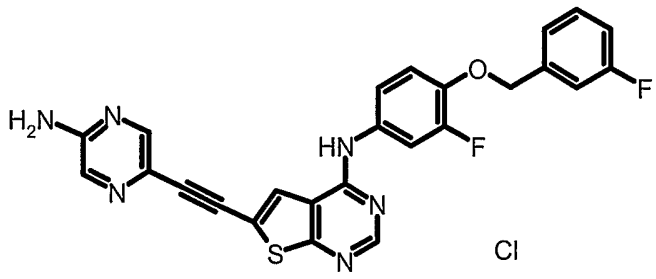
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[4-(phenylsulfonyl)phenyl]thieno[2,3-d]pyrimidin-4-amine (1:1) Formate



The title product was prepared from 4-(phenylsulfonyl)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 28

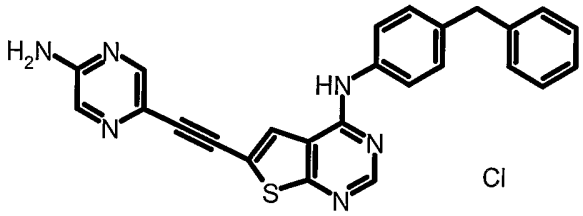
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-fluoro-4-[(3-fluorobenzyl)oxy]aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 29

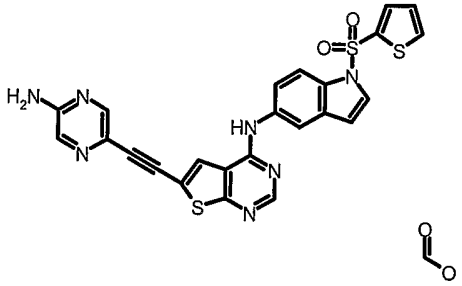
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-(4-benzylphenyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 4-benzylaniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 30

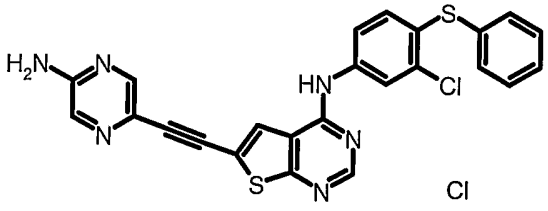
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[2,3-d]pyrimidin-4-amine Formate



The title product was prepared from 1-(thien-2-ylsulfonyl)-1H-indol-5-amine and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 31

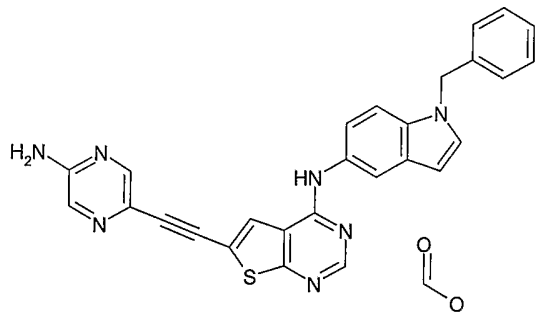
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(phenylthio)phenyl]thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title product was prepared from 3-chloro-4-(phenylthio)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 32

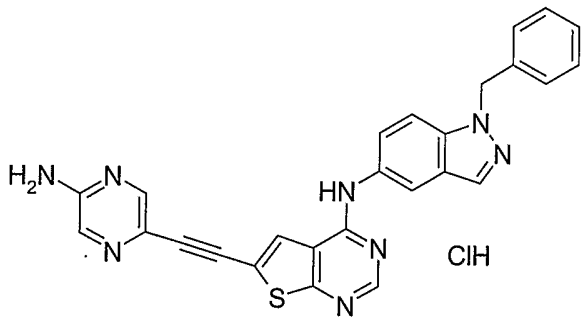
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indol-5-yl)thieno[2,3-d]pyrimidin-4-amine (1:1) Formate



The title compound was prepared from 1-benzyl-1H-indol-5-amine and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 33

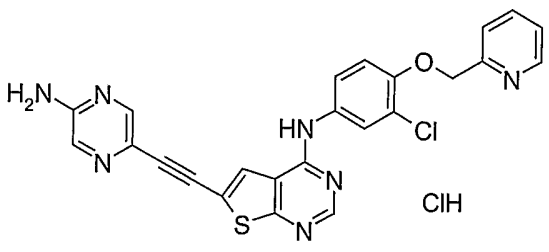
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[2,3-d]pyrimidin-4-amine hydrochloride



The title compound was prepared from 1-benzyl-1H-indazol-5-amine and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 34

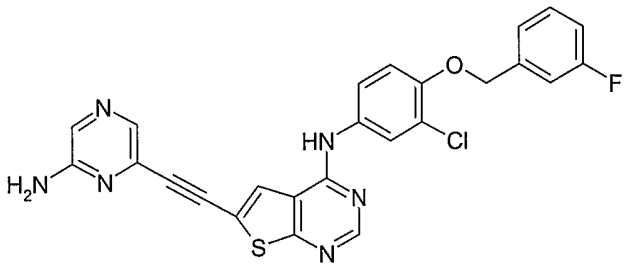
6-[(5-Aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine hydrochloride



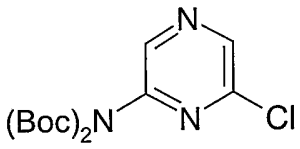
The title compound was prepared from 3-chloro-4-(pyridin-2-ylmethoxy)aniline and 5-[(4-chlorothieno[2,3-d]pyrimidin-6-yl)ethynyl]-2-pyrazinamine.

Example 35

6-[(6-aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine

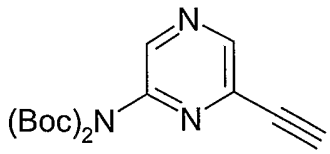


Step A - Di(tert-butyl) 6-chloropyrazin-2-ylimidodicarbonate



A solution of 2-amino-6-chloropyrazine (750 mn, 5.8 mmol), 4-dimethylaminopyridine (37 mg, 0.30 mmol) and di-tert-butyldicarbonate (2.5g, 11.4 mmol) were stirred in CH_2Cl_2 (15 mL) at room temperature overnight. The crude material was absorbed onto Celite and purified by chromatography (hexanes:ethyl acetate) on silica gel column to yield 1.6 g of the title compound as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 1.41 (s, 18H), 8.80 (s, 1H), 8.84 (s, 1H).

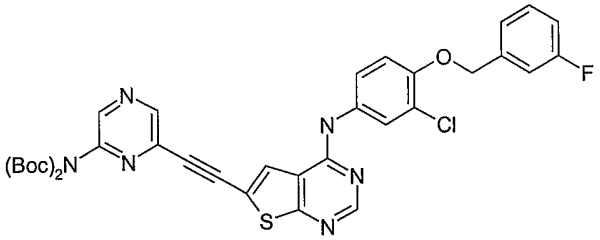
Step B - Di(tert-butyl) 6-ethynylpyrazin-2-ylimidodicarbonate



The procedure used was similar to that used to generate the isomeric acetylenic pyrazine intermediate (di(tert-butyl) 5-bromopyrazin-2-ylimidodicarbonate)

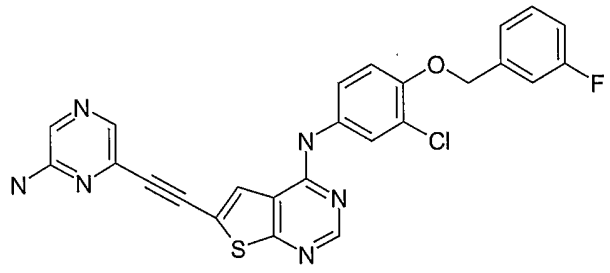
described previously. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (s, 18H) 4.78 (s, 1H), 8.78 (s, 1H), 8.82 (s, 1H).

Step C - Di(tert-butyl) 6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl} amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyrazin-2-ylimidodicarbonate



Di(tert-butyl) 6-ethynylpyrazin-2-ylimidodicarbonate (249 mg, 0.780 mmol) and 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride (390 mg, 0.716 mmol) were allowed to react in the manner described in procedure of example 1 to supply, after purification, 626.6 mg of the title compound as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.26 (s, 2H), 7.19 (t, 1H, J = 8.4), 7.29 (d, 1H, J = 9.2), 7.33 (d, 1H, J = 7.2), 7.45-7.48 (m, 1H), 7.66 (dd, 1H, J = 9.2, 2.8), 8.02 (d, 1H, J = 2.4), 8.32 (s, 1H), 8.59 (s, 1H), 8.86 (s, 1H), 8.94 (s, 1H), 9.88 (s, 1H).

