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CA 2718123 C 2017/08/22

(11)(21) 2 718 123

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2009/03/17
(87) Date publication PCT/PCT Publication Date: 2009/09/24
(45) Date de délivrance/Issue Date: 2017/08/22
(85) Entrée phase nationale/National Entry: 2010/09/09
(86) N° demande PCT/PCT Application No.: US 2009/001659
(87) N° publication PCT/PCT Publication No.: 2009/117080
(30) Priorités/Priorities: 2008/03/17 (US61/069,763);
2008/10/31 (US61/110,508)

(51) Cl.Int./Int.Cl. *C07D 413/12* (2006.01),
A61K 31/517 (2006.01), *A61P 35/00* (2006.01),
C07D 239/88 (2006.01), *C07D 239/93* (2006.01),
C07D 413/14 (2006.01)

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(54) Titre : COMPOSES QUINAZOLINE UTILES EN TANT QUE DE MODULATEURS DES KINASES RAF ET METHODES D'UTILISATION DE CES DERNIERS

(54) Title: QUINAZOLINE DERIVATIVES AS RAF KINASE MODULATORS AND METHODS OF USE THEREOF

(57) Abrégé/Abstract:
Compounds according to formula (I), compositions and methods are provided for modulating the activity of RAF kinases, including BRAF kinase and for the treatment, prevention, or amelioration of one or more symptoms of disease or disorder mediated by RAF kinases. Formula (I): or a pharmaceutically acceptable salt, solvate, clathrate of hydrate thereof, wherein X is O or $S(O)_t$; R^a is O or S.

CA 2718123 C 2017/08/22

(11)(21) **2 718 123**

(13) **C**

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 September 2009 (24.09.2009)

PCT

(10) International Publication Number
WO 2009/117080 A8

(51) International Patent Classification:
C07D 239/88 (2006.01) *A61K 31/517* (2006.01)
C07D 239/93 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2009/001659

(22) International Filing Date:
17 March 2009 (17.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/069,763 17 March 2008 (17.03.2008) US
61/110,508 31 October 2008 (31.10.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

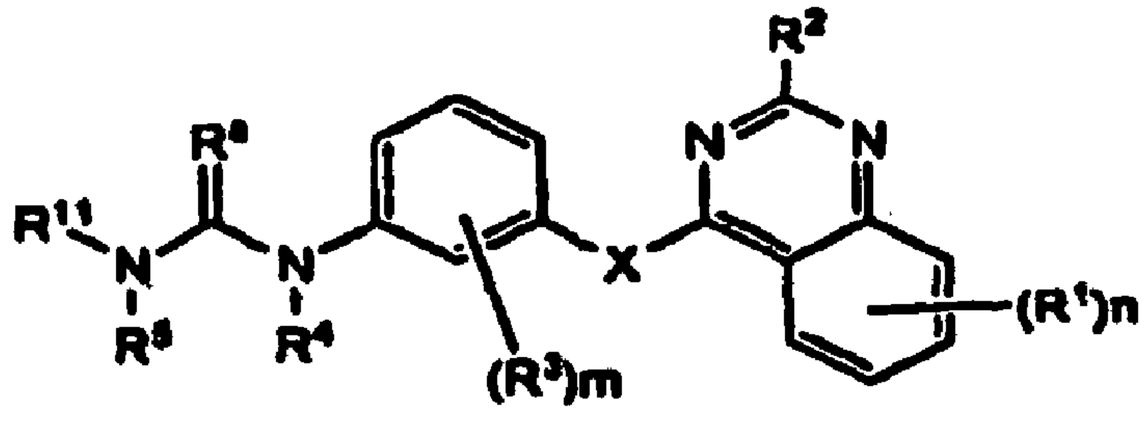
Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
4 November 2010

(15) Information about Correction:
see Notice of 4 November 2010

(54) Title: QUINAZOLINE DERIVATIVES AS RAF KINASE MODULATORS AND METHODS OF USE THEREOF



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WO 2009/117080 A8

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JUMBO APPLICATIONS / PATENTS

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QUINAZOLINE DERIVATIVES AS RAF KINASE MODULATORS AND METHODS OF USE THEREOF

FIELD

[0002] Provided herein are compounds that are modulators of RAF kinases, including BRAF kinase, compositions comprising the compounds and methods of use thereof. The compounds provided are useful in the treatment, prevention, or amelioration of a disease or disorder related to RAF, including BRAF kinase, activity or one or more symptoms thereof.

BACKGROUND

[0003] Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxyl groups on tyrosine, serine or threonine residues of proteins. Protein kinases act primarily as growth factor receptors and play a central role in signal transduction pathways regulating a number of cellular functions, such as cell cycle, cell growth, cell differentiation and cell death.

[0004] One important signal transduction pathway is the mitogen-activated protein kinase (MAPK) pathway. The MAPK signaling pathway is responsible for the regulation of cell growth, differentiation, proliferation and survival and its dysregulation is implicated in a broad spectrum of cancer. (Hoshino, *et al.*, *Oncogene*,**1999,** *18*, 813-822)

[0005] The MAPK signaling pathway is one of multiple signaling pathways activated by GTP-bound RAS. Initially, extracellular stimuli such as mitogens, hormones or neurotransmitters induce receptor tyrosine kinase dimerization leading to increased levels of GTP-bound RAS. Activated RAS recruits dimerized RAF kinase to the plasma membrane whereby RAF is activated by autophosphorylation or phosphorylation by other kinases. The activation of RAF initiates the phosphorylation cascade down the MEK/ERK pathway, in which activated RAF phosphorylates and activates MEK1/2 which in turn phosphorylates and activates ERK (or extracellular signal-regulated kinase, also called p44/42 MAPK) which in

turn phosphorylates a number of targets including nuclear transcription factors that lead to changes in gene expression.

[0006] RAF is a family of serine/threonine kinases comprising three isoforms called ARAF, BRAF and CRAF (also called raf-1). BRAF is currently a cancer therapeutic target, as mutations in the BRAF gene are among the most common in cancer (Haluska, et al., Clin Cancer Res **2006,** *12(7 Pt 2)*, 2301s-2307s; Ikediobi, ,et al., *Mol. Cancer Ther.* **2006** *5(11),* 2606-2612; Greenman, et al., *Nature* **2007** *226(7132)*, 153-158). The majority of mutant BRAF have been found to exhibit elevated kinase activity as measured by levels of phosphorylated MEK or ERK found endogenously in COS cells (Wan *et al. Cell* **2004** *116*, 855-867). BRAF mutations have been identified in about 7% of all known cancers, including 27-70% of melanoma (Davies et al. *Nature*, **2002** *417*, 949-954), 42-50% of papillary thyroid carcinoma, 36-53% colorectal cancers, and 5-22% serous ovarian cancers and to a lesser extent in breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, Barret's adenocarcinoma, gliomas including ependymomas and lung cancer including 1-2% of non small cell lung cancer (See Davies *et al. Nature*, **2002**, *417*, 949-954; Garnett and Marais, *Cancer Cell*, **2004** *6*, 313-319; Ouyang *et al. Clin Cancer Res* **2006** *12(6)*, 1785-1793; Melillo, *et al., J. Clin. Invest.* **2005,** *115,* 1068-1081; Wilhelm, *et al., Nat. Rev. Drug Discov.,* **2006** *5*, 835-844; and Ji *et al. Cancer Res* **2007** *67(10)*, 4933-4939). Over forty different missense mutations of BRAF have been identified, but among them, the V600E mutation, has been found to be the most predominant (Fecher, *et al., J. Clin. Oncology* **2007**, *25(12)*,1606-1620), accounting for nearly 90% of the mutations in melanoma and thyroid cancer and for a high proportion in colorectal cancer, which makes this mutation a particularly attractive target for molecular therapy. A study of the crystal structures of both wild type and V600 mutants suggests that substitution at the 600 position destabilizes the inactive conformation of the enzyme (Wan *et al. op cit.*). However, V600E mutation is comparatively rare in non-small cell lung cancer, which is more likely than not to be associated with non-V600E BRAF missense mutations (Brose et al. *Cancer Res.*, **2002** *62*, 6997-7000). Other non-V600E BRAF missense mutations are also implicated in melanoma, breast cancer, lung cancer, colorectal cancer, liver cancer, ovarian cancer, leukemia including acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma, Barret's adenocarcinoma, endometrial cancer, liver cancer, stomach cancer, thyroid cancer and endometrial cancer (Garnett and Marais, *op. cit.*).

[0007] *In vivo* efficacy has been demonstrated for BRAF inhibitors NVP-AAL881-NX (also AAL881) and NVP-L T613-AG-8 (LBT613) in mouse tumor xenograft models using human cell lines (*See*, Ouyang *et al. op. cit.*). Preclinical studies have also shown that BRAF inhibition by siRNA or by the small molecule RAF kinase inhibitor Sorafenib resulted in a decrease in tumor growth or metastases in animals (Sharma *et al. Cancer Res.*, **2005**, *65(6),* 2412-2421; Sharma *et al. Cancer Res.*, **2006**, *(66)16, 8200-8209).* RAF inhibitors that have entered clinical trials include antisense oligonucleotides against CRAF such as ISIS 5132 and LErafAON and small molecule BRAF inhibitors such as BAY 43-9006 (Sorafenib), Raf-265 (formerly CHIR-265, Novartis), PLX-4032 (Plexxikon) and XL281 (Exelixis).

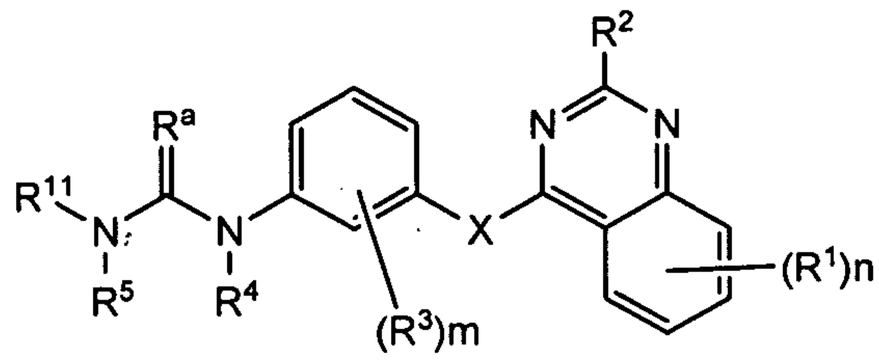
[0008] Although most BRAF mutations are activating mutations, mutants having impaired kinase activity have been identified, and shown to stimulate ERK activity, presumably through recruitment of CRAF (Wan *op cit.*). Therefore, CRAF represents another target for the treatment of diseases associated with this particular subset of BRAF mutants.

[0009] Outside of cancer, the MAPK (Raf-Mek-Erk) signaling pathway could provide targets for inflammation and inflammatory diseases. The MAPK pathway is known to control cell survival and apoptosis of inflammatory cells such as basophils, macrophages, neutrophils and monocytes (See Dong et al., *Annu. Rev. Immunol.*, **2002**, *20*, 55-72; Johnson, *et al.*, *Curr. Opin. Chem. Biol.*, **2005**, *9*, 325-331; R. Herrera and J. S. Sebolt-Leopold, *Trends Mol. Med.*, **2002**, *8*, S27-S3; and Kyriakis *et al.*, *Physiol. Rev.*, **2002**, *81*, 807-869). In the carrageenan-induced pleurisy rat model, it has been shown that the Erk1/2 inhibitor PD98059 inhibits eosinophilic proinflammtory cytokine release by increasing the rate of neutrophil apoptosis thereby decreasing the number of macrophage and neutrophils that perpetuate the inflammatory response (Sawatzky *et al.*, *Am J Pathol* **2006,** *168(1)*, 33-41). It is therefore possible that one downstream effect of inhibiting RAF might be the resolution of an inflammatory response and BRAF inhibitors could be useful for the treatment of inflammatory diseases or immune system disorders including inflammatory bowel disease, Crohn's disease, ulcerative colitis, systemic lupus erythematosis (SLE), rheumatoid arthritis, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, asthma, COPD (chronic obstructive pulmonary disease) (See Stanton *et al. Dev. Biol.* **2003** *263*,165-175, Hofman *et al.* Curr. *Drug Targets. Inflamm. Allergy* **2004** *2*,1-9).

[0010] Given the multitude of diseases attributed to the dysregulation of MAPK signaling, there is an ever-existing need to provide novel classes of compounds that are useful as inhibitors of enzymes in the MAPK signaling pathway, as discussed herein.

SUMMARY

[0011] Provided herein are compounds of formula I. In one embodiment, compounds provided herein have activity as modulators of RAF kinase, including BRAF kinase. The compounds are useful in medical treatment, pharmaceutical compositions and methods for modulating the activity of RAF kinase, including BRAF kinase such as wildtype and/or mutated forms of BRAF kinase. In one embodiment, the compounds have formula (I):



I

or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein

[0012] X is O, $S(O)_t$;

[0013] R^a is O or S;

[0014] R^1 is selected as follows:

i) each R^1 is independently selected from a group consisting of halo, nitro, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(NR^7)N(R^7)_2$, $-R^6C(O)N(R^7)R^9N(R^7)_2$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$, $-R^6S(O)_tN(R^7)_2$, $-R^6S(O)_tN(R^7)N(R^7)_2$, $-R^6S(O)_tN(R^7)N{=}C(R^7)_2$, $-R^6S(O)_tN(R^7)C(O)R^8$, $-R^6S(O)_tN(R^7)C(O)N(R^7)_2$, $-R^6S(O)_tN(R^7)C(NR^7)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$, $-R^6N(R^7)C(O)R^8$, $-R^6N(R^7)C(O)OR^8$, $-R^6N(R^7)C(O)N(R^7)_2$, $-R^6N(R^7)C(NR^7)N(R^7)_2$, $-R^6N(R^7)C(S)N(R^7)_2$, and $-R^6N(R^7)S(O)_tR^8$, or

[0015] ii) any two adjacent R^1 groups together form an alkylenedioxy group;

[0016] each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

[0017] each R^7 is independently selected from (i) or (ii) below:

[0018] (i) each R^7 is selected from a group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

[0019] (ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

[0020] each R^8 is independently selected from a group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl;

[0021] each R^9 is independently an alkylene chain or an alkenylene chain;

[0022] R^2 is hydrogen, halo, alkyl, amino or alkylamino;

[0023] R^3 is halo or alkyl;

[0024] R^4 and R^5 are each independently selected as follows:

[0025] a) R^4 and R^5 are each independently hydrogen or alkyl, or

[0026] b) R^4 and R^5, together with the N atom to which they are attached, form an oxo-substituted heterocyclyl;

[0027] R^{11} is aryl, heteroaryl or heterocyclyl;

[0028] m is an integer from 0 to 4;

[0029] n is an integer from 0 to 4;

[0030] t is an integer from 0 to 2; and

[0031] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally subtituted with one or more substituents independently selected from Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_tR^w$, $-R^uN(R^x)$ $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[0032] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[0033] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy, hydroxyl, oxo or cyano,

[0034] each R^u is independently alkylene or a direct bond;

[0035] each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,-OR^x or -$N(R^y)(R^z)$;

[0036] R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[0037] each R^x is independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[0038] each R^y and R^z is independently selected from (i) or (ii) below:

[0039] (i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, or

[0040] (ii) R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl; and

[0041] J is O, NR^x or S.

[0042] In one embodiment, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I). In one embodiment, the compound provided herein is a solvate of the compound of formula (I). In one embodiment, the compound provided herein is a hydrate of compound of formula (I).

[0043] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates, and hydrates thereof, and optionally comprising at least one pharmaceutical carrier.

[0044] Such pharmaceutical compositions deliver amounts effective for the treatment, prevention, or amelioration of diseases or disorders that are modulated or otherwise affected by RAF kinases, including BRAF kinase, or one or more

symptoms or causes thereof. Such diseases or disorders include without limitation: cancers, including melanoma, papillary thyroid carcinoma, colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, Barret's adenocarcinoma, glioma (including ependymoma), lung cancer (including small cell lung cancer and non small cell lung cancer), head and neck cancer, acute lymphoblastic leukemia and non-Hodgkin's lymphoma; and inflammatory diseases or immune system disorders, including inflammatory bowel disease, Crohn's disease, ulcerative colitis, systemic lupus erythematosis (SLE), rheumatoid arthritis, multiple sclerosis (MS), thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, asthma, and chronic obstructive pulmonary disease (COPD).

[0045] Also provided herein are combination therapies using one or more compounds or compositions provided herein, or or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, in combination with other pharmaceutically active agents for the treatment of the diseases and disorders described herein.

[0046] In one embodiment, such additional pharmaceutical agents include one or more chemotherapeutic agents, anti-proliferative agents, anti-inflammatory agents, immunomodulatory agents or immunosuppressive agents.

[0047] The compounds or compositions provided herein, or or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

[0048] In certain embodiments, provided herein are methods of treating, preventing or ameliorating a disease or disorder that is modulated or otherwise affected by RAF kinases, including BRAF kinase such as wild type and/or mutant BRAF kinase, or one or more symptoms or causes thereof. In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application are administered to an individual exhibiting the symptoms of the disease or disorder to be treated. The amounts are effective to ameliorate or eliminate one or more symptoms of the disease or disorder.

[0049] Further provided is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (e.g., separately, sequentially or concurrently), or the like.

[0050] These and other aspects of the subject matter described herein will become evident upon reference to the following detailed description.

DETAILED DESCRIPTION

[0051] Provided herein are compounds of formula (I) that have activity as RAF kinase, including BRAF kinase, modulators. Further provided are methods of treating, preventing or ameliorating diseases that are modulated by RAF kinases, including BRAF kinase, and pharmaceutical compositions and dosage forms useful for such methods. The methods and compositions are described in detail in the sections below.

A. DEFINITIONS

[0052] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0053] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

[0054] "Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to ten carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

[0055] "Alkynyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms, and which is attached to the rest of the molecule

by a single bond or a triple bond, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl and the like.

[0056] "Alkylene" and "alkylene chain" refer to a straight or branched divalent hydrocarbon chain consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene and the like. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

[0057] "Alkenylene" or "alkenylene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to eight carbon atoms, wherein the unsaturation is present only as double bonds and wherein the double bond can exist between any two carbon atoms in the chain, *e.g.*, ethenylene, prop-1-enylene, but-2-enylene and the like. The alkenylene chain may be attached to the rest of the molecule through any two carbons within the chain.

[0058] "Alkoxy" refers to the radical having the formula -OR wherein R is alkyl or haloalkyl. An "optionally substituted alkoxy" refers to the radical having the formula -OR wherein R is an optionally substituted alkyl as defined herein.

[0059] "Alkynylene" or "alkynylene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to eight carbon atoms, wherein the unsaturation is present only as triple bonds and wherein the triple bond can exist between any two carbon atoms in the chain, *e.g.*, ethynylene, prop-1-ynylene, but-2-ynylene, pent-1-ynylene, pent-3-ynylene and the like. The alkynylene chain may be attached to the rest of the molecule through any two carbons within the chain.

[0060] "Amino" refers to a radical having the formula -NR'R'' wherein R' and R'' are each independently hydrogen, alkyl or haloalkyl. An "optionally substituted amino" refers to a radical having the formula –NR'R'' wherein one or both of R' and R'' are optionally substituted alkyl as defined herein.

[0061] "Aryl" refers to a radical of carbocylic ring system, including monocyclic, bicyclic, tricyclic, tetracyclic C_6-C_{18} ring systems, wherein at least one of the rings is aromatic. The aryl may be fully aromatic, examples of which are phenyl, naphthyl, anthracenyl, acenaphthylenyl, azulenyl, fluorenyl, indenyl and pyrenyl. The aryl may also contain an aromatic ring in combination with a non-aromatic ring, examples of which are acenaphene, indene, and fluorene.

[0062] "Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above, substituted by R_b, an aryl radical, as defined above, *e.g.*, benzyl. Both the alkyl and aryl radicals may be optionally substituted as defined herein.

[0063] "Aralkoxy" refers to a radical of the formula $-OR_aR_b$ where $-R_aR_b$ is an aralkyl radical as defined above. Both the alkyl and aryl radicals may be optionally substituted as defined herein.

[0064] "Cycloalkyl" refers to a stable monovalent monocyclic or bicyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane and the like.

[0065] "Cycloalkylalkyl" refers to a radical of the formula $-R_aR_d$ where R_a is an alkyl radical as defined above and R_d is a cycloalkyl radical as defined above. The alkyl radical and the cylcoalkyl radical may be optionally substituted as defined herein.

[0066] "Halo", "halogen" or "halide" refers to F, Cl, Br or I.

[0067] "Haloalkyl" refers to an alkyl group, in certain embodiments, C_{1-4}alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl 1-chloro-2-fluoroethyl, 2,2-difluoroethyl, 2-fluoropropyl, 2-fluoropropan-2-yl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, 1,3-difluoro-2-methylpropyl, (trifluoromethyl)cyclopropyl and 2,2,2-trifluoro-1,1-dimethyl-ethyl.

[0068] "Haloalkenyl" refers to an alkenyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, 1-chloro-2-fluoroethenyl.

[0069] "Heterocyclyl" refers to a stable 3- to 15-membered non-aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from a group consisting of nitrogen, oxygen and sulfur. In one embodiment, the heterocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen or sulfur atoms in the heterocyclic ring system radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. The heterocyclic ring system may be

attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Exemplary heterocylic radicals include, morpholinyl, tetrahydropyranyl, piperidinyl, piperazinyl and pyrrolidinyl.

[0070] "Heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, a heterocyclyl radical as defined above which is aromatic, in certain embodiments, of about 5 to about 20 members where one or more, in one embodiment 1 to 5, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. The heteroaryl radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heteroaryl radicals include, but are not limited to: acridinyl, benzimidazolyl, benzindolyl, benzisoxazinyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzofuranyl, benzonaphthofuranyl, benzothiadiazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β-carbolinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indolizinyl, indolyl, isobenzothienyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, isoxazolyl, oxiranyl, perimidinyl, phenanthridinyl, phenathrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl and triazolyl.

[0071] In certain embodiments, the heterocyclic or heteroaryl radicals include, but are not limited to: acridinyl, azepinyl, benzimidazolyl, benzindolyl, benzoisoxazolyl, benzisoxazinyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzofuranyl, benzonaphthofuranyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiadiazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β-carbolinyl, carbazolyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dibenzofuranyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydropyranyl,

dioxolanyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrazolyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indolinyl, indolizinyl, indolyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxadiazolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, oxiranyl, perimidinyl, phenanthridinyl, phenathrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, 4-piperidonyl, pteridinyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuryl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, tetrazolyl, thiadiazolopyrimidinyl, thiadiazolyl, thiamorpholinyl, thiazolidinyl, thiazolyl, thienyl, triazinyl, triazolyl and 1,3,5-trithianyl.

[0072] "Heteroaralkyl" refers to a radical of the formula $-R_aR_f$ where R_a is an alkyl radical as defined above and R_f is a heteroaryl radical as defined herein. The alkyl radical and the heteroaryl radical may be optionally substituted as defined herein.

[0073] "Heterocyclylalkyl" refers to a radical of the formula $-R_aR_e$ wherein R_a is an alkyl radical as defined above and R_e is a heterocyclyl radical as defined herein, where the alkyl radical R_a may attach at either the carbon atom or the heteroatom of the heterocyclyl radical R_e. The alkyl radical and the heterocyclyl radical may be optionally substituted as defined herein.

[0074] "IC_{50}" refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as cell growth or proliferation measured via any the *in vitro* or cell based assay described herein.

[0075] Unless stated otherwise specifically described in the specification, it is understood that the substitution can occur on any atom of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group.

[0076] "Oxo" refers to =O.

[0077] Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to *N,N'*-dibenzylethylenediamine, chloroprocaine,

choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, *N*-methylglucamine, procaine, *N*-benzylphenethylamine, 1-*para*-chlorobenzyl-2-pyrrolidin-1'-ylmethyl- benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

[0078] As used herein and unless otherwise indicated, the term "hydrate" means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometeric amount of water bound by non-covalent intermolecular forces.

[0079] As used herein and unless otherwise indicated, the term "solvate" means a solvate formed from the association of one or more solvent molecules to a compound provided herein. The term "solvate" includes hydrates (e.g., mono-hydrate, dihydrate, trihydrate, tetrahydrate and the like).

[0080] "Sulfide" refers to the radical having the formula –SR wherein R is an alkyl or haloalkyl group. An "optionally substituted sulfide" refers to the radical having the formula –SR wherein R is an optionally substituted alkyl as defined herein.

[0081] As used herein, "substantially pure" means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

[0082] Unless specifically stated otherwise, where a compound may assume alternative tautomeric, regioisomeric and/or stereoisomeric forms, all alternative isomers are intended to be encompassed within the scope of the claimed subject matter. For example, where a compound is described as having one of two tautomeric forms, it is intended that the both tautomers be encompassed herein.

[0083] Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α-amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

[0084] It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof.

[0085] Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC.

[0086] As used herein, the term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the desired enantiomer.

[0087] Where the number of any given substituent is not specified (*e.g.*, haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[0088] In the description herein, if there is any discrepancy between a chemical name and chemical structure, the structure preferably controls.

As used herein, "isotopic composition" refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural isotopic composition.

As used herein, "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

As used herein, "isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0089] "Anti-cancer agents" refers to anti-metabolites (e.g., 5-fluoro-uracil, methotrexate, fludarabine), antimicrotubule agents (e.g., vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel, docetaxel), alkylating agents (e.g., cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosurea and hydroxyurea), platinum agents (e.g. cisplatin, carboplatin, oxaliplatin, JM-216 or satraplatin, CI-973), anthracyclines (e.g., doxrubicin, daunorubicin), antitumor antibiotics (e.g., mitomycin, idarubicin,

adriamycin, daunomycin), topoisomerase inhibitors (e.g., etoposide, camptothecins), anti-angiogenesis agents (*e.g.* Sutent® and Bevacizumab) or any other cytotoxic agents, (estramustine phosphate, prednimustine), hormones or hormone agonists, antagonists, partial agonists or partial antagonists, kinase inhibitors, and radiation treatment.

[0090] "Anti-inflammatory agents" refers to matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (e.g., anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (e.g., choline magnesium salicylate, salicylsalicyclic acid), COX-1 or COX-2 inhibitors), or glucocorticoid receptor agonists such as corticosteroids, methylprednisone, prednisone, or cortisone.

[0091] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, *Biochem.* 1972, *11*:942-944).

B. COMPOUNDS

[0092] In one embodiment, the compounds provided are of formula (I) as described above. In one embodiment, the compounds provided are of formula (I) as described above, where X is O. In one embodiment, the compounds provided are of formula (I) as described above, where X is $S(O)_t$ and t is an integer from 0 to 2 .

[0093] In one embodiment, the compounds have formula (I) or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, wherein

[0094] X is O, $S(O)_t$;

[0095] R^a is O or S;

[0096] R^1 is selected as follows:

i) each R^1 is independently selected from a group consisting of halo, nitro, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(NR^7)N(R^7)_2$, $-R^6C(O)N(R^7)R^9N(R^7)_2$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$,

$-R^6S(O)_tN(R^7)_2$, $-R^6S(O)_tN(R^7)N(R^7)_2$, $-R^6S(O)_tN(R^7)N=C(R^7)_2$, $-R^6S(O)_tN(R^7)C(O)R^8$, $-R^6S(O)_tN(R^7)C(O)N(R^7)_2$, $-R^6S(O)_tN(R^7)C(NR^7)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$, $-R^6N(R^7)C(O)R^8$, $-R^6N(R^7)C(O)OR^8$, $-R^6N(R^7)C(O)N(R^7)_2$, $-R^6N(R^7)C(NR^7)N(R^7)_2$, $-R^6N(R^7)C(S)N(R^7)_2$, and $-R^6N(R^7)S(O)_tR^8$, or

[0097] ii) any two adjacent R^1 groups together form an alkylenedioxy group;

[0098] each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

[0099] each R^7 is independently selected from (i) or (ii) below:

[00100] (i) each R^7 is selected from a group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

[00101] (ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

[00102] each R^8 is independently selected from a group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl;

[00103] each R^9 is independently an alkylene chain or an alkenylene chain;

[00104] R^2 is hydrogen, halo, alkyl, amino or alkylamino;

[00105] R^3 is halo or alkyl;

[00106] R^4 and R^5 are each independently selected as follows:

[00107] a) R^4 and R^5 are each independently hydrogen or alkyl, or

[00108] b) R^4 and R^5, together with the N atom to which they are attached, form an oxo-substituted heterocyclyl;

[00109] R^{11} is aryl, heteroaryl or heterocyclyl;

[00110] m is an integer from 0 to 4;

[00111] n is an integer from 0 to 4;

[00112] t is an integer from 0 to 2; and

[00113] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally subtituted with one or more substituents independently selected from Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$,

$-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_tR^w$, $-R^uN(R^x)$ $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[00114] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00115] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxyl,

[00116] each R^u is independently alkylene or a direct bond;

[00117] each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$;

[00118] R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00119] each R^x is independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

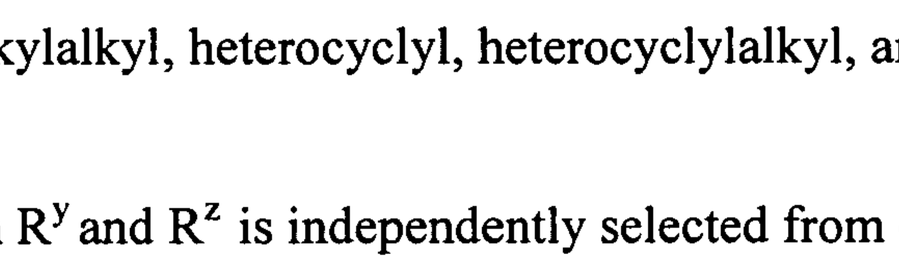
[00120] each R^y and R^z is independently selected from (i) or (ii) below:

[00121] (i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, or

[00122] (ii) R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl; and

[00123] J is O, NR^x or S.

[00124] In one embodiment, the compounds provided are of formula (II):



II

or a pharmaceutically acceptable salt, solvate, clathrate or hydrate thereof, wherein

[00125] X is O, S, S(O) or SO_2;

[00126] R^1 is selected as follows:

i) each R^1 is independently selected from the group consisting of, halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$, $-R^6OC(O)N(R^7)_2$, $-R^6N(R^7)C(O)R^8$, $-R^6S(O)_tN(R^7)_2$; or

ii) any two adjacent R^1 groups form an alkylenedioxy group;

[00127] each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

[00128] each R^7 is independently selected from (i) or (ii) below:

[00129] (i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

[00130] (ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

[00131] each R^9 is independently an alkylene chain or an alkenylene chain;

[00132] R^2 is hydrogen, halo, alkyl, amino or alkylamino;

[00133] R^3 is halo or alkyl;

[00134] R^4 and R^5 are each independently hydrogen or alkyl;

[00135] R^{11} is aryl or heteroaryl;

[00136] m is an integer from 0 to 4;

[00137] n is an integer from 0 to 4;

[00138] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally subtituted with one or more substituents independently selected from Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_2R^w$, $-R^uN(R^x)$

$R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[00139] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00140] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxyl,

[00141] each R^u is independently alkylene or a direct bond;

[00142] each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$;

[00143] R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00144] each R^x is independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00145] R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00146] R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocycle or heteroaryl;

[00147] t is an integer from 0 to 2; and

[00148] J is O, NR^x or S.

[00149] In one embodiment, the compounds provided are of formula (II) or a pharmaceutically acceptable salt, solvate, clathrate or hydrate thereof, wherein

[00150] X is O, S, S(O) or SO_2;

[00151] R^1 is selected as follows:

i) each R^1 is independently selected from the group consisting of, halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$,

$-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$, $-R^6OC(O)N(R^7)_2$, $-R^6N(R^7)C(O)R^8$, $-R^6S(O)_tN(R^7)_2$; or

ii) any two adjacent R^1 groups form an alkylenedioxy group;

[00152] each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

[00153] each R^7 is independently selected from (i) or (ii) below:

[00154] (i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

[00155] (ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

[00156] each R^9 is independently an alkylene chain or an alkenylene chain;

[00157] R^2 is hydrogen, halo, alkyl, amino or alkylamino;

[00158] R^3 is halo or alkyl;

[00159] R^4 and R^5 are each independently hydrogen or alkyl;

[00160] R^{11} is aryl or heteroaryl;

[00161] m is an integer from 0 to 4;

[00162] n is an integer from 0 to 4;

[00163] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally subtituted with one or more substituents independently selected from Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_2R^w$, $-R^uN(R^x)R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[00164] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00165] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, oxo, cyano, thioxo, alkoxy or hydroxyl,

[00166] each R^u is independently alkylene or a direct bond;

[00167] each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,-OR^x or -$N(R^y)(R^z)$;

[00168] R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00169] each R^x is independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00170] R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00171] R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocycle or heteroaryl;

[00172] t is an integer from 0 to 2; and

[00173] J is O, NR^x or S.

[00174] In one embodiment, the compound is a single isomer, including a stereoisomer, a mixture of isomers, a racemic mixture of isomers, a solvate, a hydrate or a pharmaceutically acceptable salt thereof.

[00175] In one embodiment, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I). In one embodiment, the compounds provided herein is a solvate of the compound of formula (I). In one embodiment, the compounds provided herein is a hydrate of compound of formula (I).

[00176] In one embodiment, X is O or S. In one embodiment, X is O. In one embodiment, X is $S(O)_t$ and t is an integer from 0 to 2. In one embodiment X is S. In one embodiment, R^a is O.

[00177] In one embodiment, n is an integer from 1 to 4. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3.

[00178] In one embodiment, m is an integer from 0 to 2. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, m is 2.

[00179] In one embodiment, R^2 is hydrogen.

[00180] In one embodiment, R^3 is lower alkyl or halo. In one embodiment, R^3 is methyl, chloro or fluoro. In another embodiment, R^3 is methyl, chloro or fluoro.

[00181] In one embodiment, R^4 is hydrogen or alkyl and R^5 is hydrogen. In one embodiment, R^5 is hydrogen or alkyl and R^4 is hydrogen. In one embodiment, R^4 and R^5 are each independently hydrogen or methyl. In one embodiment, R^4 and R^5 are each hydrogen.

[00182] In one embodiment, Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_2R^w$, $-R^uN(R^x)\ R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[00183] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00184] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxyl, wherein the variables are as described elsewhere herein.

[00185] In one embodiment, Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_2R^w$, $-R^uN(R^x)\ R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ and $-R^uC(R^x)=NN(R^y)(R^z)$,

[00186] when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00187] when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, oxo, thioxo, alkoxy or hydroxyl, wherein the variables are as described elsewhere herein.

[00188] In one embodiment, Q^1 is halo, alkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^uC(J)OR^x$, $-R^uS(O)_tR^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x) R^uS(O)_2R^w$, when Q^1 is alkyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy, wherein the variables are as described elsewhere herein.

[00189] In one embodiment, Q^1 is halo, alkyl, cycloalkyl, haloalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^uC(J)OR^x$, $-R^uS(O)_tR^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x) R^uS(O)_2R^w$,

[00190] when Q^1 is alkyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy,

[00191] each R^u is independently alkylene or a direct bond;

[00192] R^w is alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00193] R^x is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

[00194] R^y and R^z are each independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or

[00195] R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl.

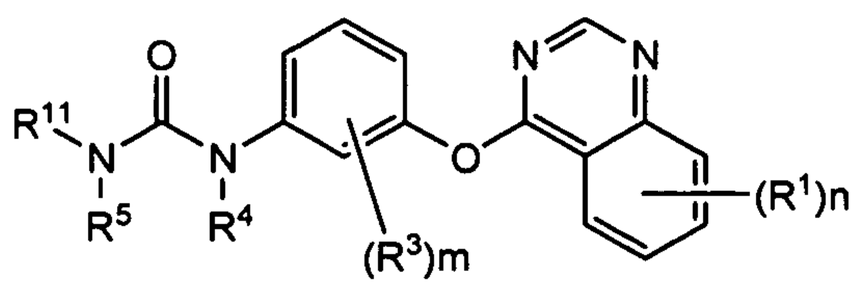
[00196] In one embodiment, Q^1 is halo, alkyl, cycloalkyl, haloalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^uC(J)OR^x$, $-R^uS(O)_tR^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x) R^uS(O)_2R^w$,

[00197] where Q^1, when alkyl is optionally substituted with halo, cyano, and where Q^1, when cycloalkyl is optionally substituted with haloalkyl and the other variables are as described ehsewhere herein.

[00198] In one embodiment, Q^1 is haloalkyl, alkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$-$R^uC(J)OR^x$, $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x)$ $R^uS(O)_2R^w$, wherein R^u is direct bond or alkylene, R^x is hydrogen or alkyl; R^w is alkyl and J is O, S or NR^x.

[00199] In one embodiment, Q^1 is halo, hydroxy, alkyl, hydroxyalkyl, alkyloxycarbonyl, alkylsulfonyl or haloalkyl.

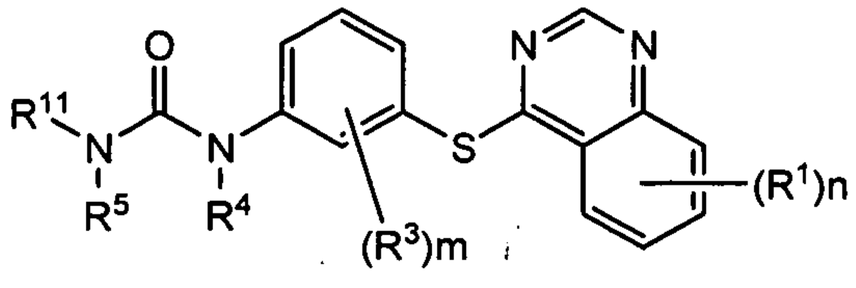
[00200] In one embodiment, the compounds provided herein have formula III:



, III

[00201] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein m is an integer from 0 to 4 and wherein the other variables are as described elsewhere herein.

[00202] In one embodiment, the compounds provided herein have formula IV:



IV

[00203] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein m is an integer from 0 to 4 and wherein the other variables are as described elsewhere herein.

[00204] In one embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents, when present are selected from one or more R^{10} groups, wherein each R^{10} is independently selected from halo, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00205] In one embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents, when present are selected from one or more R^{10} groups, wherein each R^{10} is independently selected from halo, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, hydroxy, alkoxy, cycloalkyl, aryl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00206] In another embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents, when present, are selected from one or more R^{10} groups, wherein each R^{10} is independently selected from halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, aralkyl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl and where the cycloalkyl, aryl and heteroaryl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, alkyl, haloalkyl, hydroxy and alkoxy. In another embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents, when present, are selected from one or more R^{10} groups, wherein each R^{10} is independently selected from halo, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, and cycloalkyl, and where the cycloalkyl, aryl and heteroaryl group is optionally substituted with 1, 2 or 3 groups selected from Q^1. In another embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents, when present, are selected from one or more R^{10} groups, wherein each R^{10} is independently selected from halo, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, and cycloalkyl, and where the cycloalkyl, aryl and heteroaryl groups are optionally substituted with 1, 2 or 3 groups selected halo, cyano, alkyl and haloalkyl.

[00207] In one embodiment, R^{11} is 5-12 membered optionally substituted heteroaryl having one or more heteroatoms, wherein the heteroatoms are each independently selected from nitrogen, sulfur and oxygen. In one embodiment, R^{11} is 5-6 membered optionally substituted heteroaryl. In one embodiment, R^{11} is 5-membered optionally substituted heteroaryl. In one embodiment, R^{11} is pyrazole optionally substituted with one, two or three substitutents, each independently selected from R^{10}. In another embodiment, R^{11} is isoxazole optionally substituted with one, two or three substituents, each independently selected from R^{10}.

[00208] In one embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, and cycloalkyl and where the cycloalkyl, aryl and heteroaryl is optionally substituted with 1 or 2 groups selected from Q^1. In another embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, and cycloalkyl and where the cycloalkyl, aryl and heteroaryl is optionally substituted with 1 or 2 groups selected from halo, cyano, alkyl and haloalkyl.

[00209] In one embodiment, R^{10} is independently selected from halo, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1, 2 or 3 groups selected from halo, cyano, haloalkyl, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00210] In one embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, and cycloalkyl and where the cycloalkyl, aryl and heteroaryl is optionally substituted with 1 or 2 groups selected from Q^1. In another embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, and cycloalkyl and where the cycloalkyl, aryl and heteroaryl is optionally substituted with 1 or 2 groups selected from halo, cyano, alkyl and haloalkyl.

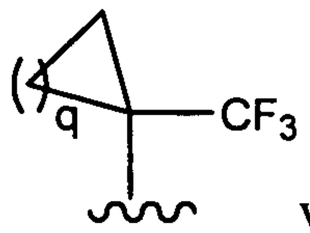
[00211] In one embodiment, each R^{10} is independently selected from hydrogen, halo, alkyl, haloalkyl, cyanoalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylalkyl, heterocyclylalkyl and heteroaryl.

[00212] In one embodiment, one R^{10} is alkyl or haloalkyl and the other R^{10} is cycloalkyl, aryl or heteroaryl optionally substituted with 1, 2 or 3 groups selected from Q^1.

[00213] In one embodiment, R^{10} is alkyl or haloalkyl.

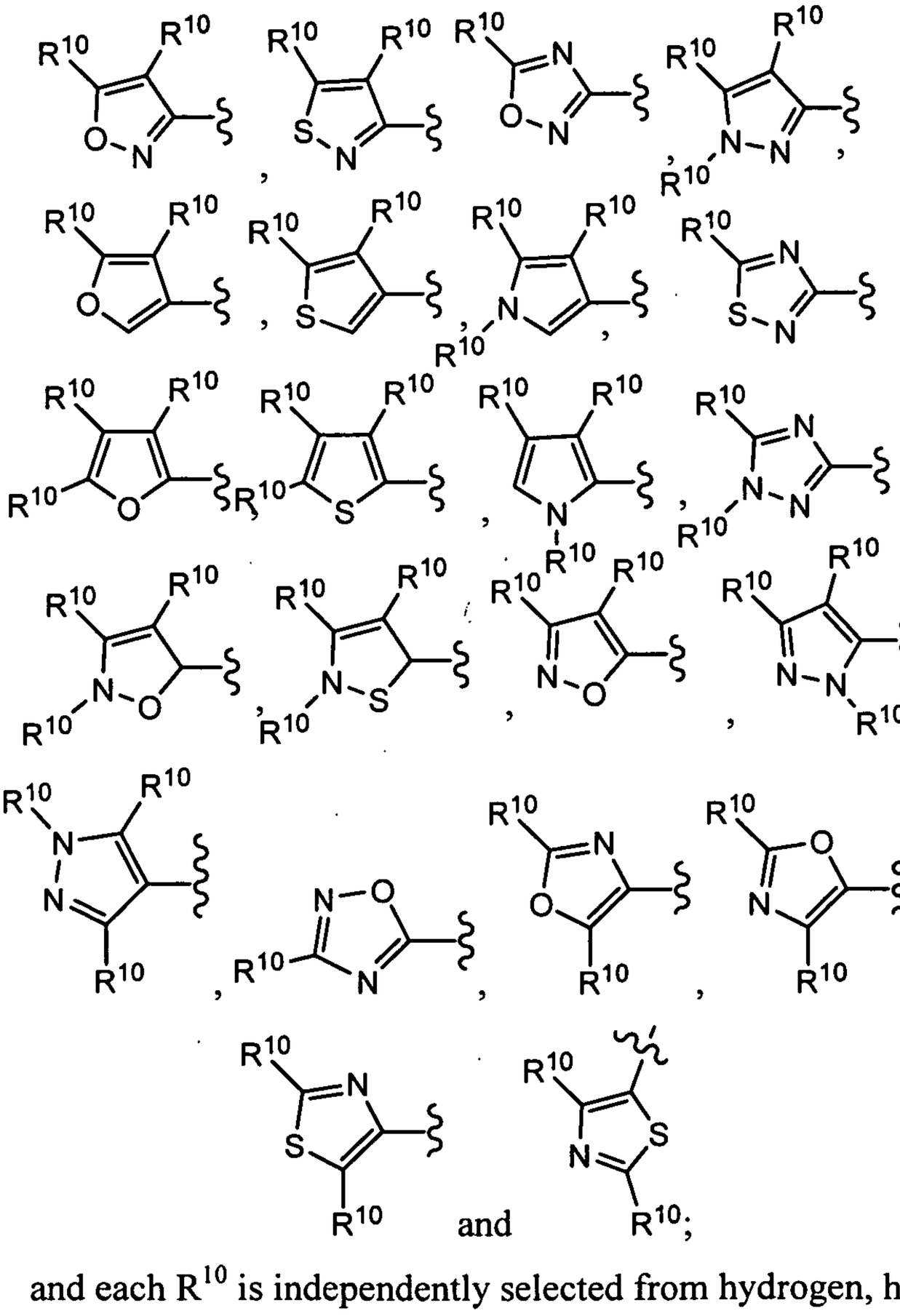
[00214] In another embodiment, R^{11} is optionally substituted aryl, optionally substituted heterocyclyl or optionally substituted heteroaryl, wherein the substituents,

when present are selected from F, Cl, methyl, ethyl, n-propyl, $-C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$, $-C(CH_3)(CH_2F)_2$, $-CF_3$, phenyl,

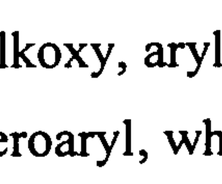


pyridinyl, cyclopropyl, cyclopentyl, cyclohexyl and where q is an integer from 1 – 5 and where the phenyl, pyridinyl, cyclopropyl, cyclopentyl or cyclohexyl may be optionally substituted with 1 or 2 groups selected from halo, cyano, alkyl, haloalkyl and cyanoalkyl.

