FUSED HETEROCYCLIC KINASE INHIBITORS

RELATED APPLICATIONS

This application claims priority benefit under Title 35 § 119(e) of United States Provisional Application Nos. 60/583,459, filed June 28, 2004, and 60/612,563, filed September 23, 2004, the contents of which are herein incorporated by reference.

FIELD OF INVENTION

This invention relates to compounds that inhibit the protein tyrosine kinase activity of growth factor receptors such as c-Met, thereby making them useful as anti-cancer agents. The pharmaceutical compositions that comprise these compounds are also useful in the treatment of diseases, other than cancer, which are associated with signal transduction pathways operating through growth factor and anti-angiogenesis receptors such as c-Met.

BACKGROUND

Hepatocyte growth factor (HGF), also known as scatter factor (SF), because of its ability to disrupt colony formation *in vitro*, is a mesenchymally derived cytokine known to induce multiple pleiotropic responses in normal and neoplastic cells (Sonnenberg et al., *J. Cell Biol.* 123:223-235, 1993; Matsumato et al., *Crit. Rev. Oncog.* 3:27-54,1992; and Stoker et al., *Nature* 327:239-242, 1987). These responses are known to include proliferation in both epithelial and endothelial cells, dissociation of epithelial colonies into individual cells, stimulation of motility (motogenesis) of epithelial cells, cell survival, induction of cellular morphogenesis (Montesano et al., *Cell* 67:901-908, 1991), and promotion of invasion (Stella et al., *Int. J. Biochem. Cell Biol.* 12:1357-62, 1999 and Stuart et al., *Int. J. Exp. Path.* 81:17-30, 2000), all critical processes underlying metastasis. HGF has also been reported to promote angiogenesis (Bussolino et al., *J. Cell Biol.* 119:629-641, 1992). In addition, HGF plays a critical role in tissue regeneration, wound healing, and normal embryonic processes, all of which are dependent on both cell motility and proliferation.

HGF initiates these physiological processes through high affinity binding to its cognate receptor, the Met protein tyrosine kinase receptor, an identified

protooncogene (Park et al., *Proc. Natl. Acad. Sci. USA* 84:6379-83, 1987 and Bottaro et al., *Science* 251:802-4, 1991). The mature form of Met consists of a highly glycosylated external α-subunit as well as a β-subunit with a large extracellular domain, a transmembrane segment and a cytoplasmic tyrosine kinase domain. Ligand engagement induces Met dimerization that results in an autophosphorylated activated receptor. Activation of Met promotes signal transduction cascades as defined by transphosphorylation of key cytoplasmic tyrosine residues responsible for recruiting multiple effector proteins (Furge et al., *Oncogene* 19:5582-9, 2000). These include the p85 subunit of the PI3-kinase, phospholipase Cγ (Gaul et al., *Oncogene* 19:1509-18, 2000), Grb2 and Shc adaptor proteins, the protein phosphatase SHP2 and Gab1. The latter adapter has emerged as the major downstream docking molecule that becomes tyrosine phosphorylated in response to ligand occupancy (Schaeper et al., *J. Cell Biol.* 149:1419-32, 2000; Bardelli, et al., *Oncogene* 18:1139-46, 1999 and Sachs et al., *J. Cell Biol.* 150:1375-84, 2000). Activation of other signaling molecules has been reported in HGF stimulated cells, most notably Ras, MAP kinases, STATs, ERK-1, -2 and FAK (Tanimura et al., *Oncogene* 17:57-65,1998; Lai et al., *J. Biol. Chem.* 275:7474-80 2000 and Furge et al., *Oncogene* 19:5582-9, 2000). The role of many of these signaling molecules has been well established in cell proliferation.

Met, also referred to as hepatocyte growth factor receptor (HGFR), is expressed predominantly in epithelial cells but has also been identified in endothelial cells, myoblasts, hematopoietic cells and motor neurons. Overexpression of HGF and activation of Met has been associated with the onset and progression in a number of different tumor types as well as in the promotion of metastatic disease. Initial evidence linking Met to cancer has been supported by the identification of kinase domain missense mutations, which predisposes individuals to papillary renal carcinomas (PRC) and hepatocellular carcinomas (HCC) (Lubensky et al., *Amer. J. Pathology*, 155:517-26, 1999). Mutated forms of Met have also been identified in ovarian cancer, childhood HCC, gastric carcinoma, head and neck squamous cell carcinoma, non-small cell lung carcinoma, colorectal metastasis (Christensen et al., *Cancer Res.*, 63:7345-55, 2003; Lee et al., *Oncogene*, 19:4947-53, 2000 and Direnzo et al., *Clin. Cancer Res.*, 1:147-54, 1995). In addition, further evidence supporting the role of the Met in cancer is based on the overexpression of HGF and Met receptor in

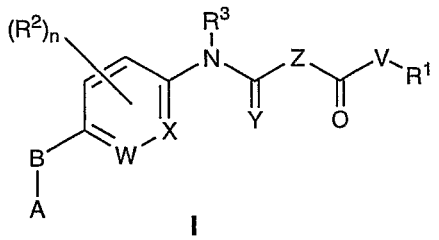
various tumors including thyroid, ovarian and pancreatic carcinomas. It has also been demonstrated to be amplified in liver metastases of colorectal carcinomas (Rong et al. *Cancer Res.* 55:1963-1970, 1995; Rong et al., *Cancer Res.* 53:5355-5360, 1993; Kenworthy et al., *Br. J. Cancer* 66:243-247, 1992 and Scarpino et al. *J. Pathology* 189:570-575, 1999). TPR-Met (an activated form similar to BCR/Abl in CML) has been described and identified in human gastric carcinoma (PNAS **88**:4892-6, 1991). In patients with invasive breast carcinoma and in a recent study in non small cell lung cancer patients, expression of either the receptor or ligand is a predictor of decreased survival, further linking Met to tumor progression (Camp et al., *Cancer* 86:2259-65 1999 and Masuya et al., *Br. J. Cancer,* 90:1555-62, 2004). In general, most human tumors and tumor cell lines of mesenchymal origin inappropriately express HGFR and/or HGF.

Numerous experimental data support the role of HGF and Met in tumor invasion, growth, survival and progression ultimately leading to metastases. Preclinically, transgenic expression of HGF results in a metastatic phenotype (Takayama et al., *PNAS*, 94:701-6, 1997) and an amplified/overexpressed Met spontaneously transforms NIH-3T3 cells (Cooper et al., *EMBO J.*, 5:2623-8, 1986).

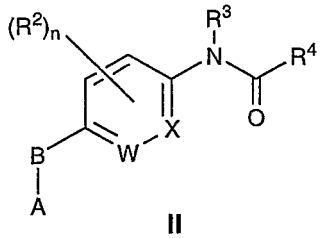
Biological agents, such as ribozymes, antibodies and antisense RNA targeting either HGF or Met have been shown to inhibit tumorogenesis (Stabile et al., *Gene Therapy*, 11:325-35, 2004, Jiang et al., *Clin. Cancer Res*, 9:4274-81, 2003 and Genentech US 6,214,344, 2001). Thus, selective, small molecule kinase modulators targeting Met are expected to have therapeutic potential for the treatment of cancers in which Met receptor activation plays a critical role in the development and progression of primary tumors and secondary metastases. HGF is also known to regulate angiogenesis, a process critical in tumor growth and dissemination. Therefore, there is a potential for this class of modulators to impact angiogenesis-dependent diseases as well that may include among others, diabetic retinopathy, macular degeneration, obesity and inflammatory disease such as rheumatoid arthritis.

SUMMARY

The present invention is directed to compounds having the following Formulas I and II:



I



II

including pharmaceutically acceptable salts, enantiomers, diastereomers, and solvates thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_p-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

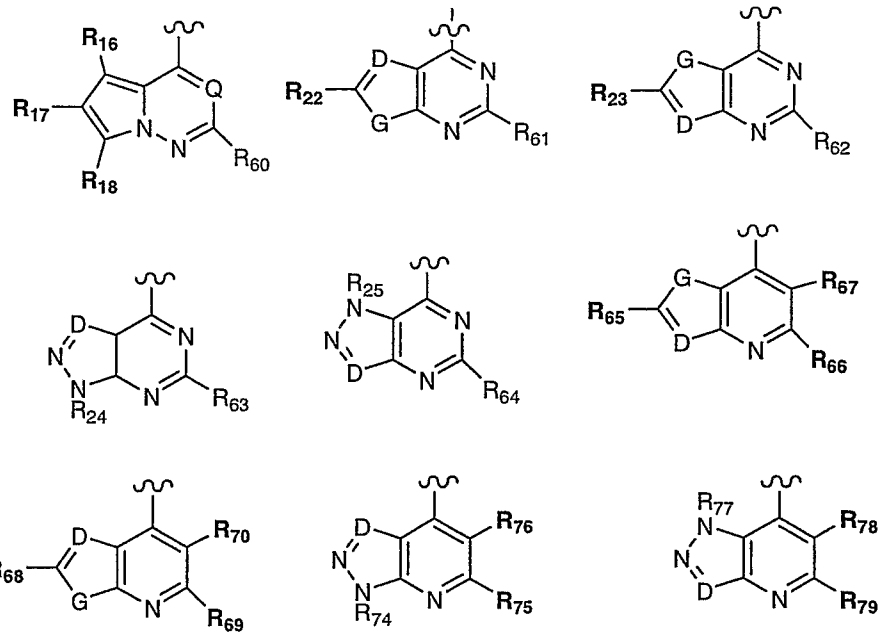
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

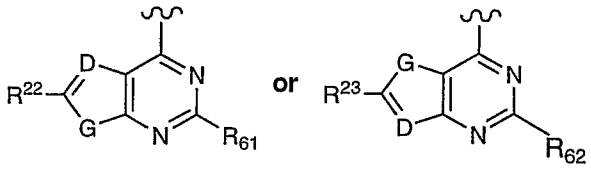
A is:



Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$,

$-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

$R^{21}$and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

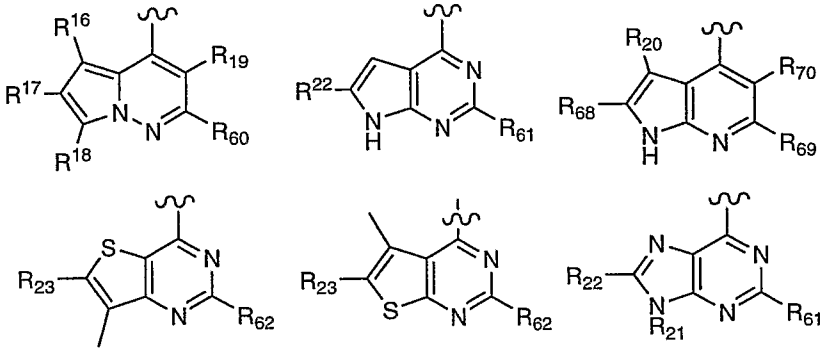
R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

In some embodiments of the present invention, R^1 is an optionally substituted C_{1-6} alkyl, alkenyl, alkynyl, optionally substituted C_{3-7} cycloalkyl, C_{3-7} eterocycloalkyl, optionally substituted phenyl, optionally substituted biphenyl, or a C_5 to C_{11} optionally substituted monocyclic or bicyclic heteroaryl. Preferably, R^1 is phenyl, optionally substituted with at least one of Cl, F, OCH_3, C_{1-4} alkyl, alkenyl, alkynyl, CN, hydroxy, amido, phenoxy, CH_2CN, benzyl, $NHCO_2CH_3$; biphenyl, pyridyl, azepanyl, pyrazolyl, thiazolyl, indolyl, indazolyl, indenyl, cyclopropyl, isopropyl, phenylethyl, aminoalkyl, benzyl, amidoalkyl, morpholine, and furanylmethyl.

In some embodiments of the present invention, R^2 is H, alkoxy, halo, methyl, haloalky or CN.

In some embodiments of the present invention, R^4 is an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted pyrrolidinyl, an optionally substituted pyridyl-N-oxy, or an optionally substituted pyridinone, wherein said substituent is selected, for example, from hydroxyl, halo, C_1 to C_4alkyl, C_3 to C_7 cycloalkyl, CN, alkylthio, alkoxy, phenyl, amino, heterocycloalkyl, aminoalkylamino and alkylaminoalkoxy. In some embodiments of the present invention, the substituent is F, Br, Cl, methyl, pentyl, methoxy, phenyl, morpholinyl, NH_2, or $NHCHNH_2$.

According to some embodiments of the present invention, A is one of the following:



According to one embodiment of the present invention, R^{19} is H or CN and R^{16}, R^{17}, and R^{18} are independently H, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, or $-C(O)_2R^{29}$ wherein R^{29} is C_1 to C_4 alkyl.

According to one embodiment of the present invention, $R^{22}$and R^{61} are H.

According to another embodiment of the present invention, R^{68}, R^{69} and R^{70} are H; R^{20} is C_1 to C_4 alkyl; alkenyl; alkynyl; C_5 to C_6 heterocycloaryl; $-CO(CH_2)_1R^{41}$, wherein R^{41} is C_1 to C_4 alkyl; haloalkyl; amino; alkylamino; C_5 to C_7 heterocycloalkyl; C_5 to C_7 heteroaryl; or $C(O)_2R^{29}$ wherein R^{29} is ethyl; CN; alkoxy; phenylmethyl; alkylaminoalkynyl; alkylaminoalkyl, hydroxyalkyl; or methoxyalkyl.

According to one embodiment of the present invention, Y is O or S.

According to one embodiment of the present invention, B is O.

In some embodiments of the present invention, Z is $-CR^{13}R^{14}$ or NR^{15} wherein R^{13}, R^{14}, and R^{15} are each H or R^{13} and R^{14} together with the carbon to which they are attached form a cyclopropyl.

The present invention is also directed to pharmaceutical compositions comprising therapeutically effective amounts of a compound of Formula I or II, or a salt or solvate thereof, together with a pharmaceutically acceptable carrier.

The present invention also provides methods for the treatment of cancer comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of Formula I or II or a salt or solvate thereof, optionally including administering to the patient at least one additional anticancer agent.

DESCRIPTION

The present invention provides for compounds of Formulas I and II defined above, pharmaceutical compositions employing such compounds, methods of making and methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The term "alkyl" herein alone or as part of another group refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. Preferred alkyl groups have from 1 to 6 carbon atoms. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. Alkyl groups may be substituted at any available point of attachment. An alkyl group substituted with another alkyl group is also referred to as a "branched alkyl group". Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents include but are not limited to one or more of the following groups: alkyl, aryl, halo (such as F, Cl, Br, I), haloalkyl (such as CCl_3 or CF_3), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino ($-NH_2$), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). In some preferred embodiments of the present

invention, alkyl groups are substituted with, for example, amino, heterocycloalkyl, such as morpholine, piperazine, piperidine, azetidine,hydroxyl, methoxy, or heteroaryl groups such as pyrrolidine,

The term "alkenyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond. Alkenyl groups may also be substituted at any available point of attachment. Exemplary substituents for alkenyl groups include those listed above for alkyl groups, and especially include C_3 to C_7 cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl, which may be further substituted with, for example, amino, oxo, hydroxyl, etc.

The term "alkynyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Alkynyl groups may also be substituted at any available point of attachment. Exemplary substituents for alkenyl groups include those listed above for alkyl groups such as amino, alkylamino, etc.

The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C_1 to C_6 alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C_1 to C_6 alkyl" can also refer to C_1 to C_6 alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C_2 to C_6 alkyenyl means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C_2 to C_6 alkenyl" can also refer to C_2 to C_6 alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C_2 to C_6 alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

The terms "alkoxy" or "alkylthio" herein alone or as part of another group denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkoxycarbonyl" herein alone or as part of another group denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: -C(O)OR, where the R group is a straight or branched C_{1-6} alkyl group, cycloalkyl, aryl, or heteroaryl.

The term "alkylcarbonyl" herein alone or as part of another group refers to an alkyl group bonded through a carbonyl group or –C(O)R.

The term "alkylcarbonyloxy" herein alone or as part of another group denotes an alkylcarbonyl group bonded through an oxygen linkage.

The term "arylalkyl" herein alone or as part of another group denotes an aromatic ring bonded through an alkyl group (such as benzyl) as described above.

The term "aryl" herein alone or as part of another group refers to monocyclic or bicyclic aromatic rings, *e.g.* phenyl, substituted phenyl and the like, as well as groups which are fused, *e.g.*, napthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, such as Br, F, or Cl, alkyl, such as methyl, ethyl, propyl, alkoxy, such as methoxy or ethoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, alkenyloxy, trifluoromethyl, amino, cycloalkyl, aryl, heteroaryl, cyano, alkyl $S(O)_m$ (m=O, 1, 2), or thiol.

The term "amino" herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl. carbonyl or carboxyl. These substituents may be further substituted with a carboxylic acid, any of the alkyl or aryl substituents set out herein. In some embodiments, the amino groups are substituted with carboxyl or carbonyl to form *N*-acyl or *N*-carbamoyl derivatives.

The term "cycloalkyl" herein alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Further, a cycloalkyl may be substituted. A substituted cycloalkyl refers to such rings having one, two, or three substituents, selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, oxo (=O), hydroxy, alkoxy, thioalkyl, $-CO_2H$, $-C(=O)H$, CO_2-alkyl, $-C(=O)$alkyl, keto, $=N$-OH, $=N$-O-alkyl, aryl, heteroaryl, heterocyclo, a five or six membered ketal (*i.e.* 1,3-dioxolane or 1,3-dioxane), $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, and $-NR'SO_2R''$, wherein each of R' and R" are independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R" together form a heterocyclo or heteroaryl ring.

The term "heteroaryl" herein alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, nitro, cyano, hydroxy, alkoxy, thioalkyl, $-CO_2H$, $-C(=O)H$, $-CO_2$-alkyl, $-C(=O)$alkyl, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, heteroaryl, $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, and $-NR'SO_2R''$, wherein each of R' and R" is independently selected from hydrogen,

alkyl, substituted alkyl, and cycloalkyl, or R' and R" together form a heterocyclo or heteroaryl ring.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, diazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heterocycloalkyl" herein alone or as part of another group refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms. The term "heterocycloalkyl" herein alone or as part of another group refers to a stable, saturated, or partially unsaturated monocyclic ring system containing 5 to 7 ring members of carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. A heterocyclic ring may be a 5, 6 or 7-membered monocyclic ring and contain one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The heterocyclic ring may be optionally substituted which means that the heterocyclic ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), heterocycloalkyl, heteroaryl, alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino),cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

Examples of such heterocycloalkyl groups include piperazine, piperidine, morpholine, homomorpholine, thiomorpholine, pyrrolidine, and azetidine.

A heteroaryl or heterocycloalkyl group may also be an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. Some preferred bicyclic rings include benzodioxole, quinoxaline, indolyl, and quinolinyl. The term "optionally substituted" as it refers to "heteraryl" or heterocycloalkyl herein indicates that the heterocyclyl group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

The term "heteroatom" means O, S or N, selected on an independent basis. It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

The term "anticancer" agent includes any known agent that is useful for the treatment of cancer including 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex, matrix metalloproteinase inhibitors, VEGF inhibitors, including as anti-VEGF antibodies such as Avastin, and small molecules such as ZD6474 and SU6668, vatalanib, BAY-43-9006, SU11248, CP-547632, and CEP-7055 are also included. Anti- Her2 antibodies from Genentech (such as Herceptin) may also be utilized.

Suitable EGFR inhibitors include gefitinib, erlotinib, and cetuximab. Pan Her inhibitors include canertinib, EKB-569, and GW-572016. Also included are Src inhibitors, dasatinib (BMS-354825) as well as Casodex® (bicalutamide, Astra Zeneca), Tamoxifen, MEK-1 kinase inhibitors, MAPK kinase inhibitors, PI3 inhibitors, and PDGF inhibitors, such as imatinib. Also included are anti-angiogenic and antivascular agents which, by interrupting blood flow to solid tumors, render cancer cells quiescent by depriving them of nutrition. Castration, which also renders androgen dependent carcinomas non-proliferative, may also be utilized. Also included are IGF1R inhibitors, inhibitors of non-receptor and receptor tyrosine kinases, and inhibitors of integrin signaling. Additional anticancer agents include microtubule-stabilizing agents such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthiomethylpaclitaxel (disclosed in U.S. 5,646,176), 4-desacetyl-4-methylcarbonatepaclitaxel, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 09/712,352 filed on November 14, 2000), C-4 methyl carbonate paclitaxel, epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7-11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17 oxabicyclo [14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4-17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione (disclosed in USP 6,262,094) and derivatives thereof; and microtubule-disruptor agents. Also suitable are CDK inhibitors, an antiproliferative cell cycle inhibitor, epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Additional cytotoxic agents include, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, topotecan, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

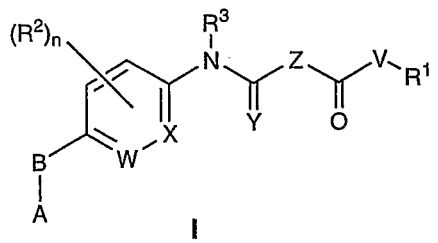
Pyridine-N-oxy refers to a pyridine ring having an oxygen substituted on the N atom of the pyridine ring.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

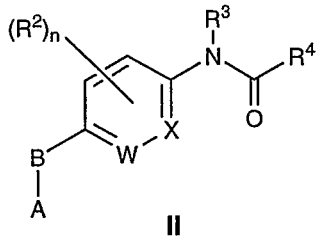
As used herein, the term "patient" encompasses all mammalian species.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formulas I and II. The compounds of formulas I and II that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formulas I and II are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The compounds of the present invention have the following Formula I or II:



I



II

including pharmaceutically acceptable salts thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl,

substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_p-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

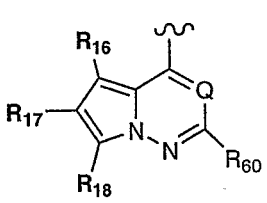
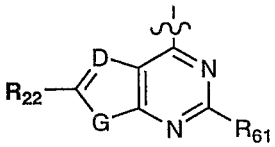
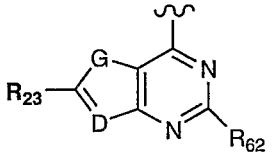
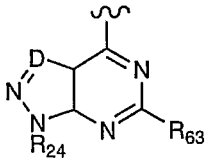
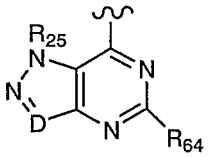
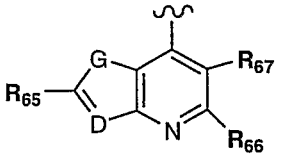
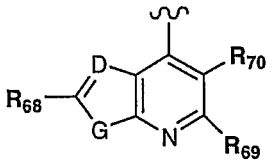
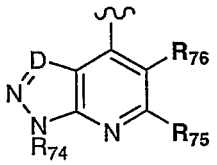
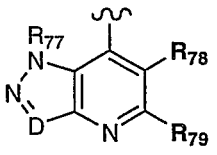
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

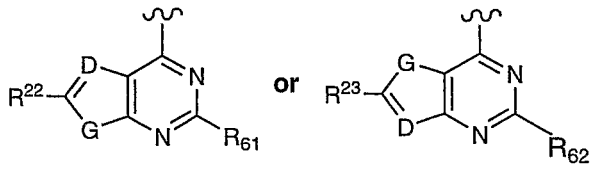
A is:

Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

$R^{21}$and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

The invention also provides a method for treating a proliferative disease, such as cancer, by administering to a patient in need of such treatment an effective amount of a compound of formula I or II, as defined above.

In another embodiment, the invention provides a method for treating a proliferative disease via modulation of Met kinase by administering to a patient in need of such treatment an effective amount of a compound of formula I or II, as defined above, in combination (simultaneously or sequentially) with at least one other anti-cancer agent. In a preferred embodiment, the proliferative disease is cancer.

The invention further provides pharmaceutical compositions comprising compounds having formula I or II together with a pharmaceutically acceptable carrier.

More specifically, the compounds of Formulas I and II are useful in the treatment of a variety of cancers, including, but not limited to, the following:

a) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

b) hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

c) hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

d) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

e) tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

f) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role protein kinases in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formulas I and II as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned herein above), viral infections (including but not limited to herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formulas I and II may modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formulas I and II may be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formulas I and II may also be useful in inhibiting tumor angiogenesis and metastasis.

Some compounds of the present invention have been found to inhibit protein kinases other than Met, such as those in the Trk family of protein kinases.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate, other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2).

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example,

microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening

agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS.TM. model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formulas I and II may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than

intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of Formulas I and II may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formulas I and II may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

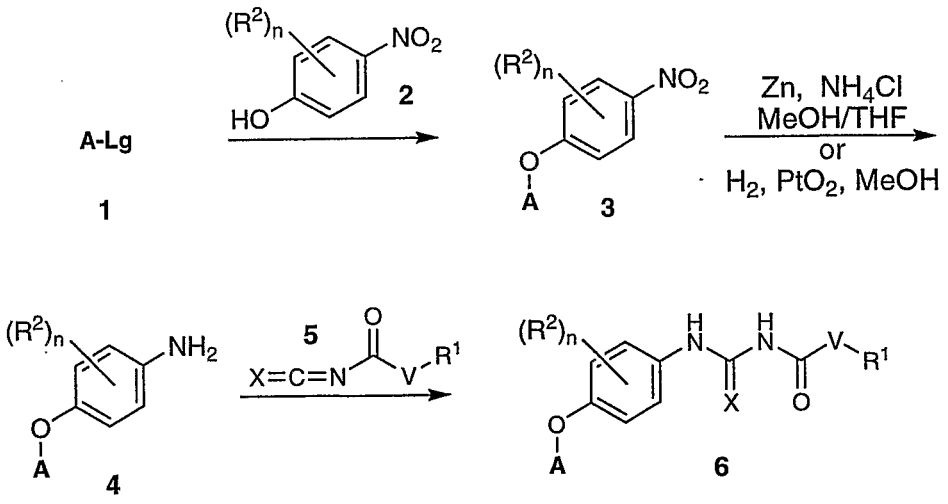
Certain compounds of Formulas I and II may generally be prepared according to the following Schemes 1-16. The compounds are synthesized readily using synthetic methods known to one skilled in the art. Tautomers and solvates (e.g., hydrates) of the compounds of Formulas I and II are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes below.

In general, the desired fused heterocycles can be prepared using the synthetic routes outlined in Schemes 1-3. The leaving group (Lg), such as a halogen (or triflate) of a heterocycle (**A**, whereby open positions may be optionally substituted) **1** can be displaced with a substituted phenol **2** to provide ether **3** (Scheme 1). Groups **A**-Lg can be prepared according to the general procedures outlined in, for example, Hunt, J. T. *et al.* WO 00/071129; Hunt, J. T. *et al. J. Med. Chem.* **2004**, *47*, 4054-4059; Leftheris, K. *et al.* WO 02/040486; Mastalerz, H. *et al.* WO 03/042172; Dyckman, A. *et al.* WO 03/091229; Vite, G. D. *et al.* WO 04/054514; Salvati, M. E. *et al.* WO 03/082208; Thibault, C. *et al. Org. Lett.* **2003**, *5*, 5023-5025; Zhang, Z. *et al. J. Org.*

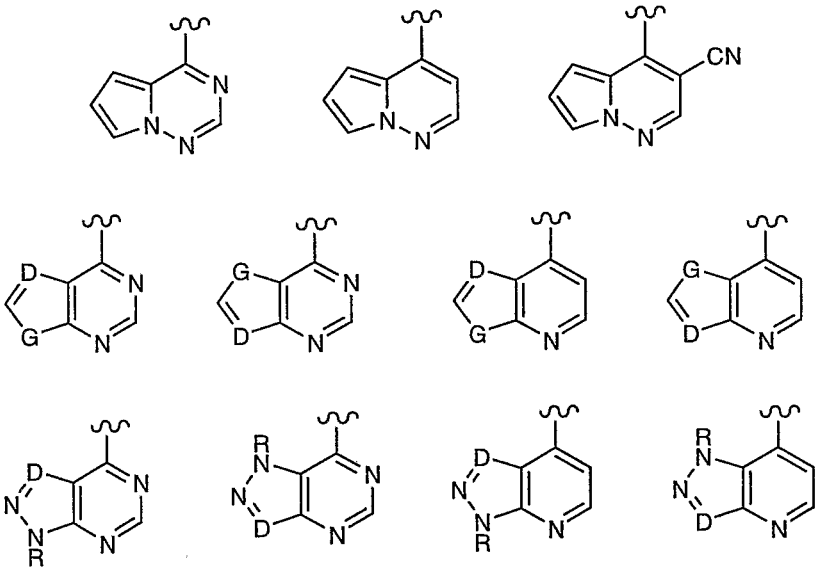
Chem. **2002**, *67*, 2345-2347; Itoh, T. *et al. J. Heterocyclic Chem.* **1982**, *19*, 513-517; Tedder, M. E. *et al. Bioorg. Med. Chem. Lett.* **2004**, *14*, 3165-3168; Dorn, H. *et al. J. Prakt. Chem.* **1982**, *324*, 557; Sanghvi, Y. S. *et al. J. Med. Chem.* **1989**, *32*, 945-951; Temple, C. Jr. *et al. J. Org. Chem.* **1972**, *37*, 3601-3604; Hurst, J. *et al.* EP119774; Hurst, J. *et al.* EP151962; Ward, R. W. *et al.* EP152910; Luzzio, M. J. *et al.* WO 01/094353; Marx, M. A. *et al.* WO 03/000194; Boschelli, D. H. *et al.* WO 04/048386; He, M. *et al.* WO 05/021554; Barker, J. M. *et al. J. Chem. Res., Synopses* **1986**, *4*, 122-123, the disclosures of which are herein incorporated by reference.

Reduction of the nitro group of intermediate **3** with, for example either zinc dust and ammonium chloride or Adam's catalyst (platinum(IV) oxide) under catalytic hydrogenation conditions can furnish the aniline **4**. Treatment of the aniline **4** with an isocyanate **5** (X = O) or isothiocyanate **5** (X = S) affords the desired acylurea or acylthiourea **6**, respectively.

SCHEME 1



A =



Lg = leaving group, such as a halogen

X = O or S

G is O, S, or NR^{21}

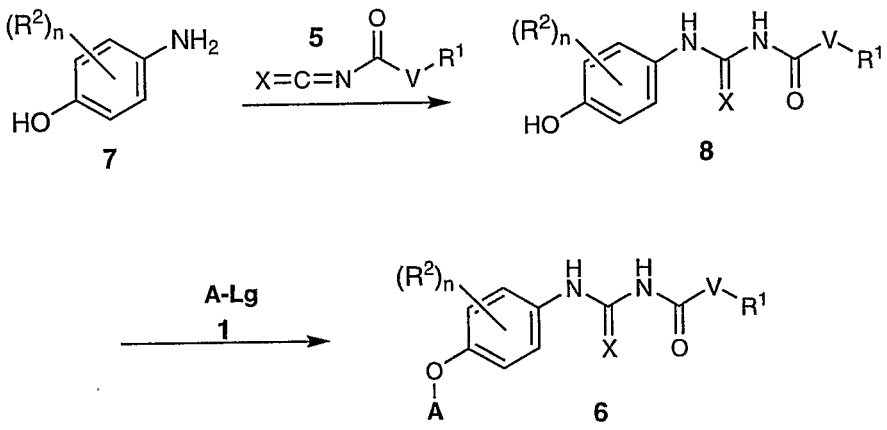
D is CR^{20} or N

V = as defined above

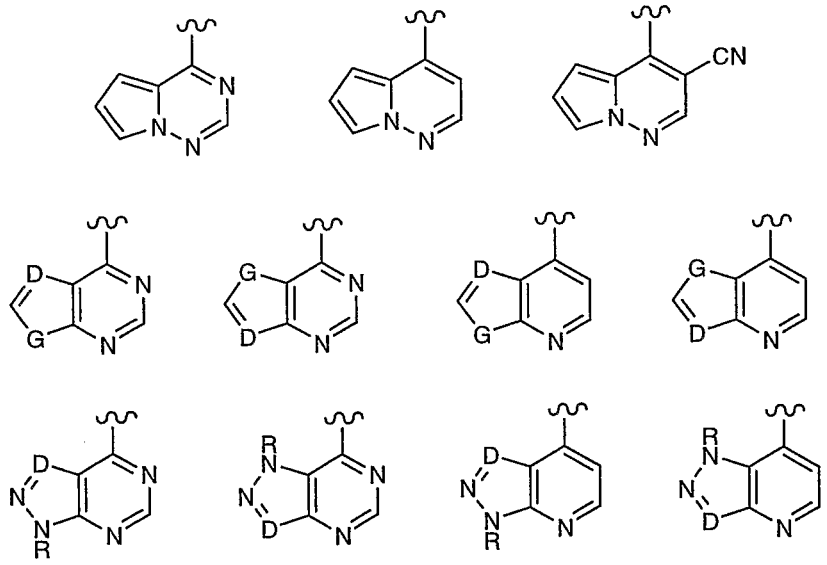
Alternatively, the appropriately substituted aniline **7** can be treated with an isocyanate **5** (X = O) or isothiocyanate **5** (X = S) to give the phenol **8** (Scheme 2).

Reaction of intermediate **8** with a heterocycle (**A-Lg**) **1** can provide the desired compound **6**.

SCHEME 2



A =



Lg = leaving group, such as a halogen

X = O or S

G is O, S, or NR^{21}

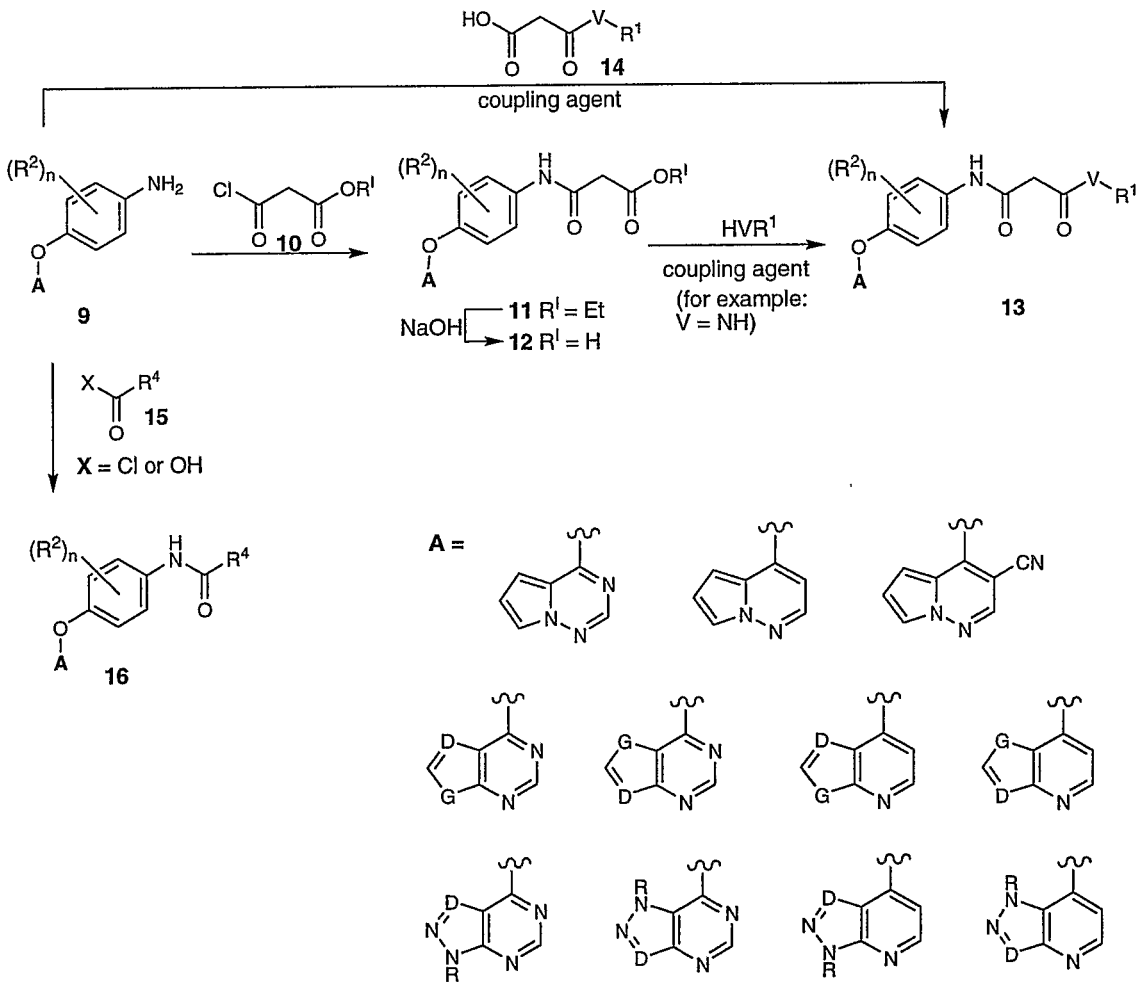
D is CR^{20} or N

V = as defined above

In general, amide derivatives described in the invention can be prepared using the chemistry outlined in Scheme 3. For example, aniline **9** (derived from Scheme 1)

can be acylated with compound **10** to provide amide **11**. Hydrolysis of the ester **11** with, for example sodium hydroxide can afford carboxylic acid **12**. Desired compound **13** can then be obtained from intermediate **12** using known amide-bond forming conditions. Alternatively, aniline **9** can be converted directly to compound **13** using carboxylic acid **14** and a coupling agent, such as benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate, 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, or bromotripyrrolidinophosphonium hexafluorophosphate. Treatment of aniline **9** with an acid chloride **15** (X = Cl) or a carboxylic acid **15** (X = OH) and a coupling reagent can provide amides of the type **16**.

SCHEME 3



G is O, S, or NR^{21}

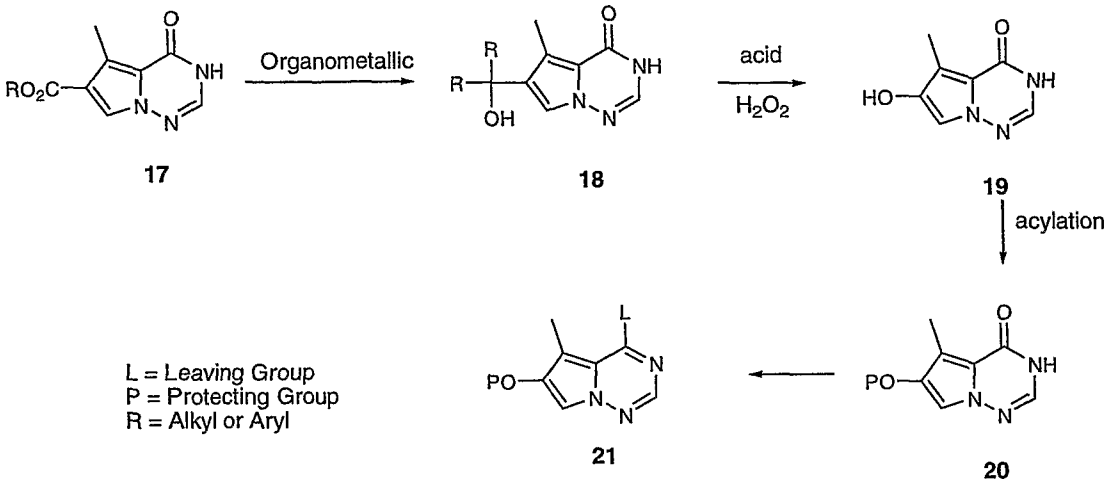
D is CR^{20} or N

V = as defined above

A substituted heterocyclic derivative, for example pyrrolotriazine compound **26a/b** (Scheme 5), can be prepared using the synthetic routes outlined in Schemes 4 and 5. Carboxylic esters, wherein R can be an alkyl or an aryl (such as phenyl) **17** can be contacted with no less than 2 equivalents of an alkyl or aryl organometallic agent such as a Grignard reagent, organolithium, organozinc, etc. to produce the tertiary alcohol **18** (Scheme 4). The reaction is generally performed in an ether solvent, such as tetrahydrofuran, dibutylether, or diethyl ether, or any other non-reactive solvent such as benzene, toluene, or hexane, for example. Tertiary alcohol **18** can be treated with a mixture of acid in the presence of hydrogen peroxide or organic peroxides such as *t*-butylhydroperoxide, cumenehydroperoxide to affect the rearrangement to hydroxypyrrolotriazine **19.** Almost any acid could be used as the catalyst for the oxidative rearrangement, the reaction has been demonstrated with organic acids, mineral acids, and Lewis acids. Some acids which have been used for this type of reaction include: *p*-toluenesulfonic acid, methansulfonic acid, formic acid, sulfuric acid, nitric acid, BF_3-OEt_2, trifluoroacetic acid, acidic zeolites, and acidic ion exchange resins. The concentration of the acid can be varied, the concentration and strength of the acid is used to control the kinetics of the reaction. The concentration of the peroxide can be varied from 30-50%. Any reducing agent which reacts to decompose hydrogen peroxide could be used in the quenching of this reaction, including, but not limited to sodium metabisulfite, sodium hydrogen sulfite, sodium thiosulfate, sodium hydrosulfite. A variety of bases can be used while quenching the reaction to control the pH. Hydroxypyrrolotriazine **19** can be reacted with a variety of acylating reagents, to furnish **20** (where, for example, P can be pivalate ester). Compound **20** can be contacted with an appropriate halogenating agent (for example, phosphorous oxychloride, $POCl_3$) to afford **21** (L = Cl). Other reagents can be used to accomplish this transformation besides $POCl_3$, including PCl_5, mixtures of PCl_5/$POCl_3$, $PhP(O)Cl_2$, $SOCl_2$. Usually an amine is used to catalyze the reaction, including Et_3N, $PhNMe_2$, DABCO, etc. Additionally, formamides such as, for example N,N-dimethylformamide and alkylamides such as *N*-methylpyrrolidinone can

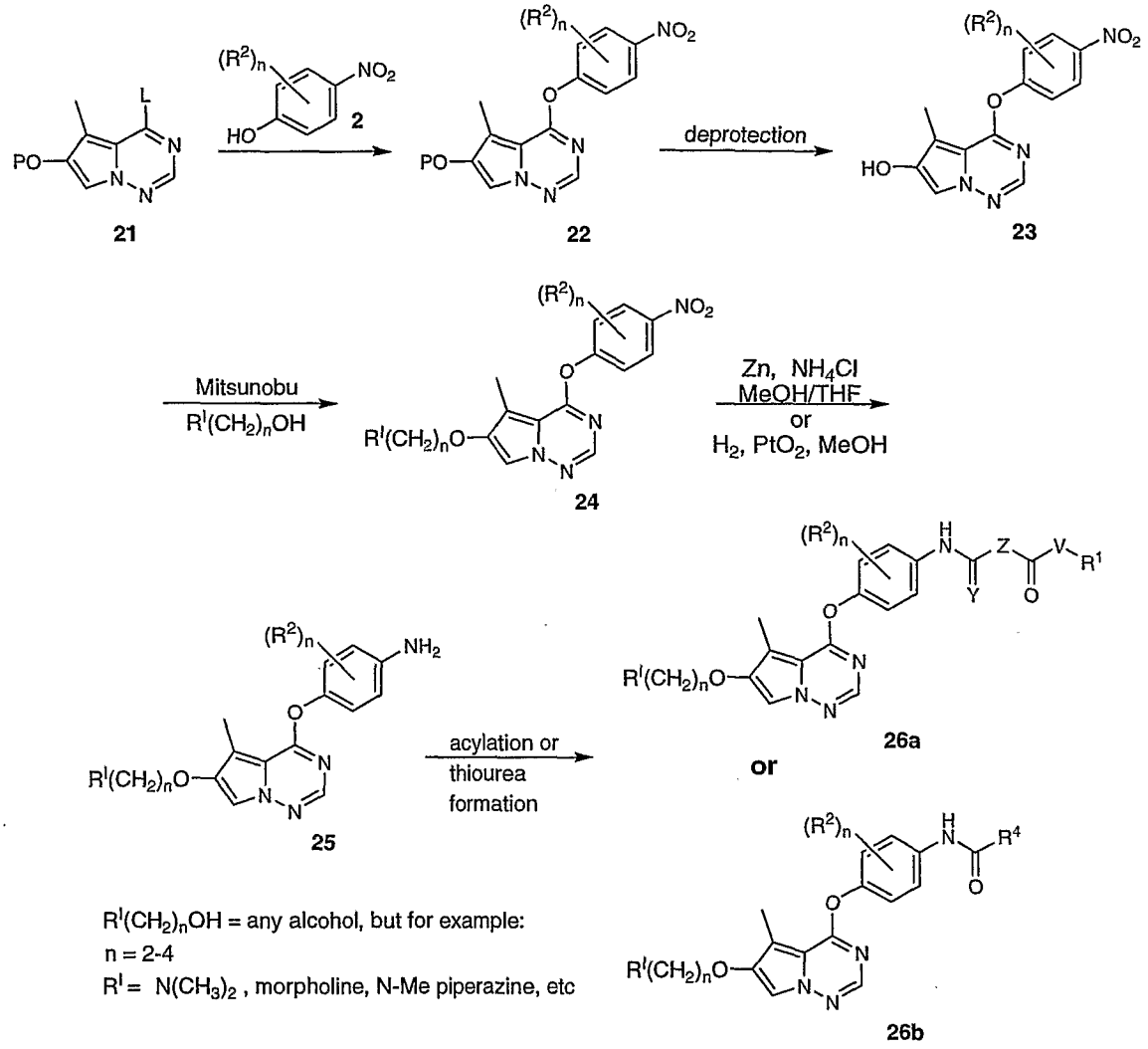
also be used to catalyze the reaction. The reaction can be run in any solvent inert to the haloginating agent, including benzene, toluene, THF, etc.

SCHEME 4



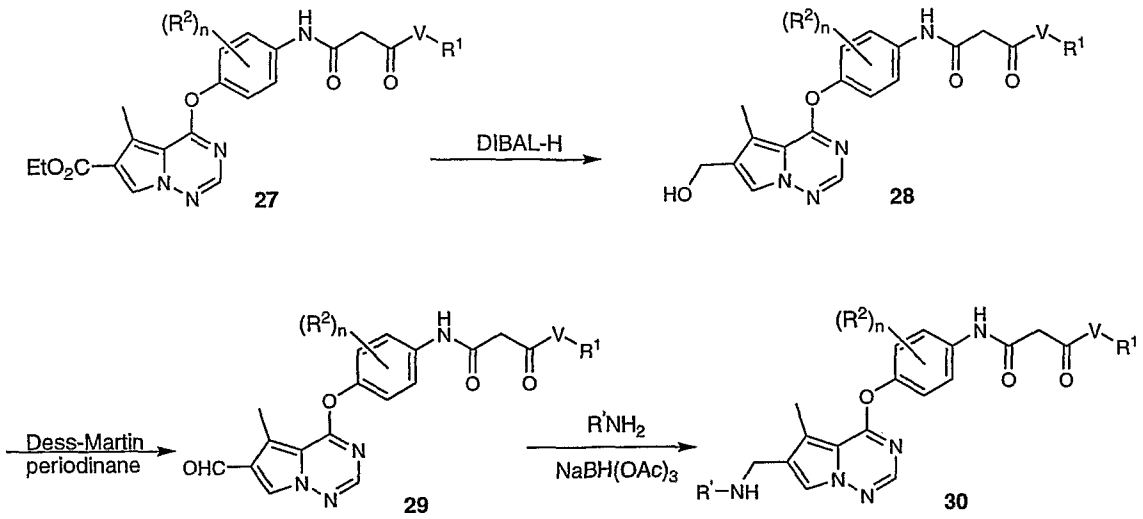
The appropriately protected imidate **21** (Scheme 5) can be treated with an optionally substituted phenol **2** to provide intermediate **22**. Phenol **23**, derived from deprotection of compound **22** (using sodium hydroxide in the case where P = pivalate) can be converted to ether **24** via a Mitsunobu reaction with an alcohol. Reduction of the nitro substituent of **24** using the same conditions described above in Scheme 1 can furnish the aniline **25**. Conversion of aniline **25** to the desired acylurea, acylthiourea or amide **26a/b** can be accomplished using chemistry previously described in Schemes 1 and 3.

SCHEME 5



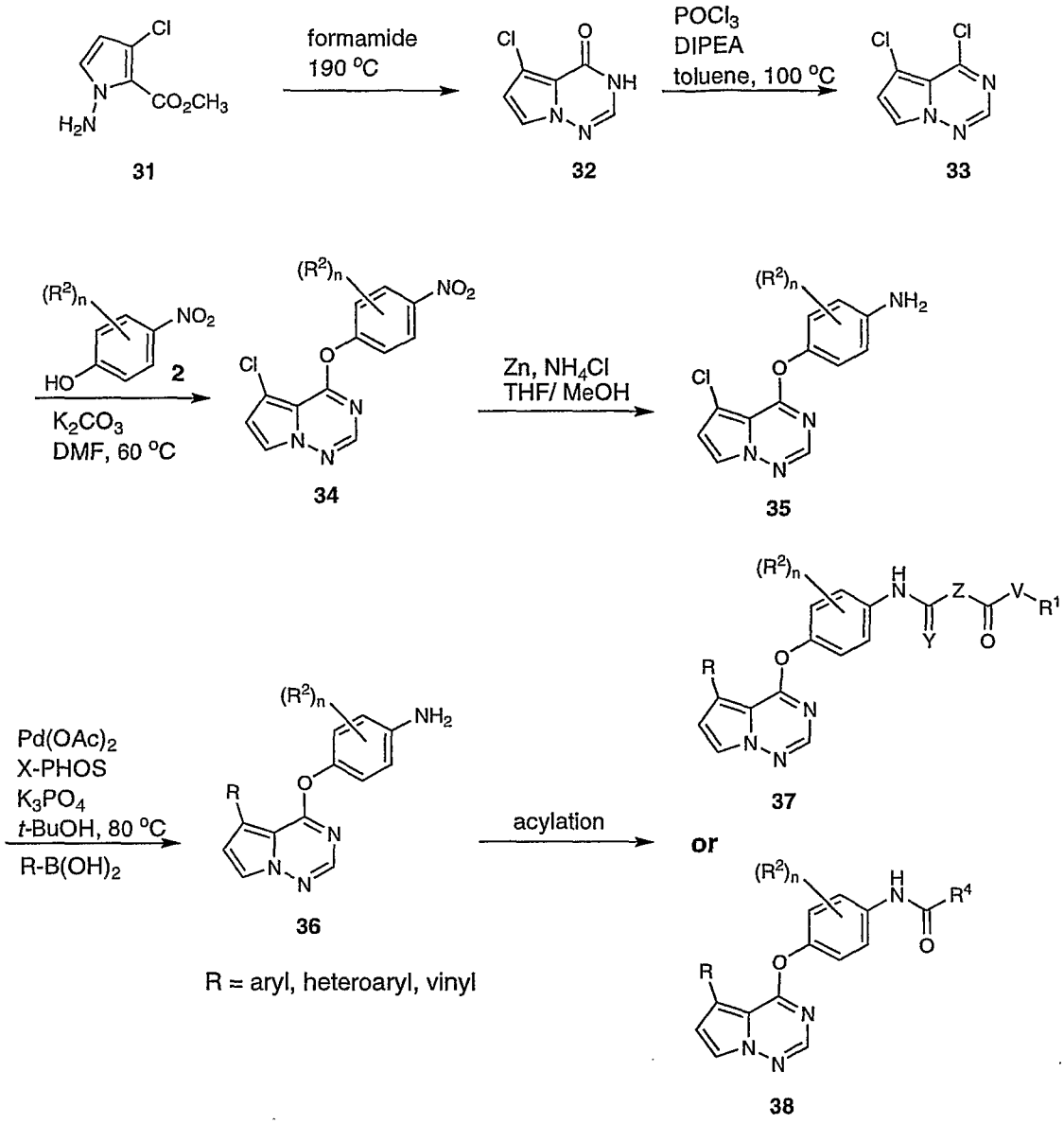
Amine compounds **30** can be prepared using the chemistry described in Scheme 6. Reduction of ester **27** with for example, diisobutylaluminum hydride (DIBAL-H) can provide alcohol **28**. Oxidation of compound **28** with for example Dess-Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one) can afford aldehyde **29**. Reductive amination of aldehyde **29** with an appropriately substituted amine in the presence of a reducing agent, such as sodium triacetoxyborohydride can furnish the desired amine **30**.

SCHEME 6



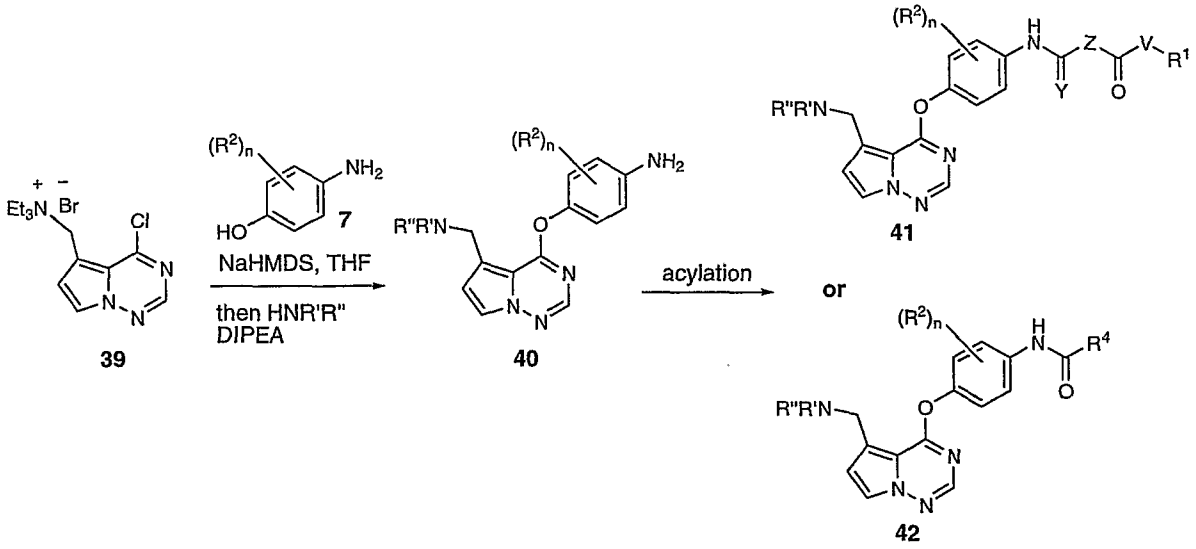
Various substituents, such as optionally substituted aryl, heteroaryl or vinyl groups can be introduced onto the 5-position of the pyrrolo[2,1-*f*][1,2,4]triazine ring using the chemistry outlined in Scheme 7. The aminopyrrole derivative **31** can be cyclized in the presence of formamide to produce 5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (**32**). Treatment of intermediate **32** with $POCl_3$ in the presence of a base, such as Hunig's base at elevated temperatures can afford 4,5-dichloropyrrolo[2,1-*f*][1,2,4]triazine (**33**). The coupling of an appropriately substituted phenol **2** with compound **33** in the presence of a base, such as potassium carbonate can provide intermediate **34**. The nitro group of **34** can be reduced using zinc dust and ammonium chloride to generate the aniline **35**. Palladium-mediated coupling reactions with various boronic acids can provide intermediate **36**, which can be converted to the desired compounds **37** or **38** using chemistry described above.

SCHEME 7



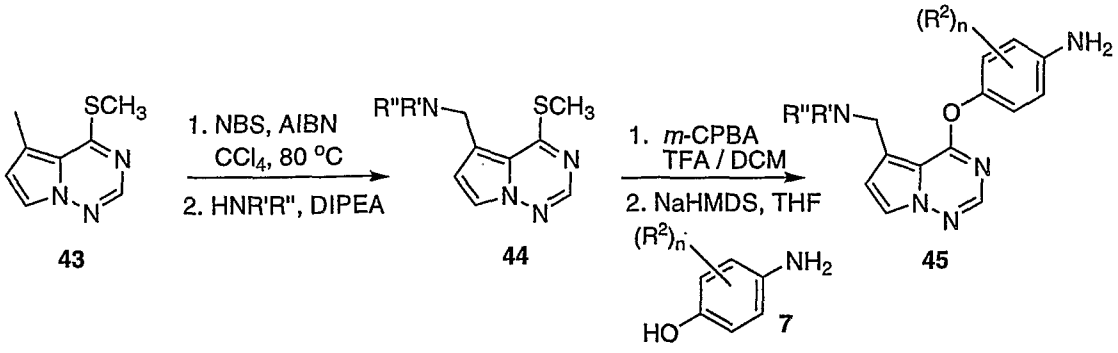
Substitution at the 5-position of the pyrrolo[2,1-*f*][1,2,4]triazine ring can also be accomplished by coupling the triethylammonium salt **39** with an appropriately substituted phenol **7** followed by treatment with an amine (HNR'R") in the presence of a base, such as Hunig's base to afford the aniline **40** (Scheme 8). Aniline **40** can be further processed as described previously to produce the desired compounds **41** or **42**.

SCHEME 8



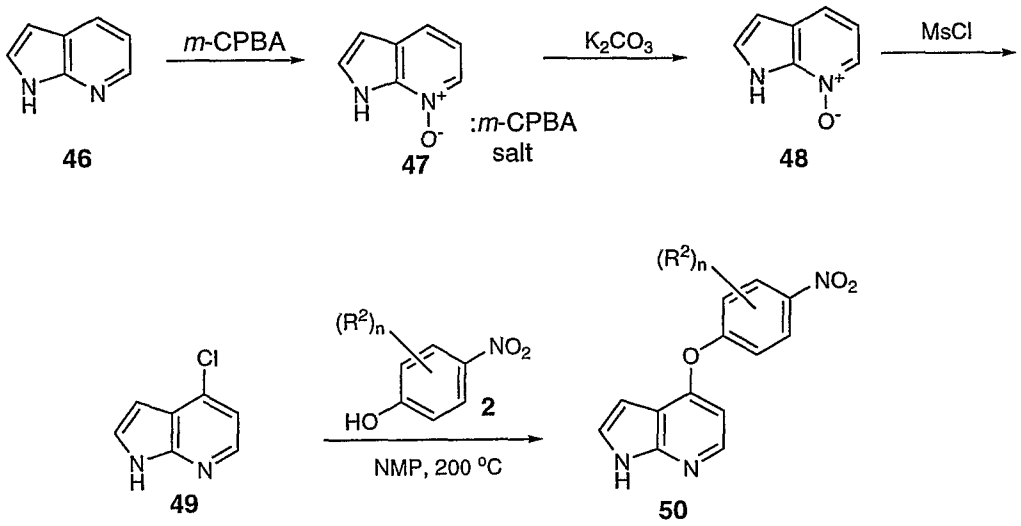
Alternatively, 5-methyl-4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazine (**43**) can be brominated with, for example *N*-bromosuccinimide (NBS) and 2, 2'-azobisisobutyronitrile (AIBN) in carbontetrachloride at elevated temperatures (Scheme 9). Treatment of the bromide intermediate with an amine (HNR'R") in the presence of a base, such as Hunig's base can provide intermediate **44**. Oxidation of the thiomethyl group of **44** can be accomplished with, for example 3-chloroperbenzoic acid (*m*-CPBA). Treatment of the sulfone intermediate with the phenoxide generated from compound **7** and sodium bis(trimethylsilyl)amide (NaHMDS) can provide the aniline intermediate **45**.

SCHEME 9



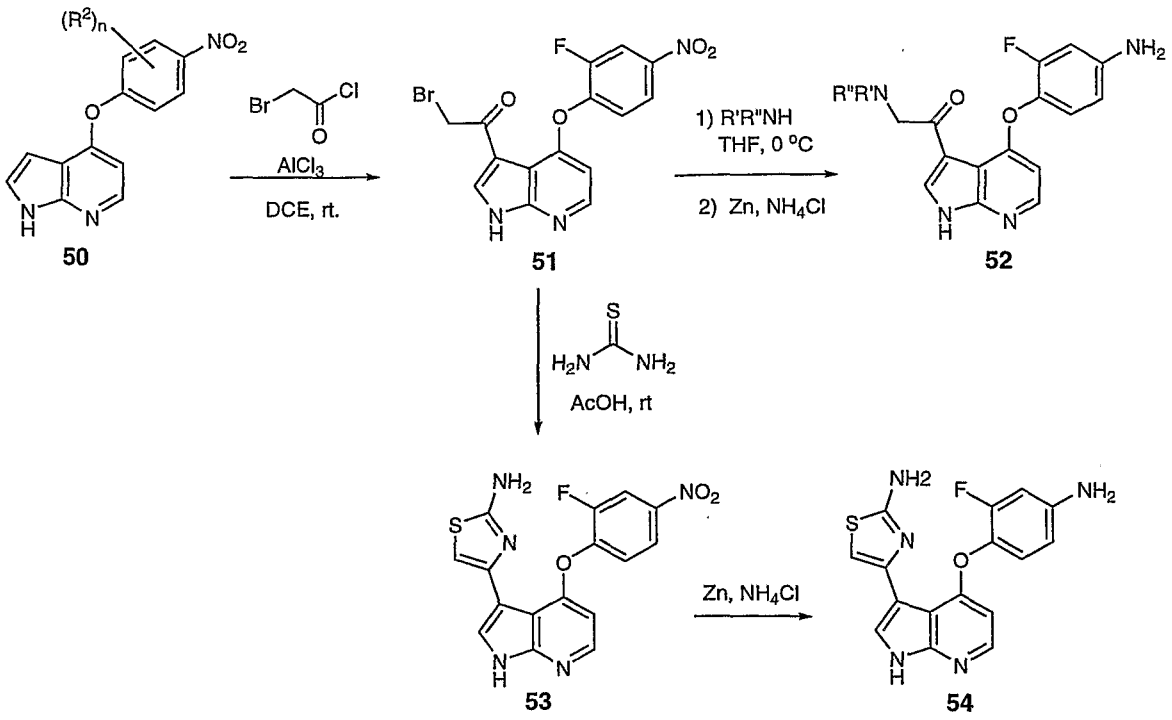
The pyrrolo[2,3-*b*]pyridine intermediate **50** can be prepared using chemistry outlined in Scheme 10. 4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**49**) can be obtained from commercially available 1*H*-pyrrolo[2,3-*b*]pyridine (**46**) using the synthetic sequence described by Thibault C. and coworkers (*Org. Lett.* **2003**, *5*, 5023-5025) which is illustrated in Scheme 10. Treatment of intermediate **49** with the phenol **2** at elevated temperatures can afford the key intermediate **50**, which can be converted to the desired compounds using chemistry described in Schemes 1 and 3.

SCHEME 10



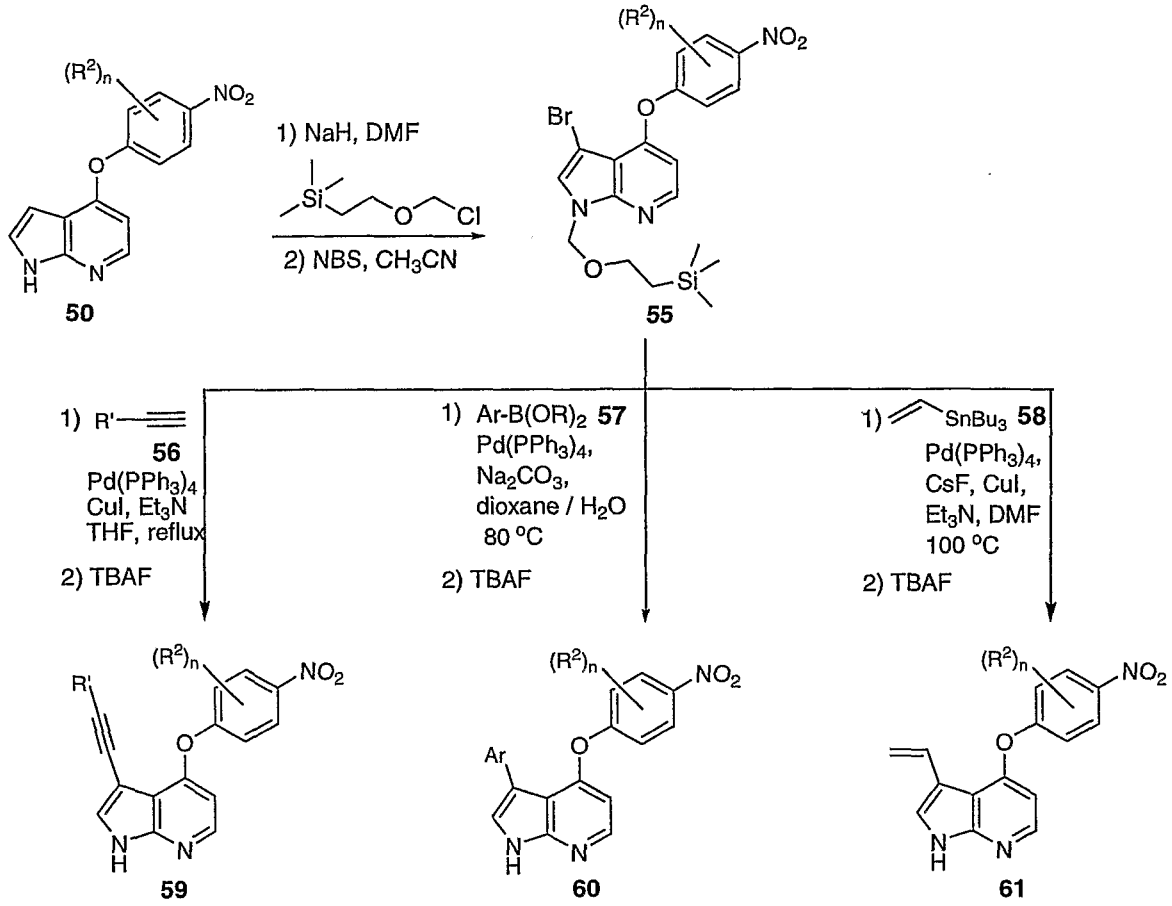
Incorporation of various substituents on the 3-position of the pyrrolo[2,3-*b*]pyridine ring can be accomplished using chemistry described in Schemes 11 and 12. For example, acylation of intermediate **50** with 2-bromoacetyl chloride in the presence of aluminum trichloride can provide compound **51** (Scheme 11). Treatment of intermediate **51** with an amine (R"R'NH) or thiourea, followed by subsequent reduction with zinc dust and ammonium chloride can provide the anilines **52** and **54,** respectively.