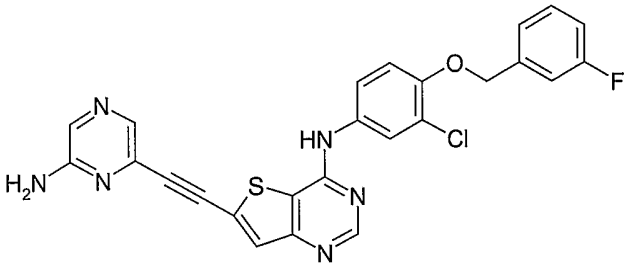
Step D - 6-[(6-Aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl) oxy]phenyl} thieno[2,3-d]pyrimidin-4-amine



The di(tert-butyl) 6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyrazin-2-ylimidodicarbonate obtained from the foregoing procedure was treated with TFA in CH_2Cl_2 to give 62 mg of the title compounds as an orange solid. HRMS: (M+H)+ 503.0867 ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 2H), 6.75 (s, 2H), 7.14-7.20 (m, 1H), 7.33-7.21 (m, 3H), 7.43-7.50 (m, 1H), 7.66 (dd, 1H, J=8.9, 2.5 Hz), 7.90(s, 1H), 7.97 (s, 1H), 8.02 (d, 1H, J=2.5 Hz), 8.19 (s, 1H), 8.56 (s, 1H), 9.78 (s, 1H).

Example 36

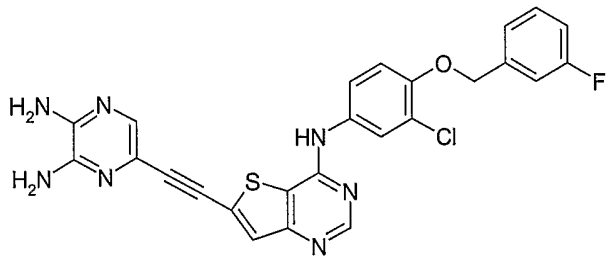
6-[(6-Aminopyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine



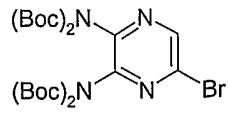
The procedure used was similar to the foregoing example using 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine hydrochloride and di(tert-butyl) 6-chloropyrazin-2-ylimidodicarbonate to give, after TFA deprotection of the Boc aminopyrazine intermediate, 187 mg of product as a yellow solid. HRMS: (M+H)+ 503.0872 ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.26 (s, 3H), 6.78 (s, 2H), 7.14-7.34 (m, 4H), 7.43-7.51 (m, 1H), 7.62 (dd, 1H, J=8.9, 2.6 Hz), 7.83 (s, 1H), 7.92 (s, 2H), 8.00 (s, 1H), 8.61 (s, 1H), 9.83 (s, 1H).

Example 37

5-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine



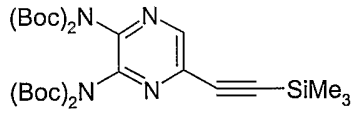
Step A - 2-Bromo-5,6-tetraboc Diaminopyrazine



The 5-bromo-2,3-diaminopyrazine (prepared according to the method of Olivier Vitse (Biorg. and Medicinal Chem. 7 (1999) 1059-1065) (438 mg, 2.32 mmoL) was partially dissolved in THF (6 mL) and treated with di-tert-butyl-dicarbonate (2.52g, 11.6 mmoL). The mixture was stirred at ambient temperature for 2 h, then heated at 50 °C until all solids dissolved. The mixture was allowed to cool to ambient

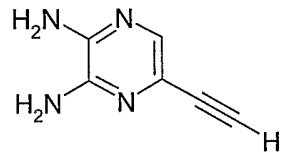
temperature and the product was isolated by silica gel chromatography (eluting with 9:1 Hexane:EtOAc to 100% EtOAc) to supply 750 mg of the product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (s, 36H), 8.86 (s, 1H).

Step B - 5-[(Trimethylsilyl)ethynyl]pyrazine-2,3-tetra-(di-tert-butyldicarbonyl)-diamine



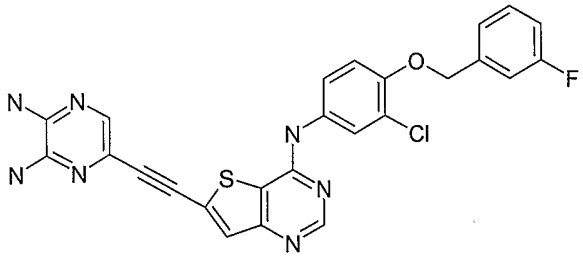
The Pd-mediated coupling procedure followed was similar to that of example 1 except using the tetraboc diaminopyrazine of the foregoing procedure and trimethylsilylacetylene to give 500 mg of the Boc diaminopyrazine intermediate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.29 (s, 9H), 1.40 (s, 18H), 1.41 (s, 18H), 8.75 (s, 1H).

Step C - 5-Ethynylpyrazine-2,3-diamine



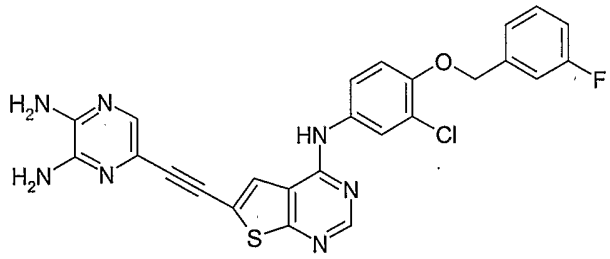
The foregoing intermediate (500 mg, .82 mmoL) was dissolved in methylene chloride (20 mL) and treated with trifluoroacetic acid (3 mL). Stirred 1 h and concentrated to dryness. Placed on vacuum pump for 1 h. Dissolved in methanol (20mL) and added potassium carbonate (570 mg, 4.12 mmoL). The mixture was filtered and the filtrate was concentrated and purified by silica gel chromatography (1:1 hexanes:EtOAc to 100% EtOAc) to obtain 81 mg of product as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.92 (s, 1H), 6.25 (broad s, 2H), 5.47 (broad s, 2H), 7.34 (s, 1H).

Step D - 5-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine



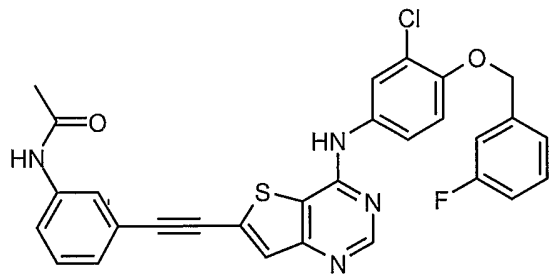
The procedure followed was similar to the Pd-mediated coupling procedure of example 1 using the 5-ethynylpyrazine-2,3-diamine and 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine hydrochloride to give 32.4 mg of the title compound as a yellow solid . HRMS: (M+H)+ 518.0982.
^{1}H NMR (400 MHz, DMSO-d_6): δ 5.29 (s, 2H), 6.32 (broad s, 2H), 6.66 (broad s, 2H), 7.19-7.37 (m, 4H), 7.47-7.57 (m, 1H), 7.61-7.66 (m, 3H) m 7.96 (d, 1H, J=2.4 Hz), 8.61 (s, 1H), 9.77 (s, 1H).

Example 38
5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine



The foregoing sequence was used with 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine hydrochloride to supply 25.7 mg of the title compound as a yellow solid. HRMS: (M+H)+ 518.0968. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 2H), 6.27 (broad s, 2H), 6.57 (broad s, 2H), 7.17-7.19 (m, 1H), 7.21-7.34 (m, 2H), 7.45-7.48 (m, 2H), 7.50 (s, 1H), 7.67 (dd, 1H, J=8.9, 2.5 Hz), 8.02 (d, 1H, J=2.8 Hz), 8.53 (s, 1H), 9.68 (s, 1H).

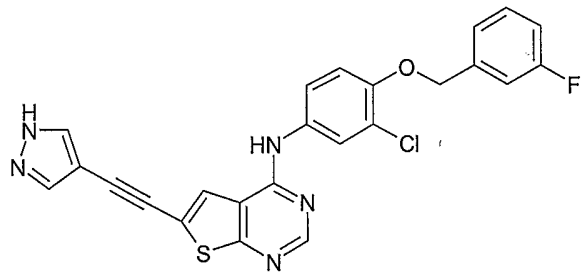
Example 39
N-(3-{[4-({3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}phenyl)acetamide hydrochloride



The title compound was prepared as the HCl salt from 6-bromo-4-chlorothieno[2,3-d]pyrimidine by a procedure similar to example 1 using commercially available N-(3-ethynylphenyl)-acetamide and known 3-chloro-4-[(3-fluorobenzyl)oxy]aniline. HPLC RT: 4.18 min. HRMS: $(M+H^+)^+$ 543.1057.