[00215] In another embodiment, R^{11} is selected from a group consisting of:



and

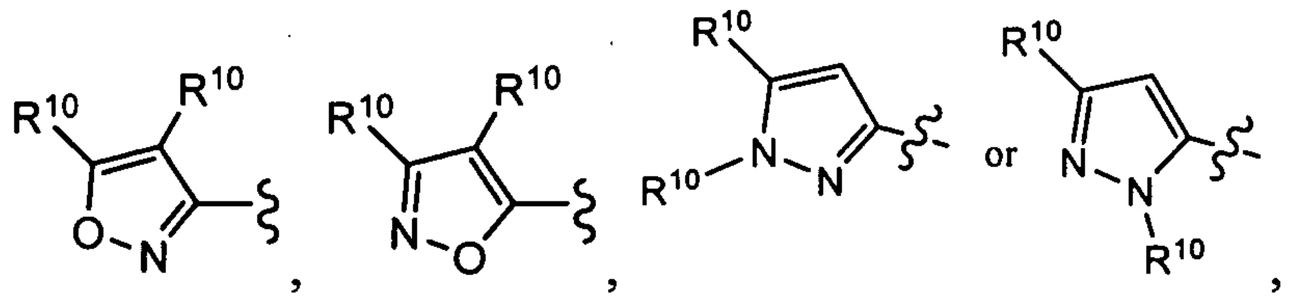


;

[00216] and each R^{10} is independently selected from hydrogen, halo, haloalkyl, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with, in one embodiment, 1 to 5, in another embodiment, 1 or 2 groups selected from halo, cyano, hydroxy, alkoxy, cycloalkyl, heterocyclyl,

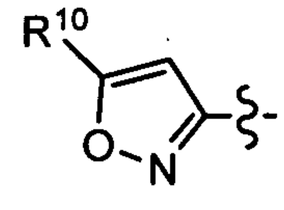
alkylcarbonyl and alkoxycarbonyl. In one embodiment, alkyl, cycloalkyl, heterocyclyl and heteroaryl groups in R^{10} are each independently optionally substituted with 1, 2 or 3 groups selected from halo, cyano, hydroxyl and alkoxy. In one embodiment, R^{10} is C_{3-5} alkyl optionally substituted with 1, 2 or 3 groups selected from halo, cyano, hydroxyl and alkoxy. In one embodiment, R^{10} is C_4 alkyl optionally substituted with 1, 2 or 3 groups selected from halo, cyano, hydroxyl and alkoxy.

[00217] In one embodiment, R^{11} is

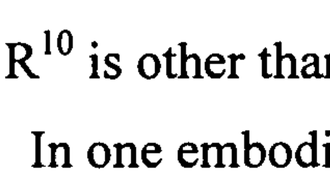


where R^{10} is as described elsewhere herein. In one embodiment, R^{10} is hydrogen, alkyl, hydroxyalkyl, cycloalkyl, haloalkyl, cyanoalkyl, alkoxyalkyl, aryl or heteroaryl. In one embodiment, R^{10} is alkyl. In one embodiment, one R^{10} is alkyl and the other R^{10} is hydrogen. In one embodiment, one R^{10} is haloalkyl and the other R^{10} is hydrogen. In one embodiment, one R^{10} is alkyl and the other R^{10} is aryl. In one embodiment, R^{10} is other than methyl. In one embodiment, R^{10} is *t*-butyl.

[00218] In one embodiment, R^{11} is

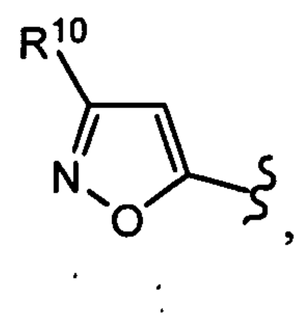


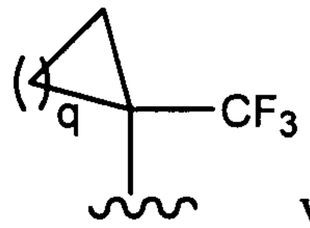
where R^{10} is as described elsewhere herein. In one embodiment, R^{10} is hydrogen, alkyl, hydroxyalkyl, cycloalkyl, haloalkyl, cyanoalkyl, alkoxyalkyl or aryl. In one embodiment, R^{10} is $-C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$, $-C(CH_3)_2CH_2OH$, $-C(CH_3)(CH_2F)_2$, $-C(CH_3)_2CH_2OCH_3$, CF_3, phenyl,



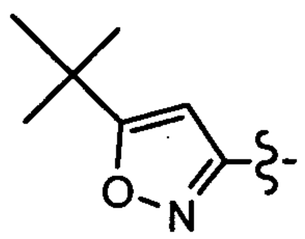
cyclopentyl or where q is an integer from 1 - 5.

[00219] In one embodiment, R^{11} is

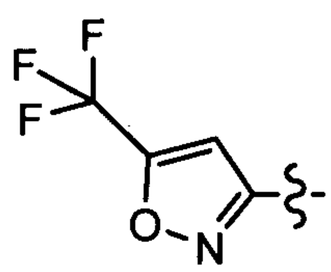


where R^{10} is as described elsewhere herein. In one embodiment, R^{10} is hydrogen, alkyl, hydroxyalkyl, cycloalkyl, haloalkyl, cyanoalkyl, alkoxyalkyl or aryl. In one embodiment, R^{10} is $-C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$, $-C(CH_3)_2CH_2OH$, $-C(CH_3)(CH_2F)_2$, $-C(CH_3)_2CH_2OCH_3$, CF_3, phenyl, cyclopentyl or  where q is an integer from 1 - 5.

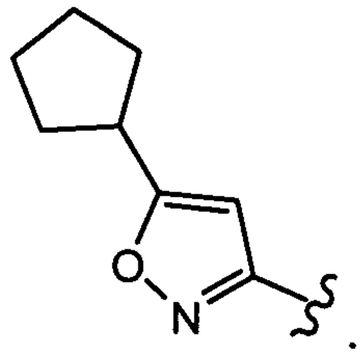
[00220] In one embodiment, R^{11} is



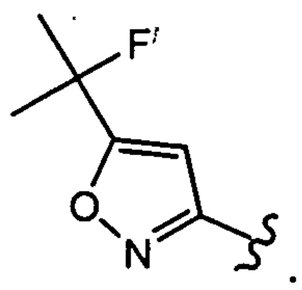
[00221] In one embodiment, R^{11} is



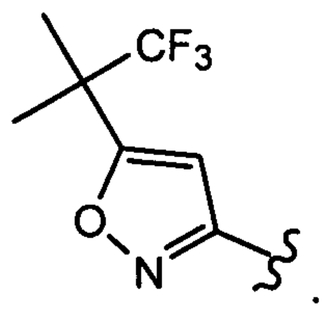
[00222] In one embodiment, R^{11} is



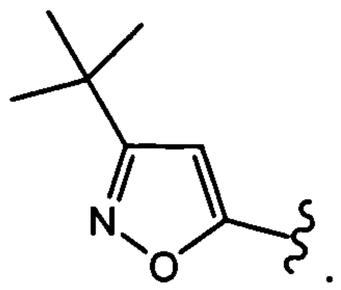
[00223] In one embodiment, R^{11} is



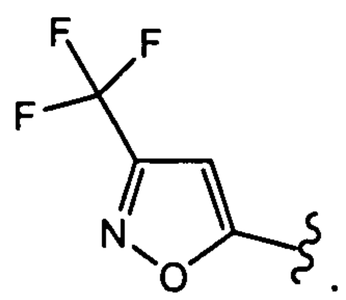
[00224] In one embodiment, R^{11} is



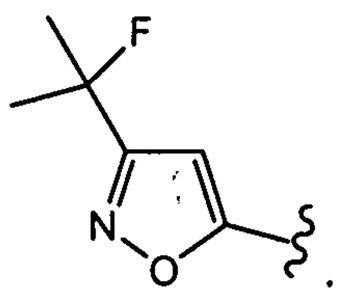
[00225] In one embodiment, R^{11} is



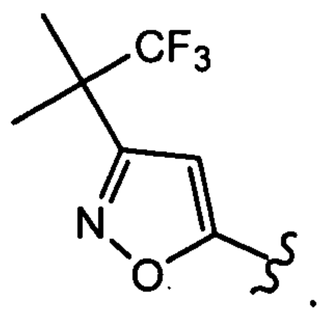
[00226] In one embodiment, R^{11} is



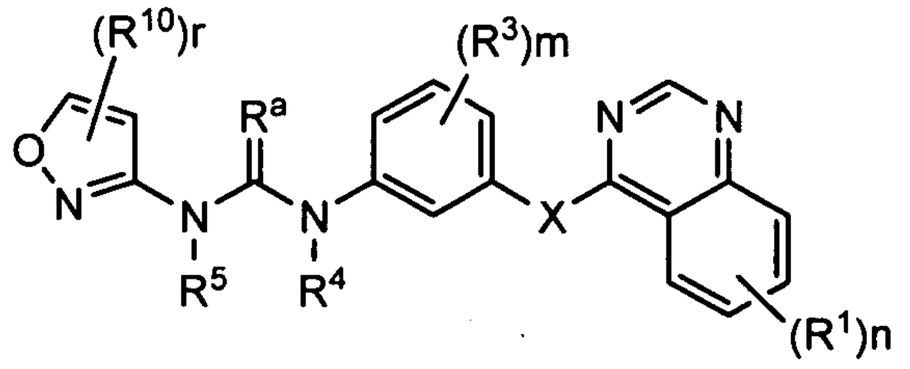
[00227] In one embodiment, R^{11} is



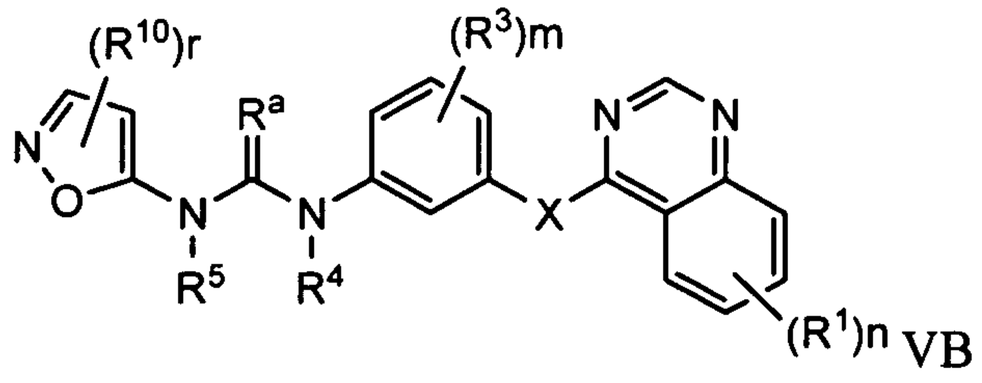
[00228] In one embodiment, R^{11} is



[00229] In one embodiment, the compounds provided herein have formula VA or VB:



VA

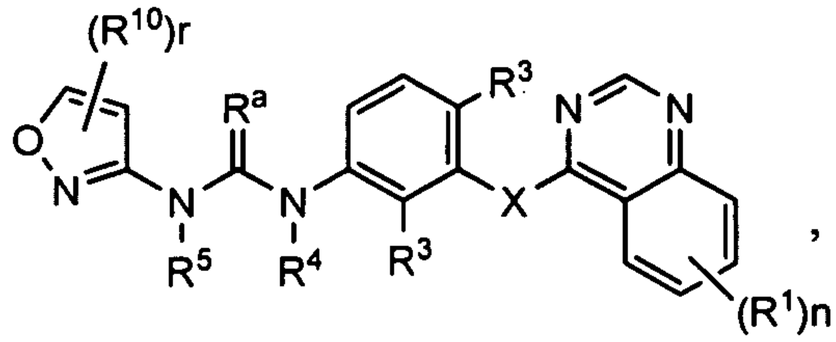


VB

[00230] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein r is 0, 1 or 2 and the other variables are as described elsewhere herein. In one embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl,

alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00231] In one embodiment, the compounds provided herein have formula: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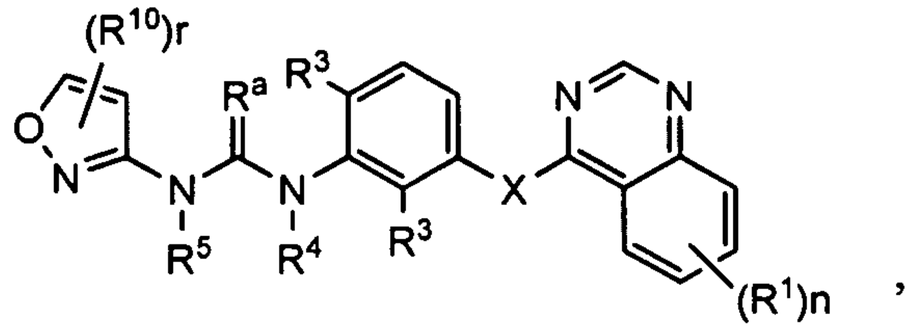
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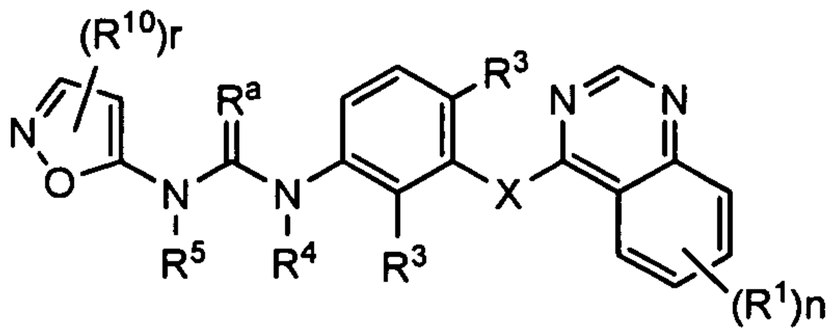
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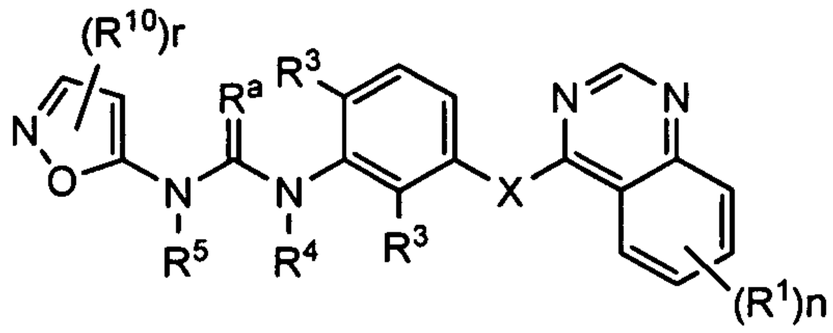
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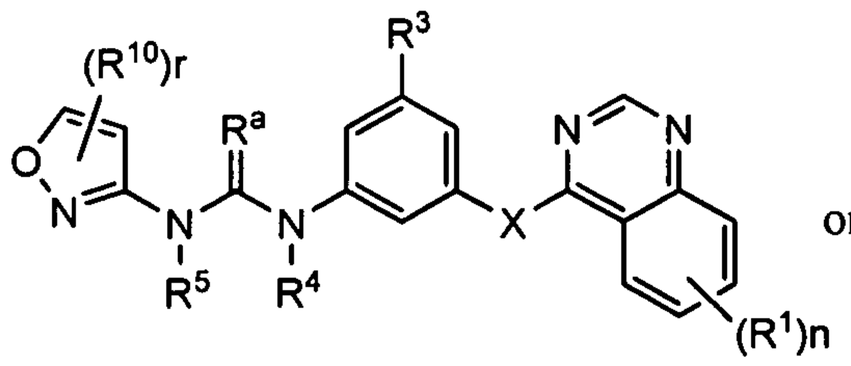
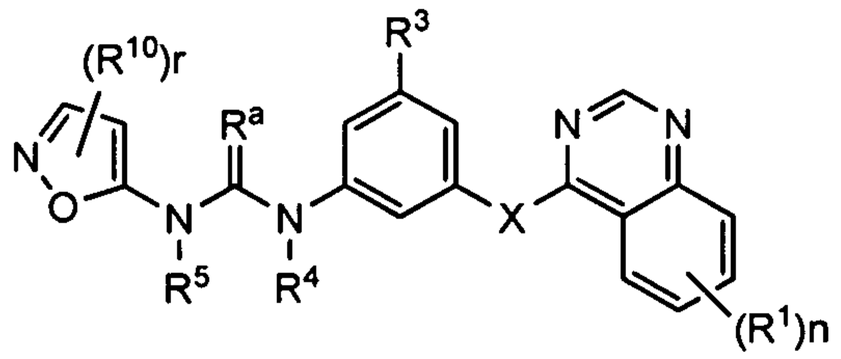
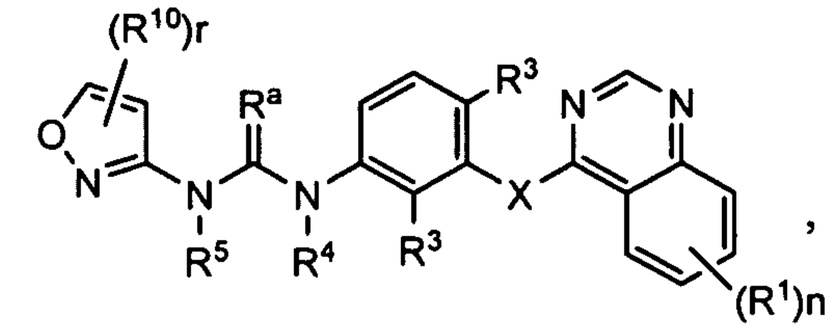

or


[00232] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein r is 0, 1 or 2 and the other variables are as described elsewhere herein. In one embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00233] In one embodiment, the compounds provided herein have formula: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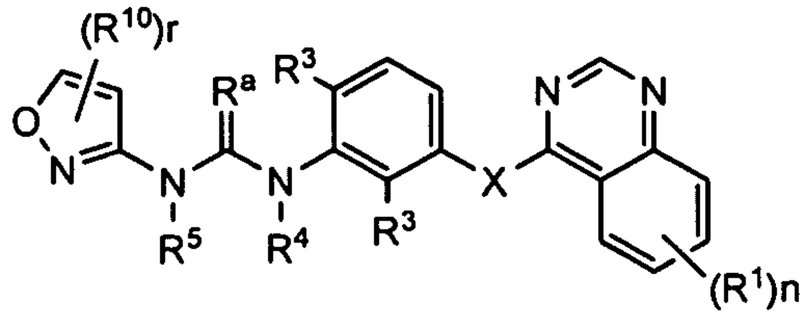
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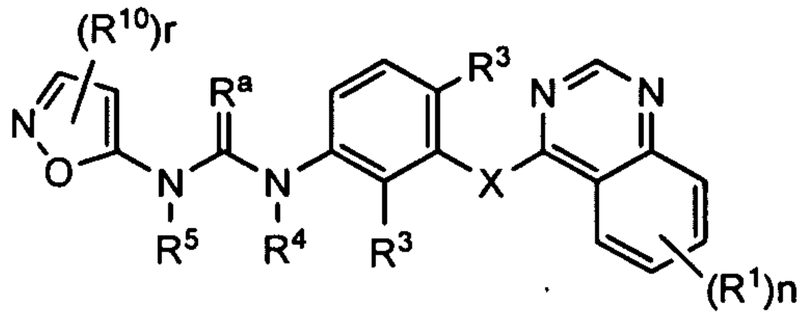
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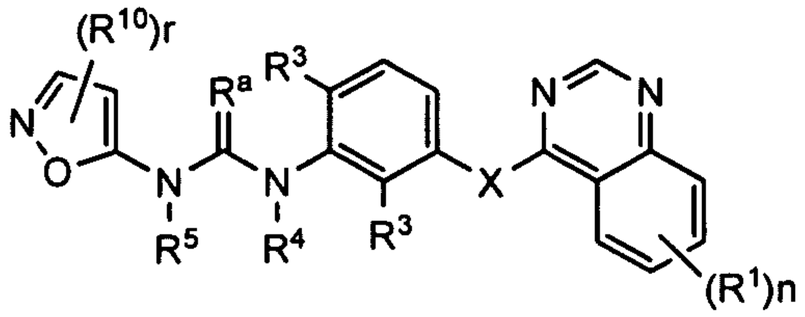
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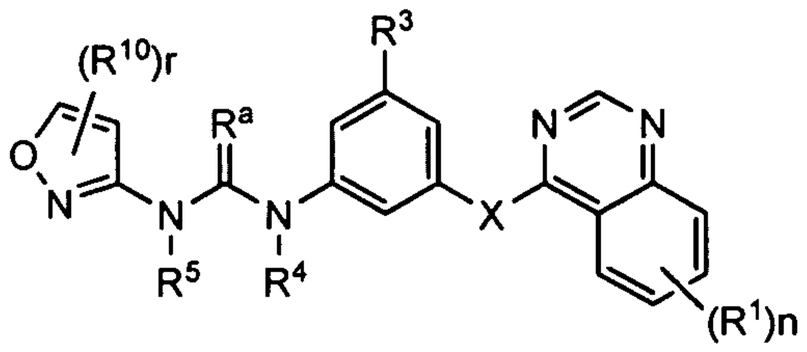
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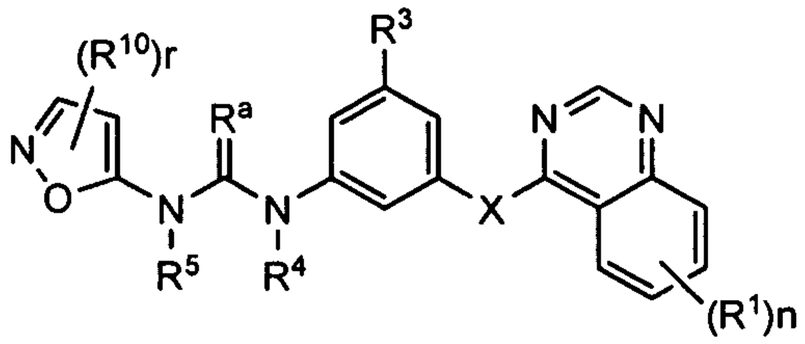
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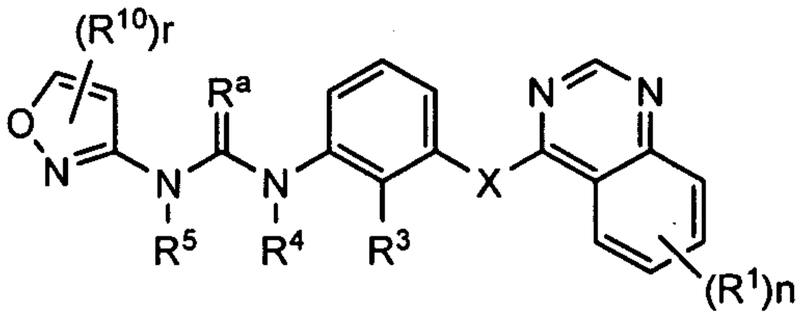
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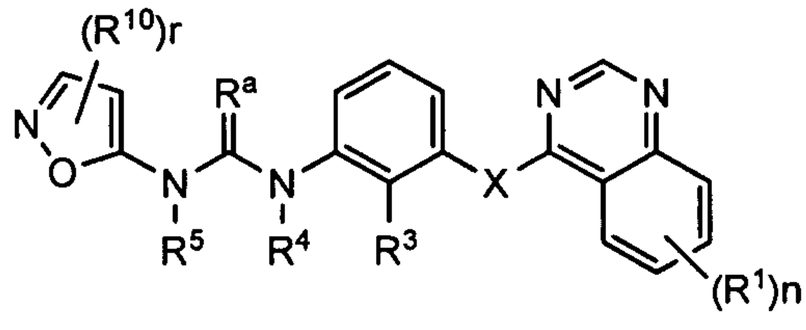
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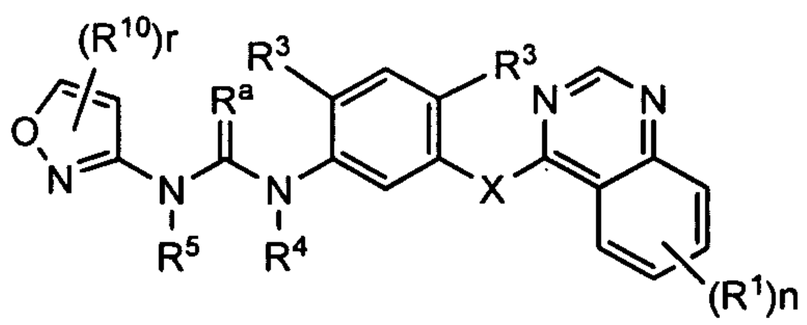
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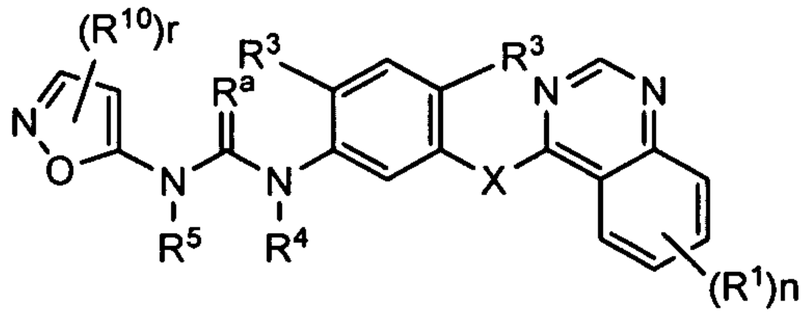
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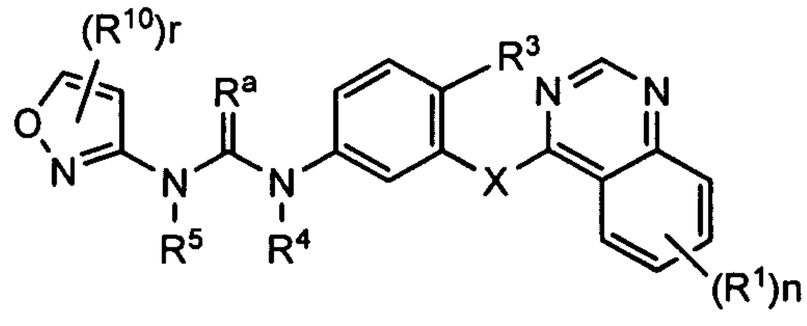
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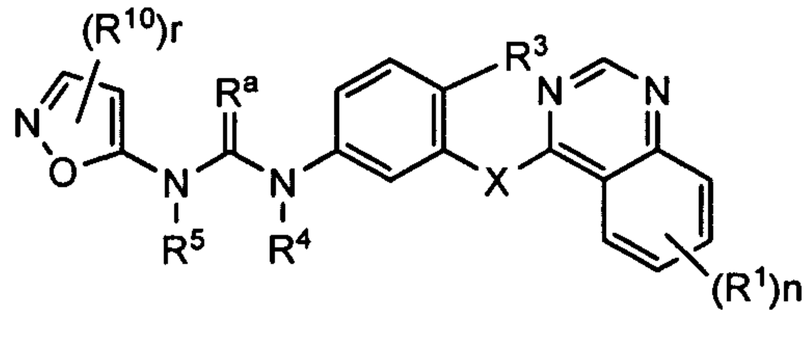
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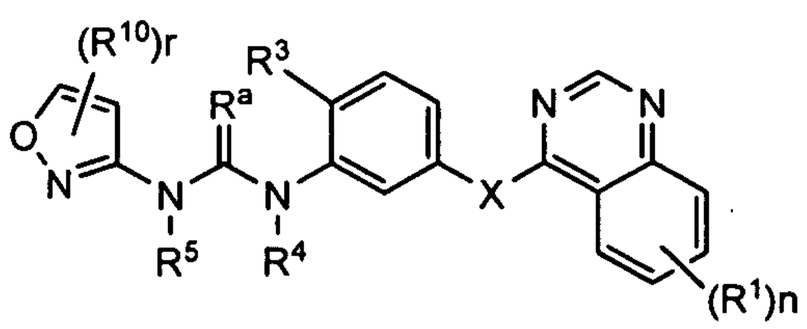
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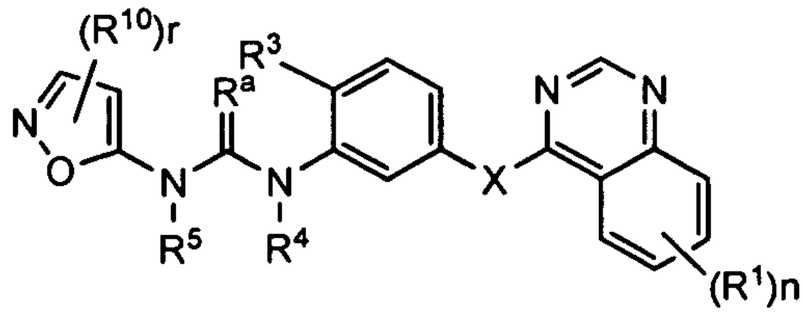
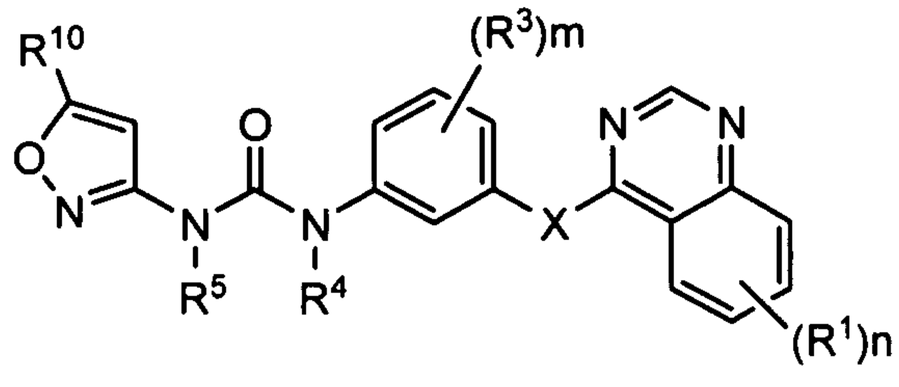


[00234] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein r is 0, 1 or 2 and the other variables are as described elsewhere herein. In one embodiment, R^{10} is independently selected from halo, haloalkyl, alkyl, alkoxy,

haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, cyano, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

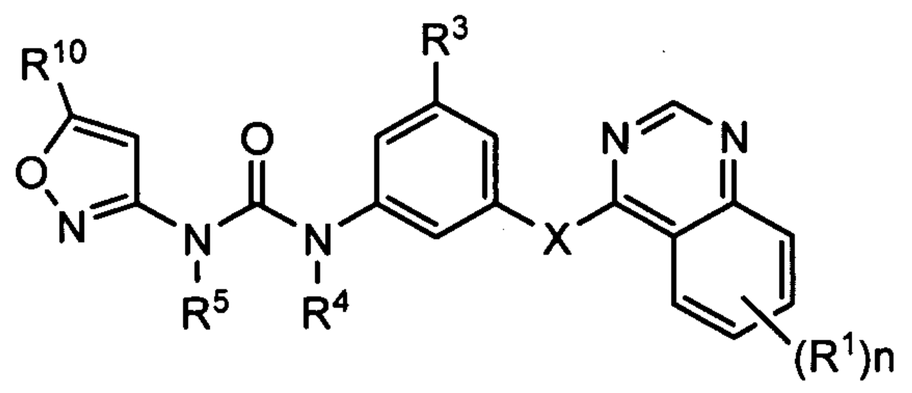
[00235] In one embodiment, the compounds provided herein have formula VI:



VI

[00236] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

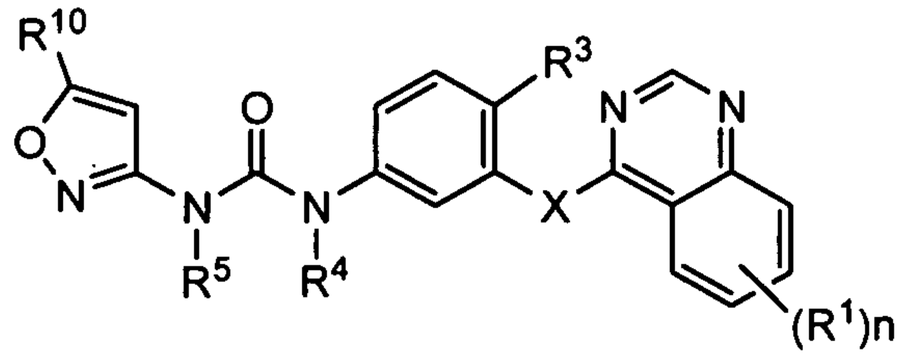
[00237] In one embodiment, the compounds provided herein have formula VIa:



VIa

[00238] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[00239] In one embodiment, the compounds provided herein have formula VIb:

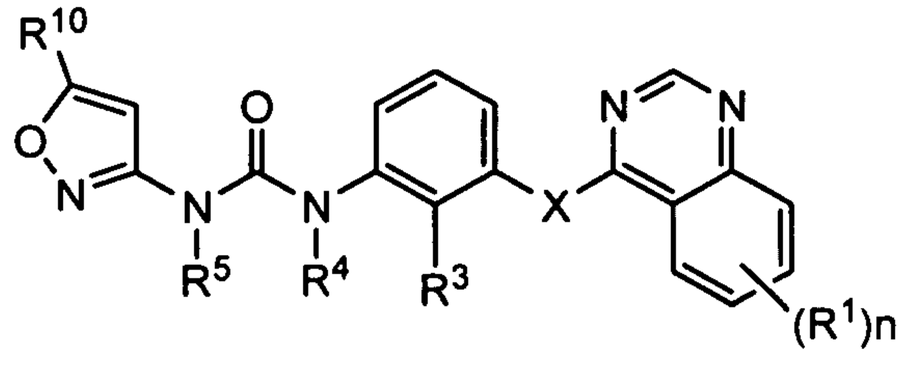


VIb

[00240]

[00241] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

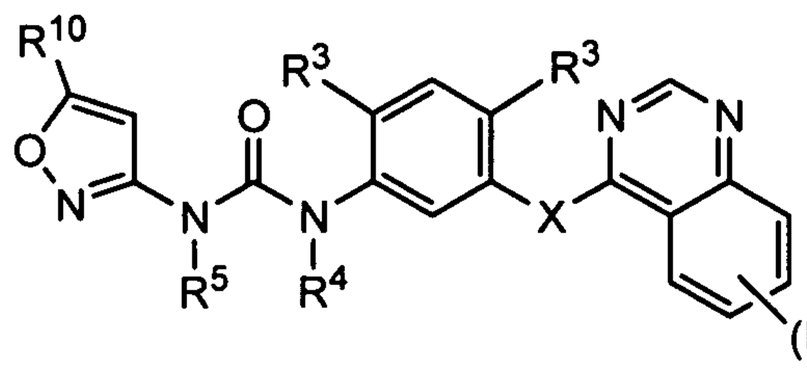
[00242] In one embodiment, the compounds provided herein have formula VIc:



VIc

[00243] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

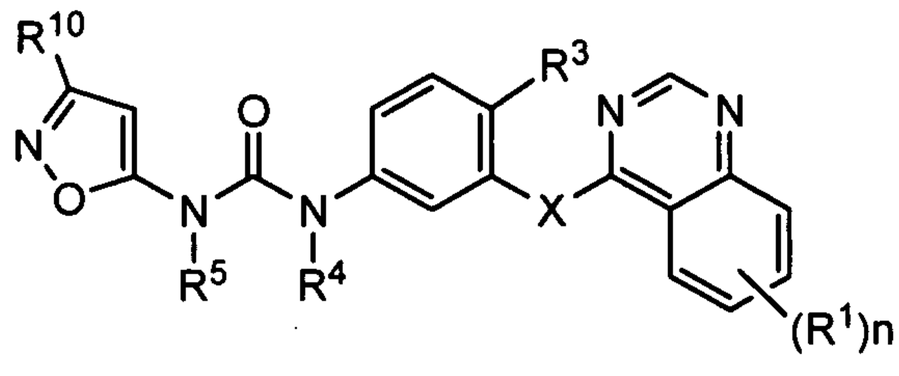
[00244] In one embodiment, the compounds provided herein have formula VId:



VId

[00245] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

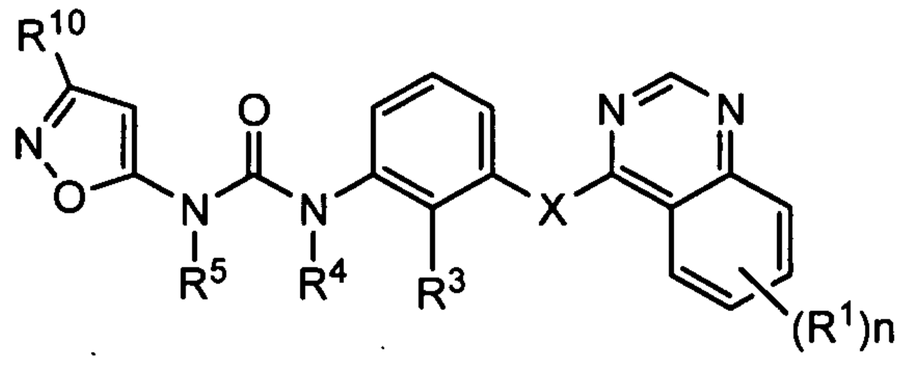
[00246] In one embodiment, the compounds provided herein have formula VIe:



VIe

[00247] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

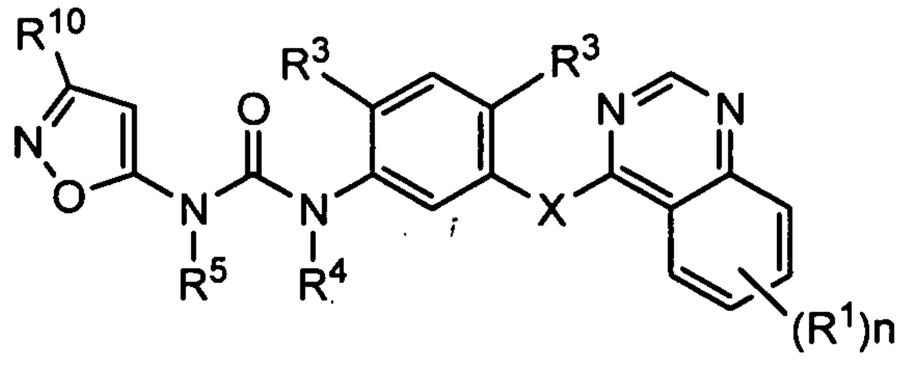
[00248] In one embodiment, the compounds provided herein have formula VIf:



VIf

[00249] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

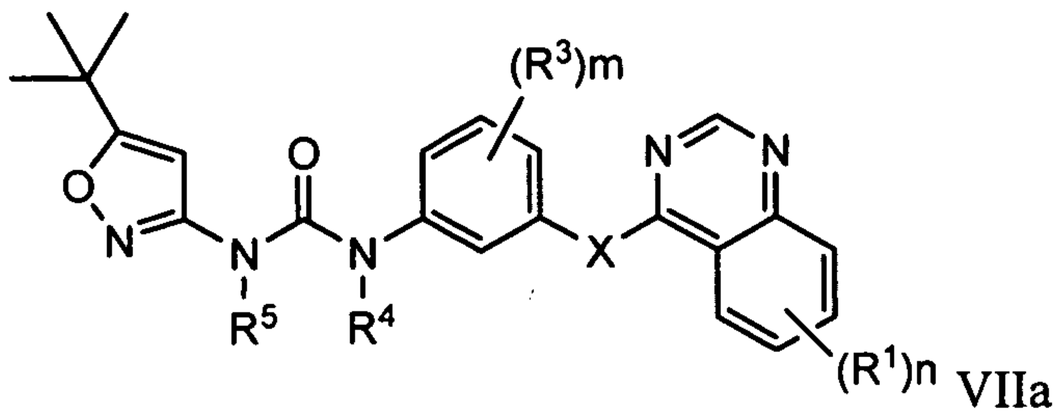
[00250] In one embodiment, the compounds provided herein have formula VIg:



VIg

[00251] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

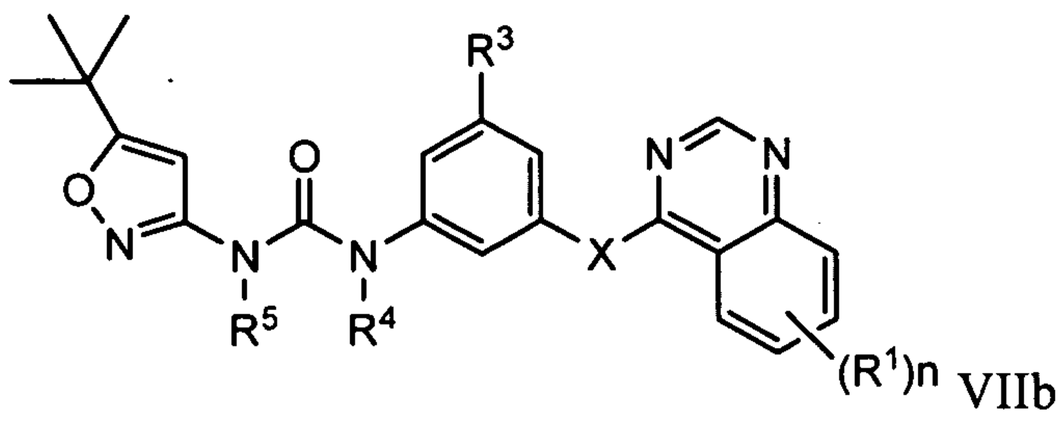
[00252] In one embodiment, the compounds provided herein have formula VIIa:



VIIa

[00253] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

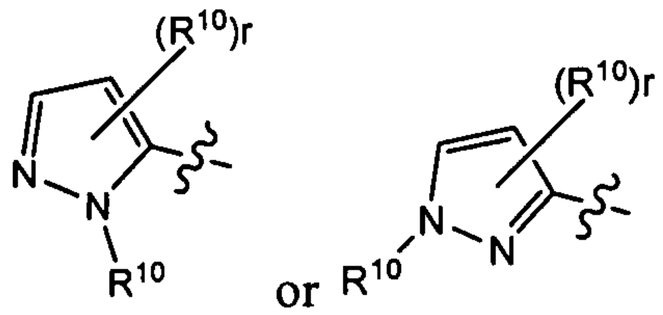
[00254] In one embodiment, the compounds provided herein have formula VIIb:



VIIb

[00255] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

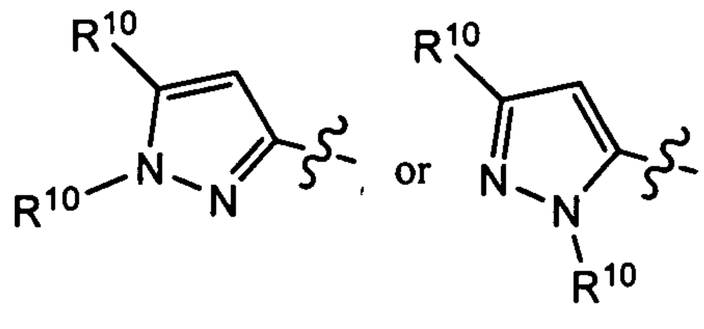
[00256] In one embodiment, R^{11} is



[00257] where each R^{10} is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, aryl, haloaryl, alkylaryl, heteroaryl and alkoxycarbonylalkyl, and r is 1 or 2. In one embodiment, r is 1, and the R^{10} on the N atom of the pyrazole is phenyl optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxy and the other R^{10} is selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl and alkoxyalkyl. In one embodiment, r is 1 and the R^{10} on the N atom of the pyrazole is 5 or 6-membered heteroaryl and the other R^{10} is selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl and alkoxyalkyl. In one embodiment, r is 1 and the R^{10} on the N atom of the pyrazole is selected from pyridinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolinyl, quinazolinyl, thiazolyl, thiadiazolyl, imidazolyl,

thienyl and furanyl and the other R^{10} is selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl and alkoxyalkyl. In one embodiment, each R^{10} is independently selected from hydrogen, *tert*-butyl, methyl, isopropyl or phenyl; and r is 1.