SCHEME 11



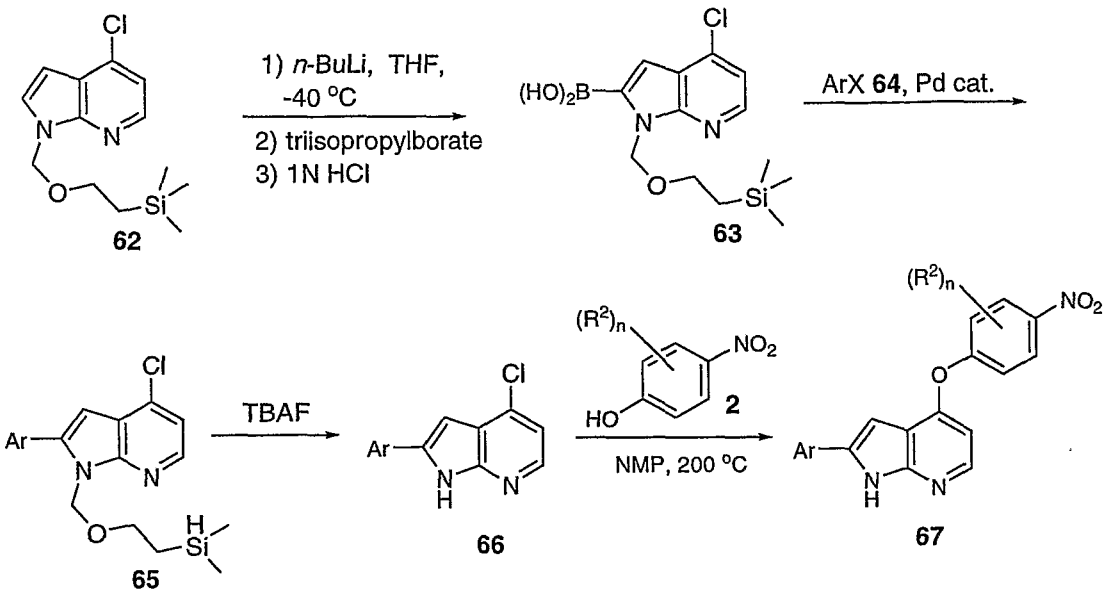
Alternatively, protection of compound **50** with, for example (2-(chloromethoxy)ethyl)trimethylsilane in the presence of a base, such as sodium hydride, followed by bromination with NBS can provide intermediate **55** (Scheme 12). The bromide **55** can then be treated with substituted alkynes **56**, arylboronates / arylboronic acids **57**, or vinylstannanes **58** in the presence of a palladium and/or copper catalyst to afford the intermediates **59-61**, respectively. Removal of the protecting group of **59-61** with tetrabutylammonium fluoride (TBAF) followed by reduction of the nitro groups can provide the corresponding aniline intermediates, which can be acylated using chemistry previously described in Schemes 1 and 3.

SCHEME 12



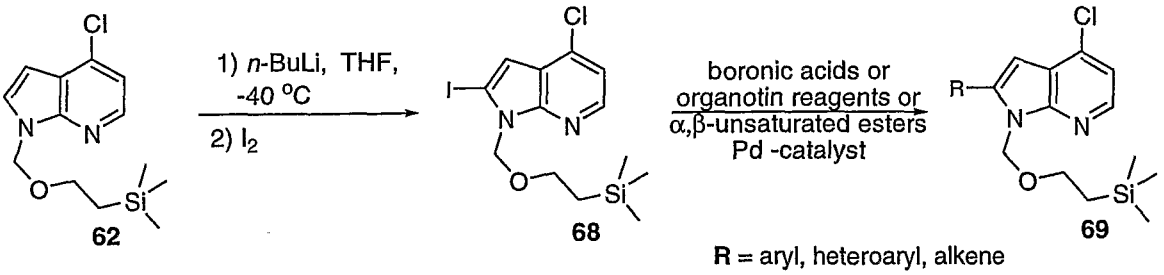
Incorporation of various substituents at the 2-position of the pyrrolo[2,3-*b*]pyridine nucleus can be accomplished using the chemistry outlined in Schemes 13 and 14. The protected azaindole derivative **62**, derived from compound **49** (Scheme 10) can be treated with *n*-butyllithium at low temperature followed by triisopropylborate (Scheme 13). The requisite intermediate can then be hydrolyzed to generate the boronic acid **63**. Coupling of the boronic acid **63** with various aryl or heteroaryl halides **64** can be accomplished using a palladium catalyst to furnish intermediate **65**. Removal of the protecting group of **65** with TBAF can afford compound **66**, which can be treated with phenol **2** at elevated temperature to provide the intermediate **67**. Compound **67** can be further modified to furnish the desired compounds using similar chemistry described above.

SCHEME 13



Alternatively, compound **62** can be converted to iodide **68** using chemistry described in Scheme 14. Intermediate **68** can be coupled with a variety of reagents, such boronic acids, organostannes or substituted olefins in the presence of a transition metal catalyst [i.e., $Pd(OAc)_2$ – *cf.* Chi, S. M. *et al. Tetrahedron Lett.* **2000**, 919-922] to give **69**. Intermediate **69** can be converted to the desired analogues using chemistry previously described.

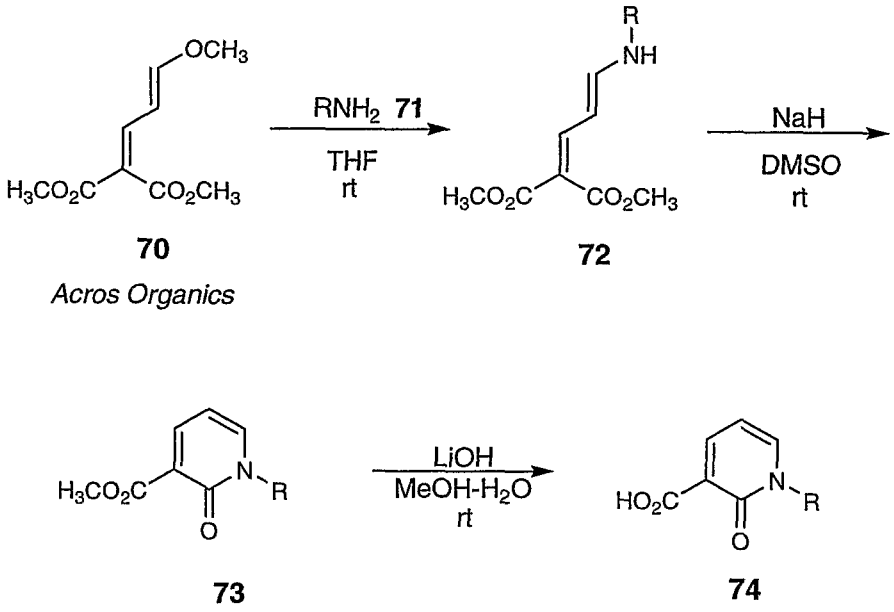
SCHEME 14



The pyridinone intermediate **74** can be obtained by a two step process beginning with commercially available (*E*)-dimethyl 2-(3-methoxyallylidene)malonate (**70**) (Scheme 15). Thus, treatment of compound **70** with an amine or aniline **71** at room temperature can provide intermediate **72**, which can then be cyclized in the

presence of a base, such as sodium hydride in dimethylsulfoxide to generate **73**. Hydrolysis of intermediate **73** under basic conditions can provide the desired pyridinone intermediate **74**, which can be coupled to various anilines as described in the aforementioned Schemes.

SCHEME 15



70

Acros Organics

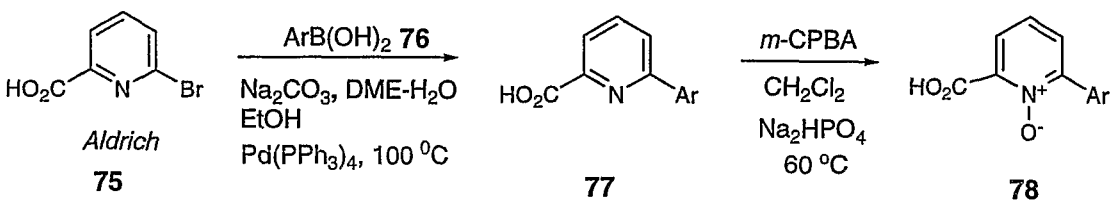
72

73

74

The pyridyl *N*-oxide intermediate **78** (Scheme 16) can be obtained by a two-step process in which the commercially available 6-bromopicolinic acid (**75**) is coupled with boronic acid or borinate **76** in the presence of a palladium(0) catalyst and sodium carbonate, followed by oxidation of the requisite intermediate **77** at elevated temperature. Intermediate **78** can then be coupled to various anilines as described in the aforementioned Schemes.

SCHEME 16



Aldrich

75

77

78

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

ASSAYS

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and/or their pharmaceutically acceptable salts.

Met Kinase assay

Reagents	Substrate Mix Final Concentration
Stock Solution	
Tris-HCl, (1M, pH 7.4)	20 mM
$MnCl_2$ (1M)	1 mM
DTT(1M)	1 mM
BSA (100 mg/ml)	0.1 mg/ml
$polyGlu_4$/tyr (10 mg/ml)	0.1 mg/mL
ATP (1mM)	1 μM
γ-ATP (10μCi/μl)	0.2 μCi/ml

Buffer	Enzyme mix
20ul 1M DTT	4ul GST/Met enzyme(3.2mg/ml) = 10ng/rxn
200ul 1M Tris-HCL, pH 7.4	qs 12ml Buffer
20ul 100mg/ml BSA	
qs 20ml H_20	

Incubation mixtures employed for the Met kinase assay contain the synthetic substrate polyGlu:Tyr, (4:1), ATP, ATP-γ-^{33}P and buffer containing Mn^{++} and/or Mg^{++}, DTT, BSA, and Tris buffer. Reactions are incubated for 60 minutes at 27°C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 4%. TCA precipitates are collected onto GF/C unifilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters are quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves

are generated to determine the concentration required to inhibit 50% of kinase activity (IC_{50}). Compounds are dissolved at 10 mM in dimethyl sulfoxide (DMSO) and evaluated at six concentrations, each in quadruplicate. The final concentration of DMSO in the assay is 1%. IC_{50} values are derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

The compounds of the invention inhibit the Met kinase enzyme with IC_{50} values between 0.01 to 100 μM. Preferred compounds have IC_{50} values less than 1.0μM, and more preferably, less than about 0.5 μM.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

EXAMPLES

All reactions were carried out with continuous magnetic stirring under an atmosphere of dry nitrogen or argon. All evaporations and concentrations were carried out on a rotary evaporator under reduced pressure. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying or purification. Flash chromatography was performed using silica gel (EMerck Kieselgel 60, 0.040-0.060 mm).

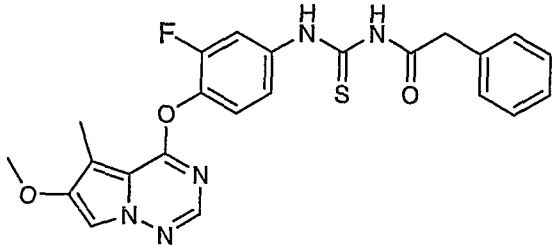
Analytical Reverse Phase (RP) HPLC was performed using a Phenomenex Luna C18 S5 4.6 mm × 50 mm column or a YMC S5 ODS 4.6 x 50 mm column. In each case a 4 min linear gradient (from 100% A: %0 B to 0% A: 100 % B) was used with the following mobile phase system: A = 90% H_2O/MeOH + 0.2% H_3PO_4; B = 90% MeOH/H_2O + 0.2% H_3PO_4 at flow rate = 4mL/min and detection at 220 nm.

Preparative Reverse Phase (RP) HPLC was performed with a linear gradient elution using H_2O/MeOH mixtures buffered with 0.1% trifluoroacetic acid and detection at 220 nm on one of the following columns: Shimadzu S5 ODS-VP 20 x 100 mm (flow rate = 9 mL/min), or YMC S10 ODS 50 x 500 mm (flow rate = 50 mL/min), or YMC S10 ODS 30 x 500 mm (flow rate = 20 mL/min).

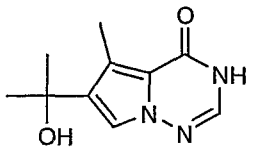
All final products were characterized by ^{1}H NMR, RP HPLC, electrospray ionization (ESI MS) or atmospheric pressure ionization (API MS) mass spectrometry. ^{1}H NMR spectra were obtained on either a 500 MHz JEOL or a 400 MHz Bruker instrument. ^{13}C NMR spectra were recorded at 100 or 125 MHz. Field strengths are expressed in units of δ (parts per million, ppm) relative to the solvent peaks, and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dm, doublet of multiplets; t, triplet; q, quartet; br s, broad singlet; m, multiplet.

The following abbreviations are used for commonly used reagents : Boc or BOC: *t*-butyl carbamate; Fmoc: 9*H*-fluorenylmethyl carbamate; NMM: *N*-methylmorpholine; Ms: methanesulfonyl; DIEA or DIPEA: diisopropylethylamine or Hunig's base; NMP: *N*-methylpyrrolidinone; BOP reagent: benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate; DCC: 1,3-dicyclohexylcarbodiimide; EDCI: 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; RT: room temperature; t_R: retention time; h: hour(s); min: minute(s); PyBrOP: bromotripyrrolidinophosphonium hexafluorophosphate; TBTU: *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate; DMAP: 4-*N*,*N*-dimethylaminopyridine; HOBt: hydroxybenzotriazole; HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate; DIBAL-H: diisobutylaluminum hydride; $Na(OAc)_3BH$: sodium triacetoxyborohydride; HOAc: acetic acid; TFA: trifluoroacetic acid; LiHMDS: lithium bis(trimethylsilyl)amide; *m*-CPBA: *m*-chloro: 3-chloroperbenzoic acid; AIBN: 2, 2'-azobisisobutyronitrile; DMSO: dimethyl sulfoxide; MeCN: acetonitrile; MeOH: methanol; EtOAc: ethyl acetate; DMF: dimethyl formamide; THF: tetrahydrofuran; DCE: 1,2-dichloroethane; Et_2O: diethyl ether.

EXAMPLE 1

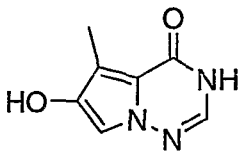


1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-phenylacetyl)thiourea



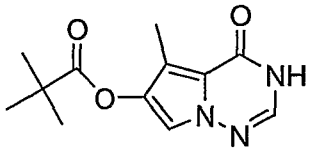
A) **6-(1-Hydroxy-1-methyl-ethyl)-5-methyl-*3H*-pyrrolo[2,1-*f*]1,2,4]triazin-4-one**

A mixture of 1.9 kg of 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid ethyl ester, prepared generally according to the procedures described in, United States Patent Application Serial No. 09/573829, and 17.9 kg of THF was prepared under an inert atmosphere and cooled to -10 °C. To this mixture was added 14.2 kg methylmagnesium chloride as a 3 M solution in THF at a rate to maintain the reaction temperature < 35 °C. The reaction mixture was held at 25-45 °C until complete, then cooled to 0 °C. A solution of 9.9 kg ammonium chloride in 36.7 kg water was prepared and cooled to 5 °C. The organic reaction mixture was added to the ammonium chloride solution at a rate to maintain the internal temperature < 15 °C. The phases were allowed to settle and the lower aqueous phase drained off and re-extracted with 9.5 kg additional THF. To the combined organic phases was added 8.6 kg EtOAc and the mixture washed with 7.6 kg of saturated aqueous sodium chloride solution. The reaction mixture was filtered, then solvent was removed *in vacuo* (temperature < 40 °C) to about 1/3 the original volume. Additional EtOAc was added with continuing distillation until the THF level was < 7%. The resulting slurry was cooled to 0-5 °C, then the solid collected by filtration. The wet cake was washed with cold (-10 °C) EtOAc, then dried in vacuo at 40 °C to produce 1.5 kg 6-(1-hydroxy-1-methyl-ethyl)-5-methyl-*3H*-pyrrolo[2,1-*f*]1,2,4]triazin-4-one with a purity of 96-99%.



B) 6-Hydroxy-5-methyl-3*H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one

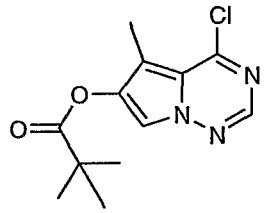
A one liter, 3-neck, round bottom flask as equipped with mechanical stirrer and a cooling bath of ice/acetone. To this was charged 20 g of 6-(1-hydroxy-1-methyl-ethyl)-5-methyl-*3H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 235 mL of THF and 47 mL 50% aqueous hydrogen peroxide. An exotherm from -7 °C to 7.3 °C was observed and the mixture became a solution. To this was added a pre-cooled solution of 28.5 mL water and 63 mL methanesulfonic acid over 40 min, keeping the temperature between -5 °C and -0.7 °C. The solution was stirred at -2 °C for 95 min until HPLC indicated reaction was complete; reaction mixture was quenched, while keeping it at -2 °C, by adding it portion wise to a cooled solution of 28.5 mL water, 89 g $NaHSO_3$ and 128 mL 28% aqueous ammonium hydroxide over 40 min, at 15 °C to 25 °C. The mixture was stirred at room temperature for 20 min; pH was 6.80 and a peroxide test was negative. The layers were separated and the aqueous layer was extracted with 100 mL THF. The two organic layers were combined and concentrated, removing 280 mL solvent. To the thick slurry was added 250 mL water and the concentration continued until 88 mL of solvent was removed. The slurry was filtered and the cake was washed with 25 mL water twice and then 25 mL acetonitrile. It was dried by suction on the filter to constant weight to yield 12.51 g of 6-hydroxy-5-methyl-3*H*- pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 75.9% yield, 96.5% purity.



C) 2,2- Dimethyl-propionic acid 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazin-6-yl ester

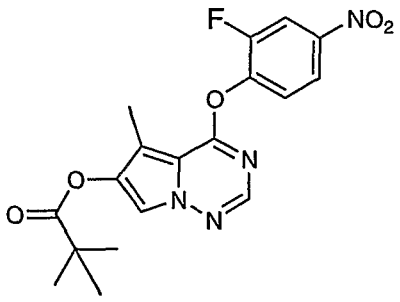
A mixture of 2.9 kg 6-hydroxy-5-methyl-3*H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 4.6 kg of diisopropylethylamine and 17.0 kg of THF was cooled to 0-10 °C, then treated with 2.6 kg pivaloyl chloride at a rate to maintain the temperature < 20 °C. The mixture was stirred until the reaction was complete by HPLC, then 17.8 kg of toluene was added, followed by 20.6 kg of 15% aqueous potassium dihydrogen phosphate solution. The phases were separated and the organic was washed with 10.2

kg water. The organic phase was filtered, then distilled under vacuum with a maximum temperature of 65 °C. Additional toluene can be added and distillation continued until the concentration of THF was < 8%, and the total reactor volume was reduced to 31 L. The resulting slurry was cooled to 20-25 °C and treated with 20.3 kg heptane over 1.5 h. The slurry was cooled to 0-5 °C and held for 1 h, then the solid was collected by filtration and dried to yield 4.0 kg of 2,2-dimethyl-propionic acid 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazin-6-yl ester with a purity of 95-99%.



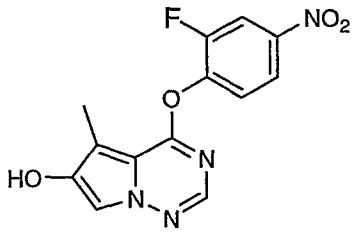
D) 4-Chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

To a mixture of 5-methyl-4-oxo-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (300 mg, 1.20 mmol), phosphorus oxychloride (2.0 mL, 21.4 mmol) and DIEA (0.5 mL, 2.80 mmol) was added toluene (10 mL). The reaction was heated at 110 °C for 4 hours and then cooled to room temperature. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and dried with sodium sulfate, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 – 25% EtOAc/CH_2Cl_2) to give the title compound (250 mg, 78%) as a white solid.



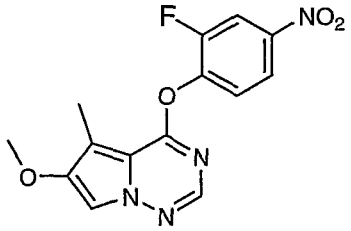
E) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

To a mixture 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (250 mg, 0.94 mmol), 2-fluoro-4-nitrophenol (176 mg, 1.12 mmol, Aldrich) and K_2CO_3 (154 mg, 1.12 mmol) was added DMF (5 mL). The reaction was stirred at room temperature for 24 h. The reaction was quenched with water (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica gel flash chromatography (eluted with 1 – 25% EtOAc/CH_2Cl_2) to give the title compound (160 mg, 44%) as a white solid.



F) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol

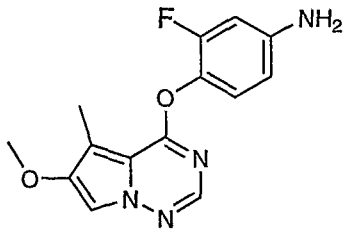
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (80 mg, 0.2 mmol) in THF (1 mL) was added a solution of NaOH in MeOH / H_2O (0.2 mL, 1 M). The solution turned red instantly. After 5 minutes, the reaction was quenched with EtOAc (5 mL) and H_2O (5 mL). The organic layer was separated, dried with sodium sulfate and concentrated *in vacuo* to give the title compound (52 mg, 85%) as a yellow solid.



G) 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine

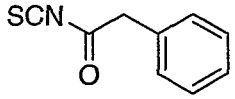
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (52 mg, 0.17 mmol) in DMF (2 mL) was added Cs_2CO_3 (65 mg, 0.2 mmol) and the mixture was stirred at RT for 10 minutes. A solution of methyl iodide in DMF (0.2 mL, 0.2 mmol, 1 M) was added and the reaction solution was stirred at RT for 2 h. The reaction was quenched with EtOAc (5 mL) and H_2O (5

mL). The organic layer was separated, dried with sodium sulfate and concentrated *in vacuo* to give the title compound (35 mg, 65%) as a yellow solid.



H) 3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

To a solution of 4-(2-fluoro-4-nitrophenoxy)-6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (35 mg, 0.11 mmol) in THF (1.0 mL) was added MeOH (1.0 mL) followed by Zn (100 mg, 1.5 mmol) and NH_4Cl (43 mg, 0.80 mmol). The reaction was heated at 60 °C for 3 h. The solution was filtered through Celite® and concentrated *in vacuo*. The product mixture was purified by a SCX cartridge (eluted with ammonia in methanol (2 M) to give the title compound (15 mg, 50%) as a white solid.



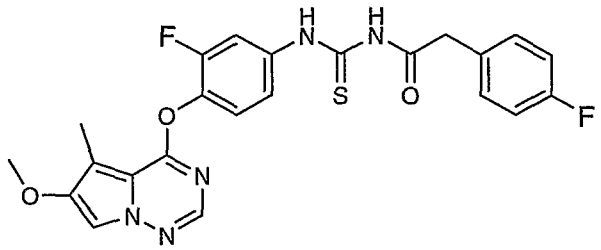
I) 2-Phenyl-1-thiocyanatoethanone

To a solution of NaSCN (49 mg, 0.60 mmol) in EtOAc (2 mL) was added phenylacetyl chloride (0.066 mL, 0.50 mmol, Aldrich) to provide a 0.25 M solution of 2-phenyl-1-thiocyanatoethanone. After 10 min, completion of the reaction was determined by reacting an aliquot of the reaction mixture with 4-(phenyloxy)aniline to form the corresponding thiocyanate which was detected by LCMS(ESI^+) *m/z* 363 $(M + H)^+$. The 2-phenyl-1-thiocyanatoethanone was used directly without isolation or further purification.

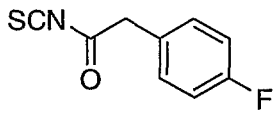
J) 1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-phenylacetyl)thiourea

To a solution of 3-fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (7.5 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) was added a solution of 2-phenyl-1-thiocyanatoethanone (0.133 mL, 0.033 mmol, 0.25 M in ethyl acetate). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (6.1 mg, 50%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.87 (m, 1H), 7.83 (s, 1H), 7.47 (m, 5H), 7.31 (m, 4H), 3.89 (s, 3H) 3.74 (d, 2H, J = 10.5 Hz), 2.44 (s, 3H); MS(ESI$^+$) *m/z* 466 $(M + H)^+$.

EXAMPLE 2



1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) 2-(4-Fluorophenyl)-1-thiocyanatoethanone

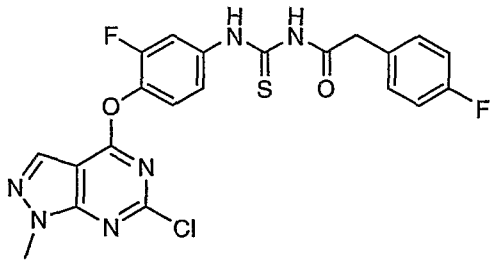
To a solution of NaSCN (49 mg, 0.60 mmol) in EtOAc (2 mL) was added 4-fluorophenylacetyl chloride (0.066 mL, 0.50 mmol, Aldrich). The reaction was stirred at room temperature for 1 h to give a 0.25 M solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone in EtOAc, which was used directly without further purification.

B) 1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

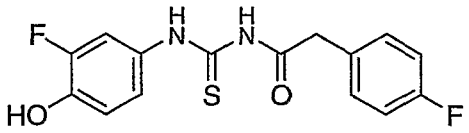
The title compound was prepared from 3-fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine and 2-(4-fluorophenyl)-1-thiocyanatoethanone in a similar manner as described for Compounds H and J of

Example 1. ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 7.88 (m, 1H), 7.83 (s, 1H), 7.45 (s, 1H), 7.28 (m, 5H), 7.12 (m, 2H), 3.89 (s, 3H), 3.71 (s, 2H) 2.44 (s, 3H); MS(ESI$^+$) *m/z* 484 $(M + H)^+$.

EXAMPLE 3



1-(4-(6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) 1-(3-Fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

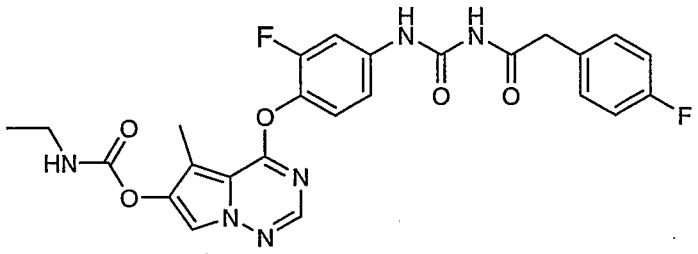
To a solution of 4-amino-2-fluorophenol (50 mg, 0.3 mmol, Indofine Chemical Co.) in CH_2Cl_2 (5 mL) was added a 0.25 M solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (prepared using a similar procedure for the synthesis of Compound A of Example 2) in EtOAc (1.6 mL, 0.4 mmol). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (100 mg, 95%) as a white solid.

B) 1-(4-(6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

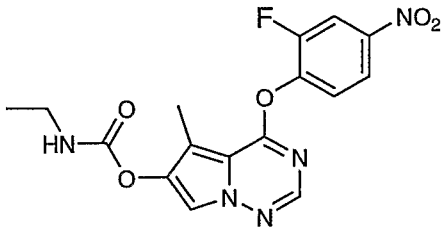
To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol), 4,6-dichloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (15.3 mg, 0.075 mmol, preparation: *J. Org. Chem.* **1958**, *23*, 852, the disclosure of which is herein incorporated by reference) and K_2CO_3 (10 mg, 0.075 mmol) was added DMF (2 mL). The reaction was stirred at RT for 24 h.

The reaction was quenched with water (2 mL) and CH_2Cl_2 (5mL). The organic layer was separated, dried with sodium sulfate, concentrated *in vacuo* and purified by reverse phase preparative HPLC to give the title compound (22.9 mg, 60%) as a white solid. MS(ESI$^+$) *m/z* 457 $(M + H)^+$.

EXAMPLE 4

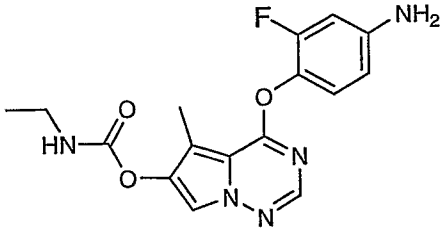


4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate



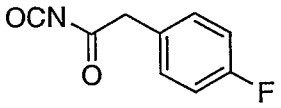
A) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (25 mg, 0.082 mmol, Compound F of Example 1), DIEA (0.017 mL, 0.1 mmol) in CH_2Cl_2 (5 mL) was added ethyl isocyanate (0.078 mL, 0.1 mL) and stirred at room temperature for 2 h. The reaction was quenched with water (5 mL). The organic layer was separated, dried and concentrated *in* vacuo. The mixture was purified by flash chromatography (1-5% Methanol/CH_2Cl_2) to give the title compound (12.5 mg, 32%) as a white solid.



B) 4-(4-Amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (12.5 mg, 0.033 mmol) in ethanol (2 mL) was added Zn (20 mg, 0.3 mmol) and NH_4Cl (20 mg, 0.37 mmol). The reaction was stirred at room temperature for 1 h, filtered through Celite® and concentrated *in vacuo* to give the title compound (8 mg, 70%) as a white solid.



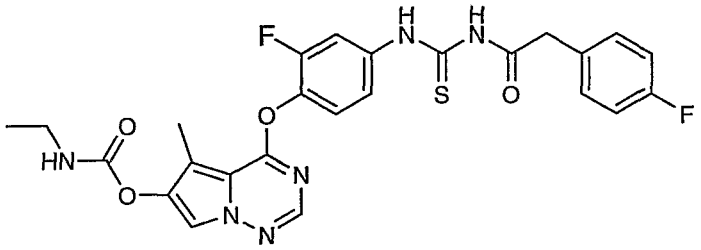
C) 2-(4-Fluorophenyl)acetyl isocyanate

To a solution/suspension of 4-fluorophenylacetamide (77 mg, 0.50 mmol, see generally, *J. Med. Chem.* **2003**, *46*, 4333-4341, the disclosure of which is herein incorporated by referene) in dichloroethane (2 mL) was added oxalyl chloride (0.175 mL, 2.00 mmol). The reaction was heated at 80 °C for 24 h and then 70 °C for two days. By this time, most of the solids had dissolved and the reaction was yellow. LC/MS analysis found a peak with a molecular weight of 211 corresponding to methyl 2-(4-fluorophenyl)acetylcarbamate, resulting from quenching of the isocyanate with methanol. The reaction was concentrated *in vacuo* to give a yellow slurry. The slurry was redissolved in dichloroethane (2 mL) and again concentrated *in vacuo*. The resulting residue was redissolved again in dichloroethane (2 mL) to give a 0.25 M solution of 2-(4-fluorophenyl)acetyl isocyanate in dichloroethane, which was used directly in subsequent reactions.

D) 4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (10 mg, 0.029 mmol) in CH_2Cl_2 (1 mL) was added a solution of 2-(4-fluorophenyl)acetyl isocyanate (2 mL, 0.25 M in dichloroethane). The reaction was stirred at room temperature for 1 h, LC/MS analysis indicated consumption of starting carbamate. The mixture was concentrated *in vacuo* and the residue was suspended in methanol and filtered to give the title compound. The filtrate was purified by flash chromatography to provide more of the title compound as a pale yellow solid (combined yield 5.9 mg, 40%). ^{1}H NMR ($CDCl_3$) δ 10.63 (s, 1H), 8.42 (s, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.67 (dd, 1H, J = 12.1, 2.2 Hz), 7.28 (m, 4H), 7.10 (m, 2H), 3.73 (s, 3H), 3.36 (m, 2H), 2.48 (s, 3H), 1.26 (m, 3H); MS(ESI$^+$) *m/z* 525 $(M + H)^+$.

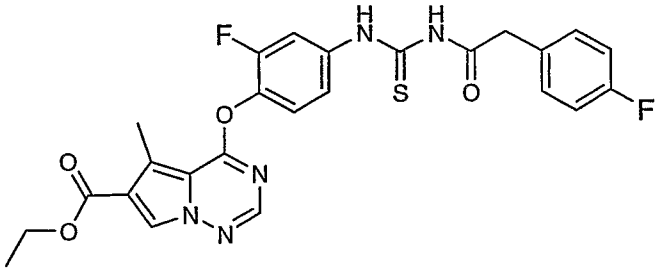
EXAMPLE 5



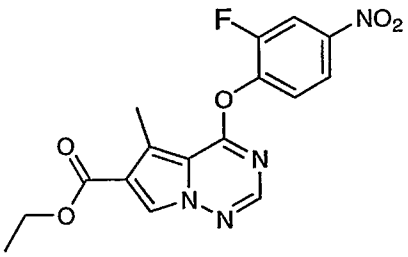
4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (8 mg, 0.023 mmol, preparation Compound B of Example 4) in CH_2Cl_2 (1 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.120 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction was stirred at room temperature for 1 h, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (5.4 mg, 43%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.58 (s, 1H), 7.88 (m, 3H), 7.28 (m, 5H), 7.12 (m, 2H), 3.72 (s, 2H), 3.37 (m, 2H), 2.46 (m, 3H), 1.26 (m, 3H); MS(ESI$^+$) *m/z* 541 $(M + H)^+$.

EXAMPLE 6

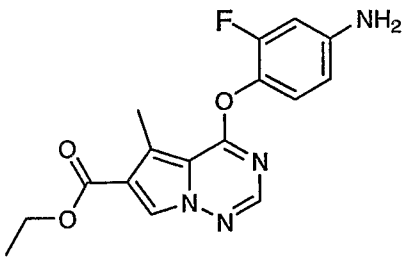


Ethyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



A) Ethyl 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a mixture of ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (24 mg, 0.10 mmol, preparation: See, US Pat. No. 6,670,357, especially example 61, the disclosure of which is hererin incorporated by reference), 2-fluoro-4-nitrophenol (20 mg, 0.125 mmol) and K_2CO_3 (28 mg, 0.20 mmol) was added DMF (0.5 mL). The reaction was heated at 70 °C for 20 minutes, cooled to room temperature and 2 mL of water was added. The mixture was filtered, the solid was washed with water, and dried to give the title compound (36 mg, 100%) as a light yellow solid.



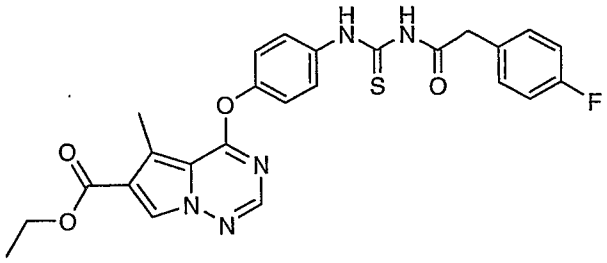
B) Ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a solution of ethyl 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (36 mg, 0.1 mmol) in THF (1.0 mL) was added MeOH (0.7 mL) followed by Zn (130 mg, 2.0 mmol) and NH_4Cl (53 mg, 1.0 mmol). The reaction was heated at 70 °C overnight. LC/MS analysis indicated mostly starting material. The solution was shaken vigorously and then heated to 75 °C. LC/MS analysis after 4 h showed the desired product and many other peaks. The reaction was filtered through a coarse filter, and the filtrate was concentrated to a give 55 mg of a brown residue. The residue was suspended in THF and passed through an HPLC filter resulting in a clear filtrate. The filtrate was concentrated *in vacuo* to give 54 mg of the title compound as a crude mixture which was used in the next step without further purification.

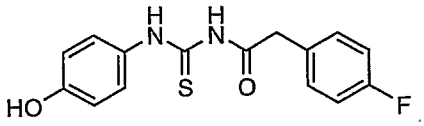
C) Ethyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a suspension of ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (54 mg) in CH_2Cl_2 (0.6 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.5 mL, 0.12 mmol, 0.25 M in ethyl acetate Compound A of Example 2). The reaction was stirred at room temperature for 15 minutes, LC/MS analysis indicated mostly starting material. The reaction was warmed to 45 °C, after 30 min most of the suspension had dissolved to give a cloudy solution. LC/MS analysis indicated mostly desired product. The reaction was shaken at room temperature for an additional 2 h, evaporated to dryness, and purified by column chromatography eluting with 1-7% ethyl acetate/dichloromethane to the title compound (9 mg, 17% overall yield for 3 steps) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.45 (s, 1H), 8.66 (s, 1H), 8.18 (s, 1H), 7.92 (dd, 1H, J = 11.4, 2.4 Hz), 7.90 (s, 1H), 7.41 (m, 1H), 7.29 (m, 3H), 7.12 (m, 2H), 4.38 (q, 2H, J = 7.1 Hz), 3.73 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 526 $(M + H)^+$.

EXAMPLE 7



Ethyl 4-(4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



A) **1-(2-(4-Fluorophenyl)acetyl)-3-(4-hydroxyphenyl)thiourea**

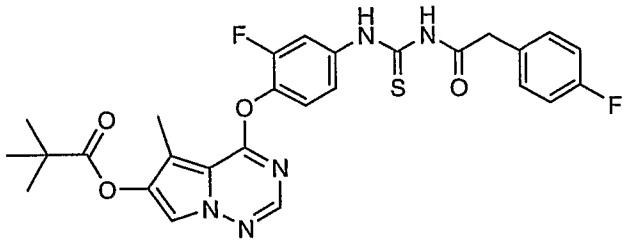
To a solution of 4-amino-phenol (11 mg, 0.1 mmol, Aldrich) in CH_2Cl_2 (0.55 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.5 mL, 0.125 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction was stirred at room temperature for 10 minutes, LC/MS analysis indicated formation of the title compound. The crude reaction mixture was used directly in the next reaction.

B) **Ethyl 4-(4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate**

To a room temperature solution of ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (7.2 mg, 0.03 mmol) (for preparation see U.S. Pat. 6,670,357, the disclosure of which is herein incorporated by reference) and DABCO (7 mg, 0.06 mmol) in acetonitrile (0.5 mL) was added 1-(2-(4-fluorophenyl)acetyl)-3-(4-hydroxyphenyl)thiourea (0.5 mL, 0.05 mmol). The reaction was shaken at room temperature. After 30 min, LC/MS analysis indicated mostly product. The reaction was stirred at room temperature overnight. The mixture was evaporated to dryness. Purification by silica gel chromatography (eluting with 1% methanol/dichloromethane) provided the desired product contaminated with impurities. A second purification by silica gel chromatography (1-6% Ethyl acetate/dichloromethane) again did not remove all of the impurities. The resulting solid mixture was washed with methanol and dried to provide the title compound (6

mg, 39%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 12.32 (s, 1H), 8.62 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.76 (m, 2H), 7.29 (m, 4H), 7.12 (m, 2H), 4.38 (q, 2H, J = 7.1 Hz), 3.72 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 508 $(M + H)^+$.

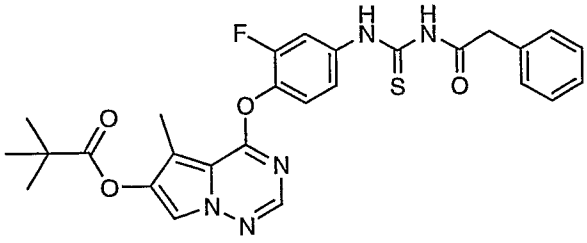
EXAMPLE 8



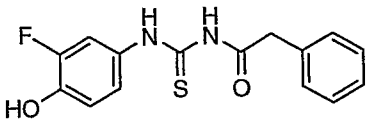
4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (60 mg, 0.19 mmol, Compound A of Example 3), 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (50 mg, 0.19 mmol, Compound D of Example 1) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 21.3 mg, 0.19 mmol) was added MeCN (5 mL). The reaction was stirred at RT for 1 h and concentrated *in vacuo*. The residue was purified by flash chromatography (eluted with 1 – 15% MeOH / CH_2Cl_2) to give the title compound (91 mg, 86 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.40 (s, 1H), 8.54 (s, 1H), 7.87 (m, 3H), 7.29 (m, 4H), 7.12 (m, 2H), 3.71 (s, 2H), 2.43 (s, 3H), 1.39 (s, 9H); MS(ESI$^+$) m/z 554 $(M + H)^+$.

EXAMPLE 9



4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate



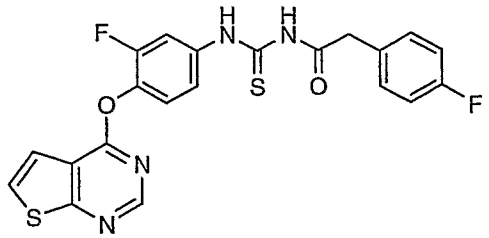
A) 1-(3-Fluoro-4-hydroxyphenyl)-3-(2-phenylacetyl)thiourea

To a solution of 4-amino-3-fluorophenol (50 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added a solution of 2-phenyl-1-thiocyanatoethanone (2 mL, 0.4 mmol, 0.2 M in ethyl acetate, Compound I of Example 1). The reaction was stirred at room temperature for 20 minutes, LC/MS analysis indicated formation of the title compound. The mixture was concentrated to give a residue that was used without further purification.

B) 4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

A vial was charged with 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (13.3 mg, 0.19 mmol, Compound D of Example 1), 1-(3-fluoro-4-hydroxyphenyl)-3-(2-phenylacetyl)thiourea (16 mg, 0.05 mmol), cesium carbonate (spatula tip) and DMF (2 mL) and warmed to 100 °C for 26 h. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatography to give the title compound (6.2 mg, 25 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.50 (s, 1H), 7.88 (m, 3H), 7.40 (m, 4H), 7.31 (m, 2H), 3.75 (s, 3H), 2.44 (s, 3H), 1.40 (s, 9H); MS(ESI$^+$) *m/z* 536 $(M + H)^+$.

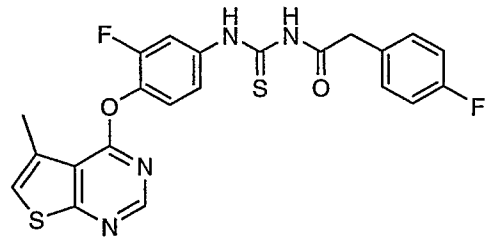
EXAMPLE 10



1-(4-(4a,7a-Dihydrothieno[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-5-thieno[2,3-*d*]pyrimidine (12.8 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC to give the title compound (13.8 mg, 40%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.62 (s, 1H), 8.53 (s, 1H), 7.93 (dd, 1H, J = 13.8, 2.2 Hz), 7.56 (m, 2H) 7.46 (m, 1H), 7.29 (m, 3H), 7.12 (m, 2H), 3.73 (s, 2H); MS(ESI$^+$) *m/z* 457 $(M + H)^+$.

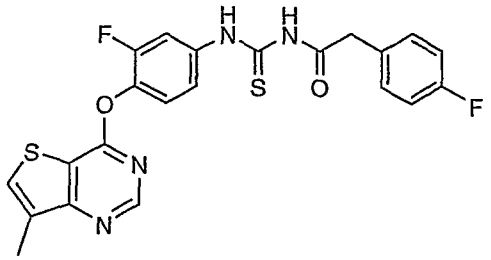
EXAMPLE 11



1-(3-Fluoro-4-(5-methyl-4a,7a-dihydrothieno[2,3-*d*]pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

In a similar manner as described for the preparation of Example 10, the title compound was prepared from commercially available 4-chloro-5-methylthieno[2,3-*d*]pyrimidine and 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3). ^{1}H NMR ($CDCl_3$) δ 12.42 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.88 (dd, 1H, J = 13.8, 2.2 Hz), 7.43 (s, 1H), 7.32 (m, 3H), 7.09 (m, 3H), 3.72 (S, 2H), 2.67 (s, 3H); MS(ESI$^+$) *m/z* 471 $(M + H)^+$.

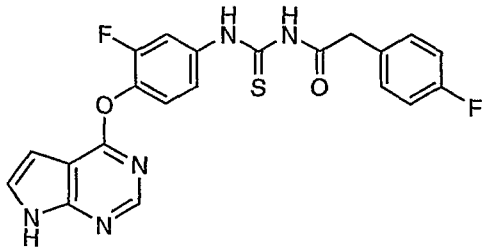
EXAMPLE 12



1-(3-Fluoro-4-(7-methyl-4a,7a-dihydrothieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-7-methylthieno[3,2-*d*]pyrimidine (13.8 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC to give the title compound (11.2 mg, 31%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.45 (s, 1H), 8.79 (s, 1H), 8.61 (s, 1H), 7.93 (dd, 1H, J = 13.8, 2.2 Hz), 7.46 (s, 1H), 7.43 (m, 1H), 7.28 (m, 3H), 7.12 (m, 2H), 3.72 (s, 2H), 2.51 (s, 3H); MS(ESI$^+$) *m/z* 471 $(M + H)^+$.

EXAMPLE 13

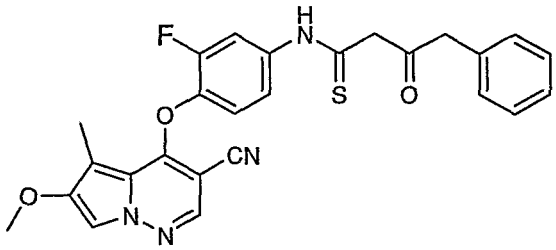


1-(4-(7,7a-Dihydro-4a*H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

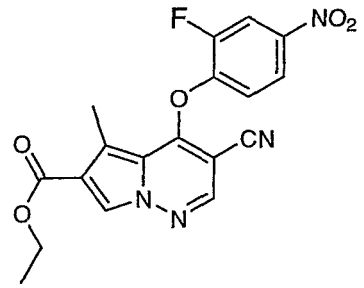
To a mixture 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (11 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified reverse phase preparative HPLC to give the title compound (5.3

mg, 16%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 7.95 (dd, 1H, J = 11.6, 2.8 Hz), 7.43 (m, 1H), 7.34 (m, 1H), 7.29 (m, 4H), 7.13 (app. T, 2H, J = 8.6 Hz), 6.80 (s, 1H), 3.72 (s, 2H); MS(ESI$^+$) m/z 440 $(M + H)^+$.

EXAMPLE 14

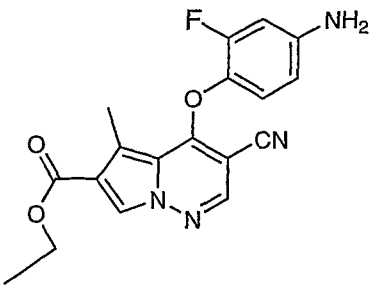


***N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-oxo-4-phenylbutanethioamide**



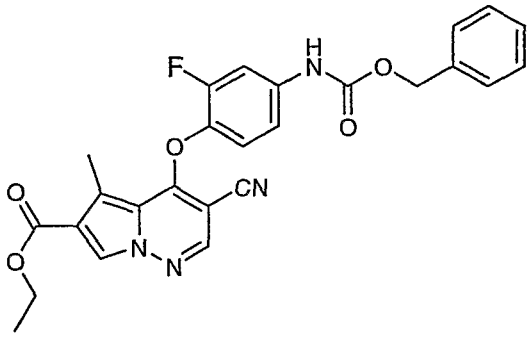
A) Ethyl 3-cyano-4-(2-fluoro-4-nitrophenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a mixture of ethyl 4-chloro-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (500 mg, 1.90 mmol, see U.S. Pat. Application No. 2004/063712, especially example 1, the disclosure of which is herein incorporated by reference in its entirety), 2-fluoro-4-nitrophenol (361 mg, 2.3 mmol) and K_2CO_3 (315 mg, 2.3 mmol) was added DMF (5 mL). The reaction stirred at RT for 2 h. The reaction was quenched with water (5 mL). The mixture was filtered and the solid was washed with water, dried to give the title compound (630 mg, 86%) as a light yellow solid.



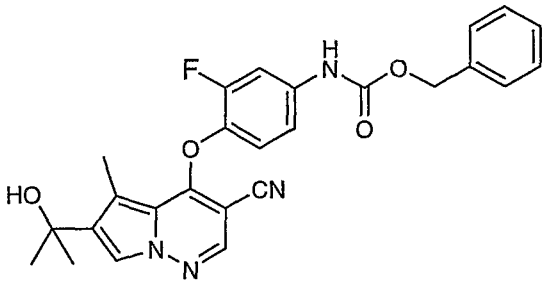
B) Ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a solution of ethyl 3-cyano-4-(2-fluoro-4-nitrophenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (630 mg, 1.64 mmol) in THF (5 mL) was added MeOH (5 mL) followed by Zn (200 mg, 3.0 mmol) and NH_4Cl (200 mg, 3.7 mmol). The reaction was heated at 60 °C for 2 h, filtered and concentrated *in vacuo*. The filtrate was purified by a SCX cartridge (eluted with 2M ammonia in MeOH) to give the title compound (420 mg, 72%) as a white solid.



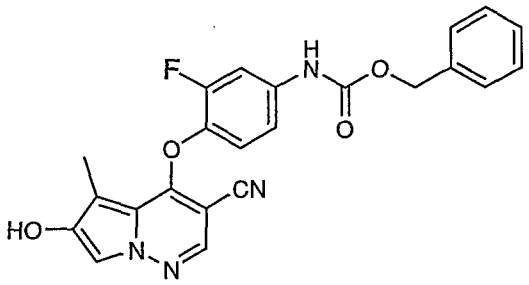
C) Ethyl 4-(4-(benzyloxycarbonyl)-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (420 mg, 1.19 mmol) in CH_2Cl_2 (10 mL) was added potassium carbonate (200 mg. 1.43 mmol) and benzyl chloroformate (0.261 mL, 1.43 mmol). The solution was stirred at RT for 24 h. The solution was filtered, concentrated *in vacuo* and recrystallized from EtOAc/CH_2Cl_2 to give the title compound (490 mg, 84%) as a white solid.



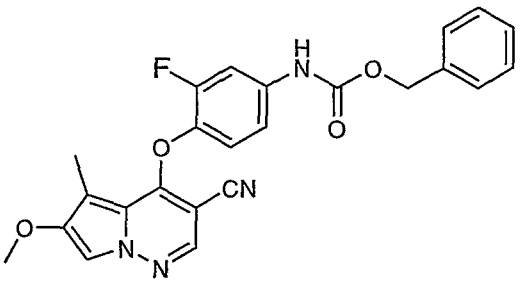
D) **Benzyl 4-(3-cyano-6-(2-hydroxypropan-2-yl)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate**

A solution of ethyl 4-(4-(benzyloxycarbonyl)-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (123 mg, 0.25 mmol) in THF (5 mL) was cooled to 0°C. A solution of methylmagnesium bromide (0.336 mL, 1.00 mmol, 3 M in THF) was added and the solution stirred at RT for 30 minutes. More methylmagnesium bromide (0.336 mL, 1.00 mmol, 3 M in THF) was added, and the solution was heated to 60 °C for 30 minutes. Ethyl acetate (10 mL) and water (5 mL) was added and the organic layer was washed, separated, dried and concentrated *in vacuo*. The mixture was purified by flash chromatography (20 - 50% EtOAc in CH_2Cl_2) to give the title compound (97 mg, 81%) as a white solid.



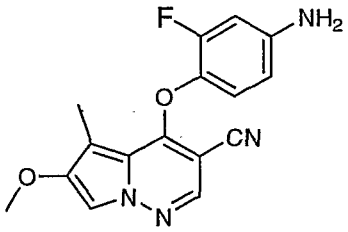
E) **Benzyl 4-(3-cyano-6-hydroxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate**

To a solution of benzyl 4-(3-cyano-6-(2-hydroxypropan-2-yl)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (97 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added to a premixed solution of hydrogen peroxide (0.033 mL) in water and boron trifluoride diethyerate (0.570 mL) at -5 °C. After 10 minutes, the reaction was quenched with sodium sulfite solution, dried, concentrated *in vacuo* and the residue recrystallized with EtOAc and hexane to give the title compound (70 mg, 80%) as a white solid.



F) Benzyl 4-(3-cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate

To a solution of benzyl 4-(3-cyano-6-hydroxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (25 mg, 0.06 mmol) in DMF (1 mL) was added cesium carbonate (39 mg. 0.12 mmol) and methyl iodide (0.05 mL, 0.072 mmol). The solution was stirred at RT for 2 h. Water (1 mL) was added and the product was extracted with ethyl acetate (2 x 5 mL), dried and concentrated to give the title compound (20 mg, 74%) as a white solid.



G) 4-(4-Amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile

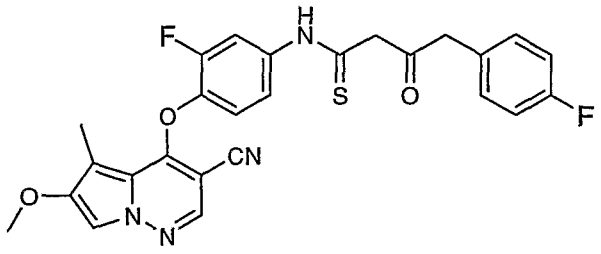
To a solution of benzyl 4-(3-cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (20 mg, 0.045 mmol) in ethanol (3 mL) was added 10% palladium on carbon (20 mg) and the mixture was stirred under balloon of hydrogen for 2 h. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to give the title compound (12 mg, 85%).

H) *N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-oxo-4-phenylbutanethioamide

To a solution of 4-(4-amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile (6 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was

added a solution of 2-phenyl-1-thiocyanatoethanone (0.1 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound F of Example 1). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to afford the title compound (3.90 mg, 40%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 8.01 (d, 1H, J = 12.7 Hz), 7.86 (s, 1H), 7.72 (s, 1H), 7.19 (m, 5H), 6.75 (m, 2H), 3.79 (s, 3H), 3.20 (m, 2H), 2.18 (s, 3H); MS(ESI$^+$) *m/z* 490 $(M + H)^+$.

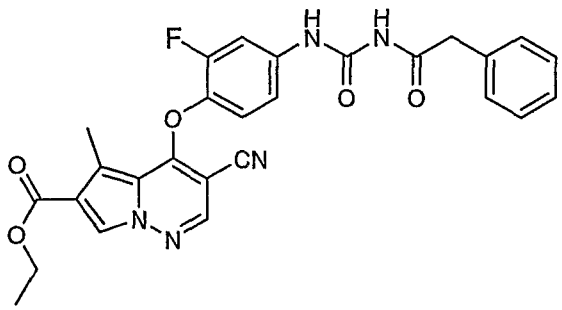
EXAMPLE 15



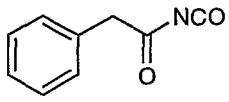
***N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-4-(4-fluorophenyl)-3-oxobutanethioamide**

The title compound was prepared from 4-(4-amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile (Compound G of Example 14) and 2-(4-fluorophenyl)-1-thiocyanatoethanone (Compound A of Example 2) by the procedure described for Compound H of Example 14. ^{1}H NMR (CD_3OD) δ 8.08 (dd, 1H, J = 12.7, 1.7 Hz), 7.95 (s, 1H), 7.80 (s, 1H), 7.34 (m, 3H), 7.19 (m, 1H), 7.04 (s, 2H), 6.87 (m, 2H), 3.89 (s, 3H), 3.30 (m, 2H), 2.27 (s, 3H); MS(ESI$^+$) *m/z* 508 $(M + H)^+$.

EXAMPLE 16



Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)ureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate



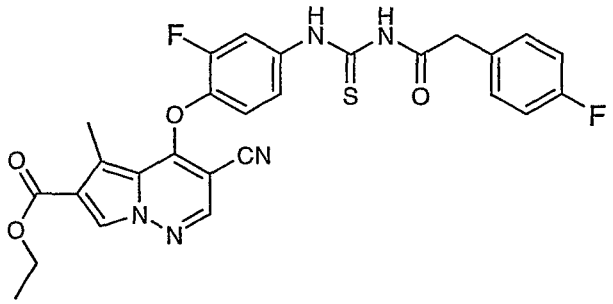
A) **2-Phenylacetyl isocyanate**

To a suspension of 2-phenylacetamide (68 mg, 0.5 mmol) in dichloroethane (2 mL) was added oxalyl chloride (0.175 mL, 2.0 mmol). The suspension dissolved quickly and a new suspension formed. LC/MS analysis of the reaction mixture after 5 min indicated none of the desired product had formed. The mixture was warmed to 80 °C, LC/MS after 30 min indicated a small amount of product. The reaction was heated at 70 °C for 2 days and became mostly clear. LC/MS analysis indicated mostly product. The mixture was shaken and heated at 80 °C for another 4 h. Almost all of the yellow solid on the walls of the reaction vessel had dissolved. The mixture was concentrated *in vacuo*. The residue dissolved in dichloroethane (1.5 mL), concentrated, and redissolved in dichloroethane (2 mL). The resulting 0.25 M solution was used without further purification.

B) **Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)ureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate**

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (7 mg, 0.02 mmol, Compound B of Example 14) in dichloromethane (0.3 mL) was added a solution of 2-phenylacetyl isocyanate (0.04 mmol, 0.25 M in dichloroethane,). The reaction was shaken at room temperature and monitored by LC/MS. After 2 h, all of the starting material had been consumed. The mixture was concentrated and the residue was purified by silica gel chromatography (1-10% ethyl acetate/dichloromethane) to give the title compound (8 mg, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 7.86 (s, 1H), 7.73 (dd, 1H, J = 12.2, 2.2 Hz), 7.43 – 7.21 (m, 7H), 4.37 (q, 2H, J = 7.1 Hz), 3.76 (s, 2H), 2.80 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 516 (M + H)$^+$.

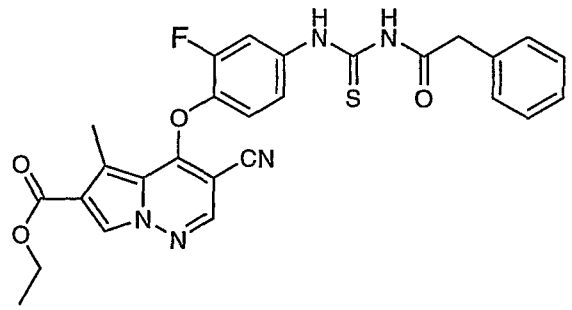
EXAMPLE 17



Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (10.6 mg, 0.03 mmol, Compound B of Example 14) in dichloromethane (0.5 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.04 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction instantly became cloudy. The reaction was shaken at room temperature for 2 h and then at 40 °C for 1 h. LC/MS analysis indicated that the reaction was complete. The reaction was concentrated and the residue was purified by silica gel chromatography (1-6% ethyl acetate/dichloromethane) to give the title compound (16 mg, 97%) as a yellow film/solid. ^{1}H NMR ($CDCl_3$) δ 12.52 (s, 1H), 8.63 (s, 1H), 8.24 (s, 1H), 8.01 (dd, 1H, J = 11.9, 2.4 Hz), 7.88 (s, 1H), 7.41 (m, 1H), 7.29 (m, 3H), 7.11 (m, 2H), 4.37 (q, 2H, J = 7.1 Hz), 3.71 (s, 2H), 2.78 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 550 $(M + H)^+$.

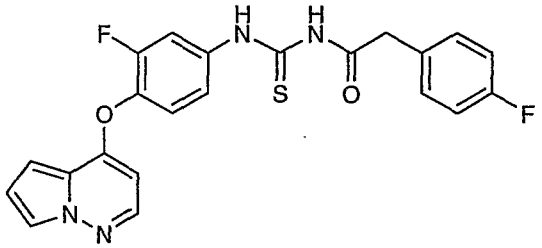
EXAMPLE 18



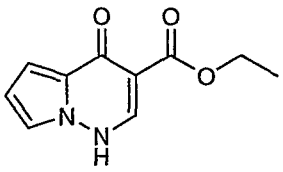
Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

The title compound was prepared from ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (Compound B of Example 14) and 2-phenyl-1-thiocyanatoethanone (0.1 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound I of Example 1) by the method described in Example 17. ^{1}H NMR ($CDCl_3$) δ 12.55 (s, 1H), 8.58 (s, 1H), 8.23 (s, 1H), 8.01 (dd, 1H, J = 11.9, 2.4 Hz), 7.88 (s, 1H), 7.42 (m, 4H), 7.30 (m, 3H), 4.37 (q, 2H, J = 7.1 Hz), 3.74 (s, 2H), 2.78 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 532 $(M + H)^+$.

EXAMPLE 19

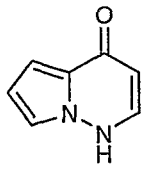


1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



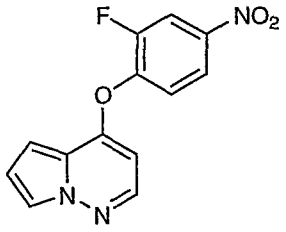
A) **Ethyl 4-oxo-1,4-dihydropyrrolo[1,2-*b*]pyridazine-3-carboxylate**

A mixture of *N*-aminopyrrole (575 mg, 7.0 mmol, commercially available) and diethyl ethoxymethylenemalonate (1.82 g, 8.4 mmol) was heated at 125 °C for 2 hours to give crude diethyl 2-((1*H*-pyrrol-1-ylamino)methylene)malonate. To this intermediate was added diphenyl ether (2 mL). The reaction was put under nitrogen and heated at 220 °C for 2 hours, while allowing the ethanol formed in the reaction to be distilled off. The reaction was cooled to room temperature and purified by silica gel flash chromatography (eluted with 100% CH_2Cl_2) to give the title compound (1.03 g, 71%) as a yellow solid.



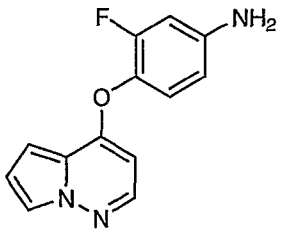
B) Pyrrolo[1,2-*b*]pyridazin-4(1*H*)-one

A mixture of ethyl 4-oxo-1,4-dihydropyrrolo[1,2-*b*]pyridazine-3-carboxylate (206 mg, 1.0 mmol), NaCl (64 mg, 1.1 mmol), water (0.054 mL, 3.0 mmol) and DMSO (2 mL) was heated at 150 °C for 3 hours. At the end of the reaction DMSO was distilled off and the residue was purified by silica gel flash chromatography (eluted with 1 - 10% EtOAc/CH_2Cl_2) to give the title compound (90 mg, 67%) as a light yellow solid.



C) 4-(2-Fluoro-4-nitrophenoxy)*H*-pyrrolo[1,2-*b*]pyridazine

To a mixture of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-one (13.4 mg, 0.10 mmol), 3,4-difluoronitrobenzene (24 mg, 0.15 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 22 mg, 0.20 mmol) was added MeCN (0.7 mL). The reaction was heated at 70 °C for 72 h and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (eluted with 100% CH_2Cl_2) to give the title compound (20 mg, 73%) as a yellow solid.



D) 4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine

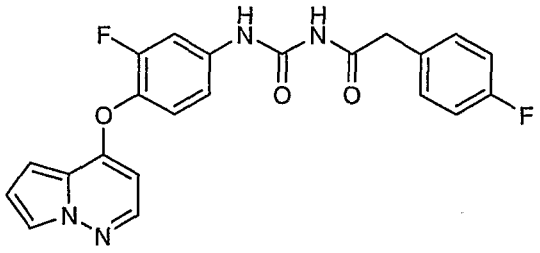
To a solution of 4-(2-fluoro-4-nitrophenoxy)*H*-pyrrolo[1,2-*b*]pyridazine (17 mg, 0.062 mmol) in THF (1.2 mL) was added MeOH (0.8 mL) followed by Zn (100

mg, 1.5 mmol) and NH_4Cl (43 mg, 0.80 mmol). The reaction was heated at 70 °C for 90 minutes and concentrated *in vacuo*. To the residue was added CH_2Cl_2 (2 mL) and a few drops of Et_3N. The solid was partially dissolved and the mixture was filtered. The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 6% EtOAc/CH_2Cl_2) to give the title compound (15 mg, 99%) as a white solid.

E) 1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a solution of 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (7 mg, 0.03 mmol) in CH_2Cl_2 (0.3 mL) was added a 0.25 M solution of isocyante (0.16 mL, 0.04 mmol, 0.25 M in ethyl acetate, Compound A of Example 2) in EtOAc. The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 5% EtOAc/CH_2Cl_2) to give the title compound (12 mg, 95%) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.67 (s, 1H), 7.92 (dd, 1H, J = 11.5, 2.4 Hz), 7.85 (d, 1H, J = 5.3 Hz), 7.77 (dd, 1H, J = 2.6, 1.5 Hz), 7.39 (m, 1H), 7.28 (m, 3H), 7.13 (m, 2H), 6.83 (dd, 1H, J = 4.3, 2.6 Hz), 6.74 (dd, 1H, J = 4.3, 1.5 Hz), 5.70 (d, 1H, J = 5.3 Hz), 3.73 (s, 2H); MS(ESI$^+$) *m/z* 439 $(M + H)^+$.

EXAMPLE 20

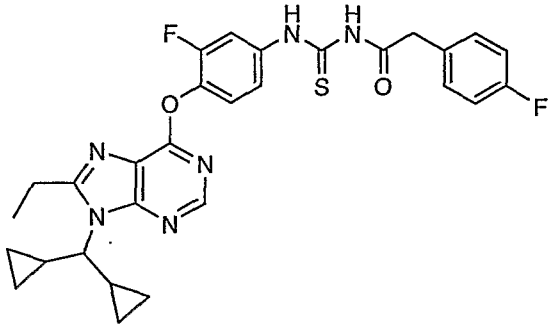


1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of the 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (5 mg, 0.02 mmol, Compound D of Example 19) in CH_2Cl_2 (0.3 mL) was added a solution of 2-(4-fluorophenyl)acetyl isocyanate (0.16 mL, 0.04 mmol, 0.25 M in dichloromethane, Compound C of Example 4). The reaction was

stirred at room temperature for 2 h, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 15% EtOAc/CH_2Cl_2) to give the title compound (5.5 mg, 63%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.68 (s, 1H), 8.69 (s, 1H), 7.83 (d, 1H, J = 5.3 Hz), 7.77 (dd, 1H, J = 2.6, 1.5 Hz), 7.68 (dd, 1H, J = 11.5, 2.4 Hz), 7.33 – 7.17 (m, 4H), 7.09 (m, 2H), 6.82 (dd, 1H, J = 4.3, 2.6 Hz), 6.74 (dd, 1H, J = 4.3, 1.5 Hz), 5.69 (d, 1H, J = 5.3 Hz), 3.76 (s, 2H); MS(ESI$^+$) m/z 423 $(M + H)^+$.

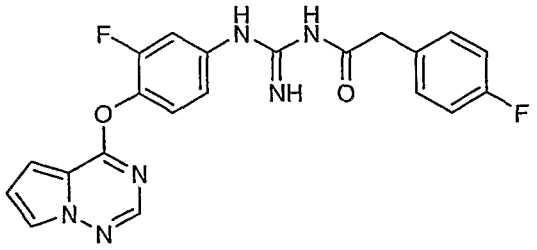
EXAMPLE 21



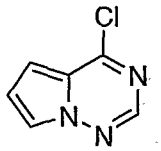
1-(4-(9-(Dicyclopropylmethyl)-8-ethyl-9*H*-purin-6-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 6-chloro-9-(dicyclopropylmethyl)-8-ethyl-9*H*-purine (20.7 mg, 0.075 mmol, PCT Appl. WO 99/01454, U.S. Pat. 6,143,743, example 831, the disclosure of which is herein incorporated by reference) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phased preparative HPLC to give the title compound (15.3 mg, 36%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.43 (m, 1H), 8.48 (m, 1H), 8.40 (m, 1H), 7.92 (m, 1H), 7.28 (m, 4H), 7.13 (m, 2H), 3.72 (s, 2H), 3.34 (m, 3H), 1.53 (m, 3H), 0.81 (m, 2H), 0.46 (m, 4H), 0.23 (m, 2H); MS(ESI$^+$) m/z 489 $(M + H)^+$.