Example 40

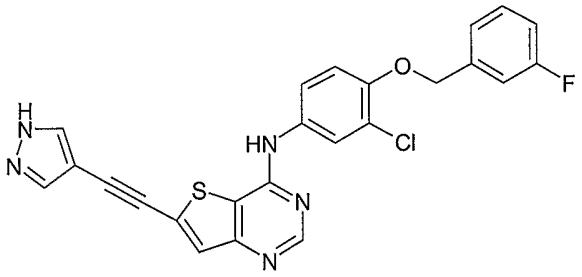
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[2,3-d]pyrimidin-4-amine



An N_2-flushed flask was charged with N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[2,3-d]pyrimidin-4-amine (301 mg, 0.735 mmol, prepared from 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine and trimethylsilyl acetylene in a manner similar to procedure 1, followed by removal of the TMS group by TBAF in THF), 4-iodopyrazole (249 mg, 1.29 mmol), $PdCl_2(PPh_3)_2$ (26 mg, 0.037 mmol), Cu(I)I (11.5 mg, 0.06 mmol), THF (3.6 mL) and Et_3N (270 mL, 1.94 mmol) and the mixture was heated at 37 °C for 20 h. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic layer was separated, dried and concentrated to give the crude product. Purification by silica gel chromatography (eluting with 0-4% methanol in $CHCl_3$ gradient) supplied 93.1 mg of the title compound as a pale reddish solid. Electrospray MS 476 (ES+). ^1H NMR (400 MHz, DMSO-d_6) δ 5.25 (s, 2H), 7.19 (dt, 1H, J = 8.8, 3.3), 7.27 (d, 1H, J = 9.2), 7.30-7.34 (m, 2H), 7.45-7.50 (m, 1H), 7.66 (dd, 1H, J = 9.2, 2.8), 7.84 (s, 1H), 8.02 (s, 2H), 8.27 (s, 1H), 8.53 (s, 1H), 9.68 (s, 1H).

Example 41

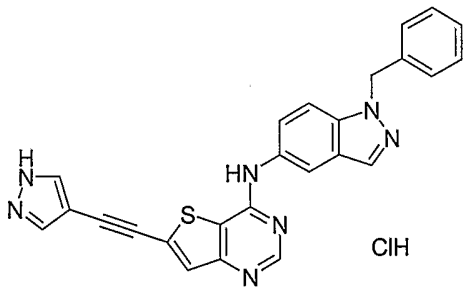
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



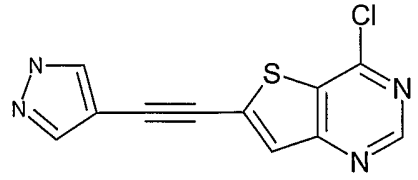
The procedure of Example 40 was utilized except that the starting materials were N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine.

Example 42

N-(1-Benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



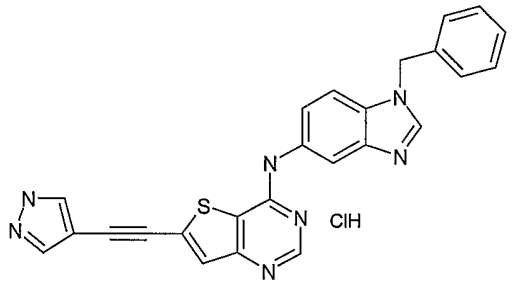
Step A - 4-Chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine



A round bottom flask equipped with a stirring bar was purged with nitrogen. The flask was charged with 1.0g (4.0 mmol) 6-bromo-4-chlorothieno[3,2-d]pyrimidine, 140 mg (0.2 mmol), $Pd(PPh_3)_2Cl_2$, 76 mg (0.4mmol), CuI, 25 mL THF and 1.6 mL (12 mmol) Et_3N. Next, 443 mg (4.8 mmol) 4-ethynyl-1H-pyrazole (Prepared in a manner similar to that described by Heinisch, Holzer and Obala, Monatshefte fuer Chemie,

119, 253-62, 1988) was added, the mixture heated to 60 ^{0}C and the progress of the reaction was monitored by TLC. When all the bromide had reacted, the mixture was cooled to room temperature, filtered through a pad of Celite, and the crude absorbed onto silica gel. The crude mixture was purified by silica gel chromatography to yield the title compound (780 mg, 75 % yield). ^{1}H NMR 300 MHz, $(CD_3)_2CO$ δ 13.44 (brs, 1H); 9.05 (s, 1H); 8.34 (s, 1H); 7.93 (s, 1H); 7.88 (s, 1H).

Step B - N-(1-benzyl-1H-benzimidazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine 2 Hydrochloride

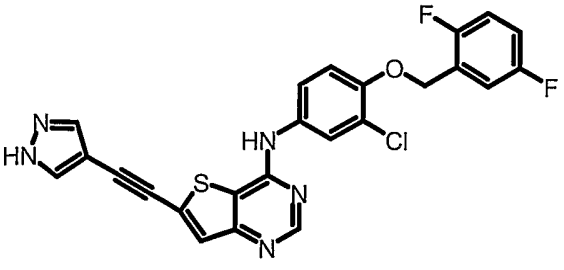


A mixture of 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine and 1-benzyl-1H-benzimidazole-5-diazonium were heated in isopropanol as described in previous examples. The resulting solid that formed was collected by suction filtration to afford the title compound as the hydrochloride salt. ^{1}H NMR (400 MHz, $(CD_3)_2CO$ δ 13.67 (brs, 1H); 9.77 (s, 1H); 8.51 (s, 1H); 8.45 (s, 1H); 8.27 (brs, 1H); 7.95 (s, 1H); 7.84 (brs, 1H); (s, 1H); 7.52 (d, 1H); 7.41-7.27 (m, 6H); 5.52 (s, 2H). LCMS (Electrospray): 445 $[M+H]^+$.

The following Examples 43-50 were prepared similar to the procedure of Example 42 from the indicated starting materials and were characterized as the indicated product.

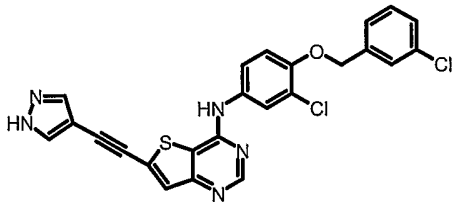
Example 43

N-{3-chloro-4-[(2,5-difluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



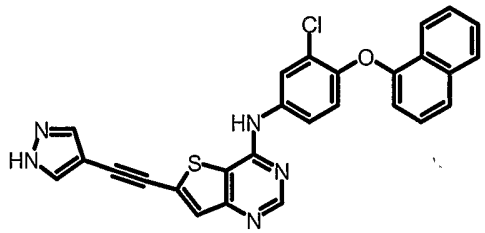
The title compound was prepared from 3-chloro-4-[(2,5-difluorobenzyl)oxy]aniline and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 44
N-{3-Chloro-4-[(3-chlorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



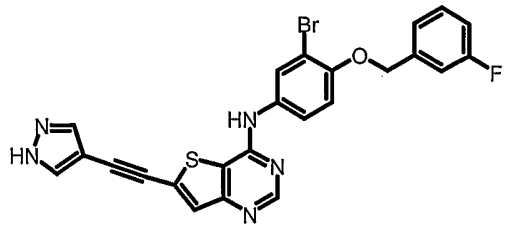
The title compound was prepared from 3-chloro-4-[(3-chlorobenzyl)oxy]aniline and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 45
N-[3-Chloro-4-(1-naphthyloxy)phenyl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



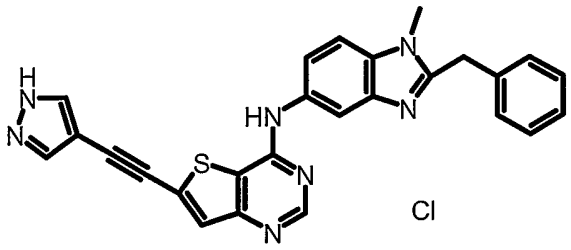
The title compound was prepared from 3-chloro-4-(1-naphthyloxy)aniline and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 46
N-{3-bromo-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



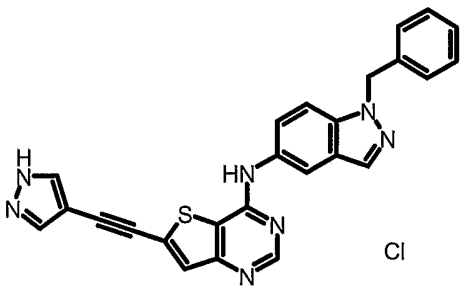
The title compound was prepared from 3-bromo-4-[(3-fluorobenzyl)oxy]aniline and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 47
N-(2-benzyl-1-methyl-1H-benzimidazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



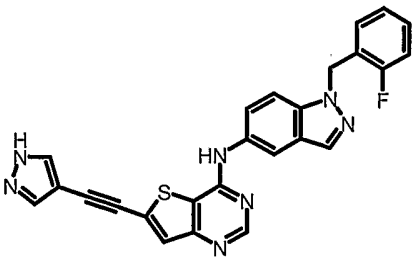
The title compound was prepared from 2-benzyl-1-methyl-1H-benzimidazol-5-amine and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 48
N-(1-benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title compound was prepared from 1-benzyl-1H-indazol-5-amine and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

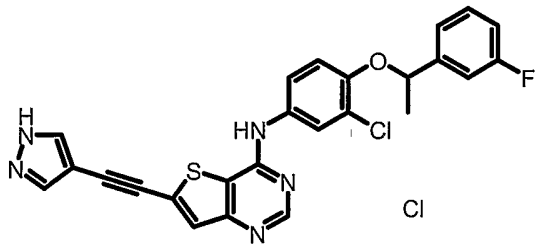
Example 49
N-[1-(2-fluorobenzyl)-1H-indazol-5-yl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine



The title compound was prepared from 1-benzyl-1H-indazol-5-amine and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

Example 50

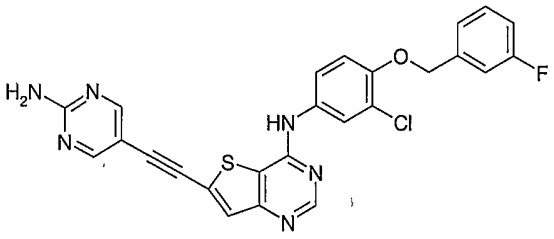
(R,S)-N-{3-Chloro-4-[1-(3-fluorophenyl)ethoxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine hydrochloride



The title compound was prepared from (R,S)-3-chloro-4-[1-(3-fluorophenyl)ethoxy]aniline and 4-chloro-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidine.