[00258] In one embodiment, R^{11} is

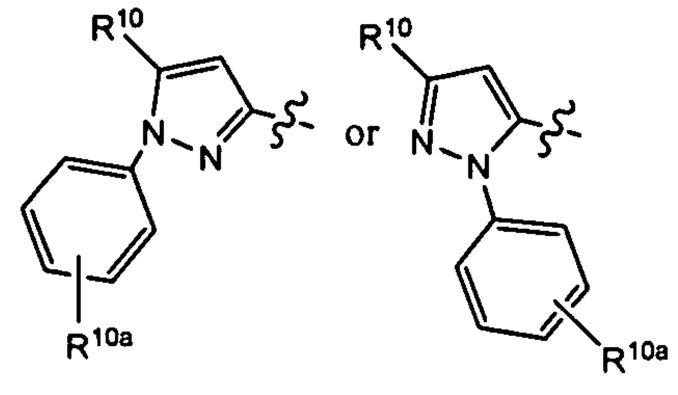


,

[00259] where R^{10} is as defined elsewhere herein. In one embodiment, R^{10} on the N atom of the pyrazole is phenyl optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxy and the other R^{10} on the carbon atom of the pyrazole is selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkyl. In one embodiment, R^{10} on the N atom of the pyrazole is heteroaryl optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy or hydroxy and the other R^{10} on the carbon atom of the pyrazole is selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkyl.

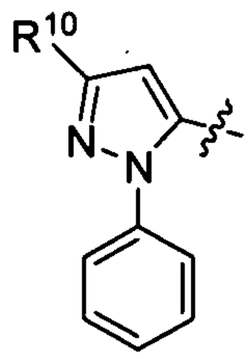
[00260] In one embodiment, each R^{10} of the pyrazole is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, cycloalkyl, heterocyclyl, aryl, aralkyl, heteroaryl and heteroaralkyl wherein each cycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl is optionally substituted with halo, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl and alkoxyalkyl. In another embodiment, R^{10} on the N atom of the pyrazole is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, cycloalkyl, heterocyclyl, aryl, aralkyl, heteroaryl and heteroaralkyl wherein each cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl is optionally substituted with halo, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl and alkoxyalkyl and R^{10} on the C atom of the pyrazole is independently selected from halo, alkyl, haloalkyl, cyanoalkyl and cycloalkyl.

[00261] In one embodiment, R^{11} is



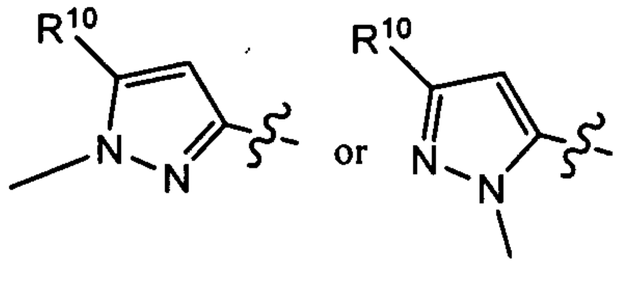
[00262] where R^{10} is hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl or alkoxyalkyl; and R^{10a} is hydrogen, halo or alkyl.

[00263] In one embodiment, R^{11} is



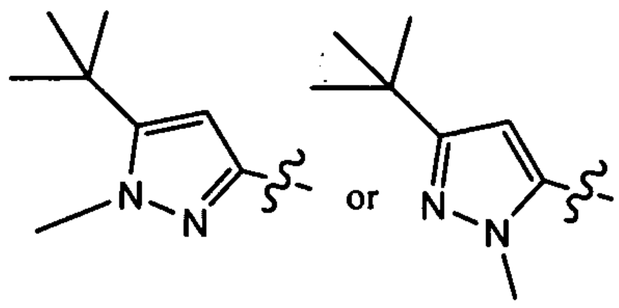
[00264] where R^{10} is as defined elsewhere herein.

[00265] In one embodiment, R^{11} is

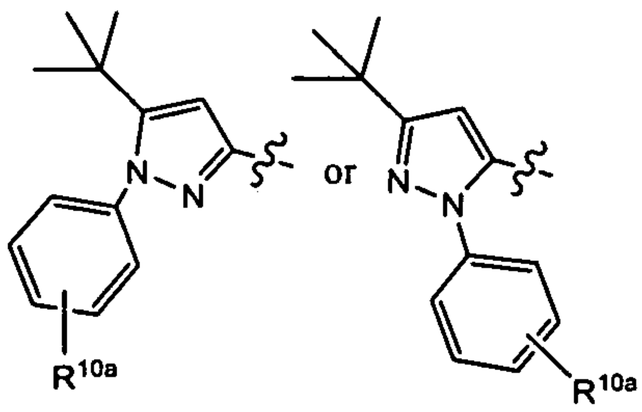


[00266] where R^{10} is hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl or alkoxyalkyl.

[00267] In one embodiment, R^{11} is

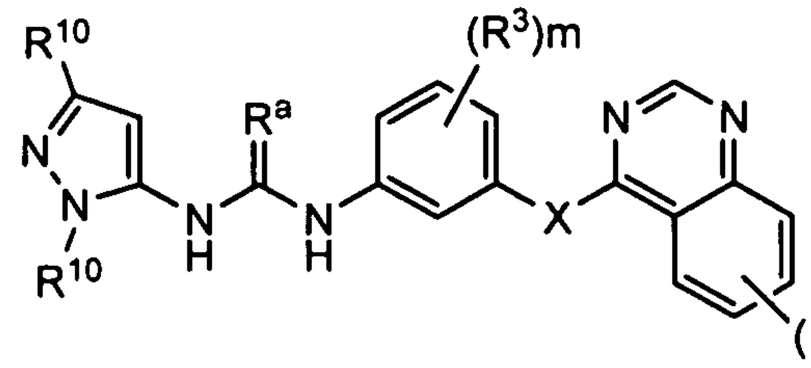


[00268] In one embodiment, R^{11} is

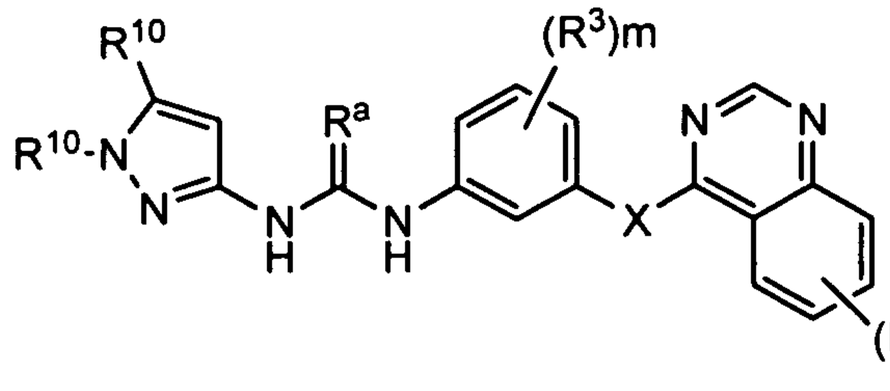


[00269] where R^{10a} is hydrogen, halo, haloalkyl, cyano, alkyl, alkoxy, aminoalkoxy, haloalkoxy or alkylsulfonyl.

[00270] In one embodiment, the compounds provided herein have formula VIIIA or VIIIB:



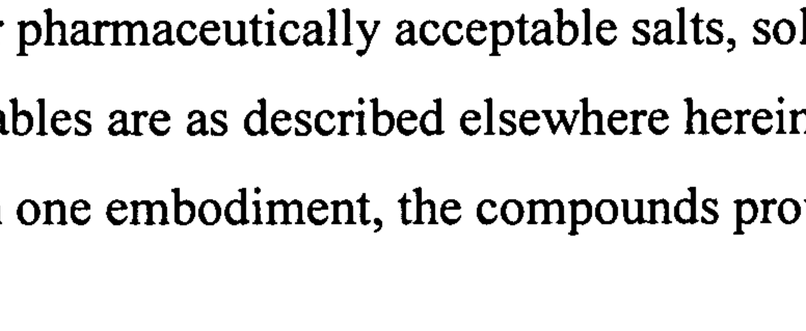
VIIIA or



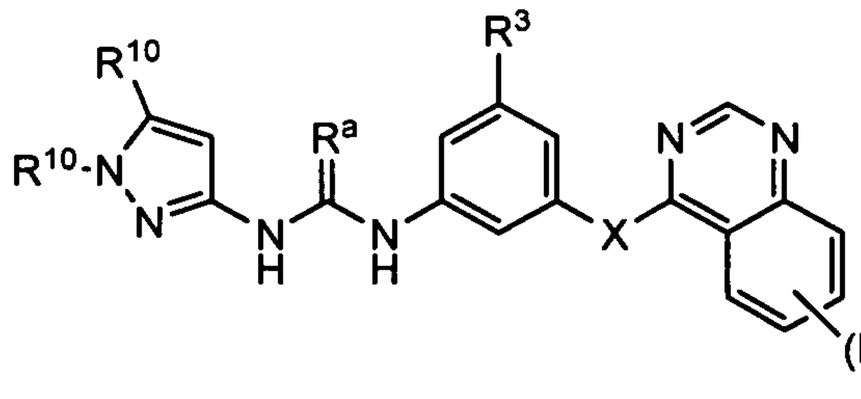
VIIIB

[00271] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[00272] In one embodiment, the compounds provided herein have formula VIIIC or VIIID:



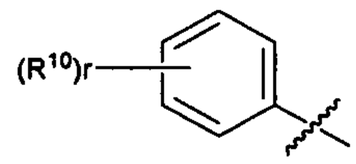
VIIIC or



VIIID

[00273] or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

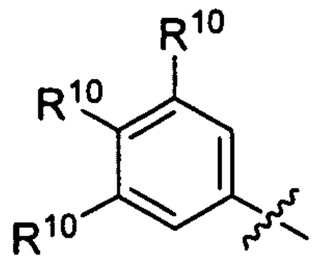
[00274] In one embodiment, R^{11} is



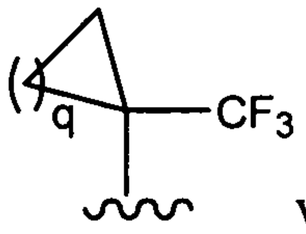
[00275] where each R^{10} is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, cycloalkyl, alkoxyalkyl, alkoxyalkoxy, aryl, heterocyclylalkyl and heterocyclylcarbonyl; and r is an integer from 0 to 3. In one

embodiment, r is 1, 2 or 3. In one embodiment, r is 1 or 2. In one embodiment, r is 1. In one embodiment, r is 0.

[00276] In one embodiment, R^{11} is

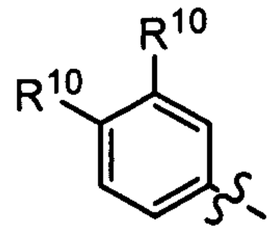


[00277] where each R^{10} is absent or is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, cycloalkyl, alkoxyalkyl, alkoxyalkoxy, aryl, heterocyclylalkyl and heterocyclylcarbonyl. In one embodiment, at least one R^{10} is absent and the other two R^{10} are each independently selected from –F, Cl, $C(CH_3)_3$, -$CH(CH_3)_2$, -$C(CH_3)_2CN$, -$C(CH_3)_2CF_3$, -$CF(CH_3)_2$, -$CF_2(CH_3)$,-$C(CH_3)(CH_2F)_2$, -$C(CH_3)_2CH_2OCH_3$, -$C(CH_3)_2CH_2OH$, CF_3, -OCH_3, -$O(CH_2)_2OCH_3$, -$O(CH_2)_2CH(CH_3)_2OCH_3$, morpholinomethyl, phenyl, cyclopentyl, or

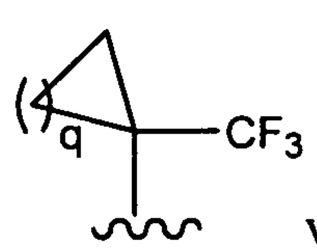


where q is an integer from 1 - 5.

[00278] In one embodiment, R^{11} is

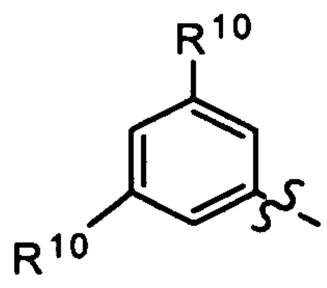


[00279] where each R^{10} is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, cycloalkyl, alkoxyalkyl, alkoxyalkoxy, aryl, heterocyclylalkyl and heterocyclylcarbonyl. In one embodiment, each R^{10} is –F, Cl, $C(CH_3)_3$, -$CH(CH_3)_2$, -$C(CH_3)_2CN$, -$C(CH_3)_2CF_3$, -$CF(CH_3)_2$, -$CF_2(CH_3)$,-$C(CH_3)(CH_2F)_2$, -$C(CH_3)_2CH_2OCH_3$, -$C(CH_3)_2CH_2OH$, CF_3, -OCH_3, -$O(CH_2)_2OCH_3$, -$O(CH_2)_2CH(CH_3)_2OCH_3$, morpholinomethyl, phenyl, cyclopentyl or

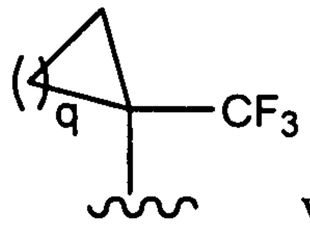


where q is an integer from 1 - 5.

[00280] In one embodiment, R^{11} is

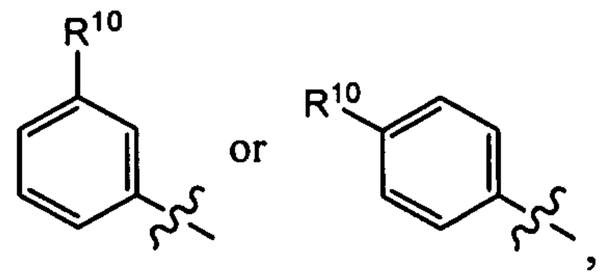


[00281] where each R^{10} is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, cycloalkyl, alkoxyalkyl, alkoxyalkoxy, aryl, heterocyclylalkyl and heterocyclylcarbonyl. In one embodiment, R^{10} is –F, Cl, $C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$,- $C(CH_3)(CH_2F)_2$, $-C(CH_3)_2CH_2OCH_3$, $-C(CH_3)_2CH_2OH$, CF_3, $-OCH_3$, $-O(CH_2)_2OCH_3$, $-O(CH_2)_2CH(CH_3)_2OCH_3$, morpholinomethyl, phenyl,

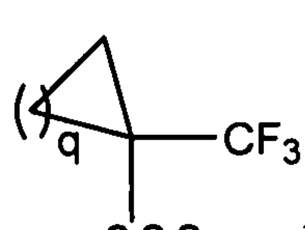


cyclopentyl or where q is an integer from 1 - 5.

[00282] In one embodiment, R^{11} is

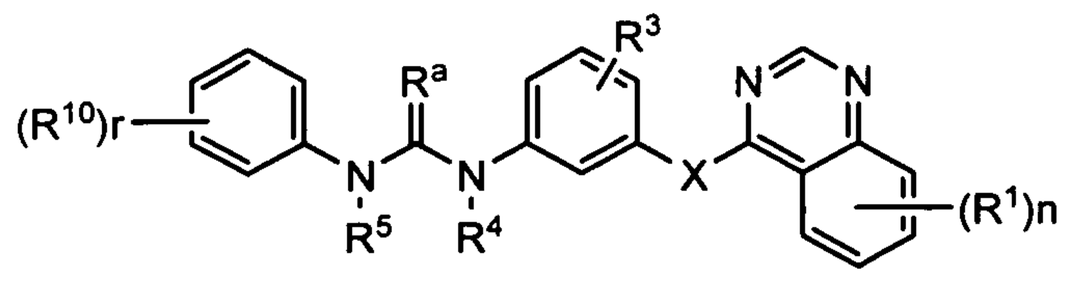


where R^{10} is as defined elsewhere herein. In one embodiment, R^{10} is —F, Cl, $C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$,- $C(CH_3)(CH_2F)_2$, $-C(CH_3)_2CH_2OCH_3$, $-C(CH_3)_2CH_2OH$, CF_3, $-OCH_3$, $-O(CH_2)_2OCH_3$, $-O(CH_2)_2CH(CH_3)_2OCH_3$, morpholinomethyl, phenyl,



cyclopentyl or where q is an integer from 1 - 5.

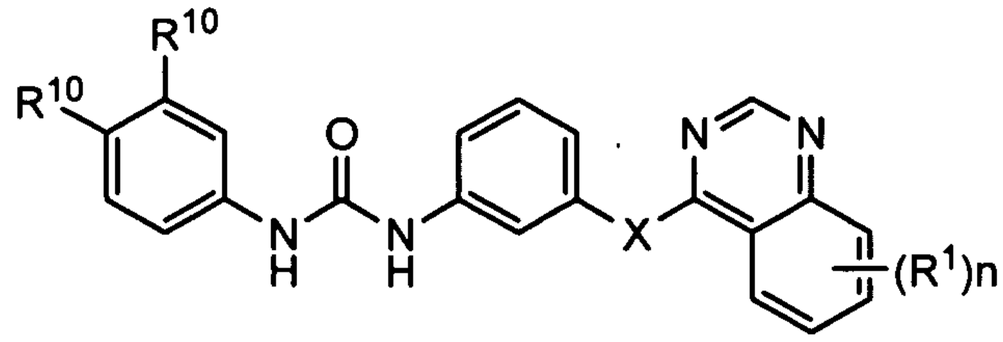
[00283] In one embodiment, the compounds provided herein have formula IX:

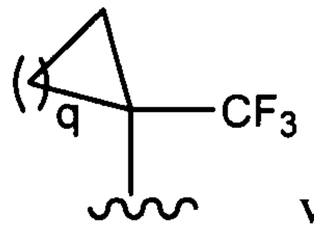


IX

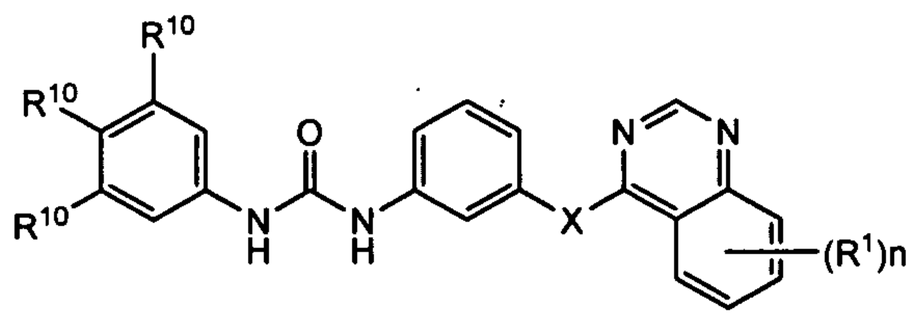
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In one embodiment, r is 0, 1 or 2. In one embodiment, X is $S(O)_t$ where t is an integer from 0 to 2. In one embodiment, X is S. In one embodiment, X is O.

[00284] In one embodiment, compounds provided have formula IXa:

[00285]  IXa

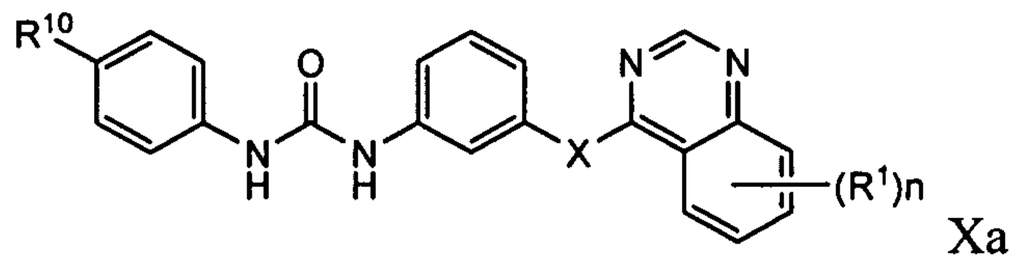
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In one embodiment, one R^{10} is $-C(CH_3)_3$, $-CH(CH_3)_2$, $-C(CH_3)_2CN$, $-C(CH_3)_2CF_3$, $-CF(CH_3)_2$, $-CF_2(CH_3)$, $-C(CH_3)_2CH_2OH$, $-C(CH_3)(CH_2F)_2$, $-C(CH_3)_2CH_2OCH_3$, CF_3, phenyl, cyclopentyl or  where q is an integer from 1 – 5 and the other R^{10} is alkoxy, haloalkoxy, alkoxyalkoxy or aminoalkoxy.

[00286] In one embodiment, the compounds provided herein have formula X:

 , X

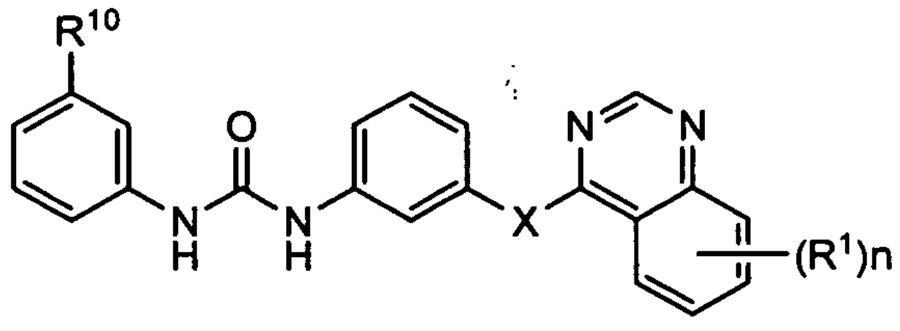
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[00287] In one embodiment, the compounds provided herein have formula Xa:

 Xa

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[00288] In one embodiment, the compounds provided herein have formula XI:

 XI

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[00289] In one embodiment, each R^1 is selected as follows:

i) each R^1 is absent or is independently selected from the group consisting of halo, nitro, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9N(R^7)_2$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$ and $-R^6N(R^7)C(O)R^8$; or

ii) any two adjacent R^1 groups form an alkylenedioxy group,

wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00290] In one embodiment, each R^1 is selected as follows:

i) each R^1 is absent or is independently selected from the group consisting of halo, nitro, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6CN$, $-R^6C(O)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$ and $-R^6N(R^7)C(O)R^8$; or

ii) any two adjacent R^1 groups form an alkylenedioxy group,

wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00291] In one embodiment, each R^1 is selected as follows:

i) each R^1 is absent or is independently selected from the group consisting of halo, nitro, amino, alkyl, cycloalkylalkyl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylcarbonylamino, $-R^6OR^7$, $-R^6OR^9OR^7$ and $-R^6OR^9N(R^7)_2$; or

ii) any two adjacent R^1 groups form an alkylenedioxy group;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently selected from (i) or (ii) below:

(i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

(ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

each R^9 is independently an alkylene chain or an alkenylene chain,

wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups, wherein each Q^1 is independently haloalkyl, alkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, -

$R^uC(J)OR^x$, $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x)\ R^uS(O)_2R^w$, wherein R^u is direct bond or alkylene, R^x is hydrogen or alkyl; R^w is alkyl and J is O, S or NR^x.

[00292] In one embodiment, each R^1 is absent or is independently selected from the group consisting of halo, amino, alkyl, heteroaryl, alkoxy, hydroxy, alkoxyalkoxy and cycloalkylcarbonylamino, wherein each R^1 is optionally substituted with one, two or three Q^1 groups, wherein each Q^1 is independently haloalkyl, alkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uC(J)OR^x$, $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x)\ R^uS(O)_2R^w$, wherein R^u is direct bond or alkylene, R^x is hydrogen or alkyl; R^w is alkyl and J is O, S or NR^x.

[00293] In one embodiment, each R^1 is absent or is independently selected from the group consisting of $-R^6OR^7$, $-R^6SR^7$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9N(R^7)_2$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$ and $-R^6N(R^7)C(O)R^8$;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently selected from (i) or (ii) below:

(i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

(ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl; and

each R^9 is independently an alkylene chain or an alkenylene chain;

wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00294] In one embodiment, each R^1 is selected from the group consisting of $-R^6OR^7$, $-R^6OR^9OR^7$ and $-R^6OR^9N(R^7)_2$;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently selected from (i) or (ii) below:

(i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

(ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

each R^9 is independently an alkylene chain or an alkenylene chain,

wherein each R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00295] In one embodiment, n is 2, and each R^1 is independently $-R^6OR^7$ or $-R^6OR^9OR^7$;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

each R^9 is independently an alkylene chain or an alkenylene chain,

wherein each R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00296] In one embodiment, n is 2, one R^1 is $-R^6OR^7$ or $-R^6OR^9OR^7$ and the other R^1 is heterocylylalkoxy;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

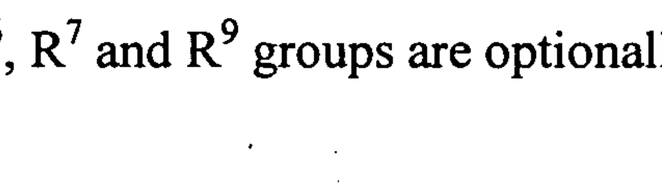
each R^9 is independently an alkylene chain or an alkenylene chain,

wherein each R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups.

[00297] In one embodiment, each R^1 is absent or is independently selected from the group consisting of fluoro, amino, methyl, methoxy, ethoxy, methoxyethoxy, ethoxyethoxy, cyclopropylcarbonylamino, furyl, and hydroxy, wherein furyl is substituted with $-R^uNH\ R^uS(O)_2R^w$, wherein R^u is methylene or ethylene and R^w is methyl.

[00298] In one embodiment, two adjacent R^1 groups form an alkylenedioxy group. In one embodiment, two adjacent R^1 groups form an ethylenedioxy group.

[00299] In one embodiment, each R^1 is independently



,

[00300] where each K is independently a direct bond, alkylene, alkenylene or alkynylene;

[00301] A is N or CR^{16};

[00302] Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

[00303] p is an integer from 0 to 2;

[00304] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl, cycloalkyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, $S(O)_tR^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, or $-C(O)SR^{12}$;

[00305] R^{15} is hydrogen, halo, nitro, cyano, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})_2$, $-S(O)_tR^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-C(O)SR^{12}$, or $-N(R^{12})S(O)_tR^{13}$;

[00306] R^{16} is hydrogen or alkyl;

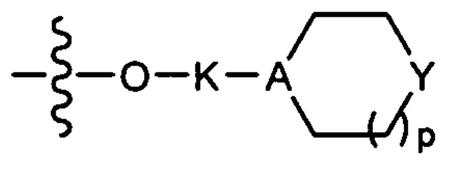
[00307] t is 1 or 2;

[00308] each R^{12} is independently selected from a group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl;

[00309] each R^{13} is independently selected from a group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl; and

[00310] each K is optionally substituted with one, two or three hydroxy or alkyl groups.

[00311] In one embodiment, each R^1 is independently



,

[00312] where K is a direct bond or alkylene, optionally substituted with one or two hydroxy groups;

[00313] A is N or CH;

[00314] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00315] p is an integer from 0 to 2;

[00316] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00317] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00318] t is 1 or 2;

[00319] R^{12} is hydrogen or alkyl; and

[00320] R^{13} is alkyl.

[00321] In certain embodiments, K is ethylene or propylene, optionally substituted with hydroxy. In one embodiment, K is a direct bond.

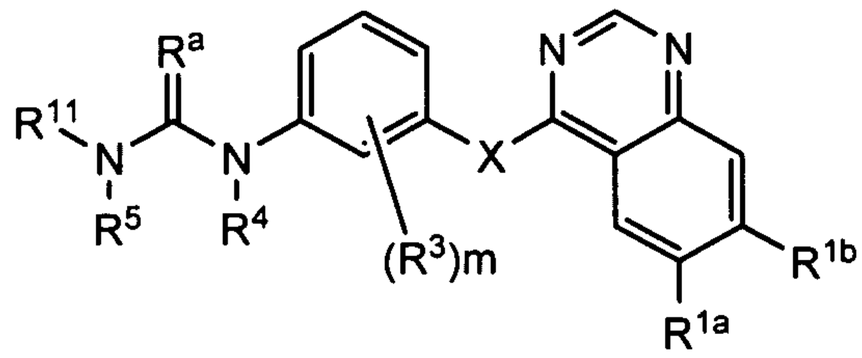
[00322] In one embodiment, R^{13} is methyl.

[00323] In certain embodiments, R^{14} is –H, -OH, $-CH_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2OH$ or $–S(O)_2CH_3$.

[00324] In certain embodiments, R^{15} is –H, -OH, $-CH_3$, CH_2OH or $-CH_2CH_2OH$.

[00325] In one embodiment, p is 0 or 1. In one embodiment, p is 0. In one embodiment, p is 1.

[00326] In another aspect, provided herein is a compound of formula XII:



XII

[00327] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^a is O or S;

[00328] X is O or S;

[00329] R^{1a} and R^{1b} are each independently selected from the group consisting of $-R^6OR^7$, $-R^6SR^7$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9N(R^7)_2$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6OC(O)N(R^7)_2$ and $-R^6N(R^7)C(O)R^8$;

[00330] each R^6 is a direct bond;

[00331] each R^7 is independently selected from (i) or (ii) below:

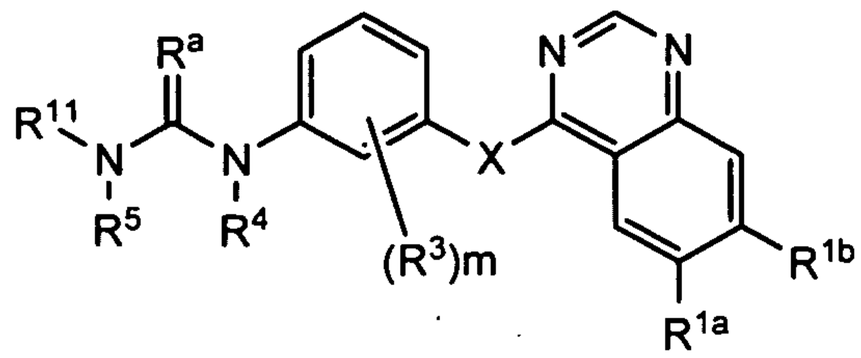
[00332] (i) each R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl, or

[00333] (ii) two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

[00334] each R^9 is independently an alkylene chain or an alkenylene chain;

[00335] wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups; and the other variables are as defined elsewhere herein.

[00336] In another aspect, provided herein is a compound of formula XII:



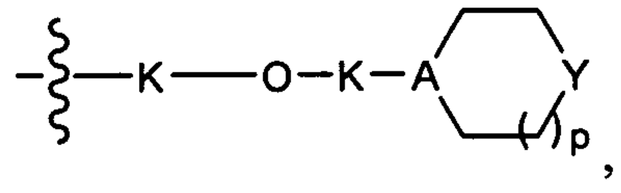
XII

[00337] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^a is O or S;

[00338] X is O or S;

[00339] R^{1a} and R^{1b} are selected as follows:

[00340] i) R^{1a} and R^{1b} are each independently selected from hydrogen, halo, amino, alkyl, alkoxy, hydroxy, heteroaryl, alkoxyalkoxy, cycloalkylcarbonylamino and a group of formula:



,

[00341] where each K is independently a direct bond or alkylene;

[00342] A is N or CR^{16};

[00343] Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

[00344] p is an integer from 0 to 2;

[00345] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl, cycloalkyl, heteroarylalkyl, arylalkyl, $S(O)_tR^{13}$ or $-C(O)R^{12}$;

[00346] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00347] R^{16} is hydrogen or alkyl;

[00348] t is 1 or 2;

[00349] each R^{12} is independently selected from a group consisting of hydrogen or alkyl;

[00350] R^{13} is alkyl;

[00351] each K is optionally substituted with one, two or three hydroxy or alkyl groups; or

[00352] ii) R^{1a} and R^{1b} groups form an alkylenedioxy group;

[00353] each R^{1a} and R^{1b} is independently optionally substituted with one or two Q^1 groups selected from haloalkyl, alkyl, $-R^uOR^x$, $-R^uC(J)OR^x$, $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2R^w$ and $-R^uN(R^x)\,R^uS(O)_2R^w$, wherein R^u is direct bond or alkylene, R^x is hydrogen or alkyl; R^w is alkyl and J is O, S or NR^x; and

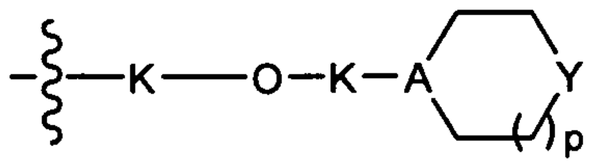
[00354] the other variables are as defined elsewhere herein.

[00355] In one embodiment, at least one of R^{1a} or R^{1b} is other than hydrogen. In one embodiment, A is CH. In one embodiment, p is 0 and A is CH.

[00356] In one embodiment, R^{1b} is hydrogen and R^{1a} is heteroaryl group substituted with $-R^uN(R^x)\ R^uS(O)_2R^w$, wherein R^u is direct bond or alkylene, R^x is hydrogen or alkyl; R^w is alkyl. In one embodiment, R^{1b} is hydrogen and R^{1a} is furyl substituted with $-R^uN(R^x)\ R^uS(O)_2R^w$, wherein R^u is methylene or ethylene, R^x is hydrogen and R^w is methyl.

[00357] In one embodiment, one of R^{1a} and R^{1b} is $-OR^7$ where R^7 is alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl; and the other of R^{1a} and R^{1b} is a group of formula

[00358]



[00359] where each K is independently a direct bond or alkylene;

[00360] A is N or CR^{16};

[00361] Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

[00362] p is an integer from 0 to 2;

[00363] R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heteroarylalkyl, arylalkyl, $S(O)_tR^{13}$ or $-C(O)R^{12}$;

[00364] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00365] R^{16} is hydrogen or alkyl;

[00366] t is 1 or 2;

[00367] each R^{12} is independently selected from a group consisting of hydrogen or alkyl;

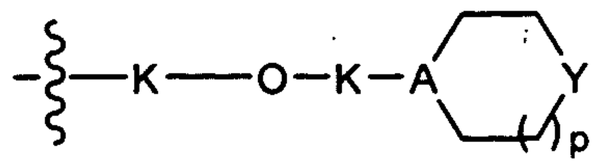
[00368] R^{13} is alkyl;

[00369] each K is optionally substituted with one, two or three hydroxy or alkyl groups; and

[00370] each R^{1a} and R^{1b} is independently optionally substituted with one or two Q^1 groups described elsewhere herein.

[00371] In one embodiment, R^{1a} is $-OR^7$ where R^7 is alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl; and R^{1b} is a group of formula

[00372]



[00373] where each K is independently a direct bond or alkylene;

[00374] A is N or CR^{16};

[00375] Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

[00376] p is an integer from 0 to 2;

[00377] R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heteroarylalkyl, arylalkyl, $S(O)_tR^{13}$ or $-C(O)R^{12}$;

[00378] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00379] R^{16} is hydrogen or alkyl;

[00380] t is 1 or 2;

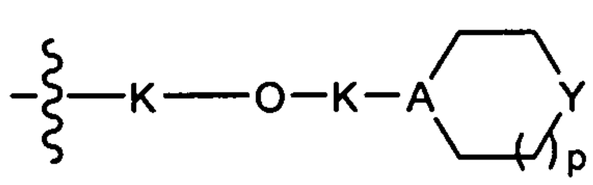
[00381] each R^{12} is independently selected from a group consisting of hydrogen or alkyl;

[00382] R^{13} is alkyl;

[00383] each K is optionally substituted with one, two or three hydroxy or alkyl groups; and

[00384] each R^{1a} and R^{1b} is independently optionally substituted with one or two Q^1 groups described elsewhere herein.

[00385] In one embodiment, R^{1b} is $-R^uOR^x$, and R^{1a} is a group of formula

[00386] 

[00387] where each K is independently a direct bond or alkylene;

[00388] A is N or CR^{16};

[00389] Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

[00390] p is an integer from 0 to 2;

[00391] R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heteroarylalkyl, arylalkyl, $S(O)_tR^{13}$ or $-C(O)R^{12}$;

[00392] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00393] R^{16} is hydrogen or alkyl;

[00394] t is 1 or 2;

[00395] each R^{12} is independently selected from a group consisting of hydrogen or alkyl;

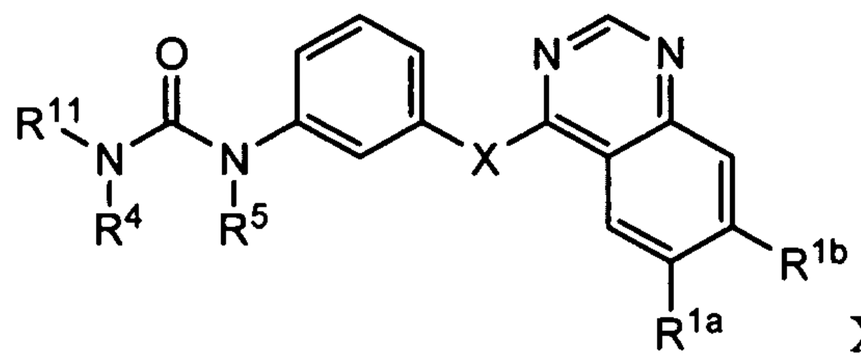
[00396] R^{13} is alkyl;

[00397] each K is optionally substituted with one, two or three hydroxy or alkyl groups; and

[00398] each R^{1a} and R^{1b} is independently optionally substituted with one or two Q^1 groups described elsewhere herein.

[00399] In another aspect, provided herein is a compound of formula XIII:

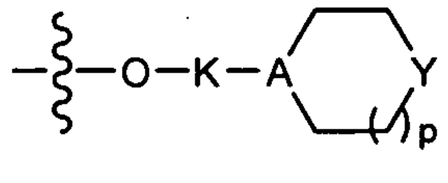
[00400]



XIII

[00401] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^{1a} and R^{1b} are selected as follows:

[00402] i) R^{1a} and R^{1b} are each independently hydrogen, alkoxy, alkoxyalkoxy, substituted or unsubstituted heteroaryl, or a group of formula:



,

[00403] where K is a direct bond or alkylene, optionally substituted with a hydroxy group;

[00404] A is N or CH;

[00405] Y is –O-, $-S(O)_2-$, $-N(R^{14})-$ or $-C(H)R^{15}-$;

[00406] p is an integer from 0 to 2;

[00407] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00408] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00409] t is 1 or 2;

[00410] R^{12} is hydrogen or alkyl; and

[00411] R^{13} is alkyl; or

[00412] ii) R^{1a} and R^{1b} groups together form an alkylenedioxy group;

[00413] where the substitutents on the heteroaryl, when present, are selected from one two or three groups selected from halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy and hydroxyl;

[00414] X is O or S;

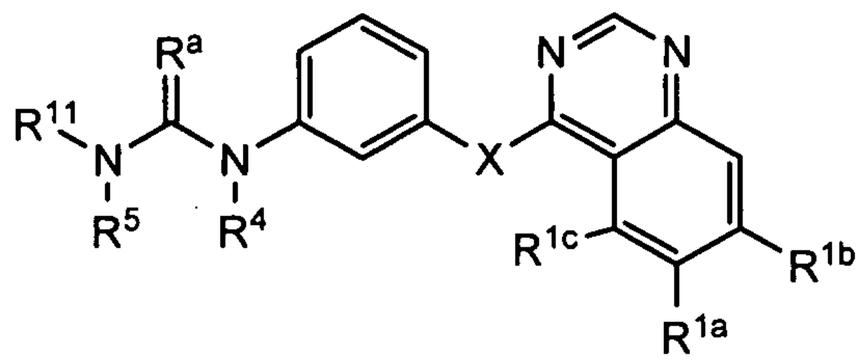
[00415] R^3 is halo;

[00416] R^4 and R^5 are each hydrogen; and

[00417] R^{11} is optionally substituted phenyl, isoxazolyl or pyrazolyl, wherein substituents when present are selected from one or two R^{10} groups, each of which is independently selected from hydrogen, halo, alkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl and heteroaryl, where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl.

[00418] In one embodiment, the compound has formula XII or XIII, wherein A is CH and the other variables are as described elsewhere herein. In one embodiment, the compound has formula XII or XIII, wherein p is 0; A is CH and the other variables are as described elsewhere herein.

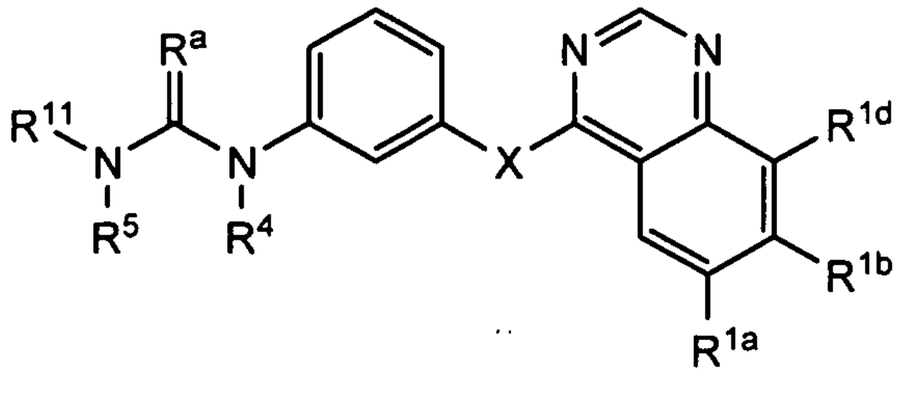
[00419] In another aspect, provided herein is a compound of formula XIV:



XIV

[00420] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^{1c} is hydrogen, halo, alkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, heterocyclyloxy or aryl; and the other variables are as described elsewhere herein.

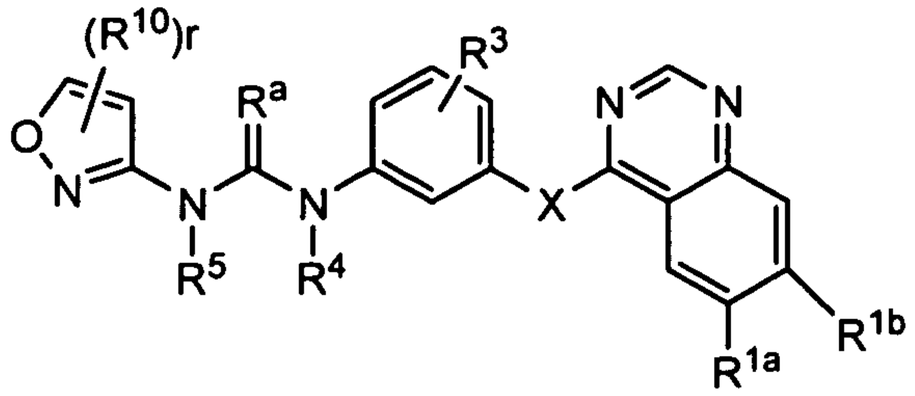
[00421] In another aspect, provided herein is a compound of formula XV:



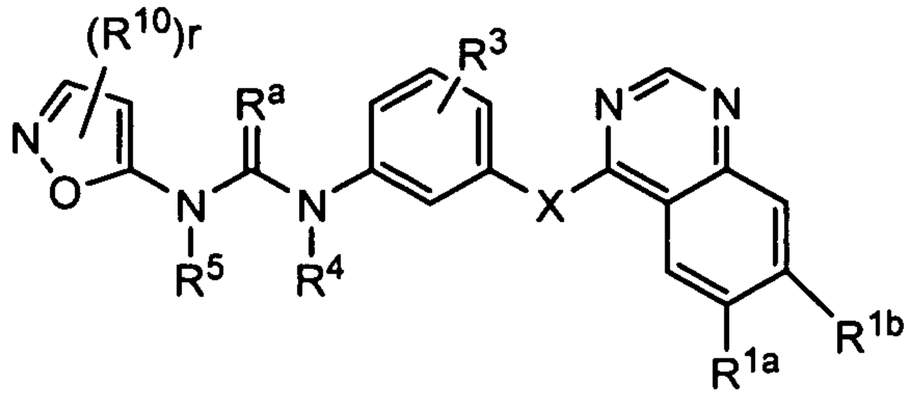
XV

[00422] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^{1d} is hydrogen, halo, alkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy or aryl; and the other variables are as described elsewhere herein.

[00423] In another aspect, provided herein is a compound of formula XVIA or XVIB:



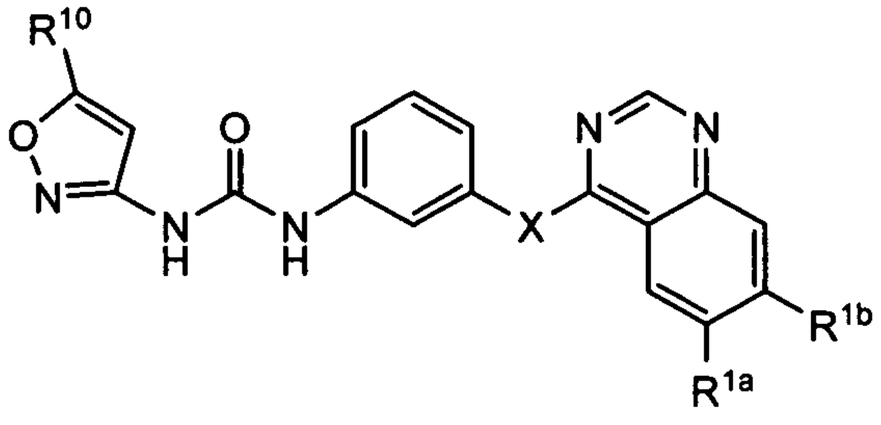
XVIA



XVIB

[00424] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R^{1a} and R^{1b} are selected from Q^1 and the other variables are described elsewhere herein. In one embodiment, the compounds have formula XVIA or XVIB wherein R^{10} is selected from hydrogen, halo, alkyl, cyanoalkyl, haloalkyl or cycloalkyl; and the other variables are as described elsewhere herein.