EXAMPLE 22

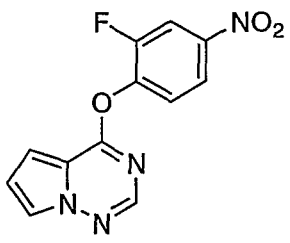


1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)guanidine



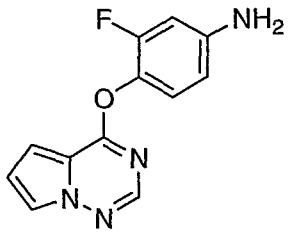
A) 4-Chloropyrrolo[2,1-*f*][1,2,4]triazine

To a solution of pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (3.70 g, 27.4 mmol, see generally, PCT Appl. WO 2000/071129 the disclosure of which is herein incorporated by reference in its entirety) in 40 mL of toluene at room temperature was added 4.77 mL (27.4 mmol) of diisopropylethylamine followed by 7.70 mL (82.6 mmol) of phosphorus oxychloride. The reaction mixture was heated at 100 °C for 18 h. After cooling to room temperature, the reaction was slowly added to a solution of 5% aq $NaHCO_3$ solution (100 mL) at 0 °C. Upon completion of the addition, the biphasic mixture was allowed to stir at room temperature for 30 min. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the pooled organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude product (4.10 g, 97%) as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.80 (dd, 1H, J = 2.4, 1.5 Hz), 6.91 (m, 2H).



B) 4-(2-Fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine

4-Chloropyrrolo[2,1-*f*][1,2,4]triazine (4.1g, 27 mmol), 2-fluoro-4-nitrophenol (5.0 g, 32 mmol), and potassium carbonate (7.4 g, 53 mmol) in 100 mL of dimethylformamide was stirred at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude product was purified by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:4) to give the title compound (4.25 g, 58%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.09 (m, 2H), 7.88 (s, 1H), 7.77 (dd, 1H, J = 2.6, 1.2 Hz), 7.46 (t, 1H, J = 7.6 Hz), 6.98 (dd, 1H, J = 4.6, 1.4 Hz), 6.84 (dd, 1H, J = 4.5, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 160.6, 154.3 (J = 254 Hz), 146.5, 145.8, 144.8 (J = 12.9 Hz), 125.0, 121.7, 120.7, 114.5, 113.9, 113.6 (J = 23.2 Hz), 103.6.



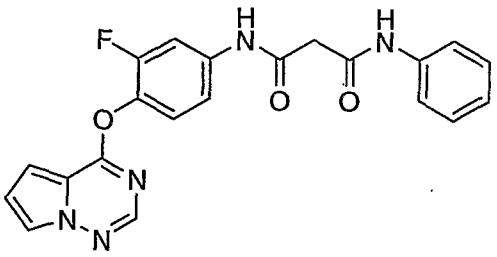
C) 3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (4)

To a solution of 4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine (4.25 g, 15.5 mmol) in 40 mL of tetrahydrofuran and 60 mL of methanol at 0 °C was added zinc dust (3.04 g, 46.5 mmol, <10 micron) followed by ammonium chloride (2.49 g, 46.5 mmol). The mixture was stirred at room temperature overnight. Additional zinc dust (6.08 g, 93 mmol) and ammonium chloride (5.0 g, 93 mmol) were added and the reaction was allowed to stir at room temperature for 4 h. The heterogeneous mixture was filtered through a thin pad of Celite® with methanol and the filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:1) gave the title compound (3.5 g, 92%) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.70 (dd, 1H, J = 2.5, 1.6 Hz), 6.98 (t, 1H, J = 8.5 Hz), 6.92 (dd, 1H, J = 4.4, 1.4 Hz), 6.77 (m, 1H), 6.42 (m, 2H), 3.71 (br s, 2H); MS(ESI$^+$) *m/z* 245.2 $(M + H)^+$.

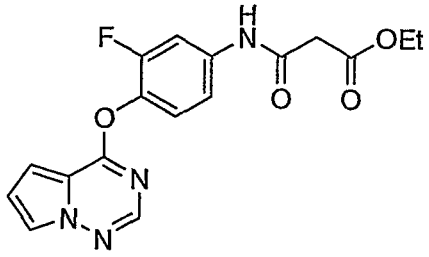
D) 1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)guanidine

To a test tube containing 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.082 mmol) and 1-(2-(4-fluorophenyl)acetyl)-2-methylisothiourea (20 mg, 0.086 mmol) was added 0.3 mL of toluene followed by diisopropylethylamine (15 µL, 0.086 mmol). The reaction was stirred at 110 °C for 6 h. Additional portions of 1-(2-(4-fluorophenyl)-acetyl)-2-methylisothiourea (20 mg, 0.086 mmol) and diisopropylethylamine (15 µL, 0.086 mmol) were added. After stirring at 110 °C overnight, the reaction was cooled to room temperature and purified directly by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:1) to give the title compound as a white solid. The solid was treated with 4 N HCl in dioxane at 0°C for 30 min. The solution was concentrated *in vacuo* to give the HCl salt of the title compound (15 mg, 40%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 13.8 (br s, 1H), 11.5 (br s, 1H), 9.48 (br s, 1H), 7.85 (s, 1H), 7.78 (dd, 1H, J = 2.5, 1.4 Hz), 7.30 (m, 5H), 7.01 (m, 3H), 6.85 (m, 1H); MS(ESI$^+$) *m/z* 423.1 $(M+H)^+$.

EXAMPLE 23

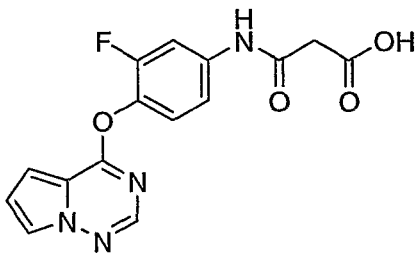


N^1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-phenylmalonamide



A) Ethyl 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoate

To a solution of 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (112 mg, 0.459 mmol, Compound C of Example 22) in methylene chloride (4 mL) at 0 °C was added 96 µL (0.55 mmol) of diisopropylethylamine followed by 61 µL (0.48 mmol) of ethyl 3-chloro-3-oxopropanoate. The reaction was stirred at 0 °C for 1 h and was then quenched with 10 mL of saturate $NaHCO_3$ solution. The aqueous layer was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product as a yellow oil that solidified on standing (180 mg). ^1H NMR ($CDCl_3$) δ 9.45 (br s, 1H), 7.89 (s, 1H), 7.71 (dd, 1H, J = 2.5, 1.5 Hz), 7.68 (dd, 1H, J = 11.8, 2.2 Hz), 7.18 (m, 2H), 6.93 (dd, 1H, J = 4.4, 1.4 Hz), 6.78 (dd, 1H, J = 4.4, 2.6 Hz), 4.19 (q, 2H, J = 7.2 Hz), 3.41 (s, 2H), 1.25 (t, 3H, J = 7.2 Hz); MS(ESI$^+$) *m/z* 359.1 $(M + H)^+$.



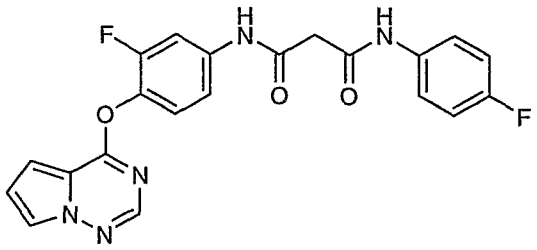
B) 3-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid

To a solution of the above crude ethyl 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoate (180 mg) in ethanol (10 mL) at 0 °C was added 1 N aq NaOH solution (10 mL). After stirring at 0 °C for 3 h, the reaction was washed with 20 mL of EtOAc. The EtOAc layer was back-extracted with 20 mL of 1 N aq NaOH solution. The combined aqueous solution was acidified to pH 5 with 1 N aq HCl solution. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude acid which was used without further purification (150 mg). MS(ESI$^+$) *m/z* 331.1 $(M^+ + H)^+$.

C) N^1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-phenylmalonamide

A solution of 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid (17 mg, 0.052 mmol), BOP reagent (34 mg, 0.077 mmol), 4-methylmorpholine (28 μL, 0.26 mmol), and aniline (4.7 μL, 0.052 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 16 h. The reaction was diluted with EtOAc (4 mL) and washed with water, 10% aq LiCl solution, and brine (1 x 3 mL each). The organic solution was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 7:3) gave the desired compound as a white solid. The product was lyophilized with acetonitrile / water to give the title compound (12 mg, 57%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 9.23 (br s, 1H), 8.22 (br s, 1H), 7.90 (s, 1H), 7.72 (m, 1H), 7.46 (d, 1H, J = 8.2 Hz), 7.20 (m, 7H), 6.95 (m, 1H), 6.78 (m, 1H), 3.47 (s, 2H); MS(ESI$^+$) *m/z* 406.1 $(M+H)^+$.

EXAMPLE 24

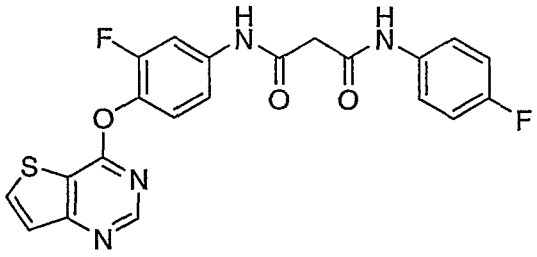


N^1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

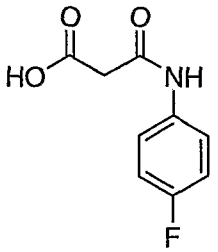
A solution of 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid (18 mg, 0.55 mmol, Compound B of Example 23), BOP reagent (36 mg, 0.082 mmol), 4-methylmorpholine (30 μL, 0.27 mmol), and 4-fluoroaniline (5.2 μL, 0.055 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 16 h. The reaction was diluted with EtOAc (4 mL) and washed with water, 10% aq LiCl solution, and brine (1 x 3 mL each). The organic solution was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 7:3) gave the desired compound as a white solid. The product was lyophilized with acetonitrile / water to give the title compound (14 mg, 61%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 9.28 (br s, 1H), 8.64 (br s, 1H), 7.89 (s, 1H), 7.73 (dd, 1H, J = 2.5, 1.5 Hz), 7.69 (dd,

1H, J = 11.6, 1.9 Hz), 7.42 (m, 3H), 7.21 (m, 1H), 6.97 (m, 3H), 6.80 (dd, 1H, J = 4.5, 2.6 Hz), 3.49 (s, 2H); MS(ESI$^+$) m/z 424.1 $(M+H)^+$.

EXAMPLE 25



N^1-(3-Fluoro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

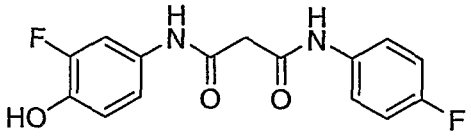


A) **3-(4-Fluorophenylamino)-3-oxopropanoic acid**

To a solution of ethyl 3-chloro-3-oxopropanoate (5.0 mL, 40 mmol, Aldrich) in methylene chloride (100 mL) at 0 °C was added diisopropylethylamine (8.4 mL, 48 mmol) followed by 4-fluoroaniline (3.6 mL, 38 mmol, Aldrich). The reaction was stirred at room temperature overnight and was then quenched with 100 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with chloroform (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product as a yellow oil that solidified on standing (10 g). ^{1}H NMR ($CDCl_3$) δ 9.30 (br s, 1H), 7.55 (m, 2H), 7.05 (t, 2H, J = 8.8 Hz), 4.28 (q, 2H, J = 7.2 Hz), 3.49 (s, 2H), 1.35 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 226.1 $(M+H)^+$.

The above ester was dissolved in 100 mL of ethanol and cooled to 0 °C. 1 N aq NaOH solution (100 mL) was added and the reaction was stirred at 0 °C for 1 h. The reaction was concentrated to remove ethanol. The aqueous solution was extracted with EtOAc (50 mL) and was then made acidic with 1 N aq HCl solution. The

aqueous solution was extracted with EtOAc (5 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product (6.31 g, 84%) as a yellow solid which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 12.9 (br s, 1H), 10.3 (br s, 1H), 7.59 (m, 2H), 7.16 (t, 2H, J = 8.9 Hz), 3.34 (s, 2H); MS(ESI$^+$) m/z 198.4 $(M+H)^+$.



B) N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide

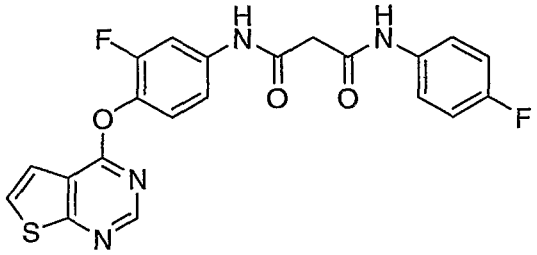
To a solution of 2-fluoro-4-nitrophenol (1.00 g, 6.37 mmol) in 4 mL of tetrahydrofuran and 6 mL of methanol at 0 °C was added zinc dust (2.08 g, 31.8 mmol, <10 micron) followed by ammonium chloride (1.70 g, 31.8 mmol). The mixture was stirred at room temperature overnight. The heterogeneous mixture was filtered through a thin pad of Celite® with methanol and the filtrate was concentrated *in vacuo* to give a brown solid which was used without further purification (656 mg, 81%).

3-(4-Fluorophenylamino)-3-oxopropanoic acid (197 mg, 1.00 mmol) was dissolved in 4 mL of dimethylformamide. Triethylamine (140 µL, 1.00 mmol) was added and the solution was cooled to 0 °C. 4-Amino-2-fluorophenol (127 mg, 1.00 mmol, Aldrich) was added followed BOP reagent (442 mg, 1.00 mmol). The reaction was allowed to warm to room temperature and was then stirred at room temperature for 3 h. The reaction mixture was concentrated to remove methylene chloride and water was added to precipitate the product. Filtration and trituration with water gave the title compound (211 mg, 69%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.61 (m, 2H), 7.51 (dd, 1H, J = 13, 2.5 Hz), 7.08 (m, 3H), 6.88 (t, 1H, J = 9.4 Hz), 3.51 (s, 2H); MS(ESI$^+$) m/z 307.4 $(M+H)^+$.

C) N^1-(3-Fluoro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide (46 mg, 0.15 mmol), 4-chlorothieno[3,2-*d*]pyrimidine (17 mg, 0.10 mmol), cesium carbonate (49 mg, 0.15 mmol), and copper(I) chloride (10 mg, 0.10 mmol) were placed in a test tube. The tube was sealed, flushed with nitrogen, charged with 1-methyl-2-pyrrolidinone (0.3 mL) followed by 2,2,6,6-tetramethyl-3,5-heptanedione (4.0 µL, 0.02 mmol). The reaction was stirred at 120 °C for 2 h. The reaction mixture was purified by preparative HPLC. The appropriate fraction was concentrated to remove methanol and the resulting aqueous solution was made basic with saturated $NaHCO_3$ solution (5 mL). The aqueous solution was extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired product as a colorless oil. Lyophilization with methanol / water gave the title compound (23 mg, 52%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.54 (s, 1H), 8.21 (d, 1H, J = 5.5 Hz), 7.69 (dd, 1H, J = 12.4, 2.0 Hz), 7.49 (m, 3H), 7.27 (m, 2H), 6.96 (t, 2H, J = 8.9 Hz), 3.47 (s, 2H); MS(ESI$^+$) *m/z* 441.1 $(M+H)^+$.

EXAMPLE 26

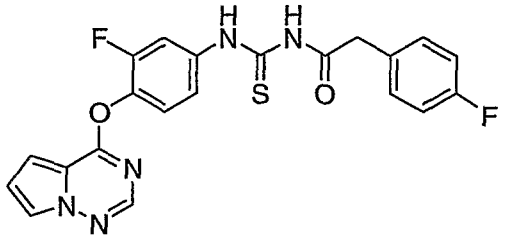


N^1-(3-Fluoro-4-(thieno[2,3-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide (46 mg, 0.15 mmol, Compound B of Example 25), 4-chlorothieno[2,3-*d*]pyrimidine (17 mg, 0.10 mmol), cesium carbonate (49 mg, 0.15 mmol), and copper(I) chloride (10 mg, 0.10 mmol) were placed in a test tube. The tube was sealed, flushed with nitrogen, charged with 1-methyl-2-pyrrolidinone (0.3 mL) followed by 2,2,6,6-tetramethyl-3,5-heptanedione (4.0 µL, 0.02 mmol). The reaction was stirred at 120 °C for 1 h. The reaction mixture was purified by preparative HPLC. The appropriate fraction was concentrated to remove methanol and the resulting aqueous solution was made basic with saturated $NaHCO_3$ solution (5 mL). The aqueous solution was extracted with

EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired product as a colorless oil. Lyophilization with methanol / water gave the title compound (27 mg, 61%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.7 (s, 1H), 10.4 (s, 1H), 8.77 (s, 1H), 8.15 (d, 1H, J = 5.9 Hz), 7.95 (dd, 1H, J = 12.8, 2.0 Hz), 7.85 (d, 1H, J = 5.9 Hz), 7.77 (m, 2H), 7.54 (m, 2H), 7.30 (t, 2H, J = 8.8 Hz), 3.48 (s, 2H); MS(ESI$^+$) m/z 441.1 (M + H)$^+$.

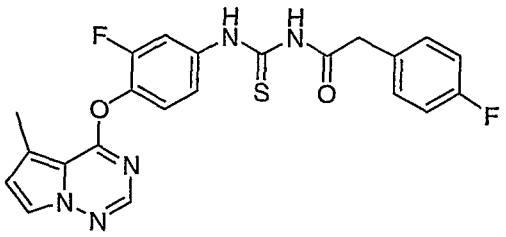
EXAMPLE 27



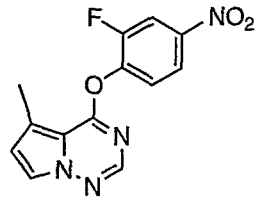
1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)-acetyl)thiourea

To a homogeneous solution of sodium thiocyanate (21 mg, 0.26 mmol) in ethyl acetate (1 mL), at room temperature under a nitrogen atmosphere, was added 4-fluorophenyl-acetyl chloride (28 µL, 0.20 mmol). The mixture was stirred for 30 minutes before being added directly to a homogeneous solution of 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]-triazin-4-yloxy)benzenamine (37 mg, 0.15 mmol, Compound C of Example 22) in anhydrous dichloromethane (3 mL), under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 4 h before being concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with chloroform, afforded the title compound (55 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.50 (s, 1H), 7.97 (s, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.42 (m, 1H), 7.35-7.25 (m, 3H), 7.17-7.10 (m, 2H), 7.05-7.02 (m, 1H), 6.85-6.90 (m, 1H), 3.72 (s, 2H); HRMS(ESI), 440.0993 (M + H)$^+$ calc, 440.0988 (M + H)$^+$ found.

EXAMPLE 28

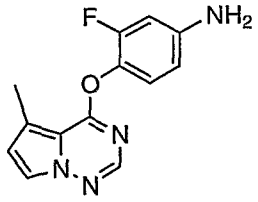


1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine**

To a mixture of 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (3.37 g, 20.11 mmol, PCT Appl.WO 2000/071129, U.S. pat. application 2003/0186982, the disclosure of which is herein incorporated by reference) and 2-fluoro-4-nitrophenol (3.48 g, 22.12 mmol) in anhydrous DMF (100 mL), stirred for 5 minutes under a nitrogen atmosphere, was added anhydrous potassium carbonate (6.11 g, 44.24 mmol). The mixture was heated at 60 °C for 15 h before 2-fluoro-4-nitrophenol (1.00 g, 6.37 mmol) was added and stirring continued at 60 °C for 4.5 h. The mixture was cooled to room temperature, diluted with dichloromethane, washed sequentially with water and 10% aqueous lithium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a tan solid. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with chloroform, afforded the title compound (4.19 g, 72%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.13 (m, 2H), 7.83 (s, 1H), 7.73 (d, 1H, J = 2.6 Hz); 7.58-7.53 (m, 1H), 6.69 (d, 1H, J = 2.4 Hz), 2.62 (s, 3H); HRMS(ESI), 289.0737 $(M + H)^+$ calc, 289.0733 $(M + H)^+$ found.



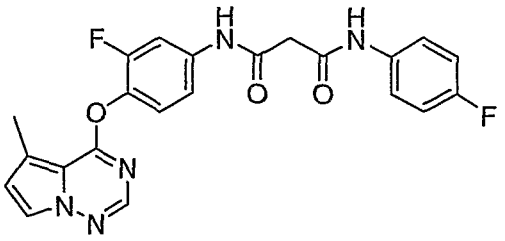
B) 3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (3.04 g, 10.55 mmol) in anhydrous methanol (60 mL) and anhydrous tetrahydrofuran (40 mL), at ambient temperature under nitrogen atmosphere, was added zinc dust (6.90 g, 105 mmol) and ammonium chloride (5.64g, 105 mmol). The mixture was stirred for 7 h before the catalyst was filtered off and the filtrate was concentrated *in vacuo* to a pale yellow solid which was partitioned between chloroform and water. The aqueous layer was then extracted twice with chloroform. The combined chloroform layers were washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield the title compound (2.51 g, 92%) as a solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.64 (d, 1H, J = 2.6 Hz); 7.08-7.03 (m, 1H), 6.61 (d, 1H, J = 2.4 Hz), 6.55-6.45 (m, 2H), 3.78 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 259.0995 $(M + H)^+$ calc, 259.0997 $(M + H)^+$ found.

C) 1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (39 mg, 0.15 mmol) was converted to the title compound (42 mg, 62%) in a manner similar to the preparation of Example 27. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.48 (s, 1H), 7.92-7.82 (m, 2H), 7.68 (d, 1H, J = 2.5 Hz), 7.39-7.27 (m, 4H), 7.15-7.10 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.72 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 454.1149 $(M + H)^+$ calc, 454.1154 $(M + H)^+$ found.

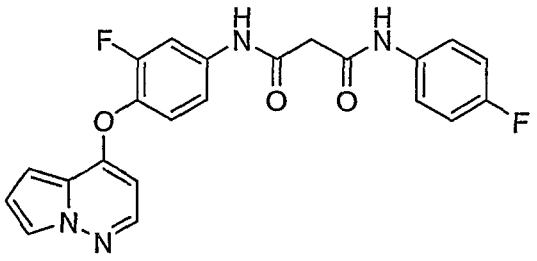
EXAMPLE 29



N^1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluoro-phenyl)malonamide

To a homogeneous solution of 3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (52 mg, 0.20 mmol, Compound B of Example 28) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (39 mg, 0.20 mmol, Compound A of Example 25) in anhydrous DMF (2 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (52 µL, 0.30 mmol). The mixture was stirred for 5 minutes before o-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (96 mg, 0.30 mmol) was added in one portion. The mixture was stirred for 17.5 h before the reaction was concentrated *in vacuo* to remove volatiles. The resultant residue was diluted with ethyl acetate and washed twice with 10% aqueous lithium chloride before being concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 1% methanol in chloroform, afforded an off-white solid that was triturated and sonicated in the presence of anhydrous ethyl ether (3 mL). The title compound (66 mg, 75%) was isolated by filtration as a white solid. ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1H), 8.67 (s, 1H), 7.83 (s, 1H), 7.80-7.73 (m, 1H), 7.67 (d, 1H, J = 2.5 Hz), 7.54-7.49 (m, 2H), 7.28-7.26 (m, 2H), 7.10-7.02 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.56 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 436.1221 $(M + H)^+$ calc, 436.1230 $(M + H)^+$ found.

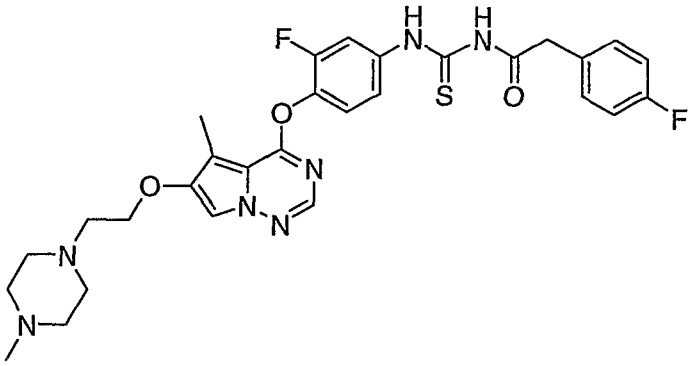
EXAMPLE 30



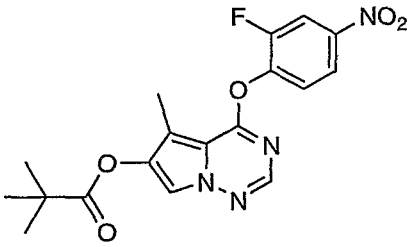
N^1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

A solution of 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (51 mg, 0.21 mmol, Compound D of Example 19) in DMF (1 mL) was treated with 3-(4-fluorophenylamino)-3-oxopropanoic acid (41 mg, 0.21 mmol, Compound A of Example 25), DIPEA (42 μL, 0.25 mmol) and TBTU (81 mg, 0.25 mmol) and the mixture stirred at RT for 16 h. The mixture was concentrated *in vacuo* to remove the DMF and the residue was partitioned between EtOAc (2 mL) and saturated sodium bicarbonate solution (2 mL). The EtOAc phase was washed with 10% aqueous LiCl (2 mL), brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was triturated twice with EtOAc and two times with MeOH to give the title compound (17 mg, 19%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.56 (s, 1H), 10.28 (s, 1H), 8.01, (d, 1H, J = 5.4 Hz), 7.92-7.91 (m, 1H), 7.65-7.62 (m, 2H), 7.48-7.44 (m, 2H), 7.22-7.15 (m, 3H), 6.86 (dd, 1H, J = 4.2, 2.7 Hz), 6.72 (dd, 1H, J = 4.4, 1.4 Hz), 5.81 (d, 1H, J = 5.4 Hz), 3.51 (s, 2H); MS(ESI$^+$) *m/z* 423.3 $(M+H)^+$.

EXAMPLE 31

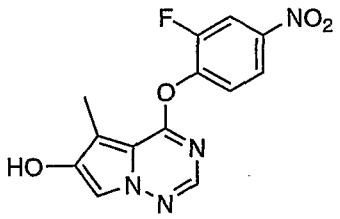


1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*]-[1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, bis-hydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-yl pivalate

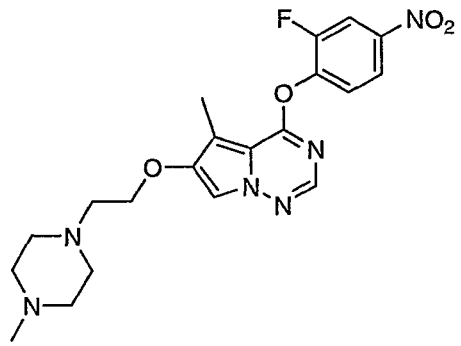
To a homogeneous solution of 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (1.00 g, 3.74 mmol, Compound D of Example 1) and 2-fluoro-4-nitrophenol (588 mg, 3.74 mmol) in anhydrous acetonitrile (25 mL), at room temperature under a nitrogen atmosphere, was added DABCO (462 mg, 4.12 mmol). The mixture was then heated at 50 °C for 3 h. The mixture was cooled to room temperature then partitioned between chloroform and saturated aqueous ammonium chloride. The aqueous layer was extracted twice with chloroform. The combined organic layers were washed once each with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a pale yellow solid that was used in the next step without further purification. MS(ESI$^+$) *m/z* 389.1 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-yl pivalate (1.45 g, 3.74 mmol) in absolute ethanol (19 mL), at room temperature under a nitrogen atmosphere, was added 1 N aqueous sodium hydroxide. The reaction mixture was stirred at ambient temperature for 1.5 h before being neutralized to pH 7 with 1 N aqueous hydrochloride. The reaction mixture was concentrated to remove ethanol, before being partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed twice with water, once with

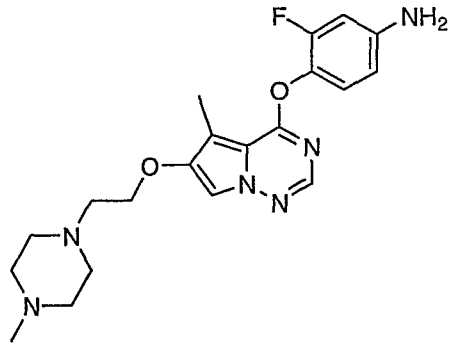
saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 2:1 hexane/ethyl acetate, afforded the title compound (602 mg, 53% for Steps A-B) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.12 (m, 2H), 7.84 (s, 1H), 7.58-7.53 (m, 1H), 7.53 (s, 1H), 4.76 (s, 1H), 2.48 (s, 3H); MS(ESI$^+$) *m/z* 305.2 $(M + H)^+$.



C) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)-ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

To a homogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (100 mg, 0.33 mmol) and triphenylphosphine (129 mg, 0.49 mmol) in 4 mL of 1:1 anhydrous dichlormethane/anhydrous tetrahydrofuran, cooled to 0 °C under a nitrogen atmosphere, was added dropwise a mixture of 2-(4-methylpiperazin-1-yl)ethanol (71 mg, 0.49 mmol) and diisopropylazodicarboxylate (0.10 μL, 0.49 mmol) in 2mL of 1:1 anhydrous dichlormethane/anhydrous tetrahydrofuran. The mixture was stirred and allowed to warm to room temperature. The reaction was stirred for twelve hours before being concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500 mm, 30 minute gradient from 50% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined, neutralized with saturated aqueous sodium bicarbonate, and then concentrated *in vacuo* to remove methanol. The mixture was extracted with chloroform (3 x 10 mL). The combined organic layers were washed once each with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield the title compound (34 mg, 24%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.10 (m, 2H), 7.82 (s, 1H), 7.58-7.52 (m, 1H),

7.49 (s, 1H), 4.16 (t, 2H, J = 5.7 Hz), 2.87 (t, 2H, J = 5.7 Hz), 2.80-2.40 (m, 8H), 2.45 (s, 3H), 2.31 (s, 3H); MS(ESI$^+$) m/z 431.3 $(M + H)^+$.



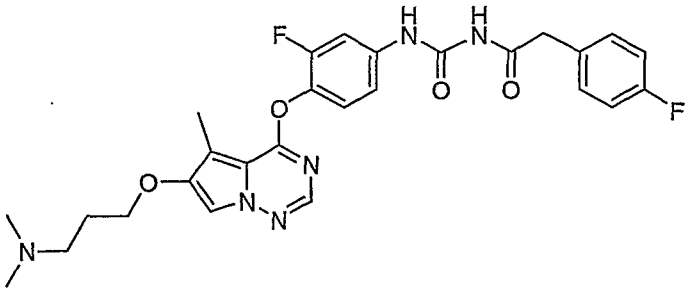
D) **3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*]-[1,2,4]triazin-4-yloxy)benzenamine**

4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (20 mg, 0.05 mmol) was converted to the title compound (16 mg, 87%) in a manner similar to the preparation of Compound B of Example 28. ^{1}H NMR ($CDCl_3$) δ 7.86-7.83 (m, 1H), 7.50-7.38 (m, 2H), 7.09-7.00 (m, 1H), 6.56-6.45 (m, 1H), 4.14 (t, 2H, J = 5.5 Hz), 2.99-2.38 (m, 18H); MS(ESI$^+$) m/z 401.4 $(M + H)^+$.

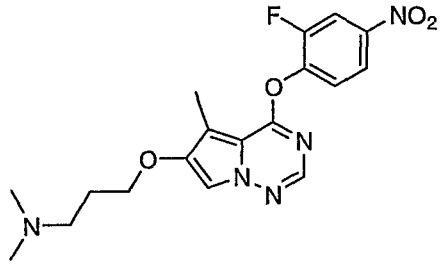
E) **1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, bis-hydrochloride salt**

3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]-triazin-4-yloxy)benzenamine (18 mg, 0.05 mmol) was converted to the title compound (7 mg, 26%) in a manner similar to the preparation of Example 27. Treatment with 1 N aqueous hydrochloric acid (0.05 mL, 0.05 mmol), followed by lyophilization, resulted in the title compound as a pale yellow solid (5 mg, 64%). ^{1}H NMR (CD_3OD) δ 8.06-7.99 (m, 2H), 7.83 (s, 1H), 7.79 (s, 1H), 7.48-7.30 (m, 4H), 7.13-7.02 (m, 2H), 4.56-4.45 (m, 2H), 3.87-3.59 (m, 4H), 3.09-2.44 (m, 15H); HRMS(ESI), 596.2255 $(M+H)^+$ calc, 596.2261 $(M + H)^+$ found.

EXAMPLE 32

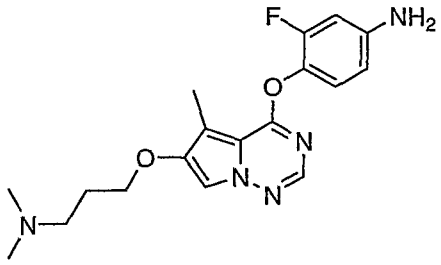


1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) **3-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N*,*N*-dimethylpropan-1-amine**

To a mixture of polymer bound triphenylphosphine (3 mmol triphenylphosphine per 1 g of resin, 583 mg, 1.75 mmol) in anhydrous tetrahydrofuran (5 mL), at 0 °C under a nitrogen atmosphere, was added diethylazodicarboxylate (138 µL, 0.87 mmol) dropwise via syringe. The mixture was stirred for 15 minutes before 3-dimethyl-aminopropanol (103 µL, 0.87 mmol) was added. After 30 minutes at 0 °C, 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (133 mg, 0.44 mmol, Compound B of Example 31) was added, and the mixture was allowed to slowly warm to room temperature. After 14.5 h, the resin was removed by filtration and rinsed with 1:1 methanol/tetrahydrofuran. The combined filtrate was concentrated *in vacuo* to a yellow residue that was used in the next step without further purification. MS(ESI$^+$) *m/z* 390.2 $(M + H)^+$.



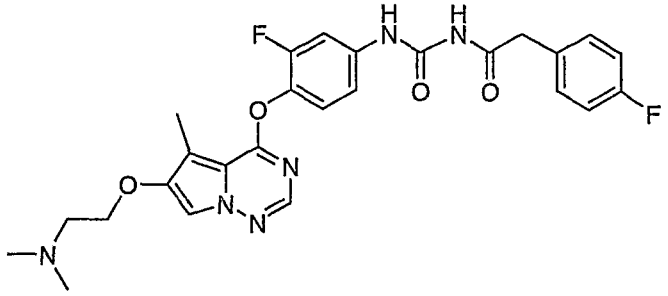
B) 4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine

3-(4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N,N*-dimethylpropan-1-amine (170 mg, 0.44 mmol) was converted to the title compound in a manner similar to the preparation of Compound B of Example 28. The resultant yellow solid was used in the next step without further purification. MS(ESI$^+$) *m/z* 360.3 $(M + H)^+$.

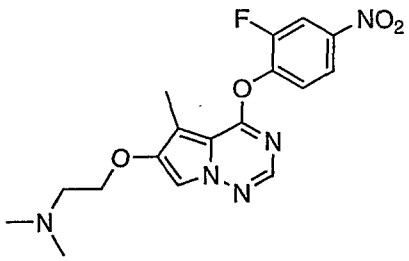
C) 1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (12 mg, 0.03 mmol) was converted to the title compound (2.5 mg, 13%) in a manner similar to the preparation of Compound E of Example 31, except that 2-(4-fluorophenyl)-acetyl isocyanate (0.10 mL, 0.04 mmol, Compound C of Example 4) was used instead of benzenesulfonyl isocyanate. ^{1}H NMR (CD_3OD) δ 10.77 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.40-7.23 (m, 5H), 7.11-7.02 (m, 3H), 4.15-4.12 (m, 2H), 3.71 (s, 2H), 3.41-3.36 (m, 2H), 2.97 (s, 6H), 2.44 (s, 3H), 2.31-2.22 (m, 2H); HRMS(ESI), 539.2218 $(M + H)^+$ calc, 539.2218 $(M + H)^+$ found.

EXAMPLE 33

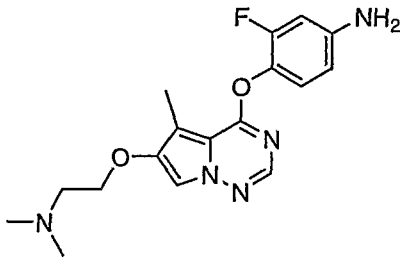


1-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) **2-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N,N*-dimethylethanamine**

4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (91 mg, 0.30 mmol, Compound B of Example 31) was converted to the title compound in a manner similar to the preparation of Compound A of Example 32, except that *N,N*-dimethylethanolamine (75 µL, 0.75 mmol) was used instead of 3-dimethylaminopropanol and diisopropylazodicarboxylate (148 µL, 0.75 mmol) was used instead of diethylazodicarboxylate. The residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500 mm, 30 minute gradient from 70% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined, neutralized with saturated aqueous sodium bicarbonate, and then concentrated *in vacuo* to remove methanol. The mixture was extracted with chloroform (3 x 10mL). The combined organic layers were washed once each with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield the title compound (22 mg, 19%) as a solid. MS(ESI$^+$) *m/z* 376.2 $(M+H)^+$.



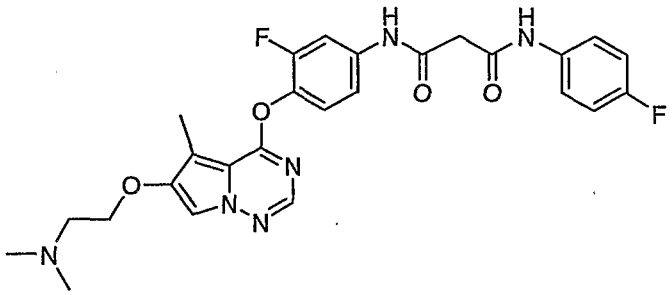
B) **4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine**

2-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N,N*-dimethylethanamine (22 mg, 0.06 mmol) was converted to the title compound (20 mg, 100%) in a manner similar to the preparation of Compound B of Example 28. The resultant yellow glass was used in the next step without further purification. MS(ESI$^+$) *m/z* 346.3 $(M + H)^+$.

C) 1-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (20 mg, 0.06 mmol) was converted to the title compound (6.5 mg, 19%) in a manner similar to the preparation of Compound C of Example 32. ^{1}H NMR (CD_3OD) δ 10.79 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.40-7.21 (m, 5H), 7.10-6.97 (m, 3H), 4.43-4.39 (m, 2H), 3.71 (s, 2H), 3.68-3.62 (m, 2H), 3.03 (s, 6H), 2.48 (s, 3H); HRMS(ESI), 525.2062 $(M + H)^+$ calc, 525.2079 $(M + H)^+$ found.

EXAMPLE 34

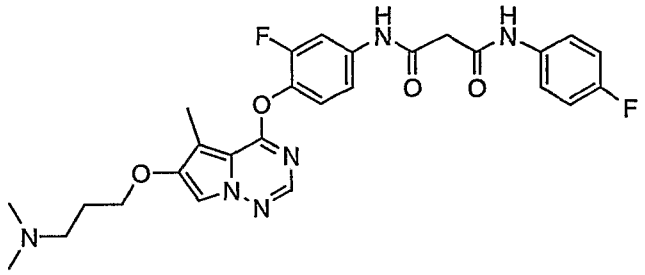


***N*^{1}-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenyl)malonamide, hydrochloride salt**

4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.10 mmol, Compound B of Example 33) was converted to the title compound (4.2 mg, 8%) in a manner similar to the preparation of Example 29, except that PyBroP (52 mg, 0.11 mmol) was used instead of o-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium tetrafluoroborate. Treatment with 1 N aqueous hydrochloric acid (1 mL, 1 mmol), followed by lyophilization, resulted in

the title compound (1.7 mg, 38%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 7.83 (s, 1H), 7.77 (s, 1H), 7.62-7.58 (m, 2H), 7.40-7.27 (m, 5H), 7.09-7.04 (m, 2H), 4.43-4.41 (m, 2H), 3.70-3.54 (m, 4H), 3.04 (s, 6H), 2.50 (s, 3H); HRMS(ESI), 525.2062 $(M + H)^+$ calc, 525.2059 $(M + H)^+$ found.

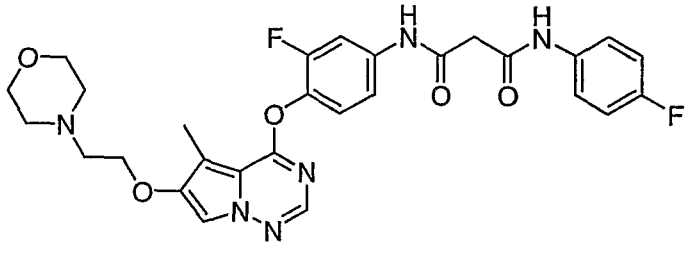
EXAMPLE 35



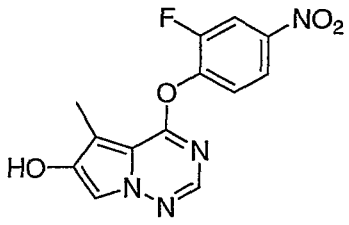
N^1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (54 mg, 0.15 mmol, Compound B of Example 32) was converted to the title compound (13 mg, 15%) in a manner similar to the preparation of Example 34. ^{1}H NMR (CD_3OD) δ 7.83-7.75 (m, 2H), 7.67 (s, 1H), 7.63-7.57 (m, 2H), 7.39-7.27 (m, 2H), 7.09-7.02 (m, 2H), 4.18-4.13 (m, 2H), 3.58 (s, 2H), 3.42-3.36 (m, 2H), 2.96 (s, 6H), 2.48-2.42 (m, 4H), 2.32-2.25 (m, 2H); HRMS(ESI), 537.2062 $(M-H)^-$ calc, 537.2073 $(M-H)^-$ found.

EXAMPLE 36

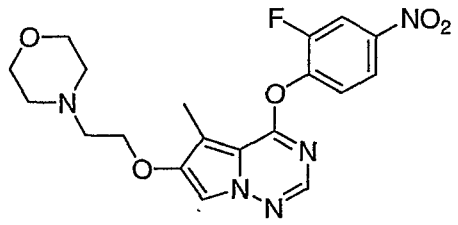


N^1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt



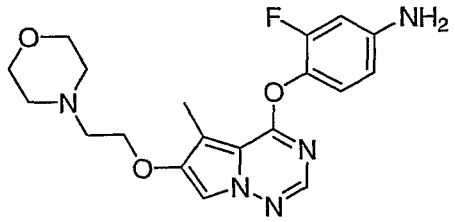
A) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (2.40 g, 6.19 mmol, Compound E of Example 1) in a mixture of 20 mL of THF and 30 mL of EtOH was added 1 N NaOH (12 mL, 12 mmol) dropwise at room temperature. The resulting solution was allowed to stir for 45 min, by that time HPLC analysis indicated the completion of the reaction. The reaction was thus quenched with 13 mL of 1 N HCl. After the organic solvent was removed under reduced pressure, the product precipitated out and was collected through filtration. The product obtained is 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (1.65 g, 88%). MS(ESI$^+$) *m/z* 305.1 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazine

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (55 mg, 0.18 mmol), 2-morpholinoethanol (47 mg, 0.36 mmol), and polymer-bound PPh_3 (3.0 mmol/g, 167 mg, 0.50 mmol) in 1 mL of THF at room temperature was added DIAD (72 mg, 0.36 mmol). The mixture was stirred for 1 h and HPLC analysis indicated most of the starting material disappeared. The polymer was filtered off through Celite® and the filtrate was concentrated and purified by preparative HPLC to afford the title compound (50 mg, 67%). MS(ESI$^+$) *m/z* 418.2 $(M + H)^+$.



C) **3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

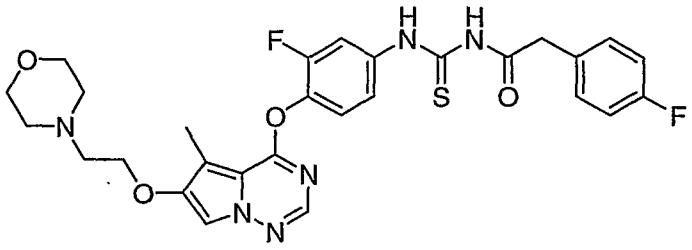
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (54 mg, 0.13 mmol) in a mixture of 0.8 mL of THF and 1.2 mL of MeOH were added NH_4Cl (70 mg, 1.3 mmol) and Zn powder (85 mg, 1.3 mmol). The suspension was allowed to stir at room temperature for 2 h. Both HPLC analysis and LC-MS analysis indicated the completion of the reaction and the solid was thus filtered off. After concentration of the filtrate, the residue was taken into 10% MeOH in CH_2Cl_2. The solution was then filtered again and the filtrate was concentrated *in vaco* to provide the title compound (50 mg, 92%). MS(ESI$^+$) *m/z* 388.4 $(M + H)^+$.

D) **N^1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt**

To a solution of 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.041 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (12 mg, 0.06 mmol, Compound A of Example 25) in 1 mL of THF were added DIEA (0.04 mL) and PyBrOP (32 mg, 0.06 mmol) at room temperature. The reaction was allowed to stir over the weekend and LC-MS analysis indicated the formation of the product, although there was still some staring material left. The solution was directly subject to preparative HPLC purification and the HPLC fraction containing the desired product was passed through a Waters Oasis® MCX 20cc 500mg LP Extraction cartridge and washed with MeOH to remove TFA. After that, the cartridge was eluted with 7 N NH_3 in MeOH and the ammonia solution was concentrated under reduced pressure to dryness. The residue was then suspended in a mixture of MeOH and H_2O and a few drops of 1 N HCl was added. The suspension

became a clear solution and it was frozen in dry ice-acetone bath. The frozen solution was then lyophilized to afford the title compound (20 mg, 80%). ^{1}H NMR (CD_3OD) δ 7.71 (m, 2H), 7.60 (s, 1H), 7.53 (m, 2H), 7.28 (m, 2H), 7.00 (m, 2H), 4.13 (s, 2H), 3.67 (s, 4H), 2.80 (s, 2H), 2.58 (s, 4H), 2.37 (s, 3H); MS(ESI$^+$) *m/z* 567.2 $(M + H)^+$.

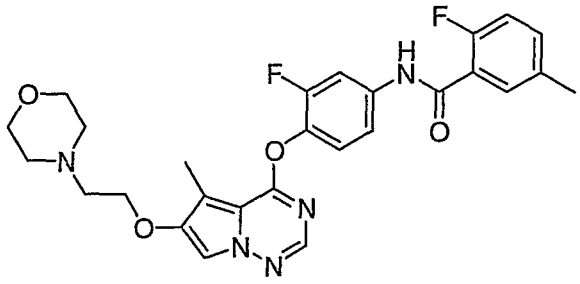
EXAMPLE 37



1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt

To a solution of 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (30 mg, 0.072 mmol, Compound C of Example 36) in 1 mL of THF was added 2-(4-fluorophenyl)ethanoyl isothiocyanate (19 mg, 0.1 mmol, Compound A of Example 2). The solution was allowed to stir at room temperature for 2 h and HPLC analysis indicated the completion of the reaction. The reaction was then quenched with NH_3 in propanol and the resulting solution was loaded on a preparative HPLC to be purified. Following a work-up procedure similar to that for Compound D of Example 36, the title compound (13 mg, 30%) was obtained as a HCl salt. ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H), 11.85 (s, 1H), 11.50 (br s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.20 (m, 2H), 4.50 (br s, 2H), 4.00 (m, 2H), 3.85 (s, 2H), 3.25-3.70 (m, 8H), 2.40 (s, 3H); MS(ESI$^+$) *m/z* 583.2 $(M + H)^+$.

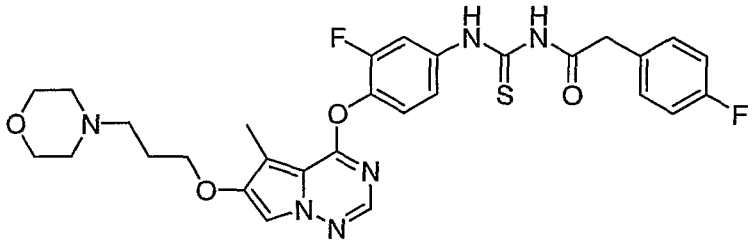
EXAMPLE 38



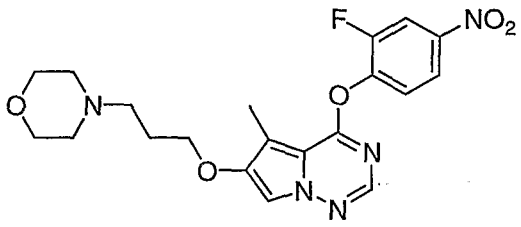
2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide, hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.042 mmol, Compound C of Example 36) was converted to the title compound (5.6 mg, 23%) as a HCl salt. ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.35 (m, 2H), 7.13 (m, 1H), 4.22 (m, 2H), 3.73 (m, 4H), 2.88 (m, 2H), 2.66 (m, 4H), 2.44 (s, 3H), 2.38 (s, 3H); MS(ESI$^+$) *m/z* 262.3 $(M + H)^+$.

EXAMPLE 39

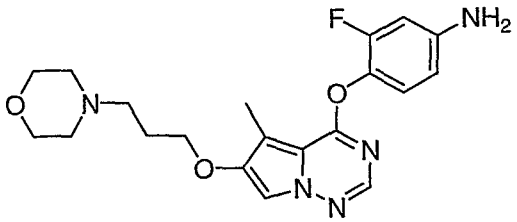


1-(3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazine

Following a procedure similar to that for the synthesis of Compound B of Example 36 , 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (50 mg, 0.16 mmol, Compound A of Example 36) was converted to the title compound (32 mg, 46%). MS(ESI$^+$) *m/z* 432.2 $(M + H)^+$.



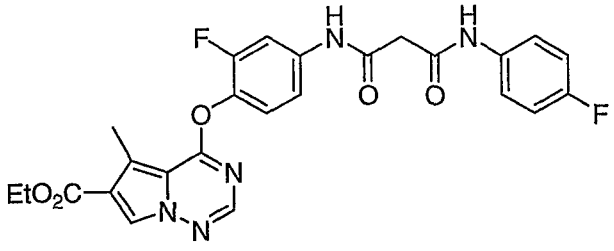
B) 3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazine (31 mg, 0.072 mmol) was converted to the title compound (28 mg, 95%). MS(ESI$^+$) *m/z* 402.3 $(M + H)^+$.

C) 1-(3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt

Following a procedure similar to Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (28 mg, 0.07 mmol) was converted to the title compound (30 mg, 68%) as a HCl salt. ^{1}H NMR (DMSO-d_6) 12.45 (s, 1H), 11.80 (s, 1H), 11.65 (br s, 1H), 8.00 (s, 2H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.25 (m, 2H), 3.10-4.10 (m, 16H), 2.40 (s, 3H); MS(ESI$^+$) *m/z* 597.2 $(M + H)^+$.

EXAMPLE 40

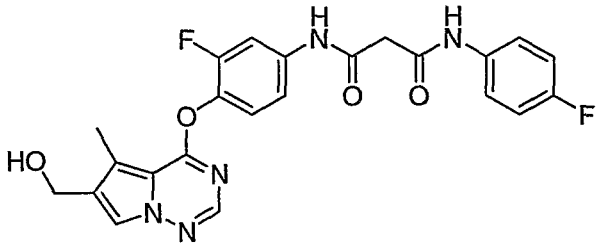


Ethyl 4-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

Following a procedure similar to that for the synthesis of Compound D of Example 36, ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (70 mg, 0.21 mmol, Compound B of Example 6) was

converted to the title compound (50 mg, 47%). ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 10.30 (s, 1H), 8.45 (s, 1H), 8.16 (s, 1H), 7.90 (d, 1H), 7.67 (m, 2H), 7.51 (t, 1H), 7.40 (t, 1H), 7.20 (m, 2H), 4.33 (q, 2H), 3.52 (s, 2H), 2.77 (s, 3H), 1.35 (t, 3H); MS(ESI$^+$) *m/z* 510.1 $(M + H)^+$.

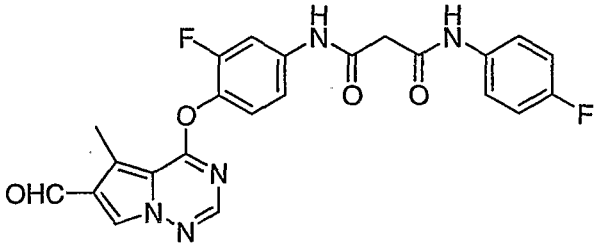
EXAMPLE 41



N^1-(3-Fluoro-4-(6-(hydroxymethyl)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

To a solution of ethyl 4-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (66 mg, 0.13 mmol, Example 40) in 20 mL of THF at -78 °C was added DIBAL-H (1 M, 1.65 mL). The reaction mixture was allowed to stir at -78 °C for 1 h and then at room temperature for 2 h. At that time, HPLC analysis indicated the completion of the reaction. The reaction was quenched with 4 mL of MeOH, followed by addition of 4 mL of H_2O. The mixture was allowed to stir for 0.5 h and then Na_2SO_4 was added. The stirring was continued for 1 h. Filtration and concentration gave rise to the title compound (50 mg, 82%). ^{1}H NMR (CD_3OD) δ 7.70 (m, 3H), 7.50 (m, 2H), 7.25 (m, 2H), 7.00 (m, 2H), 4.60 (s, 2H), 3.45 (s, 2H), 2.50 (s, 3H); MS(ESI$^+$) *m/z* 468.2 $(M + H)^+$.

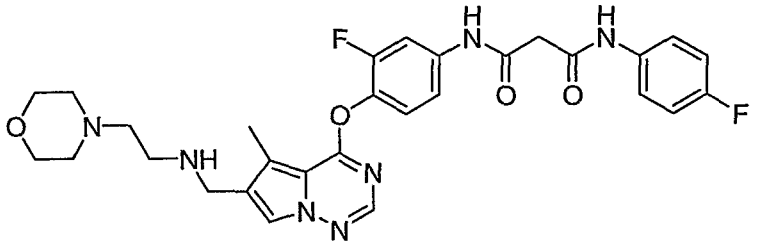
EXAMPLE 42



N^1-(3-Fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl) N^3-(4-fluorophenyl)malonamide

To a solution of N^1-(3-fluoro-4-(6-(hydroxymethyl)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (12 mg, 0.026 mmol, Example 41) in 1 mL of THF was added Dess-Martin periodinane (48 mg, 0.11 mmol, Aldrich) at room temperature. The mixture was allowed to stir for 2 h and HPLC analysis indicated total consumption of the starting material. The mixture was filtered through a plug of SiO_2, washed with EtOAc. The organic solvent was then removed under reduced pressure and the residue was purified on preparative HPLC to afford the title compound (10 mg, 83%). MS(ESI$^+$) *m/z* 466.2 $(M + H)^+$.

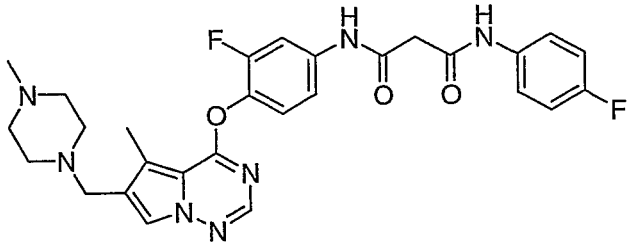
EXAMPLE 43



N^1-(3-Fluoro-4-(5-methyl-6-((2-morpholinoethylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis-trifluoroacetic acid salt

To a solution of N^1-(3-fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (15 mg, 0.032 mmol, Example 42) in 1 mL of DMF were added 2-morpholinoethanamine (21 mg, 0.16 mmol), DIEA (0.04 mL) and $NaBH(OAc)_3$ (52 mg, 0.2 mmol). The mixture was allowed to stir at room temperature for 4 days. HPLC analysis and LC-MS analysis indicated formation of the product. The solution was then dissolved in MeOH and purified by preparative HPLC to give the title compound (4 mg, 21%) as a 2•TFA salt. ^{1}H NMR (CD_3OD) δ 7.92 (s, 1H), 7.82 (s, 1H), 7.70 (d, 1H), 7.50 (m, 2H), 7.28 (m, 2H), 6.98 (m, 2H), 4.31 (s, 2H), 3.68 (s, 4H), 3.20 (m, 4H), 2.82 (m, 2H), 2.65 (s, 4H), 2.56 (s, 3H); MS(ESI$^+$) *m/z* 580.2 $(M + H)^+$.

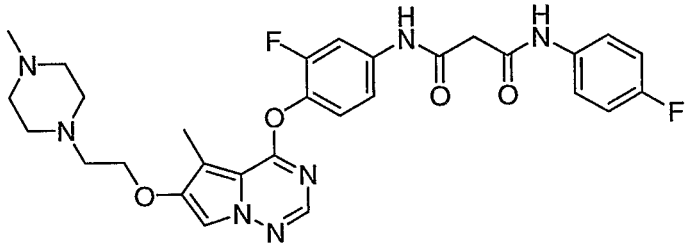
EXAMPLE 44



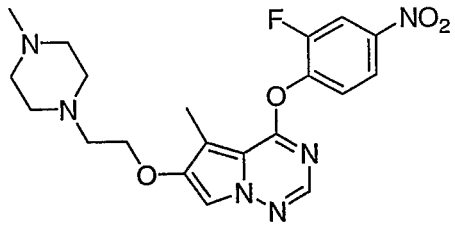
N^1-(3-Fluoro-4-(5-methyl-6-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis-trifluoroacetic acid salt

Following a procedure similar to that for the synthesis of Example 43, N^1-(3-fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (15 mg, 0.032 mmol, Example 42) was converted to the title compound (4 mg, 23%) as a 2•TFA salt. MS(ESI$^+$) *m/z* 550.2 $(M + H)^+$.

EXAMPLE 45



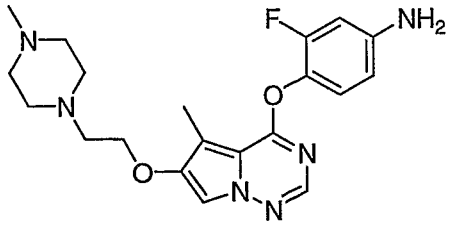
N^1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis hydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine

Following a procedure similar to that for the synthesis of Compound B of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (55 mg, 0.18 mmol, Compound A of Example 36), 2-morpholinoethanol (304 mg, 1.0

mmol) was converted to the title compound (352 mg, 82%). MS(ESI$^+$) *m/z* 431.2 (M + H)$^+$.



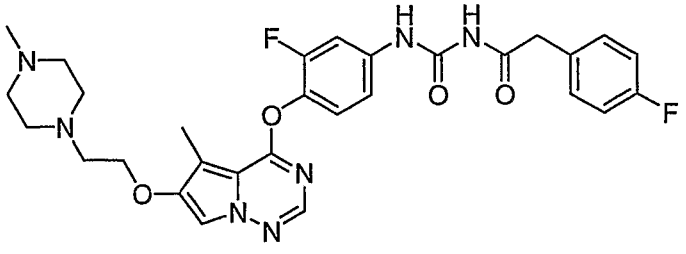
B) 3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (2.90 g, 6.74 mmol) was converted to the title compound (1.38 g, 51%). MS(ESI$^+$) *m/z* 401.3 (M + H)$^+$.

C) N^1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis-hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (60 mg, 0.15 mmol) was converted the title compound (30 mg, 46%) as a 2•HCl salt. ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 1H), 10.37 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.80 (d, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 7.16 (m, 2H), 4.42 (br s, 2H), 3.38-3.60 (m, 10H), 2.81 (s, 3H), 2.40 (s, 3H);). MS(ESI$^+$) *m/z* 580.3 (M + H)$^+$:

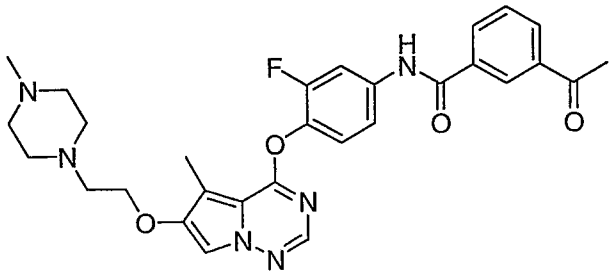
EXAMPLE 46



1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-hydrochloride salt

To a solution of 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) in 1 mL of THF at room temperature was added a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.36 M, 0.18 mL, Compound C of Example 4) and the solution was allowed to stir overnight. HPLC analysis and LC-MS analysis indicated the completion of the reaction and the organic solvent was thus removed under reduced pressure. The residue was purified on preparative HPLC. The title compound (15 mg, 46%) was finally obtained as a 2•HCl salt after a work-up similar to that described for Compound D of Example 36. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.58 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.70 (d, 1H), 7.35 (m, 4H), 7.16 (m, 2H), 4.44 (br.s, 2H), 3.40-3.70 (m, 12H), 2.81 (s, 3H), 2.39 (s, 3H); MS(ESI$^+$) *m/z* 580.1 $(M + H)^+$.

EXAMPLE 47

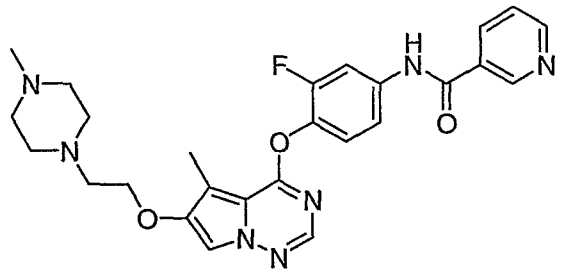


3-Acetyl-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, bis-hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) was converted to the title compound (11 mg, 35%) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 8.20 (m, 1H), 7.90 (m, 2H), 7.84 (s, 1H), 7.80 (s, 1H), 7.70 (m, 1H), 7.50

(m, 2H), 7.32 (m, 1H), 4.54 (m, 2H), 3.60-4.10 (m, 10H), 3.08 (s, 3H), 2.50 (s, 3H); MS(ESI$^+$) *m/z* 547.2 $(M + H)^+$.

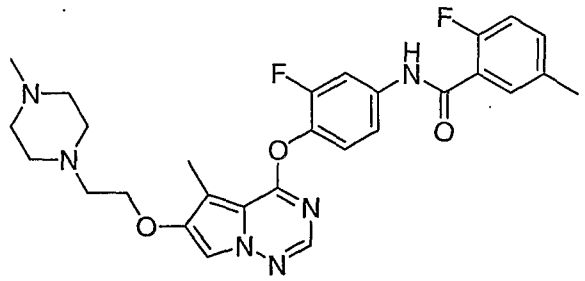
EXAMPLE 48



***N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide, tris hydrochloride salt**

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) was converted the tile compound (10 mg, 32%) as a 3•HCl salt. ^{1}H NMR (CD_3OD) δ 9.46 (s, 1H), 9.20 (d, 1H), 9.08 (d, 1H), 8.29 (m, 1H), 7.92 (d, 1H), 7.81 (s, 1H), 7.82 (s, 1H), 7.61 (m, 1H), 7.42 (m, 1H), 4.54 (m, 2H), 3.82-4.05 (m, 10H), 3.05 (s, 3H), 2.51 (s, 3H); MS(ESI$^+$) *m/z* 506.2 $(M + H)^+$.

EXAMPLE 49

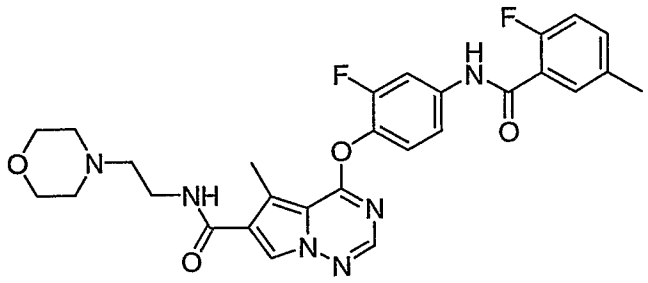


2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide, bis-hydrochloride salt

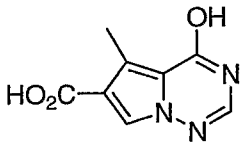
Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example

45) was converted to the title compound (8 mg, 26% yield) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.33 (m, 2H), 7.13 (t, 1H), 4.54 (m, 2H), 3.70-4.10 (m, 10H), 3.04 (s, 3H), 2.50 (s, 3H), 2.37 (s, 3H); MS(ESI$^+$) *m/z* 537.2 $(M + H)^+$.

EXAMPLE 50

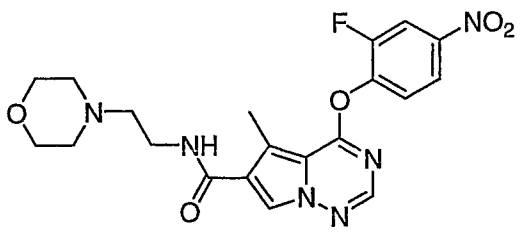


4-(2-Fluoro-4-(2-fluoro-5-methylbenzamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, hydrochloride salt



A) 4-Hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid

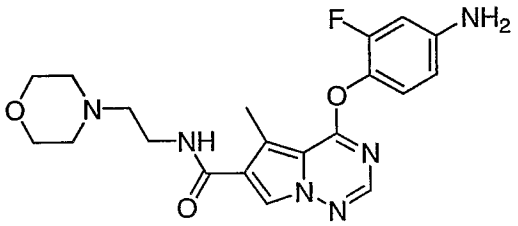
To a solution of ethyl 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (442 mg, 2.0 mmol) (see example 6 of US Pat. App. 2003/0186982, the disclosure of which is herein incorporated by reference) in 10 mL of THF was added a solution of NaOH (1 N, 6.0 mL). The mixture was heated at 60 °C overnight and HPLC analysis indicated the completion of the reaction. After cooling down, the solution was neutralized with 6.0 mL of 1 N HCl. The organic solvent was then removed and the solid was collected after filtration to the title compound (350 mg, 91%). MS(ESI$^+$) *m/z* 194.2 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide

A suspension of 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (100 mg, 0.52 mmol) in 2 mL of $POCl_3$ was heated at 110 °C for 4 h. The suspension became a clear solution and the excess of $POCl_3$ was removed with toluene. The residue was then dissolved in 5 mL of acetonitrile at 0 °C. To this solution were added Et_3N (0.72 mL, 5.2 mmol) and 2-morpholinoethanamine (0.13 mL, 1.04 mmol). The mixture was stirred for 0.5 h and HPLC analysis indicated the formation of the product. The solution was then diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$. After filtration and concentration, the crude material was carried to the next reaction.

The crude material was dissolved in 2 mL of acetonitrile and to it were added 2-fluoro-4-nitrophenol (94 mg, 0.60 mmol) and DABCO (78 mg, 0.70 mmol). The reaction was allowed to stir for 1 h and HPLC analysis indicated the completion of the reaction. After concentration, the residue was purified on preparative HPLC to give the title compound (75 mg, 33%). MS(ESI$^+$) *m/z* 445.2 $(M + H)^+$.



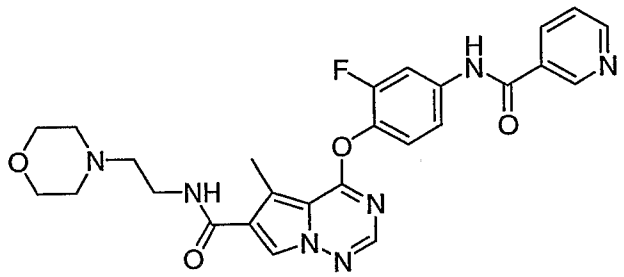
C) 4-(4-Amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (75 mg, 0.17 mmol) was converted to the title compound (65 mg, 92%). LCMS(ESI$^+$) *m/z* 415.3 $(M + H)^+$.