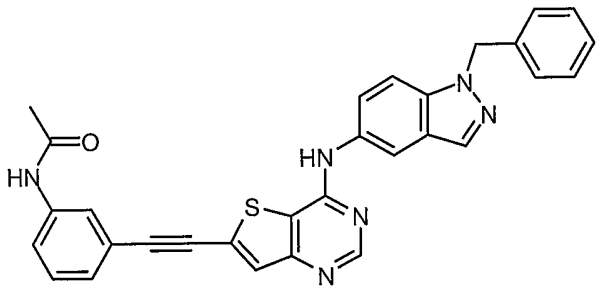
Example 51

6-[(2-Aminopyrimidin-5-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine



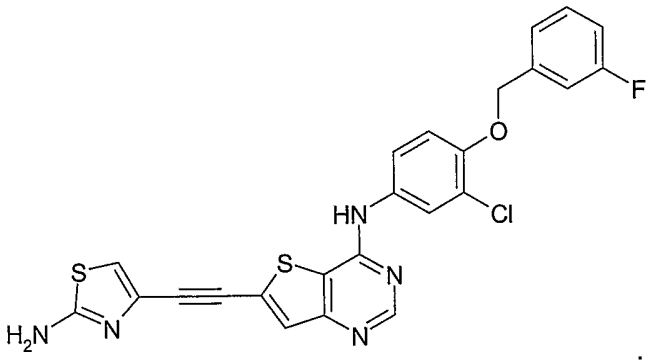
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine (300 mg, 0.735 mmol) was allowed to react with 2-amino-4-iodopyrimidine (195 mg, 0.882 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (31 mg, 0.044 mmol), Cu(I)I (3.6 mg, 0.019 mmol) and Et_3N (300 mL, 2.15 mmol) in procedure similar to the foregoing procedure to afford, after workup, 106.4 mg of the title compound as a light green solid. ^1H NMR (400 MHz, DMSO-d6) δ 5.26 (s, 2H), 7.19 (t, 1H), J = 9.0), 7.26 (d, 1H, J = 9.0), 7.30-7.36 (m, 3H), 7.45-7.50 (m, 1H), 7.61 (dd, 1H, J = 8.8, 2.0), 7.66 (s, 1H), 7.92 (d, 1H, J = 2.4 (8.52 (s, 2H), 8.61 (bs, 1H), 9.78 (s, 1H). HRMS (M+H) 503.0857.

Example 52
N-[3-({4-[(1-Benzyl-1H-indazol-5-yl)amino]thieno[3,2-d]pyrimidin-6-yl}ethynyl)phenyl]acetamide hydrochloride

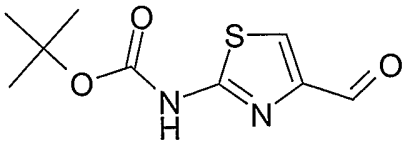


The title compound was prepared as the HCl salt from 6-bromo-4-chlorothieno[2,3-d]pyrimidine by a procedure analogous to example 1 using commercially available N-(3-ethynylphenyl)-acetamide and known 5-amino-1-benzyl-indazole. HPLC RT: 3.70 min. HRMS: 515.1664 (MH^+).

Example 53
6-[(2-Amino-1,3-thiazol-4-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[3,2-d]pyrimidin-4-amine



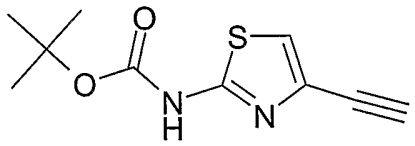
Step A - tert-Butyl 4-formyl-1,3-thiazol-2-ylcarbamate



Ethyl 2-[(tert-butoxycarbonyl)amino]-1,3-thiazole-4-carboxylate (prepared according to the method of Kim, H.-O.; Kahn, M. Synlett 1999, 8, 1239-1240) (0.28 g, 1.02 mmol) was dissolved into THF (5 mL) and cooled to 0 °C for 10

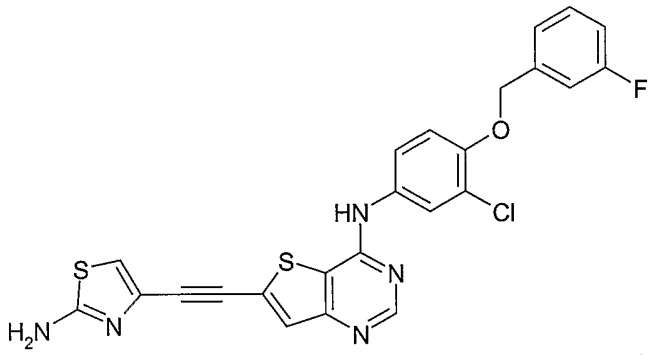
min. Added lithium aluminum hydride (0.077 g, 2.04 mmol) in one portion, vigorous gas evolution ocurred. The reaction became green in color, stirred for 10 min at 0°C, warmed reaction to RT. After stirring for 1 hr at RT, reaction was cooled to 0 °C, diluted with Et_2O (3 mL) and quenched with dropwise addition of saturated aqueous Na_2SO_4 (10 mL). The resulting suspension was stirred for 30 min at RT, partitioned the reaction with EtOAc (20 mL), and 0.5 M HCl (20 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, reduced in vacuo to afford a white fluffy solid that was carried on crude without further purification. The crude alcohol was dissolved into CH_2Cl_2 (10 mL) at RT. Added MnO_2 (0.865 g, 9.95 mmol), and after one hour added an additional 5 eq of MnO_2. The reaction was very sluggish, and the reaction was filtered through Celite, and the pad was washed with CH_2Cl_2 (4x10 mL), before completion of the reaction had occurred. The reaction was absorbed onto silica and purified via ISCO chromatography (hexanes:EtOAc) to afford a solid; 85 mg, 37% over two steps. LRMS (ES, m/z) 229 $(m+H)^+$.

Step B - tert-Butyl 4-ethynyl-1,3-thiazol-2-ylcarbamate



The aldehyde (0.083 g, 0.364 mmol) was dissolved into MeOH (0.6 mL) at RT. Added K_2CO_3 (0.125 g, 0.91 mmol), and dimethyl 1-(1λ^5-diazenylidene)-2-oxopropylphosphonate (0.14 g, 0.728 mmol, prepared according to the method of P. Callant, L. D'Haenens and M. Vandewalle. Synth. Commun. 14 (1984), pp. 155–161) at RT. The reaction was allowed to stir for 12 h at RT. The reaction was partitioned between water and EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo onto silica and purified silica gel chromatography (hexanes:EtOAc) to afford a white solid; 63 mg, 74% yield. ^1H NMR (400 MHz, CDCl3): δ. 9.23 (bs, 1H); 7.12 (s, 1H); 3.04 (s, 1H); 1.54 (s, 9H).