[00425] In another aspect, provided herein is a compound of formula XVII:

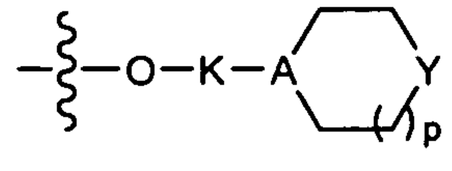


XVII

[00426] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein the variables are as described elsewhere herein. In one embodiment, the compounds have formula XVII, wherein X is O or S;

[00427] R^{1a} and R^{1b} are selected as follows:

[00428] i) R^{1a} and R^{1b} are each independently methoxy, methoxyethoxy, methylsulfonylpropyloxy, or a group of formula:



[00429] where K is ethylene or propylene, optionally substituted with a hydroxy group;

[00430] A is N or CH;

[00431] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

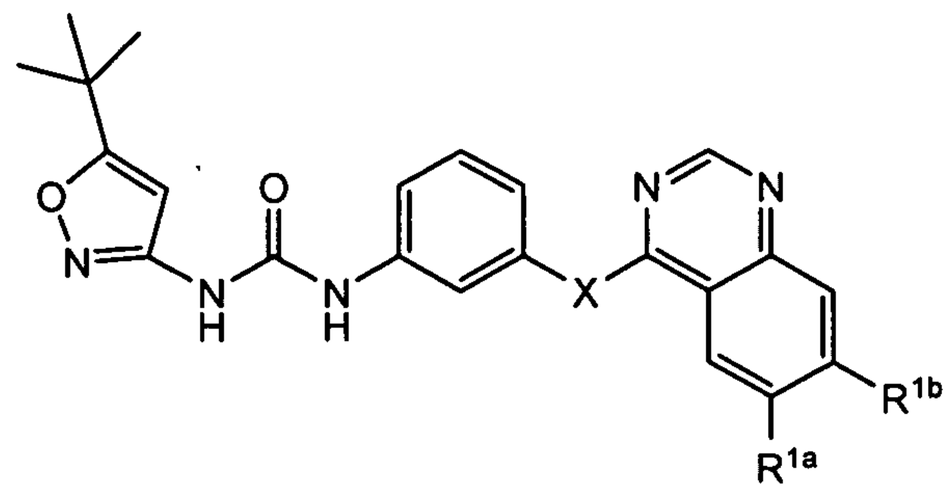
[00432] p is 1;

[00433] R^{14} is hydrogen, methyl, hydroxyethyl, or methylsulfonyl;

[00434] R^{15} is hydrogen, hydroxymethyl, hydroxyethyl or hydroxy; and

[00435] ii) R^{1a} and R^{1b} groups together with the carbon atoms on which they are substituted form an ethylenedioxy group.

[00436] In another aspect, provided herein is a compound of formula XVIII:

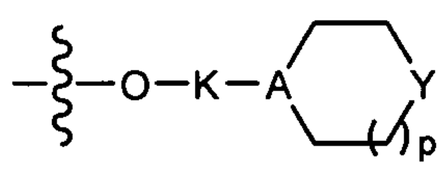


XVIII,

[00437] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X is O or S;

[00438] R^{1a} and R^{1b} are selected as follows:

[00439] i) R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy, alkylsulfonylalkoxy or a group of formula:



,

[00440] where K is a direct bond or alkylene, optionally substituted with a hydroxy group;

[00441] A is N or CH;

[00442] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00443] p is 0 or 1;

[00444] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00445] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00446] t is 1 or 2;

[00447] R^{12} is hydrogen or alkyl; and

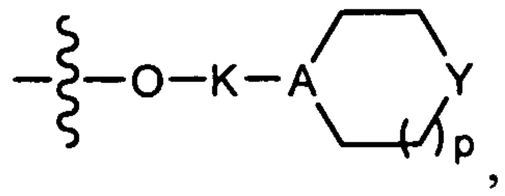
[00448] R^{13} is alkyl; or

[00449] ii) R^{1a} and R^{1b} groups together form an alkylenedioxy group.

[00450] In one embodiment, the compound is of formula XVIII or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X is O or S;

[00451] R^{1a} and R^{1b} are selected as follows:

[00452] i) R^{1a} and R^{1b} are each independently methoxy, methoxyethoxy, methylsulfonylpropyloxy, or a group of formula:



[00453] where K is ethylene or propylene, optionally substituted with a hydroxy group;

[00454] A is N or CH;

[00455] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00456] p is 1;

[00457] R^{14} is hydrogen, methyl, hydroxyethyl, or methylsulfonyl;

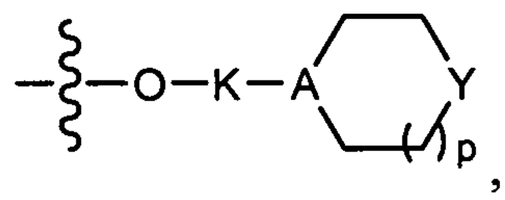
[00458] R^{15} is hydrogen, hydroxymethyl, hydroxyethyl or hydroxy; or

[00459] ii) R^{1a} and R^{1b} groups together with the carbon atoms on which they are substituted form an ethylenedioxy group.

[00460] In another aspect, provided herein is a compound of formula XVII or XVIII or a pharmaceutically acceptable salt, solvate or hydrate thereof,

[00461] wherein X is O or S;

[00462] R^{1a} and R^{1b} are each independently hydrogen, fluoro, methoxy, ethoxy, methoxyethoxy, or a group of formula:



[00463] where K is a direct bond or alkylene;

[00464] A is CH;

[00465] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00466] p is 0;

[00467] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00468] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00469] t is 1 or 2;

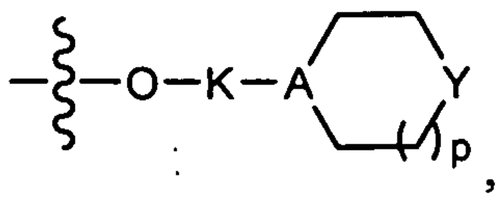
[00470] R^{12} is hydrogen or alkyl; and

[00471] R^{13} is alkyl.

[00472] In another aspect, provided herein is a compound of formula XVII or XVIII or a pharmaceutically acceptable salt, solvate or hydrate thereof,

wherein X is O or S;

at least one of R^{1a} or R^{1b} is hydrogen and the other is hydrogen, fluoro, methoxy, ethoxy, methoxyethoxy or a group of formula:



where K is a direct bond or alkylene;

A is CH;

Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

p is 0;

R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

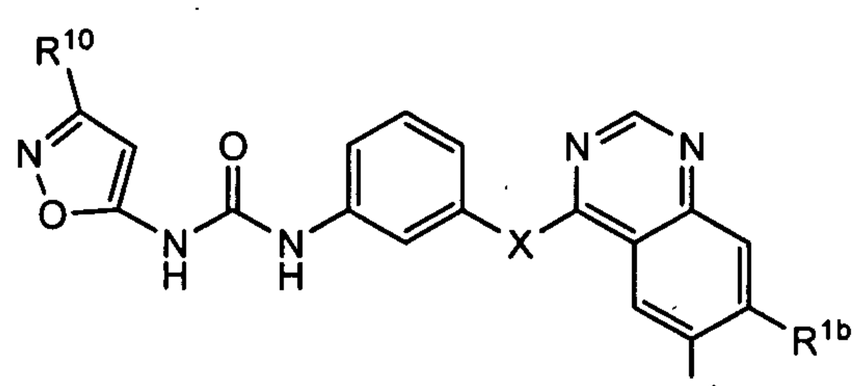
R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

t is 1 or 2;

R^{12} is hydrogen or alkyl; and

R^{13} is alkyl.

[00473] In another aspect, provided herein is a compound of formula XIX:

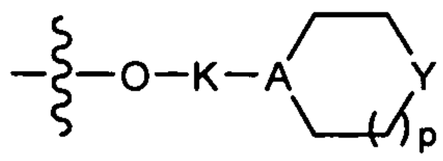


XIX

[00474] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein the variables are as described elsewhere herein. In one embodiment, the compounds have formula XIX, wherein X is O or S;

[00475] R^{1a} and R^{1b} are selected as follows:

[00476] i) R^{1a} and R^{1b} are each independently methoxy, methoxyethoxy, methylsulfonylpropyloxy, or a group of formula:



[00477] where K is ethylene or propylene, optionally substituted with a hydroxy group;

[00478] A is N or CH;

[00479] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00480] p is 1;

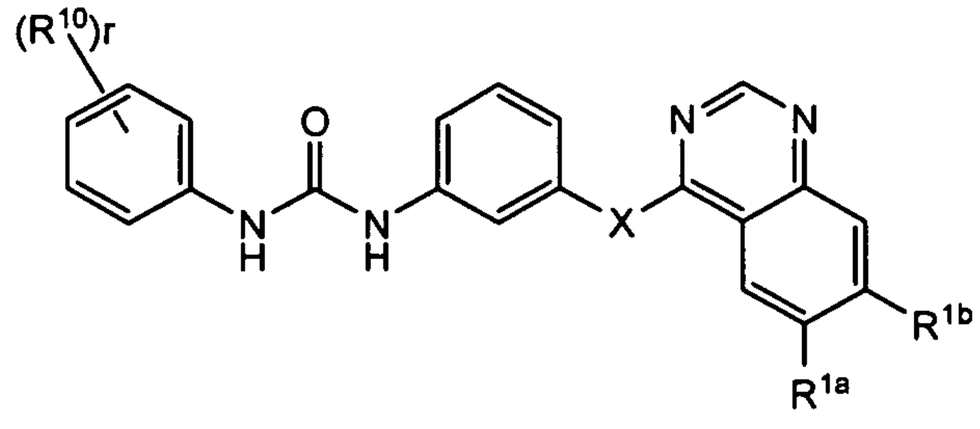
[00481] R^{14} is hydrogen, methyl, hydroxyethyl, or methylsulfonyl;

[00482] R^{15} is hydrogen, hydroxymethyl, hydroxyethyl or hydroxy; and

[00483] ii) R^{1a} and R^{1b} groups together with the carbon atoms on which they are substituted form an ethylenedioxy group;

[00484] R^{10} is selected from hydrogen, halo, alkyl, cyanoalkyl, haloalkyl or cycloalkyl.

[00485] In another aspect, provided herein is a compound of formula XX:



XX,

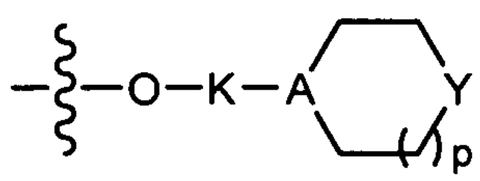
[00486] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein each R^{10} is independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclylalkyl and heterocyclylcarbonyl, where the alkyl group is optionally substituted with 1 or 2 groups selected from halo, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl and alkoxycarbonyl; r is an integer from 0 to 3; and the other variables are as described elsewhere herein. In one embodiment, each R^{10} is independently selected from hydrogen, halo, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl and alkoxy and r is 0, 1 or 2.

[00487] In another aspect, provided herein is a compound of formula XX or a pharmaceutically acceptable salt, solvate or hydrate thereof,

[00488] wherein X is O or S;

[00489] R^{1a} and R^{1b} are selected as follows:

[00490] i) R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy or a group of formula:



;

[00491] where K is a direct bond or alkylene, optionally substituted with a hydroxy group;

[00492] A is N or CH;

[00493] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00494] p is an integer from 0 to 2;

[00495] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00496] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or -OR^{12};

[00497] t is 1 or 2;

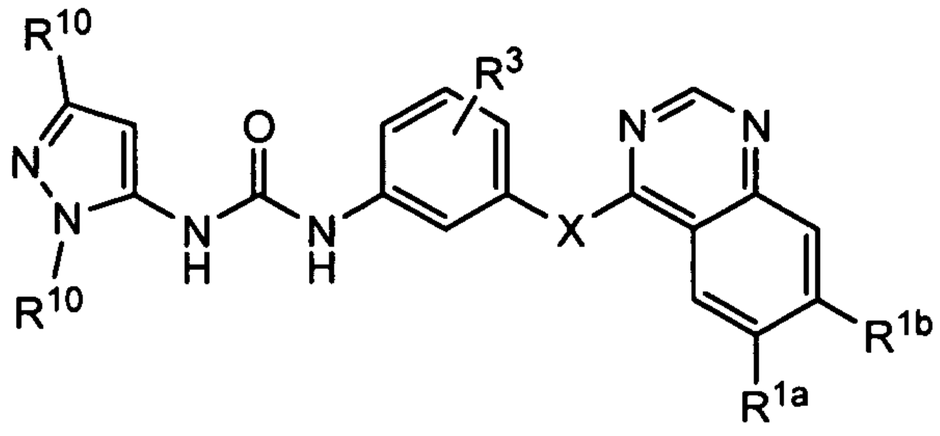
[00498] R^{12} is hydrogen or alkyl; and

[00499] R^{13} is alkyl; or

[00500] ii) R^{1a} and R^{1b} groups together form an alkylenedioxy group; and

[00501] r is 0, 1, 2 or 3.

[00502] In another aspect, provided herein is a compound of formula XXI:

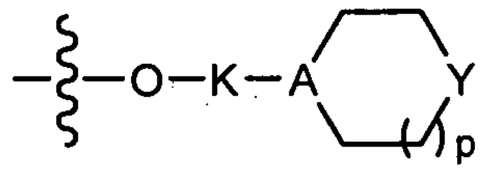


XXI,

[00503] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X is O or S;

[00504] R^{1a} and R^{1b} are selected as follows:

[00505] i) R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy, alkylsulfonylalkoxy or a group of formula:



,

[00506] where K is a direct bond or alkylene, optionally substituted with a hydroxy group;

[00507] A is N or CH;

[00508] Y is –O, -$S(O)_2$, -$N(R^{14})$ or -$C(H)R^{15}$;

[00509] p is 0 or 1;

[00510] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00511] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or -OR^{12};

[00512] t is 1 or 2;

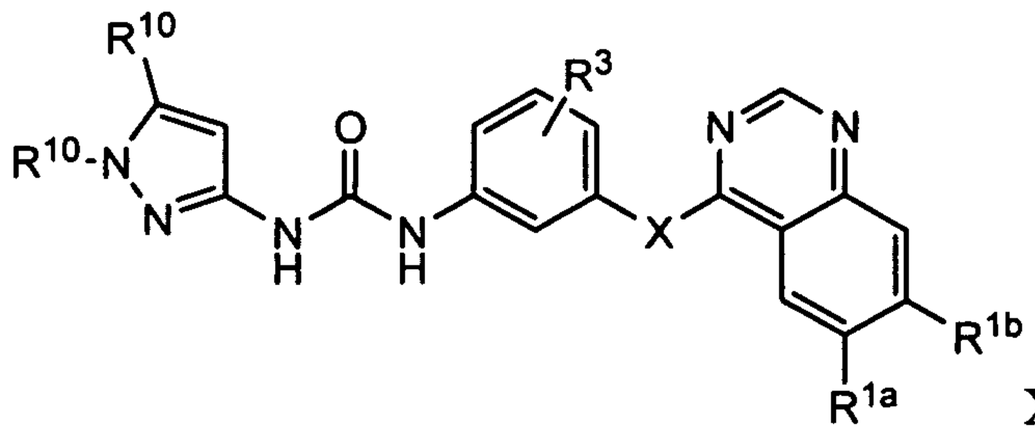
[00513] R^{12} is hydrogen or alkyl; and

[00514] R^{13} is alkyl; or

[00515] ii) R^{1a} and R^{1b} groups together form an alkylenedioxy group

[00516] each R^{10} is independently selected from alkyl, haloalkyl, hydroxyalkyl, aryl, haloaryl, alkylaryl or heteroaryl.

[00517] In another aspect, provided herein is a compound of formula XXII:

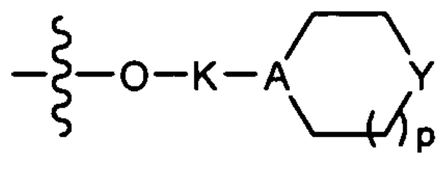


XXII,

[00518] or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X is O or S;

[00519] R^{1a} and R^{1b} are selected as follows:

[00520] i) R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy, alkylsulfonylalkoxy or a group of formula:



,

[00521] where K is a direct bond or alkylene, optionally substituted with a hydroxy group;

[00522] A is N or CH;

[00523] Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

[00524] p is 0 or 1;

[00525] R^{14} is hydrogen, alkyl, haloalkyl, hydroxy(C_2-C_6)alkyl or $S(O)_tR^{13}$;

[00526] R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

[00527] t is 1 or 2;

[00528] R^{12} is hydrogen or alkyl; and

[00529] R^{13} is alkyl; or

[00530] ii) R^{1a} and R^{1b} groups together form an alkylenedioxy group

[00531] each R^{10} is independently selected from alkyl, haloalkyl, hydroxyalkyl, aryl, haloaryl, alkylaryl or heteroaryl.

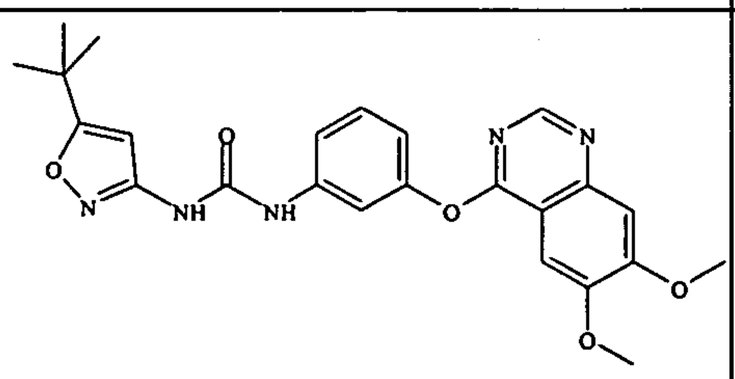
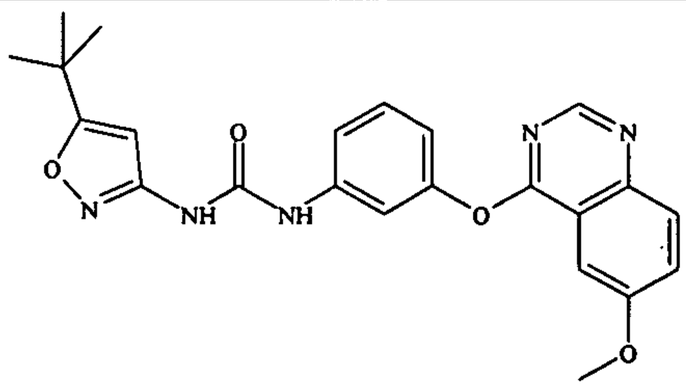
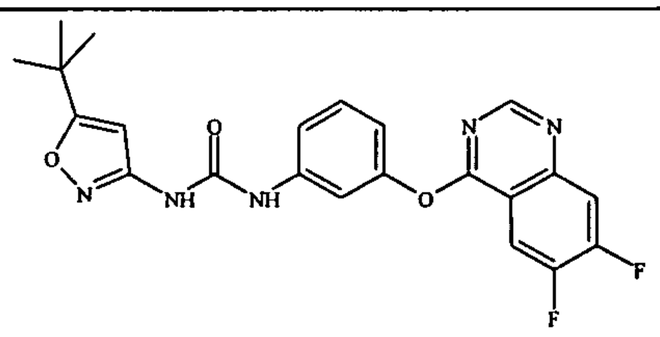
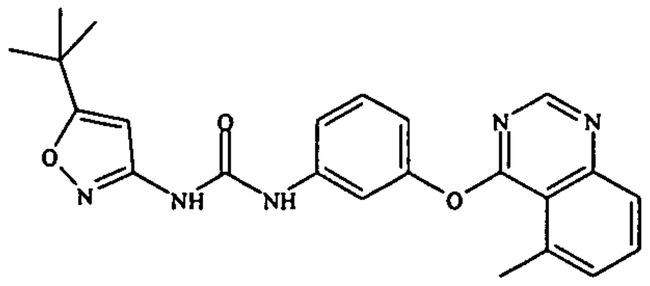
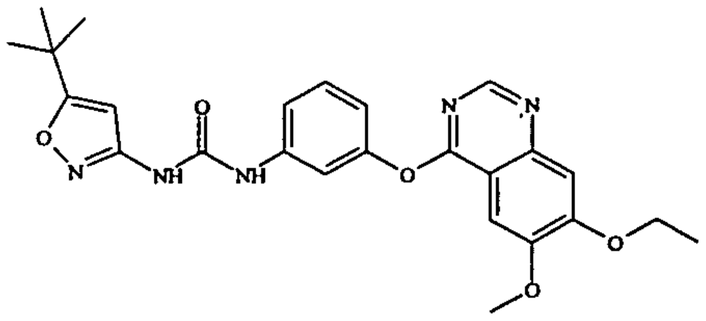
[00532] In one embodiment, the compound has formula XXI or XXII or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein each R^{10} is independently selected from *tert*-butyl, methyl, trifluoro *tert*-butyl, phenyl, p-fluorophenyl or p-methylphenyl.

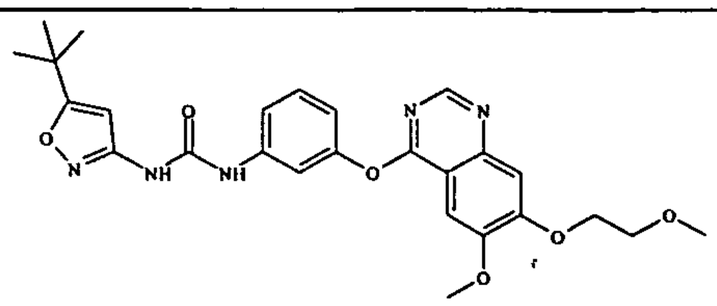
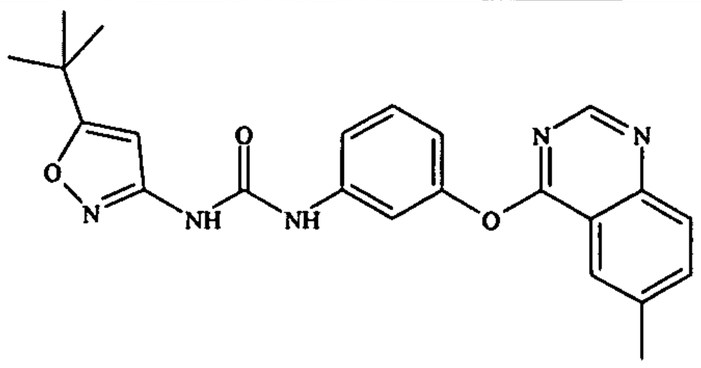
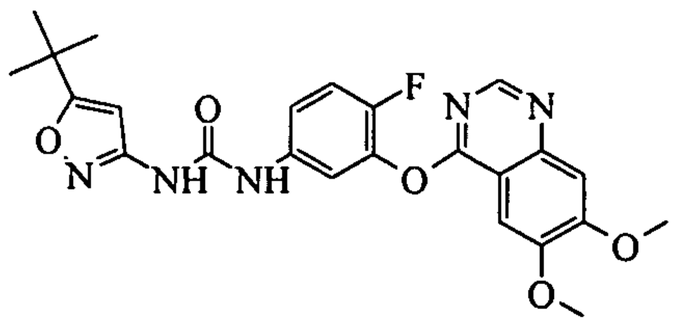
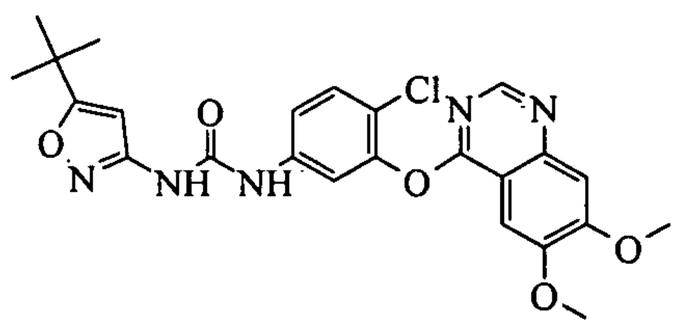
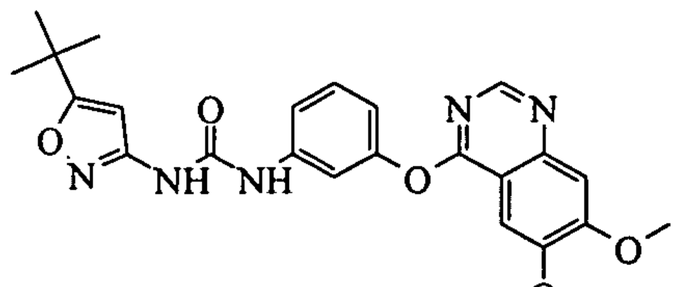
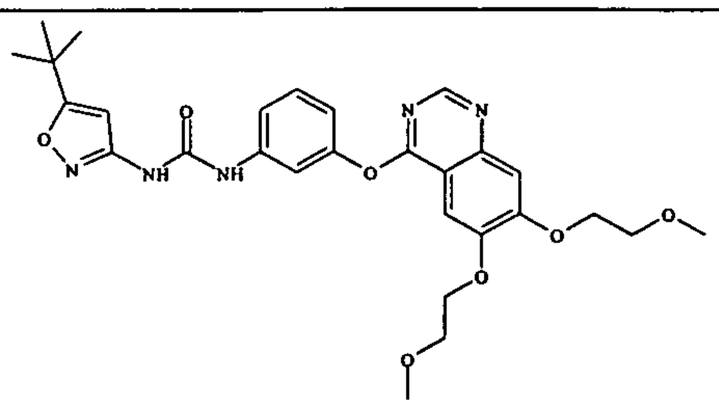
[00533] In one embodiment, the compound is selected from formula XVI-XXIII, wherein p is 0; A is CH and the other variables are as described elsewhere herein.

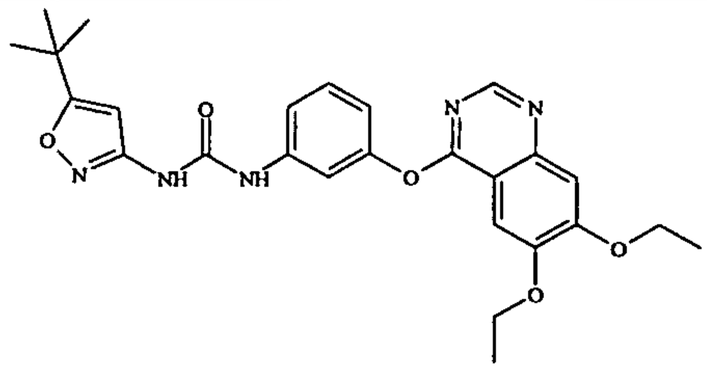
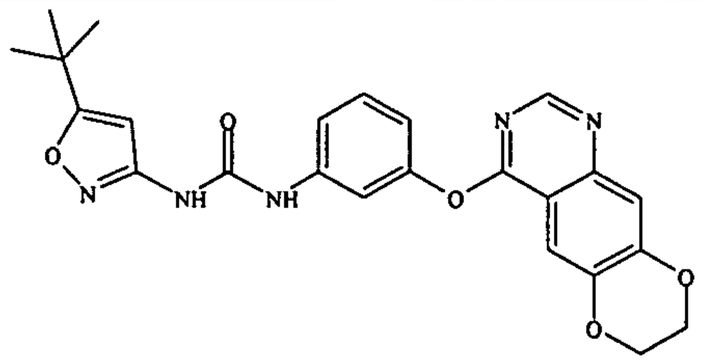
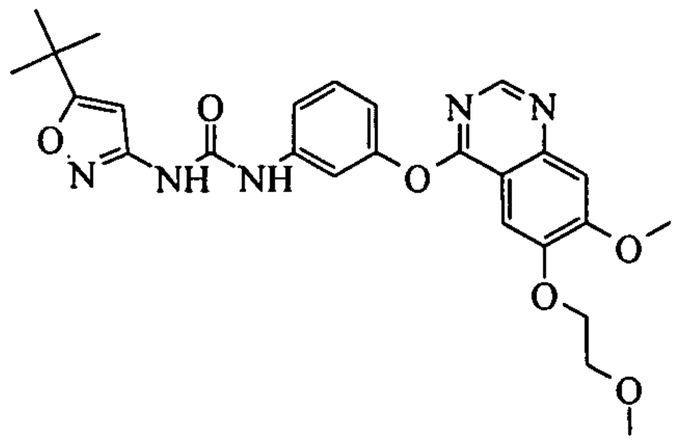
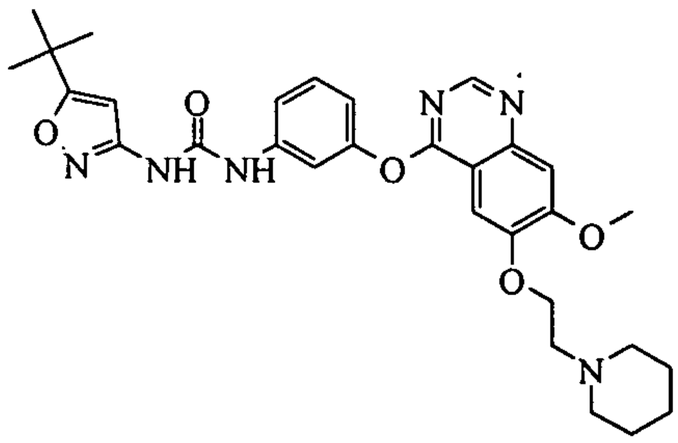
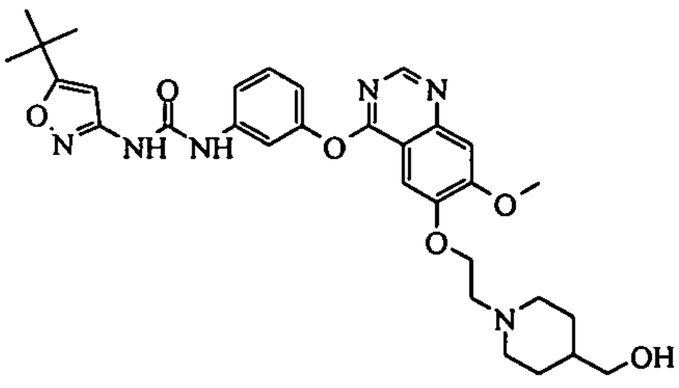
[00534] In one embodiment, the compound is selected from a group consisting of the compounds in Table 1.

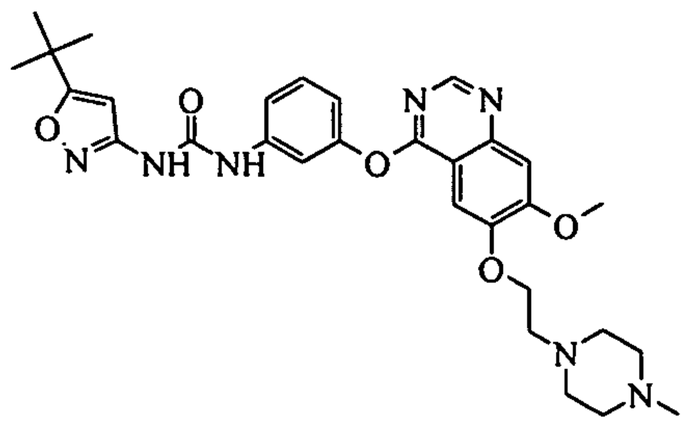
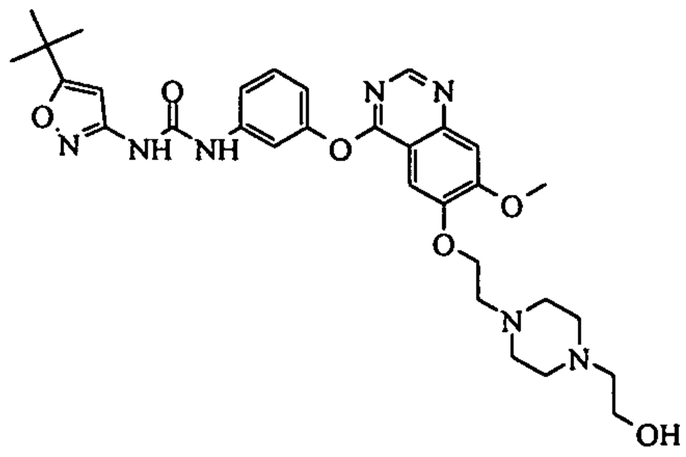
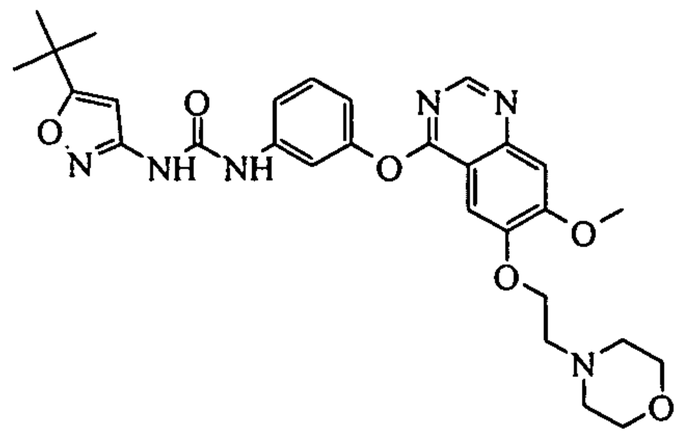
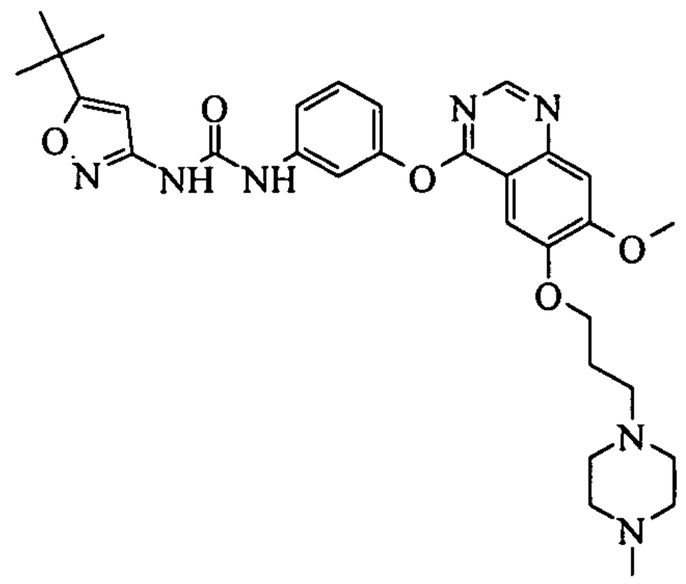
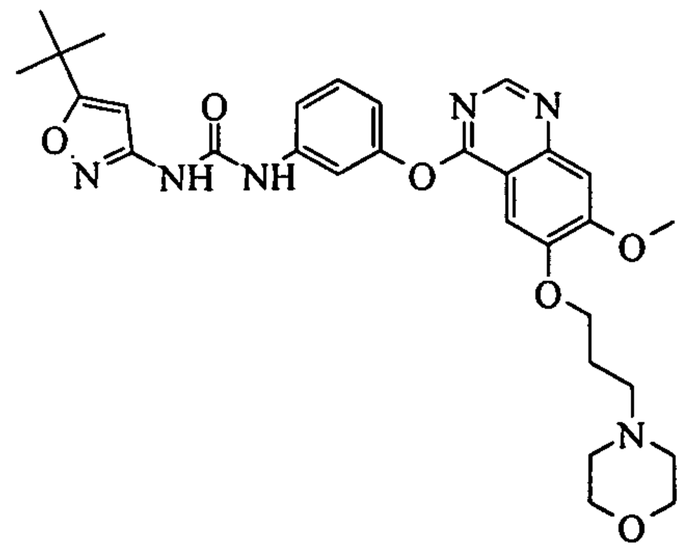
[00535] Certain exemplary compounds are provided in Table 1.

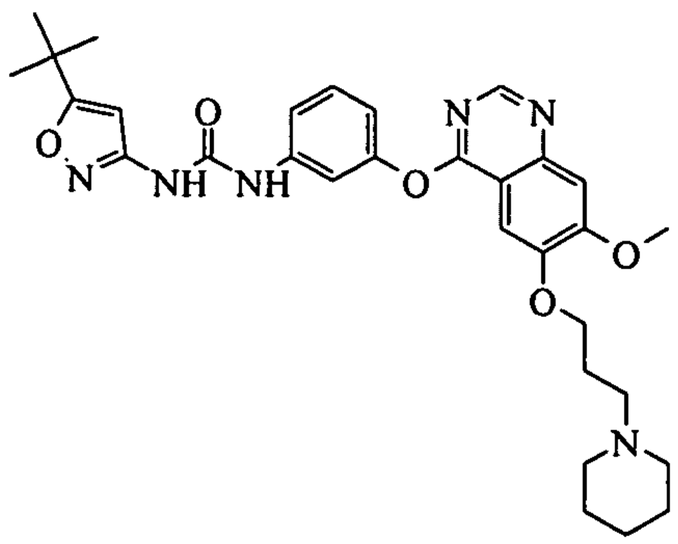
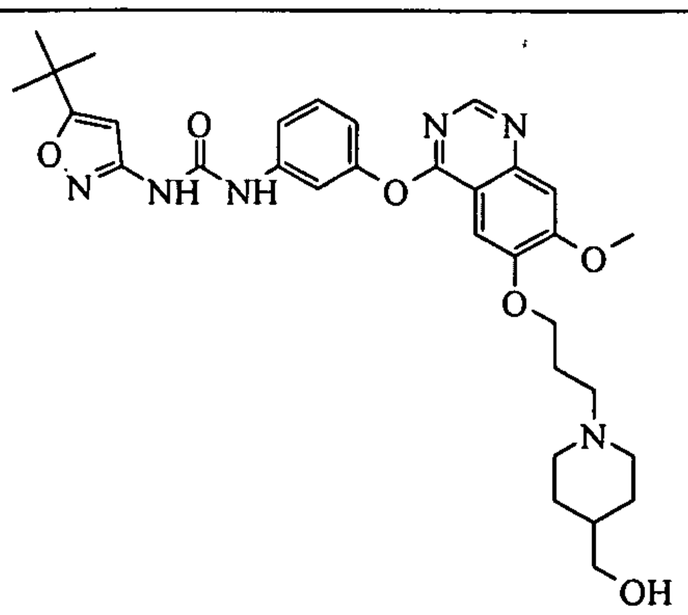
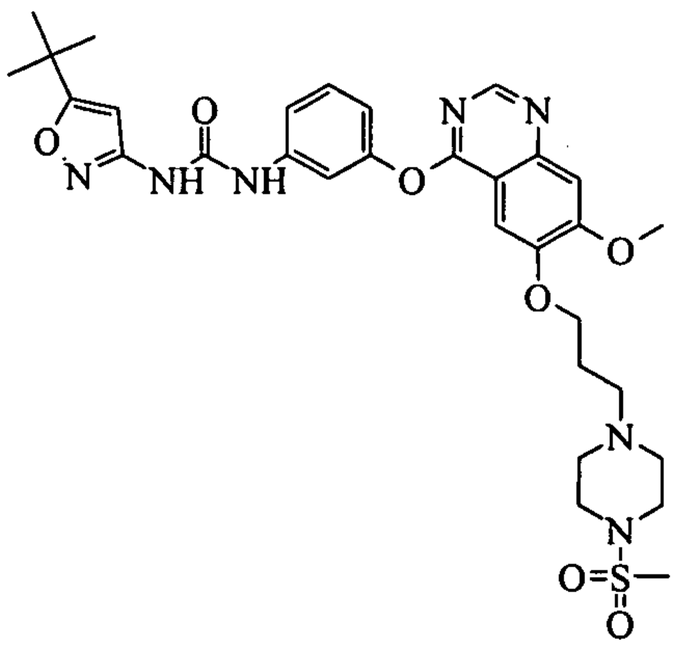
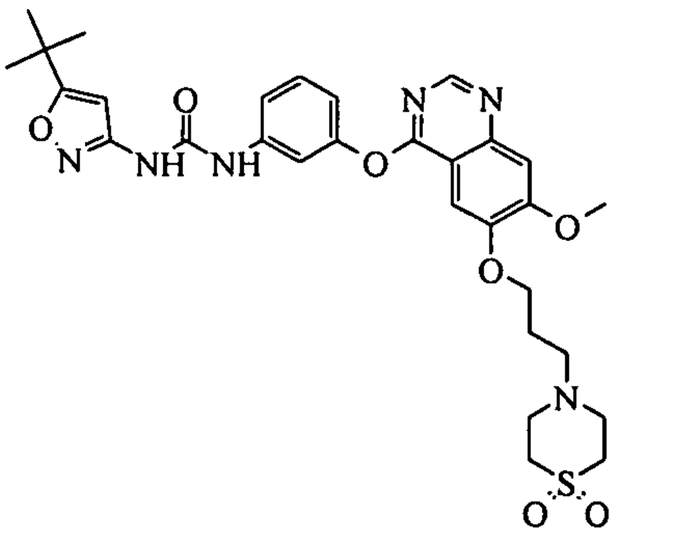
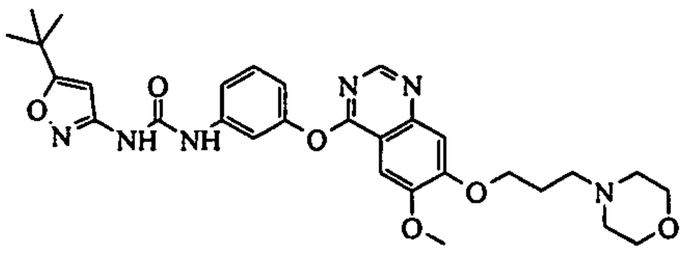
Table 1:

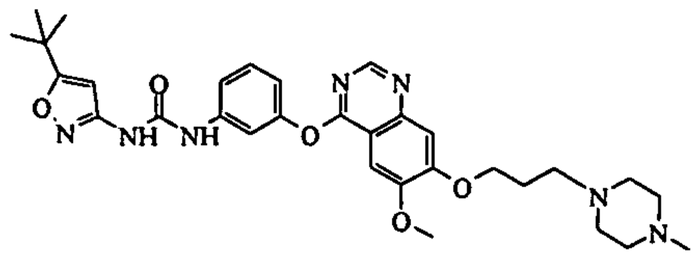
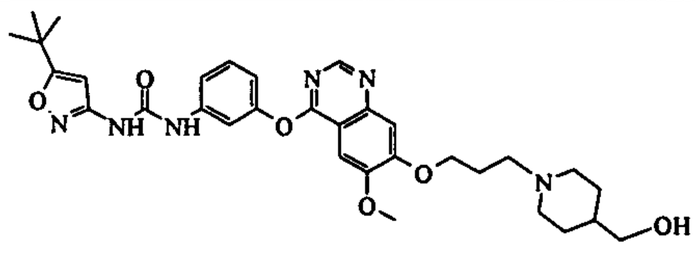
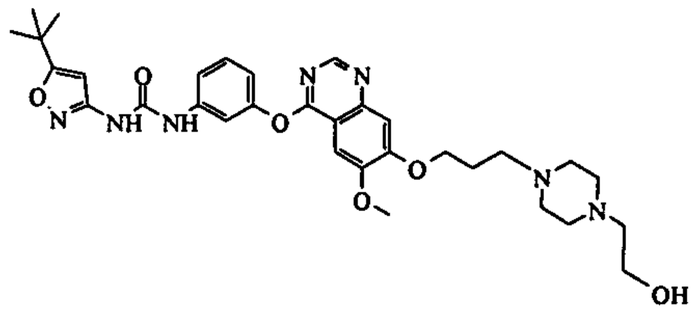
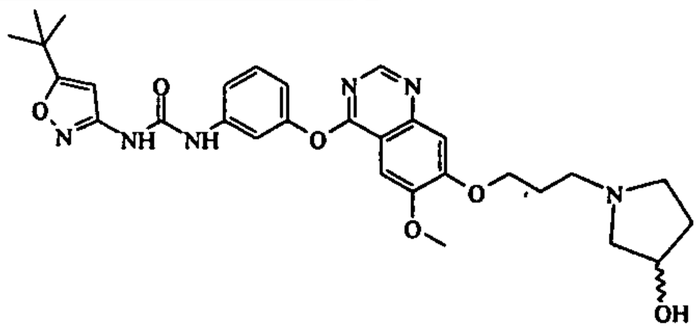
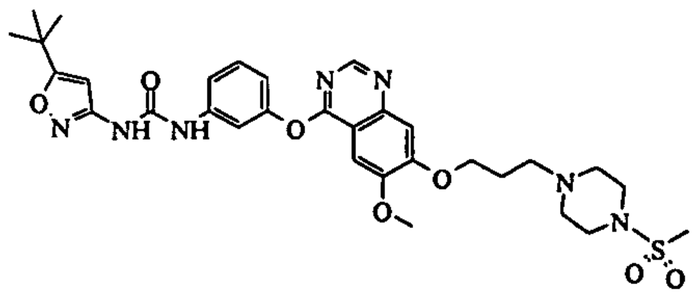
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 1 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	A	C	A	D	B	C
	Ex 2 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-yloxyphenyl) urea	ND	ND	ND	ND	ND	ND
	Ex 3 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-yloxy)phenyl) urea	ND	ND	ND	ND	ND	ND
	Ex 4 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-yloxy)phenyl) urea	ND	ND	ND	ND	ND	ND
	Ex 5 1-(5-tert-butylisoxazol-3-yl)-3-(3-(5-methylquinazolin-4-yloxy)phenyl)urea	ND	ND	ND	ND	ND	ND
	Ex 6 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy) phenyl] urea hydrochloride	A	B	A	D	C	D