D) 4-(2-Fluoro-4-(2-fluoro-5-methylbenzamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, hydrochloride salt

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (25 mg, 0.06 mmol) in 1 mL of THF were added Et_3N (0.2 mL) and a solution of 2-fluoro-5-methylbenzoyl chloride (20 mg, 0.11 mmol) in 1 mL of THF at room temperature. The mixture was allowed to stir for 1 h and HPLC analysis indicated the consumption of the starting material. The reaction was quenched with MeOH. The solution was then concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound (8.0 mg, 23%) as a HCl salt. ^{1}H NMR (CD_3OD) δ 8.48 (d, 1H), 7.83 (m, 3H), 7.28 (m, 3H), 7.00 (m, 1H), 2.90-4.00 (m, 12H), 2.76 (s, 3H), 2.33 (s, 3H); MS(ESI$^+$) *m/z* 551.2 $(M + H)^+$.

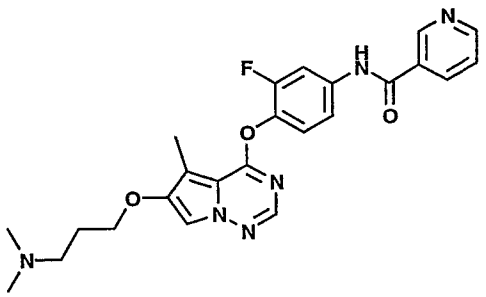
EXAMPLE 51



4-(2-Fluoro-4-(nicotinamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, bis-hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of Example 50, 4-(4-amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (30 mg, 0.07 mmol, Compound C of Example 50) was converted the title compound (16 mg, 39%) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 9.08 (s, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 7.87 (m, 2H), 7.38 (m, 2H), 7.22 (m, 2H), 3.82 (s, 4H), 3.61 (m, 2H), 2.75 (m, 9H); MS(ESI$^+$) *m/z* 520.2 $(M + H)^+$.

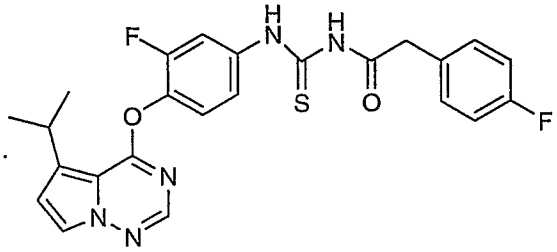
EXAMPLE 52



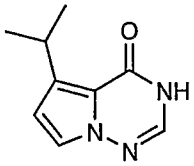
***N*-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide, dihydrochloride salt**

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (54 mg, 0.15 mmol, Compound B of Example 32) as converted to the title compound (8.7 mg, 11%) in a manner similar to the preparation of Compound D of Example 36. ^{1}H NMR (CD_3OD) δ 9.47 (s, 1H), 9.20-9.19 (m, 1H), 9.08-9.07 (m, 1H), 8.30-8.27 (m, 1H), 7.97-7.93 (m, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.64-7.61 (m, 1H), 7.43-7.39 (m, 1H), 4.26-4.11 (m, 2H), 3.43-3.39 (m, 2H), 2.98 (s, 6H), 2.46 (s, 3H), 2.34-2.30 (m, 2H); HRMS(ESI), 463.1894 $(M-H)^-$ calc, 463.1905 $(M-H)^-$ found.

EXAMPLE 53



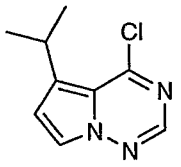
1-(3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) 5-Isopropylpyrrolo[2,1-*f*][1,2,4]triazin-4(3H)-one

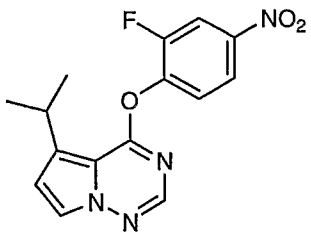
5-Isopropyl-4-oxo-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (0.025 g, 1.13 mmol, 1.0 equiv, prepared in a manner similar to that described in

patent application : US 2004/063708, herein incorporated by reference in its entiretyz) was added to polyphosphoric acid (5.0 g) and the reaction mixture was heated to 160 °C for 1 h. The reaction was cooled to room temperature and quenched with water (50 ml). The solution was extracted with ethyl acetate (3 x 50 ml), the combined organic fractions washed with sat $NaHCO_3$ (1 x 100 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 3/1 ethyl acetate / hexane, afforded the title compound (0.060 g, 30%). MS(ESI$^-$) *m/z* 176 $(M-H)^-$; HRMS(ESI), 176.0824 $(M-H)^-$ calc, 176.0818$(M-H)^-$ found.



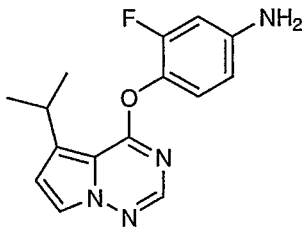
B) 4-Chloro-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

5-Isopropylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (0.035 g, 0.198 mmol, 1.0 equiv) was added to phosphorous oxychloride (2.0 ml, 21.5 mmol, 109 equiv) under a nitrogen atmosphere. The reaction mixture was heated to reflux for 1.5 h. The mixture was cooled to room temperature then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate. The combined organic washes were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a tan solid that was used in the next step without further purification. MS(ESI$^+$) *m/z* 196 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine

To a mixture of 4-chloro-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (0.038g, 0.194 mmol, 1.0 equiv) and 2-fluoro-4-nitrophenol (0.062 g, 0.388 mmol, 2.0 equiv) in anhydrous CH_3CN (2mL), stirred for five minutes under a nitrogen atmosphere then was added DABCO (0.044 g, 0.388 mmol, 2.0 equiv) and the reaction mixture was heated at 50 °C for 2 h. The mixture was cooled to room temperature and quenched with 1 N HCl. The solution was extracted with CH_2Cl_2 (3 x 30 ml), the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 2/1 hexane / ethyl acetate, afforded the title compound (0.048g, 79%). ^{1}H NMR ($CDCl_3$) δ 8.07-8.13 (m, 2H), 7.77 (s, 1H), 7.68-7.69 (m, 1H), 7.46-7.50 (m, 1H), 6.71-6.72 (m, 1H), 3.53-3.56 (m, 1H), 1.29-1.31 (m, 6H); HRMS(ESI), calc, 317.1050 $(M + H)^+$ found, 317.1039.



D) 3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine (0.044 g, 1.39 mmol, 10 equiv) in 1/1 anhydrous methanol / tetrahydrofuran (2 mL), at ambient temperature under nitrogen atmosphere, was added zinc dust (0.090 g, 0.139 mmol, 1.0 equiv) and ammonium chloride (0.075 g, 1.39 mmol, 10 equiv). The mixture was stirred for 4 h before the catalyst was filtered off and the filtrate was concentrated *in vacuo* to yield the title compound (0.040g, 100%) as a solid, that was used without further purification. HRMS(ESI), 287.1308 $(M + H)^+$ calc, 287.1300 $(M + H)^+$ found.

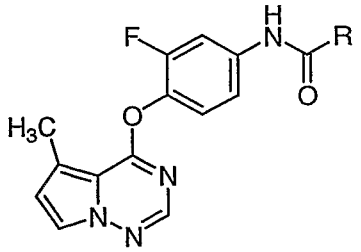
E) 1-(3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

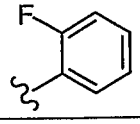
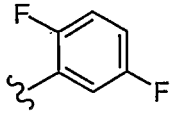
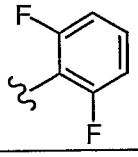
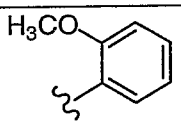
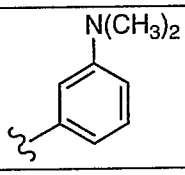
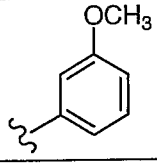
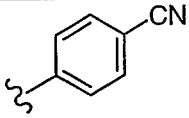
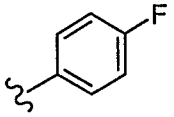
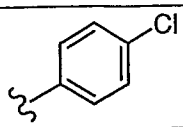
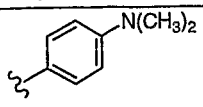
To a homogeneous solution of sodium thiocyanate (0.037 g, 0.46 mmol, 3.3 equiv) in ethyl acetate (1 mL), at room temperature under a nitrogen atmosphere, was added 4-fluorophenyl-acetyl chloride (0.048 ml, 0.35mmol, 2.5 equiv). The mixture was stirred for 2 h before being added directly to a homogeneous solution of 3-fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (0.040g, 0.139 mmol, 1.0 equiv) in anhydrous 1/1 THF/dichloromethane (3 mL), under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 16 h before being quenched with 1 N HCl. The solution was extracted with CH_2Cl_2 (3 x 50 ml), the combined organic fractions washed with 1 N NaOH (50 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 4/1 hexane/ ethyl acetate, afforded the title compound (0.050 g, 75%). ^{1}H NMR ($CDCl_3$) δ 12.34 (s, 1H), 8.47 (m, 1H), 7.65-7.78 (m, 2H), 7.63-7.64 (m, 1H), 7.19-7.32 (m, 4H), 7.03-7.08 (m, 2H), 6.66-6.67 (m, 1H), 3.65 (s, 2H), 3.40-3.50 (m, 1H), 1.28-1.30 (m, 6H); HRMS(ESI) 482.1462, calc, $(M+H)^+$ 482.1461 found. Elemental Analysis: $C_{24}H_{21}N_5O_2SF_2$. 0.23 H_2O. calc: C; 59.35, H; 4.45, N; 14.42, found: C; 59.36, H; 4.44, N; 14.03.

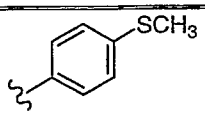
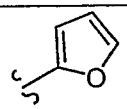
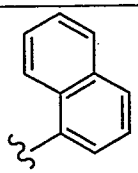
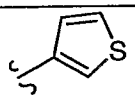
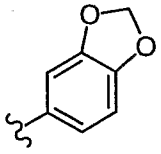
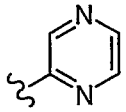
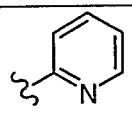
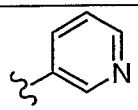
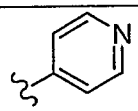
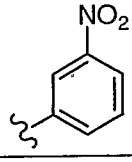
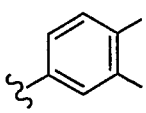
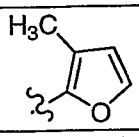
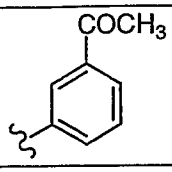
EXAMPLES 54 TO 85

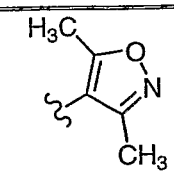
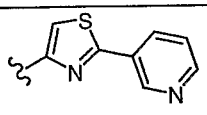
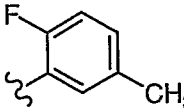
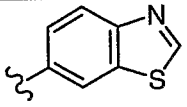
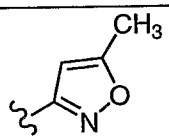
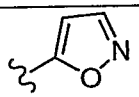
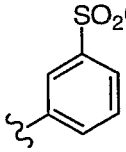
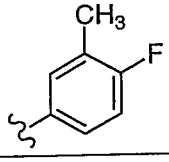
Examples **54** to **85** illustrated in Table 1 below were synthesized from 3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (Compound B of Example 28) using one equivalent of the corresponding carboxylic acid, (1 eq) PyBrOP (1 eq), DIEA (1 eq) in DMF. The reaction mixture was heated to 70 °C and the crude products were purified by preparative HPLC (H_20/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20 ×100 mm 5 μm YMC ODS-A column) utilizing mass-directed fractionation. The purified sample was reconstituted in 1:1/MeOH:DCE, transferred to a tared 2.5 mL plastic microtube, dried via centrifugal evaporation, weighed and analyzed by LCMS (H_20/MeOH/0.1% TFA).

TABLE 1



Example #	R	Compound Name	LC/MS $(M+H)^+$
54	Ph	*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	363.4
55		2-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	381.4
56		2,5-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
57		2,6-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
58		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methoxybenzamide	393.4
59		3-(Dimethylamino)-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	406.4
60		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methoxybenzamide	393.4
61		4-Cyano-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	388.4
62		4-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	381.4
63		4-Chloro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	397.8
64		4-(Dimethylamino)-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	406.4

Example #	R	Compound Name	LC/MS $(M+H)^+$
65		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(methylthio)benzamide	409.5
66		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-2-carboxamide	353.3
67		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-1-naphthamide	413.4
68		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-3-carboxamide	369.4
69		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[*d*][1,3]dioxole-5-carboxamide	407.4
70		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)pyrazine-2-carboxamide	365.3
71		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)picolinamide	364.4
72		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	364.4
73		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	364.4
74		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-nitrobenzamide	408.4
75		3,4-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
76		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylfuran-2-carboxamide	367.4
77		3-Acetyl-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	405.4

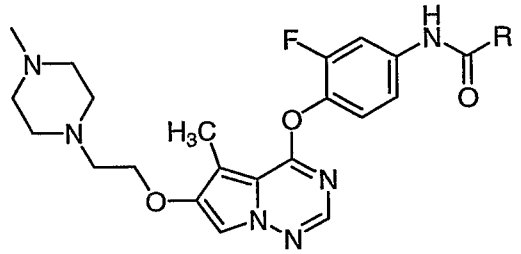
Example #	R	Compound Name	LC/MS $(M+H)^+$
78		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3,5-dimethylisoxazole-4-carboxamide	382.4
79		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(pyridin-3-yl)thiazole-4-carboxamide	447.5
80		2-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide	395.4
81		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[*d*]thiazole-6-carboxamide	420.4
82		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylisoxazole-3-carboxamide	368.3
83		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isoxazole-5-carboxamide	354.3
84		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(methylsulfonyl)benzamide	441.5
85		4-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylbenzamide	395.4

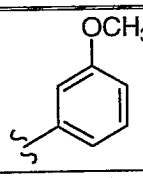
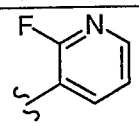
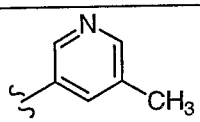
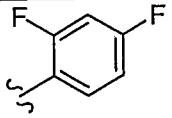
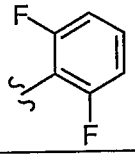
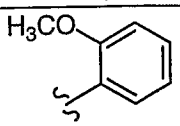
EXAMPLES 86 TO 130

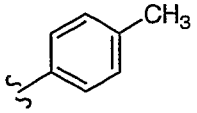
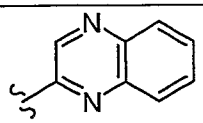
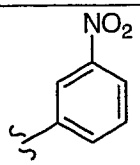
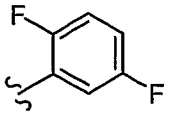
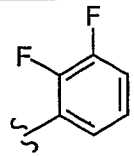
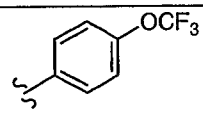
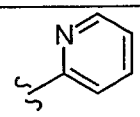
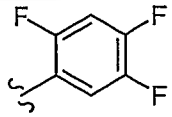
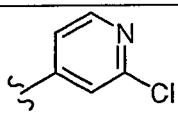
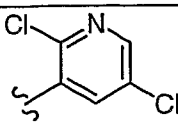
Examples **86** to **130** illustrated in Table 2 below were synthesized from 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (Compound B of Example 45). To an individual well of a 48-position MiniBlock® XT reactor was added 375 µL of a 0.2 M solution of the acid chloride in 1,2-dichloroethane (DCE) (0.075 mmol, 2.5 eq); 50 µL of pyridine (0.62 mmol, 20 eq); and 150 µL of a 0.2 M solution of the amine in DCE (0.03 mmol, 1 eq). The reactor was agitated via orbital shaker for 14 h. The crude product in DCE was diluted to a volume of 1 mL with methanol, then purified by standard preparative

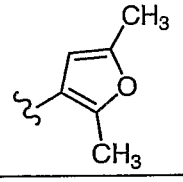
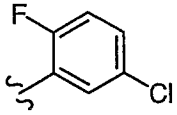
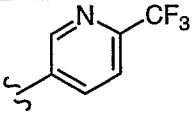
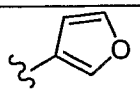
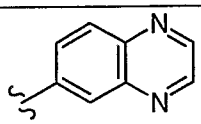
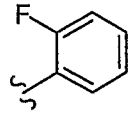
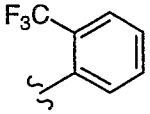
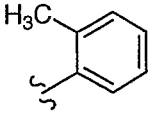
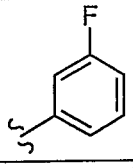
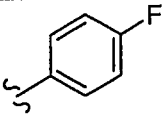
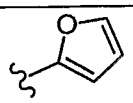
HPLC (H_2O/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20×100 mm 5μm YMC ODS-A column) utilizing mass-directed fractionation. The purified sample was reconstituted in 1:1/MeOH:DCE, transferred to a tared 2.5 mL plastic microtube, dried via centrifugal evaporation, weighed and analyzed by LCMS (H_2O/MeOH/0.1% TFA).

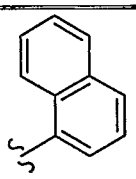
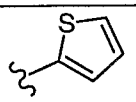
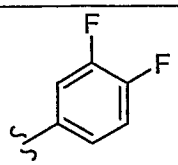
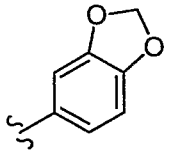
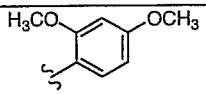
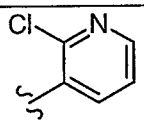
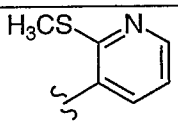
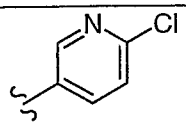
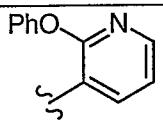
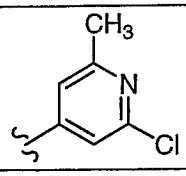
TABLE 2

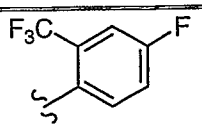
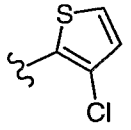
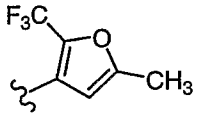
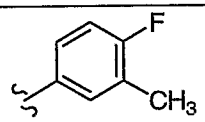
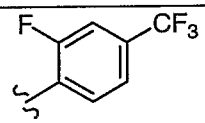
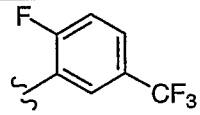
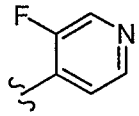
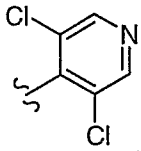


Example #	R	Compound Name	LC/MS $(M+H)^+$
86		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methoxybenzamide	535.6
87		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	524.6
88		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylnicotinamide	520.6
89		2,4-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
90		2,6-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
91		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methoxybenzamide	535.6

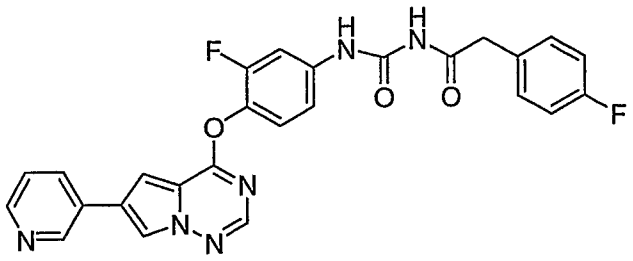
Example #	R	Compound Name	LC/MS $(M+H)^+$
92		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-methylbenzamide	519.6
93		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)quinoxaline-2-carboxamide	557.6
94		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-nitrobenzamide	550.6
95		2,5-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
96		2,3-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
97		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(trifluoromethoxy)benzamide	589.6
98		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)picolinamide	506.6
99		2,4,5-Trifluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	559.5
100		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	541.0
101		2,5-Dichloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	575.4

Example #	R	Compound Name	LC/MS $(M+H)^+$
102		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2,5-dimethylfuran-3-carboxamide	523.6
103		5-Chloro-2-fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	558.0
104		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-6-(trifluoromethyl)nicotinamide	574.6
105		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-3-carboxamide	495.5
106		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)quinoxaline-6-carboxamide	557.6
107		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
108		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(trifluoromethyl)benzamide	573.6
109		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methylbenzamide	519.6
110		3-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
111		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
112		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-2-carboxamide	495.5

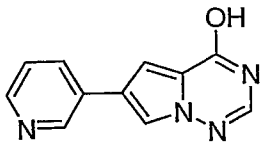
Example #	R	Compound Name	LC/MS $(M+H)^+$
113		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-1-naphthamide	555.6
114		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-2-carboxamide	511.6
115		3,4-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
116		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[d][1,3]dioxole-5-carboxamide	549.6
117		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2,4-dimethoxybenzamide	565.6
118		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	541.0
119		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(methylthio)nicotinamide	552.7
120		6-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	541.0
121		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-phenoxynicotinamide	598.7
122		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-6-methylisonicotinamide	555.0

Example #	R	Compound Name	LC/MS $(M+H)^+$
123		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(trifluoromethyl)benzamide	591.6
124		3-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-2-carboxamide	546.0
125		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methyl-2-(trifluoromethyl)furan-3-carboxamide	577.6
126		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylbenzamide	537.6
127		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(trifluoromethyl)benzamide	591.6
128		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-(trifluoromethyl)benzamide	591.6
129		3-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	524.6
130		3,5-Dichloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	575.5

EXAMPLE 131

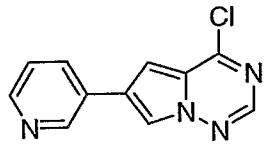


1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2(4-fluorophenyl)acetyl)urea, trifluroacetic acid salt



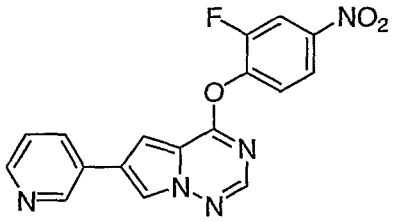
A) 6-(Pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol

A solution of 6-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, prepared from methyl 4-bromo-1*H*-pyrrole-2-carboxylate: see, generally, Kitamura, C. and Yamashita, Y. *J. Chem. Soc. Perkin Trans.* 1, **1997**, 1443, the disclosure of which is herein incorporated by reference, using a similar procedure outlined in the PCT Appl. WO 00/71129) and pyridin-3-ylboronic acid (172 mg, 1.40 mmol) in 2 mL of DMF and 2 mL of saturated aqueous K_2CO_3 was degassed and then $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) was added. The mixture was then heated to 120 °C for 3 h. LC-MS analysis indicated the disappearance of starting material. The mixture was cooled down and the solution was filtered. The filtrate was purified on preparative HPLC to afford the title compound (100 mg, 65%) as a TFA salt. MS(ESI$^+$) *m/z* 213.2 $(M + H)^+$.



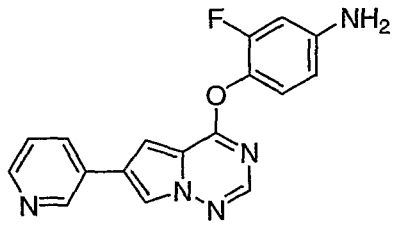
B) 4-Chloro-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine

To a suspension of 6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.30 mmol) in 10 mL of toluene were added $POCl_3$ (0.18 mL, 1.88 mmol) and DIEA (0.09 mL, 0.5 mmol). The suspension was heated at 100 °C for 7 h. After cooling down, the excess $POCl_3$ was removed under reduced pressure. The residue was suspended in EtOAc, and then neutralized with sat. $NaHCO_3$. The organic layer was then washed with brine and dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash column chromatography to afford the title compound (23 mg, 33%). MS(ESI$^+$) *m/z* 231.2/233.2 $(M + H)^+$.



C) **4-(2-Fluoro-4-nitrophenoxy)-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine**

Following a procedure similar to the that for the synthesis of Compound B of Example 2, 4-chloro-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (23 mg, 0.1 mmol) was converted to the title compound (35 mg, 95%). MS(ESI$^+$) *m/z* 352.3 $(M + H)^+$.



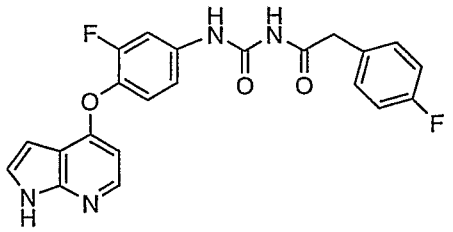
D) **3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (35 mg, 0.10 mmol) was converted to the title compound (15 mg, 46%). MS(ESI$^+$) *m/z* 322.3 $(M + H)^+$.

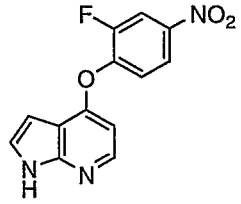
E) **1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3(2-(4-fluorophenyl)acetyl)urea, trifluoroaacetic acid salt**

The title compound was prepared using following a procedure similar to that for the syntheis of Example 46, 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.046 mmol) was converted to the title compound (5.0 mg, 18%) as a TFA salt. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.53 (s, 1H), 9.12 (s, 1H), 8.75 (s, 1H), 8.50 (m, 1H), 8.30 (m, 1H), 8.12 (s, 1H), 7.67 (m, 2H), 7.30-7.50 (m, 5H), 7.12 (m, 2H), 3.69 (s, 2H); MS(ESI$^+$) *m/z* 501.2 $(M + H)^+$.

EXAMPLE 132

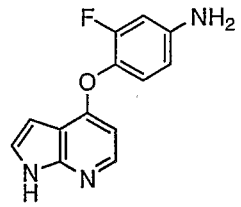


1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl) acetyl)urea, hydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine

A mixture of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (457 mg, 3.0 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) and 2-fluoro-4-nitrophenol (706 mg, 4.5 mmol), and *N,N*-diisopropylethylamine (580 mg, 4.5 mmol) in 1-methyl-2-prolidinone (NMP) (3 mL) was heated at 200 °C under microwave irradiation for 1.0 h. The mixture was diluted with ethyl acetate (150 mL), washed with sat. aq. KH_2PO_4 solution, and Na_2CO_3 (aq. 1 M), dried over Na_2SO_4. The product was purified by flash column chromatography (silica gel, eluting with CH_2Cl_2 to 30% EtOAc/CH_2Cl_2) to afford a brown solid (350 mg, 43%). MS(ESI$^+$) *m/z* 274 $(M + H)^+$.



B) 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine

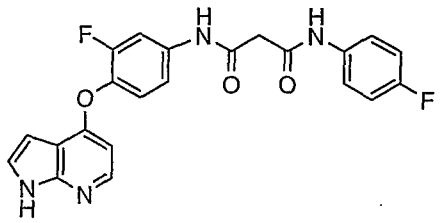
To a suspension of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (300 mg, 1.1 mmol) in tetrahydrofuran (5 mL) and methanol (10 mL), were added zinc powder (350 mg, 5.5 mmol) and ammonium chloride (294 mg, 5.5 mmol). The mixture was stirred at rt overnight. The mixture was filtered through a pad of Celite®,

rinsed with methanol. The filtrate was concentrated. The product was purified by flash column chromatography (silica gel, 1-5% MeOH in CH_2Cl_2) to afford the desired product (205 mg, 77%) as an off-white solid. MS(ESI$^+$) *m/z* 244 $(M + H)^+$.

C) **1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt**

A mixture of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (30 mg, 0.12 mmol) and 2-(4-fluorophenyl)acetyl isocyanate, (Compound C, Example 4) (0.25 M in toluene, 0.18 mmol) in THF (0.5 mL) was stirred at rt for 1 h. The mixture was concentrated *in vacuo*, purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL). This solution was then lyophilized to afford the title compound (15 mg, 27%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.74 (s, 1H), 8.12 (d, 1H, *J* = 6.4 Hz), 7.73 (dd, 1H, *J* = 2.4, 13.0 Hz), 7.39 (d, 1H, *J* = 3.6 Hz), 6.90-7.3 (m, 6H), 6.65 (d, 1H, *J* = 6.4 Hz), 6.50 (d, 1H, *J* = 3.2 Hz), 3.68 (s, 2H); MS(ESI$^+$) *m/z* 423 $(M + H)^+$.

EXAMPLE 133

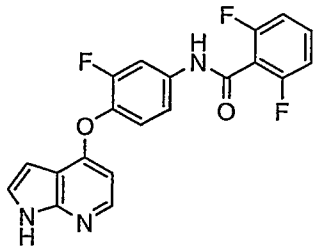


N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl) malonamide, trifluoroacetic acid salt

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132; 25 mg, 0.10 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid, Compound A, Example 25 (25 mg, 1.27 mmol) in DMF (0.5 mL), was added TBTU (48 mg, 0.15 mmol), followed by DIPEA (0.1 mL). The resulting mixture was stirred at rt for 2 h. The product was purified by preparative HPLC to afford the title compound (TFA salt, 26 mg, 62%) as a white solid. ^{1}H NMR ($CDCl_3$)

δ 7.94 (d, 1H, J = 6.4 Hz), 7.66 (dd, 1H, J = 2.4, 13.0 Hz), 7.54 (m, 2H), 6.90-7.25 (m, 5H), 6.31 (d, 2H, J = 2.8 Hz), 3.37 (s, 2H); MS(ESI$^+$) m/z 423 $(M + H)^+$.

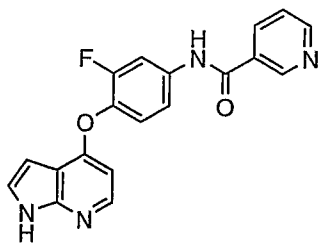
EXAMPLE 134



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide**

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132; 20 mg, 0. 08 mmol) in DMF (0.5 mL), was added 2,6-difluorobenzoyl chloride (20 mg, 0.11 mmol), followed by DIPEA (0.1 mL). The mixture was stirred at rt for 2 h and the product was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was neutralized with sat. aq. sodium bicarbonate solution. The mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried and concentrated *in vacuo* to afford the title compound (14 mg, 37%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 6.4 Hz), 7.87 (d, 1H, J = 2.4, 12.8 Hz), 7.40 (m, 4H), 7.04 (m, 2H), 6.69 (d, 2H, J = 7.6 Hz), 6.52 (m, 1H); MS(ESI$^+$) m/z 384 $(M + H)^+$.

EXAMPLE 135

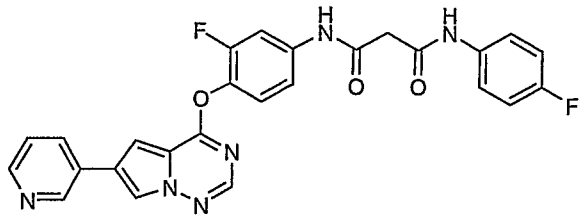


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)nicotinamide**

In a similar manner as described for the preparation of Example 134, the title compound was isolated as a TFA salt and was prepared using commercially available nicotinyl chloride and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132). Yield: 55%. ^{1}H NMR (CD_3OD) δ 9.09 (s, 1H), 8.73 (d,

1H, J = 4.4 Hz), 8.44 (d, 1H, J = 8.0 Hz), 8.22 (d, 1H, J = 6.8 Hz), 8.22 (dd, 1H, J = 2.4, 12.4 Hz), 7.40-7.80 (m, 4H), 6.79 (d, 1H, J = 6.8 Hz), 6.59 (d, 1H, J = 3.6 Hz); MS(ESI$^+$) m/z 349 $(M + H)^+$.

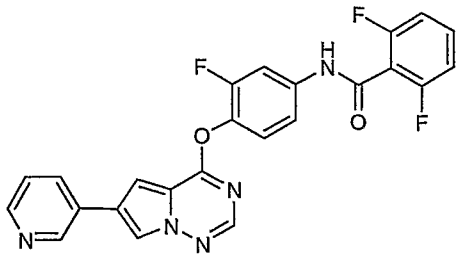
EXAMPLE 136



N^1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

To a homogeneous solution of 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (32 mg, 0.10 mmol, Compound D of Example 131) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (20 mg, 0.10 mmol, Compound A of Example 25) in anhydrous DMF (3 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (26 µL, 0.15 mmol). The mixture was stirred for five minutes before o-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (48 mg, 0.15 mmol) was added in one portion. The mixture was stirred for sixty-three hours before being partitioned between chloroform and brine. The aqueous layer was extracted three times with chloroform, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to remove volatiles. The resultant residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500mm, 30 minute gradient from 58% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined and lyophilized to afford the title compound (18 mg, 30%) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (br s, 1H), 9.49 (s, 1H), 9.18 (s, 1H), 8.80-8.65 (m, 2H), 8.36-8.29 (m, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.83-7.68 (m, 2H), 7.55-7.49 (m, 2H), 7.35-7.23 (m, 2H), 7.10-7.00 (m, 2H), 3.58 (s, 2H); HRMS(ESI), 501.1487 $(M + H)^+$ calc, 501.1491 $(M + H)^+$ found.

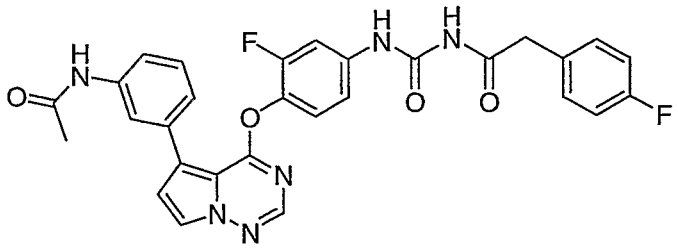
EXAMPLE 137



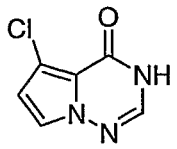
2,6-Difluoro-*N*-(3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, trifluoroacetic acid salt

To a homogeneous solution of 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (64 mg, 0.20 mmol, Compound D of Example 131) in anhydrous chloroform (5 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (49 µL, 0.28 mmol). The mixture was stirred for five minutes before 2,6-difluorobenzoyl chloride (33 µL, 0.26 mmol, Aldrich) was added. The mixture was stirred for eighty-seven hours before being partitioned between chloroform and saturated aqueous sodium bicarbonate. The organic layer was washed once with saturated aqueous sodium bicarbonate and once with brine, before the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to remove volatiles. The resultant residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500mm, 30 minute gradient from 58% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined and lyophilized to afford the title compound (24 mg, 21%) as a white solid. ^{1}H NMR (CD_3OD) δ 9.20 (s, 1H), 8.85-8.78 (m, 1H), 8.65-8.60 (m, 1H), 8.51 (d, 1H, J = 1.6 Hz), 8.00 (s, 1H), 7.98-7.90 (m, 1H), 7.81-7.74 (m, 1H), 7.58 (d, 1H, J = 1.8 Hz), 7.51-7.27 (m, 3H), 7.00-7.10 (m, 2H); HRMS(ESI), 462.1178 $(M + H)^+$ calc, 462.1168 $(M + H)^+$ found.

EXAMPLE 138



1-(4-(5-(3-Acetamidophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one

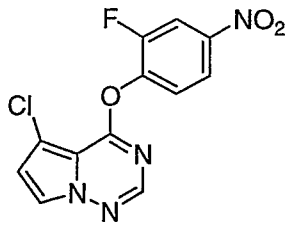
A solution of methyl 1-amino-3-chloro-1*H*-pyrrole-2-carboxylate (10.0 g, 57.3 mmol, WO 03/099286: Compound A of Example 9) in formamide (40 mL) was heated at 170 °C for 1 h and then at 190 °C for 1 h. Upon cooling to room temperature, the mixture solidified. The product was purified by recrystallization from ethyl acetate to give the title compound (6.53 g, 67%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.24 (br s, 1H), 7.48 (d, 1H, J = 3.6 Hz), 7.29 (d, 1H, J = 2.8 Hz), 6.47 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 170.1 $(M + H)^+$.



B) 4,5-Dichloropyrrolo[2,1-*f*][1,2,4]triazine

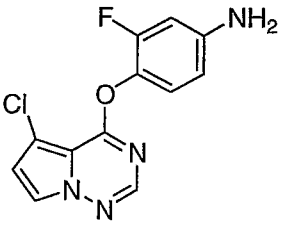
To a solution of 5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (5.00 g, 29.5 mmol) in toluene (100 mL) at rt under nitrogen was added diisopropylethylamine (5.14 mL, 29.5 mmol) followed by phosphorus(III) oxychloride (8.25 mL, 88.5 mmol). The mixture was heated at 100 °C for 20 h and was then cooled to rt. The reaction was slowly added to saturated aqueous sodium bicarbonate solution (500 mL) at 0 °C. After the addition was complete, the mixture was stirred at rt for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 500 mL), dried over anhydrous

$MgSO_4$, and concentrated *in vacuo* to give the crude product (3.73 g, 67%) as a yellow solid which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.70 (d, 1H, J = 2.8 Hz), 6.84 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) m/z 188.1 $(M + H)^+$.



C) 5-Chloro-4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine

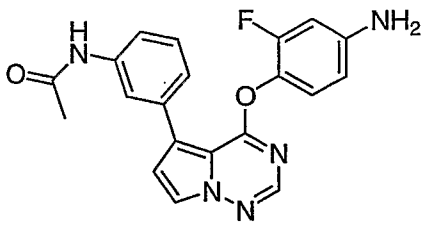
A mixture of 4,5-dichloropyrrolo[2,1-*f*][1,2,4]triazine (3.73 g, 19.8 mmol), 2-fluoro-4-nitrophenol (3.43 g, 21.8 mmol) and potassium carbonate (5.47 g, 39.6 mmol) in DMF (100 mL) was stirred at 60 °C for 1 h. After cooling to rt, the reaction was filtered through a short plug of silica gel with ethyl acetate and then concentrated *in vacuo*. The crude product was purified by recrystallization from ethyl acetate / hexanes (1:1) to give the title compound (4.37 g, 71%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.22-8.17 (m, 2H), 7.92 (s, 1H), 7.77 (d, 1H, J = 2.8 Hz), 7.58 (t, 1H, J = 7.2 Hz), 6.87 (d, 1H, J = 3.2 Hz); MS(ESI$^+$) m/z 309.3 $(M + H)^+$.



D) 4-(5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine

To a solution of 5-chloro-4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine (2.00 g, 6.48 mmol) in THF (50 mL) / MeOH (80 mL) was added zinc dust (2.12 g, 32.4 mmol) followed by ammonium chloride (1.73 g, 32.4 mmol). After stirring at rt for 8 h, the reaction mixture was filtered through Celite® with MeOH and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and washed with water (2 x 100 mL) then brine (1 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50 % EtOAc / hexanes) to give the

title compound (1.51 g, 84%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.69 (d, 1H, J = 2.8 Hz), 7.09 (t, 1H, J = 8.4 Hz), 6.79 (d, 1H, J = 2.8 Hz), 6.58 (dd, 1H, J = 11.6, 2.6 Hz), 6.51 (d, 1H, J = 8.7 Hz), 3.92 (br s, 2H); MS(ESI$^+$) *m/z* 279.2 $(M + H)^+$.



E) *N*-(3-(4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl)acetamide

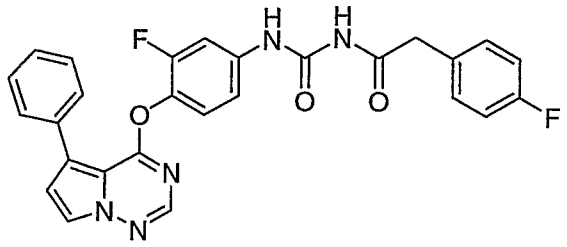
A flask was charged with palladium acetate (4.5 mg, 0.02 mmol), X-Phos ligand (24 mg, 0.05 mmol, Strem), 4-(5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (56 mg, 0.20 mmol), 3-acetamidobenzene boronic acid (72 mg, 0.40 mmol, Lancaster), and potassium phosphate (127 mg, 0.60 mmol) in that order. The flask was flushed with nitrogen and then *t*-BuOH was added (0.40 mL). The mixture was heated at 80 °C for 8 h. Additional shots of palladium acetate (4.5 mg, 0.02 mmol), X-Phos ligand (24 mg, 0.05 mmol), and 3-acetamidobenzene boronic acid (72 mg, 0.40 mmol) were added and the reaction was stirred an additional 9 h at 80 °C. After cooling to rt, the reaction was filtered using MeOH to remove the potassium phosphate and then concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo* to remove MeOH. The resulting aqueous layer was made basic with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound (20 mg, 26%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.84-7.94 (m, 2H), 7.44-7.41 (m, 1H), 7.34-7.19 (m, 3H), 6.92 (t, 1H, J = 8.8 Hz), 6.87 (d, 1H, J = 2.8 Hz), 6.50 (dd, 1H, J = 12.4, 2.4 Hz), 6.46-6.43 (m, 1H), 2.04 (s, 3H); MS(ESI$^+$) *m/z* 378.3 $(M + H)^+$.

F) **1-(4-(5-(3-Acetamidophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

To a solution of *N*-(3-(4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl)acetamide (20 mg, 0.053 mmol) in dichloromethane (0.5 mL) at rt under nitrogen was added 2-(4-fluorophenyl)acetyl isocyanate (250 μL, 0.064 mmol, 0.25 M in toluene, Compound C of Example 4). The reaction was stirred at rt for 1 h and was then concentrated *in vacuo*. The residue was suspended in methanol and filtered to collect 14 mg (47%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 8.25-8.21 (m, 2H), 8.05 (s, 1H), 7.78 (d, 1H, J = 13.2 Hz), 7.51-7.38 (m, 7H), 7.23 (t, 2H, J = 8.4 Hz), 7.13 (s, 1H), 3.81 (s, 2H), 2.10 (s, 3H); MS(ESI$^+$) *m/z* 557.4 $(M + H)^+$.

Examples 139-144 were prepared in a manner similar to Example 138.

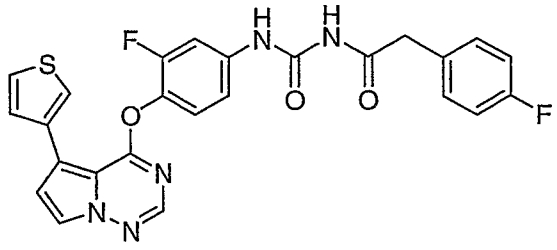
EXAMPLE 139



1-(3-Fluoro-4-(5-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 10.56 (s, 1H), 8.55 (s, 1H), 7.89 (s, 1H), 7.77 (d, 1H, J = 2.8 Hz), 7.62-7.57 (m, 3H), 7.33 (t, 2H, J = 7.7 Hz), 7.26-7.19 (m, 4H), 7.10 (m, 1H), 7.02 (t, 2H, J = 8.6 Hz), 6.88 (d, 1H, J = 2.7 Hz), 3.65 (s, 2H); MS(ESI$^+$) *m/z* 500.3 $(M + H)^+$.

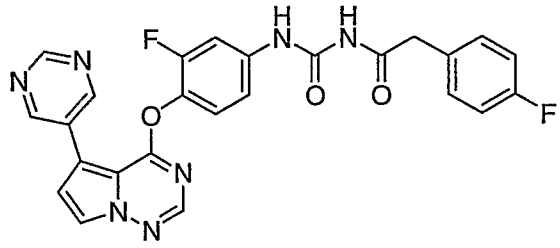
EXAMPLE 140



1-(3-Fluoro-4-(5-(thiophen-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.59 (s, 1H), 8.16 (d, 1H, J = 2.8 Hz), 8.12 (s, 1H), 7.81 (d, 1H, J = 1.6 Hz), 7.75 (dd, 1H, J = 12.4, 2 Hz), 7.62-7.49 (m, 3H), 7.39-7.36 (m, 3H), 7.21-7.16 (m, 3H), 3.76 (s, 2H); MS(ESI$^+$) *m/z* 506.3 $(M + H)^+$.

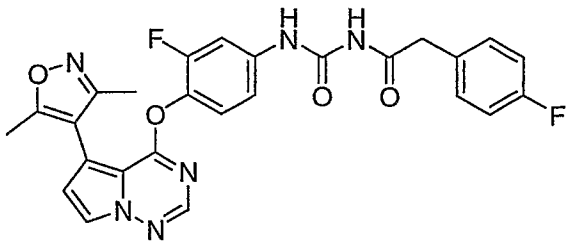
EXAMPLE 141



1-(3-Fluoro-4-(5-(pyrimidin-5-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 10.65 (s, 1H), 9.21 (s, 2H), 9.18 (s, 1H), 8.37 (d, 1H, J = 2.4 Hz), 8.31 (s, 1H), 7.80 (dd, 1H, J = 12.4, 2 Hz), 7.58 (t, 1H, J = 8.8 Hz), 7.44-7.40 (m, 4H), 7.23 (t, 2H, J = 8.4 Hz), 3.80 (s, 2H); MS(ESI$^+$) *m/z* 502.3 $(M + H)^+$.

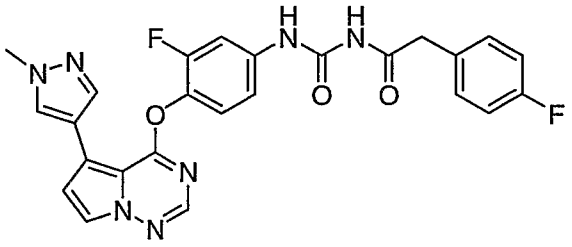
EXAMPLE 142



1-(4-(5-(3,5-Dimethylisoxazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.58 (s, 1H), 8.24 (d, 1H, J = 2.4 Hz), 8.17 (s, 1H), 7.42 (dd, 1H, J = 13.2, 2 Hz), 7.38-7.35 (m, 4H), 7.18 (t, 2H, J = 7.6 Hz), 7.06 (d, 1H, J = 2.8 Hz), 3.75 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H); MS(ESI$^+$) *m/z* 519.3 $(M + H)^+$.

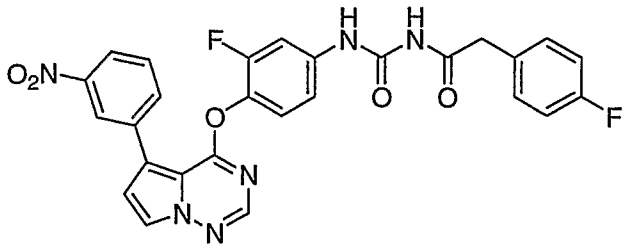
EXAMPLE 143



1-(3-Fluoro-4-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.59 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 8.05 (d, 2H, J = 2.4 Hz), 7.85 (s, 1H), 7.76 (dd, 1H, J = 12.4, 2 Hz), 7.52 (t, 1H, J = 8.4 Hz), 7.39-7.36 (m, 3H), 7.18 (t, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 2.8 Hz), 3.86 (s, 3H), 3.76 (s, 2H); MS(ESI$^+$) *m/z* 504.3 $(M + H)^+$.

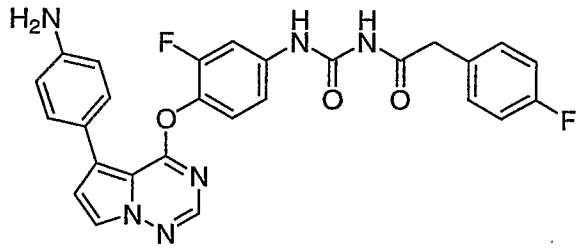
EXAMPLE 144



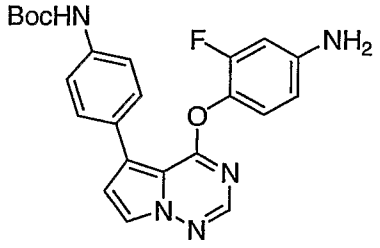
1-(3-Fluoro-4-(5-(3-nitrophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.27 (d, 1H, J = 2.4 Hz), 8.23 (s, 1H), 8.20-8.16 (m, 2H), 7.76-7.72 (m, 2H), 7.49 (t, 1H, J = 8.8 Hz), 7.39-7.34 (m, 4H), 7.18 (t, 2H, J = 9.2 Hz), 3.75 (s, 2H); MS(ESI$^+$) m/z 545.2 (M + H)$^+$.

EXAMPLE 145



1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) *tert*-Butyl 4-(4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenylcarbamate

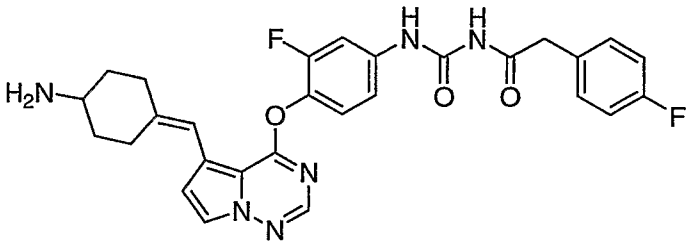
Prepared in a similar manner as Step E of Example 138 to give the title compound (46%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.73 (d, 1H, J = 4 Hz), 7.54 (d, 2H, J = 8 Hz), 7.33-7.30 (m, 2H), 6.93 (t, 1H, J = 7.6 Hz), 6.82 (d, 1H, J = 4 Hz), 6.60-6.47 (m, 2H), 1.44 (s, 9H); MS(ESI$^+$) m/z 436.4 (M + H)$^+$.

B) 1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

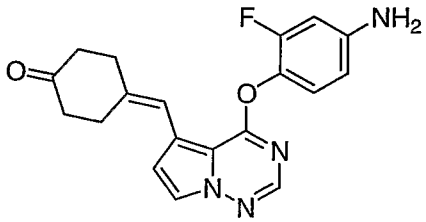
Prepared in a similar manner as Step F of Example 138 to give the Boc protected material (51%). The Boc protected material was suspended in ether (2 mL), cooled to 0 °C, and charged with TFA (0.5 mL). After stirring at rt for 1 h, the reaction was concentrated *in vacuo*. The residue was suspended in ethyl acetate (10 mL),

washed with saturated aqueous sodium bicarbonate solution (5 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash chromatography on silica gel (60 % EtOAc / hexanes). Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the title compound (38%) as a light brown solid. ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 10.50 (s, 1H), 8.02 (d, 1H, J = 2.8 Hz), 7.98 (s, 1H), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.36 (t, 1H, J = 8.8 Hz), 7.31-7.28 (m, 5H), 7.10 (t, 2H, J = 8.8 Hz), 6.89 (d, 1H, J = 2.8 Hz), 6.51 (d, 2H, J = 8.8 Hz), 5.08 (s, 2H), 3.68 (s, 2H); MS(ESI$^+$) m/z 515.3 $(M + H)^+$.

EXAMPLE 146

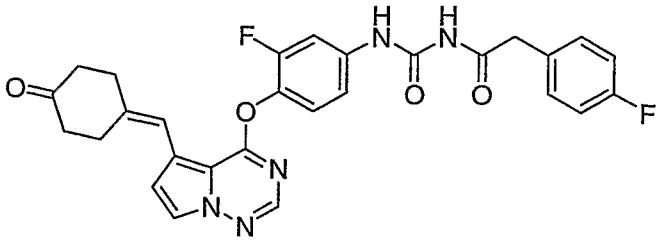


1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 4-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylene)cyclohexanone

Prepared in a similar manner as Step E of Example 138 using 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)cyclohexanone (prepared according to the procedure of Morrill, C. and Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031-6034). to give the title compound (11%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.76 (s, 1H), 7.73 (d, 1H, J = 2.8 Hz), 7.54-7.51 (m, 1H), 7.33 (d, 1H, J = 2.8 Hz), 6.92 (t, 1H, J = 7.6 Hz), 6.84 (d, 1H, J = 2.8 Hz), 6.46-6.41 (m, 1H), 2.83 (t, 2H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 2.45-2.38 (m, 4H); MS(ESI$^+$) m/z 353.2 $(M + H)^+$.



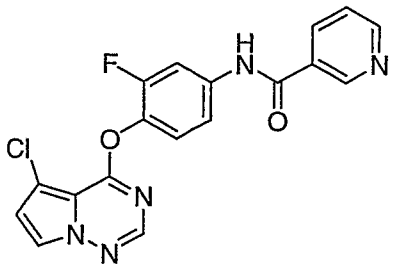
B) 1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Step F of Example 138 to give the title compound (38%) as a yellow solid. ^{1}H NMR (acetone-d_6) δ 10.62 (s, 1H), 9.87 (s, 1H), 7.80 (s, 1H), 7.79 (d, 1H, J = 2.8 Hz), 7.70 (dd, 1H, J = 12.8, 2.4 Hz), 7.33-7.19 (m, 4H), 6.96-6.93 (m, 3H), 6.16 (m, 1H), 3.75 (s, 2H), 2.82 (t, 2H, J = 6.8 Hz), 2.62 (t, 2H, J = 6.8 Hz), 2.37 (t, 2H, J = 6.8 Hz), 2.30 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) *m/z* 532.2 $(M + H)^+$.

C) 1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

A solution of 1-(4-(5-(4-aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (21 mg, 0.040 mmol) in methanol (0.5 mL) and THF (0.5 mL) at 0 °C was charged with ammonium acetate (30 mg, 0.40 mmol) followed by sodium cyanoborohydride (2.5 mg, 0.040 mmol). After stirring at 0 °C for 1 h, the reaction was concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 5 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (19%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.77 (s, 1H), 7.76 (d, 1H, J = 2.8 Hz), 7.63 (dd, 1H, J = 12.8, 2.4 Hz), 7.29-7.14 (m, 4H), 7.03-6.93 (m, 2H), 6.91 (d, 1H, J = 2.8 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.15-3.08 (m, 1H), 2.50-2.30 (m, 2H), 2.21-2.05 (m, 2H), 1.46-1.30 (m, 4H); MS(ESI$^+$) *m/z* 533.2 $(M + H)^+$.

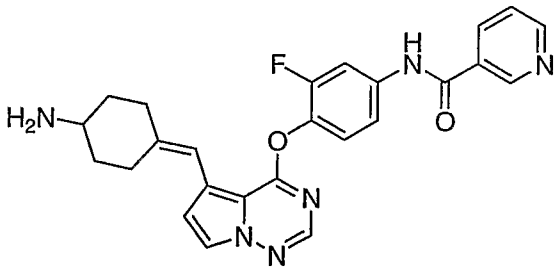
EXAMPLE 147



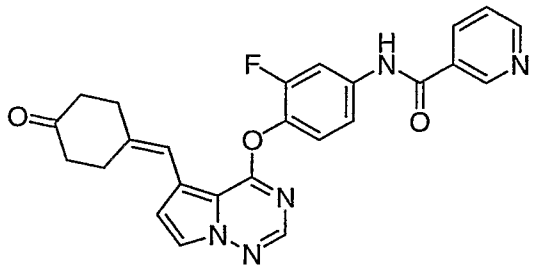
***N*-(4-(5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide**

To 4-(5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (100 mg, 0.359 mmol, Compound D of Example 138) in DMF (2 mL) was added nicotinic acid (53 mg, 0.431 mmol, Aldrich), DIPEA (300 μL, 1.80 mmol), followed by TBTU (173 mg, 0.539 mmol, Fluka). After stirring at rt overnight, the reaction was diluted with 20 mL of EtOAc, washed with 10% aqueous lithium chloride solution (2 x 10 mL) followed by brine (1 x 10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% MeOH / EtOAc) to give the title compound (125 mg, 91%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J = 2 Hz), 8.80 (dd, 1H, J = 4.8, 1.2 Hz), 8.34-8.31 (m, 1H), 8.18 (d, 1H, J = 2.8 Hz), 8.17 (s, 1H), 7.96 (dd, 1H, J = 12.8, 2 Hz), 7.66-7.60 (m, 2H), 7.54 (t, 1H, J = 8.8 Hz), 7.10 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 383.9 $(M + H)^+$.

EXAMPLE 148



***N*-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide**



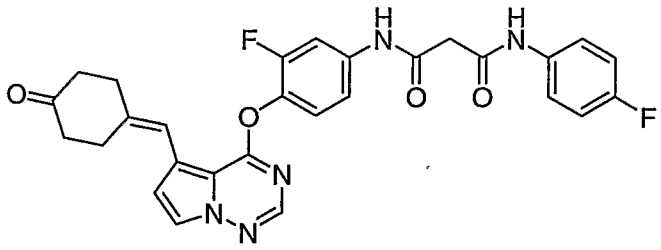
A) ***N*-(3-Fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide**

Prepared in a similar manner as Step E of Example 138 to give the title compound (66%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J = 2 Hz), 8.82 (dd, 1H, J = 4.8, 1.2 Hz), 8.36-8.33 (m, 1H), 8.13 (d, 1H, J = 2.8 Hz), 8.10 (s, 1H), 7.99-7.93 (m, 1H), 7.68-7.63 (m, 1H), 7.54 (t, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 2.8 Hz), 6.92 (s, 1H), 2.90 (t, 2H, J = 6.8 Hz), 2.74 (t, 2H, J = 6.8 Hz), 2.51 (t, 2H, J = 6.8 Hz), 2.42 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) *m/z* 458.2 (M + H)$^+$.

B) ***N*-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide**

Prepared in a similar manner as Step C of Example 146 to give the TFA salt of the title compound (6%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 9.15 (s, 1H), 8.80 (s, 1H), 8.59 (d, 1H, J = 8 Hz), 7.84-7.76 (m, 4H), 7.48 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 8 Hz), 6.80 (d, 1H, J = 4 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.10-3.08 (m, 1H), 2.48-2.05 (m, 4H), 1.47-1.20 (m, 4H); MS(ESI$^+$) *m/z* 459.2 (M + H)$^+$.

EXAMPLE 149

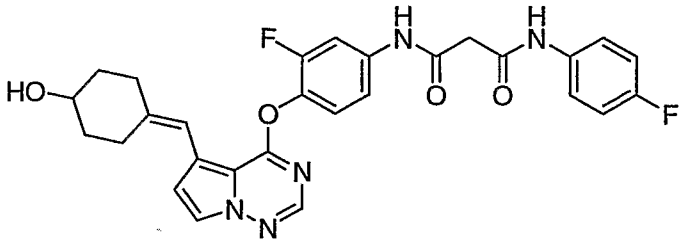


N^1-(3-Fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

Suzuki coupling in a similar manner as Step E of Example 138 followed by malonamide formation as in Step A of Example 133 gave the title compound (39%) as

a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 10.31 (s, 1H), 8.15 (d, 1H, J = 2.4 Hz), 8.11 (s, 1H), 7.86 (dd, 1H, J = 12.4, 2.8 Hz), 7.52 (t, 1H, J = 8.8 Hz), 7.44-7.42 (m, 1H), 7.25-7.19 (m, 2H), 7.09 (d, 1H, J = 2.8 Hz), 6.93 (s, 1H), 3.54 (s, 2H), 2.91 (t, 2H, J = 6.8 Hz), 2.73 (t, 2H, J = 6.4 Hz), 2.53 (t, 2H, J = 6.8 Hz), 2.45 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) m/z 532.3 $(M + H)^+$.

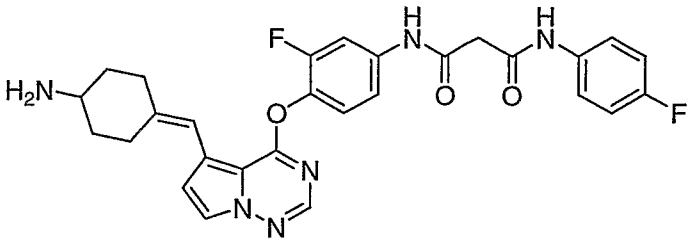
EXAMPLE 150



N^1-(3-Fluoro-4-(5-((4-hydroxycyclohexylidene)methyl)pyrrolo[2,1-*f*] [1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

To N^1-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*] [1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (80 mg, 0.15 mmol, Example 149) in methanol (2 mL) at 0 °C was added a spatula tip of sodium borohydride. The reaction was stirred at 0 °C for 30 min and was then quenched with saturated aqueous ammonium chloride solution (10 mL) and stirred at 0 °C for 5 min. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% MeOH / EtOAc) to give the title compound (30 mg, 37%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1H), 10.34 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 8.10 (s, 1H), 7.86 (dd, 1H, J = 12.8, 2.4 Hz), 7.71-7.68 (m, 2H), 7.53 (t, 1H, J = 8.4 Hz), 7.46-7.43 (m, 1H), 7.25-7.21 (m, 2H), 6.99 (d, 1H, J = 2.8 Hz), 6.64 (s, 1H), 4.65 (br s, 1H), 3.76-3.75 (m, 1H), 3.56 (s, 2H), 2.90-2.85 (m, 1H), 2.51-2.45 (m, 1H), 2.27-2.24 (m, 2H), 1.92-1.85 (m, 2H), 1.46-1.41 (m, 2H); MS(ESI$^+$) m/z 534.3 $(M + H)^+$.

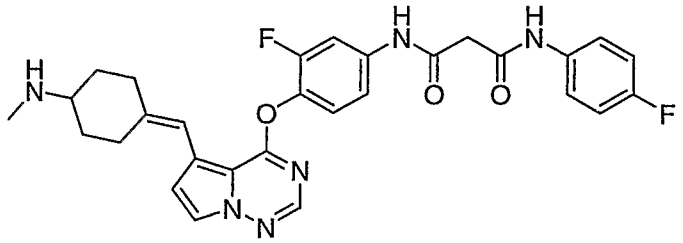
EXAMPLE 151



N^1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

Prepared in a similar manner as Step C of Example 146 to give the TFA salt of the title compound (12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J = 2.4 Hz), 7.99 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.59-7.55 (m, 2H), 7.38 (t, 1H, J = 8.4 Hz), 7.32-7.35 (m, 1H), 7.13-7.08 (m, 2H), 6.90 (d, 1H, J = 2.8 Hz), 6.59 (s, 1H), 3.44 (s, 2H), 2.95-3.00 (m, 1H), 2.20-2.41 (m, 2H), 1.96-2.11 (m, 2H), 1.32-1.39 (m, 2H), 1.17-1.13 (m, 2H); MS(ESI$^+$) *m/z* 533.3 $(M + H)^+$.

EXAMPLE 152

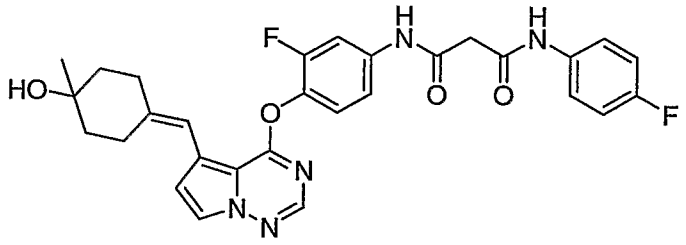


N^1-(3-Fluoro-4-(5-((4-(methylamino)cyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

To N^1-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (20 mg, 0.038 mmol, Example 149) in dichloroethane (1 mL) was added methylamine (23 μL, 0.045 mmol, 2 M THF), acetic acid (2.6 μL, 0.045 mmol), followed by sodium triacetoxyborohydride (13 mg, 0.056 mmol). After stirring at rt for 2 h, the reaction was quenched with 5% aqueous sodium bicarbonate solution (1 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase

prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 4 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (11 mg, 44%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J = 2.8 Hz), 8.00 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.59-7.55 (m, 2H), 7.40 (t, 1H, J = 8.4 Hz), 7.35-7.32 (m, 1H), 7.13-7.06 (m, 2H), 6.90 (d, 1H, J = 2.8 Hz), 6.60 (s, 1H), 3.44 (s, 2H), 3.10-3.13 (m, 1H), 3.02-2.98 (m, 1H), 2.52-2.39 (m, 4H), 2.23-2.21 (m, 1H), 2.08-2.02 (m, 3H), 1.36-1.31 (m, 2H); MS(ESI$^+$) *m/z* 547.1 (M + H)$^+$.

EXAMPLE 153

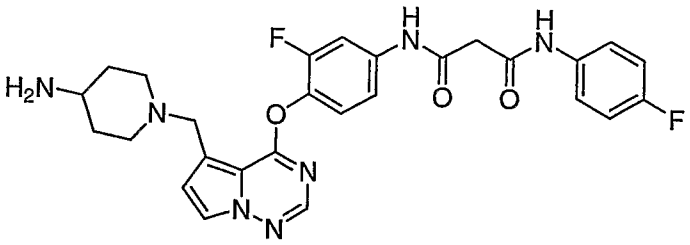


N^1-(3-Fluoro-4-(5-((4-hydroxy-4-methylcyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

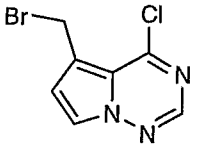
To N^1-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (10 mg, 0.019 mmol, Example 149) in THF (1 mL) at 0 °C was added methyllithium (76 µL, 0.076 mmol, 1 M THF). After stirring at rt overnight, the reaction was quenched with brine (1 mL). The layers were separated and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (3 mg, 21%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 10.21 (s, 1H), 7.98 (d, 1H, J = 2.8 Hz), 7.96 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.58-7.55 (m, 2H), 7.40 (t, 1H, J = 8 Hz), 7.33-7.31 (m, 1H), 7.13-7.08 (m, 2H), 6.87 (d, 1H, J = 2.8 Hz),

6.51 (s, 1H), 4.20 (br s, 1H), 3.43 (s, 2H), 2.60-2.45 (m, 3H), 2.09-2.06 (m, 1H), 1.56-1.52 (m, 2H), 1.41-1.36 (m, 2H), 1.07 (s, 3H); MS(ESI$^+$) *m/z* 548.3 $(M + H)^+$.

EXAMPLE 154

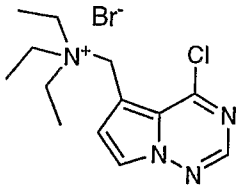


N^1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



A) 5-Bromomethyl-4-chloro-pyrrolo[2,1-*f*][1,2,4]triazine

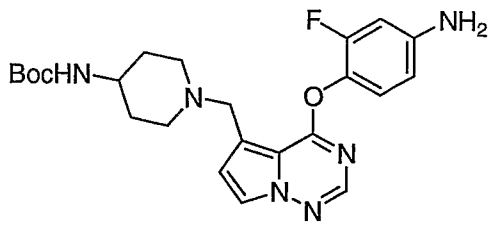
A mixture of 4-chloro-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine (2.0 g, 11.93 mmol, WO 03/042172) and AIBN (195 mg, 1.19 mmol) in CCl_4 (80 mL) under N_2 was heated to 100 °C for 5 min, NBS (2.55 g, 14.3 mmol) was added. The reaction mixture was stirred for 10 min, then cooled to rt, filtered. The CCl_4 layer was washed with dilute $NaHCO_3$ aqueous solution, dried ($MgSO_4$), filtered and concentrated to give the desired product (2.70 g, 92%).



B) (4-Chloro-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-triethylammonium bromide

A mixture of 5-bromomethyl-4-chloro-pyrrolo[2,1-*f*][1,2,4]triazine (2.7 g, 11 mmol), Et_3N (5 mL, 36 mmol) in THF (20 mL) was stirred at rt for 12 h. The solid was filtered and rinsed with THF and Et_2O, dried to give the desired product (3.38 g,

89%). Analytical HPLC retention time = 0.776 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm); MS(ESI$^+$) *m/z* 267 $(M + H)^+$.