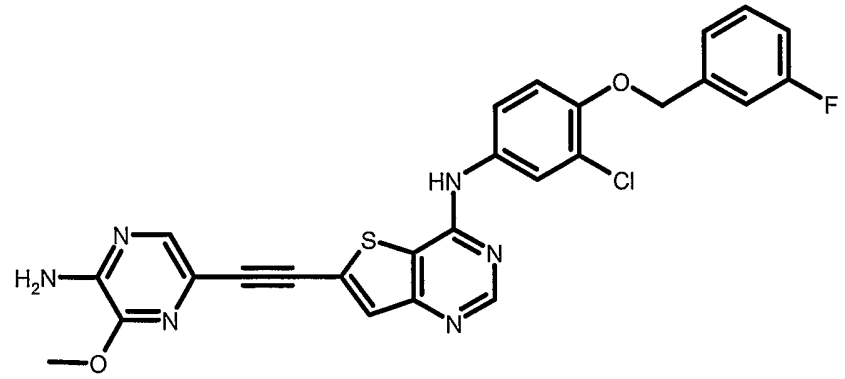
Step C - 6-[(2-Amino-1,3-thiazol-4-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[3,2-d]pyrimidin-4-amine



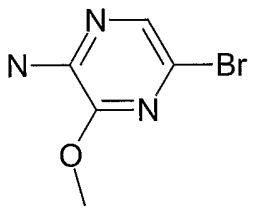
To a mixture of 6-bromo-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (0.111 g, 0.205 mmol), $(Ph_3P)_2PdCl_2$ (0.0143 g, 0.0205 mmol), CuI (0.0039 g, 0.0205 mmol) and Et_3N (0.052 g, 0.512 mmol) in THF (1 mL) added a solution of the acetlyene (0.060 g, 0.27 mmol) in THF (2x1mL) at RT. The reaction was warmed to 60 °C and stirred at 60 °C for 24 hr. The reaction was cooled to RT, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and reduced in vacuo to afford an orange solid that was dissolved into CH_2Cl_2 (5 mL), cooled and treated with a total of 1 mL of TFA. After stirring at RT for 6 h, the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, reduced in vacuo onto silica, and purified silica gel chromatography (hexanes:EtOAc) to afford a yellow solid; 25 mg, 19% over two steps. LRMS (ES, m/z) 508 $(m)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 9.78 (s, 1H); 8.59 (s, 1H); 7.93 (d, 1H); 7.70 (d, 1H); 7.62 (dd, 1H); 7.46 (m, 1H); 7.34-7.19 (m, 6H); 5.26 (s, 2H).

Example 54

6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-d]pyrimidin-4-amine

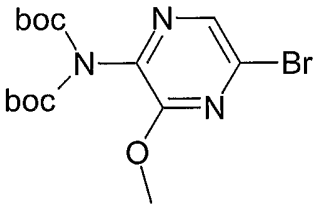


Step A - 5-Bromo-3-methoxypyrazin-2-amine



3,5-Dibromopyrazin-2-amine (1.0g, 3.95 mmol) was treated with 25% sodium methoxide in MeOH (2mL, 8.75 mmol) and heated to reflux for 2 h. The reaction was allowed to cool to room temperature and partitioned between 5:1 $CHCl_3$: MeOH and a saturated aqueous solution of $NaHCO_3$. The mixture was filtered, separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated to give a crude material that was purified by silica gel chromatography (8:2 to 1:1 hexane:ethyl acetate) to obtain the title compound as a white solid (730mg, 91%). ^1H NMR (400 MHz, DMSO) δ 3.85 (s, 3H), 6.50 (broad s, 2H), 7.55 (s, 1H).

*Step B - Di(*tert*-butyl) 5-bromo-3-methoxypyrazin-2-ylimidodicarbonate*



5-Bromo-3-methoxypyrazin-2-amine (400mg, 1.96 mmol) was dissolved in CH_2Cl_2 (8 mL) and treated with di-*tert*-butyldicarbonate (1.07 g, 4.9 mmol) and 4-dimethylaminopyridine (24.4 mg, 0.2mmol) The mixture was stirred at room temperature overnight, concentrated and purified via silica gel chromatography (hexane:ethyl acetate) to yield the title compound as a white solid (680 mg, 86%). ^1H NMR (300 MHz, DMSO) δ 1.39 (s, 18H), 4.03, (s, 1H), 8.40 (s, 1H).

Step C - 6-[(5-amino-6-methoxypyrazin-2-yl)ethynyl]-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine

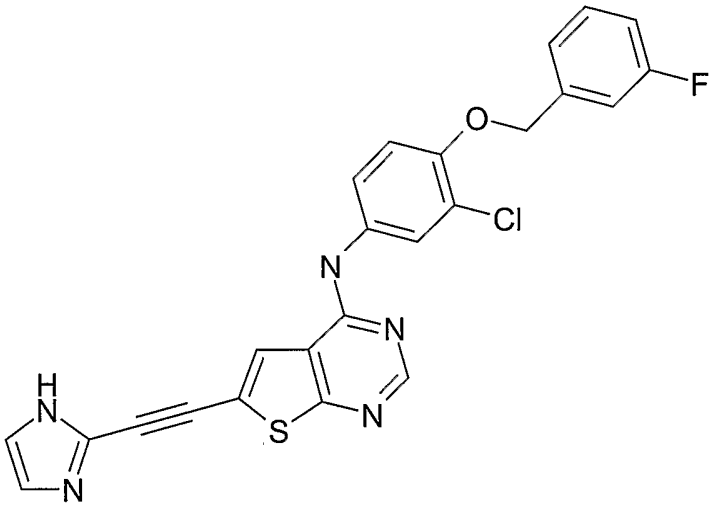
N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-ethynylthieno[3,2-d]pyrimidin-4-amine (170mg, 0.42 mmol) and di(tert-butyl)-5-bromo-3-methoxypyrazin-2-

ylimidodicarbonate (140mg, 0.35 mmol) were combined in an oven dried vial, dissolved in THF (10mL) and treated with triethylamine (154 uL, 1.1mmol). After heating the reaction to 60 °C, Cu(I)I (13 mg, 0.07 mmol) and bis(triphenylphosphine)dichloropalladium (II) (24mg, 0.036 mmol) were added. The reaction was heated at 60°C overnight, allowed to cool to room temperature and partitioned between 5:1 $CHCl_3$:MeOH and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel chromatography (hexane:ethyl acetate with 0.5% triethylamine in each solvent). The intermediate di(*tert*-butyl) 5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-3-methoxypyrazin-2-ylimidodicarbonate was obtained as a yellow solid (150mg, 55%).

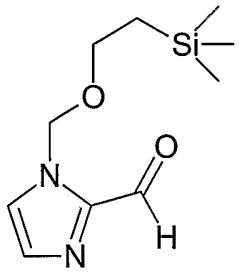
Di(tert-butyl)5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-3-methoxypyrazin-2-ylimidodicarbonate (150 mg, 0.20 mmol) was then dissolved in $CHCl_3$ (5mL) and treated with trifluoroacetic acid (1 mL, 13 mmol). The mixture was stirred at room temperature for 2.25 h and the reaction was complete. The solvent was concentrated and partitioned between 5:1 $CHCl_3$:MeOH and a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by silica gel chromatography (hexane:ethyl acetate) to yield the title compound as a yellow solid (61mg, 57%). ^{1}H NMR (400 MHz, DMSO): δ 3.90 (s, 3H), 5.23 (s, 2H), 7.05 (broad s, 2H), 7.13-7.18 (m, 1H), 7.22-7.31 (m, 3H), 7.41-7.47 (m, 1H), 7.57-7.60 (dd, J=2.5, 8.9 Hz, 1H), 7.67 (s, 1H), 7.86 (s, 1H), 7.89 (d, J=2.6 Hz, 1H), 8.56 (s, 1H), 9.73, (s, 1H). $C_{26}H_{18}ClFN_6O_2S$: MH+ calcd 533.0963, found 533.0961 Δ 0.2 mmu.

Example 55

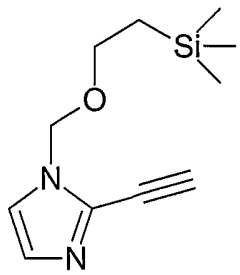
N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-imidazol-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine



Step A-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-carbaldehyde

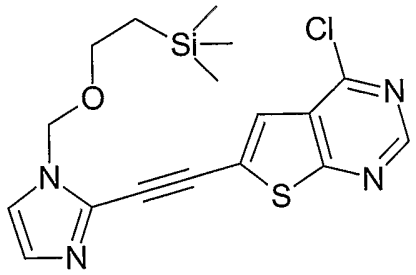


2-Formylimidizole (1.0 g, 10.4 mmol), 2-(trimethylsilyl)ethoxymethyl chloride (2.07 mL, 11.4 mmol), potassium carbonate (2.9 g, 20.8 mmol) and anhydrous DMF (50 mL) were stirred at room temperature for 3 h. The reaction was partitioned between ethyl acetate and water and the organic layer was washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified by silica gel column chromatography (20-80% ethyl acetate/hexanes). Purification yielded a clear oil (1.3 g, 67%). R_f = 0.3 (2:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.91 (m, 2H), 3.55 (m, 2H), 5.77 (s, 2H), 7.32 (s, 1H), 7.35 (s, 1H), 9.83 (s, 1H).