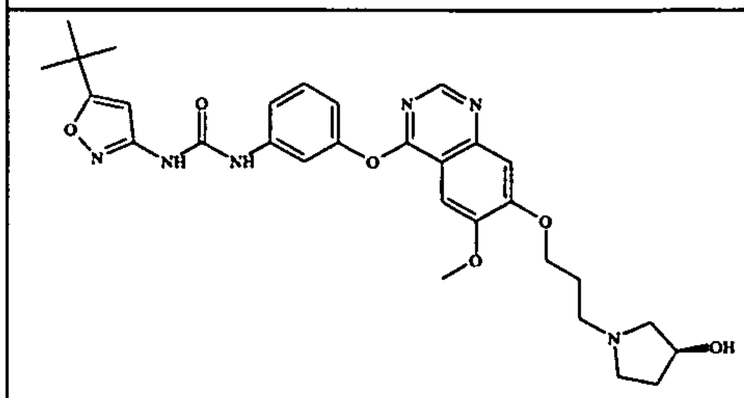
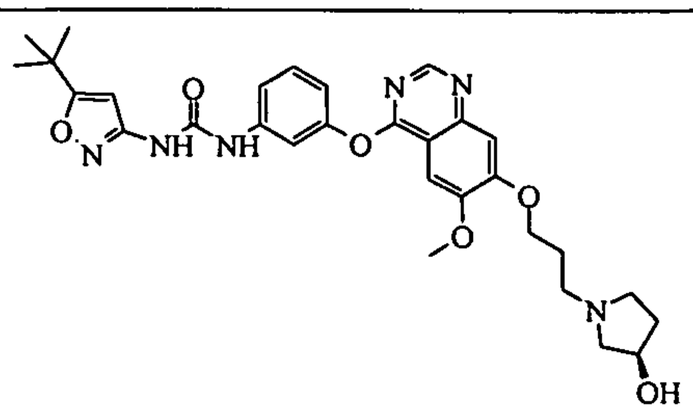
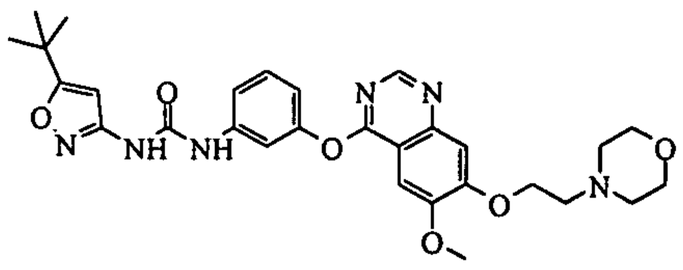
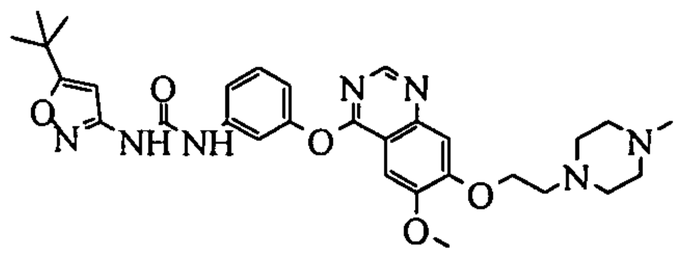
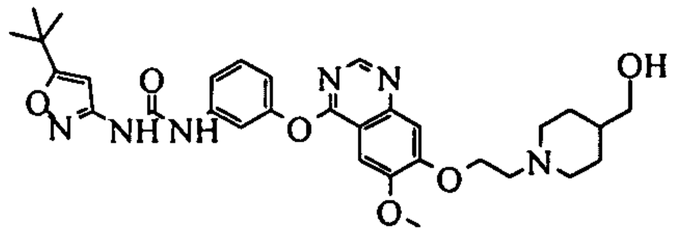
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 7 1-(5-*tert*-Butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride	A	B	A	B	B	D
	Ex 8 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methylquinazolin-4-yloxy)phenyl)urea	ND	ND	ND	ND	ND	ND
	Ex 9 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea	A	A	A	D	C	D
	Ex 10 1-(5-tert-butylisoxazol-3-yl)-3-(4-chloro-3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	C	D	D	C
	Ex 11 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	D	C	C
	Ex 12 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride	A	B	A	C	B	C

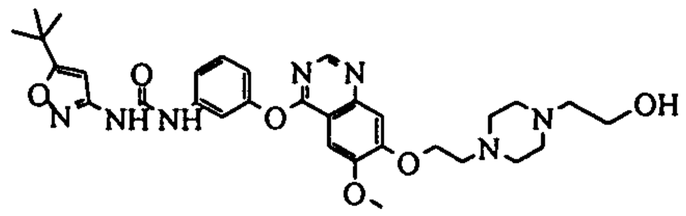
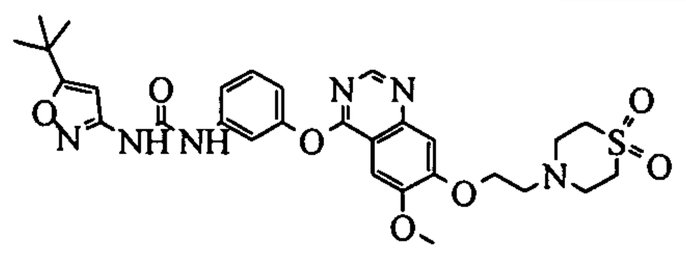
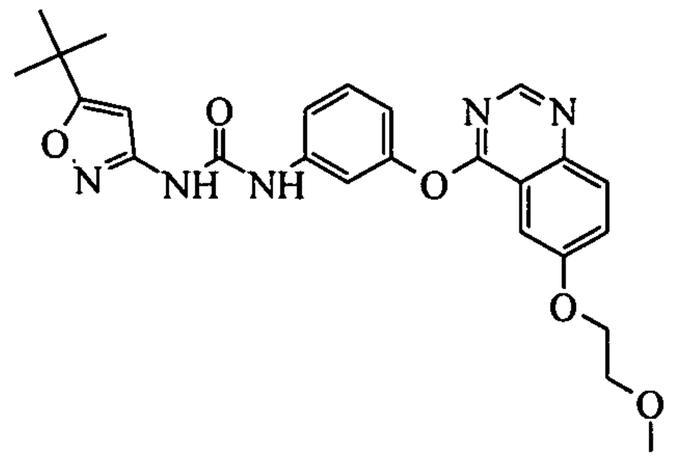
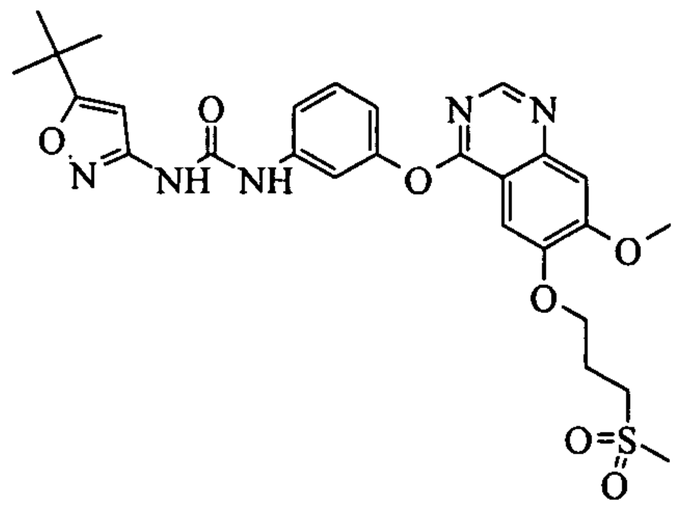
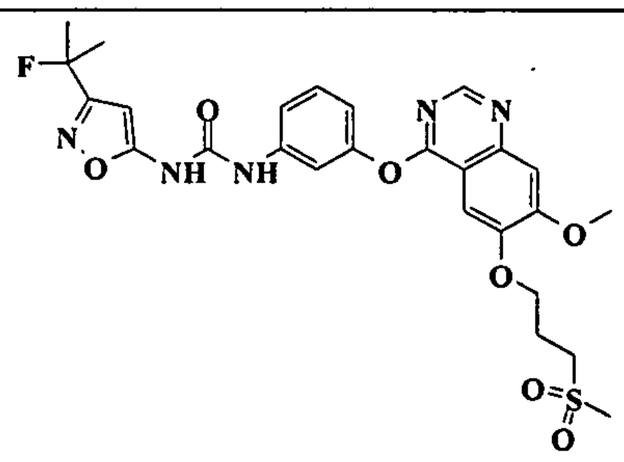
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 13 1-(5-*tert*-Butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea hydrochloride	B	C	B	D	D	C
	Ex 14 1-(5-*tert*-Butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-yloxy) phenyl]urea hydrochloride	C	D	A	C	B	C
	Ex 15 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride	A	A	A	B	B	C
	Ex 16 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea	B	D	A	C	D	C
	Ex 17 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea	B	B	A	C	C	C

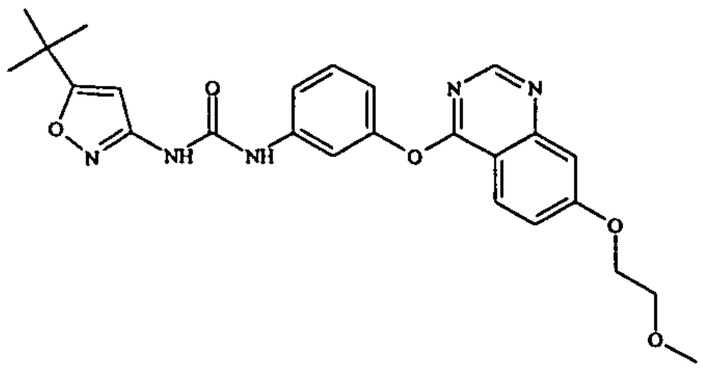
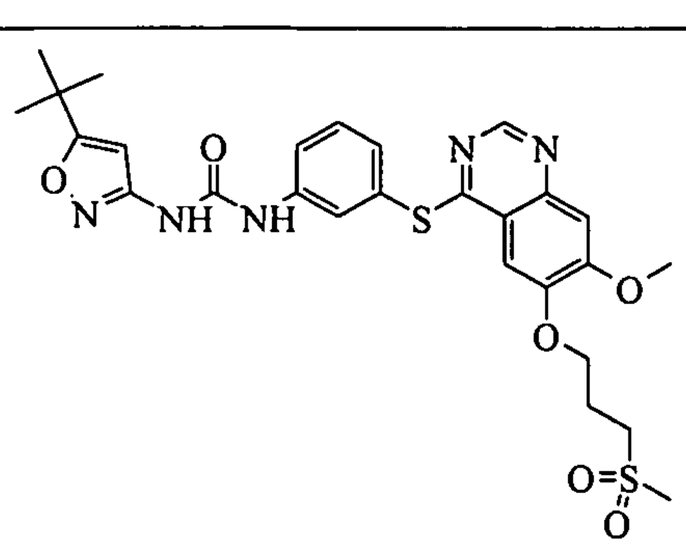
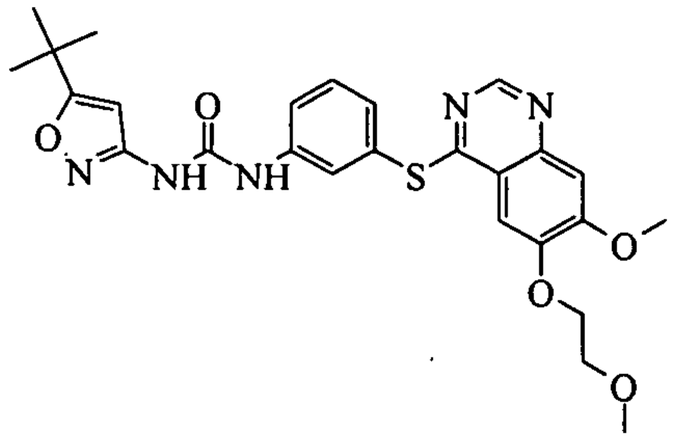
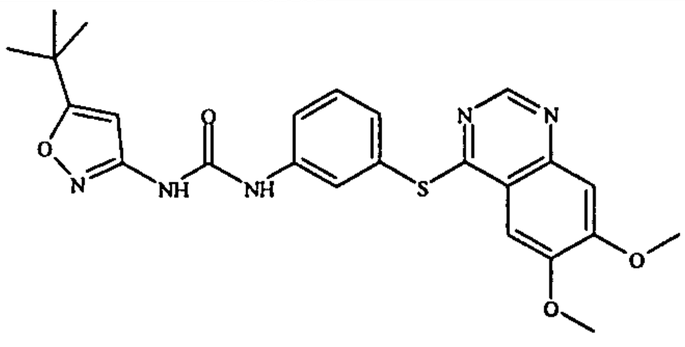
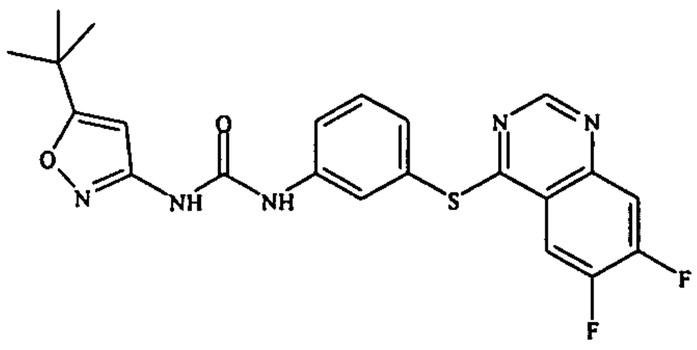
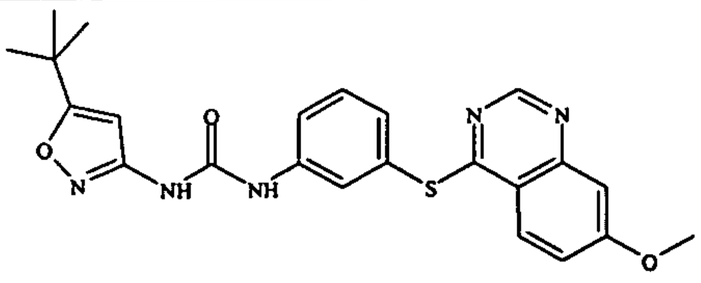
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 18 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea	A	B	A	B	C	D
	Ex 19 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	B	A	B	B	D
	Ex 20 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea	A	A	A	B	B	C
	Ex 21 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methyl piperazin-1-yl)propoxy) quinazolin-4-yloxy)phenyl) urea	A	B	A	B	B	D
	Ex 22 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yloxy)phenyl)urea	A	A	A	A	A	D

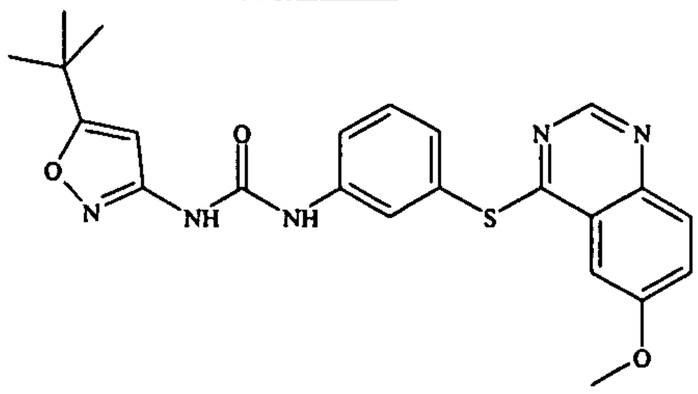
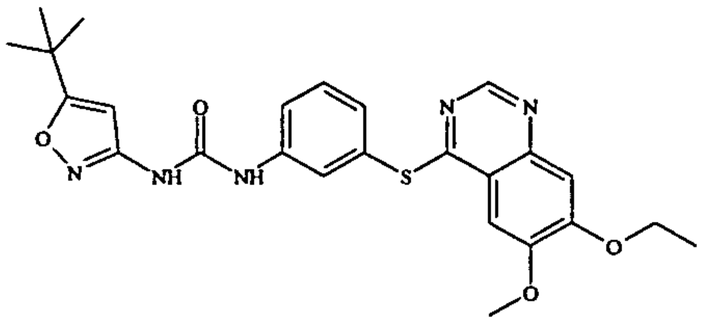
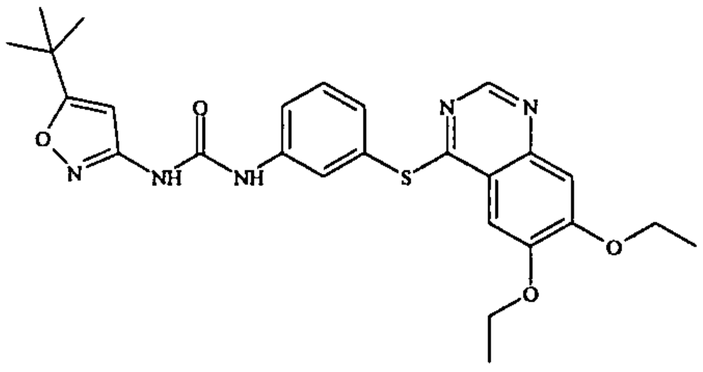
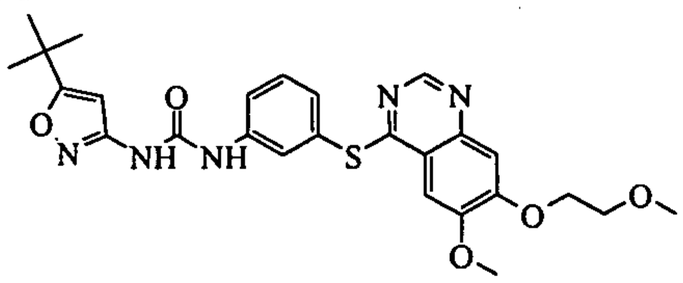
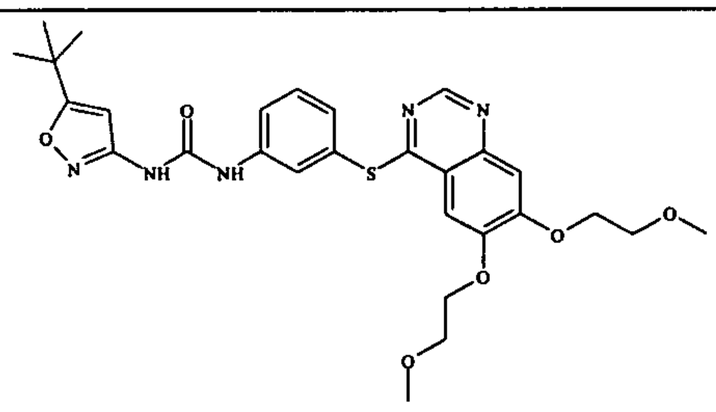
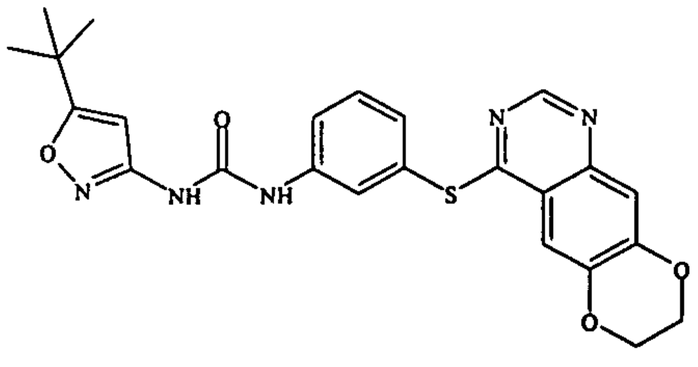
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 23 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea	A	C	A	C	C	D
	Ex 24 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	C	A	C	C	D
	Ex 25 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea	A	A	A	B	B	D
	Ex 26 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	A	A	B	A	D
	Ex 27 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-	A	A	A	B	B	D

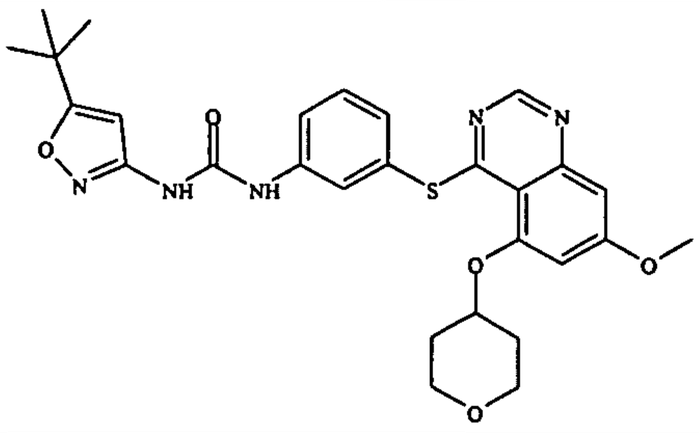
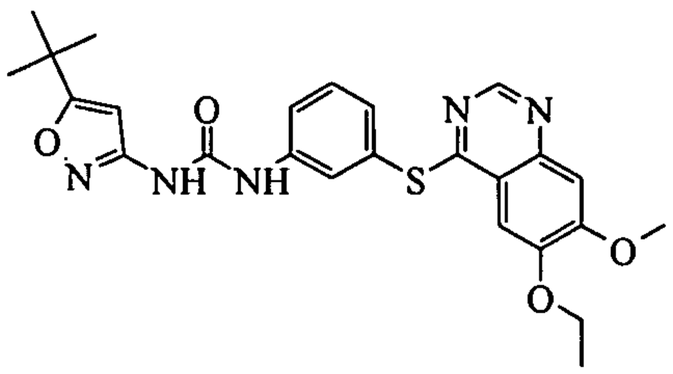
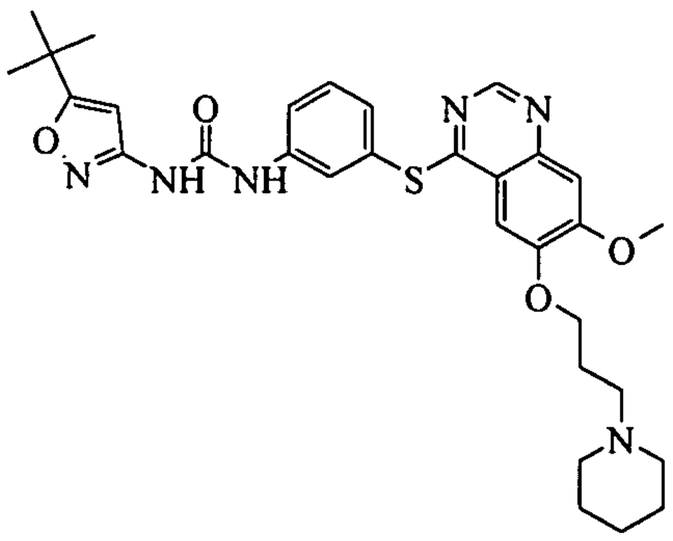
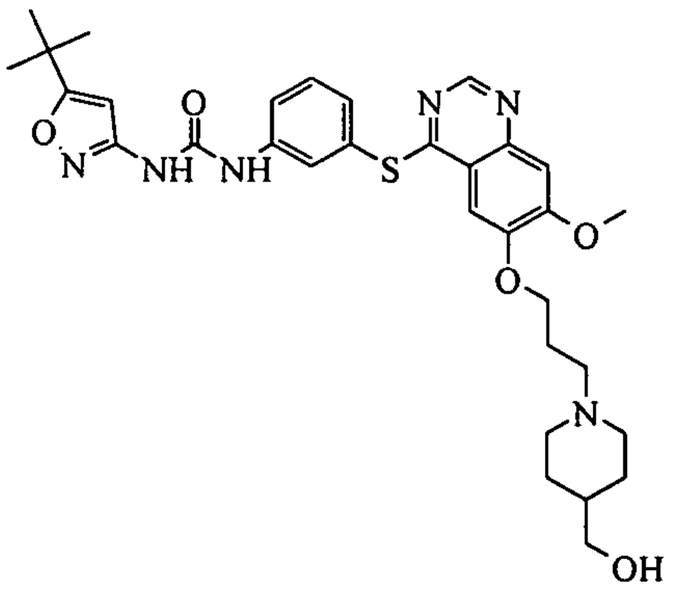
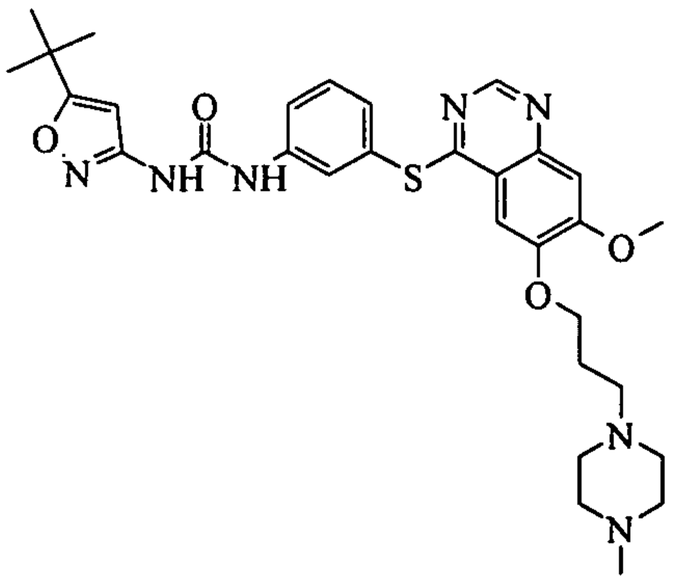
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	yloxy)phenyl)urea						
	Ex 28 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea	A	A	A	B	A	D
	Ex 29 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-hydroxymethyl) piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	B	B	D
	Ex 30 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl) piperazin-1-yl)propoxy)-6-methoxy quinazolin-4-yloxy)phenyl) urea	A	A	A	A	B	D
	Ex 31 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(3-hydroxy-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	A	A	B	B	D
	Ex 32 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methyl sulfonyl) piperazin-1-yl)propoxy) quinazolin-4-	A	B	A	C	B	D

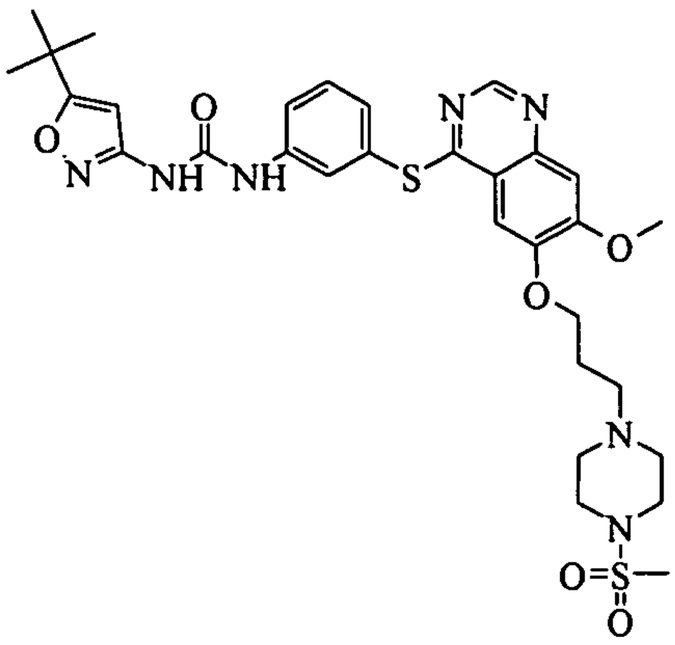
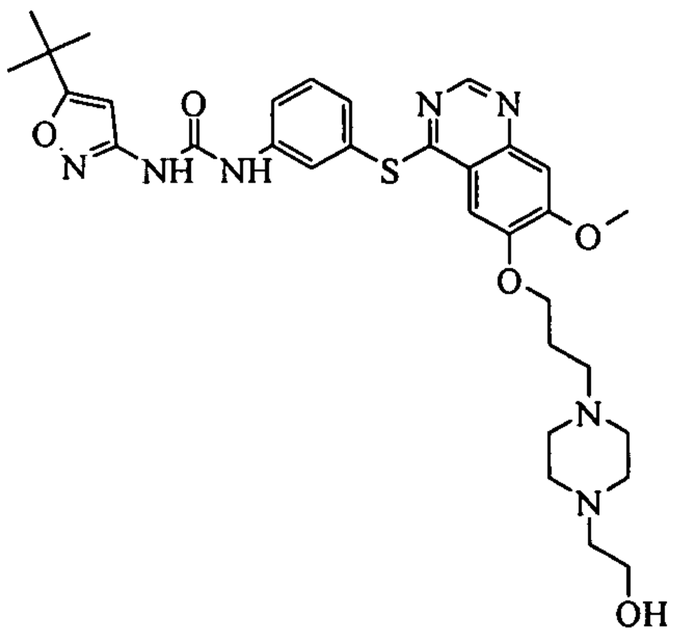
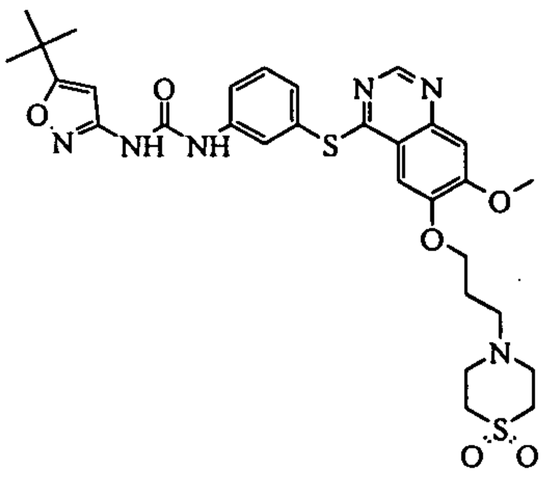
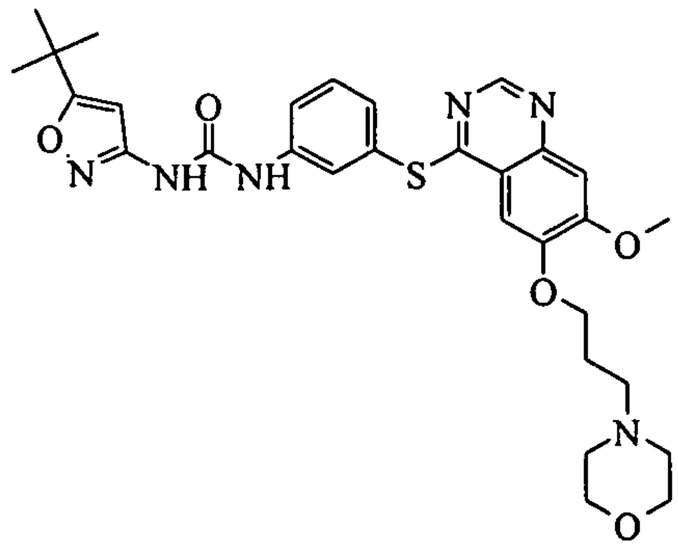
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	yloxy)phenyl) urea						
	Ex 33 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxy pyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl) urea	A	A	A	B	B	D*
	Ex 34 (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxy pyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl) urea	A	D	A	B	B	D*
	Ex 35 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy) phenyl)urea	A	C	A	B	B	C
	Ex 36 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methyl piperazin-1-yl)ethoxy) quinazolin-4-yloxy)phenyl) urea	A	B	A	B	B	C
	Ex 37 1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{7-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	B	A	B	B	C

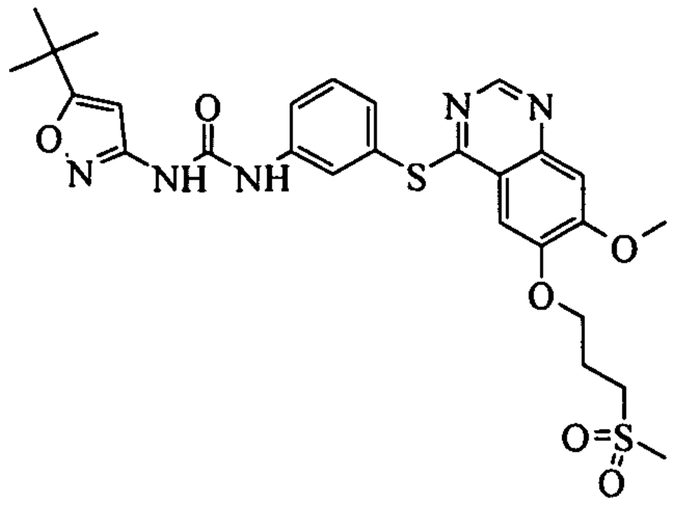
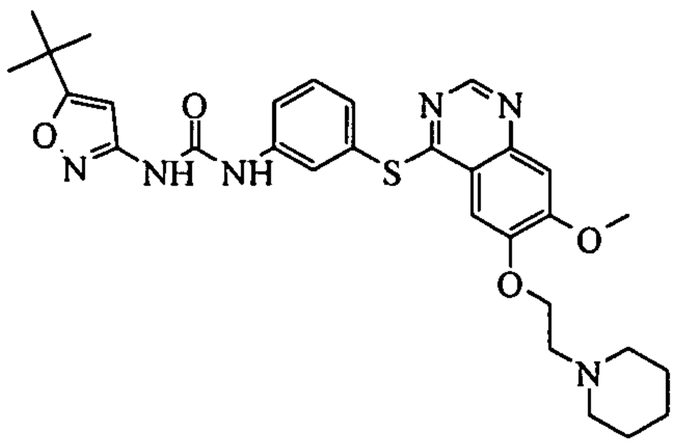
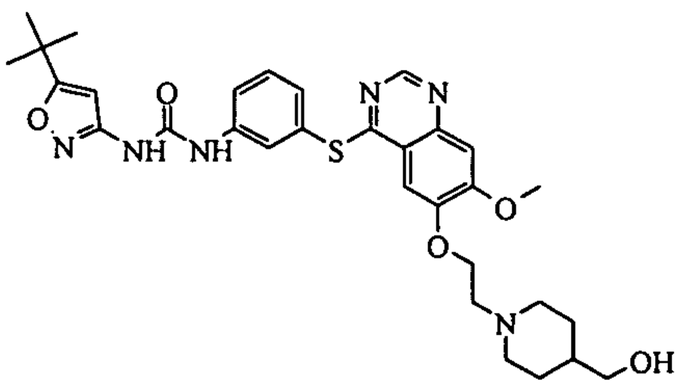
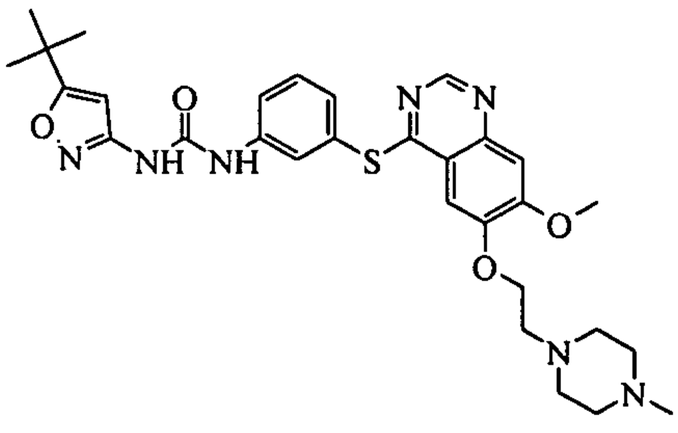
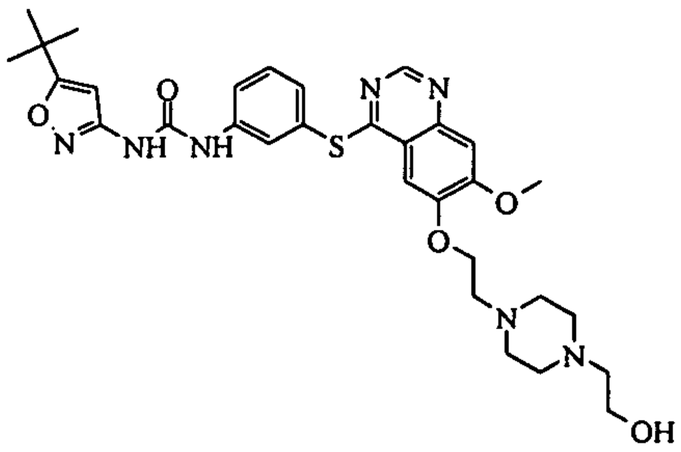
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 38 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl) ethoxy)-6 methoxy quinazolin-4yloxy) phenyl) urea	A	B	A	B	B	D
	Ex 39 1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{7-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	A	A	B	B	C
	Ex 40 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	A	C	A	D	B	C
	Ex 41 1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy) quinazolin-4-ylthio)phenyl) urea	A	A	A	A	A	C
	Ex 42 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy) quinazolin-4-yloxy)phenyl) urea	B	C	A	A	A	C*

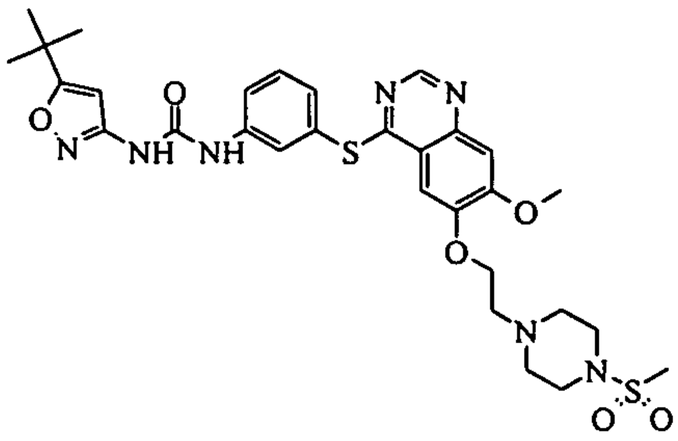
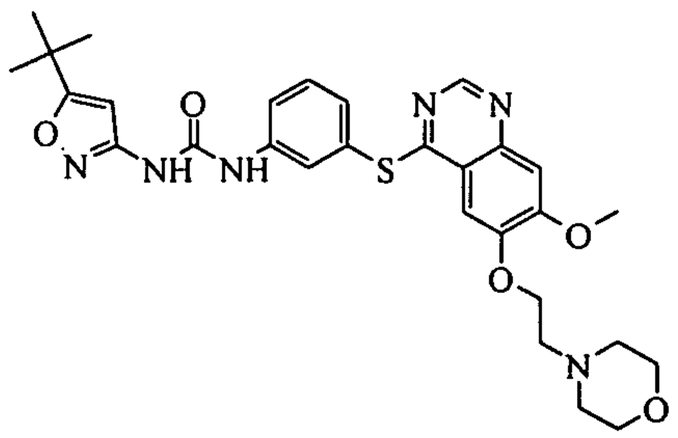
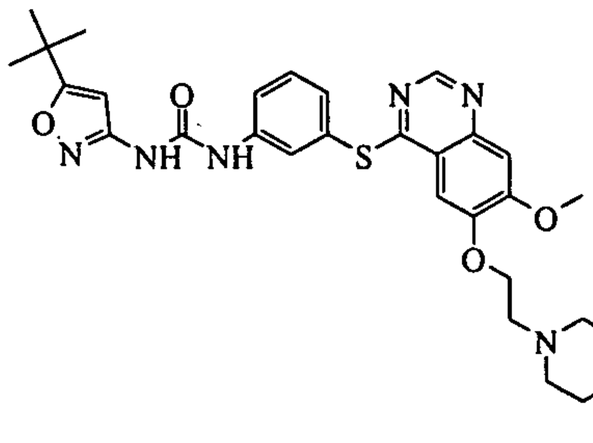
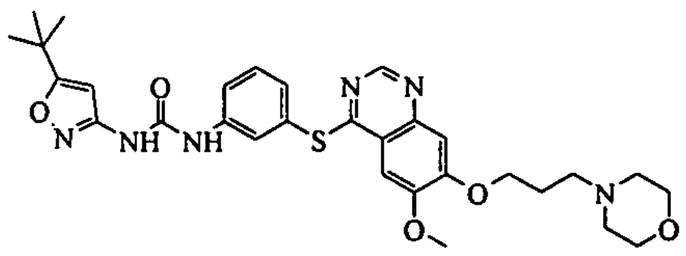
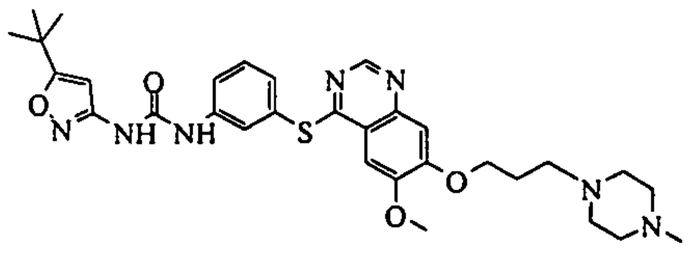
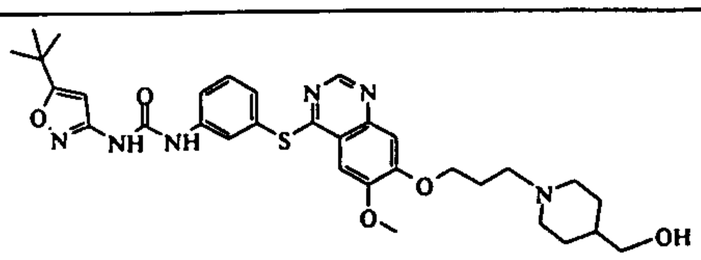
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 43 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	C	B	C
	Ex 44 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl) urea	A	B	A	A	A	C
	Ex 45 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl) urea	A	B	A	C	B	C
	Ex 46 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	A	B	A	C	B	C
	Ex 47 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-ylthio)phenyl) urea	D	D	C	D	D	A
	Ex 48 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-ylthio)phenyl) urea	C	D	B	D	D	C

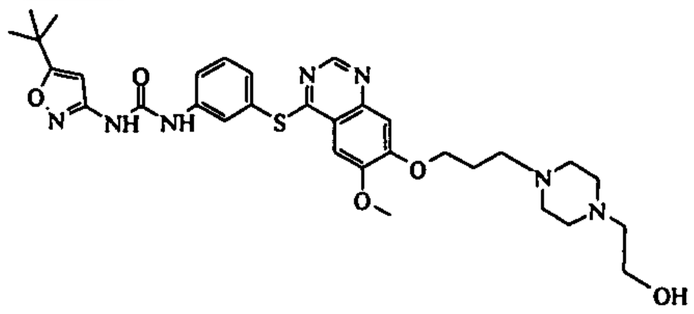
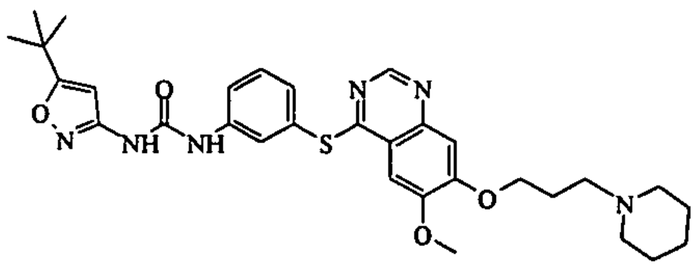
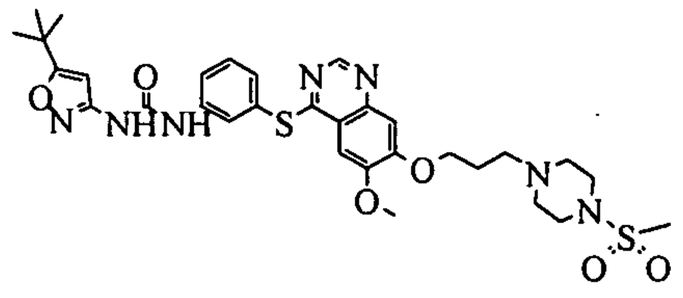
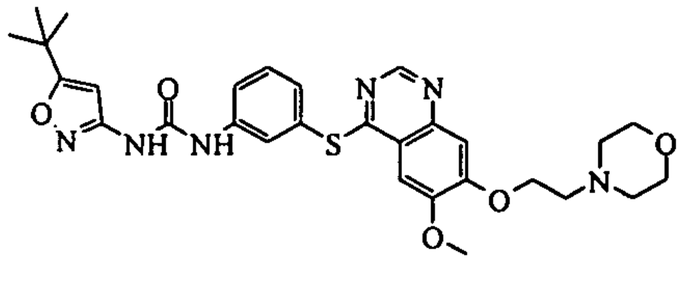
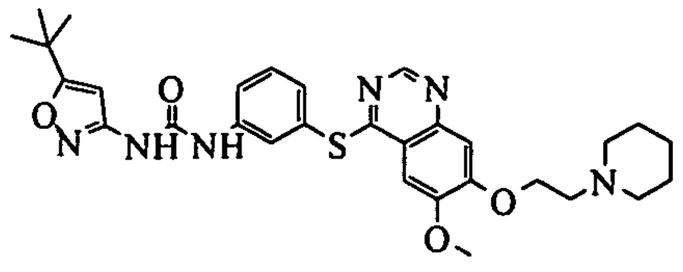
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 49 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-ylthio)phenyl) urea	C	D	B	D	C	C
	Ex 50 1-(5-*tert*-Butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl] urea	B	D	B	C	B	B
	Ex 51 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-ylthio)phenyl] urea	B	D	C	D	D	C
	Ex 52 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl} urea hydrochloride	A	C	A	B	B	C
	Ex 53 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride	A	C	A	C	B	C
	Ex 54 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-ylthio)phenyl]urea hydrochloride	C	D	C	D	D	C