C) *tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate

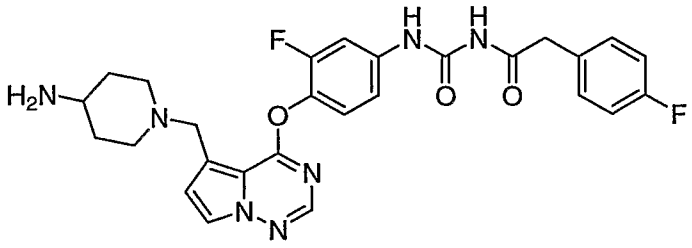
To 4-amino-2-fluorophenol (82 mg, 0.646 mmol) in THF (5 mL) at -78 °C under nitrogen was added NaHMDS (650 µL, 0.650 mmol, 1 M hexanes). After stirring at -78 °C for 20 min, the flask was transferred to a bath at 0 °C and solid *N*-((4-chloropyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-triethylammonium bromide (200 mg, 0.807 mmol) was immediately added. The reaction was allowed to warm to rt and stirred for 2 h. DIPEA (280 µL, 1.6 mmol), *tert*-butyl piperidin-4-ylcarbamate (129 mg, 0.646 mmol, Aldrich), and DMF (2 mL) was added. The reaction was heated to 120 °C for 4 h. After cooling to rt, the reaction was concentrated *in vacuo* and the crude product was purified by reverse phase prep HPLC. The appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (100 mg, 27%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.09 (s, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.23-7.13 (m, 2H), 6.83-6.61 (m, 2H), 4.73 (s, 2H), 3.67-3.64 (m, 1H), 3.30-3.19 (m, 2H), 2.31-2.24 (m, 2H), 1.76-1.63 (m, 2H), 1.49-1.45 (m, 2H), 1.45 (s, 9H); MS(ESI$^+$) *m/z* 457.5 $(M + H)^+$.

D) N^1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

Prepared in similar manner as Step A of Example 133. The resulting Boc protected material was dissolved in ether (1 mL) at 0 °C and charged with 4 N HCl in dioxane (3 mL). After stirring at 0 °C for 3 h, the reaction was concentrated *in vacuo*.

The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (4 mg, 12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.22 (s, 1H), 8.18 (s, 1H), 7.90 (d, 1H, J = 2.8 Hz), 7.76 (dd, 1H, J = 12.8, 2.4 Hz), 7.57-7.56 (m, 2H), 7.43-7.36 (m, 2H), 7.13-7.09 (m, 3H), 4.57 (s, 2H), 3.51-3.48 (m, 1H), 3.44 (s, 2H), 3.09-3.06 (m, 2H), 2.53-2.50 (m, 2H), 2.00-1.97 (m, 2H), 1.72-1.67 (m, 2H); MS(ESI$^+$) *m/z* 536.5 $(M + H)^+$.

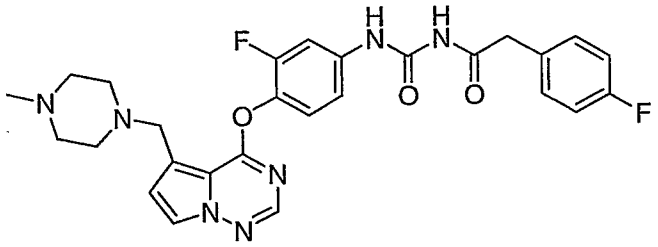
EXAMPLE 155



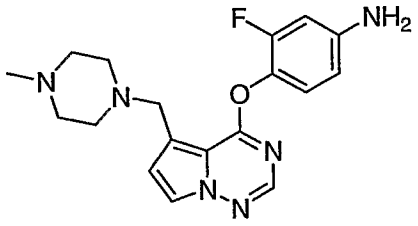
1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To *tert*-butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate (50 mg, 0.088 mmol, Compound C of Example 154) in dichloromethane (1 mL) at 0 °C was added 2-(4-fluorophenyl)acetyl isocyanate (290 uL, 0.088 mmol, 0.3 M in toluene, Compound C of Example 4). The reaction was stirred at 0 °C for 0.5 h and was purified directly by by flash chromatography on silica gel (10% MeOH / EtOAc) to give the Boc protected material (33 mg, 59%) as a colorless oil. The Boc protected material was suspended in ether (2 mL) at 0 °C and charged with 4 N HCl in dioxane (5 mL). After stirring at 0 °C for 1.5 h, the reaction was concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (3 mg, 8%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.57 (s, 1H), 8.21-8.18 (m, 2H), 7.73 (dd, 1H, J = 12.8, 2.4 Hz), 7.48-7.33 (m, 4H), 7.18-7.11 (m, 3H), 4.57 (m, 1H), 3.69 (s, 2H), 3.44 (s, 2H), 3.59-3.48 (m, 2H), 3.13-3.06 (m, 2H), 2.05-1.98 (m, 2H), 1.71-1.55 (m, 2H); MS(ESI$^+$) *m/z* 535.3 $(M + H)^+$.

EXAMPLE 156



1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



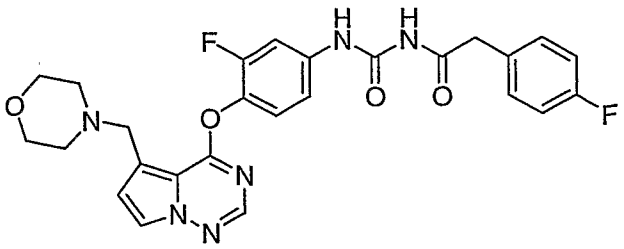
A) 1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*] [1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (9%) as a brown solid. ^{1}H NMR (CD_3OD) δ 7.90 (s, 1H), 7.85 (d, 1H, J = 2.8 Hz), 7.17 (t, 1H, J = 8.8 Hz), 6.94 (d, 1H, J = 2.8 Hz), 6.75 (dd, 1H, J = 11.6, 2.4 Hz), 6.72-6.69 (m, 1H), 4.39 (s, 2H), 3.40-3.31 (m, 8H), 2.79 (s, 3H); MS(ESI$^+$) *m/z* 357.3 $(M + H)^+$.

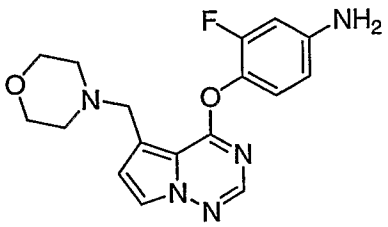
B) 1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in similar manner as Example 155 to give the title compound (83%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.80 (s, 1H), 7.77 (d, 1H, J = 2 Hz), 7.62 (dd, 1H, J = 12.4, 2.4 Hz), 7.27-7.17 (m, 4H), 6.99-6.95 (m, 2H), 6.84 (d, 1H, J = 2.4 Hz), 3.94 (s, 2H), 3.62 (s, 2H), 2.70-2.45 (m, 8H), 2.26 (s, 3H); MS(ESI$^+$) *m/z* 536.2 $(M + H)^+$.

EXAMPLE 157



1-(3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



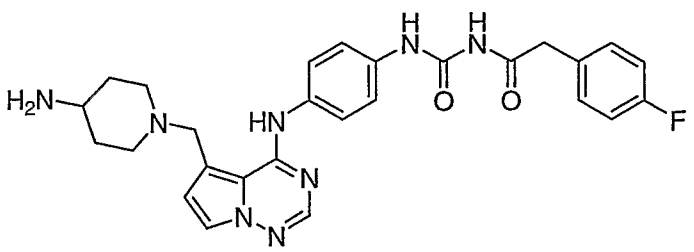
A) 3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (10%) as a light brown solid. ^{1}H NMR (CD_3OD) δ 7.98 (s, 1H), 7.91 (d, 1H, J = 2.8 Hz), 7.11 (t, 1H, J = 8.4 Hz), 7.02 (d, 1H, J = 2.8 Hz), 6.62 (dd, 1H, J = 12.4, 2.8 Hz), 6.60-6.57 (m, 1H), 4.67 (s, 2H), 4.00-3.94 (m, 2H), 3.68-3.61 (m, 2H), 3.43-3.40 (m, 2H), 3.22-3.20 (m, 2H); MS(ESI$^+$) *m/z* 344.3 $(M + H)^+$.

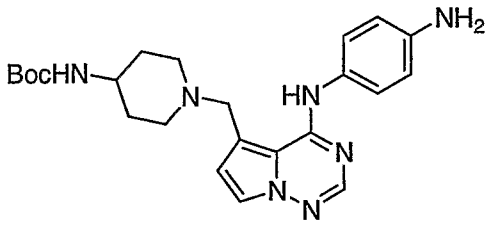
B) 1-(3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in similar manner as Example 155 to give the title compound (83%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.89 (s, 1H), 7.85 (d, 1H, J = 2.8 Hz), 7.67 (dd, 1H, J = 12.4, 2.4 Hz), 7.30-7.19 (m, 4H), 7.01-6.94 (m, 3H), 4.28 (s, 2H), 3.70-3.76 (m, 4H), 3.62 (s, 2H), 2.88-2.80 (m, 2H); MS(ESI$^+$) *m/z* 523.2 $(M + H)^+$.

EXAMPLE 158



1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



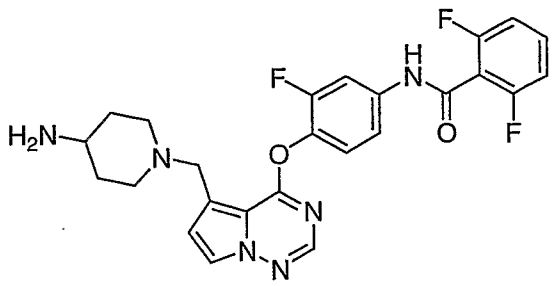
A) ***tert*-Butyl 1-((4-(4-aminophenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (38%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.57 (s, 1H), 7.33 (d, 1H, J = 2.4 Hz), 7.24-7.21 (m, 2H), 6.71-6.68 (m, 2H), 6.45 (d, 1H, J = 2.8 Hz), 3.67 (s, 2H), 3.34-3.28 (m, 1H), 2.95-2.90 (m, 2H), 1.80-1.77 (m, 2H), 1.41-1.33 (m, 2H), 1.32 (s, 9H); MS(ESI$^+$) *m/z* 438.3 $(M + H)^+$.

B) **1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (47%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 8.00-7.89 (m, 2H), 7.61-7.59 (m, 3H), 7.45-7.41 (m, 2H), 7.26-7.22 (m, 4H), 3.77 (s, 2H), 3.63 (s, 2H), 3.35-3.32 (m, 1H), 3.20-3.14 (m, 2H), 2.19-1.90 (m, 6H); MS(ESI$^+$) *m/z* 517.3 $(M + H)^+$.

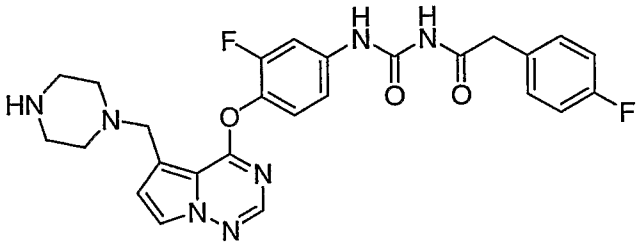
EXAMPLE 159



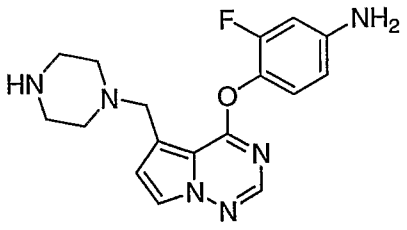
N-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide

Prepared in a similar manner as Example 147 to give the TFA salt of the title compound (5%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 8.19-8.17 (m, 2H), 7.82 (dd, 1H, J = 12.8, 2.4 Hz), 7.49 (t, 1H, J = 8.8 Hz), 7.49-7.47 (m, 2H), 7.25-7.21 (m, 2H), 7.14-7.09 (m, 1H), 4.59 (s, 2H), 3.54-3.48 (m, 3H), 3.15-3.08 (m, 2H), 2.08-2.00 (m, 2H), 1.74-1.66 (m, 2H); MS(ESI$^+$) *m/z* 497.2 $(M + H)^+$.

EXAMPLE 160



1-(3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



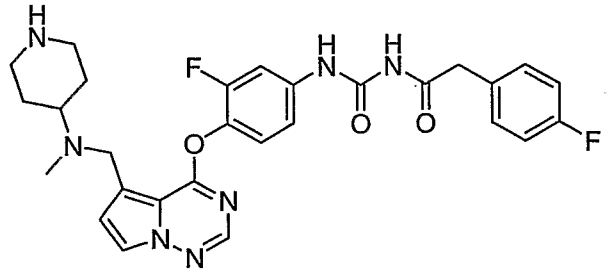
A) **3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Prepared in a similar manner as Step C of Example 154 to give the title compound as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

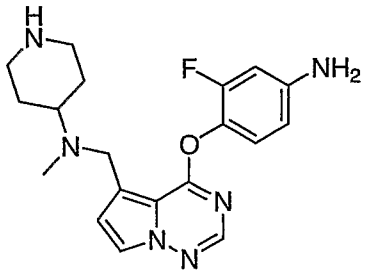
B) 1-(3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in similar manner as Example 155 to give the title compound (6%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.12 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 7.71 (dd, 1H, J = 12.8, 2.4 Hz), 7.42 (t, 1H, J = 8.8 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J = 9.2 Hz), 7.03 (m, 1H), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.59 (m, 4H), 3.32-3.05 (m, 4H); MS(ESI$^+$) *m/z* 522.3 $(M + H)^+$.

EXAMPLE 161



1-(3-Fluoro-4-(5-((methyl(piperidin-4-yl)amino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) *N*-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-*N*-methylpiperidin-4-amine

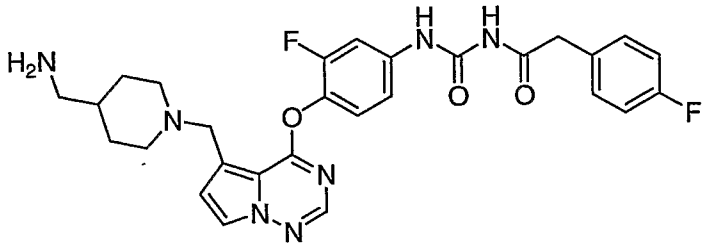
Prepared in a similar manner as Step C of Example 154 to give the title compound (38%) as a yellow oil. MS(ESI$^+$) *m/z* 471.3 $(M + H)^+$.

B) 1-(3-Fluoro-4-(5-((methyl(piperidin-4-yl)amino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

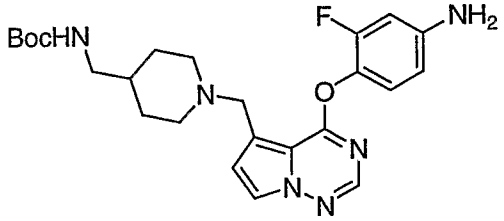
Prepared in similar manner as Example 155 to give the title compound (32%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H, J = 2.4 Hz), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.42-7.34 (m, 2H), 7.32-7.28

(m, 2H), 7.16-7.06 (m, 3H), 4.44 (s, 2H), 3.69 (s, 2H), 3.64-3.59 (m, 4H), 2.87-2.84 (m, 1H), 2.72 (s, 3H), 2.19-2.15 (m, 2H), 1.87-1.82 (m, 2H); MS(ESI$^+$) *m/z* 550.3 (M + H)$^+$.

EXAMPLE 162



1-(4-(5-((4-(Aminomethyl)piperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



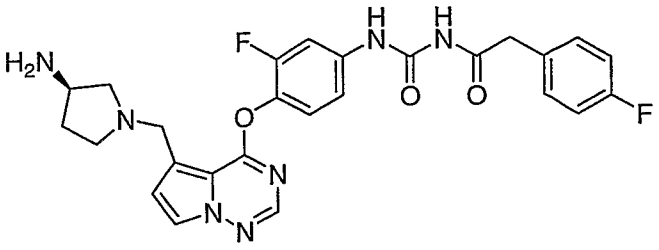
A) ***tert*-Butyl (1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-yl)methylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (29%) as a yellow oil. MS(ESI$^+$) *m/z* 471.3 (M + H)$^+$.

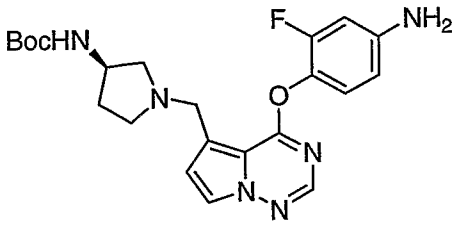
B) **1-(4-(5-((4-(Aminomethyl)piperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (26%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 7.99 (s, 1H), 7.97 (d, 1H, *J* = 2.4 Hz), 7.66 (dd, 1H, *J* = 13.2, 2.4 Hz), 7.36-7.28 (m, 4H), 7.09 (t, 2H, *J* = 8.8 Hz), 6.82 (d, 1H, *J* = 2.4 Hz), 3.77 (s, 2H), 3.68 (s, 2H), 3.84-3.82 (m, 2H), 2.38-2.36 (m, 1H), 1.88 (t, 2H, *J* = 10 Hz), 1.58-1.55 (m, 2H), 1.20-1.01 (m, 4H); MS(ESI$^+$) *m/z* 550.2 (M + H)$^+$.

EXAMPLE 163



(*R*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



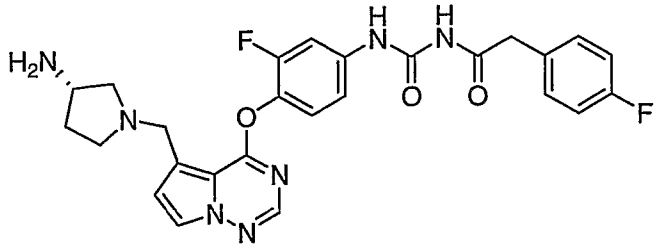
A) **(*R*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)pyrrolidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (30%) as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

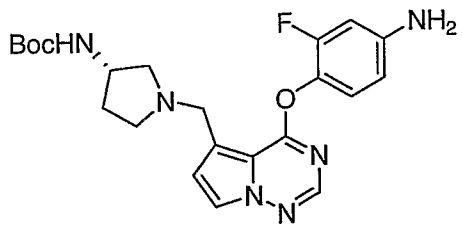
B) **(*R*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (11%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J = 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); MS(ESI$^+$) *m/z* 522.2 $(M + H)^+$.

EXAMPLE 164



(*S*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



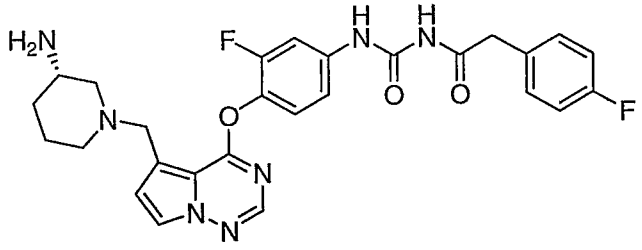
A) **(*S*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)pyrrolidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (30%) as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

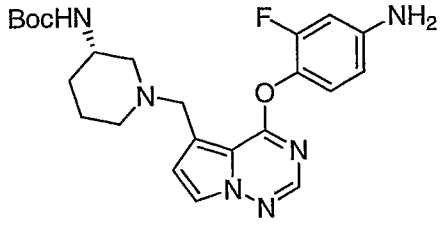
B) **(*S*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (7%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J = 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); MS(ESI$^+$) *m/z* 522.2 $(M + H)^+$.

EXAMPLE 165



(*S*)-1-(4-(5-((3-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



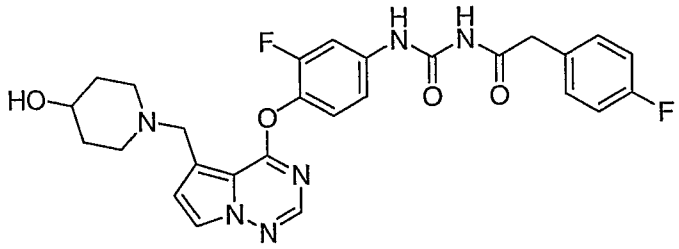
A) **(*S*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (40%) as a yellow oil. MS(ESI$^+$) *m/z* 457.3 $(M + H)^+$.

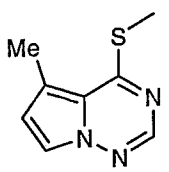
B) **(*S*)-1-(4-(5-((3-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the TFA salt of the title compound (29%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.15 (m, 2H), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.41 (t, 1H, J = 8.4 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J = 8.8 Hz), 7.05 (d, 1H, J = 2.8 Hz), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.30 (m, 5H), 1.95-1.83 (m, 2H), 1.67-1.53 (m, 1H), 1.40-1.32 (m, 1H); MS(ESI$^+$) *m/z* 536.2 $(M + H)^+$.

EXAMPLE 166

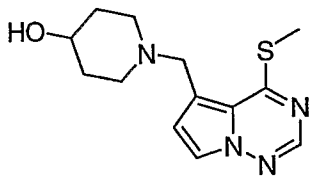


1-(3-Fluoro-4-(5-((4-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



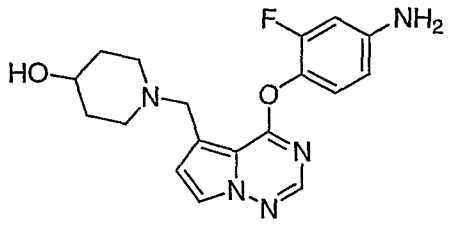
A) 5-Methyl-4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazine

To a solution of 4-chloro-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine (4.02 g, 24.0 mmol, WO 03/042172) in dry THF (200 mL) sparged with N_2 at 0°C was added NaSMe (1.85 g, 26.3 mmol). The sparging was continued for 5 min. The reaction mixture was then stirred at rt overnight, concentrated *in vacuo* to about 50 mL volume, diluted with H_2O (280 mL) and stirred at 0 °C. The solid was filtered, washed with cold water, dried to give the desired product (3.91 g, 91%). Analytical HPLC retention time = 3.38 min. (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm); MS(ESI$^+$) *m/z* 180 $(M + H)^+$.



B) 1-((4-(Methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol

A solution of 5-methyl-4-methylsulfanyl-pyrrolo[2,1-*f*] [1,2,4]triazine (200 mg, 1.12 mmol), NBS (218 mg, 1.23 mmol), and AIBN (spatula tip) in carbon tetrachloride (4 mL) was heated at 80 °C for 1 h. After cooling to rt, the solution was filtered to remove succinimide. To the filtrate was added 4-hydroxypiperidine (126 mg, 1.34 mmol, Aldrich) and DIPEA (214 µL, 1.23 mmol). The reaction was stirred at rt overnight and was then concentrated *in vacuo*. The residue was suspended in methanol and filtered. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (20% MeOH / EtOAc) to give the title compound (229 mg, 74%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 8.25 (s, 1H), 7.88 (d, 1H, J = 2 Hz), 6.81 (d, 1H, J = 2 Hz), 4.54 (br s, 1H), 3.76 (s, 2H), 3.48-3.44 (m, 1H), 2.75-2.71 (m, 2H), 2.62 (s, 3H), 2.10-2.08 (m, 2H), 1.70-1.68 (m, 2H), 1.38-1.36 (m, 2H); MS(ESI$^+$) *m/z* 279.3 $(M + H)^+$.



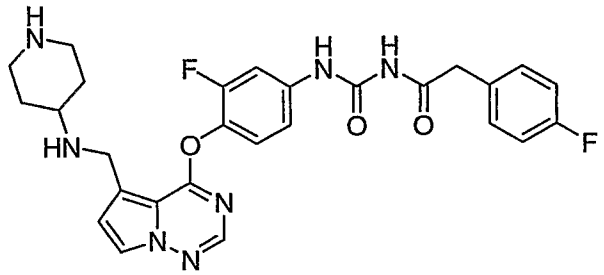
C) 1-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol

To 1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol (188 mg, 0.675 mmol) in dichloromethane (7 mL) at 0 °C was added TFA (78 µL, 1.01 mmol) followed by *m*-CPBA (166 mg, 0.675 mmol, ~70% pure). After stirring at 0 °C for 1 h, the mixture was concentrated *in vacuo*. Ether (20 mL) was added and then decanted off to remove the benzoic acid. The resulting crude sulfoxide was dried under high vacuum. 4-Amino-2-fluorophenol (343 mg, 2.7 mmol) was dissolved in THF (10 mL), cooled to -78 °C, and charged with NaHMDS (2.7 mL, 2.7 mmol, 1 M in THF). After stirring at 0 °C for 5 min, the crude sulfoxide in THF (3 mL) was added. The reaction was stirred at 0 °C for 30 min and was then concentrated *in vacuo*. The residue was suspended in EtOAc (20 mL), washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo* to remove methanol. The resulting aqueous solution was made basic with 5% aqueous sodium bicarbonate solution and extracted with EtOAc (3 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 36 mg (15%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.04 (s, 1H), 8.00 (d, 1H, J = 2.8 Hz), 7.02 (t, 1H, J = 8.8 Hz), 6.88 (d, 1H, J = 2.8 Hz), 6.51 (dd, 1H, J = 12.8, 2.8 Hz), 6.46-6.42 (m, 1H), 5.45 (br s, 2H), 3.83 (s, 2H), 3.18 (m, 1H), 2.76-2.71 (m, 2H), 2.12-2.06 (m, 2H), 1.72-1.67 (m, 2H), 1.41-1.38 (m, 2H); MS(ESI$^+$) *m/z* 358.4 $(M + H)^+$.

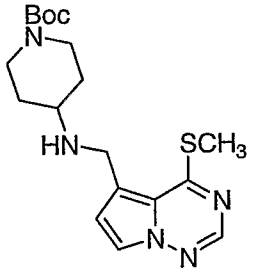
D) 1-(3-Fluoro-4-(5-((4-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

Prepared in similar manner as Example 155 to give the TFA salt of the title compound (12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18 (s, 1H), 8.16-8.14 (m, 1H), 7.71 (d, 1H, J = 12.4 Hz), 7.41-7.28 (m, 4H), 7.11-7.08 (m, 3H), 4.59-4.54 (m, 2H), 3.68 (s, 2H), 3.60-3.00 (m, 5H), 1.92-1.87 (m, 1H), 1.81-1.68 (m, 2H), 1.53-1.48 (m, 1H); MS(ESI$^+$) m/z 537.2 $(M + H)^+$.

EXAMPLE 167

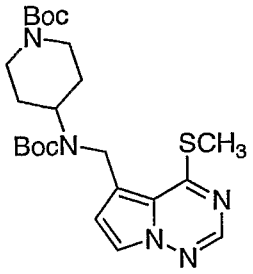


1-(3-Fluoro-4-(5-((piperidin-4-ylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



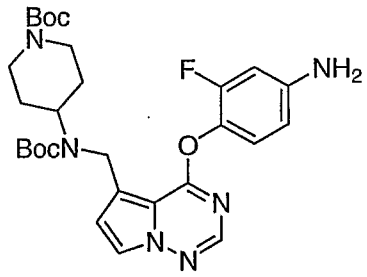
A) *tert*-Butyl 4-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylamino)piperidine-1-carboxylate

Prepared in a similar manner as Step A of Example 166 to give the title compound (50%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.8 Hz), 6.91 (d, 1H, J = 2.8 Hz), 4.21 (s, 2H), 4.10-4.07 (m, 2H), 2.83-2.77 (m, 3H), 2.71 (s, 3H), 1.99-1.97 (m, 2H), 1.48 (s, 9H), 1.34-1.31 (m, 2H); MS(ESI$^+$) m/z 378.3 $(M + H)^+$.



B) 4-[*tert*-Butoxycarbonyl-(4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester

tert-Butyl 4-((4-(methylthio)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methylamino)piperidine-1-carboxylate (210 mg, 0.556 mmol) was dissolved in dichloromethane (5 mL) and triethylamine (120 µL, 0.834 mmol) followed by di-*tert*-butyl dicarbonate (134 mg, 0.612 mmol) was added. After stirring at rt for 8 h, the reaction was diluted with methylene chloride (20 mL), washed with saturated aqueous ammonium chloride solution (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% EtOAc / hexanes) to give the title compound (207 mg, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.51 (d, 1H, J = 2.8 Hz), 6.57 (d, 1H, J = 2.8 Hz), 4.71 (s, 2H), 4.06-4.04 (m, 3H), 2.68-2.61 (m, 2H), 2.61 (s, 3H), 1.60-1.57 (m, 2H), 1.46-1.36 (m, 2H), 1.35 (s, 18H); MS(ESI$^+$) *m/z* 478.2 $(M + H)^+$.



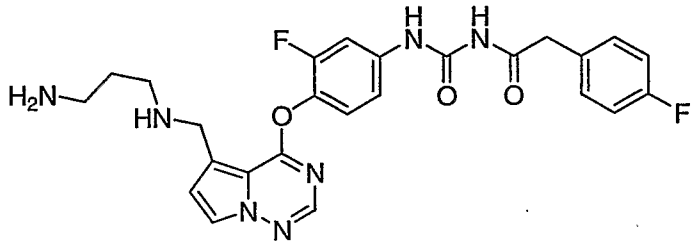
C) 4-{[4-(4-Amino-2-fluoro-phenoxy)-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl]-*tert*-butoxycarbonyl-amino}-piperidine-1-carboxylic acid *tert*-butyl ester

Prepared in a similar manner as Step C of Example 166 to give the title compound (43%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.62 (d, 1H, J = 2.8 Hz), 6.98 (t, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 2.8 Hz), 6.47-6.41 (m, 2H), 4.72 (s, 2H), 4.10-4.04 (m, 2H), 3.77-3.75 (m, 1H), 2.62-2.60 (m, 2H), 1.71-1.38 (m, 4H), 1.35 (s, 18H); MS(ESI$^+$) *m/z* 557.2 $(M + H)^+$.

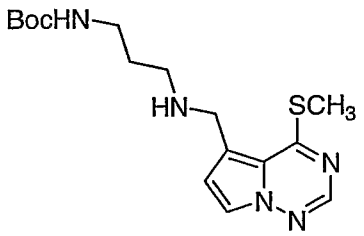
D) **1-(3-Fluoro-4-(5-((piperidin-4-ylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 155 to give the title compound (34%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.55 (s, 1H), 8.16 (s, 1H), 8.12 (d, 1H, J = 2.4 Hz), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.42-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.51 (s, 2H), 3.69 (s, 2H), 3.50-3.29 (m, 3H), 2.88-2.85 (m, 2H), 2.23-2.18 (m, 2H), 1.72-1.64 (m, 2H); MS(ESI$^+$) m/z 536.2 $(M + H)^+$.

EXAMPLE 168

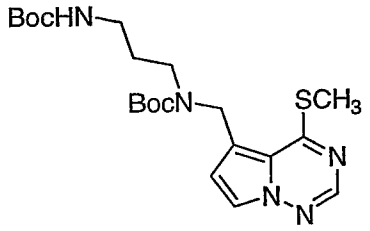


1-(4-(5-((3-Aminopropylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



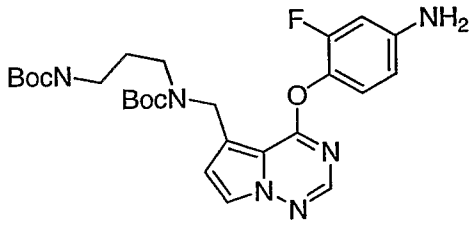
A) ***tert*-Butyl 3-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylamino)propylcarbamate**

Prepared in a similar manner as Step B of Example 166 to give the title compound (51%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.16 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J = 2.8 Hz), 4.30 (s, 2H), 3.14 (t, 2H, J = 6.4 Hz), 2.83 (t, 2H, J = 7.2 Hz), 2.72 (s, 3H), 1.82-1.75 (m, 2H), 1.40 (s, 9H); MS(ESI$^+$) m/z 352.3 $(M + H)^+$.



B) {3-[*tert*-Butoxycarbonyl-(4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-amino]-propyl}-carbamic acid *tert*-butyl ester

Prepared in a similar manner to Step B of Example 167 to give the title compound (77%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 2 Hz), 4.88 (s, 2H), 3.29-3.25 (m, 2H), 3.04-3.02 (m, 2H), 2.71 (s, 3H), 1.72-1.68 (m, 2H), 1.54 (s, 9H), 1.42 (s, 9H); MS(ESI$^+$) *m/z* 452.2 $(M + H)^+$.



C) (3-{[4-(4-Amino-2-fluoro-phenoxy)-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl]-*tert*-butoxycarbonyl-amino}-propyl)-carbamic acid *tert*-butyl ester

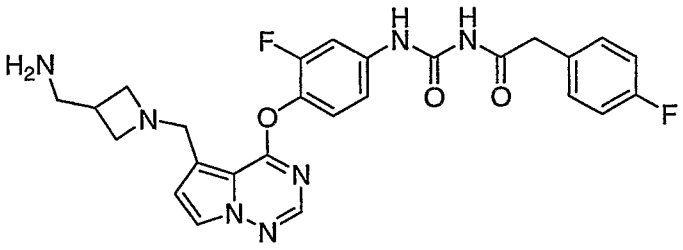
Prepared in a similar manner as Step C of Example 166 to give the title compound (29%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.64 (d, 1H, J = 2.8 Hz), 7.00 (t, 1H, J = 8.8 Hz), 6.82-6.78 (m, 1H), 6.62 (dd, 1H, J = 12.8, 2.4 Hz), 6.54-6.51 (m, 1H), 4.72 (m, 2H), 3.28-3.23 (m, 2H), 3.02-3.00 (m, 2H), 1.58-1.55 (m, 2H), 1.43 (s, 9H), 1.35 (s, 9H); MS(ESI$^+$) *m/z* 531.2 $(M + H)^+$.

D) 1-(4-(5-((3-Aminopropylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

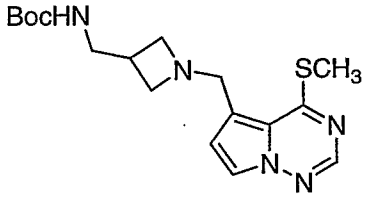
Prepared in a similar manner as Example 155 to give the title compound (17%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.52 (s, 1H), 8.00 (s, 1H), 7.98 (d, 1H, J = 2.8 Hz), 7.68 (dd, 1H, J = 12.8, 2.4 Hz), 7.34-7.28 (m, 4H), 7.13

(t, 2H, J = 9.2 Hz), 6.84 (d, 1H, J = 2.4 Hz), 3.68 (s, 2H), 3.52 (s, 2H), 2.90-2.85 (m, 2H), 2.28-2.20 (m, 2H), 1.35-1.30 (m, 2H); MS(ESI$^+$) m/z 510.2 $(M + H)^+$.

EXAMPLE 169

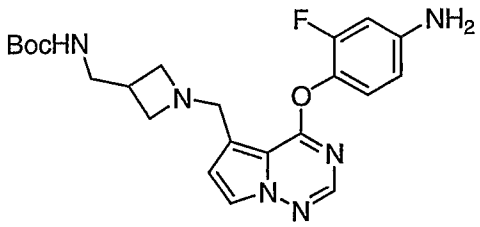


1-(4-(5-((3-(Aminomethyl)azetidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) ***tert*-Butyl (1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)azetidin-3-yl)methylcarbamate**

Prepared in a similar manner as Step B of Example 166 to give the title compound (31%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.12 (s, 1H), 7.72 (d, 1H, J = 2.4 Hz), 6.81 (d, 1H, J = 2.8 Hz), 4.07 (s, 2H), 3.46 (t, 2H, J = 8 Hz), 3.34-3.33 (m, 1H), 3.20-3.18 (m, 2H), 3.08 (t, 2H, J = 7.6 Hz), 2.65 (s, 3H), 1.44 (s, 9H); MS(ESI$^+$) m/z 364.3 $(M + H)^+$.



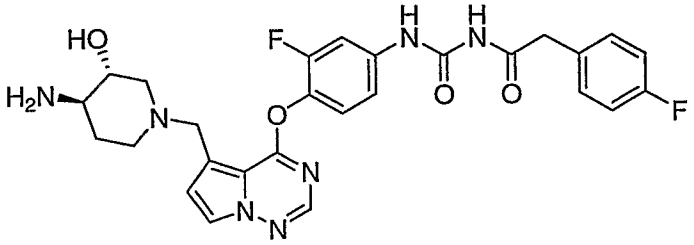
B) ***tert*-Butyl (1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)azetidin-3-yl)methylcarbamate**

Prepared in a similar manner as Step C of Example 166 to give the title compound (33%) as a brown solid. MS(ESI$^+$) m/z 443.2 $(M + H)^+$.

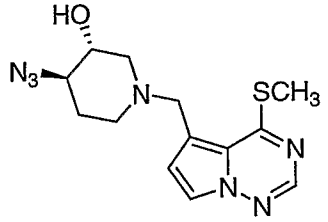
C) **1-(4-(5-((3-(Aminomethyl)azetidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 155 to give the title compound (4%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.56 (s, 1H), 8.18-8.15 (m, 2H), 7.68 (dd, 1H, J = 12.8, 2.4 Hz), 7.45-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.67 (s, 2H), 4.44-4.41 (m, 2H), 4.05-3.98 (m, 2H), 3.69 (s, 2H), 3.10-2.97 (m, 3H); MS(ESI$^+$) m/z 522.3 $(M + H)^+$.

EXAMPLE 170

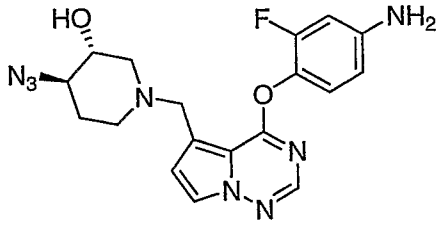


1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) **(3*R*,4*R*)-4-Azido-1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-3-ol**

Prepared in a similar manner as Step B of Example 166 to give the title compound (65%) as a yellow foam. ^{1}H NMR (CD_3OD) δ 8.36 (s, 1H), 7.99 (d, 1H, J = 2.4 Hz), 6.93 (d, 1H, J = 2.8 Hz), 3.92-3.88 (m, 2H), 3.35-3.30 (m, 1H), 3.08-2.90 (m, 2H), 2.72 (s, 3H), 2.14-2.10 (m, 2H), 2.00-1.91 (m, 2H), 1.47-1.44 (m, 1H); MS(ESI$^+$) m/z 320.2 $(M + H)^+$.



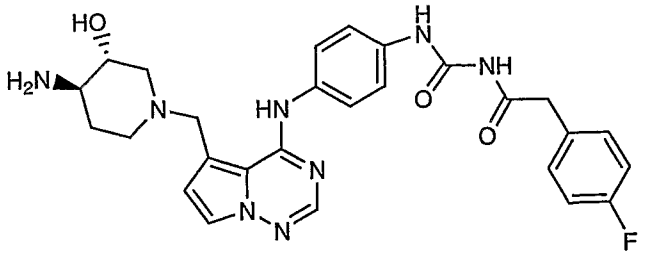
B) **(3*R*,4*R*)-1-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-4-azidopiperidin-3-ol**

Prepared in a similar manner as Step C of Example 166 to give the title compound (24%) as a brown solid. MS(ESI$^+$) *m/z* 399.2 $(M + H)^+$.

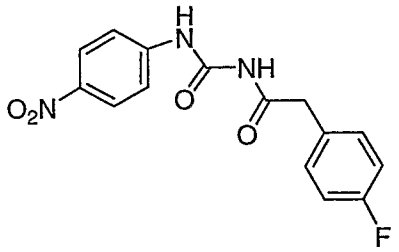
C) **1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

The acylurea was prepared in a similar manner as Example 155 to give the corresponding azide (48%). MS(ESI$^+$) *m/z* 578.16 $(M + H)^+$. The azide (35 mg, 0.06 mmol) was then dissolved in ethyl acetate (1 mL) at 0 °C and charged with trimethylphosphine (0.11 mL, 0.11 mmol) followed by water (1 drop). After stirring at rt for 3 h, the reaction was concentrated *in vacuo* and purified by reverse phase prep HPLC. The appropriate fractions were concentrated *in vacuo* and toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (8 mg, 17%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18-8.16 (m, 2H), 7.72 (dd, 1H, J = 12.8, 2.4 Hz), 7.36-7.28 (m, 4H), 7.14-7.09 (m, 3H), 4.62 (s, 2H), 3.69 (s, 2H), 3.22-2.85 (m, 6H), 2.03-1.98 (m, 1H), 1.68-1.65 (m, 1H); MS(ESI$^+$) *m/z* 510.2 $(M + H)^+$.

EXAMPLE 171

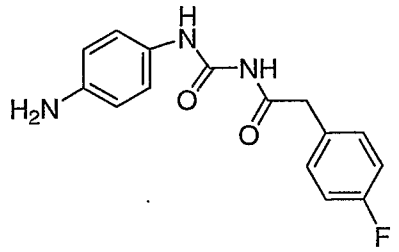


1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



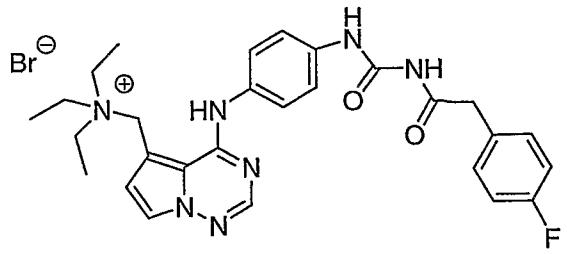
A) 1-(2-(4-Fluorophenyl)acetyl)-3-(4-nitrophenyl)urea

To a stirred solution of *p*-nitroaniline (200 mg, 1.45 mmol) in tetrahydrofuran (1 mL) at room temperature was added 2-(4-fluorophenyl)acetyl isocyanate (2 mL, 0.32 M in toluene, Compound C of Example 4). After 18 h, the mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (5 mL). The solution was slowly concentrated on rotary evaporator without heating. When a precipitate started to form, the flask was removed from the rotory evaporator and allowed to sit for 2 h. The solid formed was filtered and washed with small amount of ethyl acetate and dried in vacuo to afford light yellow crystalline compound (200 mg, 44%). MS(ESI$^+$) *m/z* 318.3 $(M+H)^+$.



B) 1-(4-Aminophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 1-(2-(4-fluorophenyl)acetyl)-3-(4-nitrophenyl)urea (200 mg, 0.63 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon (15 mg) and the flask was filled with hydrogen using a balloon. The mixture was stirred for 18 h, filtered and the catalyst was washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give a solid which was was triturated with small amount of ether and dried in vacuo to obtain the desired compound (180 mg) as pale yellow solid. MS(ESI$^+$) *m/z* 287.4 $(M+H)^+$.



C) ***N,N*-diethyl-*N*-((4-(4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)ethanaminium bromide**

To a solution of (4-chloro-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-triethylammonium bromide (75 mg, 0.22 mmol, Compound B of Example 154) in chloroform (1.5 mL) was added 1-(4-aminophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (50 mg, 0.17 mmol) and the mixture was heated at reflux for 6 h. The mixture was cooled to room temperature, concentrated in vacuo and the residue was triturated with acetonitrile. The resulting solid was used in the next step without purification.

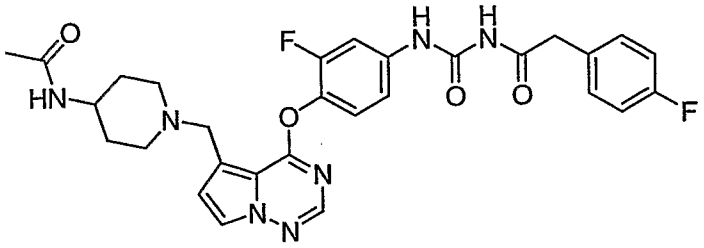
D) **1-(4-(5-(((3*R*,4*R*)-4-Azido-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

To a solution of crude *N,N*-diethyl-*N*-((4-(4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)ethanaminium bromide in chloroform (3 mL), were added (3*R*,4*R*)-4-azidopiperidin-3-ol (0.28 mg, 0.2 mmol, WO 04/058144) and triethylamine (0.2 mL). The reaction mixture was stirred at 60 °C for 2 h, cooled to room temperature and was then washed with water. The aqueous layer was extracted with chloroform (3 x 8 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product as a yellow solid.

The above crude solid was dissolved in tetrahydrofuran (3 mL), triphenylphosphine (80 mg) and water (0.02 mL) were added and the resulting reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the crude product was purified by preparative reverse phase HPLC. The appropriate fractions were collected, concentrated and treated with 1 N HCl (2 mL). The solution was concentrated *in vacuo*, dissolved in water and lyophilized to obtain the title compound (48 mg, 47%

over three steps) as a white solid. ^{1}H NMR (CD_3OD) δ 7.87 (s, 1H), 7.77 (s, 1H), 7.65 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.28 (dd, 2H , J = 5.4, 8.4 Hz), 7.06 (s, 1H), 6.98 (t, 2 H, J = 8.7 Hz), 4.7 (br s, 2H), 3.9 (br s, 2H), 3.63 (s, 2H), 3.56 (br s, 2H), 3.20-3.10 (br s, 2H), 2.99-2.87 (br s, 1H), 2.96 (br d, 1H, J = 10.8 Hz), 1.91 (br t, J = 10.8 Hz); MS(ESI$^+$) m/z 533.4 $(M+H)^+$.

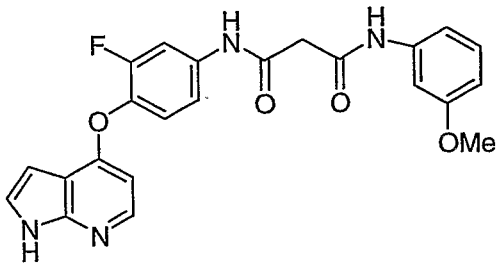
EXAMPLE 172



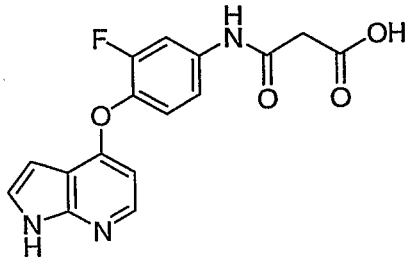
1-(4-(5-((4-Acetamidopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To 1-(4-(5-((4-aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (30 mg, 0.056 mmol, Example 155) in methylene chloride (1 mL) was added pyridine (6 µL, 0.067 mmol) followed by acetyl chloride (5 µL, 0.067 mmol). DMF (0.5 mL) was added to solubilize the reaction. After stirring at rt for 2 h, a second shot of pyridine (6 uL) and acetyl chloride (5 µL) was added. After stirring at rt for 1 h, the reaction was diluted with ethyl acetate (10 mL), washed with 10% aqueous lithium chloride solution followed by brine (1 x 5 mL each), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase prep hplc. The appropriate fractions were concentrated *in vacuo* and toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (15 mg, 39%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.14 (d, 1H, J = 2.8 Hz), 7.89 (d, 1H, J = 7.2 Hz), 7.71 (dd, 1H, J = 12.4, 2.4 Hz), 7.43-7.28 (m, 4H), 7.14-7.07 (m, 3H), 4.54 (s, 2H), 3.68 (s, 2H), 3.45-2.42 (m, 3H), 3.12-3.10 (m, 2H), 1.88-1.85 (m, 2H), 1.73 (s, 3H), 1.52-1.50 (m, 2H); MS(ESI$^+$) m/z 578.2 $(M+H)^+$.

EXAMPLE 173



N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-methoxyphenyl)malonamide, trifluoroacetic acid salt



A) 3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (900 mg, 3.7 mmol, Compound B of Example 132) in CH_2Cl_2 (30 mL) at –40 °C, was added ethyl 3-chloro-3-oxopropanoate (555 mg, 3.7 mmol, Aldrich), followed by pyridine (1 mL). The resulting mixture was stirred at –40 °C for 1 h. The mixture was diluted with CH_2Cl_2, washed with sat. KH_2PO_4, and dried over $MgSO_4$. The mixture was filtered through a short pad of silica gel, eluting with 2% MeOH/EtOAc to give a brown oil (1.1 g). The ester was saponified in EtOH (15 mL) and NaOH (1 N in H_2O, 15 mL) at 0 °C for 1 h, neutralized with 1 N HCl to pH 4. EtOH was removed from the reaction mixture under reduced pressure and the solid was collected by filtration. The solid was then rinsed with H_2O and dried ($MgSO_4$) to afford the title compound (670 mg, 55%) as a beige solid. LC/MS(ESI$^+$) *m/z* 330 $(M + H)^+$.

B) N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-methoxyphenyl)malonamide, trifluoroacetic acid salt

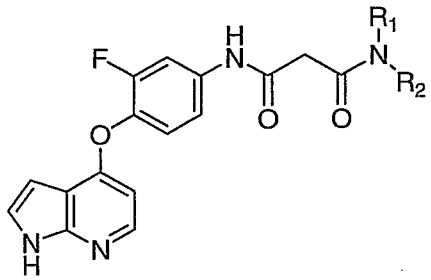
To a stirred solution of 3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (16.5 mg, 0.05 mmol) in DMF (0.4 mL), was added HATU (38 mg, 0.1 mmol), followed by 3-methoxybenzenamine (18 mg,

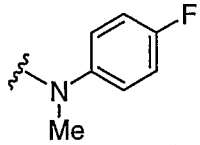
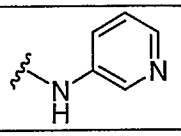
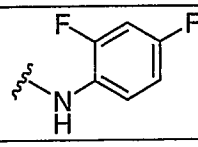
0.15 mmol) and DMAP (3 mg). The mixture was heated at 45 °C for 4 h. The desired product was purified by prep-HPLC to give the title compound (17 mg, 62%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 6.6 Hz), 7.80 (dd, 1H, J = 11.8, 2.2 Hz), 7.41 (d, 1H, J = 3.9 Hz), 7.29-7.38 (m, 2H), 7.23 (m, 1H), 7.12 (t, 1H, J = 8.3 Hz), 7.00 (dd, 1H, J = 8.3, 1.1 Hz), 6.69 (d, 1H, J = 6.6 Hz), 6.60 (dd, 1H, J = 8.3, 2.2 Hz), 6.51 (d, 1H, J = 3.3 Hz), 3.90 (s, 3H); LCMS(ESI$^+$) m/z 435 $(M + H)^+$.

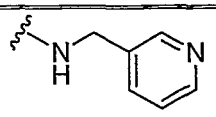
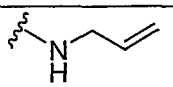
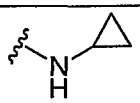
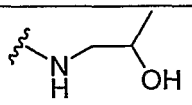
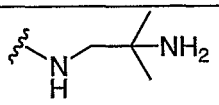
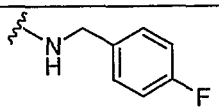
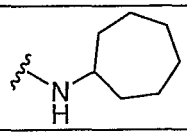
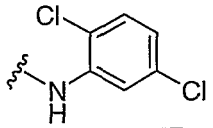
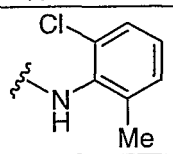
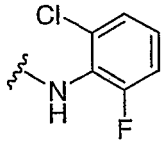
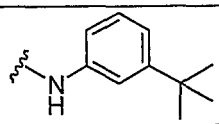
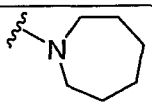
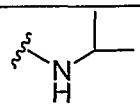
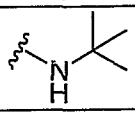
EXAMPLES 174–236

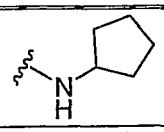
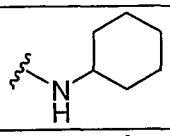
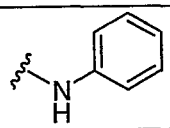
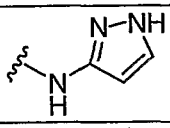
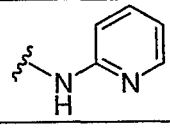
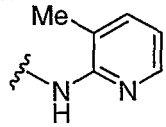
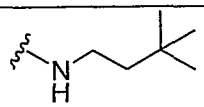
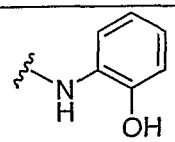
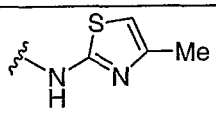
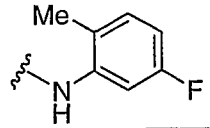
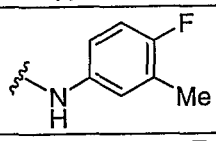
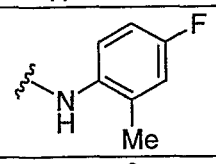
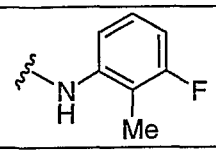
The examples **174–236** illustrated in Table 3 were prepared from 3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound A of Example 173) and the corresponding amines, in the presence of HATU, DIPEA, and DMAP in DMF. The crude products were purified by prep-HPLC (H_2O/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20 ×100 mm 5 μm YMC ODS-A column). The desired fraction(s) was/were centrifugally evaporated, weighed and analyzed by LCMS (H_2O/MeOH/0.1% TFA).

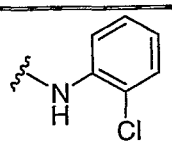
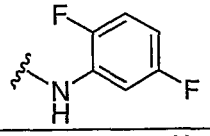
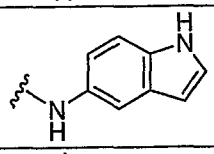
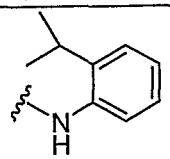
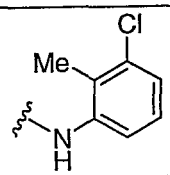
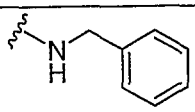
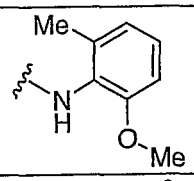
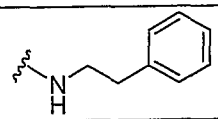
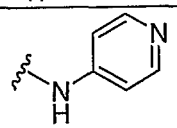
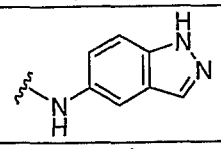
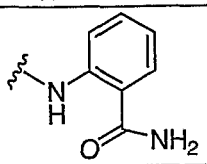
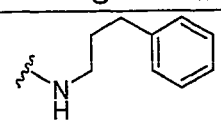
TABLE 3

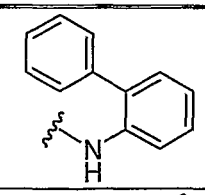
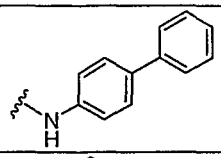
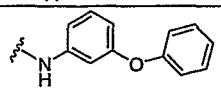
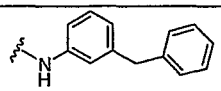
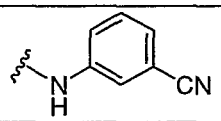
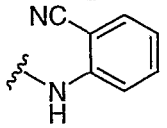
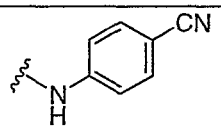
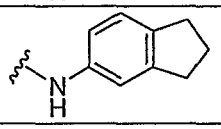
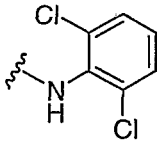
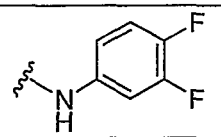
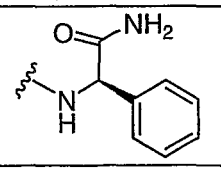
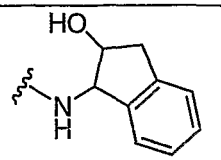


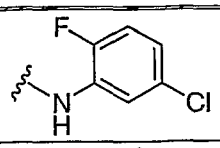
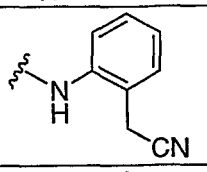
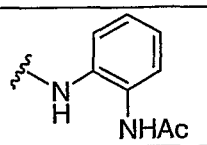
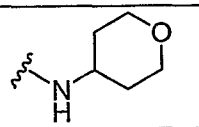
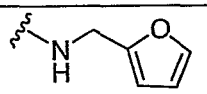
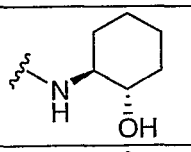
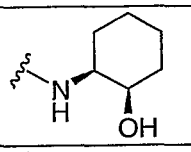
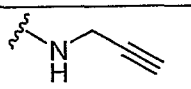
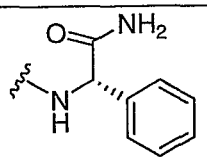
EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
174		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)-N^3-methylmalonamide	437
175		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-3-yl)malonamide	406
176		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,4-difluorophenyl)malonamide	441

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
177		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-3-ylmethyl)malonamide	420
178		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-allylmalonamide	369
179		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclopropylmalonamide	369
180		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-hydroxypropyl)malonamide	387
181		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-amino-2-methylpropyl)malonamide	400
182		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorobenzyl)malonamide	437
183		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cycloheptylmalonamide	425
184		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,5-dichlorophenyl)malonamide	474
185		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chloro-6-methylphenyl)malonamide	453
186		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chloro-6-fluorophenyl)malonamide	457
187		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-*tert*-butylphenyl)malonamide	461
188		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(azepan-1-yl)-3-oxopropanamide	411
189		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-isopropylmalonamide	371
190		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-*tert*-butylmalonamide	385

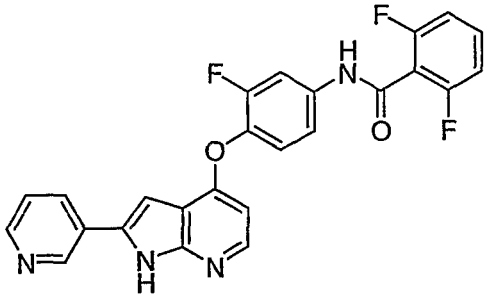
EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
191		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclopentylmalonamide	397
192		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclohexylmalonamide	411
193		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-phenylmalonamide	405
194		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(1*H*-pyrazol-3-yl)malonamide	395
195		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-2-yl)malonamide	406
196		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-methylpyridin-2-yl)malonamide	420
197		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3,3-dimethylbutyl)malonamide	413
198		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-hydroxyphenyl)malonamide	421
199		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-methylthiazol-2-yl)malonamide	426
200		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(5-fluoro-2-methylphenyl)malonamide	437
201		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluoro-3-methylphenyl)malonamide	437
202		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluoro-2-methylphenyl)malonamide	437
203		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-fluoro-2-methylphenyl)malonamide	437

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
204		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chlorophenyl)malonamide	439
205		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,5-difluorophenyl)malonamide	441
206		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(1*H*-indol-5-yl)malonamide	444
207		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-isopropylphenyl)malonamide	447
208		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-chloro-2-methylphenyl)malonamide	453
209		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-benzylmalonamide	419
210		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-methoxy-6-methylphenyl)malonamide	449
211		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-phenethylmalonamide	433
212		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-4-yl)malonamide	406
213		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(1*H*-indazol-5-yl)malonamide	445
214		2-(3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)benzamide	448
215		N^1-(4-(1*H*-Pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-phenylpropyl)malonamide	447

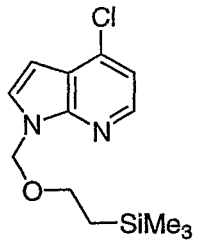
EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
216		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-biphenyl)malonamide	481
217		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-biphenyl)malonamide	481
218		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-phenoxyphenyl)malonamide	497
219		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-benzylphenyl)malonamide	495
220		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-cyanophenyl)malonamide	430
221		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-cyanophenyl)malonamide	430
222		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-cyanophenyl)malonamide	430
223		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,3-dihydro-1*H*-inden-5-yl)malonamide	445
224		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,6-dichlorophenyl)malonamide	474
225		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3,4-difluorophenyl)malonamide	441
226		(*R*)- N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-amino-2-oxo-1-phenylethyl)malonamide	462
227		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)malonamide	461

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
228		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(5-chloro-2-fluorophenyl)malonamide	457
229		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-(cyanomethyl)phenyl)malonamide	444
230		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-acetamidophenyl)malonamide	462
231		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(tetrahydro-2*H*-pyran-4-yl)malonamide	413
232		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(furan-2-ylmethyl)malonamide	409
233		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(*trans*-2-hydroxycyclohexyl)malonamide	427
234		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(*cis*-2-hydroxycyclohexyl)malonamide	427
235		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(prop-2-ynyl)malonamide	367
236		(*S*)- N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-amino-2-oxo-1-phenylethyl)malonamide	462

EXAMPLE 237

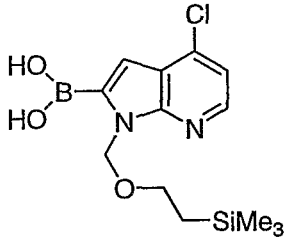


2,6-Difluoro-*N*-(3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide, hydrochloride salt



A) 4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

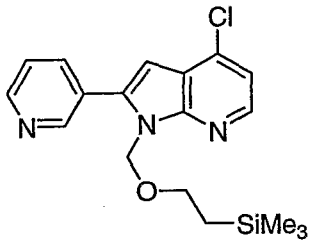
To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (3.05 g, 20 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in DMF (50 mL) at –40 °C under N_2, was added NaH (60% in mineral oil, 880 mg, 22 mmol). The mixture was stirred at rt for 15 min, then cooled to –40 °C. To this solution was added (2-(chloromethoxy)ethyl)trimethylsilane (3.67 g, 22 mmol). The resulting mixture was stirred at rt overnight. The mixture was diluted with EtOAc, washed twice with 10% LiCl, and dried over $MgSO_4$. The title compound was purified by flash column chromatography (silica gel, eluding with hexane, followed by Et_2O) to give the desired product (5.6 g, quantitiatve yield) as an oil. LC/MS(ESI$^+$) *m/z* 283 $(M + H)^+$.



B) 4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-ylboronic acid

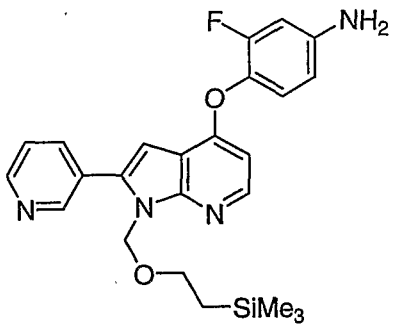
To a solution of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (565 mg, 2 mmol) in THF (5 mL) at –40 °C under N_2, was added *n*-BuLi (2.0 M in cyclohexane, Aldrich, 2.4 mmol). The reaction mixture was stirred at –40 °C for 1 h and then treated with triisopropylborate (489 mg, 2.6 mmol). The mixture was slowly warmed to rt and stirred overnight. To this solution was added 1 N HCl in

H_2O (20 mL), and the mixture was stirred for 20 min., neutralized with saturated aq. K_2HPO_4 solution and extracted with ether. The organic layer was dried over Na_2SO_4. After filtration and concentration under reduced pressure, the title compound was obtained as a light beige solid (640 mg, quantitative yield). LC/MS(ESI$^+$) *m/z* 327 (M + H)$^+$.



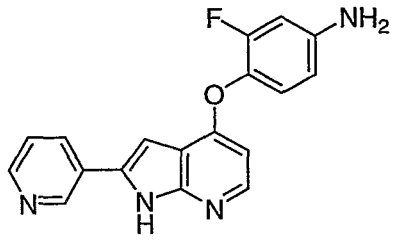
C) 4-Chloro-2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

Argon was bubbled through a mixture of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-ylboronic acid (5.55 g, 17 mmol), 3-iodopyridine (6.97 g, 34 mmol), $Pd(OAc)_2$, 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (405 mg, 0.85 mmol), and K_3PO_4 (2 M in H_2O, 34 mmol) in DME (50 mL) for 10 min and then heated at reflux overnight. The reaction mixture was diluted with EtOAc and washed with saturated aq. K_2HPO_4 solution. The title compound was purified by flash column chromatography (silica gel, 20% EtOAc/CH_2Cl_2) to afford the desired product (3.2 g, 52% yield) as an oil. LC/MS(ESI$^+$) *m/z* 361 (M + H)$^+$.



D) 3-Fluoro-4-(2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine

A mixture of 4-chloro-2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3.2 g, 8.9 mmol), 2-fluoro-4-nitrophenol (2.79 g, 17.8 mmol), and DIPEA (3.5 mL, 20 mmol) in NMP (15 mL) was heated in a sealed tube at 185 °C for 3 days. The mixture was diluted with EtOAc and filtered through a short pad of Celite® (EtOAc). The filtrate was washed with 5% aq. Na_2CO_3 solution and dried over $MgSO_4$. The title compound was purified by flash column chromatography (silica gel, 100% CH_2Cl_2 to 50% EtOAc/CH_2Cl_2) to afford the desired product (295 mg, 7.4%) as a light brown solid. LC/MS(ESI$^+$) *m/z* 451 $(M + H)^+$.



E) 3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine

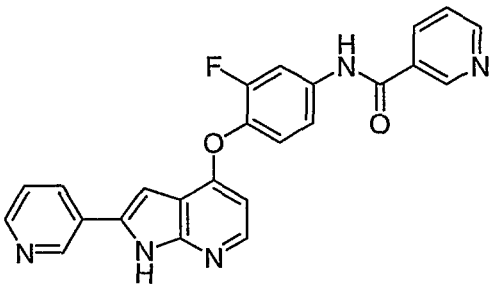
A mixture of 3-fluoro-4-(2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (275 mg, 0.61 mmol), tetrabutylammonium fluoride (1 M in THF, 4 mL), and 1,2-diaminoethane (0.2 mL) in THF (4 mL) was heated at 65 °C for 24 h. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 5% MeOH/EtOAc) to afford the desired product (180 mg, 92%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 321 $(M + H)^+$.

F) 2,6-Difluoro-*N*-(3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide, hydrochloride salt

To a solution of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (15 mg, 0.047 mmol) and pyridine (0.1 mmol) in THF at 0 °C was added 2,6-difluorobenzoyl chloride (10 mg, 0.056 mmol). The reaction mixture was stirred at 0 °C for 1 h, concentrated *in vacuo*, and the resulting residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL). This

solution was then lyophilized to afford the title compound (HCl salt, 12 mg, 48%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 9.29 (s, 1H), 8.85 (d, 1H, J = 9.6 Hz), 8.74 (d, 1H, J = 5.2 Hz), 8.26 (d, 1H, J = 6.8 Hz), 8.01 (dd, 1H, J = 8.4, 5.6 Hz), 7.88 (dd, 1H, J = 12.4, 2.4 Hz), 7.50-7.35 (m, 4H), 7.10-7.00 (m, 2H), 6.73 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) m/z 461 $(M + H)^+$.