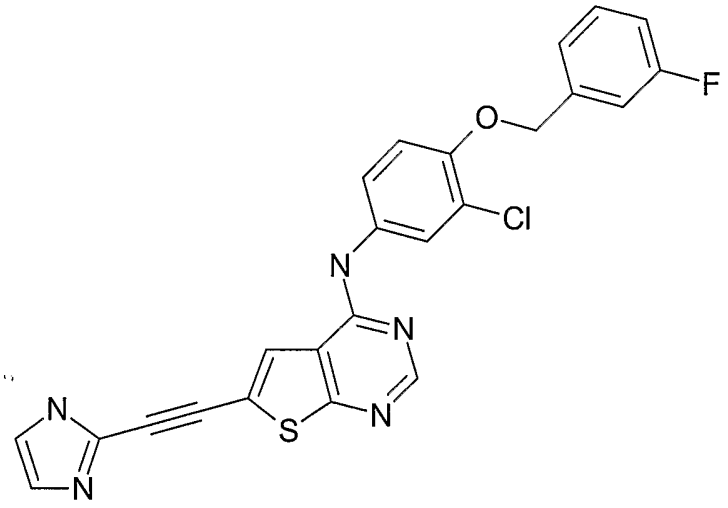
Step B- 2-ethynyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole

Dimethyl 1-diazo-2-oxopropylphosphonate (880 uL, 5.8 mmol) was injected into a suspension of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole-2-carbaldehyde (1.0 g, 4.4 mmol), potassium carbonate (1.22 g, 8.8 mmol) and methanol (50 mL). The reaction was stirred under nitrogen at room temperature for 15 h. The solvent was removed under vacuum and the resulting material was combined with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The resulting crude oil was purified by silica gel column chromatography (20 – 80% ethyl acetate/hexanes). Purification provided the product as a clear oil (660 mg, 67%). R_f = 0.3 (2:1 Hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 9H), 0.09 (t, 2H), 3.31 (s, 1H), 3.52 (t, 2H), 5.38 (s, 2H), 7.06 (s, 1H), 7.08 (s, 1H).



Step C-4-chloro-6-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)ethynyl]thieno[2,3-d]pyrimidine

2-Ethynyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole and 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine were coupled under conditions reported for example 24 (step A). R_f = 0.9 (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.06 (s, 1H), 7.60 (s, 1H), 7.16 (s, 1H), 5.51 (s, 2H), 3.57 (t, 2H), 0.87 (t, 2H), -0.08 (s, 9H). MS (ESI): M+H=391.

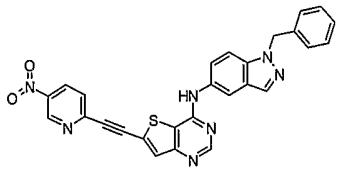


Step D- N-*{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-imidazol-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine*

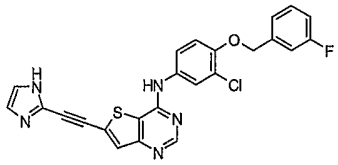
4-Chloro-6-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)ethynyl]thieno[2,3-*d*]pyrimidine and 3-chloro-4-[(3-fluorobenzyl)oxy]aniline were coupled following the protocol described for example 17 (step B) to give the SEM-protected imidazole intermediate, ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 9H), 0.92 (t, 2H), 3.57 (t, 2H), 5.16 (s, 2H), 5.42 (s, 2H), 6.97 (m, 1H), 7.02 (m, 1H), 7.15 (s, 2H), 7.22 (m, 2H), 7.35 (m, 2H), 7.44 (m, 2H), 7.74 (s, 1H), 8.59 (s, 1H). MS (ESI): M+H=606. The SEM protecting group was removed from the *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)ethynyl]thieno[2,3-*d*]pyrimidin-4-amine intermediate (160 mg, 0.26 mmol) by stirring with a solution of trifluoroacetic acid (2.0 mL) and dichloromethane (2.0 mL) at room temperature for 6 h. The reaction was diluted with 50 mL CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ was added until the pH of the aqueous layer was greater than 7.0. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined. The organics were washed with brine and dried over $MgSO_4$ and concentrated under vacuum. The crude yellow solid was purified by silica gel chromatography (50 –100% ethyl acetate/hexanes). Purification yielded the title compound, a gold-colored powder (35 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.26 (s, 2H), 7.22-7.05 (m, 2H), 7.40-7.23 (m, 4H), 7.47 (m, 1H), 7.62 (m, 1H), 7.80 (s, 1H), 7.93 (m, 1H), 8.61 (s, 1H), 9.83 (s, 1H), 13.15 (s, 1H). MS (ESI): M+H=476.

Additional compounds of formula (I), (I') and (I") were prepared according to the procedures described above in Examples 1 to 55 and were characterized as being the following:

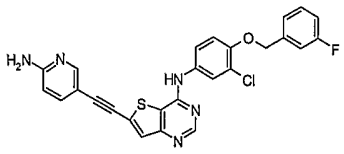
Example 56
6-[(5-nitro-2-pyridinyl)ethynyl]-*N*-[1-(phenylmethyl)-1*H*-indazol-5-yl]thieno[3,2-*d*]pyrimidin-4-amine



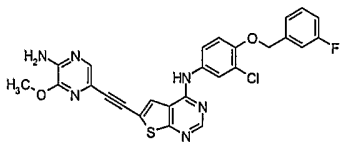
Example 57
N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-(1*H*-imidazol-2-ylethynyl)thieno[3,2-*d*]pyrimidin-4-amine



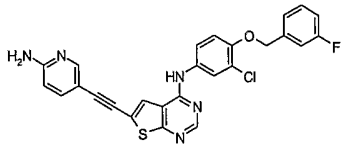
Example 58
6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-*d*]pyrimidin-4-amine



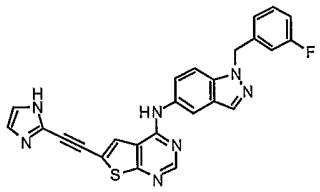
Example 59
6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;



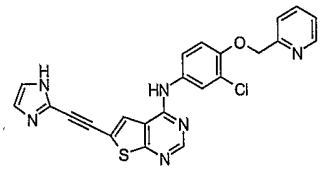
Example 60
6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;



Example 61
N-{1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine, and;



Example 62
N-{3-chloro-4-[(2-pyridinylmethyl)oxy]phenyl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine.



6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[3-({[2-(methylsulfonyl)ethyl]amino}methyl)phenyl]thieno[2,3-*d*]pyrimidin-4-amine trifluoroacetate

N-(1-benzyl-1*H*-indazol-5-yl)-6-[3-({[2-(methylsulfonyl)ethyl]amino}methyl)phenyl]thieno[2,3-*d*]pyrimidin-4-amine trifluoroacetate

formic acid - 6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1*H*-indol-5-yl)thieno[3,2-*d*]pyrimidin-4-amine (1:1)

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[2,3-*d*]pyrimidin-4-amine hydrochloride

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[1-(2-thienylsulfonyl)-1*H*-indol-5-yl]thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-(1-benzyl-1*H*-indazol-5-yl)thieno[3,2-*d*]pyrimidin-4-amine

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-(1-benzyl-1*H*-indazol-5-yl)thieno[3,2-*d*]pyrimidin-4-amine

6-[(5-aminopyridin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-*d*]pyrimidin-4-amine

6-[(5-aminopyridin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-*d*]pyrimidin-4-amine

Biological Data:

Compounds of the present invention were tested for ErbB family protein tyrosine kinase inhibitory activity in substrate phosphorylation assays and cell proliferation assays.

Enzyme Assays:

Compounds of the present invention were tested for EGFR, ErbB-2, and ErbB-4 protein tyrosine kinase inhibitory activity in substrate phosphorylation assays using enzymes purified from a baculovirus expression system. Reagent production was conducted essentially as described (Brignola, P.S., et al, (2002) J. Biol. Chem. v. 277 2, 1576-1585).

The method measures the ability of the isolated enzyme to catalyse the transfer of the γ-phosphate from ATP onto the tyrosine residue of a biotinylated synthetic peptide (biotin-Ahx-RAHEEIYHFFFAKKK-amide). The extent of tyrosine phosphorylation was measured using an anti-phosphotyrosine antibody, and quantified by homogenous time-resolved fluorescence (HTRF).

The enzymes were first diluted from their concentrated stock solutions into buffer containing 100 mM MOPS (pH7.5); 0.01% Tween-20; 0.1 mg/mL bovine serum albumin (BSA); and 80 nM EGFR, 100 nM ErbB2, or 100nM ErbB4. The enzymes were incubated in this buffer for 30 minutes at room temperature before addition to the assay plates. Reactions were performed in black 384-well polystyrene flat-bottom plates in a final volume of 20 μL. Reaction mixtures contained 100 mM MOPS (pH 7.5), 2 mM $MnCl_2$, 20 μM ATP, 0.01% Tween-20, 0.1 mg/mL (BSA), 0.8 μM peptide substrate, and 1mM dithiothreitol. Reactions were initiated by adding enzyme. 0.4 nM EGRF, 5 nM ErbB2, and 0.5 nM ErbB4 were the final enzyme concentrations.

Reactions were allowed to proceed for 90 minutes and were then terminated by the addition of 20 μL 100 mM EDTA to each well. 40 μL /well of HTRF mix were then added to the assay plates for the detection of phosphorylated substrate. Final assay concentrations were: 100mM HEPES (pH7.5), 0.1 mg/mL BSA, 15nM streptavidin-labeled allophycocyanin (PerkinElmer), and 1nM europium-labeled anti-phosphotyrosine antibody (PerkinElmer). Assay plates were left unsealed and were counted in a Wallac Multilabel Counter 1420 (PerkinElmer).