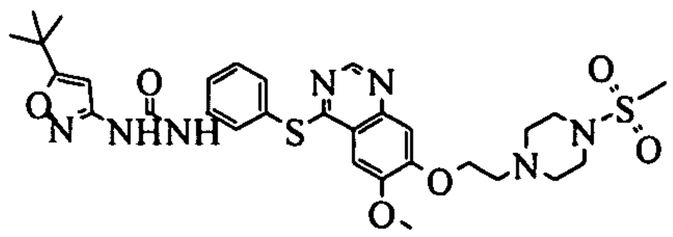
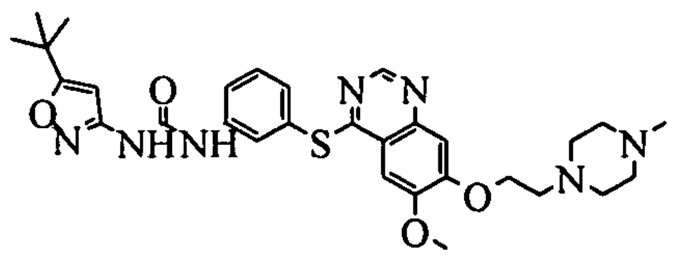
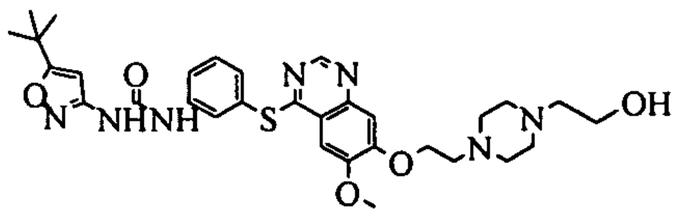
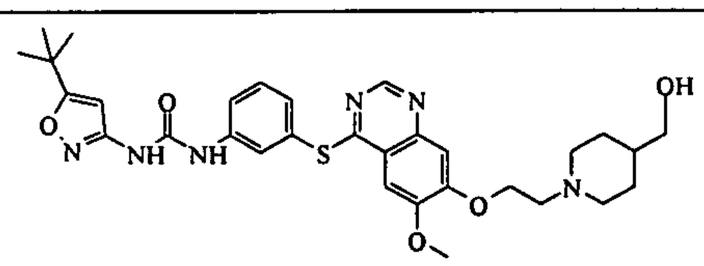
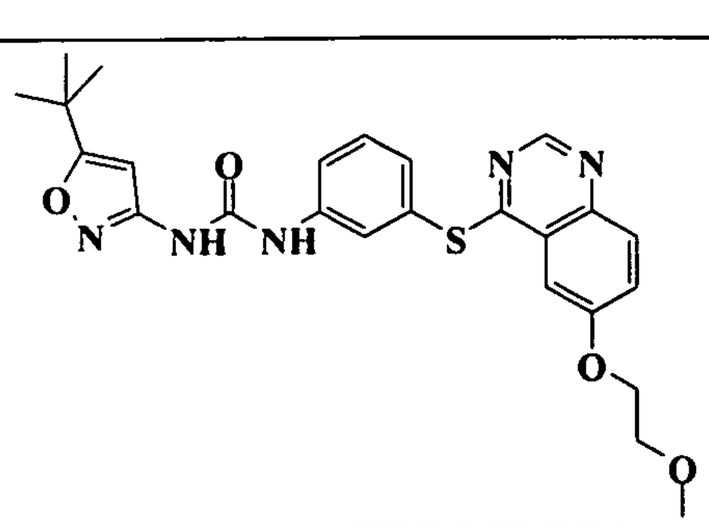
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 55 1-(5-*tert*-Butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-ylthio)quinazolin-4-yloxy]phenyl}urea	A	B	A	C	B	C
	Ex 56 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)urea	A	A	A	C	B	B
	Ex 57 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl) urea	A	D	A	C	C	C
	Ex 58 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl) urea	A	D	A	B	C	D
	Ex 59 1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl) urea	A	D	A	B	B	D

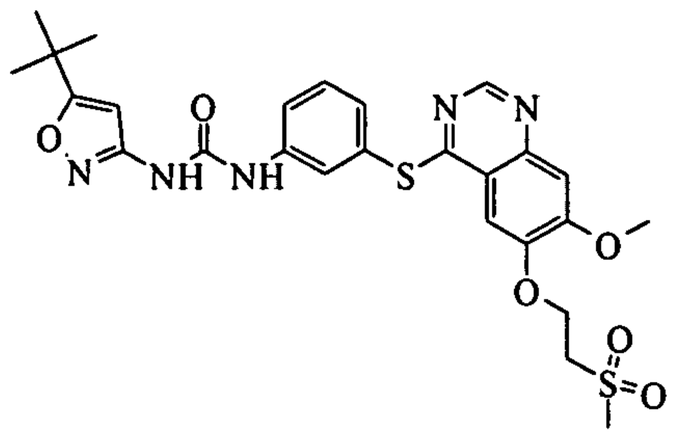
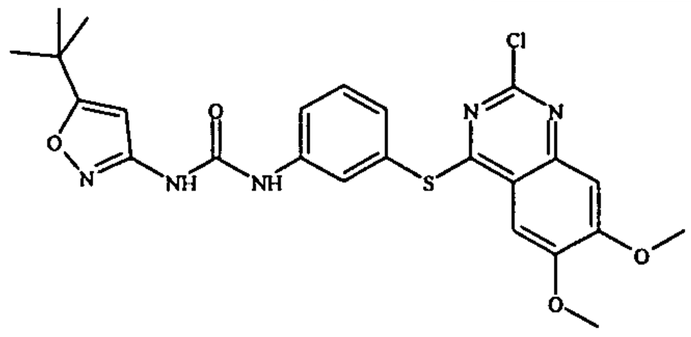
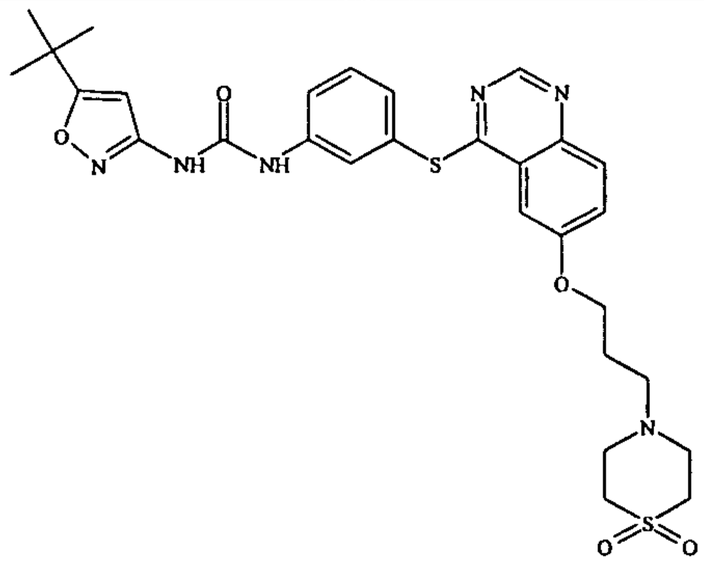
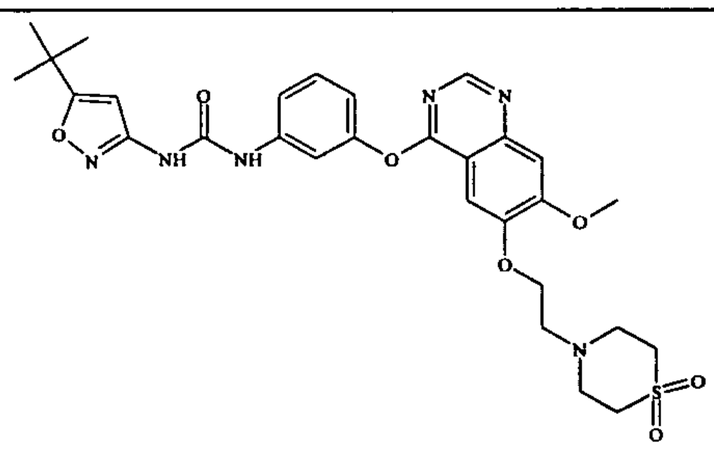
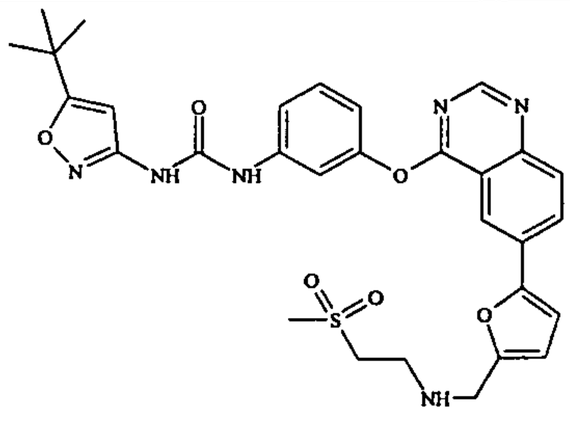
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 60 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea	A	B	A	C	B	C
	Ex 61 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea	D	D	A	B	A	D
	Ex 62 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea	A	A	A	B	A	C
	Ex 63 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylthio)phenyl)urea	A	C	A	B	A	C

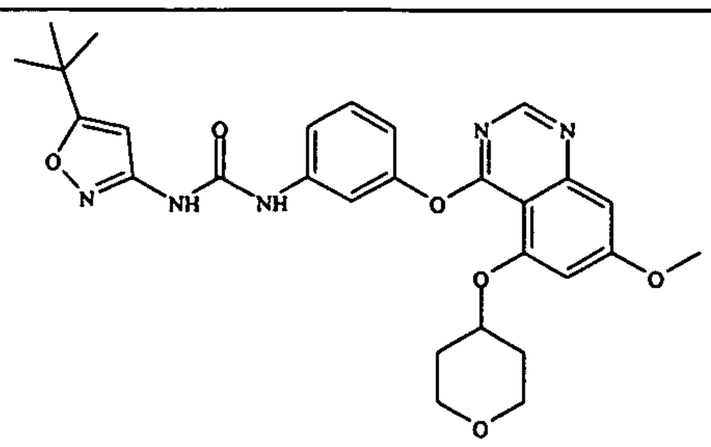
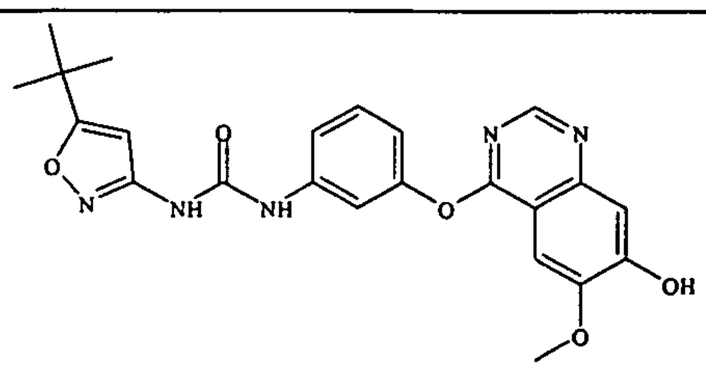
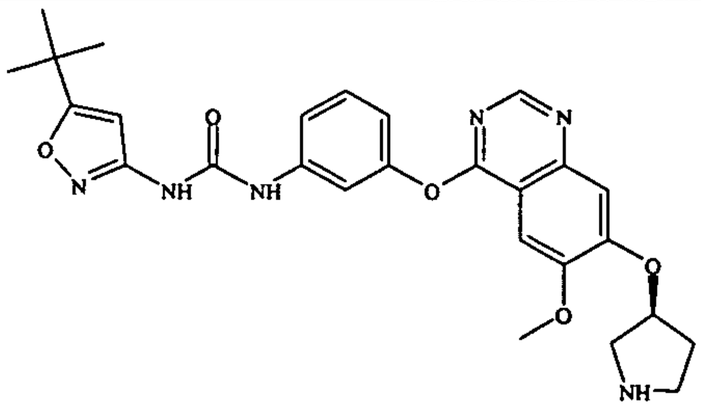
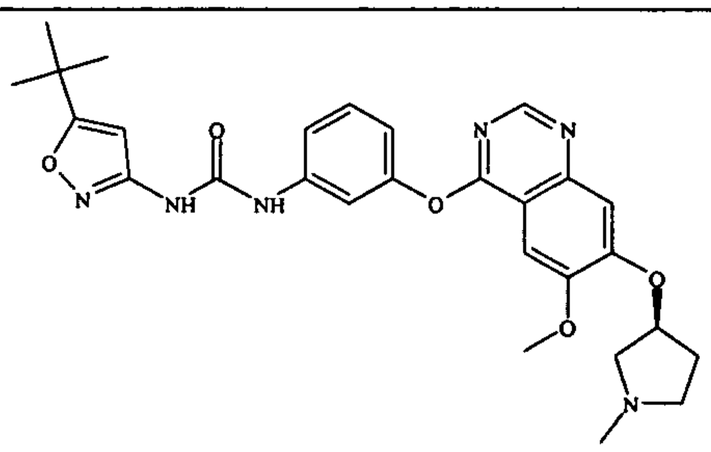
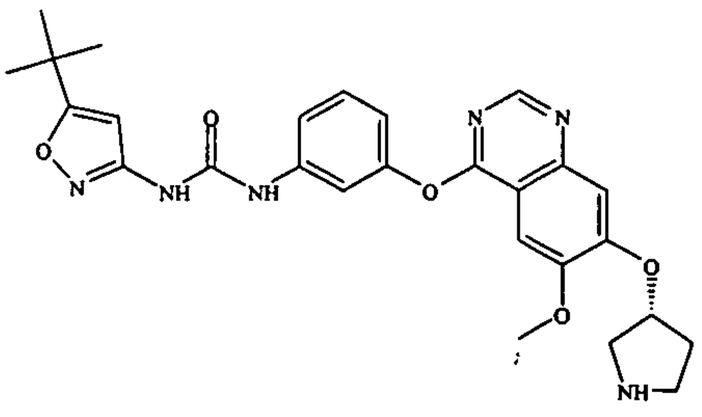
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 64 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea	A	B	A	A	A	C
	Ex 65 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	A	D	C	C
	Ex 66 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea	A	D	A	C	C	C
	Ex 67 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea	A	D	A	B	B	C
	Ex 68 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea	A	C	A	B	B	C

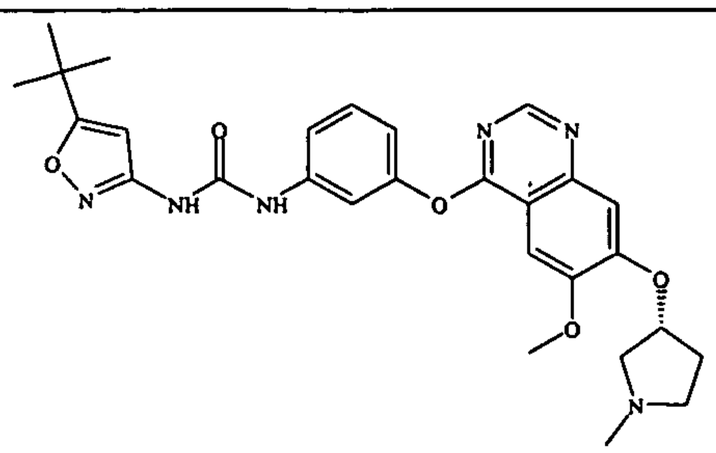
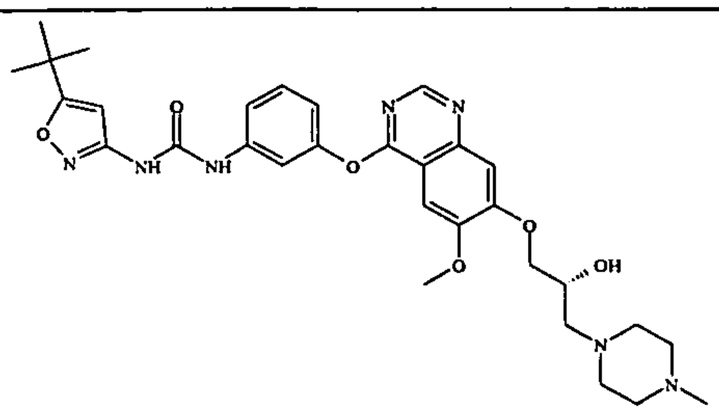
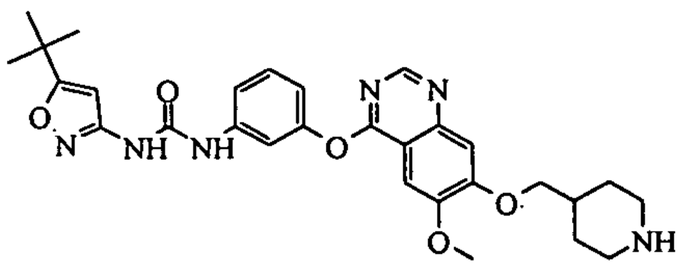
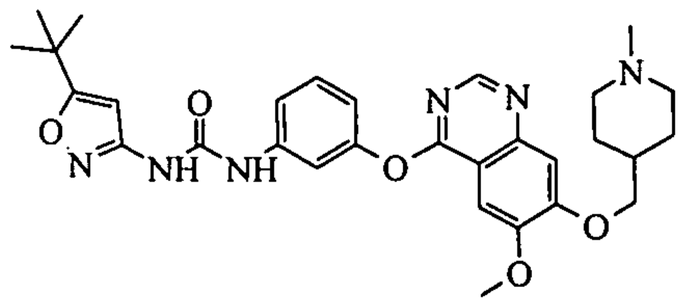
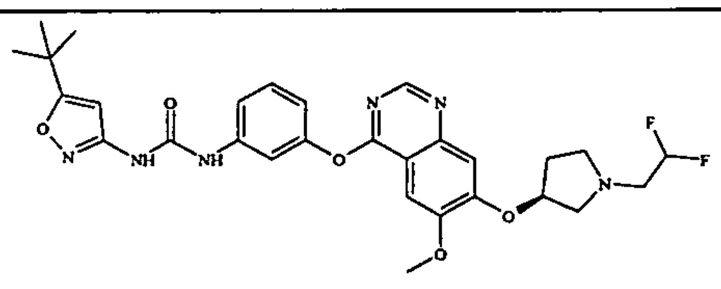
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 69 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-(methyl sulfonyl) piperazin-1-yl)ethoxy) quinazolin-4-ylthio)phenyl) urea	A	B	A	B	B	C
	Ex 70 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-ylthio) phenyl)urea	A	A	A	B	A	C
	Ex 71 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea	A	B	A	A	A	C
	Ex 72 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl) urea	A	C	A	C	B	D
	Ex 73 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methyl piperazin-1-yl)propoxy) quinazolin-4-ylthio)phenyl) urea	A	C	A	B	B	D
	Ex 74 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(hydroxyl	A	B	A	B	A	D

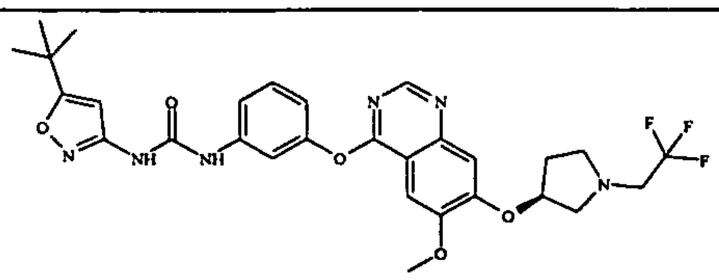
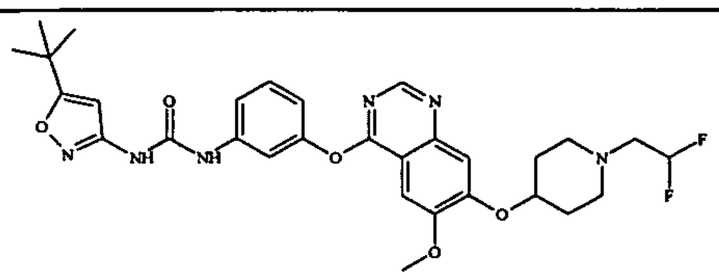
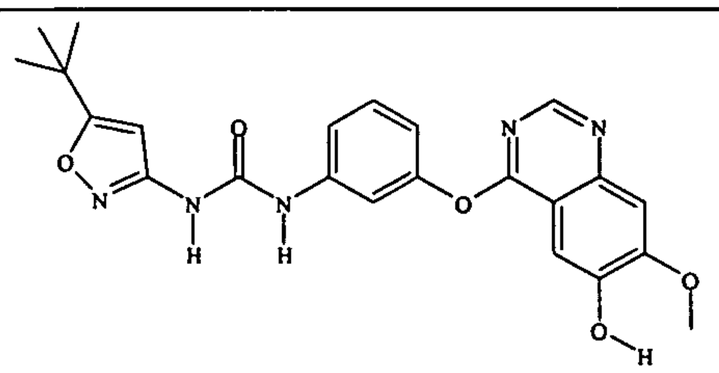
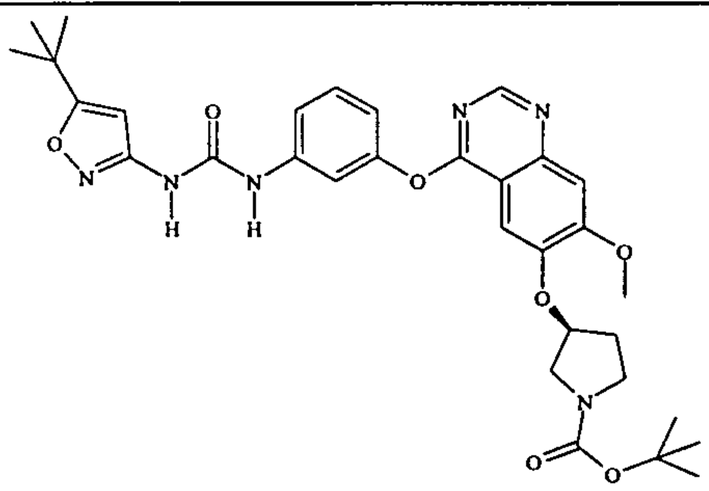
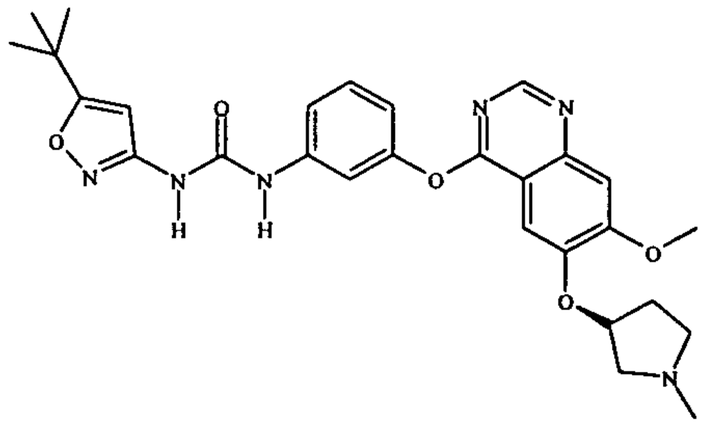
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	methyl)piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl) urea						
	Ex 75 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl) urea	A	D	A	B	B	D
	Ex 76 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl) urea	A	D	A	B	C	D
	Ex 77 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl) urea	A	B	A	C	C	D
	Ex 79 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea	A	D	A	C	C	D
	Ex 80 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl	B	D	A	B	B	C

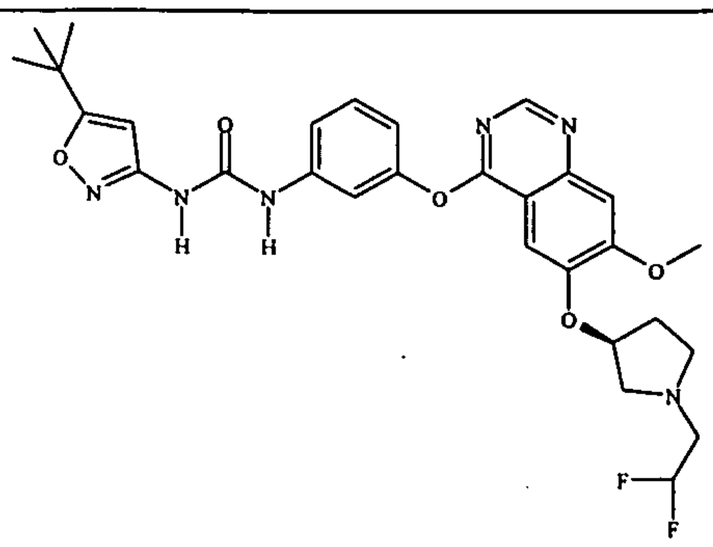
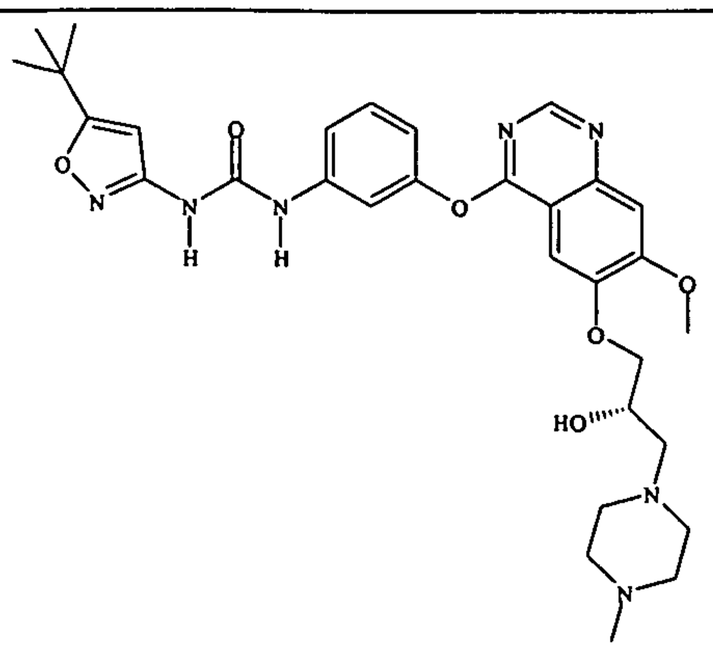
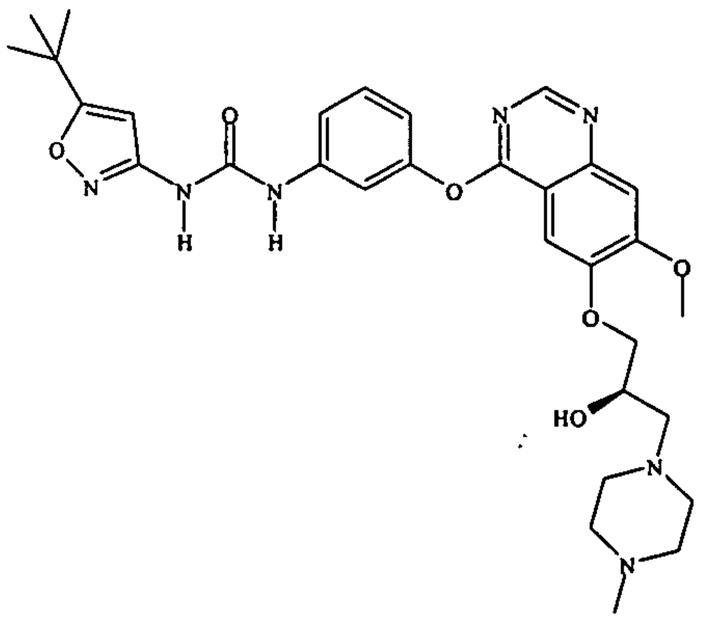
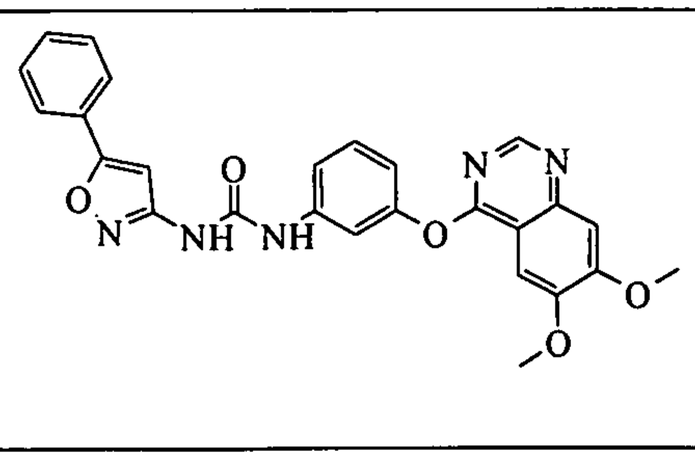
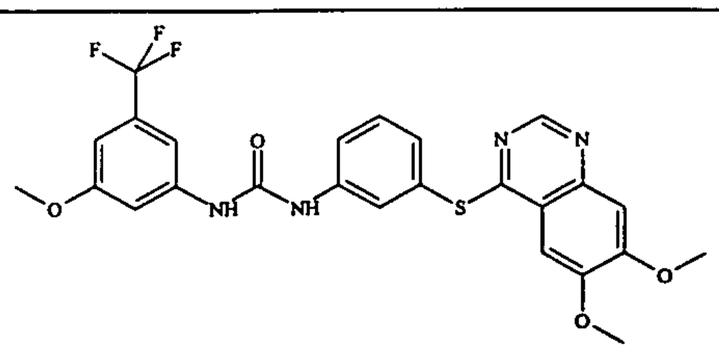
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	) urea						
	Ex 81 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea	A	B	A	C	C	C
	Ex 83 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl) urea	A	D	A	B	B	C
	Ex 84 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl) piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio) phenyl)urea	A	D	A	B	B	D
	Ex 86 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl) urea	A	D	B	D	C	C
	Ex 87 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	B	D	C	C

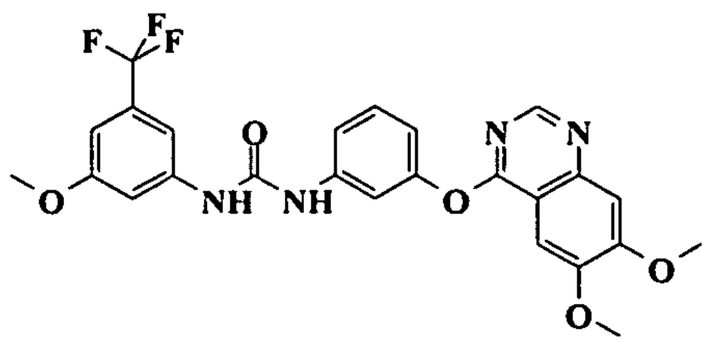
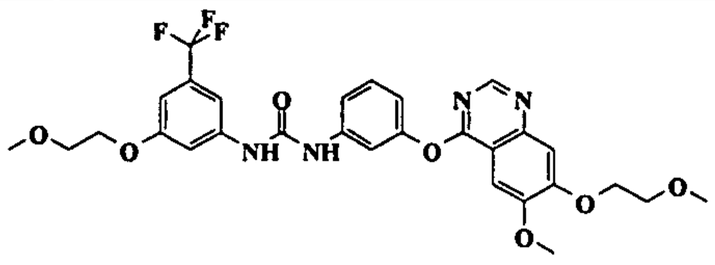
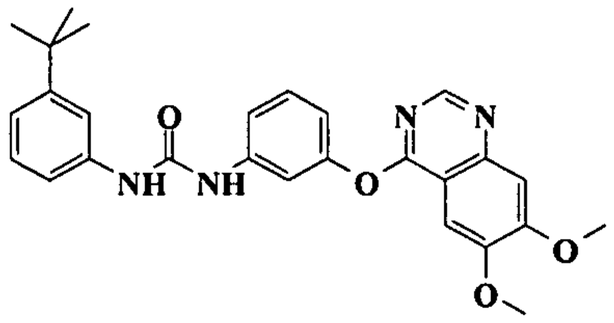
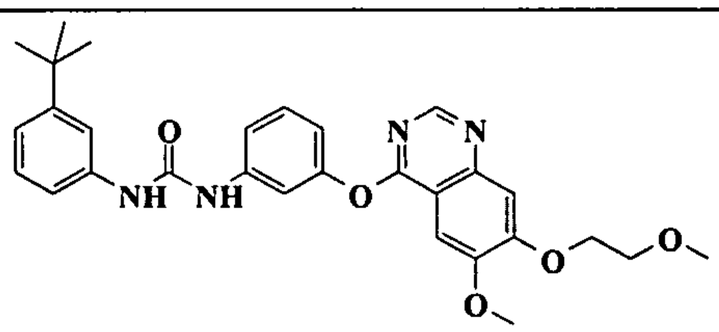
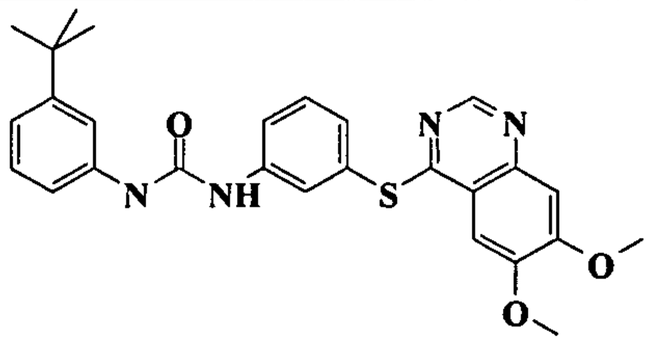
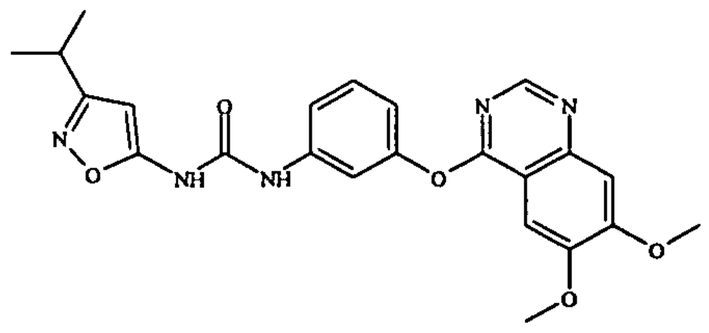
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 88 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazolin-4-ylthio)phenyl urea	A	C	A	A	A	C
	Ex 89 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio) phenyl)urea	D	ND	D	D	D	A
	Ex 90 1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo--thiomorpholin-4-yl)-propoxy]-quinazolin-4-ylsulfanyl}-phenyl)-urea	A	D	A	C	B	C
	Ex 91 1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-116-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	A	A	B	B	C
	Ex 92 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-(5-{[2-(methylsulfonyl)ethylamino]methyl}furan-2-yl)quinazolin-4-yloxy]phenyl } urea	A	A	A	C	B	C

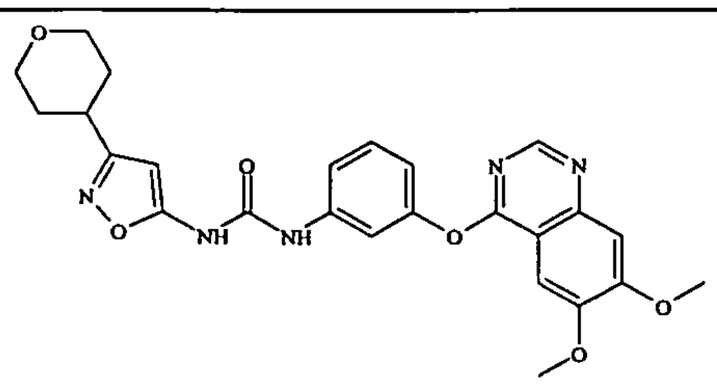
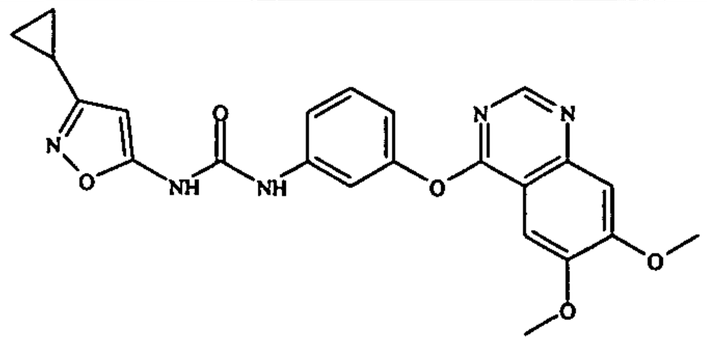
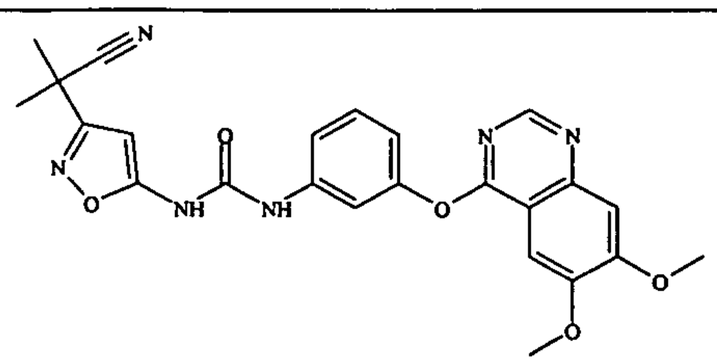
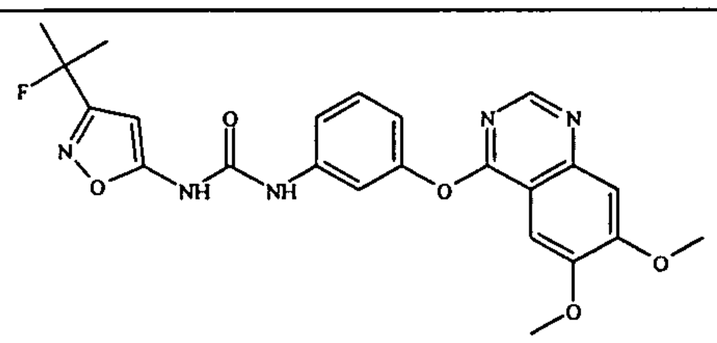
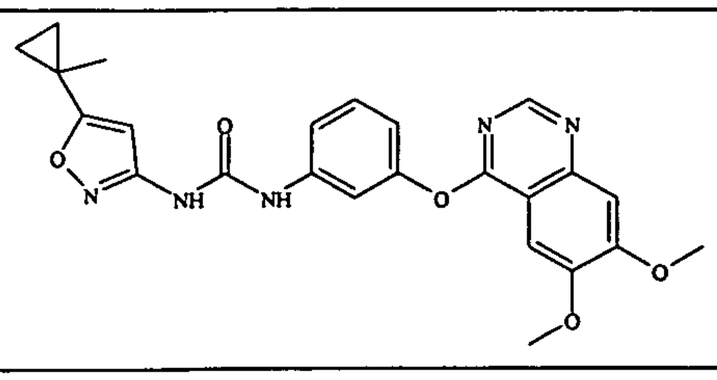
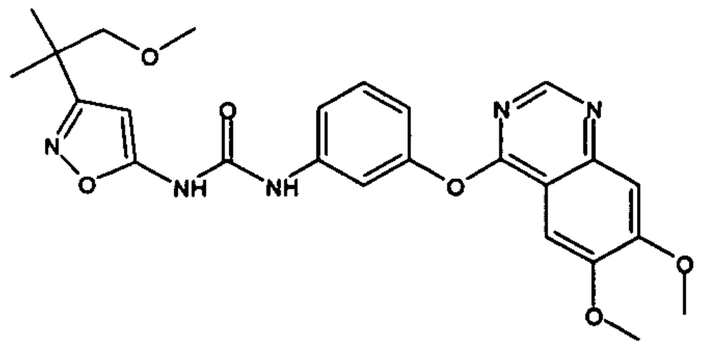
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 94 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-yloxy]phenyl} urea	B	D	B	D	B	C
	Ex 95 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl) urea	A	A	A	C	B	C
	Ex 96 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	B	A	C
	Ex 97 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea mono acetate	B	D	A	B	C	C
	Ex 98 (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea carboxylate	C	D	A	B	A	C

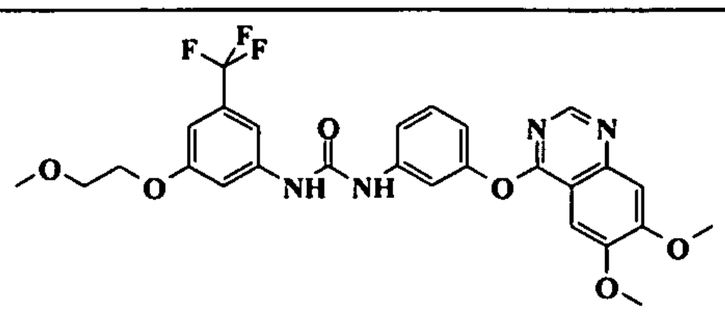
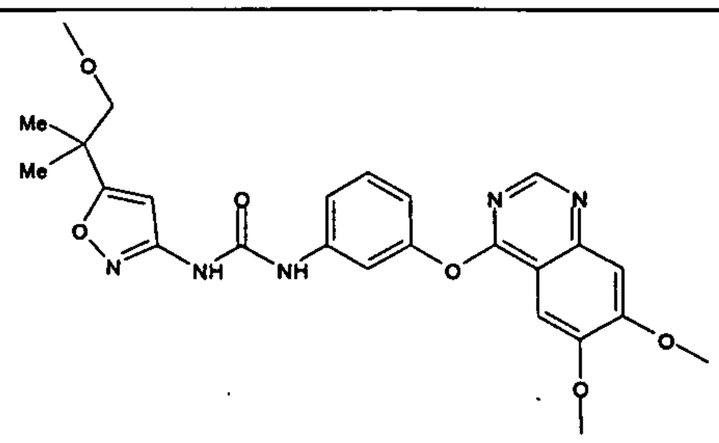
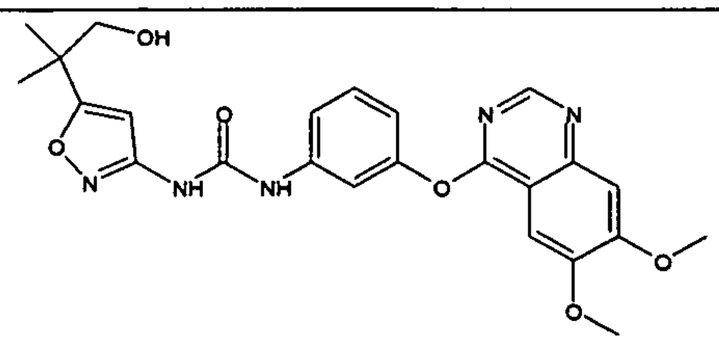
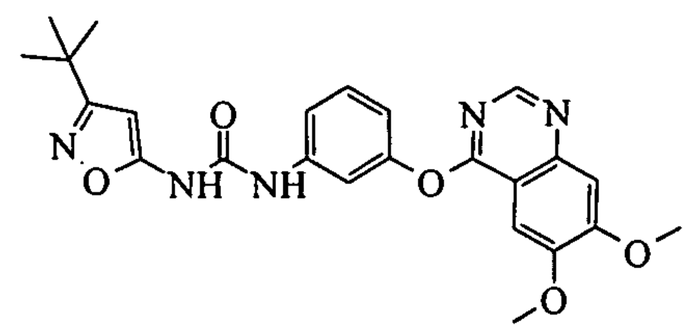
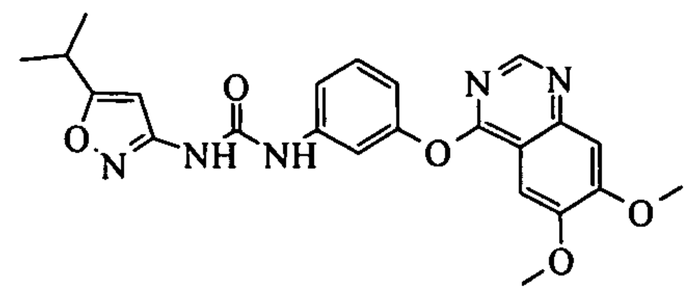
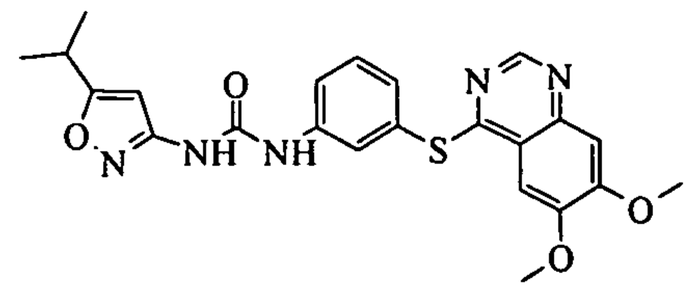
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 99 (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea mono acetate	B	D	A	B	B	C
	Ex 100 (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy quinazolin-4-yloxy)phenyl) urea	A	A	A	A	A	D
	Ex 101 1-(3-tert-Butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyl)urea	A	C	A	A	B	C
	Ex 102 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-((1-methylpiperidin-4-yl)methoxy) quinazolin-4-yloxy)phenyl)urea	A	A	A	A	B	D
	Ex 103 (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)pyrrolidin-3-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl) urea	C	D	B	D	D	C*