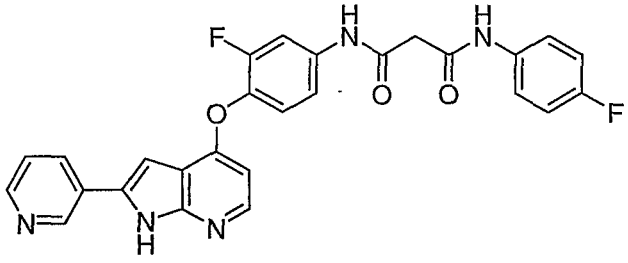
EXAMPLE 238



***N*-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)nicotinamide**

Prepared in a similar manner as Example 237. ^{1}H NMR (CD_3OD) δ 9.36 (s, 1H), 9.33 (s, 1H), 9.00-8.90 (m, 3H), 8.79 (d, 1H, J = 5.2 Hz), 8.31 (d, 1H, J = 6.8 Hz), 8.12-8.05 (m, 2H), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.52 (s, 1H), 7.48-7.40 (m, 2H), 6.78 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) m/z 461 $(M + H)^+$.

EXAMPLE 239

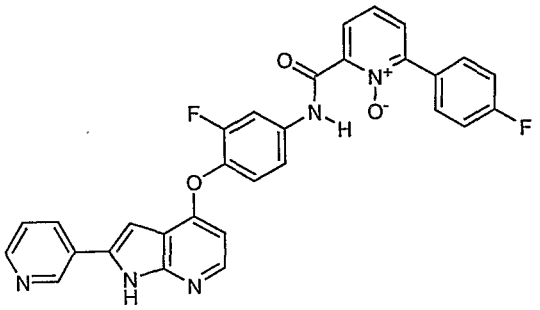


***N*^{1}-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide, hydrochloride salt**

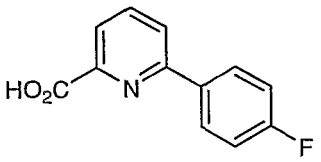
To a stirred solution of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (16 mg, 0.05 mmol, Compound E of Example 237), 3-(4-fluorophenylamino)-3-oxopropanoic acid (19.7 mg, 0.1 mmol, Compound A of Example 25), and HATU (38 mg, 0.1 mmol) in DMF (0.5 mL) was added DIPEA (0.1

mL). The mixture was stirred at rt for 2 h, concentrated *in vacuo*, and the residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL) and lyophilized to afford the title compound (HCl salt, 12 mg, 42%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 9.25 (s, 1H), 8.81 (d, 1H, J = 8.7 Hz), 8.72 (d, 1H, J = 5.4 Hz), 8.25 (d, 1H, J = 6.7 Hz), 8.00 (dd, 1H, J = 8.1, 6.1 Hz), 7.82 (dd, 1H, J = 12.1, 1.3 Hz), 7.53-7.48 (m, 2H), 7.40-7.32 (m, 3H), 7.00-6.95 (m, 2H), 6.71 (d, 1H, J = 6.72 Hz), 3.48 (s, 2H); LC/MS(ESI$^+$) *m/z* 500 $(M + H)^+$.

EXAMPLE 240



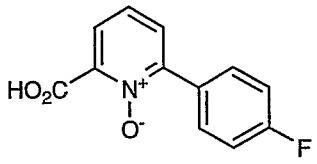
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(2-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt



A) **6-(4-Fluorophenyl)picolinic acid**

A solution of 2-bromo-picolinic acid (2.02 g, 10 mmol, Aldrich) in DME containing 4 mL of 10% aq. Na_2CO_3 was purged with Ar gas, treated with $Pd(PPh_3)_4$ followed by 2-(4-fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2.40 g, 11.5 mmol, Aldrich) and EtOH (20 mL). This mixture was then also purged with Ar gas. The reaction mixture was heated at 100 °C for 2.5 h in a sealed tube. Additional 2-bromo-picolinic acid (900 mg) and $Pd(PPh_3)_4$ was added, and after purging with Ar gas it was heated at 100 °C for 4.5 h. Trifluoroacetic acid (20 mL) was added to the reaction and the mixture was concentrated *in vacuo*. MeOH (150 mL) was added to the residue and the insoluble material was filtered. The filtrate was concentrated *in*

vacuo, and the resulting residue was purified by flash column chromatography on silica gel eluting with EtOAc/MeOH (9:1) followed by EtOAc/MeOH/HOAc (14:30:1) to afford the desired product (1.0 g, 40% based on borinane starting material) as a white solid. ^{1}H NMR (CD_3OD) δ 8.01 (d, 1H, J = 7.7 Hz), 7.94-7.87 (m, 3H), 7.73 (d, 1H, J = 7.7 Hz), 7.13 (t, 2H, J = 8.8 Hz); MS(ESI$^+$) *m/z* 234 (M + H)$^+$.



B) 6-(4-Fluorophenyl)picolinic acid-*N*-oxide

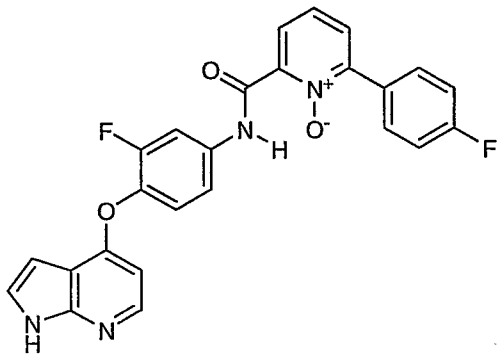
A mixture of the picolinic acid derivative above (1.0 g, 4.6 mmol), Na_2HPO_4 (1.2 g) and *m*-CPBA (1.1 g, ~70 % from Aldrich) in CH_2ClCH_2Cl (30 mL) was stirred at rt for 2 h. Additional Na_2HPO_4 (0.8 g) and *m*-CPBA (1.0 g) were added to the reaction mixture and it was stirred for 3 h at rt. Na_2HPO_4 (0.5 g) and *m*-CPBA (0.5 g) were again added to the reaction mixture and it was stirred at rt overnight. $CHCl_3$ (160 mL) and 2 N aq. HCl solution (50 mL) were added to the mixture and the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/MeOH/HOAc (70:24:6) to obtain the desired product which was contaminated with *m*-CPBA. This impure material was purified by preparative HPLC to obtain the desired product (175 mg, 16%) as a white solid. ^{1}H NMR (DMF-d_7) 8.45 (dd, 1H, J = 8.3, 2.2 Hz), 8.15 (d, 1H, J = 2.2 Hz), 8.13-8.00 (m, 4H), 7.45 (t, 2H, J = 8.7 Hz).

C) 6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(2-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt

To a solution of 6-(4-fluorophenyl)picolinic acid *N*-oxide (30 mg, 0.13 mmol), HOBT (16 mg), and EDCI.HCl (50 mg, 0.26 mmol) in DMF (4 mL) at room temperature was added 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (40 mg, 0.12 mmol, Compound E of Example 237). The reaction

mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the desired product (20 mg, 24%) as a beige solid. ^{1}H NMR (DMF-d_7) δ 14.07 (br s, 1H), 12.64 (br s, 1H), 9.35 (s, 1H), 8.65 (d, 1H, J = 4.4 Hz), 8.53 (d, 1H, J = 7.7 Hz), 8.49 (dd, 1H, J = 8.2, 2.2 Hz), 8.23 (d, 1H, J = 5.5 Hz), 8.19 (dd, 1H, J = 13.2, 2.8 Hz), 8.02-7.62 (m, 6H), 7.55 (t, 1H, J = 8.8 Hz), 7.43 (t, 2H, J = 8.8 Hz), 7.22 (s, 1H), 6.55 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 459.1 $(M + H)^+$.

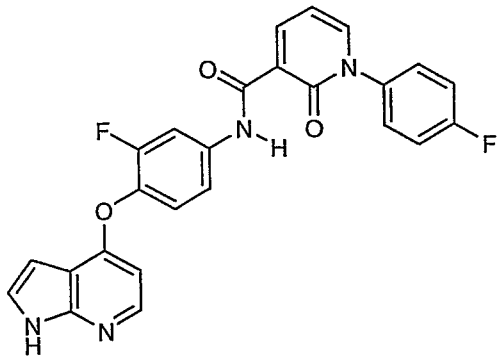
EXAMPLE 241



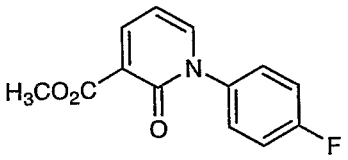
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt

To a solution of 6-(4-fluorophenyl)picolinic acid *N*-oxide (47 mg, 0.20 mmol, Compound B of Example 240), HOBT (20 mg), and EDCI.HCl (60 mg, 0.31 mmol) in DMF (4 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorobenzenamine (50 mg, 0.20 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to afford the desired product (68 mg, 12%) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.07 (br s, 1H), 12.14 (br s, 1H), 8.49 (dd, 1H, J = 7.7, 1.7 Hz), 8.26 (d, 1H, J = 6.1 Hz), 8.18 (dd, 1H, J = 12.7, 1.7 Hz), 8.02-7.96 (m, 3H), 7.84 (t, 1H, J = 8.3 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.57-7.52 (m, 2H), 7.43 (d, 2H, J = 8.8 Hz), 6.62 (d, 1H, J = 6.0 Hz), 6.46 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) m/z 536.1 $(M + H)^+$.

EXAMPLE 242

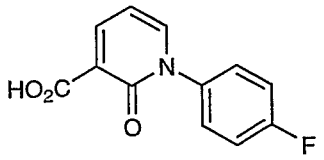


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) Methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (2.31 g, 15 mmol, Aldrich) in THF (40 mL) and DMF (10 mL) at rt was added 4-fluoroaniline (1.67 g, 15 mmol), and the reaction mixture was stirred for 2.5 h. To the 4-fluoroaniline intermediate formed *via* a Michael addition was added EDCI.HCl (3.85 g, 20 mmol) and DMAP (120 mg) at rt. The reaction mixture was stirred at rt overnight. To the reaction mixture were added 1 N aq. HCl (50 mL) and EtOAc (150 mL). The EtOAc layer was separated, and the aqueous layer was washed with EtOAc (150 mL). The combined EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo* to obtain a semi-solid material (~4.4 g). The crude product was dissolved in ether (100 mL) and methanol (15 mL), and the solid which formed after stirring was filtered off. The filtrate was concentrated *in vacuo* to afford the desired product (2.95 g, 80%) as a semi-solid, which was sufficiently pure to use in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 8.23 (dd, 1H, J = 7.2, 2.2 Hz), 7.57 (dd, 1H, J = 6.6, 1.7 Hz), 7.32-7.34 (m, 2H), 7.17 (t, 2H, J = 8.8 Hz), 6.32 (t, 1H, J = 7.1 Hz), 3.89 (s, 3H); MS(ESI$^+$) *m/z* 248.2 $(M + H)^+$.



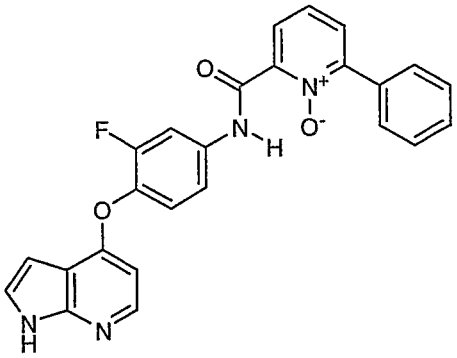
B) 1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A mixture of methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (crude 2.45 g, 12 mmol) and 6 N aq. NaOH (2.5 mL) in methanol (60 mL) was stirred at rt for 4 h. To the reaction mixture was added conc. HCl (1 mL) slowly with stirring at rt. The precipitate which formed was filtered, washed with a small amount water and dried to obtain the desired acid product (2.1 g) as a yellow solid. The filtrate was concentrated *in vacuo*. The residue was mixed with water (50 mL) and washed with EtOAc (2 × 130 mL). The EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with a small amount of ether to obtain a 2nd crop of product (195 mg, total 2.30 g, 82%). ^{1}H NMR (DMSO-d_6) δ 8.47 (dd, 1H, J = 7.2, 2.2 Hz), 8.19 (dd, 1H, J = 6.6, 1.7 Hz), 7.62-7.60 (m, 2H), 7.42 (t, 2H, J = 8.8 Hz), 6.78 (t, 1H, J = 7.1 Hz); MS(ESI$^+$) m/z 234.2 $(M + H)^+$.

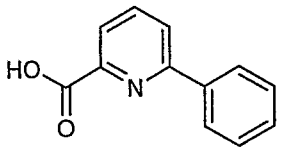
C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

To a solution of 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (70 mg, 0.30 mmol), HOBT (30 mg), and EDCI.HCl (200 mg, 1.04 mmol) in DMF (8 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (70 mg, 0.29 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (71 mg, 43%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 12.04 (br s, 1H), 11.96 (br s, 1H), 8.52 (dd, 1H, J = 7.2, 2.2 Hz), 8.08 (t, 2H, J = 5.5 Hz), 7.96 (dd, 1H, J = 12.7, 2.2 Hz), 7.55-7.53 (m, 2H), 7.84 (t, 1H, J = 8.3 Hz), 7.43 (dd, 1H, J = 8.8, 1.7 Hz), 7.38-7.32 (m, 3H), 6.67 (t, 1H, J = 7.2 Hz), 6.43 (d, 1H, J = 6.1 Hz), 6.46 (dd, 1H, J = 3.3, 1.4 Hz); MS(ESI$^+$) m/z 459.1 $(M + H)^+$.

EXAMPLE 243

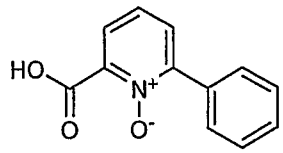


1-Oxy-6-phenyl-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt



A) 6-Phenylpicolinic acid

A mixture of 6-bromopicolinic acid (2.02 g, 10 mmol), phenyboronic acid (1.22 g, 10 mmol), cesium carbonate (5.00 g) and $PdCl_2$ [(*t*-Bu)$_2$P(OH)]$_2$ (70 mg, CombiPhos Catalysts, Inc. Princeton, NJ) in DMF (20 mL) and water (3 mL) was purged with Ar-gas and heated at 110 °C for 24 h. The reaction was incomplete and did not progress further. To the reaction mixture were added EtOAc (200 mL) and 1 N aq. HCl (40 mL). The EtOAc layer was separated, and the aqueous layer was washed with EtOAc (150 mL). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (350 mg, 18%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.18-7.96 (m, 5H), 7.51-7.53 (m, 3H).



B) 6-Phenylpicolinic acid *N*-oxide

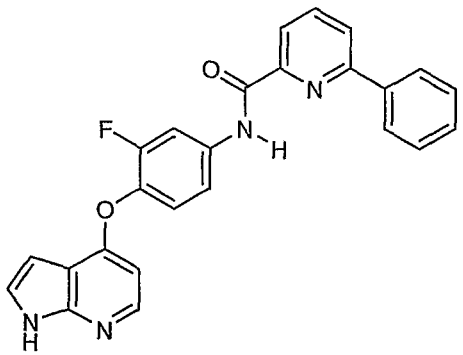
A mixture of 6-phenylpicolinic acid (150 mg, 0.75 mmol), K_2HPO_4 (600 mg) *m*-CPBA (300 mg, max 70 % from Aldrich) in dichloroethane (8.0 mL) was heated at

60 °C for 1.5 h. Additional *m*-CPBA (2 x 300 mg) was added and the mixture was heated at 60 °C for 40 min. The reaction mixture was purified by preparative HPLC to afford the desired product (110 mg, 68 %) as a white solid. ^{1}H NMR (DMF-d_7) δ 8.57 (s, 1H), 8.43 (d, 1H, J = 2.2 Hz), 8.10-7.88 (m, 5H), 7.59-7.57 (m, 3H).

C) **1-Oxy-6-phenyl-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt**

To a solution of 6-phenylpicolinic acid *N*-oxide (25 mg, 0.12 mmol), HOBT (20 mg), and EDCI.HCl (120 mg, 1.14 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (40 mg, 0.16 mmol, Compound B of Example 132). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (36 mg, 54%) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.12 (br s, 1H), 12.10 (br s, 1H), 8.48 (dd, 1H, J = 7.9, 1.6 Hz), 8.24 (d, 1H, J = 5.5 Hz), 8.18 (dd, 1H, J = 14.8, 2.2 Hz), 7.95-7.89 (m, 3H), 7.83 (t, 1H, J = 7.7 Hz), 7.67 (dd, 1H, J = 8.6, 1.2 Hz), 7.61-7.51 (m, 5H), 6.60 (d, 1H, J = 5.5 Hz), 6.44 (d, 1H, J = 3.3 Hz); MS(ESI$^+$) *m/z* 441.1 $(M + H)^+$.

EXAMPLE 244

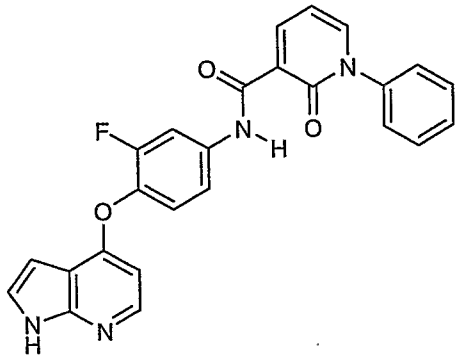


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-6-phenylpicolinamide, trifluoroacetic acid salt**

To a solution of 6-phenylpicolinic acid (48 mg, 0.24 mmol, Compound A of Example 243), HOBT (25 mg), and EDCI.HCl (155 mg, 0.81 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (65 mg, 0.26 mmol, Compound B of Example 132). The mixture

was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (25 mg, 19%) as a light brown solid. ^{1}H NMR (DMF-d_7) δ 11.93 (br s, 1H), 11.01 (br s, 1H), 8.36 (dd, 2H, J = 7.2, 1.6 Hz), 8.31-8.17 (m, 5H), 7.59-7.50 (m, 6H), 6.53 (d, 1H, J = 5.5 Hz), 6.41 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) m/z 425.1 $(M + H)^+$.

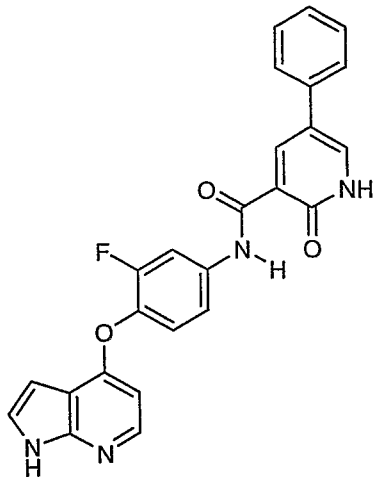
EXAMPLE 245



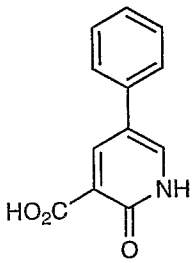
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (30 mg, 0.14 mmol, prepared in a similar manner as Steps A and B of Example 242), HOBT (20 mg), and EDCI.HCl (80 mg, 0.42 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (31 mg, 0.13 mmol, Compound B of Example 132). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (10 mg, 14 %) as a beige solid. ^{1}H NMR (acetone-d_6) δ 13.40 (br s, 1H), 12.32 (br s, 1H), 8.66 (dd, 1H, J = 7.1, 1.6 Hz), 8.43 (d, 1H, J = 6.6 Hz), 8.18 (dd, 1H, J = 13.2, 2.2 Hz), 8.03 (dd, 1H, J = 6.6, 2.2 Hz), 7.67-7.49 (m, 8H), 6.89 (d, 1H, J = 6.6 Hz), 6.75 (t, 1H, J = 6.3 Hz), 6.58 (d, 1H, J = 3.3 Hz); MS(ESI$^+$) m/z 441.1 $(M + H)^+$.

EXAMPLE 246



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



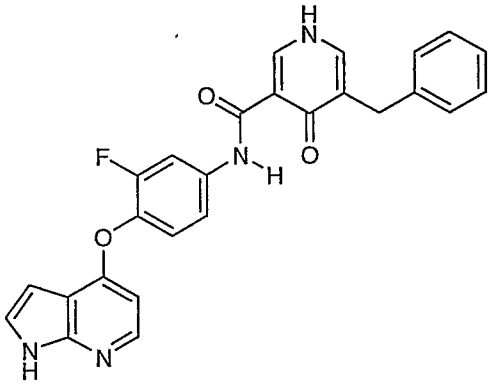
A) **2-Oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid**

A mixture of 5-bromo-2-hydroxynicotinic acid (436 mg, 2.00 mmol, *Syn. Comm.*, 19 (3&4), 553-559 (1989)), phenylboronic acid (248 mg, 2.03 mmol), Cs_2CO_3 (1.20 g) and $PdCl_2$ [(*t*-Bu) $_2$P(OH)] $_2$ (170 mg, CombiPhos Catalysts, Inc. Princeton, NJ) in DMF (10 mL) and water (1.0 mL) was purged with Ar gas and heated at 110 °C for 6 h. Additional phenylboronic acid (75 mg) was added and the mixture was heated at 110 °C for 5 h. To the reaction was added TFA (3 mL), and the mixture was concentrated *in vacuo* to a volume of ~12 mL. The mixture was purified by preparative HPLC to afford the desired product (78 mg, 18 %). ^{1}H NMR (DMF-d_7) δ 14.8 (br s, 1H), 13.8 (br s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 7.74 (d, 1H, J = 7.2 Hz), 7.53-7.42 (m, 3H), 5.81 (s, 1H).

B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxamide**

To a solution of 2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid (35mg, 0.16 mmol), HOBT (25 mg), and EDCI.HCl (80 mg, 0.42 mmol) in DMF (3.0 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (30 mg, 0.12 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (12 mg, 13%) as a light brown solid. ^{1}H NMR (CD_3OD) δ 8.81 (d, 1H, J = 2.8 Hz), 8.17 (d, 1H, J = 6.6 Hz), 8.00 (dd, 1H, J = 12.6, 2.2 Hz), 7.94 (d, 1H, J = 3.3 Hz), 7.52-7.27 (m, 7H), 6.80 (d, 1H, J = 9.3 Hz), 6.72 (d, 1H, J = 6.6 Hz), 6.54 (d, 1H, J = 3.8 Hz); MS(ESI$^+$) *m/z* 441.1 $(M+H)^+$.

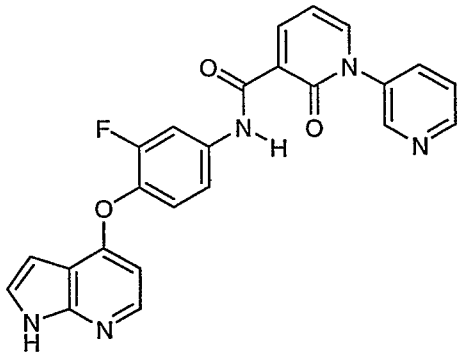
EXAMPLE 247



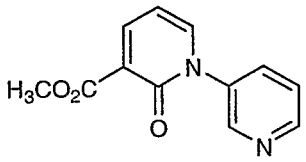
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (35 mg, 0.15 mmol) and HOBt (30 mg) in DMF (2.5 mL) at rt was added EDCI.HCl (80 mg, 0.42 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.16 mmol, Compound B of Example 132). The reaction mixture was stirred at rt for 40 h and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (38 mg, 45%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 13.21 (br s, 1H), 12.38 (s, 1H), 12.08 (br s, 1H), 8.59 (d, 1H, J = 4.4 Hz), 8.17 (d, 1H, J = 5.5 Hz), 8.03 (dd, 1H, J = 13.2, 2.2 Hz), 7.80 (d, 1H, J = 3.9 Hz), 7.48-7.19 (m, 8H), 6.52 (d, 1H, J = 5.5 Hz), 6.34 (d, 1H, J = 1.6 Hz), 3.81 (s, 2H); MS(ESI$^+$) *m/z* 455.1 $(M+H)^+$.

EXAMPLE 248

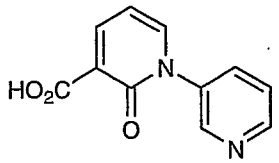


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) Methyl 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (462 mg, 3 mmol, Aldrich) in DMF (6 mL) at rt was added 3-aminopyridine (282 mg, 3 mmol). The reaction mixture was stirred overnight at rt, treated with EDCI.HCl (650 mg, 3.4 mmol) and DMAP (200 mg), stirred for an additional 24 h, and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (980 mg, 95%) as a beige solid. ^{1}H NMR ($CDCl_3$) δ 13.00 (br s, 1H), 8.83 (br s, 1H), 8.74 (br s, 1H), 8.29 (dd, 1H, J = 7.2, 1.7 Hz), 8.18 (d, 1H, J = 8.3 Hz), 7.73 (dd, 1H, J = 7.7, 5.0 Hz), 7.66 (dd, 1H, J = 6.6, 1.6 Hz), 6.42 (t, 1H, J = 7.1 Hz), 3.87 (s, 3H).



B) 2-Oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylic acid

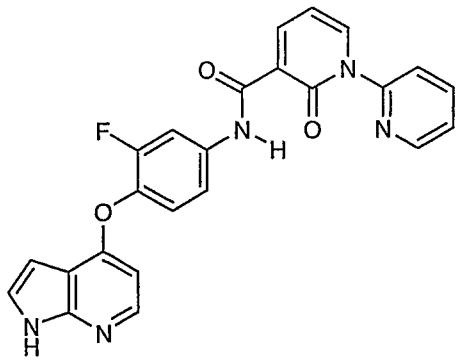
A mixture of methyl 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylate (980 mg, 2.85 mmol) and 6 N NaOH (1 mL) and methanol (20 mL) was stirred at rt overnight. To the reaction mixture was added 1 N aq. HCl (6 mL) and the mixture

was concentrated *in vacuo* to obtain the acid (1.0 g, 100 %) as a light yellow solid containing a small amount of NaCl. This material was used directly in the next step without further purification. ^{1}H NMR (CD_3OD) δ 8.85 (d, 1H, J = 1.7 Hz), 8.77 (d, 1H, J = 4.9 Hz), 8.59 (dd, 1H, J = 7.1, 1.7 Hz), 8.21 (d, 1H, J = 8.2 Hz), 8.10 (dd, 1H, J = 6.6, 2.2 Hz), 7.79 (dd, 1H, J = 8.2, 5.0 Hz), 6.80 (t, 1H, J = 6.6 Hz); MS(ESI$^+$) m/z 217.2 $(M + H)^+$.

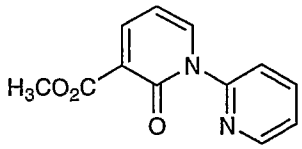
C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

To a solution of 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylic acid (22 mg, 0.10 mmol) and HOBt (5 mg) in DMF (3 mL) at rt was added EDCI.HCl (24.5 mg, 0.13 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (24 mg, 0.10 mmol, Compound B of Example 132). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (25 mg, 45%) as a beige solid. ^{1}H NMR (DMF-d_7) δ 12.26 (br s, 1H), 12.18 (s, 1H), 8.90 (d, 1H, J = 2.2 Hz), 8.78 (d, 1H, J = 3.9 Hz), 8.71 (dd, 1H, J = 7.1, 2.2 Hz), 8.28-8.15 (m, 4H), 7.72-7.48 (m, 4H), 6.87 (t, 1H, J = 7.2 Hz), 6.64 (d, 1H, J = 5.5 Hz), 6.47 (br s, 1H); MS(ESI$^+$) m/z 442.2 $(M + H)^+$.

EXAMPLE 249

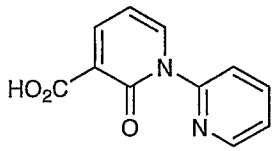


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) Methyl 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (462 mg, 3 mmol, Aldrich) in DMF (6 mL) at rt was added 3-aminopyridine (282 mg, 3 mmol). The reaction mixture was stirred at rt for 12 h and treated with EDCI.HCl (650 mg, 3.4 mmol) and DMAP (200 mg). The reaction mixture was stirred for 2.5 days at rt, and most of the DMF was removed *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (500 mg, 72%) as a glassy material. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 1H, J = 5.0 Hz), 8.20 (dd, 1H, J = 9.2, 2.2 Hz), 8.06 (dd, 1H, J = 6.0, 1.1 Hz), 7.89-7.82 (m, 2H), 7.32 (dd, 1H, J = 6.6, 5.0 Hz), 6.36 (t, 1H, J = 6.6 Hz), 3.86 (s, 3H); MS(ESI$^+$) *m/z* 231.2 $(M + H)^+$.



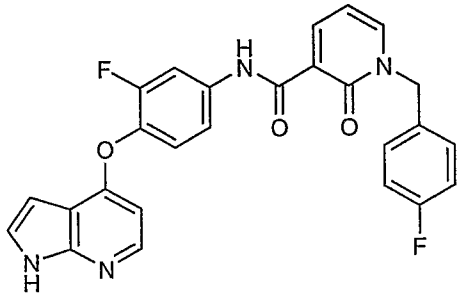
B) 2-Oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylic acid

A mixture of methyl 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylate (500 mg, 2.17 mmol) and 3 N NaOH (1 mL) and methanol (10 mL) was stirred at rt overnight. To the reaction was added TFA (0.5 mL) and the mixture was concentrated *in vacuo*. The residue was dissolved in water (3 mL) and *i*-PrOH (10 mL). The solid which formed was filtered, washed with a small amount of water and *i*-PrOH, and dried to obtain the acid (260 mg, 55 %) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.14 (br s, 1H), 8.72 (d, 1H, J = 4.9 Hz), 8.62 (dd, 1H, J = 7.7, 2.2 Hz), 8.47 (dd, 1H, J = 6.6, 2.2 Hz), 8.18-7.98 (m, 2H), 7.67 (dd, 1H, J = 7.2, 5.3 Hz), 6.97 (t, 1H, J = 6.6 Hz); MS(ESI$^+$) *m/z* 217.2 $(M + H)^+$.

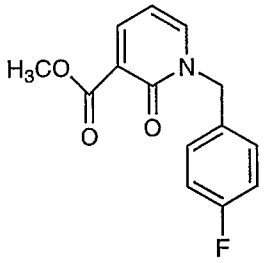
C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

To a solution of 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylic acid (200 mg, 0.93 mmol) and HOBt (100 mg) in DMF (5 mL) at rt was added EDCI.HCl (250 mg, 1.30 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (226 mg, 0.93 mmol, Compound B of Example 132) in DMF (4 mL). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (290 mg, 56%) as a white solid. ^{1}H NMR (DMF-d_7) δ 12.16 (br s, 1H), 12.15 (br s, 1H), 11.99 (br s, 1H), 8.77-8.55 (m, 2H), 8.39-8.35 (m, 1H), 8.22-8.15 (m, 4H), 7.72-7.47 (m, 3H), 6.87 (t, 1H, J = 7.2 Hz), 6.55 (t, 1H, J = 5.5 Hz), 6.42 (d, 1H, J = 2.3 Hz); MS(ESI$^+$) *m/z* 442.1 $(M + H)^+$.

EXAMPLE 250



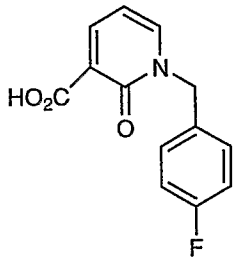
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



A) Methyl 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A heterogeneous mixture of methyl 2-oxo-2*H*-pyran-3-carboxylate (2.0 g, 13 mmol, 1.0 eq, Aldrich) and 4-fluorobenzylamine (1.5 mL, 13 mmol, 1.0 eq) in DMF (10 mL) was stirred at room temperature for 3 h. The reaction mixture was treated with EDCI (3.4 g, 18 mmol, 1.4 eq) and DMAP (0.11 g, 9.91 mmol, 0.07 eq) at room temperature and the resulting solution was stirred for 12 h. The reaction mixture was

quenched with 1 N aqueous HCl and the solution was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with 10% aqueous LiCl (3 x 70 mL), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to afford the product (2.5 g, 73%) as a solid, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.17-8.20 (m, 1H), 8.03-8.05 (m, 1H), 7.38-7.46 (m, 2H),7.16-7.22 (m, 2H), 6.37 (dd, 1H, J = 6.94 Hz), 5.13 (s, 2H), 3.73 (s, 3H); HRMS(ESI): calcd.: 262.0879, found: 262.0885.



B) 1-(4-Fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

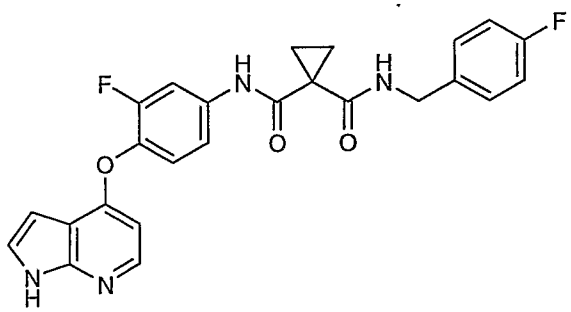
A solution of methyl 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (2.4 g, 9.2 mmol, 1.0 eq) in MeOH (25 ml) was treated with 5 N aqueous sodium hydroxide (4.6 mL, 24 mmol, 2.6 eq) at room temperature and the reaction mixture was stirred for 15 h. The reaction mixture was concentrated *in vacuo*, diluted with water and the solution was extracted with ethyl acetate (discarding the organic fraction). The aqueous fraction was cooled to 0 °C and acidified with concentrated HCl. The resulting solid was filtered, washed with water and the solid dried *in vacuo* to afford the product (1.6 g, 70%) which was sufficiently pure to use in the subsequent step without further purification.. ^{1}H NMR (DMSO-d_6) δ 8.44-8.39 (m, 2H), 7.46-7.42 (m, 2H), 7.24-7.18 (m, 2H), 6.78 (d, 1H, J = 6.98 Hz), 5.31 (s, 2H); HRMS(ESI), calcd.: 248.0723, found: 248.0718.

C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt

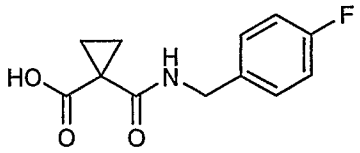
A homogeneous solution of 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0.051 g, 0.21 mmol, 1.0 eq), 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (0.50 g, 0.21 mmol, 1.0 eq, Compound B of Example 132) and

TBTU (0.086 g, 0.23 mmol, 1.1 eq) in DMF (1 mL) was treated with DIPEA (0.11 mL, 0.62 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred for 12 h and quenched with 10% aqueous LiCl (15 mL). The resulting solution was extracted with ethyl acetate (4 x 40 mL). The combined organic extracts were washed with 10% aqueous LiCl (4 x 50 mL), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting 0-2.5% MeOH in $CHCl_3$) and the appropriate fractions were isolated and concentrated *in vacuo*. The free base was dissolved in THF, cooled to 0 °C and the homogeneous solution treated with anhydrous 4 N HCl in dioxane. The reaction mixture was warmed to room temperature, concentrated *in vacuo* and the residue triturated with diethyl ether. The solid was dried *in vacuo* to afford the title compound (0.062 g, 59%) as a HCl salt. ^{1}H NMR (DMSO-d_6) δ 12.43 (s, 1H), 12.27 (s, 1H), 8.50-8.52 (m, 1H), 8.35-8.37 (m, 1H), 8.25-8.27 (m, 1H), 8.05-8.08 (m, 1H), 7.43-7.55 (m, 5H), 7.20-7.24 (m, 2H), 6.71 (t, 1H, J = 6.89 Hz), 6.65 (d, 1H, J = 6.03 Hz), 6.43 (s, 1H), 5.32 (s, 2H); HRMS(ESI$^+$): calcd: 473.1425, found: 473.1427.

EXAMPLE 251



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorobenzyl)cyclopropane-1,1-dicarboxamide, trifluoroacetic acid salt**



A) 1-((4-Fluorobenzyl)carbamoyl)cyclopropanecarboxylic acid

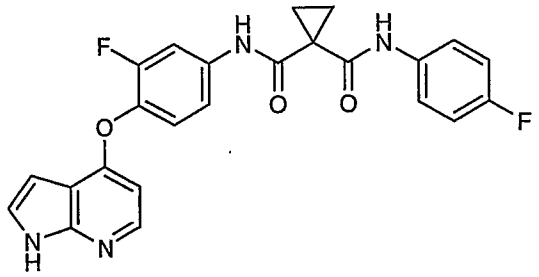
To a solution of 1,1-cyclopropanecarboxylic acid (390 mg, 3.0 mmol, Aldrich) in THF (5 mL) at 0 °C was added triethylamine (0.418 mL, 3.0 mmol). The reaction

mixture was stirred at 0 °C for 30 min and treated with thionyl chloride (0.219 mL, 3.0 mmol, Aldrich). The reaction mixture was then stirred at 0 °C for another 30 min and a solution of 4-fluorobenzylamine (375 mg, 3.0 mmol, Aldrich) in 2 mL of THF was added. The reaction mixture was stirred at 0 °C for 2 h, diluted with 100 mL of ethyl acetate and extracted with 1 N NaOH (10 mL). The aqueous phase was acidified with 1 N HCl to pH 1-2. The solid that formed was collected by filtration (343 mg, 48%). MS(ESI$^+$) *m/z* 238.2 $(M+H)^+$.

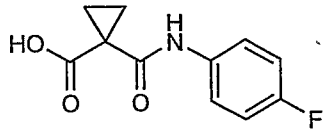
B) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorobenzyl)cyclopropane-1,1-dicarboxamide, trifluoroacetic acid salt

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (45 mg, 0.1 mmol, Compound B of Example 132) and 1-((4-fluorobenzyl)carbamoyl)cyclopropanecarboxylic acid (24 mg, 0.1 mml) in DMF (0.5 mL) at room temperature was added HATU (57 mg., 0.15 mmol, Perseptive Biosystem) and DIEA (0.05 mL, 0.3 mmol, Aldrich). The reaction mixture was stirred at rt for 2 h, and then quenched by the addition of 2 mL of methanol. The reaction mixture was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to dryness to afford the desired product (39 mg, 67%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.99 (br s, 1H), 10.81 (s, 1H), 8.46 (t, 1H, J = 5.8 Hz), 8.13 (d, 1H, J = 6.1 Hz), 7.86 (dd, 1H, J = 13.2, 2.2 Hz), 7.41-7.46 (m, 2H), 7.37 (t, 1H, J = 9.1 Hz), 7.28-7.32 (m, 2H), 7.13 (t, 3H, J = 9.1 Hz), 6.44 (d, 1H, J = 6.1 Hz), 6.30 (s, 1H), 4.30 (d, 2H, J = 5.5 Hz), 1.39 (d, 4H, J = 2.2 Hz); MS(ESI$^+$) *m/z* 463.1 $(M+H)^+$.

EXAMPLE 252



N-(4-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide



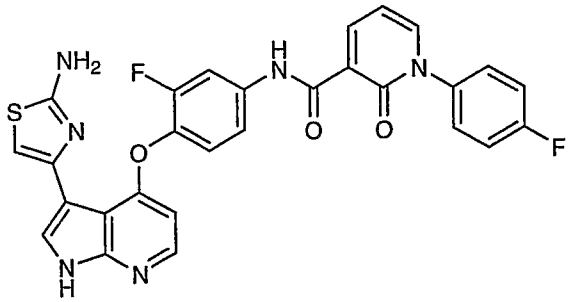
A) **1-((4-Fluorophenyl)carbamoyl)cyclopropanecarboxylic acid**

To a solution of 1,1-cyclopropanecarboxylic acid (390 mg, 3.0 mmol, Aldrich) in THF (5 mL) at 0 °C was added triethylamine (0.418 mL, 3.0 mmol). The reaction mixture was stirred at 0 °C for 30 min and treated with thionyl chloride (0.219 mL, 3.0 mmol, Aldrich). The reaction mixture was stirred at 0 °C for an additional 30 min, and treated with a solution of 4-fluoroaniline (333 mg, 3.0 mmol, Aldrich) in 2 mL of THF. The reaction mixture was stirred at 0 °C for 2 h, then diluted with 100 mL of ethyl acetate and extracted with 1 N NaOH (10 mL). The aqueous phase was acidified with 1 N HCl to pH 1-2. The solid that formed was collected by filtration (508 mg, 76%). MS(ESI$^+$) *m/z* 224.2 $(M+H)^+$.

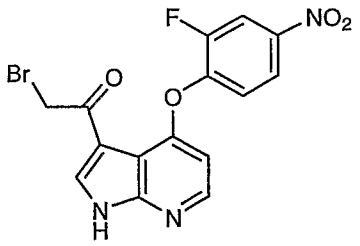
B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide**

Prepared in a similar manner as Step B of Example 251 (41 mg, 73%). ^{1}H NMR (DMSO-d_6) δ 11.97 (br s, 1H), 10.35 (s, 1H), 9.99 (s, 1H), 8.12 (d, 1H, J = 5.5 Hz), 7.85 (d, 1H, J = 13.2 Hz), 7.62 (m, 2H), 7.43 (m, 2H), 7.36 (t, 1H, J = 9.4 Hz), 7.14 (t, 2H, J = 9.1 Hz), 6.43 (d, 1H, J = 5.5 Hz), 6.29 (s, 1H), 1.46 (d, 4H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 449.1 $(M+H)^+$.

EXAMPLE 253

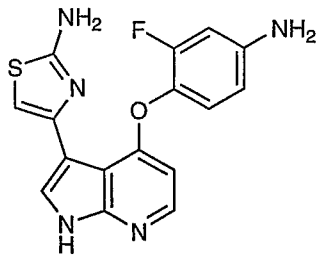


N-(4-(3-(2-Aminothiazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



A) 2-Bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)ethanone

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (1.00 g, 3.66 mmol, Compound A of Example 132) in DCE (100 mL) at rt was added aluminum chloride (2.43 g, 18.3 mmol, Alfa Aesar). The reaction mixture was stirred at rt for 1 h and then treated with bromoacetyl chloride (7.32 mmol, Aldrich). The reaction mixture was then stirred at rt for 2 h and quenched by the addition of 100 mL of EtOAc, 30 mL of MeOH, and 30 mL of saturated aq. K_2HPO_4. This mixture was filtered through a pad of Celite®. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2-5% MeOH in dichloromethane) to afford the desired product (1.12 g, 78%) as a light yellow solid. MS(ESI$^+$) *m/z* 393.9 $(M + H)^+$.



B) 4-(4-(4-Amino-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)thiazol-2-amine

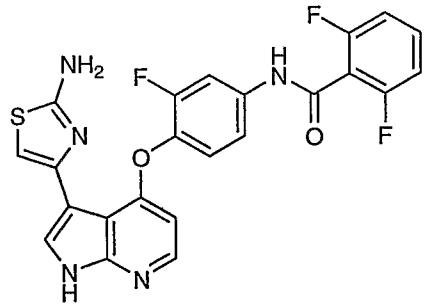
To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (392 mg, 1.0 mmol) in acetic acid (10 mL) was added thiourea (228 mg, 3.0 mmol, Aldrich). The reaction mixture was stirred at room

temperature for 3 h, and then diluted with 50 mL of EtOAc. The reaction mixture was washed with saturated aq. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow solid. The solid was dissolved in a mixed solvent (20 mL of THF and 40 mL of MeOH). Ammonium chloride (267 mg, 5.0 mmol, EMD) and Zn dust (327 mg, 5.0 mmol, Aldrich).were added then added to the resulting solution. The reaction mixture was stirred at room temperature overnight, diluted with 100 mL of EtOAc and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, neutralized with saturated aq. $NaHCO_3$ solution, and concentrated under reduced pressure. The solid that formed was collected by filtration (194 mg, 57% over two steps). MS(ESI$^+$) *m/z* 342.2 $(M + H)^+$.

D) *N*-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

Prepared in a similar manner as Step C of Example 242 (5.6 mg, 12%). ^1H NMR (CD_3OD) δ 8.60 (dd, 1H, *J* = 5.5, 1.7 Hz), 8.08 (d, 1H, *J* = 5.5 Hz), 7.90-7.88 (m, 2H), 7.67 (s, 1H), 7.45-7.42 (m, 2H), 7.29 (d, 1H, *J* = 5.5 Hz), 7.25-7.18 (m, 4H), 6.65 (t, 1H, *J* = 7.4 Hz), 6.43 (d, 1H, *J* = 6.1 Hz); MS(ESI$^+$) *m/z* 557.1 $(M + H)^+$.

EXAMPLE 254

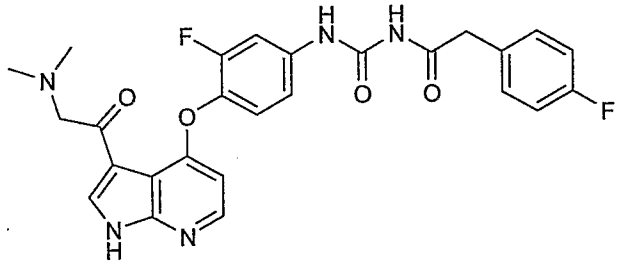


***N*-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, trifluoroacetic acid salt**

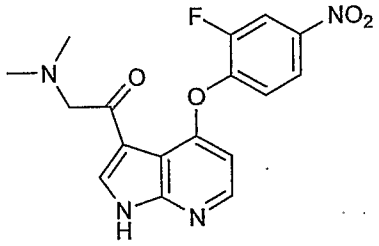
To a solution of 4-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine (20 mg, 0.06 mmol, Compound B of Example 253) in 0.5 mL of

pyridine at –20 °C was added a solution of 2,6-difluorobenzoylchloride (10.6 mg, 0.06 mmol, Aldrich) in 0.3 mL of dichloromethane. The reaction mixture was stirred at –20 °C for 30 min and quenched by the addition of MeOH (0.5 mL). The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford the desired product (TFA salt, 9.2 mg, 22%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.10 (d, 1H, J = 6.1 Hz), 7.68 (s, 1H), 7.48-7.37 (m, 2H), 7.24 (t, 1H, J = 8.3 Hz), 7.05-7.01 (m, 3H), 6.86 (s, 1H), 6.46 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) *m/z* 482.1 $(M + H)^+$.

EXAMPLE 255

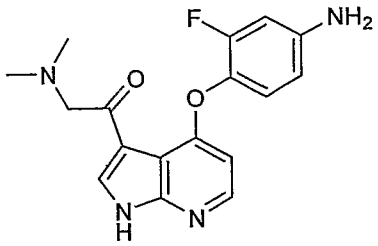


1-(4-(3-(2-(Dimethylamino)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



B) 2-(Dimethylamino)-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone

To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (96 mg, 0.24 mmol, Compound A of Example 253) in THF (5 mL) at 0 °C was added dimethylamine (1.0 M solution in THF, 0.72 mL, 0.72 mmol). The reaction mixture was stirred at 0 °C for 1 h and concentrated under reduced pressure to give the desired product (80 mg, 93%) as a light yellow solid, which was washed with cold water and air dried. MS(ESI$^+$) *m/z* 359.2 $(M + H)^+$.



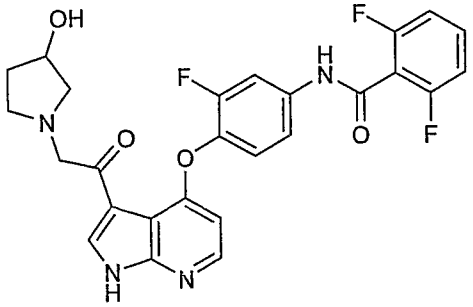
C) 1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(dimethylamino)ethanone

To a solution of 2-(dimethylamino)-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (80 mg, 0.22 mmol) in a mixed solvent (5 mL of THF and 5 mL of MeOH) were added ammonium chloride (64.2 mg, 1.2 mmol, EMD) and Zn dust (78.4 mg, 1.2 mmol, Aldrich). The reaction mixture was stirred at room temperature overnight, diluted with 30 mL of EtOAc and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, neutralized with saturated aq. $NaHCO_3$ solution, and concentrated *in vacuo*. The solid that formed was collected by filtration (51 mg, 71%). MS(ESI$^+$) *m/z* 328.1 $(M + H)^+$.

D) 1-(4-(3-(2-(Dimethylamino)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Step C of Example 132 (5.7 mg, 11%). ^1H NMR (CD_3OD) δ 10.67 (s, 1H), 8.27 (s, 1H), 8.08 (d, 1H, J = 6.1 Hz), 7.65 (d, 1H, J = 12.6 Hz), 7.24-7.16 (m, 4H), 6.96 (t, 2H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 4.74 (s, 2H), 3.60 (s, 2H), 2.86 (s, 6H); MS(ESI$^+$) *m/z* 508.2 $(M + H)^+$.

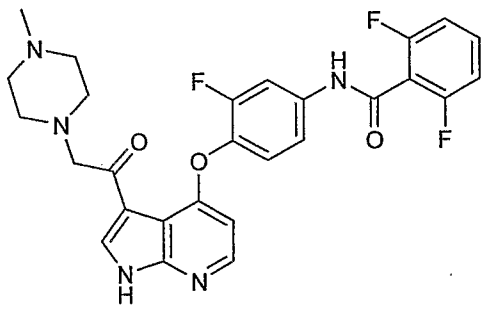
EXAMPLE 256



2,6-Difluoro-*N*-(3-fluoro-4-(3-(2-(3-hydroxypyrrolidin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (CD_3OD) δ 8.29 (d, 1H, J = 6.6 Hz), 8.13 (d, 1H, J = 5.5 Hz), 7.80 (dd, 1H, J = 12.7, 2.2 Hz), 7.46-7.38 (m, 2H), 7.23 (t, 1H, J = 9.1 Hz), 7.03 (t, 2H, J = 8.3 Hz), 6.53 (d, 1H, J = 5.5 Hz), 5.01-4.86 (m, 2H), 4.49-4.46 (m, 1H), 3.77-3.64 (m, 2H), 3.35-3.06 (m, 2H), 2.25-1.98 (m, 2H); MS(ESI$^+$) *m/z* 511.2 $(M + H)^+$.

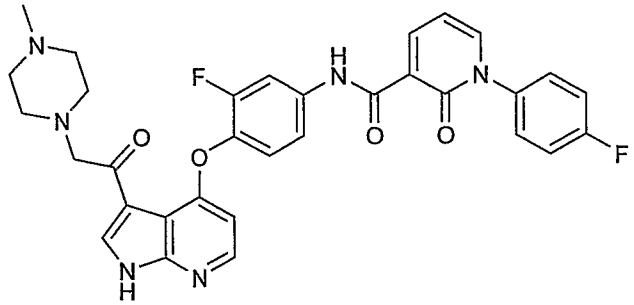
EXAMPLE 257



2,6-Difluoro-*N*-(3-fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 8.11 (d, 1H, J = 5.5 Hz), 7.79 (dd, 1H, J = 12.1, 2.2 Hz), 7.46-7.34 (m, 2H), 7.16 (t, 1H, J = 8.8 Hz), 7.03 (t, 2H, J = 8.3 Hz), 6.53 (d, 1H, J = 6.1 Hz), 4.11 (s, 2H), 3.21-2.92 (m, 8H), 2.76 (s, 3H); MS(ESI$^+$) *m/z* 524.3 $(M + H)^+$.

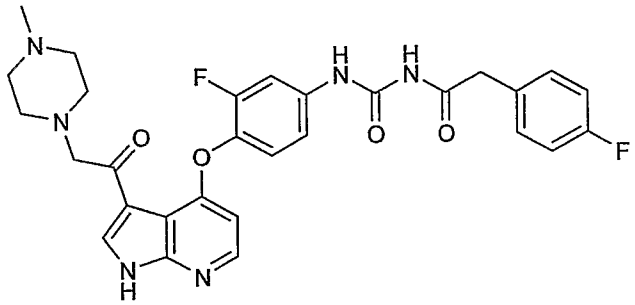
EXAMPLE 258



***N*-(3-Fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 253. ^{1}H NMR (CD_3OD) δ 8.59 (dd, 1H, J = 7.2, 2.2 Hz), 8.53 (s, 1H), 8.08 (d, 1H, J = 5.5 Hz), 7.89-7.85 (m, 2H), 7.44-7.41 (m, 2H), 7.28-7.18 (m, 3H), 7.15 (t, 1H, J = 8.8 Hz), 6.65 (t, 1H, J = 6.7 Hz), 6.48 (d, 1H, J = 5.5 Hz), 4.13 (s, 2H), 3.21-2.89 (bm, 8), 2.76 (s, 3H); MS(ESI$^+$) *m/z* 599.2 $(M + H)^+$.

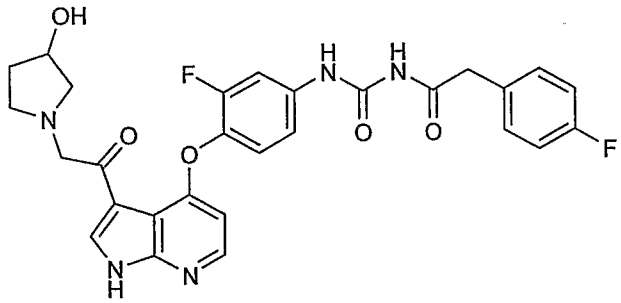
EXAMPLE 259



1-(3-Fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 255. ^{1}H NMR (CD_3OD) δ 8.28 (s, 1H), 8.12 (d, 1H, J = 6.1 Hz), 7.66 (dd, 1H, J = 10.1, 2.8 Hz), 7.28-7.16 (m, 4H), 6.97-6.92 (m, 3H), 6.51 (d, 1H, J = 6.1 Hz), 4.43 (s, 2H), 3.88 (s, 2H), 3.49 (s, 2H), 3.37-3.20 (m, 4H), 2.82 (s, 3H); MS(ESI$^+$) *m/z* 563.2 $(M + H)^+$.

EXAMPLE 260

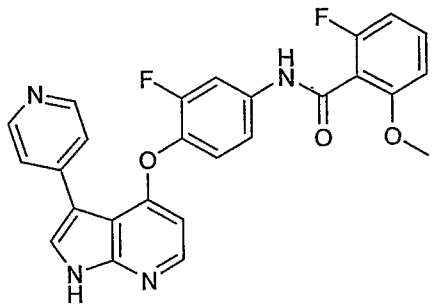


1-(3-Fluoro-4-(3-(2-(3-hydroxypyrrolidin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

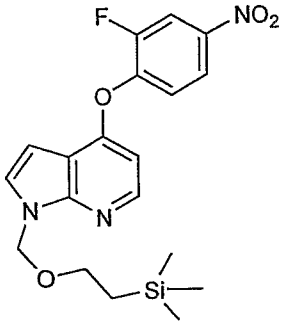
Prepared in a similar manner as Example 255. ^{1}H NMR (CD_3OD) δ 10.69 (s, 1H), 8.27 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 5.5 Hz), 7.66 (d, 1H, J = 12.7 Hz), 7.27-7.16 (m, 4H), 6.98 (t, 2H, J = 8.8 Hz), 6.47 (d, 1H, J = 5.5 Hz), 4.99 (m, 1H),

4.49-4.44 (m, 2H), 3.90-3.68 (m, 2H), 3.62 (s, 2H), 3.37-3.09 (m, 2H), 2.15-1.92 (m, 2H); MS(ESI$^+$) *m/z* 550.1 $(M + H)^+$.

EXAMPLE 261

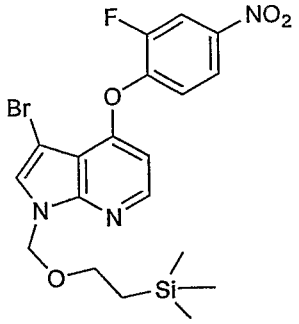


2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-6-methoxybenzamide



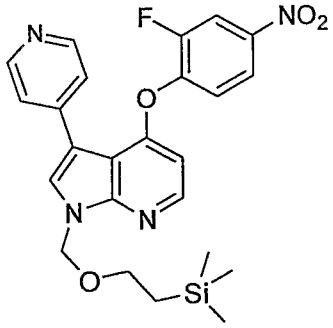
A) 4-(2-Fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (1.68 g, 6.15 mmol, Compound A of Example 132) in 20 mL of DMF at –40 °C was added sodium hydride (271 mg, 6.77 mmol, 60% in mineral oil, Aldrich). The reaction mixture was stirred at 0 °C for 30 min, cooled to –40 °C, and treated with 2-(trimethylsilyl)ethoxymethyl chloride (1.20 mL, 6.77 mmol, Aldrich). The reaction mixture was stirred at room temperature for 1 h, quenched by the addition of cold water (40 mL) and extracted with EtOAc (3 x 100mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the desired product (2.40 g, 97%) as a brown solid. MS(ESI$^+$) *m/z* 404.2 $(M + H)^+$.



B) 3-Bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl) -1*H*-pyrrolo[2,3-*b*]pyridine

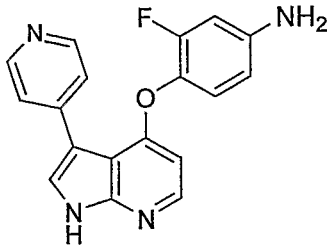
To a solution of 4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.40 g, 5.96 mmol) in 20 mL of acetonitrile at 0 °C was added a solution of NBS (1.01 g, 5.69 mmol, Aldrich) in 10 mL of acetonitrile. The reaction mixture was stirred at 0 °C for 30 min, quenched by the addition of cold water (50 mL), and extracted with EtOAc (3 x 120 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with dichloromethane) to afford the desired product (2.70 g, 94%) as a light yellow oil. MS(ESI$^+$) *m/z* 482.9 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

A sealed tube was charged with a solution of 3-bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (480 mg, 1.0 mmol) in toluene (5 mL), pyridin-4-ylboronic acid (246 mg, 2.0 mmol, Lancaster), 0.5 mL of ethanol, and potassium phosphate (1.0 mL, 2 M solution, 2.0 mmol). Argon was bubbled through the mixture for 15 minutes, and the reaction

mixture was treated with tetrakis(triphenylphosphine)Pd(0) (58 mg, 0.05 mmol, Strem). The tube was sealed and the mixture was heated at 95 °C for 18 h with vigorous stirring. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The mixture was washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2% MeOH in dichloromethane) to give the desired product (237 mg, 49%) as a thick brown oil. MS(ESI$^+$) *m/z* 481.1 $(M + H)^+$.



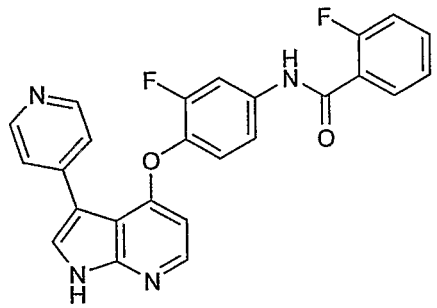
D) 3-Fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine

To a solution of 4-(2-fluoro-4-nitrophenoxy)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (237 mg, 0.49 mmol) in a mixed solvent (8 mL of MeOH and 4 mL of THF) were added ammonium chloride (131 mg, 2.49 mmol, EMC) and zinc dust (163 mg, 2.49 mmol, Aldrich). The reaction mixture was stirred at room temperature for 3 h, diluted with EtOAc (40 mL), and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give a solid. MS(ESI$^+$) *m/z* 451.3 $(M + H)^+$. The solid was dissolved in 15 mL of THF and treated with TBAF (4 mL, 1.0 M solution in THF, Aldrich) and ethane-1,2-diamine (0.4 mL, Aldrich). The reaction mixture was refluxed for 16 h, cooled to room temperature, diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2-5% MeOH in dichloromethane) to afford the desired product (127 mg, 81% for two steps). MS(ESI$^+$) *m/z* 321.2 $(M + H)^+$.

E) 2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-6-methoxybenzamide

Prepared in a similar manner as Example 254 (3.2 mg, 7%). ^{1}H NMR (DMSO-d_6) δ 12.92 (s, 1H), 10.80 (s, 1H), 8.72 (d, 2H, J = 7.2 Hz), 8.44 (s, 1H), 8.31 (d, 2H, J = 7.2 Hz), 8.16 (d, 2H, J = 5.5 Hz), 7.94-7.86 (m, 1H), 7.55-7.41 (m, 2H), 6.97-6.91 (m, 1H), 6.88 (t, 1H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 3.78 (s, 3H); MS(ESI$^+$) m/z 473.1 $(M + H)^+$.

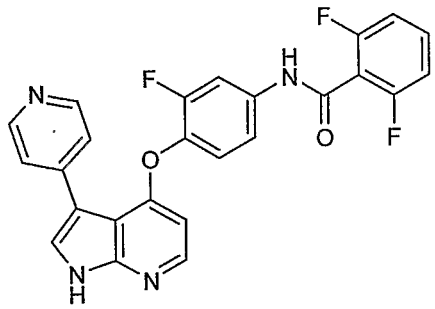
EXAMPLE 262



2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 261. ^{1}H NMR (DMSO-d_6) δ 12.97 (s, 1H), 10.76 (s, 1H), 8.78 (d, 2H, J = 8.8 Hz), 8.50 (s, 1H), 8.36 (d, 2H, J = 6.1 Hz), 8.23 (d, 1H, J = 5.5 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.70-7.54 (m, 4H), 7.39-7.35 (m, 2H), 6.50 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 443.1 $(M + H)^+$.

EXAMPLE 263

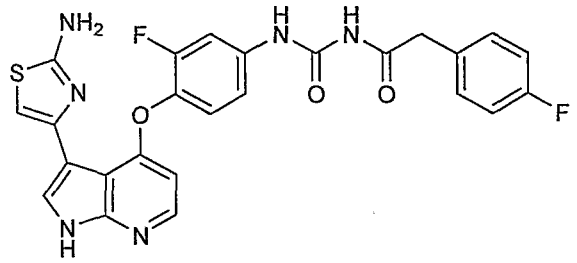


2,6-Difluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 261. ^{1}H NMR (DMSO-d_6) δ 12.89 (s, 1H), 11.10 (s, 1H), 8.70 (d, 2H, J = 6.6 Hz), 8.42 (s, 1H), 8.27 (d, 2H, J = 6.6 Hz),

8.16 (d, 1H, J = 5.5 Hz), 7.86 (d, 1H, J = 11.6 Hz), 7.58-7.48 (m, 3H), 7.23 (t, 2H, J = 8.3 Hz), 6.45 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 461.1 $(M + H)^+$.

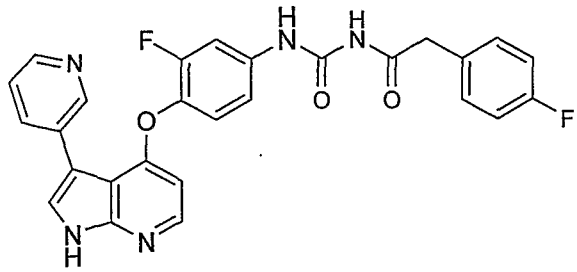
EXAMPLE 264



1-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To a solution of 4-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine (34 mg, 0.1 mmol, Compound B of Example 253) in a mixed solvent (0.5 mL of DMF and 0.5 mL of THF) at rt was added a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.4 M, 0.25 ml, 0.1 mmol, Compound C of Example 4). The reaction mixture was stirred at rt for 1 h, concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford the desired product (TFA salt, 21.2 mg, 28%) as a white solid. ^{1}H NMR (CD_3OD) δ 10.69 (s, 1H), 8.08 (d, 1H, J = 5.5 Hz), 7.68 (s, 1H), 7.66 (d, 1H, J = 12.1 Hz), 7.26-7.18 (m, 4H), 6.98 (t, 2H, J = 8.8 Hz), 6.84 (s, 1H), 6.42 (d, 1H, J = 6.1 Hz), 3.62 (s, 2H); MS(ESI$^+$) m/z 521.1 $(M + H)^+$.

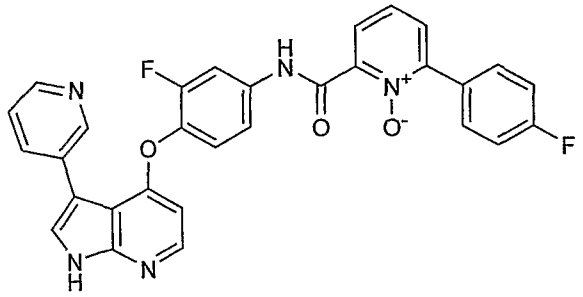
EXAMPLE 265



1-(3-Fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 264. ^{1}H NMR (DMSO-d_6) δ 12.71 (s, 1H), 11.04 (s, 1H), 10.61 (s, 1H), 9.18 (s, 1H), 8.84 (d, 1H, J = 8.3 Hz), 8.74 (d, 1H, J = 5.5 Hz), 8.20 (d, 1H, J = 5.5 Hz), 8.12 (s, 1H), 8.06 (dd, 1H, J = 8.3, 2.8 Hz), 7.78 (dd, 1H, J = 12.7, 2.2 Hz), 7.47 (t, 1H, J = 8.8 Hz), 7.40-7.34 (m, 3H), 7.16 (t, 2H, J = 8.8 Hz), 6.41 (d, 1H, J = 5.5 Hz), 3.75 (s, 2H); MS(ESI$^+$) m/z 500.1 $(M + H)^+$.

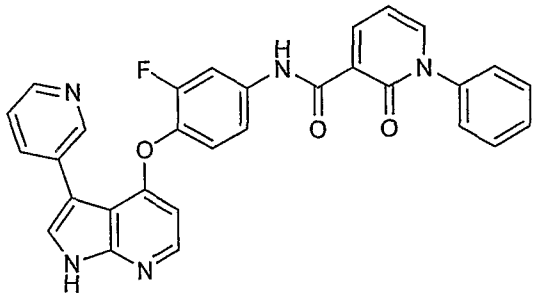
EXAMPLE 266



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(3-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. ^{1}H NMR (DMSO-d_6) δ 13.58 (s, 1H), 12.50 (s, 1H), 9.10 (s, 1H), 8.66 (d, 1H, J = 5.5 Hz), 8.32 (dd, 1H, J = 8.2, 2.2 Hz), 8.19 (d, 1H, J = 5.5 Hz), 8.05-8.02 (m, 2H), 7.89-7.85 (m, 5H), 7.73 (t, 1H, J = 7.7 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.8 Hz), 7.38 (t, 2H, J = 8.8 Hz), 6.41 (d, 1H, J = 6.5 Hz); MS(ESI$^+$) m/z 536.2 $(M + H)^+$.

EXAMPLE 267

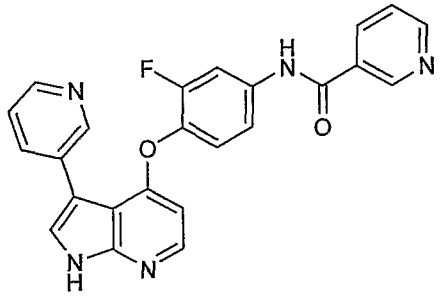


***N*-(3-Fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 245. ^{1}H NMR (DMSO-d_6) δ 12.48 (s, 1H), 12.15 (s, 1H), 9.09 (s, 1H), 8.65-8.59 (m, 3H), 8.18 (d, 1H, J = 5.5 Hz), 8.15

(dd, 1H, J = 6.6, 2.2 Hz), 8.04-7.99 (m, 2H), 7.88 (m, 1H), 7.59-7.46 (m, 7H), 6.74 (t, 1H, J = 7.2 Hz), 6.40 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 518.1 $(M + H)^+$.

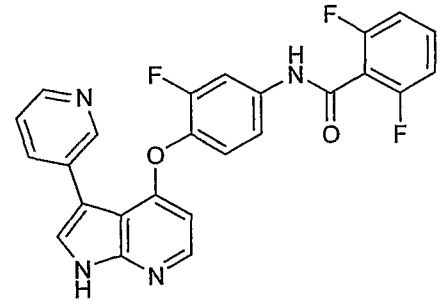
EXAMPLE 268



N-(3-Fluoro-4-(3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)nicotinamide

Prepared in a similar manner as Example 254. ^{1}H NMR (DMSO-d_6) δ 12.65 (s, 1H), 10.96 (s, 1H), 9.22 (s, 1H), 9.18 (s, 1H), 8.84 (t, 2H, J = 5.0 Hz), 8.74 (d, 1H, J = 5.5 Hz), 8.49 (d, 1H, J = 8.3 Hz), 8.21 (d, 1H, J = 5.5 Hz), 8.11 (d, 1H, J = 1.7 Hz), 8.08-8.01 (m, 2H), 7.73-7.69 (m, 2H), 7.54 (t, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 426.2 $(M + H)^+$.