Compounds under analysis were dissolved in Me_2SO to 1.0 mM and serially diluted 1 to 3 with Me_2SO through twelve dilutions. 1 μL of each concentration was transferred to the corresponding well of an assay plate. This creates a final compound concentration range from 0.00027 to 47.6 μM.

The data for dose responses were plotted as % Inhibition calculated with the data reduction formula 100*(1-(U1-C2)/(C1-C2)) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for 4.76% DMSO, and C2 is the average control value obtained for 0.035 M EDTA. Data were fitted with a curve described by:

$$y = ((Vmax * x) / (K + x)) + Y2$$

where Vmax is the upper asymptote, Y2 is the Y intercept, and K is the IC50. The results for reach compound were recorded as pIC50s, calculated as follows:

$$pIC50 = -Log10(K)$$

All exemplified Examples 1-62 were run with the recited assay and showed inhibitory activity versus erbB family kinases with a pIC_{50} of 5.5 or greater.

Cellular assays: Methylene Blue Growth Inhibition Assay

Human breast (BT474), head and neck (HN5) and gastric tumor (N87) cell lines and human foreskin Fibroblasts (HFF) were cultured in low glucose DMEM (Life Technologies 12320-032) containing 10% fetal bovine serum (FBS) at 37oC in a humidified 10% CO2, 90% air incubator. The SV40 transformed human mammary epithelial cell line HB4a was transfected with either human H-ras cDNA (HB4a r4.2) or the human c-ErbB2 cDNA (HB4a c5.2). The HB4a clones were cultured in RPMI

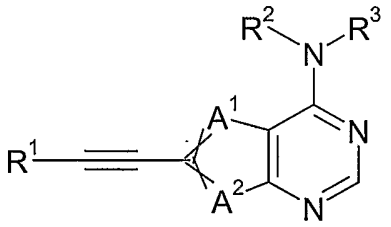
containing 10% FBS, insulin (5 μg/ml), hydrocortisone (5 μg/ml), supplemented with the selection agent hygromycin B (50μg/ml). Cells were harvested using trypsin/EDTA, counted using a haemocytometer, and plated in 100 ml of the appropriate media, at the following densities, in a 96-well tissue culture plate (Falcon 3075): BT474 10,000 cells/well, HN5 3,000 cells/well, N87 10,000 cells/well, HB4a c5.2 3,000 cells/well, HB4a r4.2 3,000 cells/well, HFF 2500 cells/well. The next day, compounds were diluted in DMEM containing 100 mg/ml gentamicin, at twice the final required concentration, from 10mM stock solutions in DMSO. 100ml/well of these dilutions were added to the 100ml of media currently on the cell plates. Medium containing 0.6% DMSO was added to control wells. Compounds diluted in DMEM were added to all cell lines, including the HB4a r4.2 and HB4a c5.2 cell lines. The final concentration of DMSO in all wells was 0.3%. Cells were incubated at 37 °C, 10% CO2 for 3 days. Medium was removed by aspiration. Cell biomass was estimated by staining cells with 100μl per well methylene blue (Sigma M9140, 0.5% in 50:50 ethanol:water), and incubation at room temperature for at least 30 minutes. Stain was removed, and the plates rinsed under a gentle stream of water, and air-dried. To release stain from the cells 100μl of solubilization solution was added (1% N-lauroyl sarcosine, Sodium salt, Sigma L5125, in PBS), and plates were shaken gently for about 30 minutes. Optical density at 620 nM was measured on a microplate reader. Percent inhibition of cell growth was calculated relative to vehicle treated control wells. Concentration of compound that inhibits 50% of cell growth (IC_{50}) was interpolated using nonlinear regression (Levenberg-Marquardt) and the equation, y = Vmax*(1-(x/(K+x))) + Y2, where "K" was equal to the IC_{50}.

All exemplified Examples 1-62 were run with the recited assay and showed inhibitory activity versus tumor cell lines with a pIC_{50} of 5.5 or greater.

CLAIMS

We claim:

1. A compound of Formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

one of A^1 and A^2 is S and the other is CH, where ⟋ indicates a single or double bond;

R^1 is the group defined by -(Z)-$(Z^1)_m$-$(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, -$(CH_2)_qS(O)_2R''$, C_1-C_3 alkyl, -$(CH_2)_qOR''$, -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

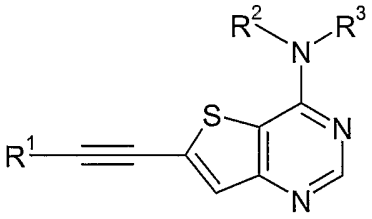
R^3 is the group defined by -(Q)-$(Q^1)_r$-(Q^2), wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

Q^2 is aralkyl, heteroaryl, or aryl.

2. A compound of Formula (I'):



(I')

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

R^1 is the group defined by $-(Z)-(Z^1)_m-(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, $-(CH_2)_qS(O)_2R''$, C_1-C_3 alkyl, $-(CH_2)_qOR''$, -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

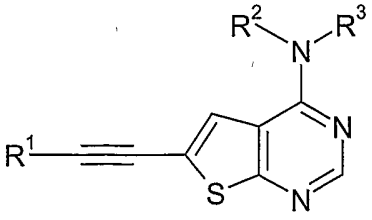
R^3 is the group defined by $-(Q)-(Q^1)_r-(Q^2)$, wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

Q^2 is aralkyl, heteroaryl, or aryl.

3. A compound of Formula (I''):



(I'')

or a salt, solvate, or physiologically functional derivative thereof:

wherein:

R^1 is the group defined by -(Z)-$(Z^1)_m$-$(Z^2)_n$, wherein

Z is heteroaryl, heteroarylene, or arylene,

Z^1 is $C(H)_2$, where m is 0 or 1,

Z^2 is –C(O)H, -N(H)R', or heterocyclyl, where n is 0 or 1;

R' is –H, -$(CH_2)_qS(O)_2R''$, C_1-C_3 alkyl, -$(CH_2)_qOR''$, -C(O)R''', or C(O)OR''';

q is 0, 1, 2, 3, or 4;

R'' is C_1-C_3 alkyl;

R''' is C_1-C_3 alkyl or N(H)R'';

R^2 is –H or C_1-C_3 alkyl;

R^3 is the group defined by -(Q)-$(Q^1)_r$-(Q^2), wherein

Q is arylene or heteroarylene

Q^1 is O, $S(O)_2$, or S, where r is 0 or 1, and

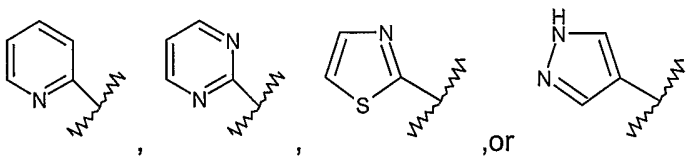
Q^2 is aralkyl, heteroaryl, or aryl.

4. A compound as claimed in claim 1, wherein A^1 is S and A^2 is CH.

5. A compound as claimed in claim 1, wherein A^1 is CH and A^2 is S.

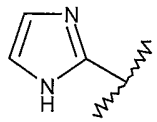
6. A compound as claimed in claim 1, wherein Z is heteroaryl and m and n are each 0.

7. A compound as claimed in claim 1, wherein Z is heteroaryl and m is 0 and n is 0, said heteroaryl group being selected from



, , ,or .

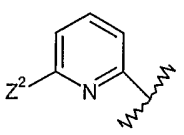
8. A compound as claimed in claim 1, wherein Z is heteroaryl and m is 0 and n is 0, where the heteroaryl group is



.

9. A compound as claimed in claim 1, wherein Z is heteroarylene, m is 0, n is 1, and Z^2 is –C(O)H, or -N(H)R'.

10. A compound as claimed in claim 1, wherein Z is heteroarylene selected from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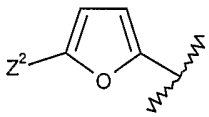
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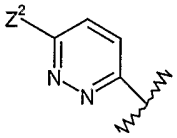
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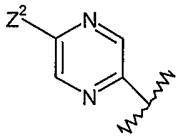
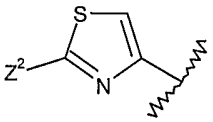
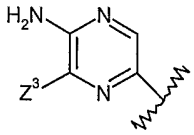

, or

,

where Z^2 is –C(O)H or -N(H)R' where R' is -H.

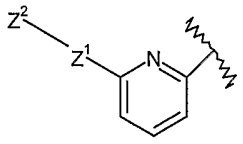
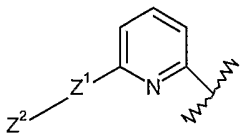
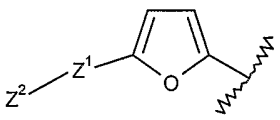
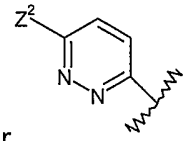
11. A compound as claimed in claim 1, wherein Z is


,

where Z^3 is $–OCH_3$ or -N(H)R' where R' is -H.