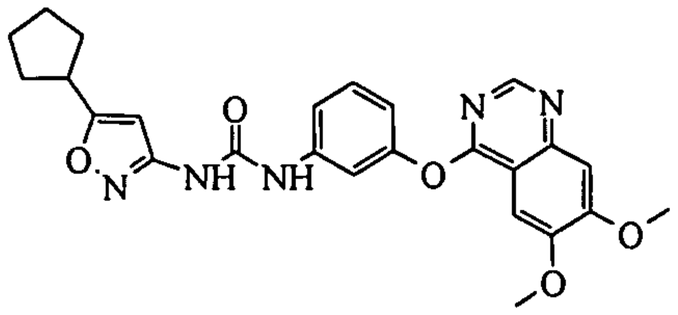
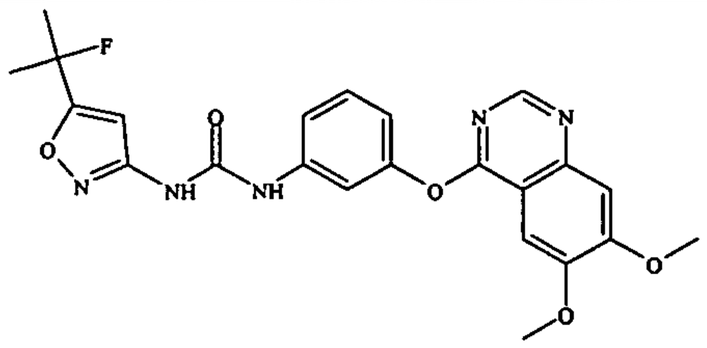
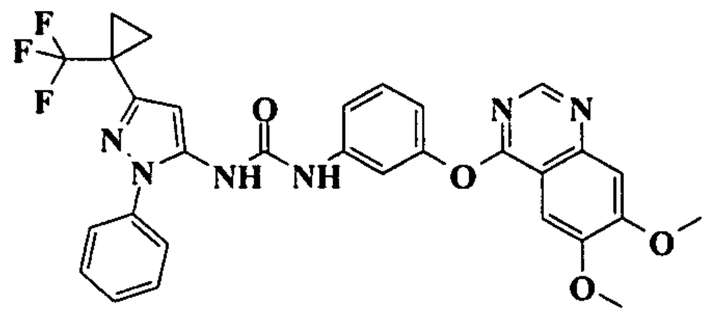
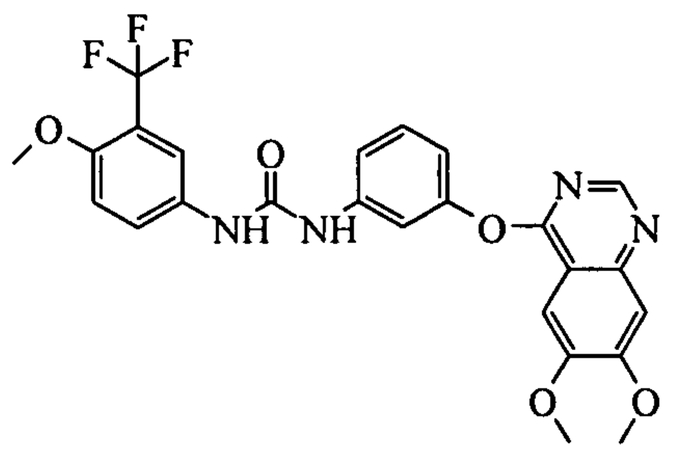
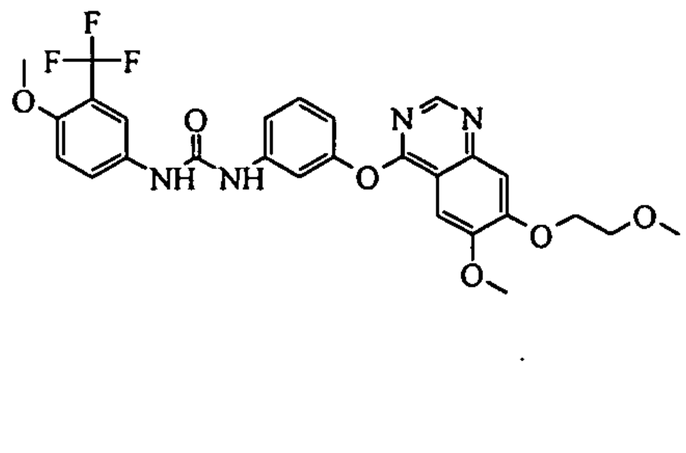
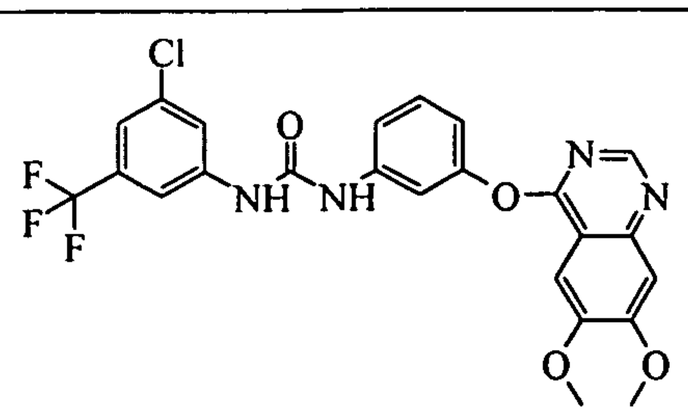
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 104 (*S*)-1-(5-*tert*-Butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yloxy]quinazolin-4-yloxy}phenyl)urea	C	D	D	D	D	B*
	Ex 105 1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)piperidin-4-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl) urea	D	D	D	D	D	C*
	Ex 107 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl) urea	A	B	A	B	A	C
	Ex 108 (S)-*tert*-butyl 3-(4-(3-(3-(5-*tert*-butylisoxazole-3-yl)ureido)phenoxy)-7-methoxyquinazolin-6-yloxy)pyrrolidine-1-carboxylate	A	C	C	D	D	C
	Ex 109 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea	A	B	A	B	A	D

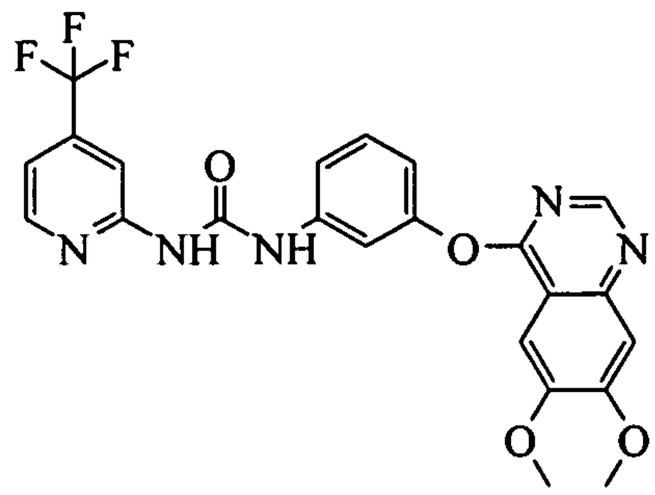
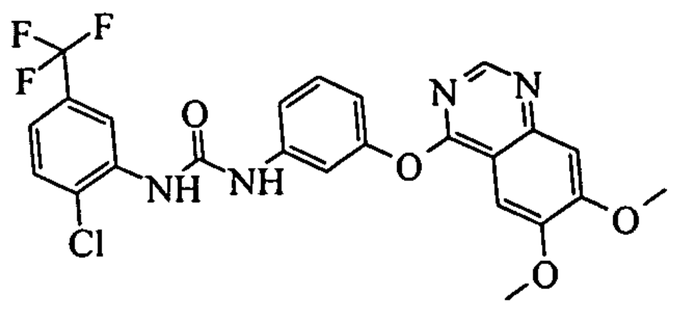
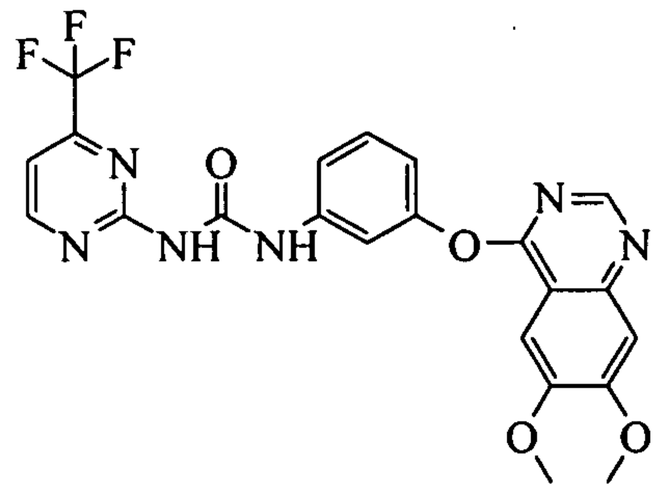
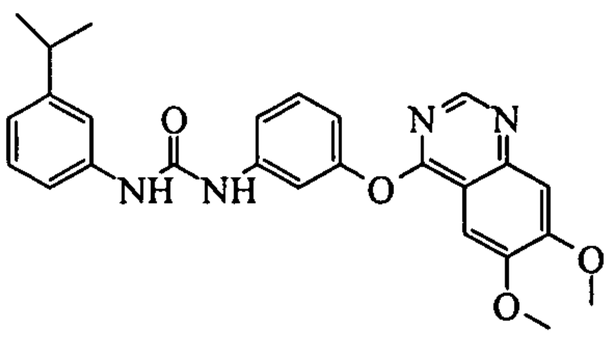
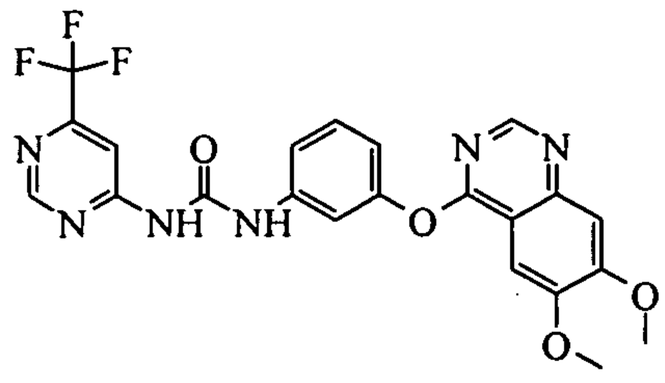
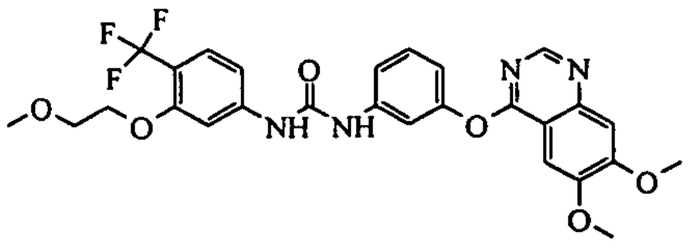
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 110 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)-7-methoxyquinazolin-4-yloxy)phenyl) urea	A	A	A	B	A	C
	Ex 111 (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-hydroxy-3-(4methylpiperazin -1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl) urea	A	B	A	B	A	D
	Ex 112 (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-hydroxy-3-(4methylpiperazin -1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl) urea	B	C	A	C	B	D
	Ex 113 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-phenylisoxazol-3-yl)urea	C	D	B	C	A	B
	Ex 115 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-methoxy-5-(trifluoromethyl)phenyl)urea	D	D	B	C	B	C

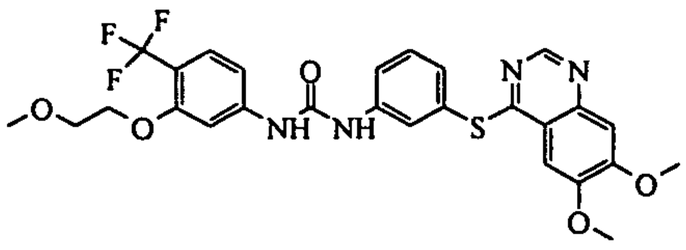
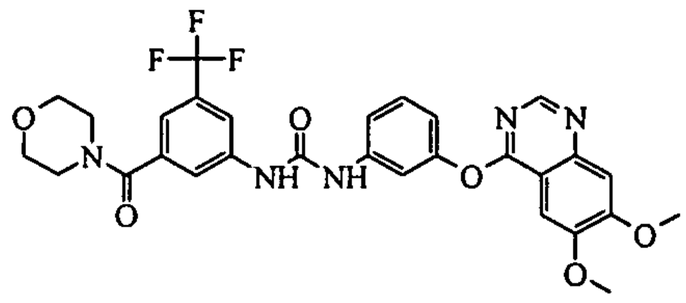
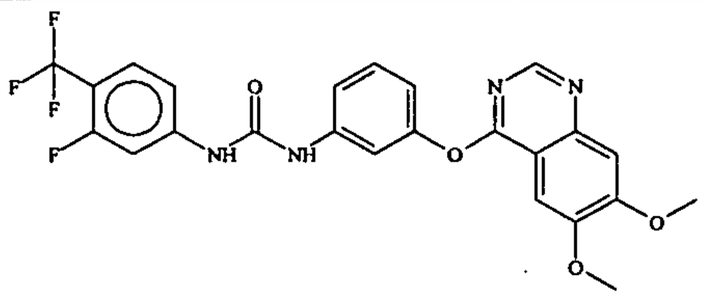
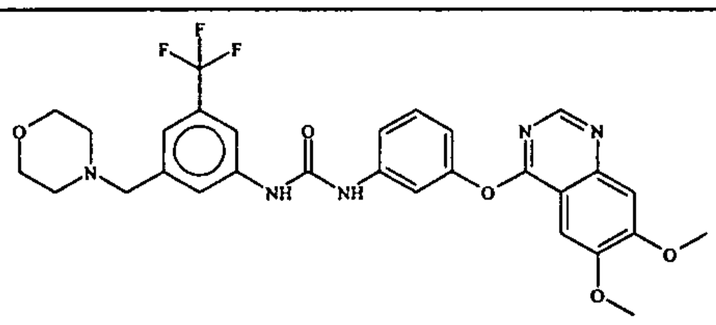
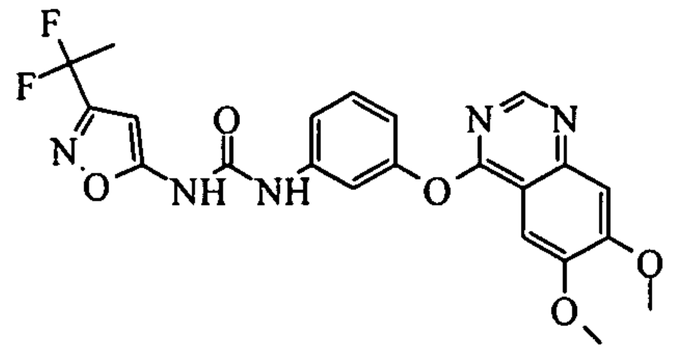
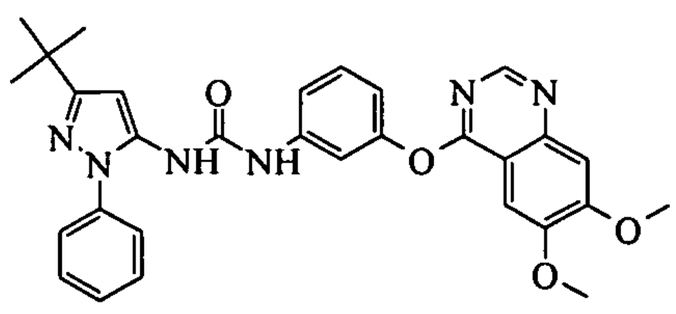
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 116 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-methoxy-5-(trifluoromethyl)phenyl)urea	D	D	B	C	B	B
	Ex 117 1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)phenyl)urea	D	D	B	C	B	C
	Ex 118 1-(3-tert-butylphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	B	D	A	B	A	C*
	Ex 119 1-(3-tert-butylphenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	B	B	C*
	Ex 120 1-(3-tert-butylphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	B	D	A	B	A	C*
	Ex 122 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropylisoxazol-5-yl)urea	B	D	A	A	A	C

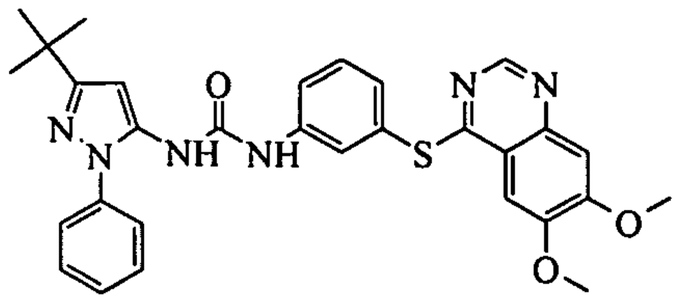
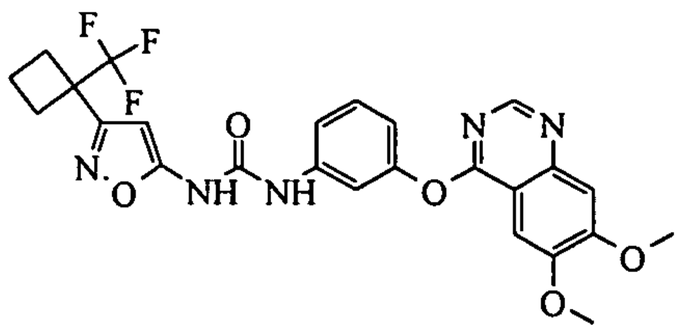
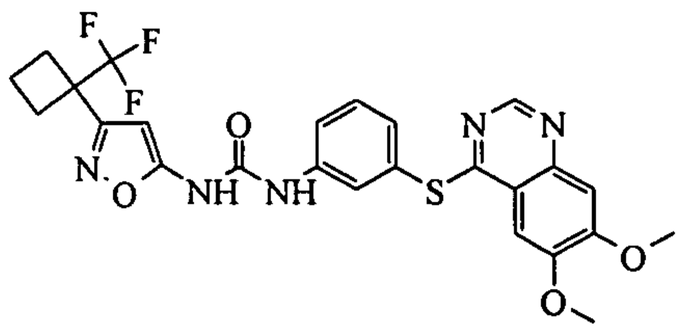
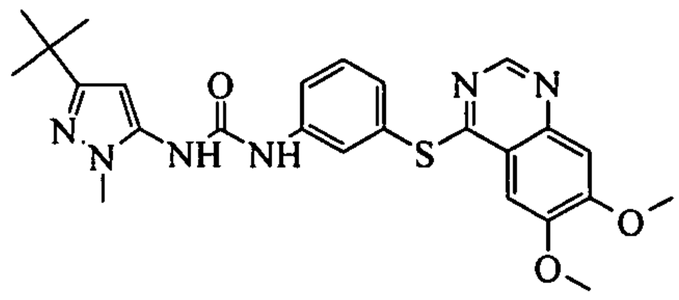
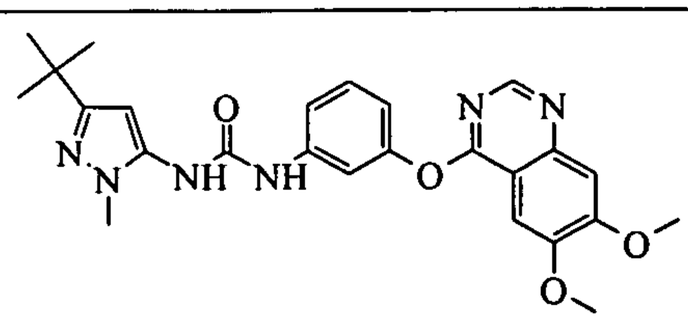
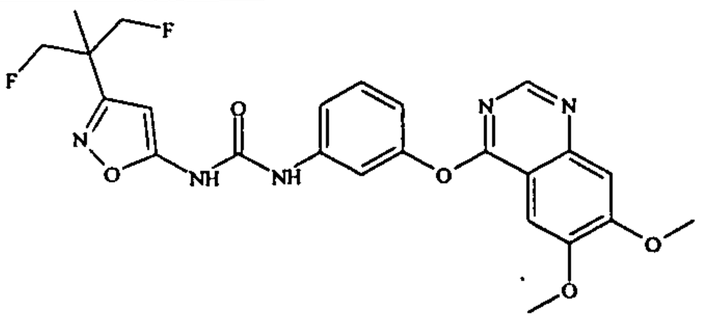
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 123 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(tetrahydro-2H-pyran-4-yl)isoxazol-5-yl)urea	D	D	B	D	C	B
	Ex 124 1-(3-cyclopropylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	D	D	A	A	A	C
	Ex 125 1-(3-(2-cyanopropan-2-yl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	B	D	A	B	B	C*
	Ex 126 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	C	A	B	A	C
	Ex 127 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-methylcyclopropyl)isoxazol-3-yl)urea	B	D	A	A	A	C
	Ex 128 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1-methoxy-2-methylpropan-2-yl)isoxazol-5-yl)urea	C	D	A	D	D	C*

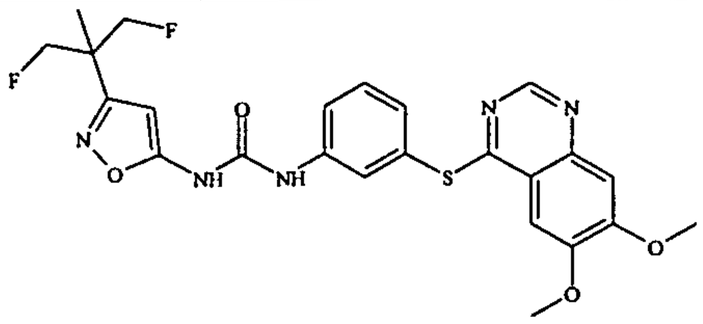
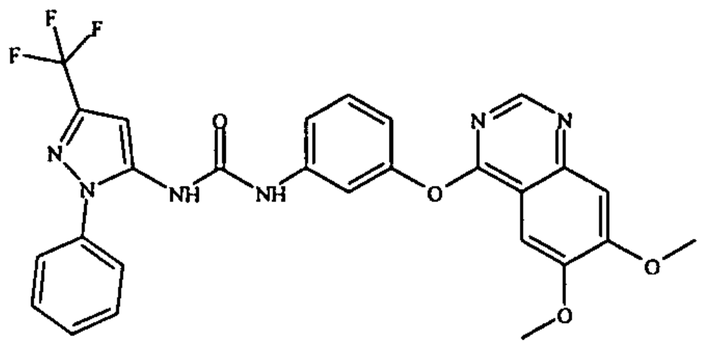
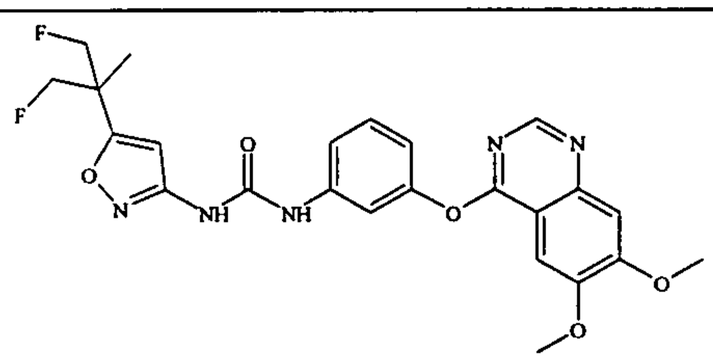
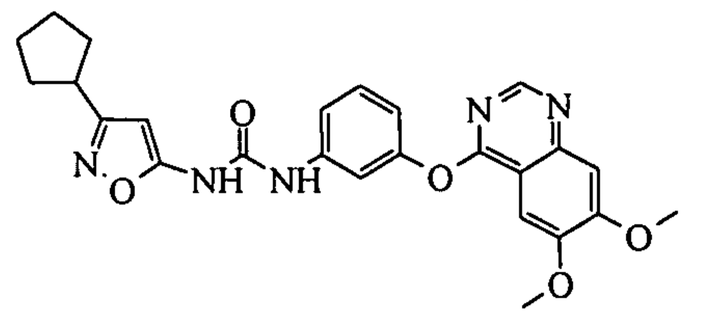
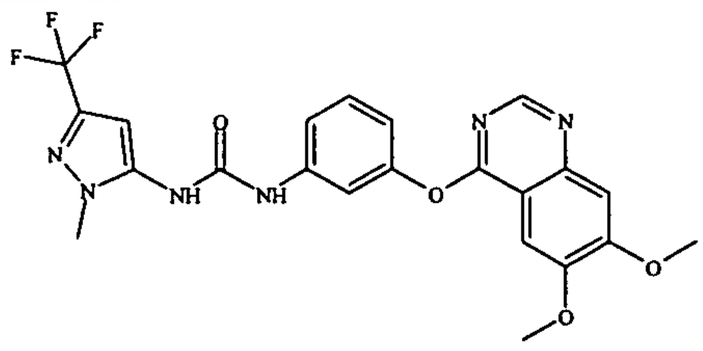
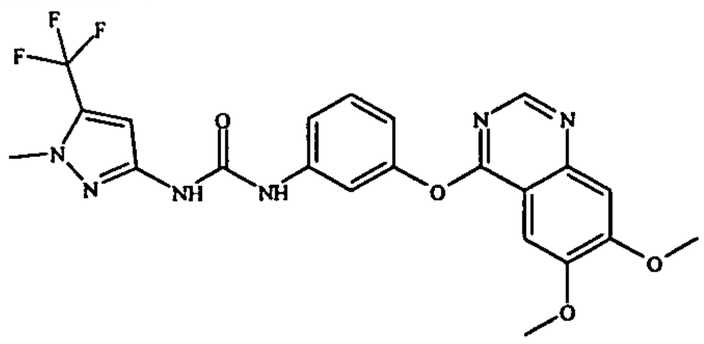
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 129 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)phenyl)urea	D	D	B	D	B	B
	Ex 130 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-yl)urea	B	D	B	D	D	C
	Ex 131 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-hydroxy-2-methylpropan-2-yl)isoxazol-3-yl)urea	C	D	A	B	A	C
	Ex 132 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	A	A	A	C	C	C
	Ex 133 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-isopropylisoxazol-3-yl)urea	B	C	A	A	A	C*
	Ex 134 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-isopropylisoxazol-3-yl)urea	B	D	A	A	A	C*

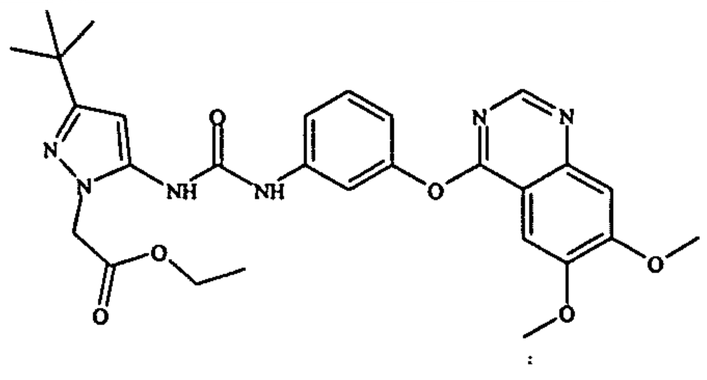
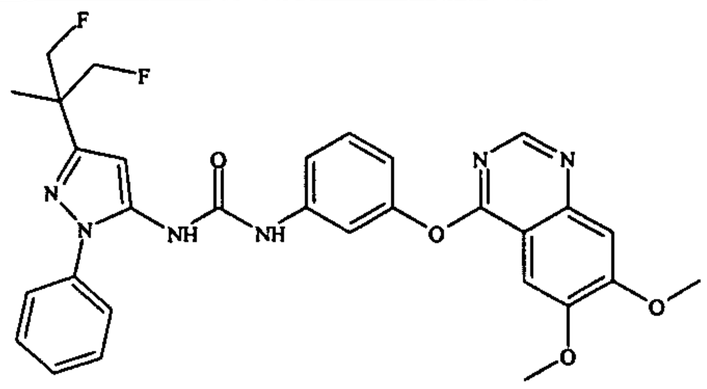
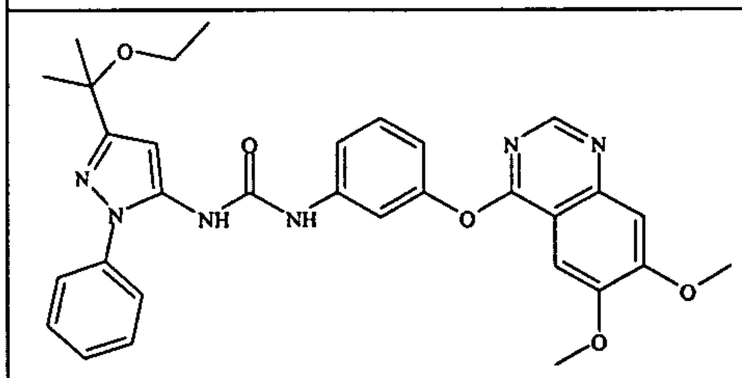
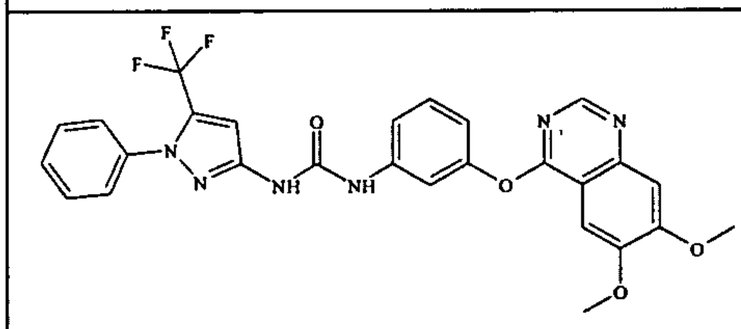
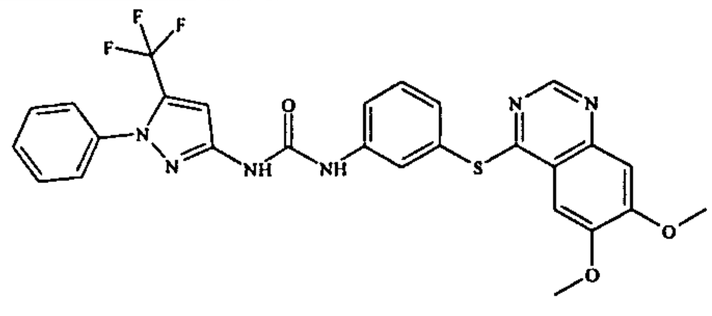
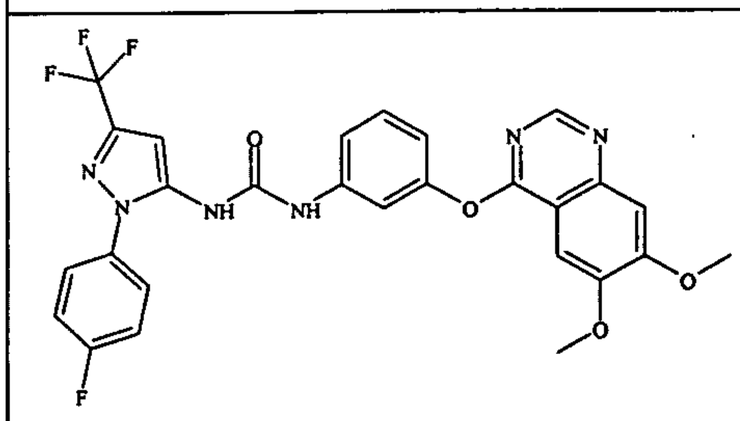
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 135 1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	A	B	A	A	A	C*
	Ex 136 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(2-fluoropropan-2-yl)isoxazol-3-yl)urea	A	B	A	A	A	C*
	Ex 137 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl) urea	A	C	C	D	D	D*
	Ex 138 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-methoxy-3-(trifluoromethyl)phenyl)urea	B	D	A	B	A	B
	Ex 139 1-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	A	A	C*
	Ex 140 1-(3-chloro-5-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy) phehyl)urea	D	D	C	D	C	B

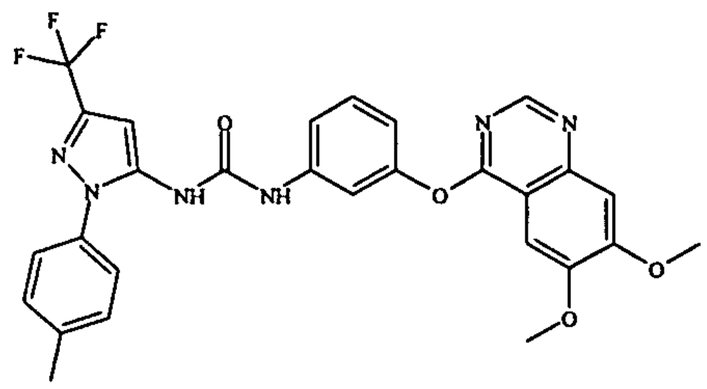
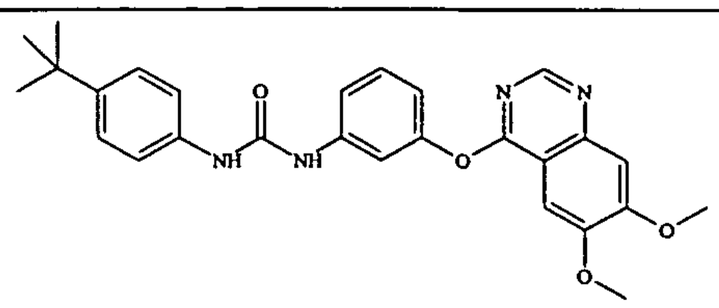
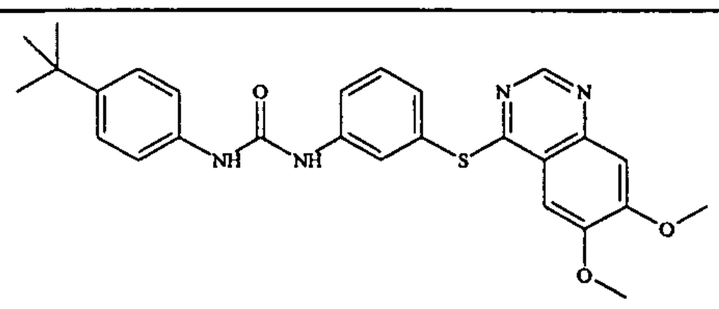
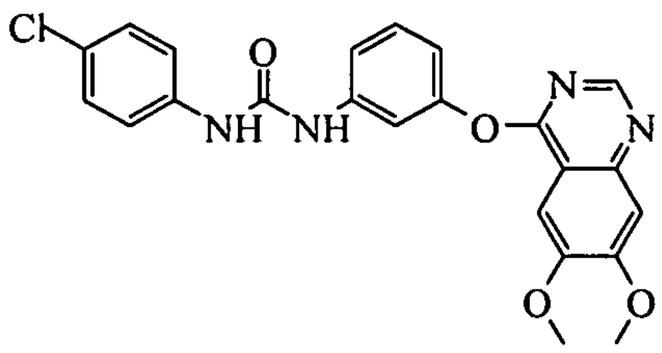
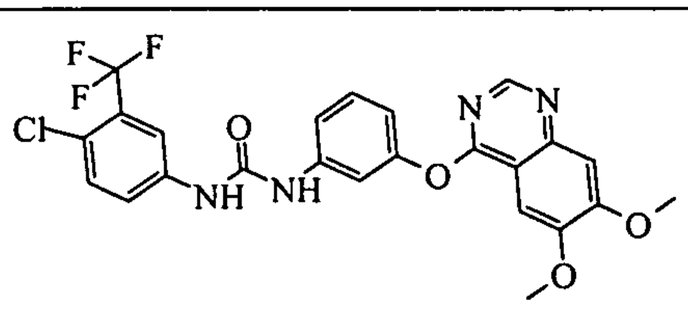
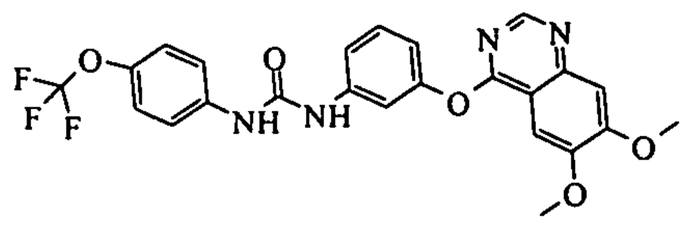
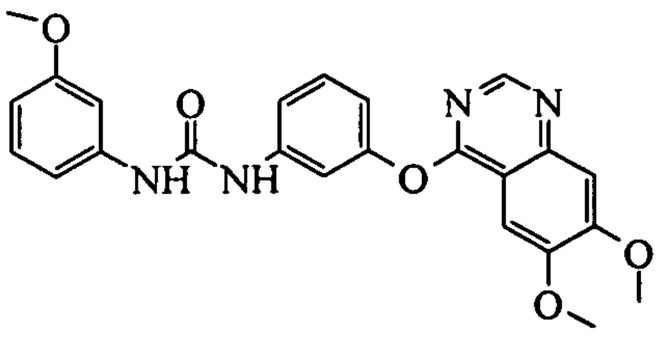
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 141 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyridin-2-yl)urea ;	C	D	A	A	A	C
	Ex 142 1-(2-chloro-5-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	D	D	B	D	B	B
	Ex 143 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyrimidin-2-yl)urea	D	D	B	D	B	A
	Ex 144 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropylphenyl)urea	B	D	A	B	A	C*
	Ex 146 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(6-(trifluoromethyl)pyrimidin-4-yl)urea	D	D	A	B	B	B*
	Ex 147 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-4-(trifluoromethyl)phenyl) urea	D	D	B	D	C	B*

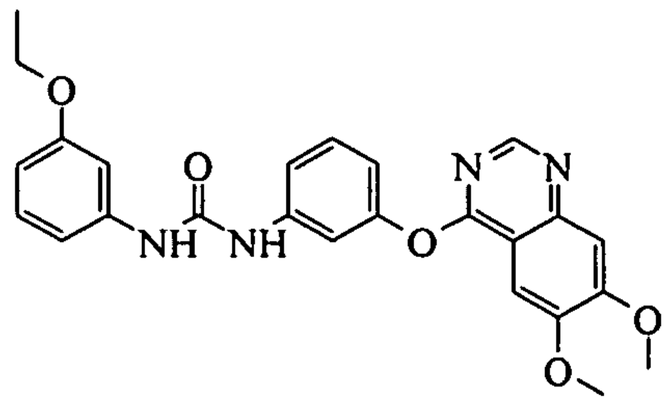
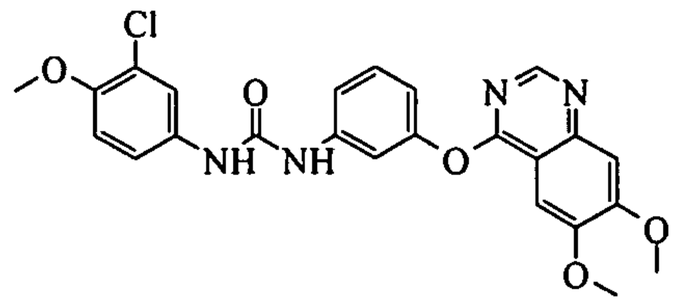
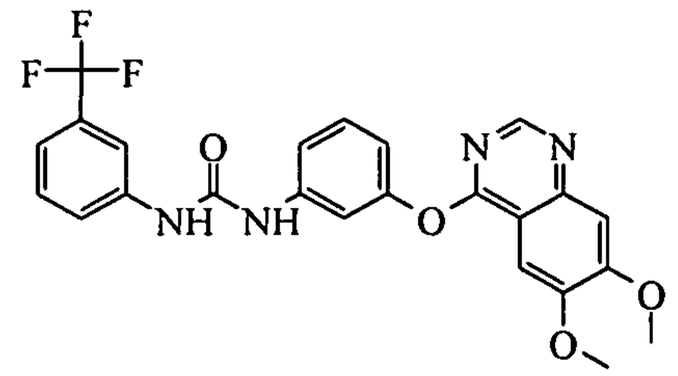
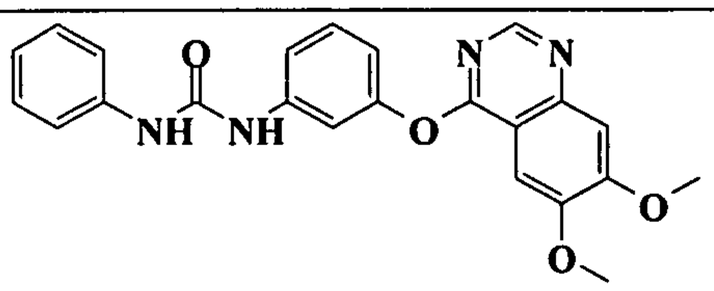
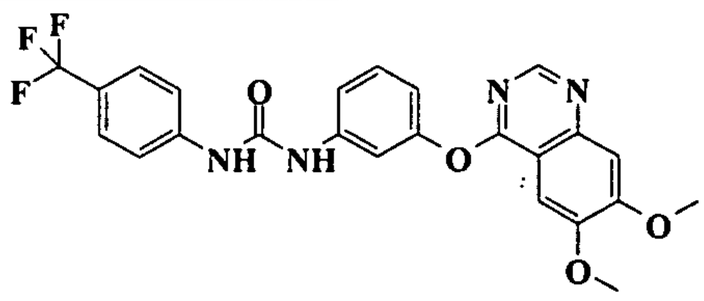
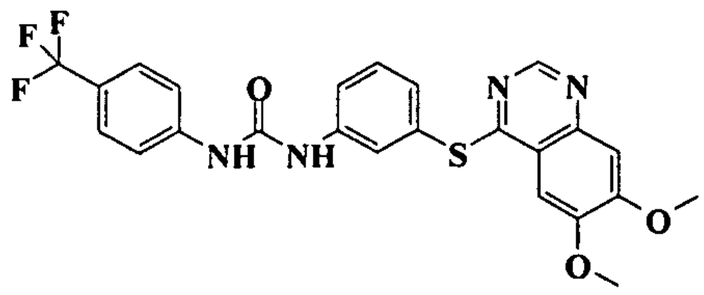
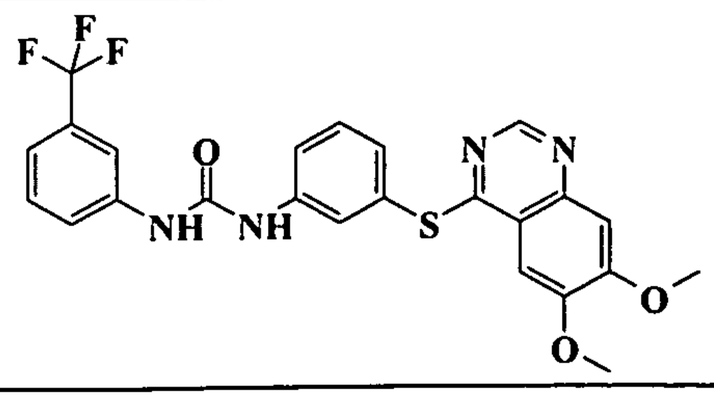
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 148 1-(3-(6,7-Dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-methoxyethoxy)-4-(trifluoromethyl)phenyl) urea	D	D	C	D	D	B*
	Ex 149 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(morpholine-4-carbonyl)-5-(trifluoromethyl)phenyl)urea	D	D	C	D	D	B*
	Ex 150 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)urea	D	D	B	C	C	C*
	Ex 151 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)urea	D	D	A	D	B	C*
	Ex 152 1-(3-(1,1-difluoroethyl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	C	C	A	B	B	C*
	Ex 153 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	A	ND	C	D	D	D*