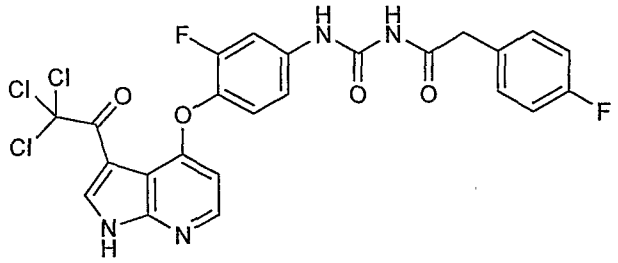
EXAMPLE 269



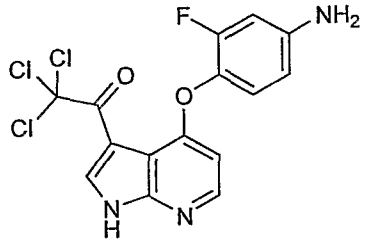
2,6-Difluoro-N-(3-fluoro-4-(3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H), 9.20 (d, 1H, J = 1.7 Hz), 8.87 (d, 1H, J = 8.3 Hz), 8.77 (d, 1H, J = 5.5 Hz), 8.23 (d, 1H, J = 5.5 Hz), 8.55 (s, 1H), 8.08 (dd, 1H, J = 8.2, 2.2 Hz), 7.90 (d, 1H, J = 13.7 Hz), 7.62-7.55 (m, 3H), 7.27 (t, 2H, J = 8.3 Hz), 6.50 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 461.1 $(M + H)^+$.

EXAMPLE 270



1-(3-Fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,2,2-trichloroethanone

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (546 mg, 2.0 mmol, Compound A of Example 132) in 100 mL of dichloroethane at room temperature was added aluminum chloride (1.33 g, 10 mmol, Alfa Aesar). The reaction mixture was stirred at rt for 30 min, treated with trichloroacetyl chloride (0.34 mL, 3.0 mmol), and then stirred at 45 °C for 5 h. After cooling to 0 °C, ice water (30 mL) was added to the mixture and the pH was adjusted to 7-8 with aq. K_2HPO_4 solution. The mixture was then filtered through a pad of Celite®. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2, eluting with 2-7% MeOH in dichloromethane) to afford 2,2,2-trichloro-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (498 mg, 60%). MS(ESI^+) *m/z* 417.9 $(M + H)^+$.

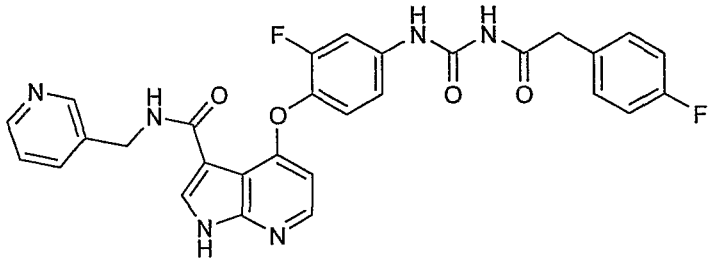
To a solution of the above intermediate (83 mg, 0.2 mmol) in a mixed solvent (3 mL of MeOH and 2 mL of THF) were added ammonium chloride (53.5 mg, 1.0 mmol, EMC) and zinc dust (65.4 mg, 1.0 mmol, Aldrich). The reaction mixture was stirred at room temperature for 3 h, diluted with EtOAc (10 mL), and filtered through

a pad of Celite®. The filtrate was concentrated *in vacuo* to give the desired product (78 mg, 100%) as a solid. MS(ESI$^+$) *m/z* 390.1, 392.1 $(M + H)^+$.

C) 1-(3-Fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 264 (33 mg, 37%). ^{1}H NMR (DMSO-d_6) δ 13.18 (s, 1H), 11.02 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.25 (d, 1H, J = 5.5 Hz), 7.78 (dd, 1H, J = 10.5, 2.2 Hz), 7.38-7.35 (m, 3H), 7.28 (t, 1H, J = 9.4 Hz), 7.18 (t, 2H, J = 8.8 Hz), 6.52 (d, 1H, J = 5.5 Hz), 3.75 (s, 2H); MS(ESI$^+$) *m/z* 567.05 $(M + H)^+$.

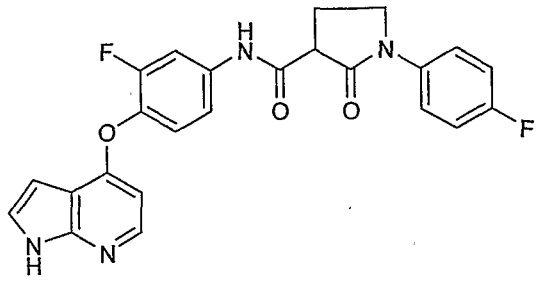
EXAMPLE 271



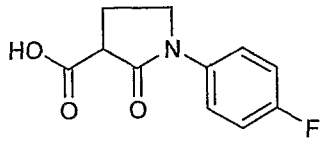
1-(4-(3-((Pyridin-3-ylmethyl)carbamoyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 1-(3-fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridine 4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (7.0 mg, 0.012 mmol, Example 270) in 0.5 mL of DMF was added 3-(aminomethyl)pyridine (10 mg, 0.092 mmol, Aldrich). The reaction mixture was stirred at rt for 1h, and quenched by the addition of 1 mL of cold water. The precipitate that formed was collected by filtration, washed with cold water (1 mL) and cold acetonitrile (1 mL) and dried under vacuum to afford the desired product (4.3 mg, 64%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.38 (s, 1H), 11.03 (s, 1H), 10.57 (s, 1H), 8.48 (s, 1H), 8.40 (t, 1H, J = 5.5 Hz), 8.34 (d, 1H, J = 3.3 Hz), 8.11 (d, 1H, J = 5.5 Hz), 8.00 (s, 1H), 7.73 (d, 1H, J = 13.2 Hz), 7.65 (d, 1H, J = 7.7 Hz), 7.37-7.29 (m, 4H), 7.16 (t, 3H, J = 8.8 Hz), 6.34 (d, 1H, J = 5.5 Hz), 4.48 (d, 2H, J = 5.5 Hz), 3.74 (s, 2H); MS(ESI$^+$) *m/z* 567.1 $(M + H)^+$.

EXAMPLE 272



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**



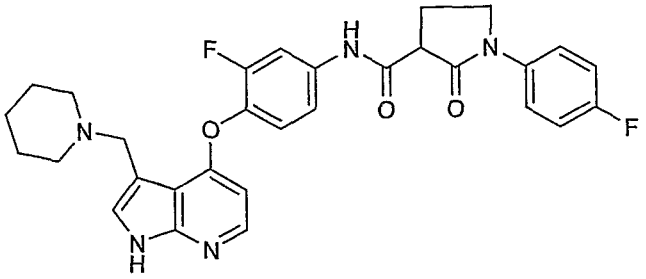
A) 1-(4-Fluorophenyl)-2-oxopyrrolidine-3-carboxylic acid

To a solution of 6,6-dimethyl-5,7-dioxaspiro[2,5]-octane-4,8-dione (1.02 g, 6.0 mmol, Aldrich) in 3 mL of DMF was added 4-fluorobenzenamine (666 mg, 6.0 mmol, Aldrich). The reaction mixture was stirred at rt overnight. The reaction mixture was poured into cold water (10 mL). The precipitate that formed was collected by filtration, washed with water, and dried under vacuum to afford the desired product (980 mg, 73%) as a tan solid. MS(ESI$^+$) *m/z* 224.3 $(M + H)^+$.

B) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

Prepared in a similar manner as Step B of Example 251 (98 mg, 49%). ^{1}H NMR (DMSO-d_6) δ 11.76 (s, 1H), 10.63 (s, 1H), 8.06 (d, 1H, J = 5.5 Hz), 7.86 (dd, 1H, J = 13.2, 2.2 Hz), 7.71-7.68 (m, 2H), 7.45-7.36 (m, 3H), 7.25 (t, 2H, J = 8.8 Hz), 6.38 (d, 1H, J = 6.5 Hz), 6.22 (dd, 1H, J = 3.3, 2.2 Hz), 3.94-3.89 (m, 2H), 3.77 (t, 1H, J = 8.5 Hz), 2.49-2.33 (m, 2H); MS(ESI$^+$) *m/z* 449.2 $(M + H)^+$.

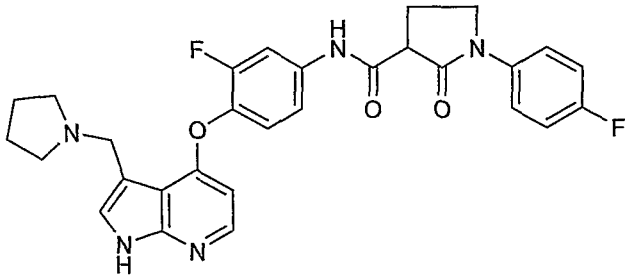
EXAMPLE 273



N-(3-Fluoro-4-(3-(piperidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide, trifluoroacetic acid salt

To a solution of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide (22.4 mg, 0.05 mmol, Compound B of Example 272) and paraformaldehyde (2.4 mg, 0.08 mmol) in a mixed solvent (1 mL of isopropanol and 0.2 mL of DMF) was added piperidine (8.5 mg, 0.1 mmol). The reaction mixture was heated at 85 °C for 7 h, concentrated *in vacuo*, and the resulting residue was purified by preparative HPLC. The desired fractions were lyophilized to give the desired product (TFA salt, 3.4 mg, 13%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 5.5 Hz), 7.91 (dd, 1H, J = 11.0, 2.2 Hz), 7.67-7.63 (m, 3H), 7.48-7.38 (m, 2H), 7.15 (t, 2H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 4.64 (s, 2H), 3.99-3.95 (m, 2H), 3.81 (t, 1H, J = 8.8 Hz), 3.61-3.59 (m, 2H), 3.10-3.06 (m, 2H), 2.61-2.47 (m, 2H), 1.97-1.93 (m, 2H), 1.81-1.71 (m, 4H); MS(ESI$^+$) *m/z* 546.2 $(M + H)^+$.

EXAMPLE 274

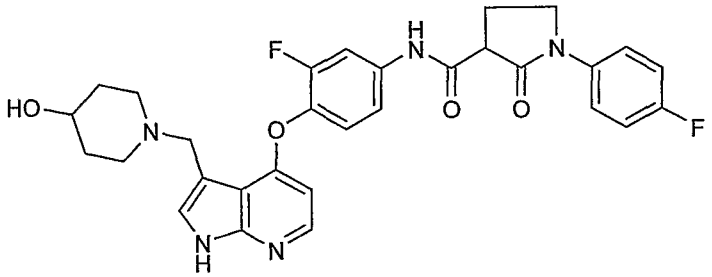


N-(3-Fluoro-4-(3-(pyrrolidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 10.62 (s, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.84 (dd, 1H, J = 13.2, 2.2 Hz), 7.65-

7.62 (m, 3H), 7.43-7.39 (m, 2H), 7.19 (t, 2H, J = 8.8 Hz), 6.25 (d, 1H, J = 6.5 Hz), 4.54 (d, 2H, J = 3.3 Hz), 3.91-3.85 (m, 2H), 3.72 (t, 1H, J = 8.5 Hz), 3.38-3.37 (m, 2H), 3.20-3.77 (m, 2H), 2.38-2.31 (m, 2H), 1.95-1.91 (m, 2H), 1.81-1.76 (m, 2H); MS(ESI$^+$) m/z 532.2 $(M + H)^+$.

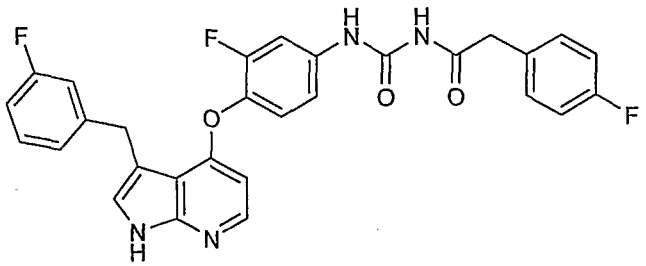
EXAMPLE 275



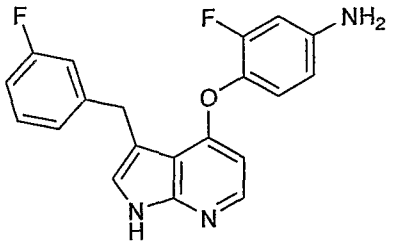
***N*-(3-Fluoro-4-(3-((4-hydroxypiperidin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 11.71 (s, 1H), 10.88 (s, 1H), 8.00 (d, 1H, J = 5.5 Hz), 7.79 (dd, 1H, J = 12.7, 2.2 Hz), 7.67-7.64 (m, 2H), 7.30-7.35 (m, 3H), 7.20 (t, 2H, J = 8.8 Hz), 6.30 (d, 1H, J = 6.5 Hz), 6.16 (s, 1H), 4.51 (d, 1H, J = 4.4 Hz), 3.83-3.79 (m, 2H), 3.38 (m, 1H), 3.70-2.69 (m, 5H), 2.28-2.19 (m, 3H), 1.65-1.62 (m, 2H), 1.37-1.26 (m, 2H); MS(ESI$^+$) m/z 562.2 $(M + H)^+$.

EXAMPLE 276



1-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



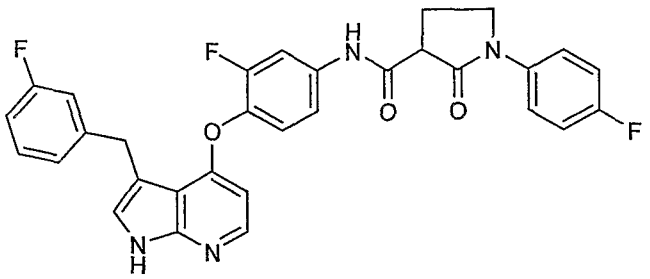
A) 4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (49 mg, 0.2 mmol, Compound B of Example 132) in 2 mL of methanol were added sodium hydroxide (40 mg, 1.0 mmol, EMD) and 3-fluorobenzaldehyde (62 mg, 0.5 mmol, Aldrich). The reaction mixture was stirred at rt for 16 h, poured into cold water (5 mL), and extracted with EtOAc (3 x 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 2 mL of dichloromethane, and treated with 1 mL of TFA and 0.2 mL of triethylsilane (Aldrich). The reaction mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by preparative HPLC and the desired fractions were combined, concentrated *in vacuo*, neutralized with saturated aq. $NaHCO_3$ solution, and extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (12.1 mg, 35% over two steps). MS(ESI$^+$) *m/z* 351.4 $(M + H)^+$.

B) 1-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 264 (3.4 mg, 11%). ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1H), 10.96 (s, 1H), 10.49 (s, 1H), 7.95 (d, 1H, J = 5.5 Hz), 7.67 (dd, 1H, J = 11.6, 2.1 Hz), 7.31-6.67 (m, 12H), 6.10 (d, 1H, J = 5.5 Hz), 4.09 (s, 2H), 3.68 (s, 2H); MS(ESI$^+$) *m/z* 531.2 $(M + H)^+$.

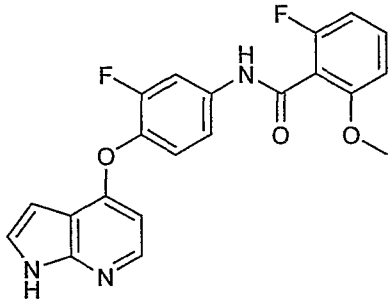
EXAMPLE 277



***N*-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 11.74 (s, 1H), 10.62 (s, 1H), 8.03 (d, 1H, J = 5.5 Hz), 7.84 (dd, 1H, J = 12.7, 2.2 Hz), 7.71-7.68 (m, 2H), 7.41 (d, 1H, J = 8.8 Hz), 7.30 (d, 1H, J = 1.7 Hz), 7.26-7.22 (m, 3H), 7.16 (t, 1H, J = 8.5 Hz), 7.08 (d, 1H, J = 7.7 Hz), 7.01 (d, 1H, J = 10.4 Hz), 6.94 (t, 1H, J = 8.8 Hz), 6.22 (d, 1H, J = 5.5 Hz), 4.17 (s, 2H), 3.94-3.90 (m, 2H), 3.76 (t, 1H, J = 8.5 Hz), 2.49-2.35 (m, 2H); MS(ESI$^+$) *m/z* 557.2 $(M + H)^+$.

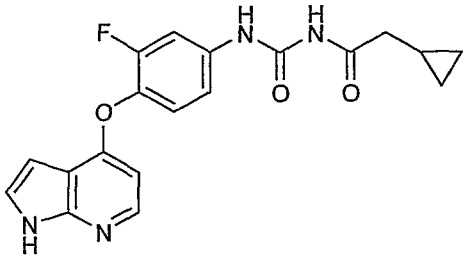
EXAMPLE 278



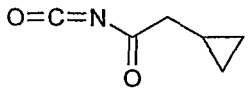
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide**

Prepared in a similar manner as Example 261 (12.1 mg, 31%). ^{1}H NMR (DMSO-d_6) δ 11.97 (s, 1H), 10.86 (s, 1H), 8.14 (d, 1H, J = 5.5 Hz), 7.92 (dd, 1H, J = 13.2, 2.2 Hz), 7.54-7.42 (m, 4H), 7.03 (d, 1H, J = 8.2 Hz), 6.95 (t, 1H, J = 8.8 Hz), 6.48 (d, 1H, J = 6.1 Hz), 6.35 (d, 1H, J = 1.4 Hz); MS(ESI$^+$) *m/z* 396.2 $(M + H)^+$.

EXAMPLE 279



1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-cyclopropylacetyl)urea



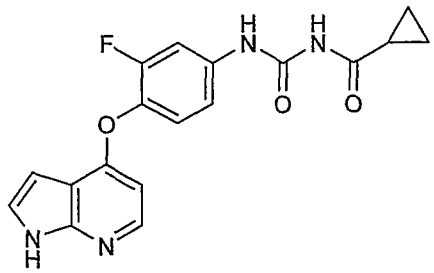
A) 2-Cyclopropylacetyl isocyanate

To a suspension of silver cyanate (435 mg, 3.0 mmol, Aldrich) in 10 mL of toluene was added cyclopropylacetyl chloride (313 mg, 3.0 mmol, Aldrich). The reaction mixture was refluxed for 2 h, cooled to rt and filtered. The filtrate was used as 0.3 M solution for next reaction.

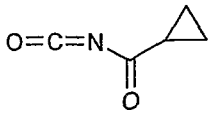
B) 1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-cyclopropylacetyl)urea

Prepared in a similar manner as Example 264 (13.5 mg, 59%). ^{1}H NMR (CD_3OD) δ 8.03 (d, 1H, J = 5.5 Hz), 7.80-7.76 (m, 1H), 7.27-7.24 (m, 3H), 6.41 (d, 1H, J = 5.5 Hz), 6.38 (d, 1H, J = 3.9 Hz), 2.25 (d, 1H, J = 7.2 Hz), 0.64-0.59 (m, 2H), 0.28-0.23 (m, 2H); MS(ESI$^+$) *m/z* 369.2 $(M + H)^+$.

EXAMPLE 280



1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(cyclopropanecarbonyl)urea



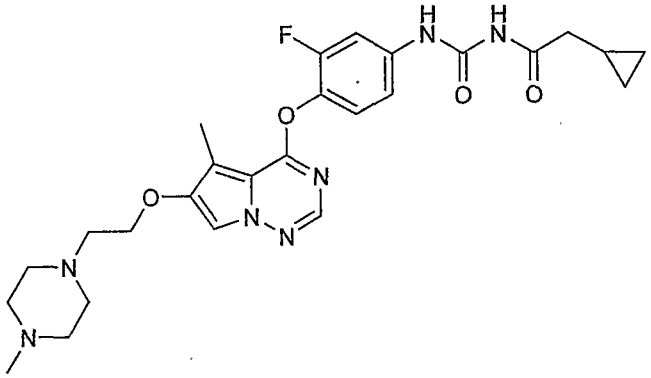
A) Cyclopropanecarbonyl isocyanate

Prepared in a similar manner as Step A of Example 279.

B) 1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(cyclopropanecarbonyl)urea

Prepared in a similar manner as Step B of Example 279 (17.2 mg, 60%). ^{1}H NMR (CD_3OD) δ 7.93 (d, 1H, J = 5.5 Hz), 7.57 (d, 1H, J = 13.8 Hz), 7.12-7.08 (m, 3H), 6.31 (m, 2H), 1.02 (m, 2H), 0.90 (m, 2H); MS(ESI$^+$) *m/z* 355.19 $(M + H)^+$.

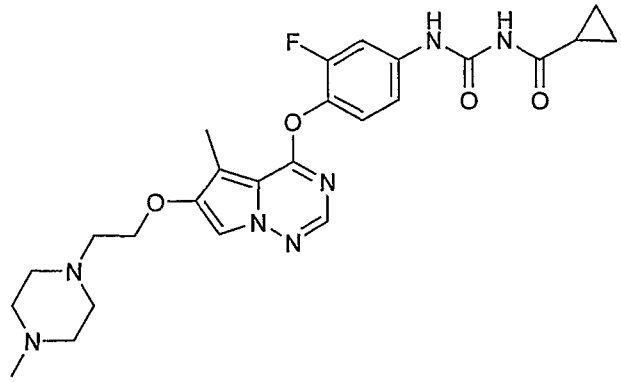
EXAMPLE 281



1-(2-Cyclopropylacetyl)-3-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)urea

Prepared in a similar manner as Example 264 using Compound B of Example 45 and Compound A of Example 279 (21.0 mg, 81%). ^{1}H NMR (CD_3OD) δ 7.81 (s, 1H), 7.74 (d, 1H, J = 5.5 Hz), 7.25 (m, 3H), 4.18 (t, 2H, J = 5.5 Hz), 3.35 (t, 2H, J = 1.7 Hz), 2.90 (t, 2H, J = 5.5 Hz), 2.74-2.54 (m, 4H), 2.45 (s, 3H), 2.33 (t, 4H, J = 2.8 Hz), 1.12 (m, 1H), 0.67-0.64 (m, 2H), 0.29-0.25 (m, 2H); MS(ESI$^+$) *m/z* 529.3 $(M + H)^+$.

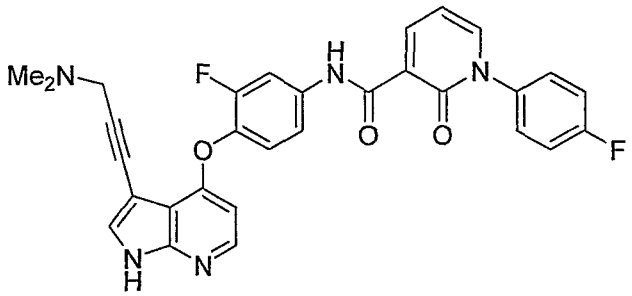
EXAMPLE 282



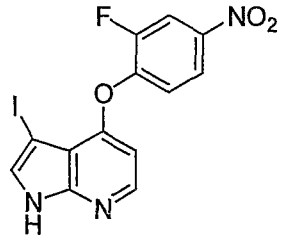
1-Cyclopropanecarbonyl-3-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)urea

Prepared in a similar manner as Example 264 using Compound B of Example 45 and Compound A of Example 280 (20.3 mg, 64%). ^{1}H NMR (CD_3OD) δ 10.85 (s, 1H), 7.70 (s, 1H), 7.76–7.72 (m, 2H), 7.22-7.14 (m, 2H), 4.14 (t, 2H, J = 5.5 Hz), 2.94 (t, 2H, J = 5.5 Hz), 2.89-2.60 (m, 4H), 2.78 (s, 3H), 2.34 (s, 4H), 1.70-1.67 (m, 1H), 0.99-0.95 (m, 2H), 0.91-0.86 (m, 2H); MS(ESI$^+$) *m/z* 512.3 $(M + H)^+$.

EXAMPLE 283

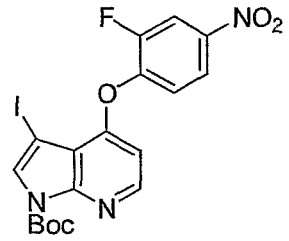


***N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



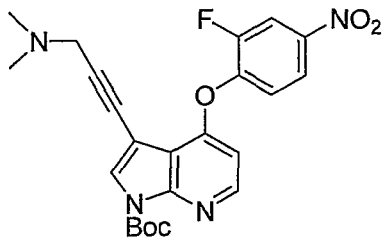
A) 4-(2-Fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine

A mixture of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (550 mg, 2 mmol, Compound A of Example 132) and *N*-iodosuccinimide (450 mg, 2 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 1 h. The mixture was washed with brine, dried over $MgSO_4$, and passed through a short pad of silica gel, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the desired product (quantitative yield) as a yellow solid. LC/MS(ESI$^+$) *m/z* 400 $(M + H)^+$.



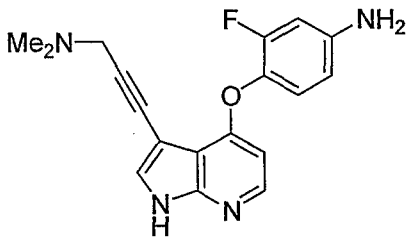
B) *tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate

To a solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (400 mg, 1 mmol) in DMF (10 mL) at –40 °C under N_2 was added NaH (60% in mineral oil, 1.2 mmol). The mixture was stirred at 0 °C for 20 min, and cooled to –40 °C. To this mixture, was added Boc_2O (330 mg, 1.5 mmol). The mixture was stirred at –40 °C for 1 h, diluted with 5% aq. sodium citrate solution, extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by flash column chromatography (silica gel, 20% EtOAc/ CH_2Cl_2) to give the desired compound (460 mg, 92%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 500 $(M + H)^+$.



C) *tert*-Butyl 3-(3-(dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate

A stream of Ar was bubbled through a mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate (200 mg, 0.4 mmol), *N,N*-dimethylprop-2-yn-1-amine (66 mg, 0.8 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (33 mg, 0.04 mmol), and CuI (20 mg) in triethylamine (0.4 mL) and THF (3 mL) for 5 min. The reaction mixture was heated in a sealed tube at 70 °C for 2 h and the solvent was removed *in vacuo*. The crude compound was purified by flash column chromatography (silica gel, 5% MeOH/EtOAc) to afford the desired product (170 mg, 95%) as a yellow oil. LC/MS(ESI$^+$) *m/z* 455 $(M + H)^+$.



D) 4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine

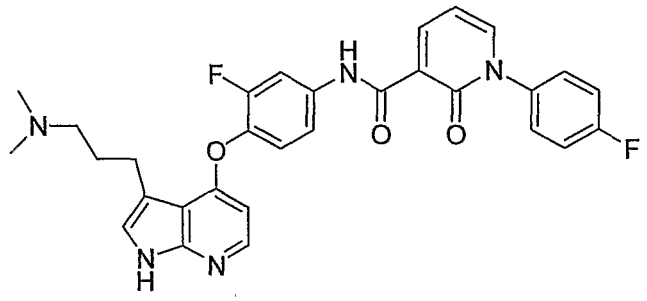
To a mixture of *tert*-butyl 3-(3-(dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (170 mg, 0.374 mmol) in THF (10 mL) and MeOH (10 mL), was added Zn powder (<10 micron, 500 mg) and NH_4Cl (500 mg). The reaction mixture was stirred at rt for 2 h, diluted with EtOAc, and filtered through a pad of Celite®. The filtrate was washed with sat. aq. KH_2PO_4 solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired product (110 mg, 90%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 325 $(M + H)^+$.

E) *N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

To a mixture of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (33 mg, 0.1 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (46 mg, 0.2 mmol, Compound B of Example 242), and HATU (Perseptive Biosystems, 76 mg, 0.2 mmol) in DMF (1 mL), was added DIPEA (0.1 mL). The reaction mixture was stirred at rt overnight and

concentrated *in vacuo*. The crude compound was purified by preparative HPLC, and the appropriate fractions were lyophilized to afford the title compound (15 mg, TFA salt, 23%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.73 (dd, 1H, J = 7.6, 2.4 Hz), 8.14 (d, 1H, J = 5.6 Hz), 8.00-8.16 (m, 2H), 7.74 (s, 1H), 7.54-7.60 (m, 2H), 7.30-7.47 (m, 4H), 6.78 (dd, 1H, J = 6.8, 6.8 Hz), 6.47 (d, 1H, J = 5.6 Hz), 4.30 (s, 2H), 2.99 (s, 6H); LC/MS (ESI$^+$) *m/z* 540 $(M + H)^+$.

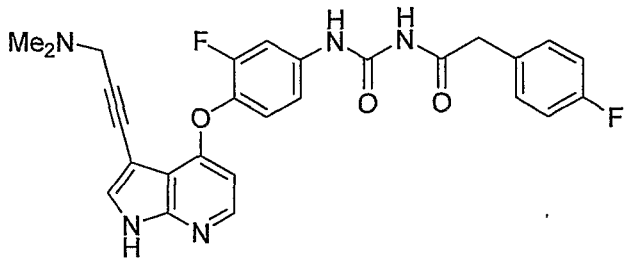
EXAMPLE 284



***N*-(4-(3-(3-(Dimethylamino)propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

A mixture of *N*-(4-(3-(3-(dimethylamino)prop-1-ynyl)-1-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32 mg, TFA salt, 0.037 mmol, obtained as a byproduct in Step E of Example 283), and Pd/C (10%, 100 mg) in MeOH (5 mL) was hydrogenated under 1 atm for 1 h. The mixture was bubbled through a stream of N_2 for 5 min, filtered through a pad Celite®. The filtrate was purified by prep-HPLC to afford the title compound as a white solid (10 mg, TFA salt, 39% yield). ^{1}H NMR (CD_3OD) δ 8.62 (dd, 1H, J = 7.2, 2.0 Hz), 8.04 (d, 1H, J = 6.4 Hz), 7.95 (dd, 1H, J = 12.8, 1.2 Hz), 7.90 (dd, 1H, J = 6.8, 2.4 Hz), 7.20-7.50 (m, 6H), 6.66 (t, 1H, J = 7.20 Hz), 6.43 (d, 1H, J = 6.4Hz), 3.11 (t, 2H, J = 8.0 Hz), 2.96 (t, 2H, J = 7.2 Hz), 2.77 (s, 6H), 2.11 (m, 2H); LC/MS(ESI$^+$) *m/z* 544 $(M + H)^+$.

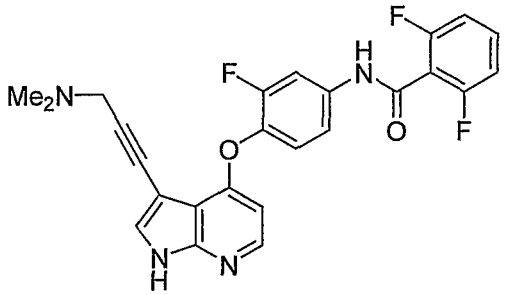
EXAMPLE 285



1-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To a solution of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (15 mg, 0.046 mmol, Compound D of Example 283) in THF (1.5 mL) was added 2-(4-fluorophenyl)acetyl isocyanate (0.05 mmol, Compound C of Example 4) at rt. The mixture was stirred for 1 h and concentrated *in vacuo*. The crude compound was purified by preparative HPLC to give the desired product (TFA salt, 12 mg, 42% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.30 (s, 1H), 10.98 (s, 1H), 10.52 (s, 1H), 10.00 (s, 1H), 8.07 (d, 1H, J = 5.6 Hz), 7.74 (d, 1H, J = 2.4 Hz), 7.73 (dd, 1H, J = 12.4, 2.4Hz), 7.25-7.40 (m, 4H), 7.10 (m, 2H), 6.26 (d, 1H, J = 5.2 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6H); LC/MS(ESI$^+$) *m/z* 504 $(M + H)^+$.

EXAMPLE 286

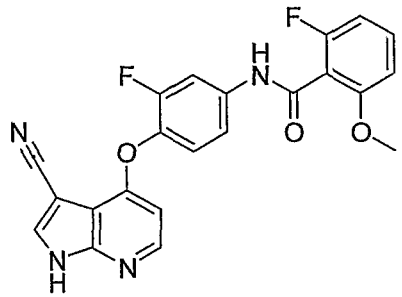


***N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, trifluoroacetic acid salt**

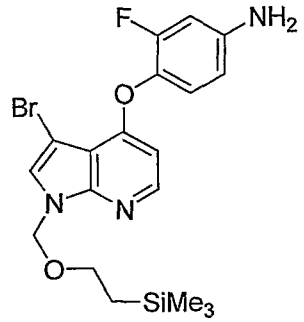
To a solution of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (15 mg, 0.046 mmol, Compound D of Example 283) and pyridine (0.05 mL) in CH_2Cl_2 (1.0 mL) at 0 °C, was added 2,6-difluorobenzoyl chloride (9 mg, 0.05 mmol). The mixture was stirred at 0 °C for 30 min and concentrated *in vacuo*. The crude compound was purified by preparative

HPLC to give the desired product (TFA salt, 11 mg, 41%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 5.6 Hz), 7.82 (dd, 1H, J = 12.4, 2.4 Hz), 7.63 (s, 1H), 7.35-7.50 (m, 2H), 7.25 (t, 1H, J = 8.8 Hz), 7.00-7.06 (m, 2H), 6.38 (d, 1H, J = 5.6 Hz), 4.19 (s, 2H), 2.87 (s, 6H); LC/MS(ESI$^+$) *m/z* 465 $(M + H)^+$.

EXAMPLE 287

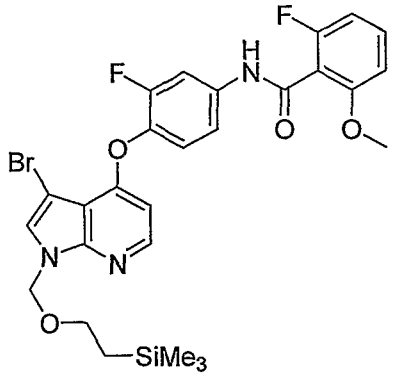


***N*-(4-(3-Cyano-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide, hydrochloride salt**



A) 4-(3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine

A mixture of 3-bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (626 mg, 1.3 mmol, Compound B of Example 261), zinc powder (1.0 g), and ammonium chloride (1.0 g) in THF (25 mL) and MeOH (25 mL) was stirred at rt overnight. The mixture was diluted with CH_2Cl_2 and filtered through a short pad of Celite®. The resulting solution was then concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, eluting with 30% EtOAc/CH_2Cl_2) to give the desired product (420 mg, 71%) as a clear oil. LC/MS(ESI$^+$) *m/z* 453 $(M + H)^+$.



B) *N*-(4-(3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide

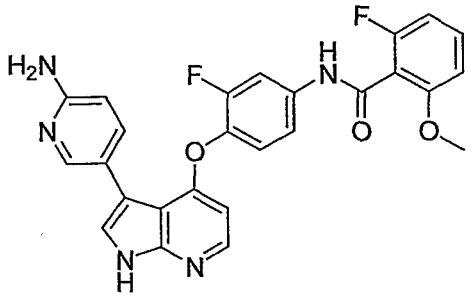
To a stirred solution of 4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (400 mg, 0.85 mmol), 2-fluoro-6-methoxybenzoic acid (226 mg, 1.33 mmol), and HATU (641 mg, 1.33 mmol) in DMF (6 mL) was added DIPEA (387 mg, 3 mmol), followed by DMAP (50 mg). The resulting mixture was stirred at rt overnight, diluted with EtOAc, and washed with saturated aq. K_2HPO_4 solution and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, eluting with 30% EtOAc/CH_2Cl_2) to give the desired product (370 mg, 72%) as a white solid. LC/MS(ESI$^+$) *m/z* 605 $(M + H)^+$.

C) *N*-(4-(3-Cyano-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide, hydrochloride salt

A mixture of *N*-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide (30 mg, 0.05 mmol), $Zn(CN)_2$ (17 mg, 0.15 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (5 mg, Aldrich), Zn(OAc)2 (1 mg) and zinc powder (1 mg) in DMF (0.6 mL) was heated in a sealed tube at 120 °C for 15 h. The mixture was diluted with CH_2Cl_2, filtered through a pad of Celite® (CH_2Cl_2). The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was treated with TBAF (1 M in THF, 1.0 mmol) and ethane-1,2-diamine (30 μL) in THF (3 mL). The mixture was refluxed for 15 h and concentrated *in vacuo*. The residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.1 mL). This

solution was then lyophilized to afford the title compound (HCl salt, 12 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1H), 8.36 (d, 1H, J = 2.8 Hz), 8.14 (d, 1H, J = 5.6 Hz), 7.87 (dd, 1H, J = 12.8, 2.0 Hz), 7.37 (m, 3H), 6.95 (d, 1H, J = 8.4 Hz), 6.88 (t, 1H, J = 8.8 Hz), 6.41 (d, 1H, J = 5.2 Hz), 3.79 (s, 3H); LC/MS(ESI$^+$) *m/z* 421 $(M + H)^+$.

EXAMPLE 288

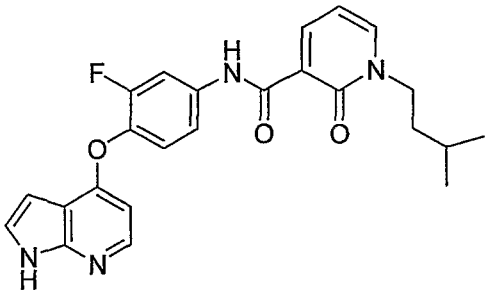


***N*-(4-(3-(6-Aminopyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide**

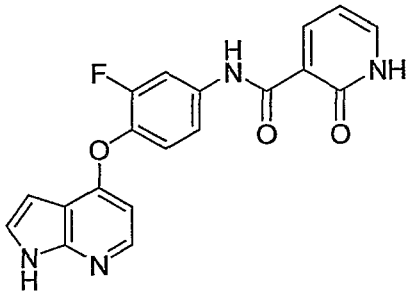
A mixture of *N*-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide (50 mg, 0.08 mmol, Compound B of Example 287), 5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyridin-2-amine (36 mg, 0.16 mmol, Oakwood), $Pd(PPh_3)_4$ (10 mg), and K_3PO_4 (2 M in H_2O, 0.32 mmol) in toluene (1 mL), EtOH (0.2 mL), and DME (0.4 mL) was purged with Ar for 10 min. The reaction mixture was heated at 95 °C for 2 h, diluted with EtOAc, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was treated with TBAF (1 M in THF, 1 mL), ethane-1,2-diamine (50 μL) in THF (3 mL) at reflux for 24 h. The mixture was diluted with EtOAc, washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 5% 2 M NH_3 in MeOH/CH_2Cl_2) to give the desired product, which was converted to the HCl salt by lyophilization with 1 N HCl in H_2O (white solid, 10 mg, 26% yield). ^{1}H NMR (CD_3OD) δ 8.32 (dd, 1H, J = 9.2, 2.0 Hz), 8.21 (d, 1H, J = 6.1 Hz), 8.15 (d, 1H, J = 2.0 Hz), 7.94 (dd, 1H, J = 12.7, 2.5 Hz), 7.70 (s, 1H), 7.44-7.50 (m, 2H), 7.36 (t, 1H, J = 8.7 Hz), 7.08 (d, 1H, J = 9.2 Hz), 6.98 (d, 1H, J = 8.7 Hz),

6.85 (t, 1H, J = 8.7 Hz), 6.56 (d, 1H, J = 5.6 Hz), 3.92 (s, 3H); LC/MS(ESI$^+$) *m/z* 488 $(M + H)^+$.

EXAMPLE 289



5 ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-isopentyl-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



10 A) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

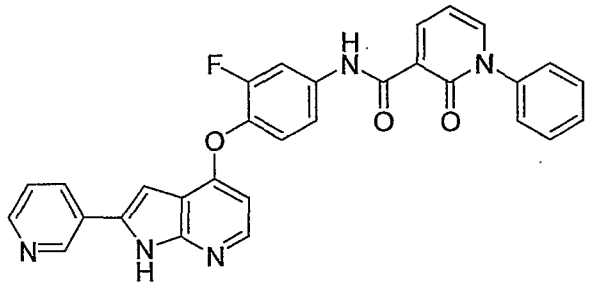
To a stirred solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (24 mg, 0.1 mmol, Compound B of Example 132), 2-hydroxynicotinic acid (27 mg, 0.2 mmol), and HATU (76 mg, 0.2 mmol) in DMF (1 **15** mL) was added DIPEA (0.1 mL) and DMAP (5 mg). The resulting mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was was purified by preparative HPLC to give the desired product (8 mg, 22%) as a white solid. LC/MS(ESI$^+$) *m/z* 365 $(M + H)^+$.

20 B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-isopentyl-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

A mixture of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (8 mg, 0.02 mmol), Na_2CO_3 (50 mg), and 1-iodo-

3-methylbutane (50 mg) in DMF (1 mL) was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was was purified by preparative HPLC to give the desired product (TFA salt, 5 mg, 42%) as a white solid. ^{1}H NMR (CD_3OD) δ 12.50 (s, 1H), 8.46 (dd, 1H, J = 7.1, 2.0 Hz), 8.16 (d, 1H, J = 6.1 Hz), 7.90-8.00 (m, 2H), 7.38-7.44 (m, 2H), 7.33 (t, 1H, J = 8.7 Hz), 6.70 (d, 1H, J = 6.6 Hz), 6.51-6.57 (m, 2H), 4.08 (t, 2H, J = 7.6 Hz), 1.51-1.53 (m, 3H), 0.92 (d, 6H, J = 6.1 Hz); LC/MS(ESI$^+$) *m/z* 435 $(M + H)^+$.

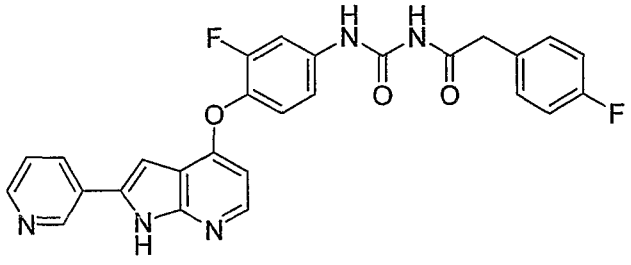
EXAMPLE 290



***N*-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 239 using 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (Compound E of Example 237) and 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid. ^{1}H NMR (DMSO-d_6) δ 12.87 (s, 1H), 12.18 (s, 1H), 9.39 (s, 1H), 8.70-8.85 (m, 2H), 8.60 (d, 1H, J = 7.1 Hz), 8.00-8.25 (m, 3H), 7.94 (s, 1H), 7.30-7.75 (m, 8H), 6.77 (t, 1H, J = 6.6 Hz), 6.45 (d, 1H, J = 4.6 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6H); LC/MS(ESI$^+$) *m/z* 518 $(M + H)^+$.

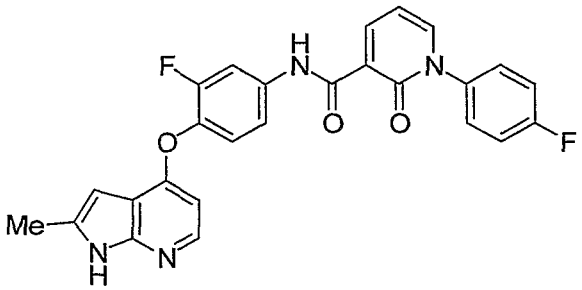
EXAMPLE 291



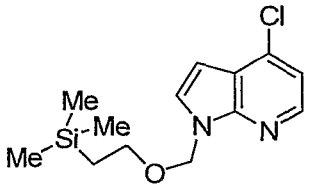
1-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

A mixture of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-b]pyridin-4-yloxy)benzenamine (25 mg, 0.078 mmol, Compound E of Example 237) and 2-(4-fluorophenyl)acetyl isocyanate (0.09 mmol in toluene, Compound C of Example 4) in THF was stirred at rt for 1 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to afford the desired product (HCl salt, 18 mg, 40%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 10.76 (s, 1H), 9.19 (s, 1H), 8.70 (d, 1H, J = 8.0 Hz), 8.66 (d, 1H, J = 5.2 Hz), 8.18 (d, 1H, J = 6.4 Hz), 8.00 (dd, 1H, J = 8.4, 5.6 Hz), 7.75 (dd, 1H, J = 13.2, 2.4 Hz), 7.10-7.35 (m, 4H), 6.90-7.03 -7.40 (m, 3H), 6.63 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) *m/z* 500 $(M + H)^+$.

EXAMPLE 292



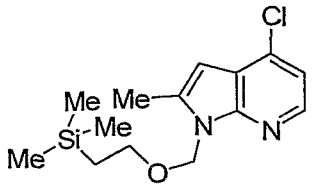
***N*-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) 4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

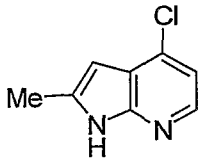
To a suspension of NaH (88 mg, 60% in mineral oil, 2.2 mmol) in DMF (1 mL) was added 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (305 mg, 2 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) at room temperature with stirring. The mixture was stirred for 5 min and trimethylsilylethyl chloromethyl ether (350 mg, 2.1 mmol, Aldrich) was added. The mixture was stirred at room temperature

for 1 h, poured onto ice, and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatograph (5% ethyl acetate in hexanes) to afford the title compound (300 mg, 1.06 mmol, 53%) as a liquid. ^{1}H NMR ($CDCl_3$) δ 8.28 (d, 1H, J = 5.5 Hz), 7.45 (d, 1H, J = 3.6 Hz), 7.18 (d, 1H, J = 5.5 Hz), 6.69 (d, 1H, J = 3.6 Hz), 5.74 (s, 2H), 3.60 (t, 2H, J = 6.8 Hz), 0.96 (t, 2H, J = 6.8 Hz), 0.07 (s, 9H); MS(ESI$^+$) *m/z* 283 and 285 (M + H, 1 Cl)$^+$.



B) 4-Chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

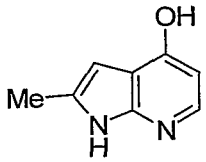
To a solution of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (150 mg, 0.53 mmol) in THF (1 mL) at -78 °C under argon was added butyllithium (0.4 mL, 1.6 M in hexanes, 6.4 mmol) dropwise. The mixture was stirred at the same temperature for 5 min, and treated with iodomethane (0.1 mL). The mixture was warmed up to room temperature, quenched by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (150 mg, 95%), which was used for the next reaction. ^{1}H NMR ($CDCl_3$) δ 8.19 (d, 1H, J = 5.5 Hz), 7.14 (d, 1H, J = 5.5 Hz), 6.42 (s, 1H), 5.74 (s, 2H), 3.60 (t, 2H, J = 6.8 Hz), 2.61(s, 3H), 0.96 (t, 2H, J = 6.8 Hz), 0.07 (s, 9H); MS(ESI$^+$) *m/z* 297 and 299 (M + H, 1 Cl)$^+$.



C) 4-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

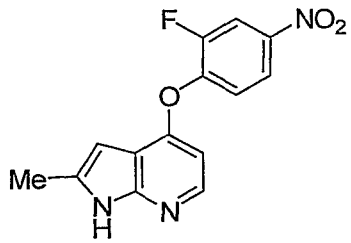
A mixture of 4-chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (296.5 mg, 1 mmol) and TBAF (5 mL, 1 M in THF, Aldrich)

was refluxed overnight. The THF was removed under reduced pressure and the residue was diluted with water (5 mL). The precipitate that formed was collected, washed with water and dried ($MgSO_4$) to afford the title compound (101 mg, 60%). ^1H NMR (CD_3OD) δ 7.99 (d, 1H, J = 5.5 Hz), 7.06 (d, 1H, J = 5.5 Hz), 6.23 (s, 1H), 2.46 (s, 3H); MS(ESI$^+$) m/z 167 and 169 $(M + H, 1\ Cl)^+$.



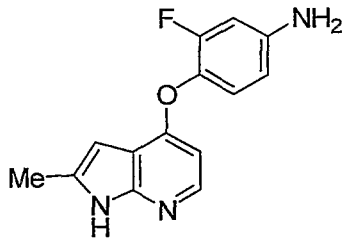
D) 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol

A mixure of 4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (120 mg, 0.72 mmol) and sodium acetate (150 mg, 1.83 mmol) in acetic acid (1.5 mL) was microwaved at 200 °C for 40 minutes. The mixture was purified by preparative HPLC and the appropriate fractions were concentrated *in vacuo* and lyophilized to afford the title compound (90 mg, 47%). ^1H NMR (CD_3OD) δ 8.09 (d, 1H, J = 5.5 Hz), 6.80 (d, 1H, J = 5.5 Hz), 6.49 (s, 1H), 2.46 (s, 3H); MS(ESI$^+$) m/z 149 $(M + H)^+$.



D) 4-(2-Fluoro-4-nitrophenoxy)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

A mixture of 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (90 mg , TFA salt, 0.34 mmol), 3,4-difluoronitrobenzene (0.05 mL) and potassium carbonate (100 mg, 0.72 mmol) in DMF (1 mL) was stirred at 50 °C for 2 h. The mixture was diluted with water and extracted with ethyl acetate (3 x 5 mL). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product, which was purified by preparative HPLC to give the title compound (45 mg, 46%). ^1H NMR (CD_3OD) δ 8.25 (dd, 2H, J = 10.4, 2.6 Hz), 8.12 (m, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.30 (t, 1H, J = 8.3 Hz), 6.67 (d, 1H, J = 5.5 Hz), 5.95 (s, 1H), 2.41 (s, 3H); MS(ESI$^+$) m/z 288 $(M + H)^+$.



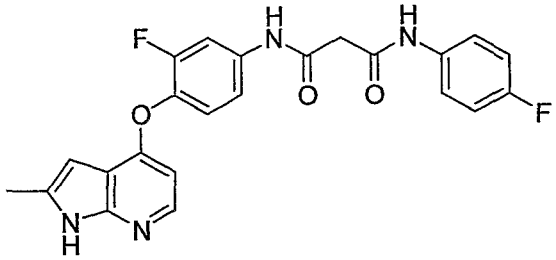
E) 3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine

A mixture of 4-(2-fluoro-4-nitrophenoxy)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (43 mg, 0.15 mmol), zinc dust (50 mg, 0.75 mmol) and ammonium chloride (50 mg) in THF/Methanol (1/2, 0.6 mL) was stirred at room temperature for 1 h, filtered and concentrated *in vacuo* to afford the desired product (35 mg, 90%), which was sufficiently pure to use in the subsequent reaction. ^{1}H NMR (DMSO-d_6) δ 11.71 (s, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.10 (t, 1H, J = 8.4 Hz), 6.64 (dd, 1H, J = 10.4, 2.6 Hz), 6.51 (m, 1H), 6.35 (d, 1H, J = 5.5 Hz), 5.95 (s, 1H), 5.50 (s 2H), 2.41 (s, 3H); MS(ESI$^+$) *m/z* 258 $(M + H)^+$.

F) *N*-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

A mixture of 3-fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (17 mg, 0.066 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20 mg, 0.086 mmol) in DMF (0.5 mL) was stirred with BOP reagent (50 mg, 0.11 mmol) and triethylamine (0.01 mL) at 50 °C for 1 h. The reaction mixture was cooled to room temperature and diluted with water. The precipitate was collected and washed with water. The crude product was purified by preparative HPLC and the appropriate fractions were collected, neutralized and concentrated *in vacuo* to give the title compound (7.85 mg, 25%) as a solid. ^{1}H NMR (DMSO-d_6) δ 12.07 (s, 1H), 11.56 (s, 1H), 8.49 (d, 1H, J = 6.2 Hz), 8.12 (d, 1H, J = 6.2 Hz), 7.98 (dd, 1H, J = 10.4, 2.6 Hz), 7.95 (d, 1H, J = 5.5 Hz), 7.61 (m, 2H), 7.43 (m, 3H), 7.29 (t, 1H, J = 8.40 Hz), 6.72 (t, 1H, J = 6.2 Hz), 6.36 (d, 1H, J = 5.5 Hz), 5.88 (s, 1H), 2.32 (s, 3H); MS(ESI$^+$) *m/z* 473 $(M + H)^+$.

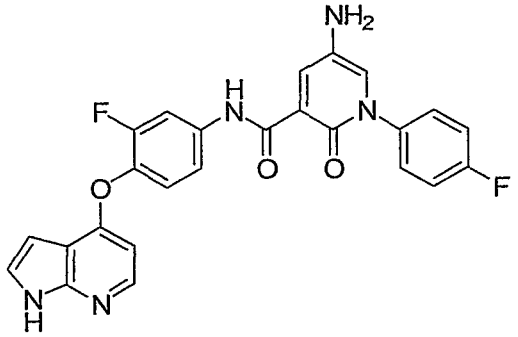
EXAMPLE 293



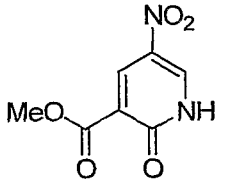
N^1-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt

To a mixture of 3-fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (20 mg, 0.078 mmol, Compound E of Example 292), 3-(4-fluorophenylamino)-3-oxopropanoic acid (20 mg, 1 mmol, Compound A of Example 25), and HATU (44 mg, 0.12 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL). The reaction mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the desired product (HCl salt, 12.5 mg, 34%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 7.2 Hz), 7.79 (dd, 1H, J = 12.7, 2.8 Hz), 7.50-7.53 (m, 2H), 7.27-7.36 (m, 2H), 6.97 (m, 2H), 6.70 (d, 1H, J = 6.6 Hz), 6.20 (s, 1H), 3.47 (s, 2H), 2.40 (s, 3H); LC/MS(ESI$^+$) *m/z* 437 $(M + H)^+$.

EXAMPLE 294

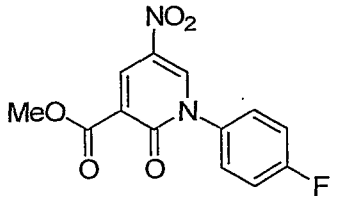


N-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt



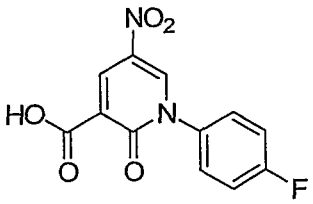
A) Methyl 5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of 2-hydroxy-5-nitronicotinic acid (0.80 g, 4.35 mmol, Combi-Blocks) in methanol (10 mL) at 0 °C was added thionyl chloride (1 mL) dropwise. The mixture was stirred at 0 °C for 1 h, then at 60 °C for 2 h. The excess methanol was removed under reduced pressure and the residue was neutralized with aqueous sodium bicarbonate solution. The solid was collected, washed with water and dried to afford the title compound (0.85 g, 99%). ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 1H), 3.67 (s, 3H); MS(ESI$^+$) *m/z* 199 $(M + H)^+$.



B) Methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate

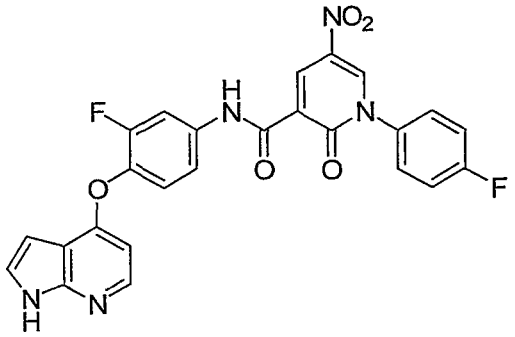
A mixture of methyl 5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (850 mg, 4.29 mmol), 4-fluorophenylboronic acid (1.40 g, 10 mmol, Combi-Blocks) and copper acetate (200 mg, 1.1 mmol) in pyridine (1 mL) and dioxane (20 mL) was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with a solution of ammonia. The solid was collected, washed with water and dried to afford the title compound (656 mg, 52%). ^{1}H NMR (DMSO-d_6) δ 8.95 (d, 1H, J = 3.2 Hz), 8.80 (d, 1H, J = 3.2 Hz), 7.40 (m, 2H), 7.25 (m, 2H), 3.95 (s, 3H); MS(ESI$^+$) *m/z* 293 $(M + H)^+$.



C) 1-(4-Fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A mixture of methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (75 mg, 0.245 mmol) and 2 N NaOH solution (1 mL) was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt and acidified with 1 N HCl solution.

The solid that formed was collected, washed with water and dried to afford the title compound (45 mg, 66%), which was used directly in the next reaction. ^{1}H NMR (DMSO-d_6) δ 13.41 (s, 1H), 9.28 (d, 1H, J = 3.2 Hz), 8.70 (d, 1H, J = 3.2 Hz), 7.60 (m, 2H), 7.41 (m, 2H); MS(ESI$^+$) m/z 279 $(M + H)^+$.



D) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxamide

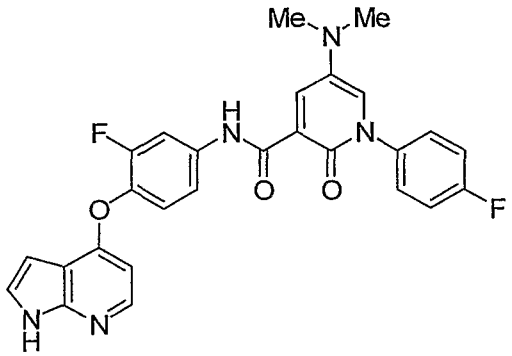
A mixture of 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40 mg, 0.14 mmol) and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.14 mmol, Compound B of Example 132) in DMF (1 mL) was stirred with BOP reagent (100 mg, 0.23 mmol) and triethylamine (0.1 mL) at 50 °C for 1 h. The reaction mixture was cooled to room temperature and diluted with water. The solid that formed was collected, washed with aqueous sodium bicarbonate solution, 1 N HCl solution, and water to afford the title compound (54 mg, 76%). ^{1}H NMR (DMSO-d_6) δ 12.19 (s, 1H), 11.04 (s, 1H), 9.37 (d, 1H, J = 2.6 Hz), 9.03 (d, 1H, J = 2.6 Hz), 8.18 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.2, 2.6 Hz), 7.71 (m, 2H), 7.61 (m, 1 H), 7.46 (m, 4H), 6.55 (d, 1H, J = 5.5 Hz), 6.36 (s, 1Hz); MS(ESI$^+$) m/z 504 $(M + H)^+$.

E) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt

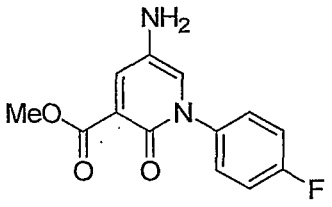
A solution of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxamide (51 mg, 0.1 mmol) in DMF (1 mL) and ethanol (5 mL) was hydrogenated in the presence of Pd/C (10%, 10

mg) under hydrogen atmosphere for 4 h at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC and the fraction containing the desired compound was collected and concentrated *in vacuo*. The product was converted to the HCl salt by adding 1 N HCl solution and lyophilizing to afford the title compound (7.6 mg, 15%) as a light yellow solid. ^{1}H NMR (CD_3OD) δ 8.56 (d, 1H, J = 3.2 Hz), 8.31 (d, 1H, J = 5.5 Hz), 8.08 (dd, 1H, J = 10.4, 2.6 Hz), 7.78 (m, 1H), 7.56 (m, 5H), 7.48 (m, 2H), 7.35 (t, 1H, J = 8.7 Hz), 6.90 (d, 1H, J = 5.5 Hz), 6.69 (s, 1H); MS(ESI$^+$) *m/z* 474 $(M + H)^+$.

EXAMPLE 295



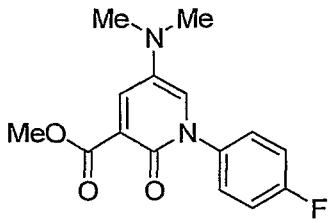
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) Methyl 5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

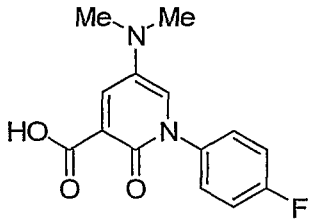
A mixture of methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (1.46 g, 5 mmol, Compound B of Example 294), zinc dust (1.63 g, 25 mmol) and ammonium chloride (1.5 g, 28 mmol) in methanol/THF (1:1, 20 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered and concentrated *in vacuo* to afford the desired product (1.30 g, 99%), which was used

directly in the next reaction without purification. ^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 7.41 (m, 2H), 7.29 (m, 3H), 3.84 (s, 3H); MS(ESI^+) *m/z* 263 $(M + H)^+$.



B) Methyl 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (30 mg, 0.11 mmol) and formalin (37%, 0.1 mL) in acetic acid (1 mL) was added sodium triacetoxyborohydride (50 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 1 h and purified by preparative HPLC. The fractions containing the desired product were collected, neutralized and concentrated *in vacuo* to afford a solid. The solid was collected, washed with water and dried to give the title compound (25 mg, 77%). ^{1}H NMR (CD_3OD) δ 8.31 (d, 1H, J = 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 3.89 (s, 3H), 2.79 (s, 6H); MS(ESI^+) *m/z* 291 $(M + H)^+$.



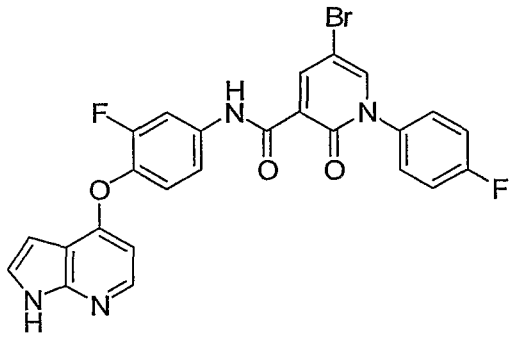
C) 5-(Dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

The title compound was prepared from methyl 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (25 mg, 0.086 mmol) utilizing the procedure described in Step C of Example 294 (20 mg, 84%). ^{1}H NMR (CD_3OD) δ 8.31 (d, 1H, J = 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 2.70 (s, 6H); MS(ESI^+) *m/z* 277 $(M + H)^+$.

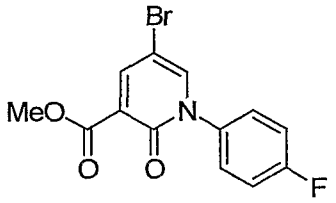
D) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

The title compound was prepared from 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20 mg, 0.072 mmol) utilizing the procedure described in Step D of Example 294 (13.5 mg, 37%). ^{1}H NMR (DMSO-d_6) δ 12.54 (s, 1H), 11.79 (s, 1H), 8.45 (d, 1H, J = 3.2 Hz), 8.10 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.62 (m, 1H), 7.44 (m, 6H), 6.40 (d, 1H, J = 5.5 Hz), 6.24 (s, 1Hz), 2.82 (s, 6H); MS(ESI$^+$) *m/z* 502 $(M + H)^+$.

EXAMPLE 296

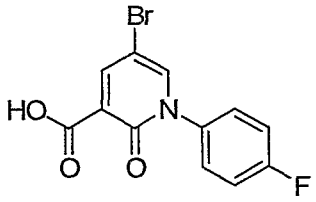


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) Methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

The title compound was prepared from 5-bromo-2-hydroxynicotinic acid (Combi-Blocks) utilizing the procedures described in Steps A and B of Example 294 in 69% yield. ^{1}H NMR (DMSO-d_6) δ 8.29 (d, 1H, J = 3.2 Hz), 8.14 (d, 1H, J = 3.2 Hz), 7.50 (m, 2H), 7.37 (m, 2H), 3.75 (s, 3H); MS(ESI$^+$) *m/z* 326 and 328 (M + H, 1 Br)$^+$.



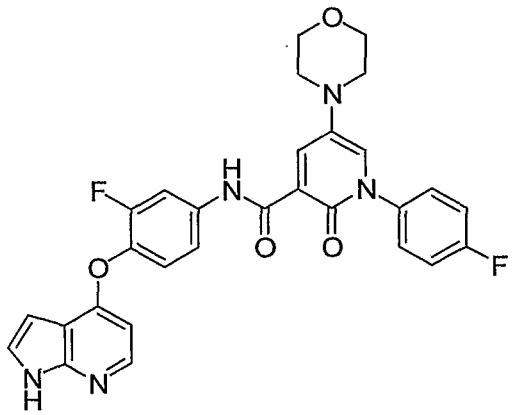
B) 5-Bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

The title compound was prepared from methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (65 mg, 0.2 mmol) utilizing the procedure described in Step C of Example 294 (55 mg, 88%). ^{1}H NMR (DMSO-d_6) δ 8.58 (d, 1H, J = 2.6 Hz), 8.44 (d, 1H, J = 2.6 Hz), 7.69 (m, 2H), 7.43 (t, 2H, J = 8.8 Hz); MS(ESI$^+$) m/z 312 and 314 (M + H, 1 Br)$^+$.

C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

The title compound was prepared from 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (31.2 mg, 0.1 mmol) utilizing the procedure described in Step D of Example 294 (28 mg, 52%). ^{1}H NMR (DMSO-d_6) δ 11.93 (s, 1H), 11.80 (s, 1H), 8.53 (m, 2H), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.64 (m, 2H), 7.41 (m, 6H), 6.41 (br.s, 1H), 6.27 (s, 1H); MS(ESI$^+$) m/z 537 and 539 (M + H, 1 Br)$^+$.

EXAMPLE 297

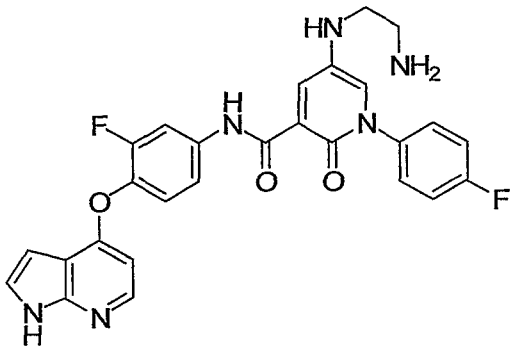


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-morpholino-2-oxo-1,2-dihydropyridine-3-carboxamide**

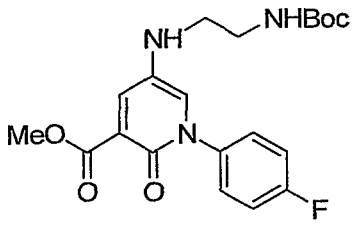
A mixture of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (40 mg, 0.074

mmol, Example 296) and morphiline (0.1 mL) in dimethylacetamide (1 mL) was microwaved at 160 °C for 30 minutes. The reaction mixture was cooled to room temperature and purified by preparative HPLC. The fractions containing the desired product were collected, neutralized and concentrated *in vacuo* to afford a solid. The solid was collected, washed with water and dried to give the title compound (7.5 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 12.38 (s, 1H), 11.75 (s, 1H), 8.50 (d, 1H, J = 2.6 Hz), 8.06 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.60 (m, 2H), 7.41 (m, 6H), 6.41 (d, 1H, J = 5.5 Hz), 6.21 (s, 1H), 3.72 (m, 4H), 3.00 (m, 4H); MS(ESI$^+$) *m/z* 544 $(M + H)^+$.