12. A compound as claimed in claim 1, wherein Z is heteroarylene, Z^1 is $C(H)_2$, m is 1, n is 1 and Z^2 is –C(O)H, or -N(H)R'.

13. A compound as claimed in claim 1, wherein Z is heteroarylene selected from

or ,

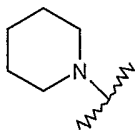
where Z^1 is $C(H)_2$ and

Z^2 is -N(H)R' where q is 2 and R' is $-(CH_2)_qS(O)_2CH_3$, or

Z^2 is -N(H)R' where q is 2 and R' is $-(CH_2)_qOCH_3$, or

Z^2 is -N(H)R' where R' is C_1-C_3 alkyl, or

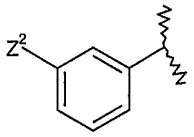
Z^2 is heterocyclyl selected from



.

14. A compound as claimed in claim 1, wherein Z is arylene, m is 0, n is 1, and Z^2 is –C(O)H or -N(H)R'.

15. A compound as claimed in claim 1, wherein Z is



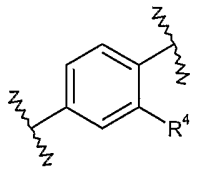
.

16. A compound as claimed in claim 1, wherein R^2 is –H.

17. A compound as claimed in claim 1, wherein R^2 is C_1-C_3 alkyl.

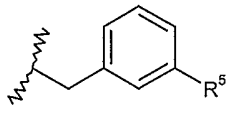
18. A compound as claimed in claim 1, wherein Q is arylene, Q^1 is O and r is 1, and Q^2 is aralkyl, aryl, or heteroaryl.

19. A compound as claimed in claim 1, wherein Q is



,

wherein R^4 is halo, preferably –Cl or -F, Q^1 is O and r is 1, and Q^2 is selected from



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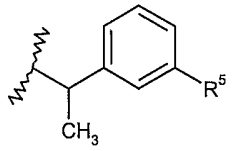

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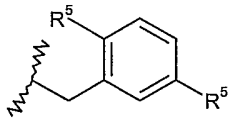

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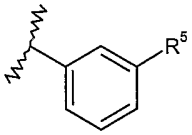

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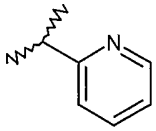

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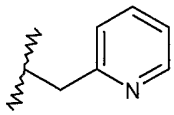

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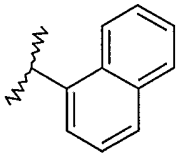


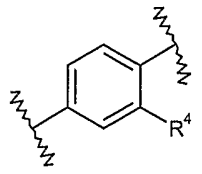
or ,

wherein each R^5 is independently a halo.

20. A compound as claimed in claim 19, wherein each R^5 is independently selected from –F, -Cl, or -Br.

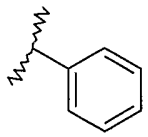
21. A compound as claimed in claim 1, wherein Q is arylene, Q^1 is S and r is 1, and Q^2 is aryl.

22. A compound as claimed in claim 1, wherein Q is



,

wherein R^4 is halo, Q^1 is S and r is 1, Q^2 is

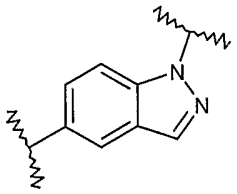


.

23. A compound as claimed in claim 22, wherein R^4 is –Cl or –F.

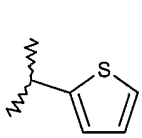
24. A compound as claimed in claim 1, wherein Q is arylene, Q^1 is $S(O)_2$ and r is 1, and Q^2 is aryl or heteroaryl.

25. A compound as claimed in claim 1, wherein Q is

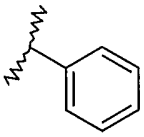


,

Q^1 is $S(O)_2$ and r is 1, and Q^2 is selected from



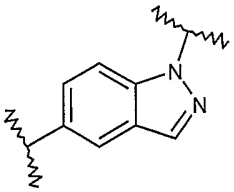
or



.

26. A compound as claimed in claim 1, wherein Q is arylene, r is 0, and Q^2 is aralkyl.

27. A compound as claimed in claim 1, wherein Q is selected from



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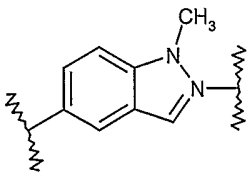
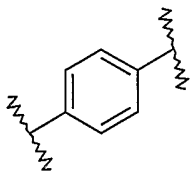
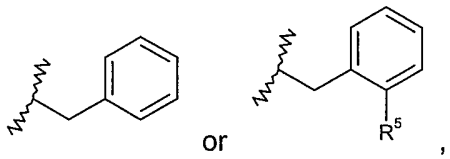


, or



,

r is 0, and Q^2 is selected from



where R^5 is halo.

28. A compound as claimed in claim 27, wherein R^5 is –F.

29. A compound as claimed in claim 1 selected from the group:

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyridin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(pyrimidin-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1,3-thiazol-2-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde;

6-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyridine-2-carbaldehyde;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-({[2-(methylsulfonyl)ethyl]amino}methyl)pyridin-2-yl]ethynyl}thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-{[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethynyl}thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({6-[(methylamino)methyl]pyridin-2-yl}ethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-({5-[(methylamino)methyl]-2-furyl}ethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[(5-{[(2-methoxyethyl)amino]methyl}-2-furyl)ethynyl]thieno[2,3-d]pyrimidin-4-amine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}-2-furaldehyde;

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(6-aminopyridazin-3-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-(1-benzyl-1H-indazol-5-yl)thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-N-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[3,2-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-yloxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(3-fluorophenoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[4-(phenylsulfonyl)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-{3-fluoro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(4-benzylphenyl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[1-(thien-2-ylsulfonyl)-1H-indol-5-yl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(phenylthio)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indol-5-yl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-(1-benzyl-1H-indazol-5-yl)thieno[2,3-d]pyrimidin-4-amine;

6-[(5-aminopyrazin-2-yl)ethynyl]-*N*-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]thieno[2,3-d]pyrimidin-4-amine;

6-[(6-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[2,3-d]pyrimidin-4-amine;

6-[(6-aminopyrazin-2-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine;

5-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[2,3-d]pyrimidin-6-yl]ethynyl}pyrazine-2,3-diamine;

N-(3-{[4-({3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}amino)thieno[3,2-d]pyrimidin-6-yl]ethynyl}phenyl)acetamide;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[2,3-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(1-benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(2,5-difluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-chloro-4-[(3-chlorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-[3-chloro-4-(1-naphthyloxy)phenyl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-{3-bromo-4-[(3-fluorobenzyl)oxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(2-benzyl-1-methyl-1H-benzimidazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-(1-benzyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

N-[1-(2-fluorobenzyl)-1H-indazol-5-yl]-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

(R,S)-*N*-{3-chloro-4-[1-(3-fluorophenyl)ethoxy]phenyl}-6-(1H-pyrazol-4-ylethynyl)thieno[3,2-d]pyrimidin-4-amine;

6-[(2-aminopyrimidin-5-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine;

N-[3-({4-[(1-benzyl-1H-indazol-5-yl)amino]thieno[3,2-d]pyrimidin-6-yl}ethynyl)phenyl] acetamide; and

6-[(2-amino-1,3-thiazol-4-yl)ethynyl]-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy] phenyl}thieno[3,2-d]pyrimidin-4-amine;

or a salt, solvate, or physiologically functional derivative thereof.

30. A compound as claimed in claim 1 selected from the group:

6-[(5-nitro-2-pyridinyl)ethynyl]-*N*-[1-(phenylmethyl)-1*H*-indazol-5-yl]thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-(1*H*-imidazol-2-ylethynyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-{[5-amino-6-(methyloxy)-2-pyrazinyl]ethynyl}-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine;

6-[(6-amino-3-pyridinyl)ethynyl]-*N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-{1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine; and

N-{3-chloro-4-[(2-pyridinylmethyl)oxy]phenyl}-6-(1*H*-imidazol-2-ylethynyl)thieno[2,3-*d*]pyrimidin-4-amine;

or a salt, solvate, or physiologically functional derivative thereof.

31. A pharmaceutical composition, comprising: a therapeutically effective amount of a compound as claimed in any one of claims 1 to 30, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

32. A method of treating a disorder in a mammal, said disorder being mediated by inappropriate activity of at least one erbB family kinase, comprising: administering to said mammal a therapeutically effective amount of a compound as claimed in any one of claims 1 to 30, or a salt, solvate or a physiologically functional derivative thereof.

33. A method of treating a disorder in a mammal, said disorder being mediated by inappropriate activity of at least two erbB family kinases, comprising: administering to said mammal a therapeutically effective amount of a compound as claimed in any one of claims 1 to 31, or a salt, solvate or a physiologically functional derivative thereof.

34. A compound as claimed in any one of claims 1 to 30, or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

35. Use of a compound as claimed in any one of claims 1 to 30, or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate activity of at least one erbB family kinase.

36. Use of a compound as claimed in any one of claims 1 to 30, or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate activity of at least two erbB family kinases.