EXAMPLE 298



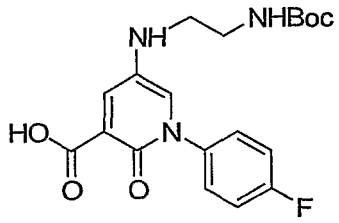
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(2-aminoethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) Methyl 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (131 mg, 0.5 mmol, Compound A of Example 296) and *tert*-butyl 2-oxoethylcarbamate (159 mg, 1 mmol, Aldrich) in acetic acid (1 mL) was added sodium triacetoxyborohydride (212 mg, 1 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched by adding water, and extracted with

ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, aqueous sodium bicarbonate solution and dried. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to afford the title compound (60 mg, 30%) as a gel. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 2.6 Hz), 7.37 (m, 2H), 7.13 (m, 2H), 6.81 (d, 1H, J = 2.6 Hz), 3.88 (s, 3H), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); MS(ESI$^+$) *m/z* 406 (M + H)$^+$.



B) 5-(2-(*tert*-Butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

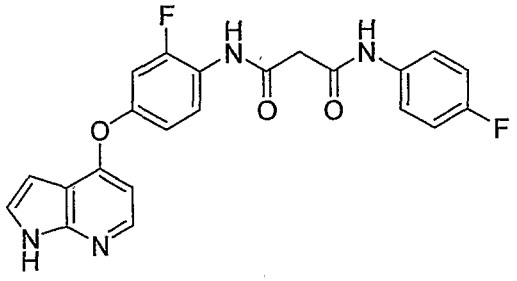
The title compound was prepared from methyl 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (60 mg, 0.15 mmol) utilizing the procedure described in Step C of Example 294 (50 mg, 85%), which was used directly in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H, J = 2.6 Hz), 7.50 (m, 2H), 7.25 (m, 2H), 6.91 (d, 1H, J = 2.6 Hz), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); MS(ESI$^+$) *m/z* 392 (M + H)$^+$.

C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridine-4-yloxy)-3-fluorophenyl)-5-(2-aminoethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

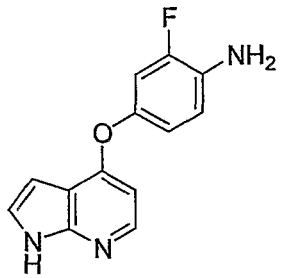
A mixture of 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (50 mg, 0.13 mmol) and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (40 mg, 0.16 mmol, Compound B of Example 132), BOP reagent (100 mg, 0.23 mmol) in DMF (1 mL) was stirred at 50 °C with triethylamine (0.1 mL) for 1 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride (3 x 10 mL).

The combined organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was stirred with TFA (1 mL) at room temperature for 30 minutes. The TFA was removed and the residue was purified by preparative HPLC. The fraction containing the desired product was collected and concentrated *in vacuo*. The residue was converted to the HCl salt by adding 1 N HCl solution and lyophilizing to give the title compound (20 mg, 27%). ^{1}H NMR (CD_3OD) δ 8.35 (d, 1H, J = 2.6 Hz), 8.26 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.48 (m, 2H), 7.41 (m, 6H), 6.81 (d, 1H, J = 5.5 Hz), 6.60 (s, 1H), 3.26 (t, 2H, J = 6.1 Hz), 3.07 (t, 2H, J = 6.1 Hz); MS(ESI$^+$) *m/z* 517 $(M + H)^+$.

EXAMPLE 299



N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



A) 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorobenzenamine

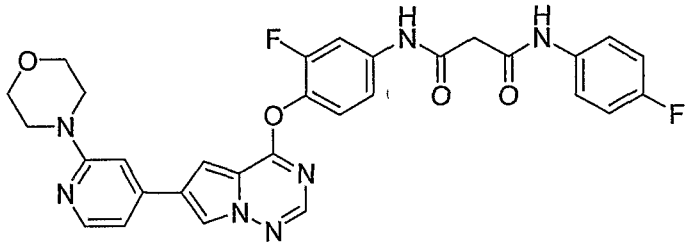
To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg, 0.33 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in NMP (0.5 mL) were added 4-amino-3-fluorophenol (51 mg, 0.40 mmol) and DIEA (0.1 mL, 0.57 mmol). The mixture was heated at 250 °C in a microwave oven for 1 h and then cooled to room temperature. To the mixture was added NaH (10 mg, 0.4 mmol) and the mixture was again heated at 250 °C for 3 h. After cooling, the mixture was diluted

with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the title compound (15 mg, 19%). MS (ESI) *m/z* 244.1 $(M+H)^+$.

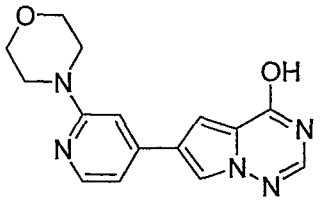
B) N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorobenzenamine (14 mg, 0.058 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (12 mg, 0.06 mmol, Compound A of Example 25) in DMF (1 mL) were added DIEA (0.04 mL, 0.23 mmol) and TBTU (22 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for 2 d and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound (18 mg, 74%). ^{1}H NMR (CD_3OD) δ 8.25 (d, 1H, *J* = 7.5 Hz), 8.19 (t, 1H, *J* = 7.5 Hz), 7.55 (m, 2H), 7.49 (d, 1H, *J* = 3.5 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.13 (d, 1H, *J* = 7.0 Hz), 7.01 (m, 2H), 6.84 (d, 1H, *J* = 7.0 Hz), 6.60 (d, 1H, *J* = 3.5 Hz), 3.60 (s, 2H); MS(ESI) *m/z* 423.1 $(M+H)^+$.

EXAMPLE 300

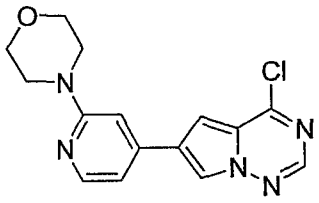


N^1-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide



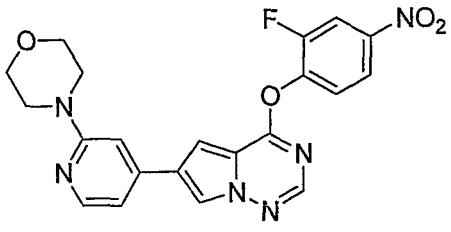
A) 6-(2-Morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol

To a solution of 6-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, prepared from methyl 4-bromo-1*H*-pyrrole-2-carboxylate: see, generally, Kitamura, C. and Yamashita, Y. *J. Chem. Soc. Perkin Trans.* 1, **1997**, 1443, the disclosure of which is herein incorporated by reference, using a similar procedure outlined in the PCT Appl. WO 00/71129) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (290 mg, 1.0 mmol) in DMF (2 mL) were added saturated aq. K_2CO_3 solution (2.0 mL) and $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). The reaction mixture was purged with N_2 for 10 min and then was heated at 80 °C for 5 h and 100 °C for 12 h. After cooling, the mixture was diluted with H_2O and filtered to afford the crude product, which was triturated with DCM to provide the title compound (114 mg, 82% yield). MS(ESI) *m/z* 298.2 $(M+H)^+$.



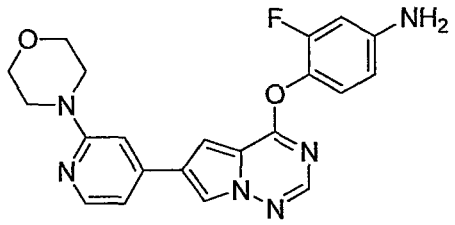
B) 4-Chloro-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

To a suspension of 6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (110 mg, 0.37 mmol) in toluene (100 mL) were added one drop of DMF and $POCl_3$ (30 mL). The flask was sealed and heated at 100 °C for 3 d. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was then dissolved in DCM, neutralized with saturated aq. $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired product, which was used directly in the next step. MS(ESI) *m/z* 316.2/318.2 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

To a suspension of the crude 4-chloro-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine in MeCN (5 mL) were added 2-fluoro-4-nitrophenol (59 mg, 0.37 mmol) and DABCO (45 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the desired compound (54 mg, 33% yield in two steps). MS(ESI) *m/z* 437.2 $(M + H)^+$.



D) 3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

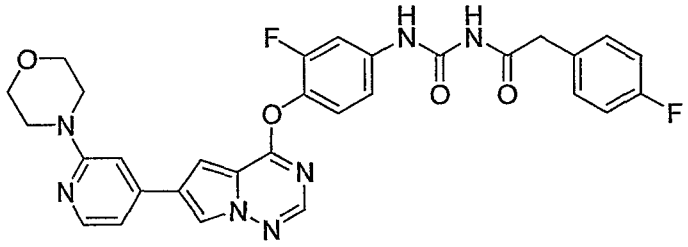
To a solution of 4-(2-fluoro-4-nitrophenoxy)-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (54 mg, 0.12 mmol) in a mixture of THF (2.0 mL) and MeOH (2.0 mL) were added NH_4Cl (127 mg, 2.4 mmol) and Zn dust (78 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the desired product (40 mg, 82% yield). MS(ESI) *m/z* 407.19 $(M + H)^+$.

E) N^1-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

To a solution of 3-fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.037 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (8 mg, 0.04 mmol, Compound A of Example 25) in DMF (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and TBTU (13 mg, 0.04 mmol). The reaction mixture was stirred at room temperature overnight and then purified using preparative HPLC. The fraction containing the desired product

was collected and concentrated *in vacuo*. The residue was neutralized with 1 N NH_4OH and concentrated again. The solid that formed was filtered, washed with 1 N NH_4OH, dissolved in $MeOH/H_2O$, and lyophilized to give the title compound (8 mg, 37%). ^1H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.23 (s, 1H), 8.63 (s, 1H), 8.55 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H, J = 7.5 Hz), 7.70 (m, 1H), 7.50 (m, 2H), 7.30-7.45 (m, 3H), 7.04-7.17 (m, 3H), 6.85-6.92 (m, 2H), 3.36 (s, 4H), 3.44 (s, 6H); MS(ESI) *m/z* 586.2 $(M + H)^+$.

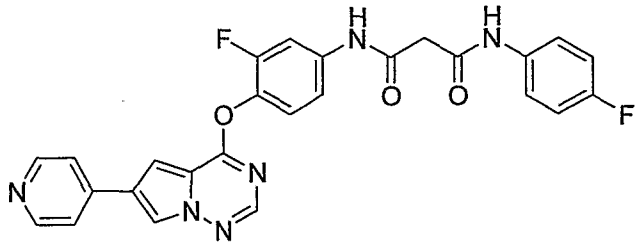
EXAMPLE 301



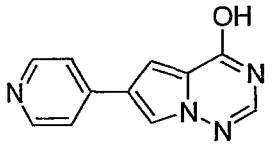
1-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 3-fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.037 mmol, Compound D of Example 300) in THF (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and 2-(4-fluorophenyl)acetyl isocyanate (0.347 M, 0.21 mL, 0.074 mmol, Compound C of Example 4). The reaction mixture was stirred at room temperature for 1 h and the precipitate was collected on a Buchner funnel and washed with toluene to give the title compound (10 mg, 46%). ^1H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.60 (s, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 8.13 (s, 1H), 8.09 (d, 1H, J = 7.5 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.35-7.54 (m, 5H), 7.18 (t, 2H, J = 7.5 Hz), 6.91 (d, 1H, J = 8.0 Hz), 3.71-3.76 (m, 6H), 3.48-3.51 (m, 4H); MS(ESI) *m/z* 586.2 $(M + H)^+$.

EXAMPLE 302

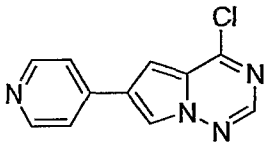


N^1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



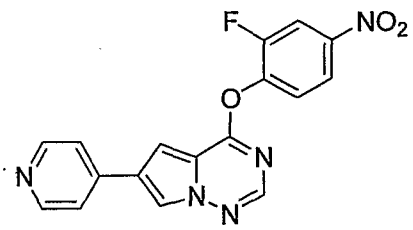
A) 6-(Pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol

Following a similar procedure as described in Step A of Example 300, 6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol) was coupled with pyridin-4-ylboronic acid (172 mg, 1.40 mmol) to provide the title compound (72 mg, 72%). MS(ESI) *m/z* 213.2 $(M + H)^+$.



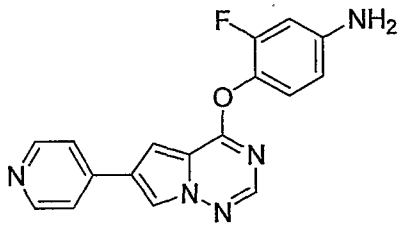
B) 4-Chloro-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Following a similar procedure as described in Step B of Example 300, 6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (62 mg, 0.29 mmol) was converted to the title compound (30 mg, 45%). MS(ESI) *m/z* 231.1/233.1 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Following a similar procedure as described in Step C of Example 300, 4-chloro-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (37 mg, 0.16 mmol) was converted to the desired compound (50 mg, 89%). MS(ESI) *m/z* 352.2 $(M + H)^+$.



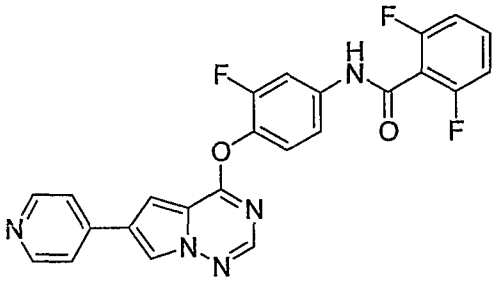
D) 3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Following a similar procedure as described in Step D of example 300, 4-(2-fluoro-4-nitrophenoxy)-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.14 mmol) was converted to the desired compound (50 mg, quantitative yield). MS(ESI) *m/z* 322.3 $(M+H)^+$.

E) N^1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

Following a similar procedure as described in Step E of Example 300, 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (8.5 mg, 28%). ^{1}H NMR (DMSO-d_6) δ 10.53 (s, 1H), 10.27 (s, 1H), 9.06 (s, 1H), 8.80 (d, 2H, J = 7.0 Hz), 8.30 (d, 2H, J = 6.0 Hz), 8.24 (s, 1H), 7.98 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.60 (m, 2H), 7.35-7.45 (m, 2H), 7.16 (t, 2H, J = 8.0 Hz), 3.49 (s, 2H); MS(ESI) *m/z* 501.2 $(M + H)^+$.

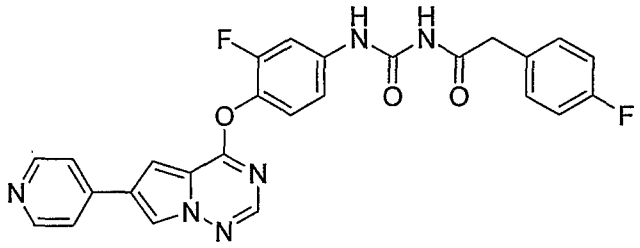
EXAMPLE 303



2,6-Difluoro-*N*-(3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, trifluoroacetic acid salt

To a solution of 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol, Compound D of Example 302) in DCM (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and a solution of 2,6-difluorobenzoyl chloride in DCM (0.5 M, 0.14 mL, 0.07 mmol) at room temperature. The reaction mixture was stirred for 0.5 h and quenched with 1 N NH_4OH. The solution was then concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound (15 mg, 54%). ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 8.96 (s, 1H), 8.70 (m, 2H), 8.18 (s, 1H), 8.10 (br. s, 2H), 7.90 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.45-7.55 (m, 3H), 7.23 (t, 2H, J = 8.0 Hz); MS(ESI) *m/z* 462.2 $(M + H)^+$.

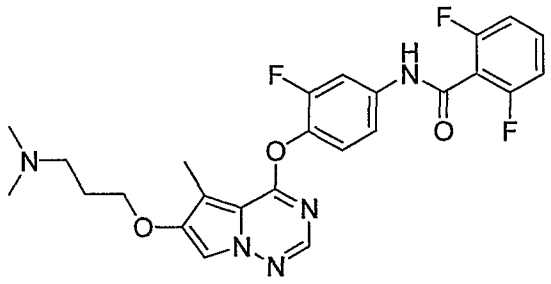
EXAMPLE 304



1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

Following a similar procedure as described in Example 301, 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.05 mmol, Compound D of Example 302) was converted to the title compound (6.5 mg, 26%). ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.55 (s, 1H), 9.04 (s, 1H), 8.78 (d, 2H, J = 6.4 Hz), 8.31 (d, 2H, J = 6.4 Hz), 8.20 (s, 1H), 7.96 (s, 1H), 7.72 (m, 1H), 7.09-7.44 (m, 6H), 3.69 (s, 2H); MS(ESI) *m/z* 501.2 $(M + H)^+$.

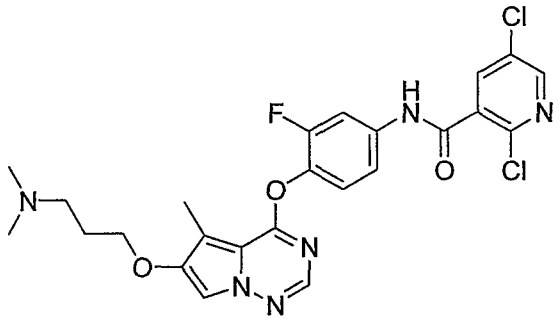
EXAMPLE 305



N-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, hydrochloride salt

Following a similar procedure as described in Example 134, 4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (36 mg, 0.1 mmol, Compound B of Example 32) was converted to the title compound (20 mg, 40%). ^{1}H NMR (DMSO-d_6) δ 11.17 (s, 1H), 10.40 (s, 1H), 8.00 (d, 2H, J = 4.0 Hz), 7.86 (d, 1H, J = 12.0 Hz), 7.65 (m, 1H), 7.51 (d, 2H, J = 5.0 Hz), 7.29 (t, 2H, J = 8.0 Hz), 4.15 (m, 2H), 3.24 (m, 2H), 2.80 (s, 6H), 2.40 (s, 3H), 2.18 (m, 2H); MS(ESI) *m/z* 500.3 $(M + H)^+$.

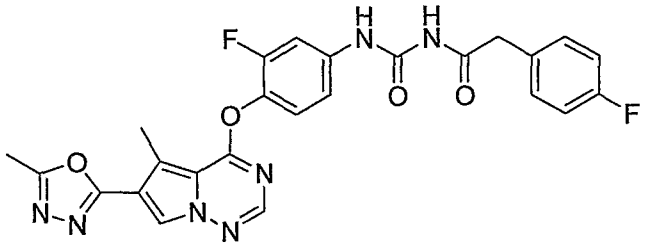
EXAMPLE 306



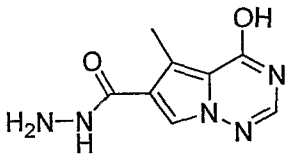
2,5-Dichloro-*N*-(4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide, hydrochloride salt

Following a similar procedure as described in Example 134, 4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (36 mg, 0.1 mmol, Compound B of Example 32) was converted to the title compound (10 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 11.12 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.00 (s, 1H), 7.86 (d, 1H, J = 12 Hz), 7.52 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 4.12 (m, 2H), 3.26 (m, 2H), 2.78 (s, 6H), 2.41 (s, 3H), 2.20 (m, 2H); MS(ESI) *m/z* 533.2 $(M + H)^+$.

EXAMPLE 307

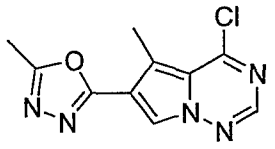


1-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



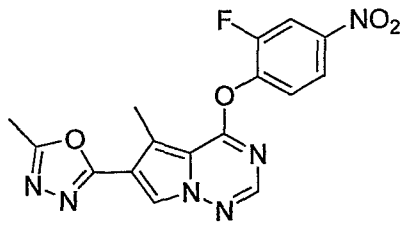
A) 4-Hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbohydrazide

Ethyl 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (467 mg, 2.11 mmol, preparation: See US Pat. No. 6,670,357) was dissolved in $N_2H_4 \cdot H_2O$/EtOH (4:1, 5 mL). The solution was heated at 88 °C for 4 h, cooled to rt, and concentrated *in vacuo* to give the title compound (450 mg, >95%). MS(ESI) *m/z* 208.1 $(M + H)^+$.



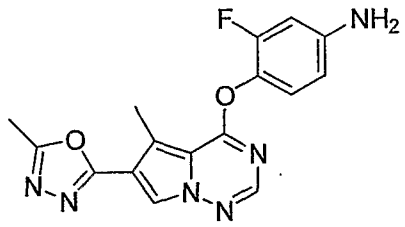
B) 4-Chloro-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

To a suspension of 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbohydrazide (100 mg, 0.48 mmol) in $POCl_3$ (5 mL) was added AcOH (50 mg, 0.83 mmol). The reaction mixture was heated at 80 °C for 3 d, cooled to rt, and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and treated with sat. aq. $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Filtration, followed by concentration, provide the title compound, which was used directly in next step. MS (ESI) *m/z* 250.1/252.1 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Following a similar procedure as described in Step C of Example 300, 4-chloro-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine was converted to the title compound (50 mg, 28% in two steps). MS(ESI) *m/z* 371.2 $(M + H)^+$.



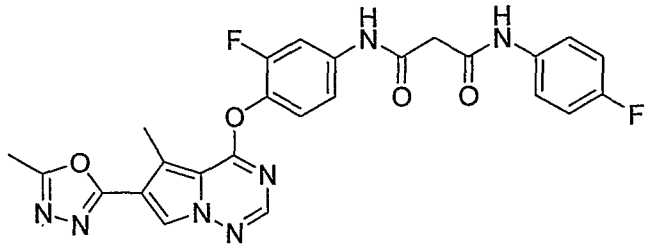
D) 3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Following a similar procedure as described in Step D of Example 300, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.13 mmol) was converted to the title compound (45 mg, >95%). MS(ESI) *m/z* 341.2 $(M + H)^+$.

E) 1-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Following a similar procedure as described for Example 301, 3-fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (11 mg, 35%). ^{1}H NMR ($CDCl_3$) δ 10.80 (s, 1H), 8.69 (s, 1H), 8.18 (s, 1H), 7.96 (s, 1H), 7.70 (m, 1H), 7.10-7.30 (m, 6H), 3.75 (s, 2H), 2.92 (s, 3H), 2.64 (s, 3H); MS(ESI) *m/z* 520.2 $(M + H)^+$.

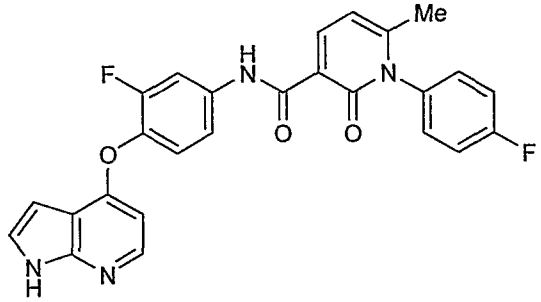
EXAMPLE 308



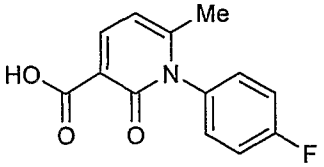
N^1-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

Following a similar procedure as described in Step E of Example 300, 3-fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (8 mg, 26%). ^{1}H NMR ($CDCl_3$) δ 9.26 (s, 1H), 8.47 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.80 (m, 1H), 7.50 (m, 2H), 7.10-7.30 (m, 4H), 3.60 (s, 2H), 2.93 (s, 3H), 2.69 (s, 3H); MS (ESI) *m/z* 520.1 $(M + H)^+$.

EXAMPLE 309



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) 1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

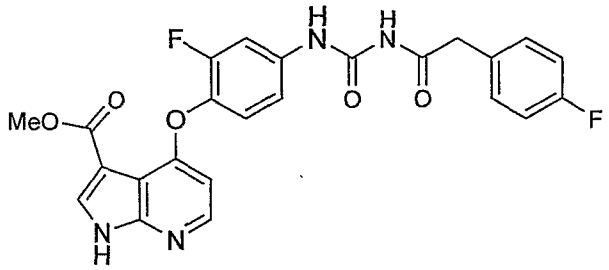
Prepared in a similar manner as Steps B and C of Example 294 using 2-hydroxy-6-methylnicotinic acid (Aldrich). ^{1}H NMR (DMSO-d_6) δ 8.41 (d, 1H, J =

6.5 Hz), 8.08 (s, 1H), 7.51-7.48 (m, 4H), 6.81 (d, 1H, J = 6.5 Hz), 2.10 (s, 3H); MS(ESI$^+$) m/z 248 $(M + H)^+$.

B) *N-(4-(1H-*Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

Prepared in a similar manner as Step D of Example 294 (21% yield). ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 11.83 (s, 1H), 8.56 (d, 1H, J = 6.5 Hz), 8.13 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.56-7.50 (m, 7H), 6.78 (d, 1H, J = 6.5 Hz), 6.44 (d, 1H, J = 5.5 Hz), 6.30 (s, 1H), 2.14 (s, 3H); MS(ESI$^+$) m/z 473 $(M + H)^+$.

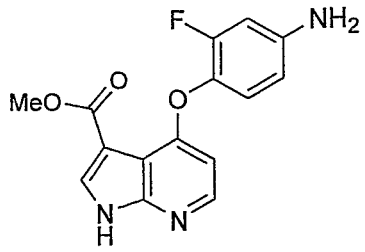
EXAMPLE 310



Methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

A) Methyl 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

To a solution of 2,2,2-trichloro-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (490 mg, 1.17 mmol, See: Step A of Example 270) in a mixed solvent (10 mL of MeOH and 10 mL of THF) was added 1 N NaOH (10 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 h, and diluted with EtOAc (30 mL). The organic layer was washed with sat. aq. $NaHCO_3$, solution, dried and concentrated *in vacuo* to give the desired product (235 mg, 61%) as a light brown solid. MS(ESI$^+$) m/z 332.2 $(M + H)^+$.



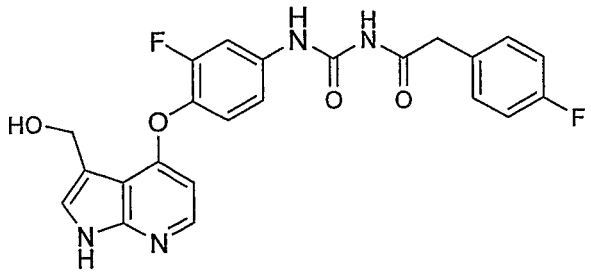
B) Methyl 4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

To a solution of methyl 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (230 mg, 0.69 mmol) in a mixed solvent (10 mL of MeOH and 10 mL of THF) were added ammonium chloride (185 mg, 3.45 mmol) and zinc dust (226 mg, 3.45 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (50 ml), and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the desired product (207 mg, 100%) as a yellow solid. MS(ESI$^+$) *m/z* 302.2 $(M + H)^+$.

C) Methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

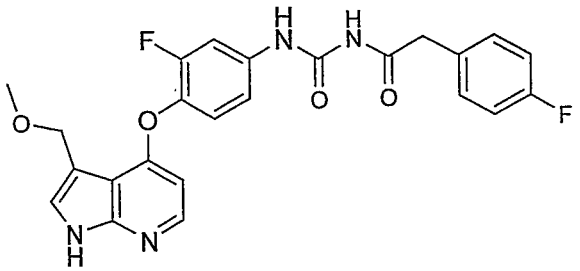
Prepared in a similar manner as Step C of Example 132 (61 mg, 36%). ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.54 (s, 1H), 8.15 (s, 1H), 8.14 (d, 1H, J = 5.5 Hz), 7.74 (dd, 1H, J = 12.5, 2.2 Hz), 7.31-7.36 (m, 3H), 7.14-7.19 (m, 3H), 6.45 (d, 1H, J = 5.5 Hz), 3.73 (s, 2H), 3.69 (s, 3H). MS(ESI$^+$) *m/z* 481.1 $(M + H)^+$.

EXAMPLE 311



1-(3-Fluoro-4-(3-(hydroxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

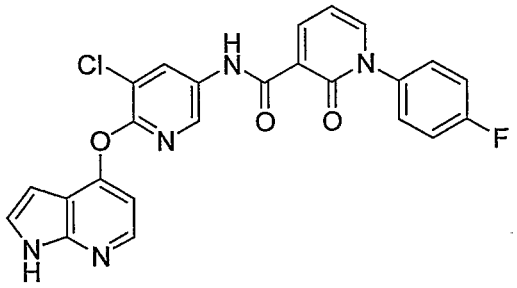
EXAMPLE 312



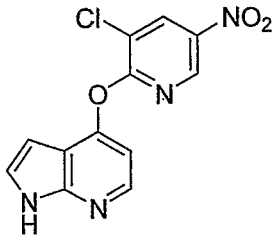
1-(3-Fluoro-4-(3-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido) phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (19.2 mg, 0.04 mmol, Compound C of Example 310) in THF (1 mL) at 0 °C was added DIBAL-H (1.5 M soln in toluene, 133 μL, 0.2 mmol, Aldrich). The reaction mixture was stirred at 0 °C for 2 h, and quenched by adding 2 mL of methanol. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC. The desired fractions were combined, concentrated *in vacuo* and lyophilized to give a white solid. LC/MS indicated that the solid contained two compounds. The solid was purified again by flash column chromatography (ISCO RediSep® silica gel cartridge, eluting with 1-10% MeOH in dichloromethane) to afford Examples 311 and 312. For 1-(3-fluoro-4-(3-(hydroxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 311, 7.47 mg, 42%): ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 10.94 (s, 1H), 10.49 (s, 1H), 7.92 (d, 1H, J = 5.5 Hz), 7.68 (dd, 1H, J = 13.2, 2.2 Hz), 7.31-7.19 (m, 5H), 7.09 (t, 2H, J = 8.8 Hz), 6.10 (d, 1H, J = 5.5 Hz), 4.68 (q, 1H, J = 5.5 Hz), 4.65 (d, 1H, J = 5.5 Hz),3.67 (s, 2H); MS(ESI$^+$) *m/z* 453.3 $(M + H)^+$. For 1-(3-Fluoro-4-(3-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 312): ^{1}H NMR (DMSO-d_6) δ 11.67 (s, 1H), 10.97 (s, 1H), 10.64 (s, 1H), 7.96 (d, 1H, J = 5.5 Hz), 7.68 (d, 1H, J = 12.5), 7.34-7.28 (m, 5H), 7.23 (t, 1H, J = 8.8 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.16 (d, 1H, J = 5.5 Hz), 4.54 (s. 2H), 3.70 (s, 2H), 3.18 (s, 3H); MS(ESI$^+$) *m/z* 467.2 $(M + H)^+$.

EXAMPLE 313

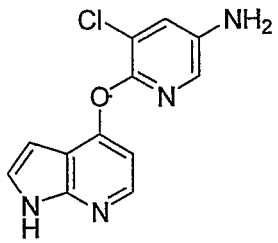


***N*-(6-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-yl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) 4-(3-Chloro-5-nitropyridin-2-yloxy)-1*H*-pyrrolo[2,3-*b*]pyridine

To a solution of 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (210 mg, 1.56 mmol, see: Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in 3 mL of MeCN was added K_2CO_3 (240 mg, 1.74 mmol). The suspension was stirred for 10 min and treated with 2,3-dichloro-5-nitropyridine (270 mg, 1.40 mmol, see: Koch, V. and Schnatterer, S. *Synthesis*, **1990**, 499). The reaction mixture was stirred for 12 h and quenched with 20 mL of H_2O. The solution was extracted with EtOAc and the organic layer was washed with brine, and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the title compound (220 mg, 54%). MS (ESI) *m/z* 291.1 $(M + H)^+$.



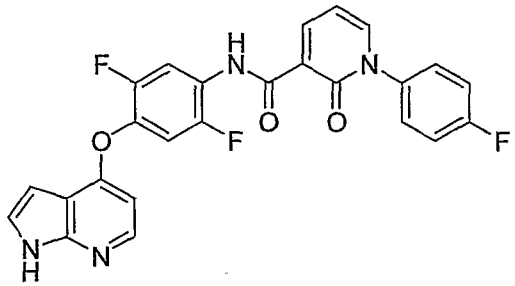
B) 6-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-amine

Following a similar procedure as described in Step B of Example 132, 4-(3-chloro-5-nitropyridin-2-yloxy)-1*H*-pyrrolo[2,3-*b*]pyridine (140 mg, 0.48 mmol) was reduced to the title compound (90 mg, 72%). MS(ESI) *m/z* 261.1 $(M + H)^+$.

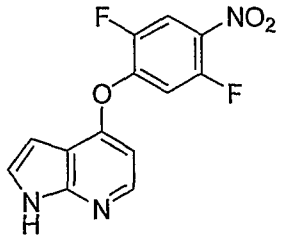
C) ***N*-(6-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-yl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

Following a similar procedure as described in Step C of Example 242, 6-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-amine, dihydrochloride (14 mg, 0.042 mmol) was converted to the title compound (5.0 mg, 20%). ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 1H), 11.86 (s, 1H), 8.67 (d, 1H, *J* = 2.0 Hz), 8.57 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.41 (d, 1H, *J* = 2.0 Hz), 8.18 (d, 1H, *J* = 5.5 Hz), 8.14 (dd, 1H, *J* = 6.5, 2.0 Hz), 7.60 (dd, 2H, *J* = 9.0, 5.0 Hz), 7.38-7.43 (m, 3H), 6.76 (d, 1H, *J* = 5.5 Hz), 6.73 (t, 1H, *J* = 7.0 Hz), 6.08 (m, 1H); MS(ESI) *m/z* 476.2 $(M + H)^+$.

EXAMPLE 314

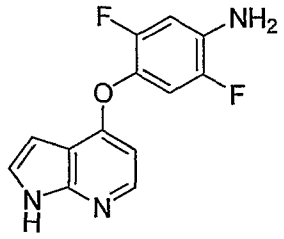


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) **4-(2,5-Difluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine**

Following a similar procedure as described in Step A of Example 313 and using 1,2,4-trifluoro-5-nitrobenzene, 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (268 mg, 2.0 mmol) was converted to the title compound (230 mg, 40%). MS(ESI) *m/z* 292.2 $(M + H)^+$.



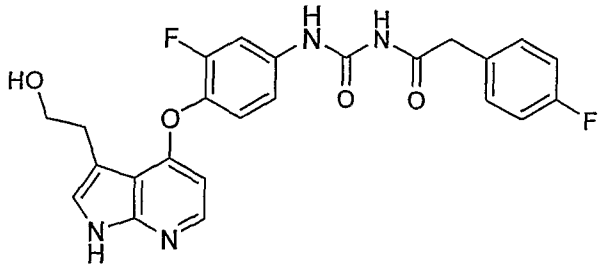
B) 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorobenzenamine

Following a similar procedure as described in Step B of Example 132, 4-(2,5-difluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (230 mg, 0.79 mmol) was converted to the title compound (34 mg, 17%). MS(ESI) *m/z* 262.2 $(M + H)^+$.

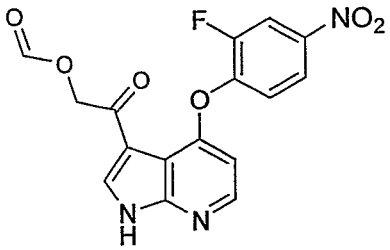
C) *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid

Following a similar procedure as described in Step C of Example 242, 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorobenzenamine, dihydrochloride (14 mg, 0.042 mmol) was converted to the title compound (4.5 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 12.42 (s, 1H), 11.86 (s, 1H), 8.61 (dd, 1H, J = 7.0, 2.0 Hz), 8.55 (dd, 1H, J = 12.5, 7.0 Hz), 8.15 (dd, 1H, J = 6.5, 2.0 Hz), 8.10 (d, 1H, J = 6.5 Hz), 7.57-7.62 (m, 3H), 7.40-7.44 (m, 3H), 6.75 (t, 1H, J = 7.0 Hz), 6.47 (d, 1H, J = 5.5 Hz), 6.29 (m, 1H); MS(ESI) *m/z* 477.2 $(M + H)^+$.

EXAMPLE 315

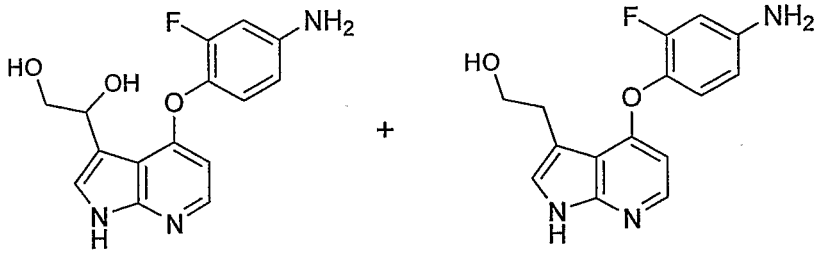


1-(3-Fluoro-4-(3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 2-(4-(2-Fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl formate

To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (100 mg, 0.25 mmol, Compound A of Example 253) in 1 mL of DMF was added sodium formate (52 mg, 0.75 mmol, Aldrich). The reaction mixture was stirred at room temperature for 4 h, and diluted with sat. aq. K_2HPO_4 (2 mL). The precipitate that formed was collected by filtration, washed with cold H_2O (2 mL) and ether (5 mL), and dried under vacuum to afford the desired product (81 mg, 90%) as a light brown solid. MS(ESI$^+$) *m/z* 360.16 $(M + H)^+$.



B) 1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol and 2-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol

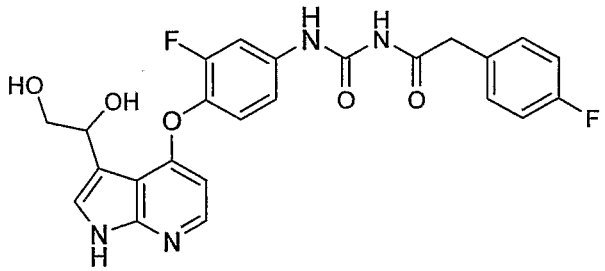
To a suspension of anhydrous aluminum hydride (266 mg, 2.0 mmol, Alfa Aesar) in 5 mL of 1,2 dimethoxyethane at 0 °C was added lithium aluminum hydride (1 M soln. in THF, 1.0 mL, 1.0 mmol). A solution of 2-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl formate (72 mg, 0.2 mmol) in 5 mL of 1,2-dimethoxyethane was added dropwise. The reaction mixture was stirred at rt for 2 h and quenched by the addition of 5 mL of cold water. The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (ISCO RediSep®

silica gel cartridge, etuting with 2-10% MeOH in dichloromethane) to give 1-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol (27 mg, 45%): MS(ESI$^+$) *m/z* 304.3(M + H)$^+$ and 2-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol (10 mg, 18%): MS(ESI$^+$) *m/z* 288.3 (M + H)$^+$.

C) 1-(3-Fluoro-4-(3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

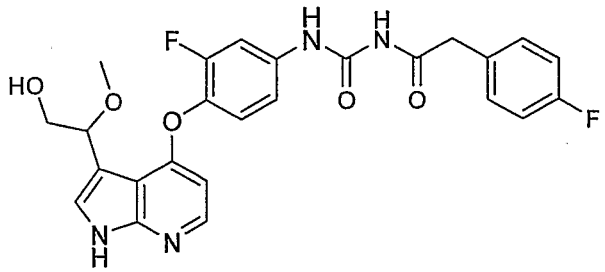
Prepared from 2-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol using a similar procedure as described for Example 264 (4.5 mg, 28%). ^{1}H NMR (CD_3OD) δ 10.74 (s, 1H), 8.06 (d, 1H, *J* = 5.5 Hz), 7.74 (d, 1H, *J* = 12.1 Hz), 7.29-7.25 (m, 4H), 7.00-6.96 (m, 3H), 6.51 (d, 1H, *J* = 5.5 Hz), 3.80 (t, 2H, *J* = 6.6 Hz), 3.62 (s, 2H), 3.06 (t, 2H, *J* = 6.6 Hz); MS(ESI$^+$) *m/z* 467.3 (M + H)$^+$.

EXAMPLE 316



1-(4-(3-(1,2-Dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

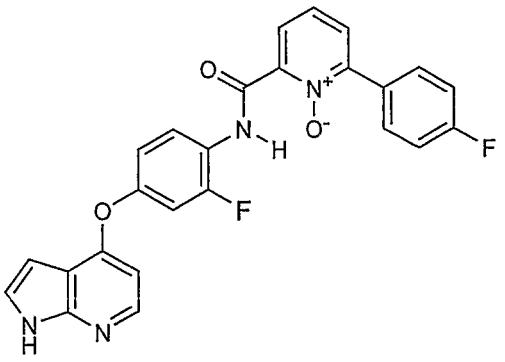
EXAMPLE 317



1-(3-Fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Examples 316 and 317 were prepared from 1-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol (see: Step B of Example 315) using a similar procedure as described for Example 264. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC. The desired fractions were combined, concentrated *in vacuo* and lyophilized to give a white solid. LC/MS indicated that the solid contained 1-(4-(3-(1,2-dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea and 1-(3-fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea. The solid was purified again by flash column chromatography (ISCO RediSep® silica gel cartridge, eluting with 1-10% MeOH in dichloromethane) to afford two products: For 1-(4-(3-(1,2-dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (6.3 mg, 16%); ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1H), 11.03 (s, 1H), 10.59 (s, 1H), 7.99 (d, 1H, J = 5.5 Hz), 7.77 (dd, 1H, J = 12.6, 2.2 Hz), 7.41-7.32 (m, 4H), 7.28 (d, 1H, J = 2.2 Hz), 7.18 (t, 1H, J = 8.8 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.15 (d, 1H, J = 5.5 Hz), 5.05 (m, 1H), 4.91 (d, 1H, J = 4.4 Hz), 4.60 (t, 1H, J = 5.8 Hz), 3.79-3.75 (m, 1H), 3.75 (s, 2H), 3.47-3.44 (m, 1H); MS(ESI$^+$) *m/z* 483.3 $(M + H)^+$. For 1-(3-fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (3.2 mg, 8%); ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 5.5 Hz), 7.71 (d, 1H, J = 12.1 Hz), 7.37 (s, 1H), 7.28-6.25 (m, 4H), 6.98 (t, 1H, J = 8.2 Hz), 6.45 (d, 1H, J = 5.5 Hz), 3.81 (m, 1H), 3.73-3.71 (m, 2H), 3.63 (s, 2H), 3.34 (s, 3H); MS(ESI$^+$) *m/z* 497.2 $(M + H)^+$.

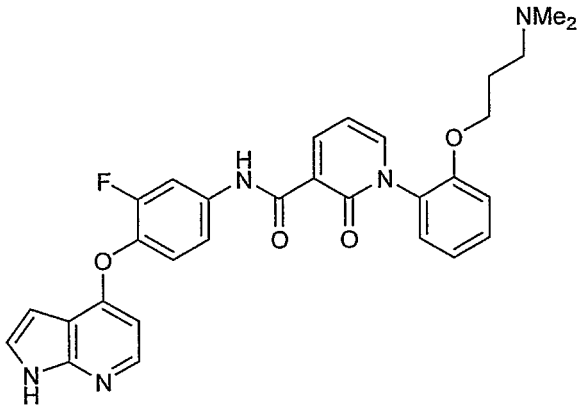
EXAMPLE 318



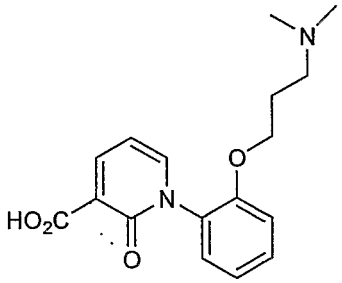
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.328 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 459.2 $(M + H)^+$.

EXAMPLE 319



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(2-(3-(dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



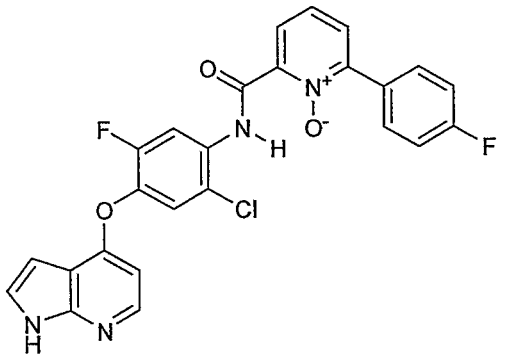
A) **1-(2-(3-(Dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid**

Prepared in a similar manner as Steps A and B of Example 242. ^{1}H NMR (DMSO-d_6) δ 10.53 (br m, 1H), 8.51-8.53 (m, 1H), 8.18-8.20 (m, 1H), 7.48-7.51 (m, 2H), 7.30 (d, 1H, J = 7.96 Hz), 7.13-7.17 (m, 1H), 6.82 (t, 1H, J = 6.95 Hz), 4.11-4.18 (m, 2H), 2.66-2.68 (m, 2H), 2.67 (s, 6H), 1.98-2.05(m, 2H); HRMS(ESI), calculated: 317.1501, found: 317.1490.

B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(2-(3-(dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

Prepared in a similar manner as Step C of Example 242. ^{1}H NMR (CD_3OD) δ 8.62-8.65 (m, 1H), 8.23 (d, 1H, J = 6.90 Hz), 7.98-8.01 (m, 1H), 7.83-7.85 (m, 1H), 7.39-7.50 (m, 2H), 7.31-7.49 (m, 3H), 7.20 (d, 1H, J = 7.93), 7.10-7.13 (m, 1H), 6.80 (d, 1H, J = 6.72 Hz), 6.69 (t, 1H, J = 6.75 Hz), 6.59-6.60 (m, 1H), 4.12 (t, 2H, J = 5.61 Hz), 3.02-3.06 (m, 2H), 2.70 (s, 6H), 2.03-2.04 (m, 2H); HRMS(ESI), calculated: 542.2204, found: 542.2194.

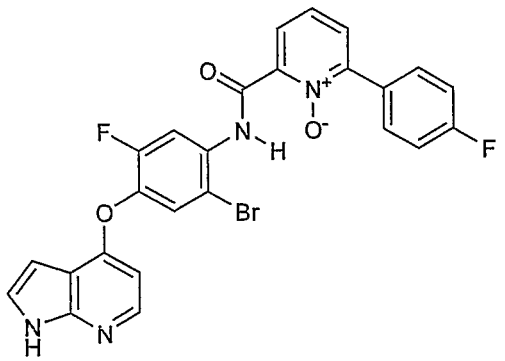
EXAMPLE 320



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-chloro-5-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.293 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

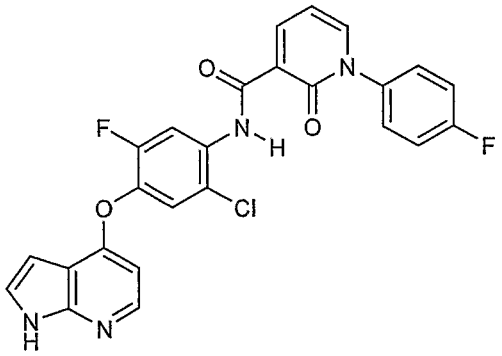
EXAMPLE 321



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-bromo-5-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.371 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 537 $(M + H)^+$.

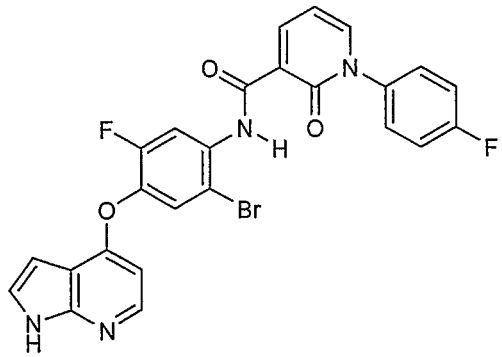
EXAMPLE 322



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chloro-5-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.070 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

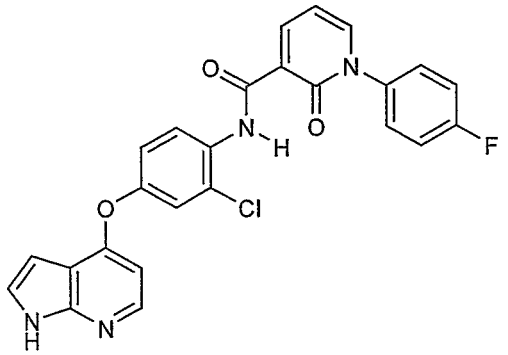
EXAMPLE 323



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-bromo-5-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.115 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 538 $(M + H)^+$.

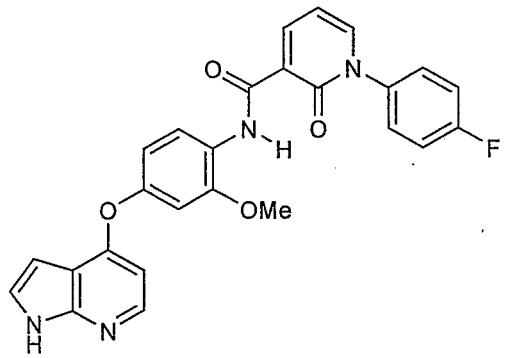
EXAMPLE 324



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chlorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.946 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 475 $(M + H)^+$.

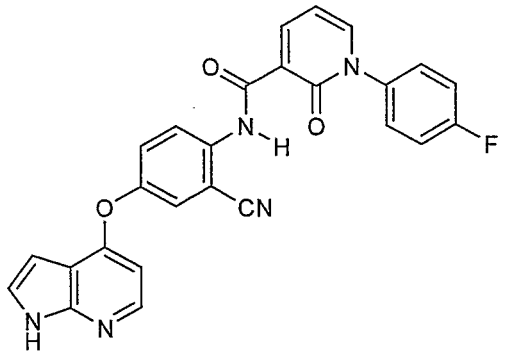
EXAMPLE 325



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-methoxyphenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.795 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 471 $(M + H)^+$.

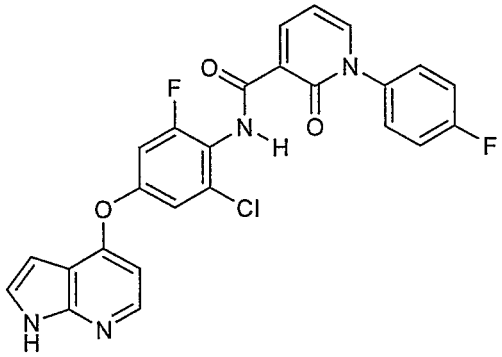
EXAMPLE 326



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-cyanophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.618 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 466 $(M + H)^+$.

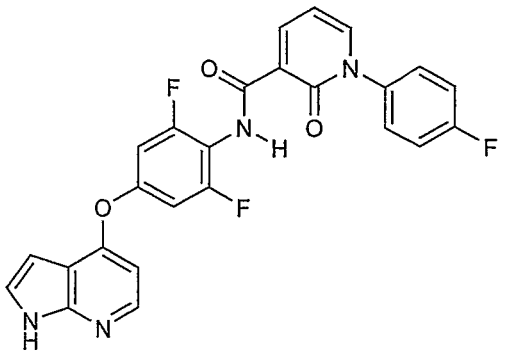
EXAMPLE 327



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chloro-6-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.805 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

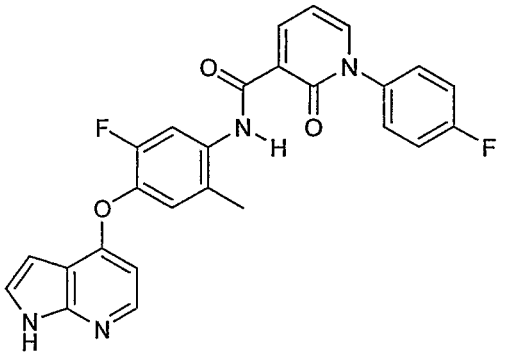
EXAMPLE 328



N-(4-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-2,6-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.653 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 477 $(M + H)^+$.

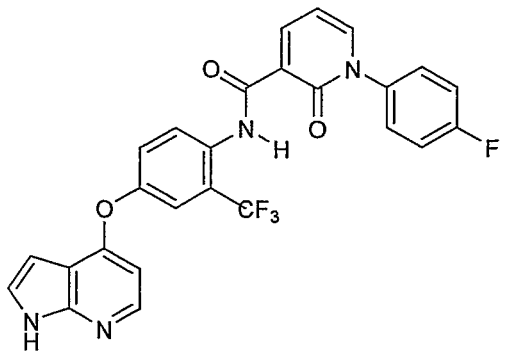
EXAMPLE 329



N-(4-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-2-methyl-4-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.010 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 473 $(M + H)^+$.

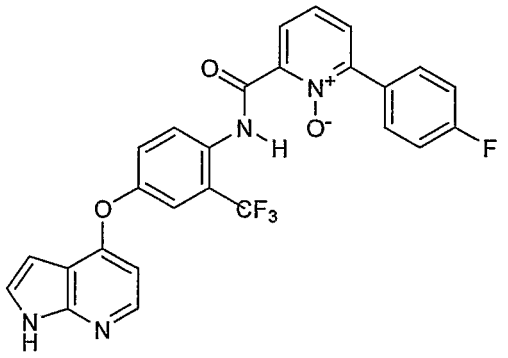
EXAMPLE 330



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-trifluoromethyl-phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.943 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 509 $(M + H)^+$.

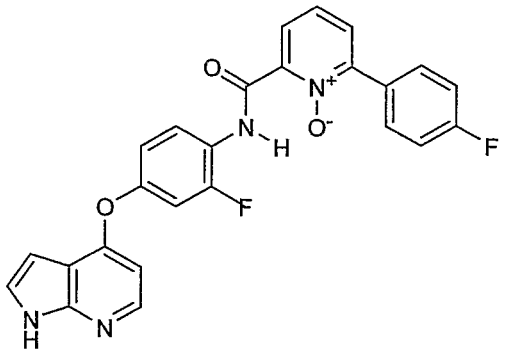
EXAMPLE 331



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-trifluoromethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.205 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 509 $(M + H)^+$.

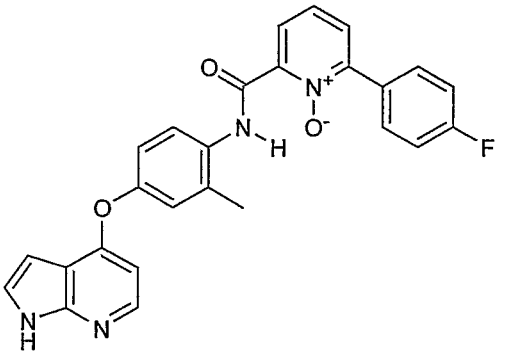
EXAMPLE 332



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 1.103 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% H_3PO_4, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 459 $(M + H)^+$.

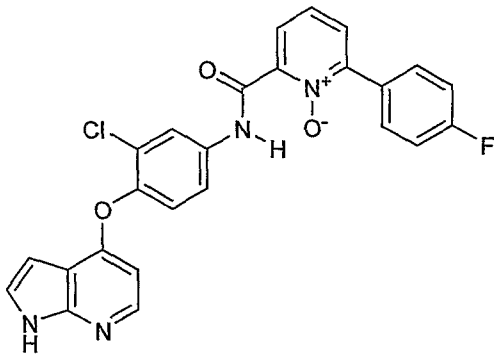
EXAMPLE 333



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.120 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 455 $(M + H)^+$.

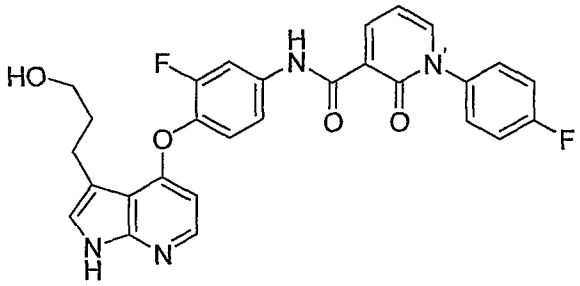
EXAMPLE 334



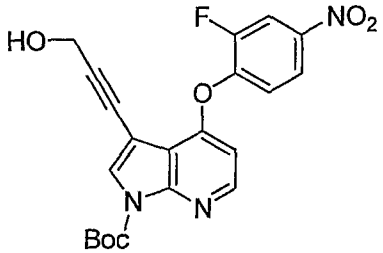
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [5-chloro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.200 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 475 $(M + H)^+$.

EXAMPLE 335



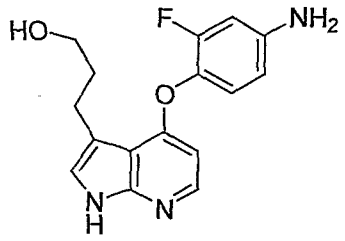
***N*-(3-Fluoro-4-(3-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) ***tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-(3-hydroxyprop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate**

A stream of Ar was bubbled through a mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (400 mg, 0.8 mmol,

Compound B of Example 283), propargyl alcohol (90 mg, 1.6 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (66 mg, 0.08 mmol), and CuI (40 mg) in triethylamine (0.8 mL) and THF (6 mL) for 5 min. The reaction mixture was sealed in a tube and heated at 75 °C for 1h. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 30% EtOAc/ CH_2Cl_2) to afford the desired product (220 mg, 64% yield) as a yellow solid. LC/MS (ESI^+) *m/z* 428 $(M + H)^+$.



B) 3-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)propan-1-ol

A mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-(3-hydroxyprop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (50 mg, 0.15 mmol) and 10% Pd/C (containing 50% H_2O, 120 mg) in THF (10 mL) and MeOH (2 mL) was hydrogenated at 1 atm for 5 h. The mixture was diluted with MeOH and filtered through a pad of Celite®. The crude mixture was purified by preparative HPLC to afford the desired product (6 mg, 13% yield) as a white solid. LC/MS (ESI^+) *m/z* 302 $(M + H)^+$.

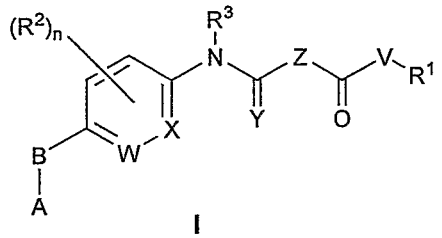
C) *N*-(3-Fluoro-4-(3-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

To a stirred mixture of 3-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)propan-1-ol (5 mg, 0.0166 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (5.8 mg, 0.025 mmol, Compound B of Example 242), and HATU (Perseptive Biosystems, 10 mg, 0.025 mmol) in DMF (0.5 mL), was added DIPEA (0.1 mL). The reaction mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title

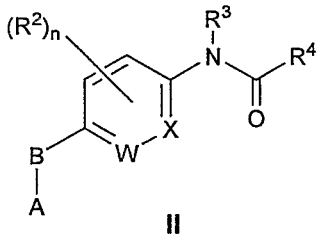
compound (6 mg, HCl salt, 66% yield) as a white solid. ^{1}H NMR (CD_3OD) δ 8.71 (dd, 1H, J = 7.2, 2.0 Hz), 8.22 (d, 1H, J = 6.8 Hz), 8.10 (dd, 1H, J = 12.4, 2.0 Hz), 8.00 (dd, 1H, J = 6.4, 2.0 Hz), 7.25-7.60 (m, 7H), 7.70-7.80 (m, 2H), 3.64 (t, 2H, J = 6.4 Hz), 3.05 (t, 2H, J = 7.2 Hz), 2.00 (m, 2H); LC/MS (ESI^+) *m/z* 517 $(M + H)^+$.

WE CLAIM:

1. A compound having the formula I or II



I



II

including pharmaceutically acceptable salts thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_p-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

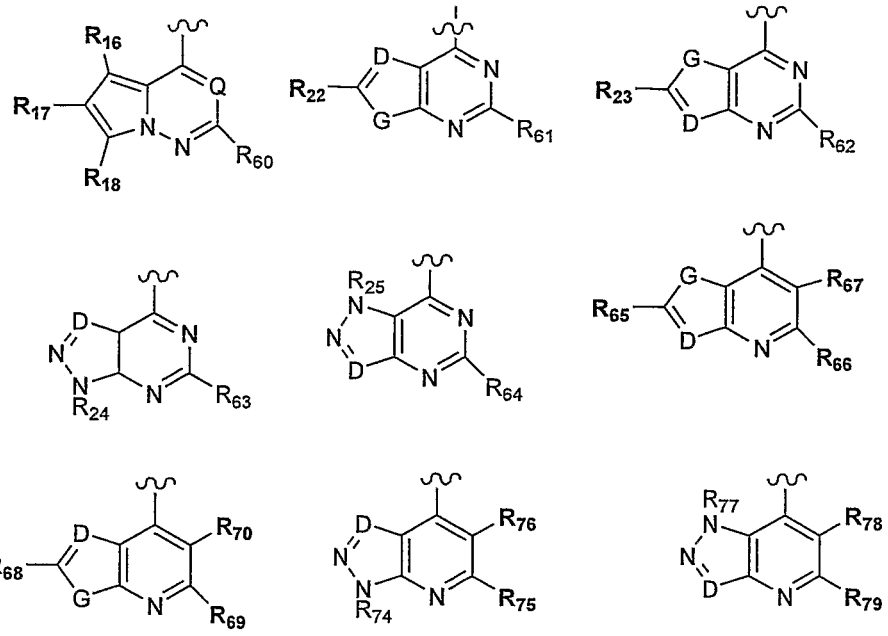
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

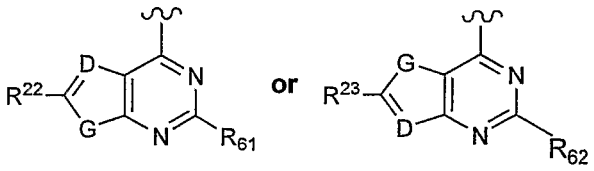
A is:



Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_lR^{41}$; $-CONH(CH_2)_lR^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

$R^{21}$and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

2. The compound according to claim 1 wherein R^1 is an optionally substituted $C_1$to C_6 alkyl, alkenyl, alkynyl, optionally substituted C_3 to C_7 cycloalkyl, C_3 to C_7 heterocycloalkyl, optionally substituted phenyl, optionally substituted biphenyl, or a C_5 to C_{11} optionally substituted monocyclic or bicyclic heteroaryl.

3. The compound according to claim 2 wherein R^1 is selected from the group consisting of phenyl, optionally substituted with Cl, F, OCH_3, alkyl, alkenyl,

alkynyl, hydroxy, cyano, amido, phenoxy, CH_2CN, benzyl, $NHCO_2CH_3$; biphenyl, pyridyl, azepanyl, pyrazolyl, thiazolyl, indolyl, indazolyl, indenyl, cyclopropyl, isopropyl, phenylethyl, aminoalkyl, benzyl, amidoalkyl, morpholine, or furanylmethyl.

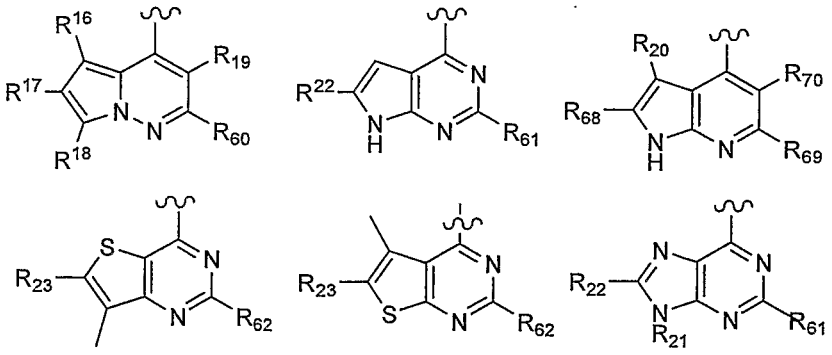
4. The compound according to claim 1 wherein R^2 is H, methyl, alkoxy, halo, haloalkyl, or cyano.

5. The compound according to claim 1 wherein R^4 is an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted pyrrolidinyl, an optionally substituted pyridyl-N-oxy, or an optionally substituted pyridinone.

6. The compound according to claim 5 wherein said phenyl, pyridyl, pyridinone, or N-oxy pyridyl is substituted with hydroxyl, halo, C_1 to C_4alkyl, C_3 to C_7 cycloalkyl, $-COCH_3$, alkoxy, amino, heterocycloalkyl, aminoalkylamino, cyano, alkylthio, phenyl or alkylaminoalkoxy.

7. The compound according to claim 6 wherein said substituent is F, Br, Cl, methyl, pentyl, methoxy, phenyl, morpholinyl, NH_2, or $NHCHNH_2$.

8. The compound according to claim 1 wherein A is

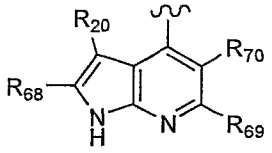


9. The compound according to claim 8 wherein R^{19} is H or CN; R^{16} and R^{17} are independently H, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, or $-C(O)_2R^{29}$ wherein R^{29} is C_1 to C_4 alkyl; and R^{18} is H.

10. The compound according to claim 8 wherein $R^{22}$and R^{61} are H.

11. The compound according to claim 8 wherein R^{68}, R^{69} and R^{70} are H; R^{20} is C_1 to C_4 alkyl; alkenyl;, alkynyl; C_5 to C_6 heterocycloaryl; $CO(CH_2)_1R^{41}$, and R^{41} is C_1 to C_4 alkyl, haloalkyl, amino, alkylamino, C_5 to C_7 heterocycloalkyl, or C_5 to C_7 heteroaryl; $C(O)_2R^{29}$ wherein R^{29} is ethyl; CN; alkoxy; phenylmethyl; alkylaminoalkynyl; alkylaminoalkyl, hydroxyalkyl; or methoxyalkyl.

12. The compound according to claim 8 wherein A is



13. The compound according to claim 1 wherein Y is O or S.

14. The compound according to claim 1 wherein B is O.

15. The compound according to claim 1 wherein Z is $-CR^{13}R^{14}$ or NR^{15}wherein R^{13}, R^{14}, and R^{15} are each H or R^{13} and R^{14} together with the carbon to which they are attached form a cyclopropyl.

16. The compound according to claim 1 wherein R^4 is phenyl.

17. The compound according to claim 1 wherein R^4 is pyridyl.

18. The compound according to claim 1 wherein R^4 is pyrrolidinyl.

19. The compound according to claim 1 wherein R^4 is pyridyl-N-oxy.

20. The compound according to claim 1 wherein R^4 is pyridinone.

21. The compound according to claim 12 wherein R^{20} is $-COCH_2$-R, wherein R is amino, pyrrolidine, or piperazine.

22. The compound according to claim 12 wherein R^{20} is pyridine or thiazole.

23. The compound according to claim 12 wherein R^{20} is is $-COC(Cl)_3$, or $CONHCH_2$pyridine.

24. The compound according to claim 12 wherein R^{20} is CH_2piperidine, CH_2phenyl, -C≡C-amino, cyano, $-CO_2CH_3$, $-CH_2OH$, CH_2OMe, hydroxyethyl,-$CHOH(CH_2)_2OH$, or $CH(OCH_3)CH_3$.

25. The compound according to claim 1 having an IC50 value of less than about 5 μM.

26. The compound according to claim 1 having an IC50 value of less than about 1 μM.

27. A method for treating cancer comprising administering to a patient in need thereof, a pharmaceutically effective amount of a compound having the formula I or II according to claim 1.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

29. The method of claim 18, further comprising administering to said patient at least one other anticancer agent.