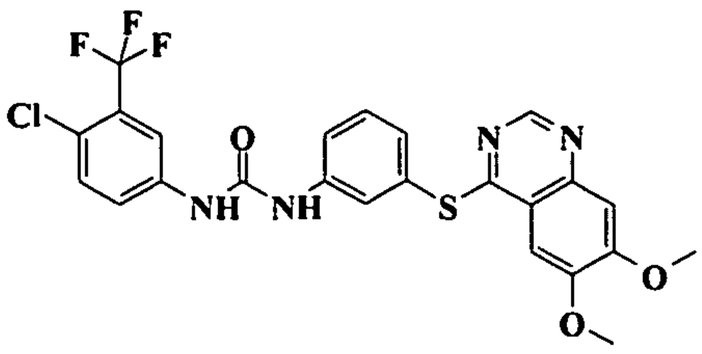
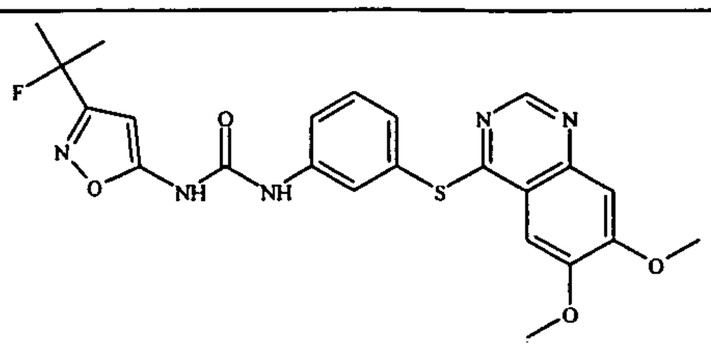
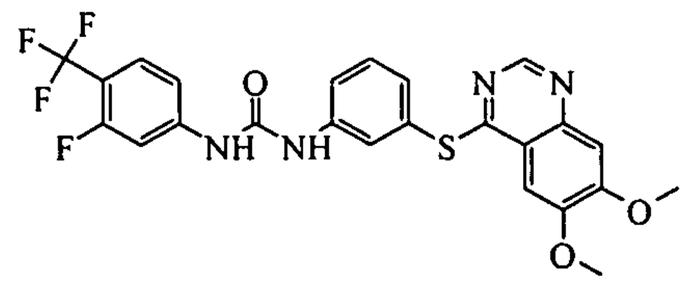
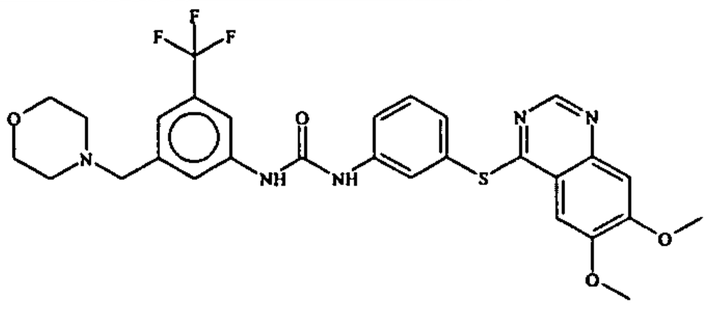
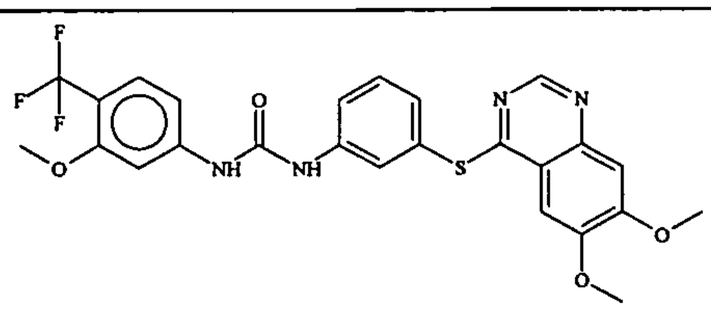
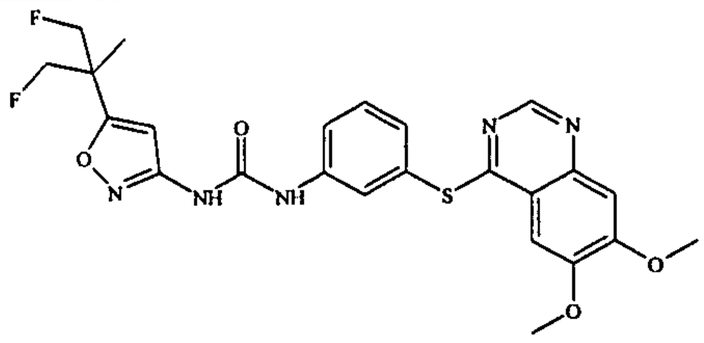
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 154 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	A	ND	D	D	D	D*
	Ex 155 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1-(trifluoromethyl)cyclobutyl)isoxazol-5-yl)urea	B	D	B	D	D	C*
	Ex 156 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(1-(trifluoromethyl)cyclobutyl)isoxazol-5-yl)urea	C	D	C	D	D	C*
	Ex 157 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	A	D	A	C	B	C*
	Ex 158 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	B	D	A	D	C	C*
	Ex 159 1-[3-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-yloxy]phenyl) urea	B	D	B	C	C	D*

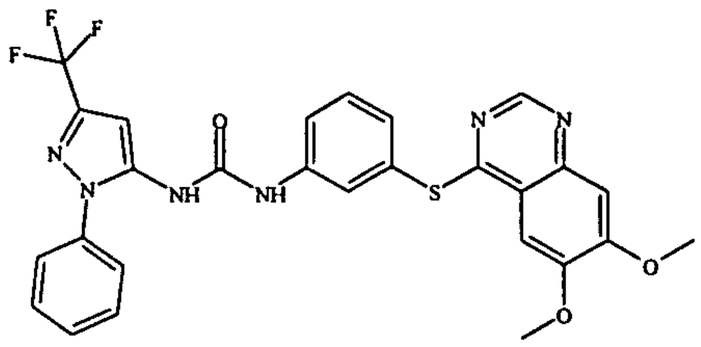
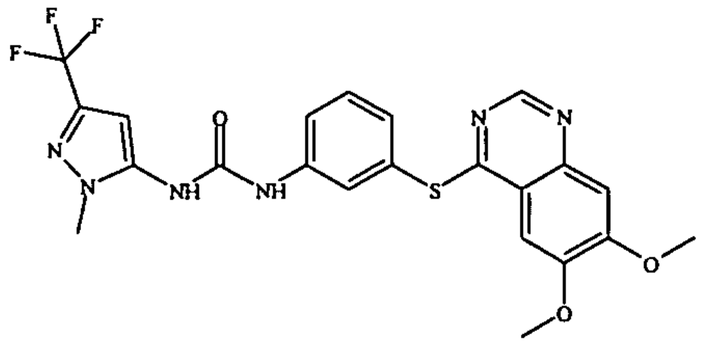
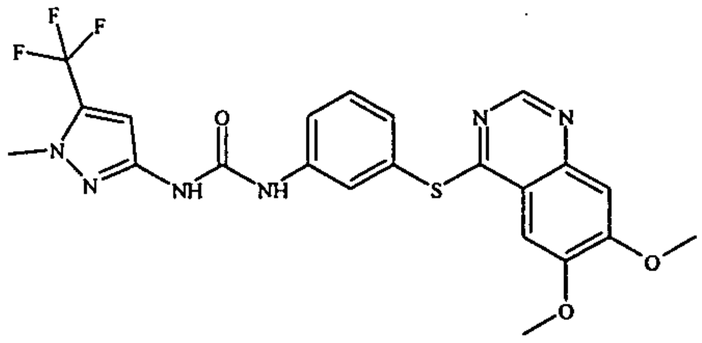
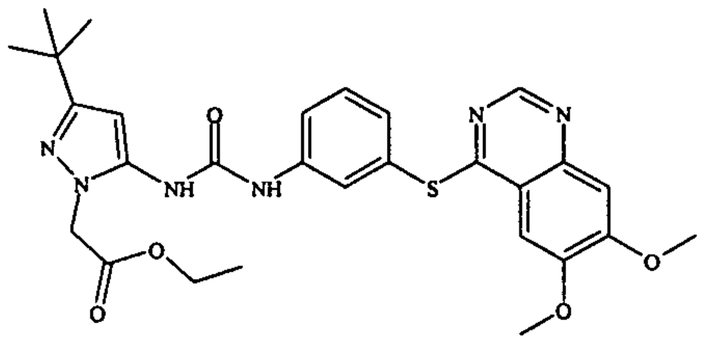
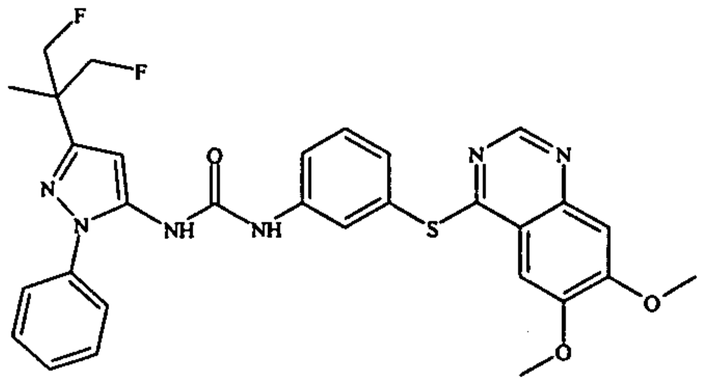
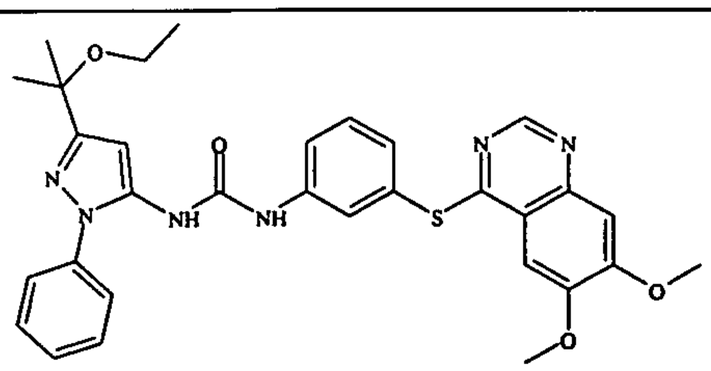
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 160 1-[3-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-ylthio]phenyl) urea	A	D	A	C	B	C*
	Ex 161 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	A	B	C	D	D	C*
	Ex 162 1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl] urea	A	A	A	B	A	C*
	Ex 163 1-(3-cyclopentylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl) urea	D	D	B	D	C	C*
	Ex 164 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	D	A	A	A	C*
	Ex 165 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	B	C	A	A	A	C*

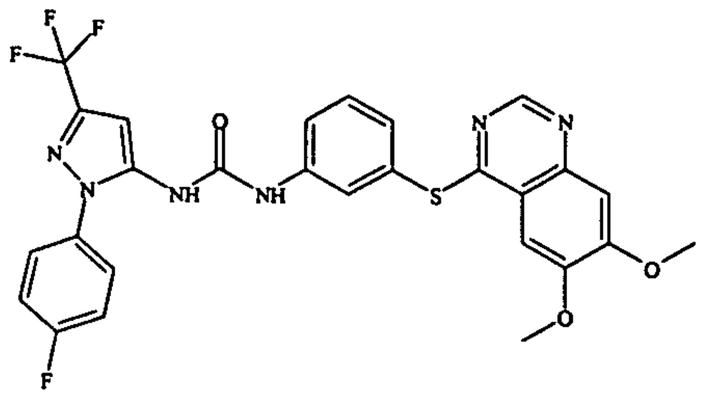
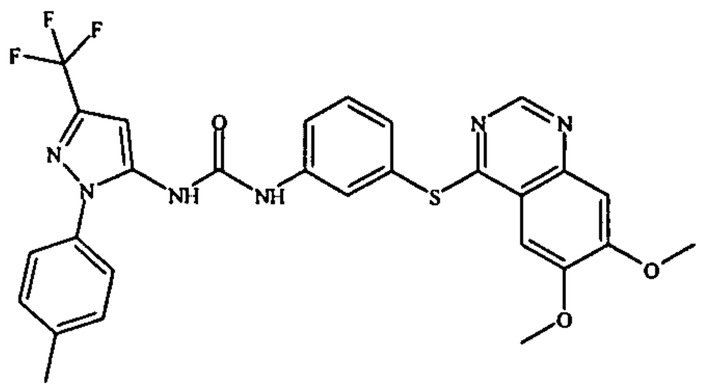
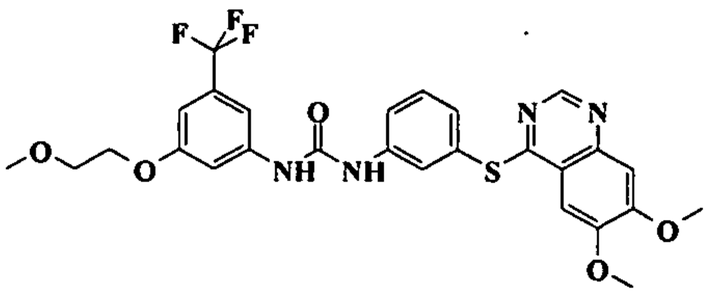
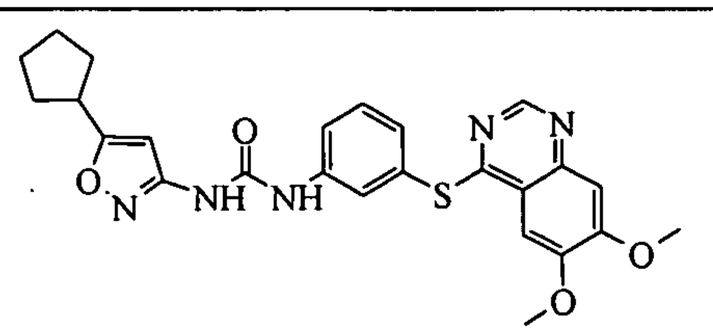
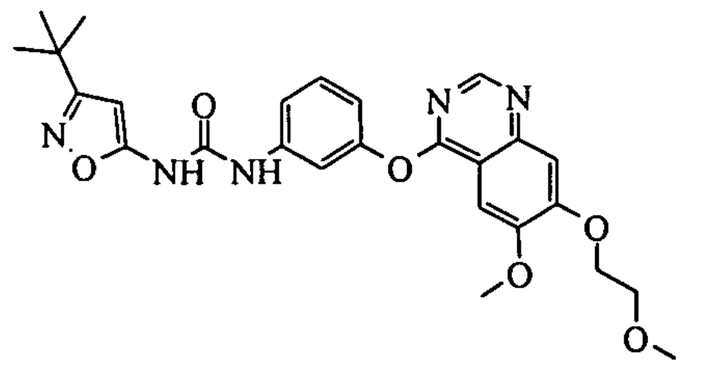
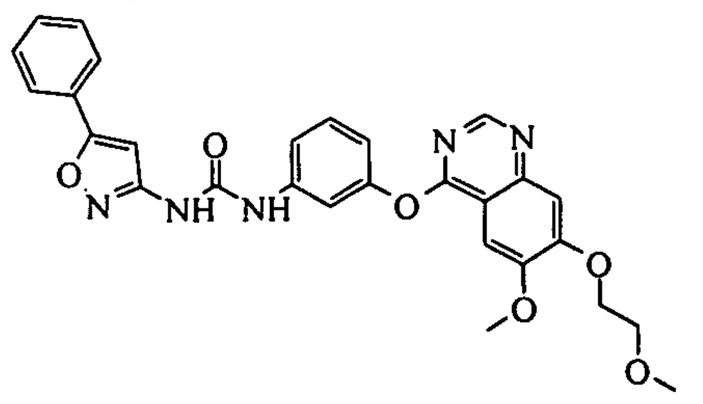
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 166 ethyl 2-(3-*tert*-butyl-5-{3-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl] ureido}-1*H*-pyrazol-1-yl)acetate	C	D	B	D	D	C*
	Ex 167 1-[3-(1,3-difluoro-2-methylpropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl] urea	A	C	D	D	D	D*
	Ex 168 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[3-(2-ethoxypropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]urea	A	D	C	D	D	C*
	Ex 169 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	B	D	B	D	C	C*
	Ex 170 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	B	B	D	D	D	B*
	Ex 171 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	B	C	D	D	C*

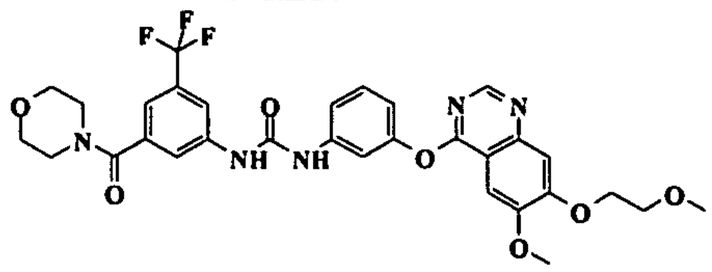
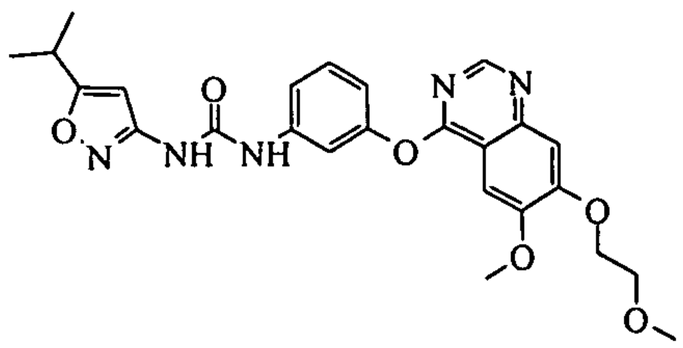
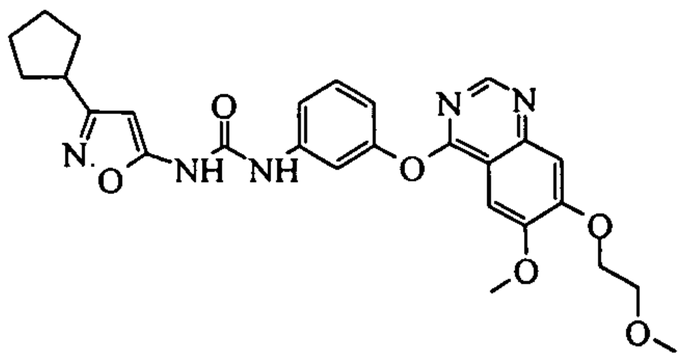
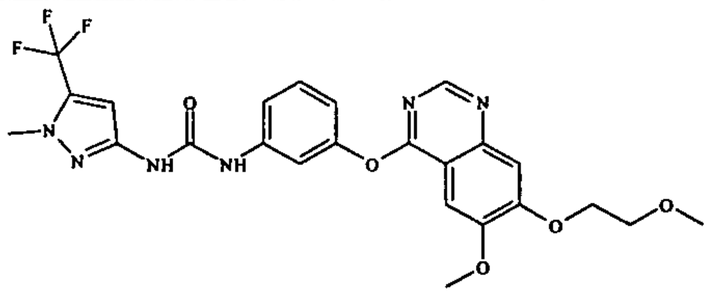
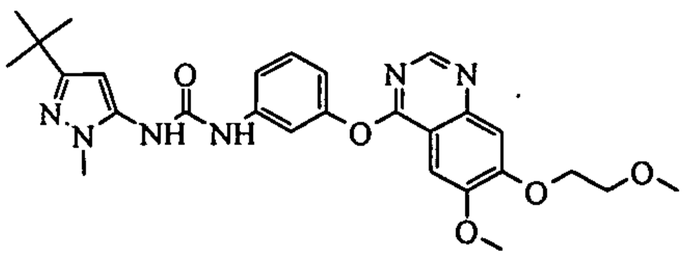
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 172 1-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-3-[1-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	A	A	C	D	D	C*
	Ex 173 1-(4-tert-butylphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	D	A	C	B	C
	Ex 174 1-(4-tert-butylphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	D	D	B	D	B	C
	Ex 175 1-(4-chlorophenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	A	A	A	C
	Ex 176 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	D	A	C	B	C
	Ex 177 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethoxy)phenyl)urea	D	D	A	B	A	C
	Ex 178 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-methoxyphenyl)urea	D	D	A	C	B	B*

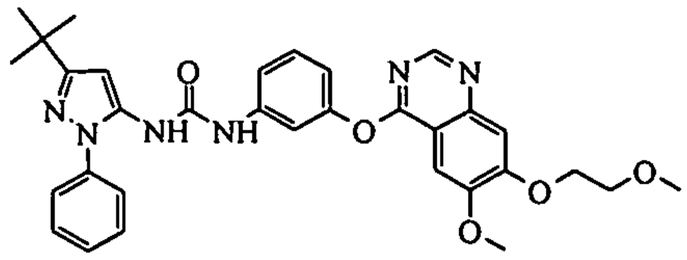
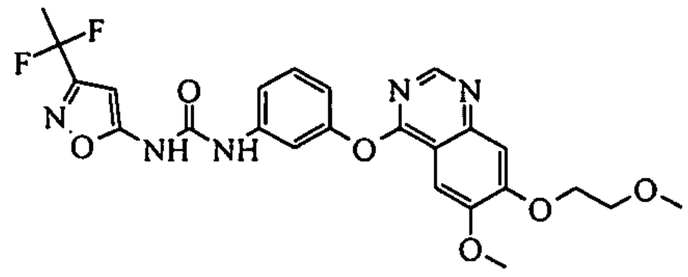
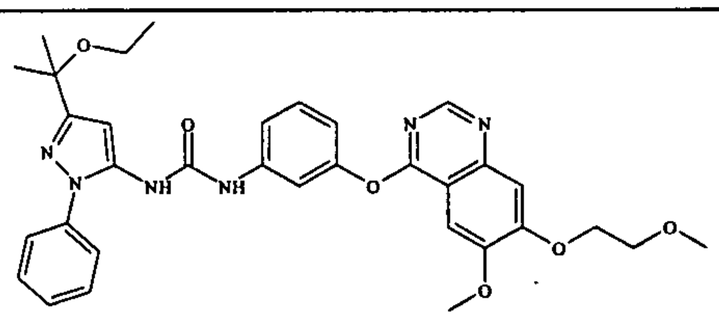
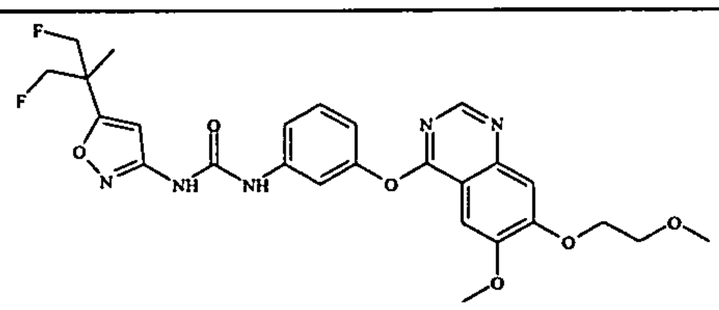
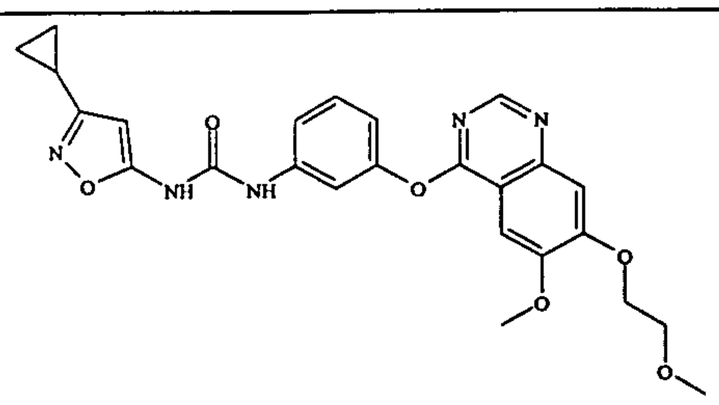
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 179 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-ethoxyphenyl)urea	D	D	A	C	B	B*
	Ex 180 1-(3-chloro-4-methoxyphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	A	A	A	B*
	Ex 181 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea	D	D	A	A	A	C*
	Ex 182 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-phenylurea	D	D	D	D	D	B
	Ex 183 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)phenyl)urea	C	D	A	B	A	C*
	Ex 184 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(4-(trifluoromethyl)phenyl)urea	B	C	B	C	B	C*
	Ex 185 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(trifluoromethyl)phenyl)urea	C	D	A	B	A	C*

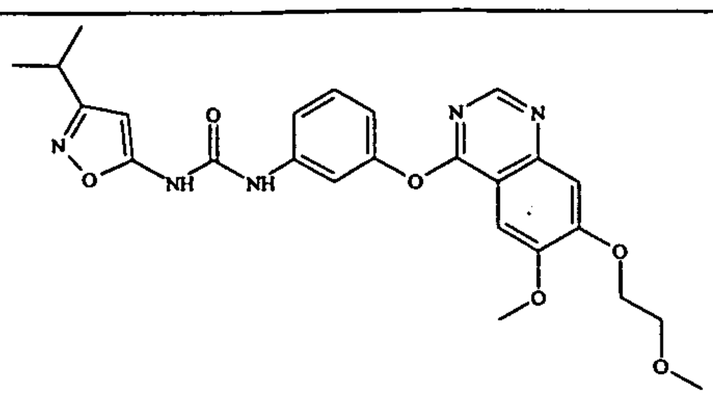
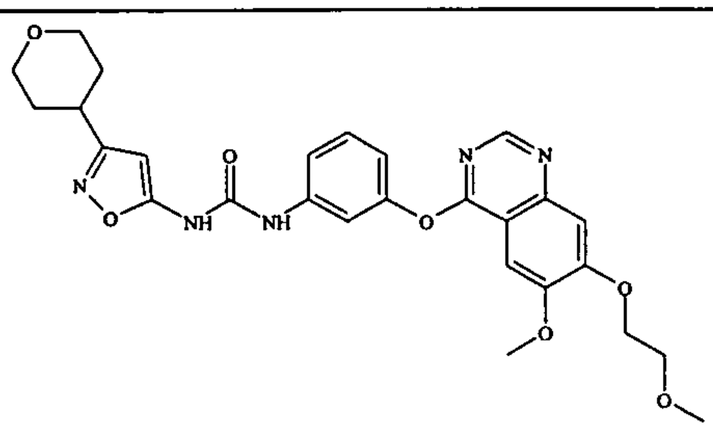
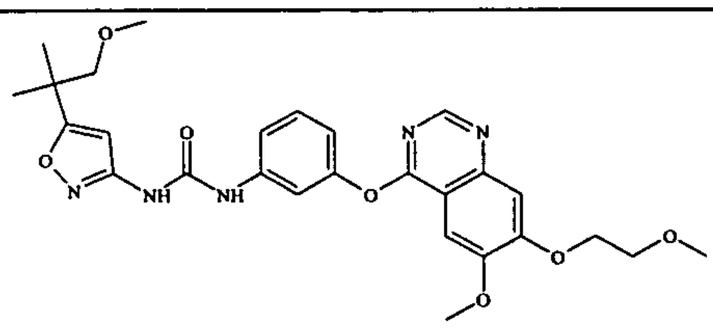
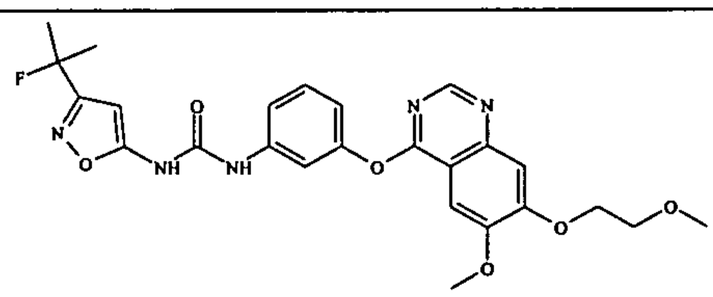
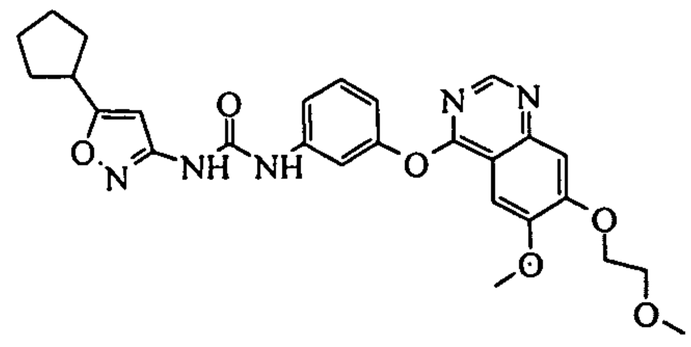
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 186 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	B	C	B	D	D	B*
	Ex 187 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	D	A	B	A	C*
	Ex 188 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)urea	D	D	B	D	C	B*
	Ex 189 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)urea	C	C	B	D	C	C*
	Ex 190 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)urea	D	D	C	D	D	B*
	Ex 191 1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl] urea	A	A	A	B	A	C*

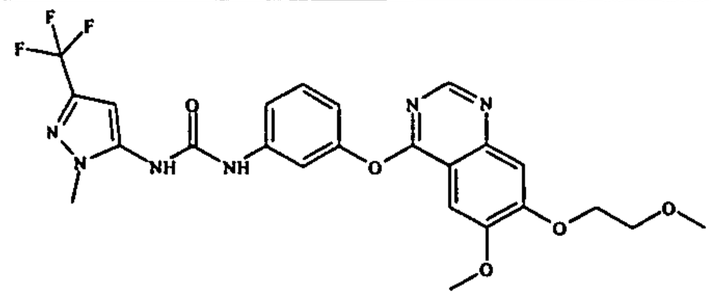
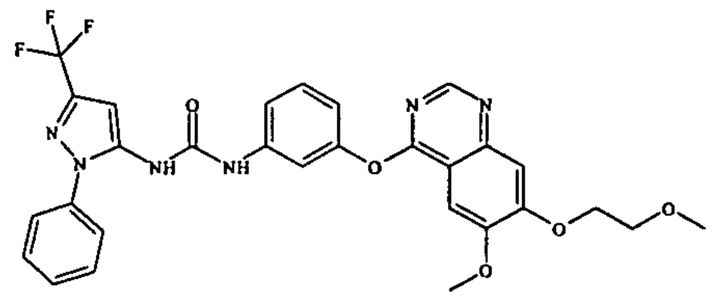
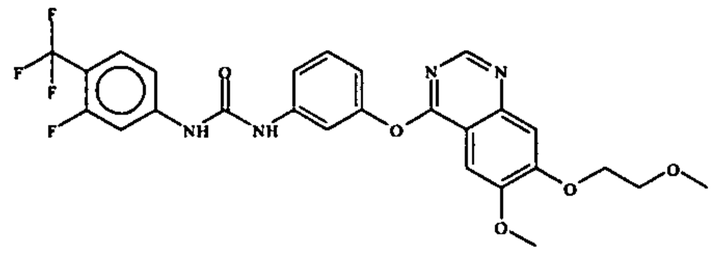
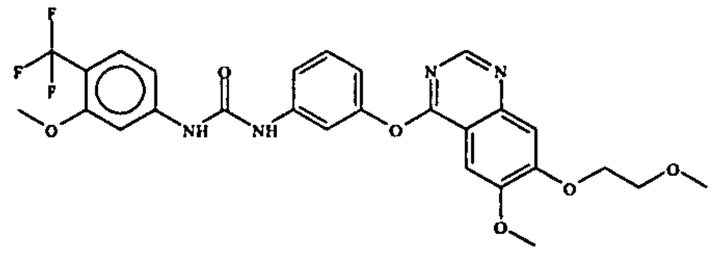
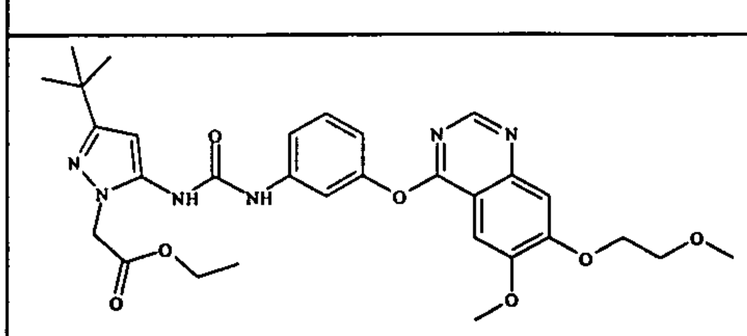
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 192 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	A	B	C	D	D	C*
	Ex 193 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	A	C	A	A	A	D*
	Ex 194 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	B	C	A	A	A	C*
	Ex 195 ethyl 2-(3-*tert*-butyl-5-{3-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]ureido}-1*H*-pyrazol-1-yl)acetate	B	D	B	D	D	C*
	Ex 196 1-[3-(1,3-difluoro-2-methylpropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl] urea	A	D	D	D	D	D*
	Ex 197 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[3-(2-ethoxypropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]urea	B	D	B	D	D	C*

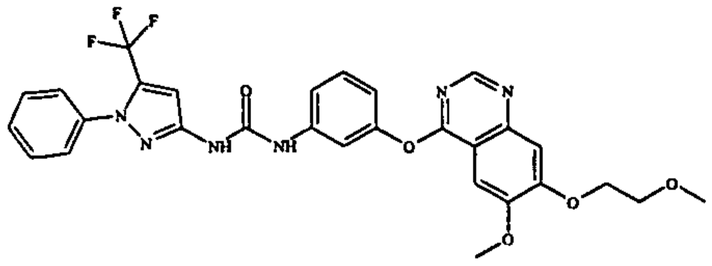
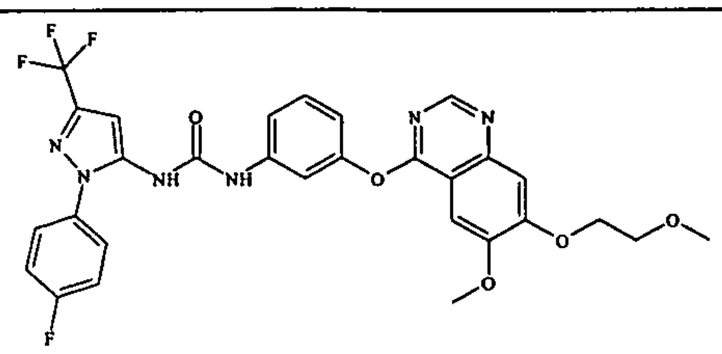
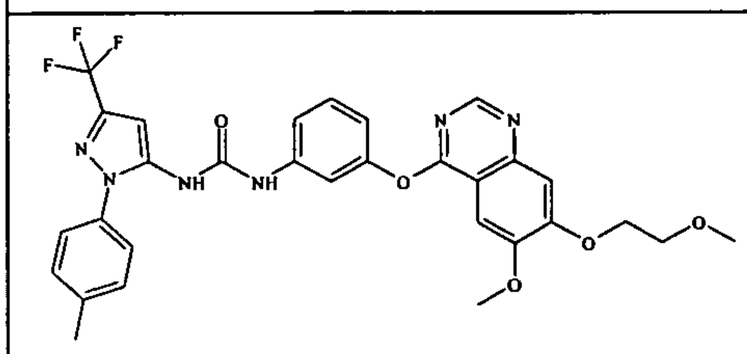
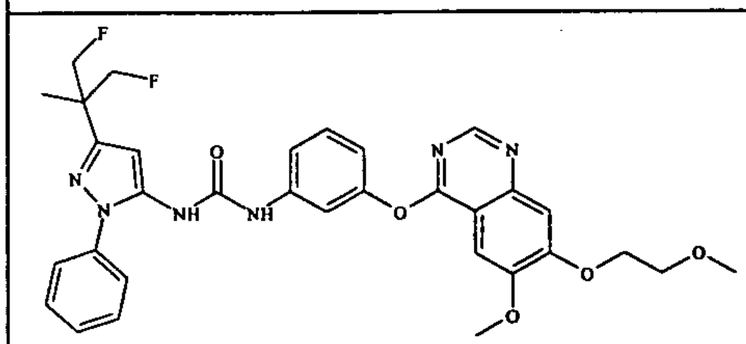
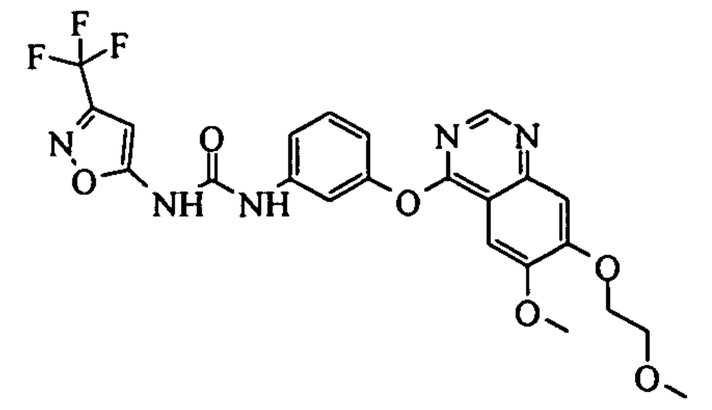
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 198 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	C	C	D	D	C*
	Ex 199 1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	A	D	D	D	D	D*
	Ex 200 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)phenyl)urea	D	D	C	C	D	C
	Ex 201 1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl) urea	B	D	A	B	A	C*
	Ex 202 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	A	D	A	B	B	C
	Ex 203 1-(3-(6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(5-phenylisoxazol-3-yl)urea	D	D	D	D	D	B

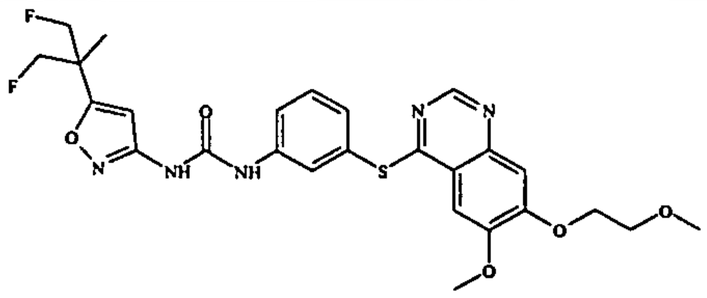
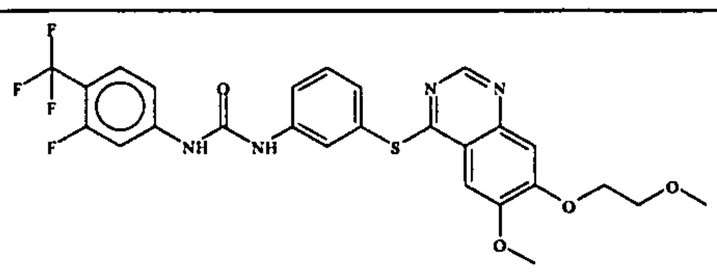
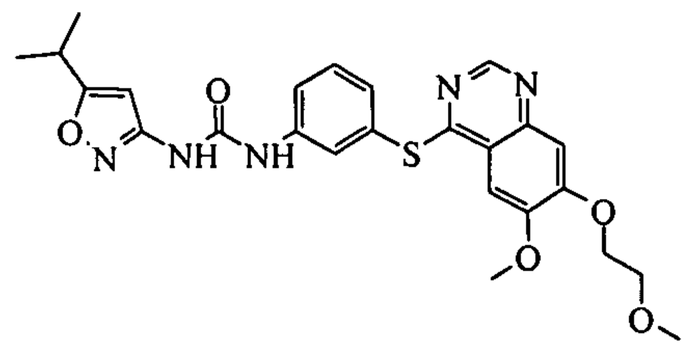
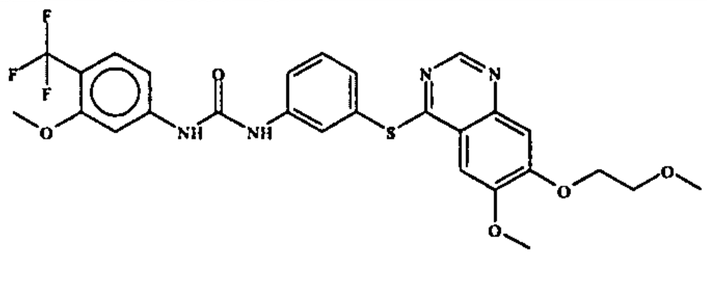
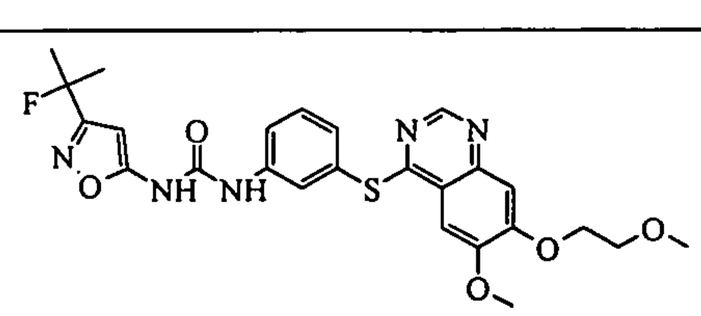
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 205 1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(morpholine-4-carbonyl)-5-(trifluoromethyl)phenyl)urea	D	D	B	D	D	C*
	Ex 206 1-(5-isopropylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	C	D	A	A	A	C*
	Ex 207 1-(3-cyclopentylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	D	D	A	C	B	C*
	Ex 208 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	D	D	A	A	A	C*
	Ex 209 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	C	D	B	D	D	C*

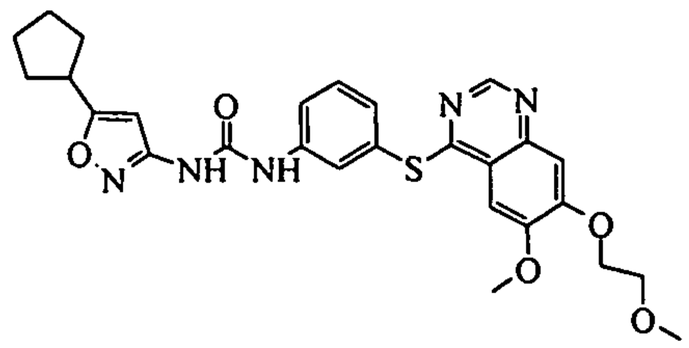
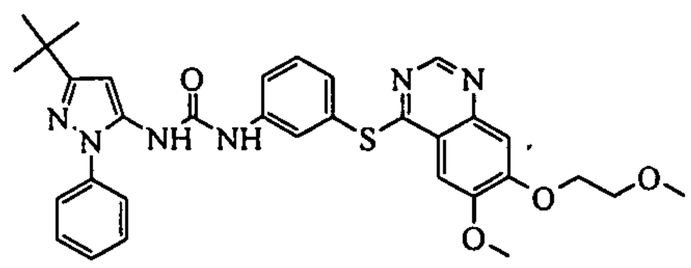
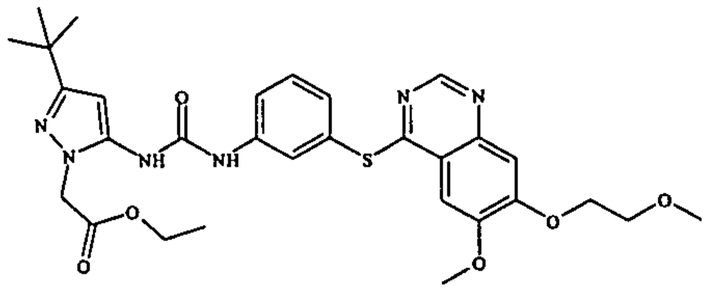
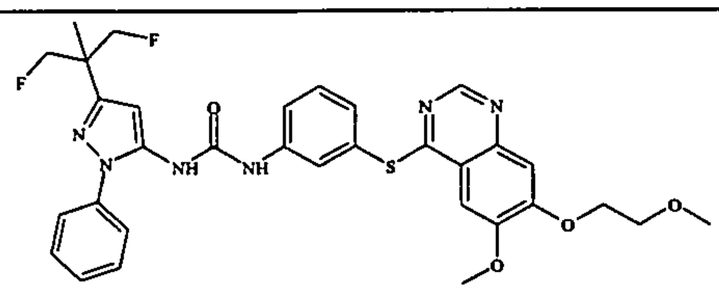
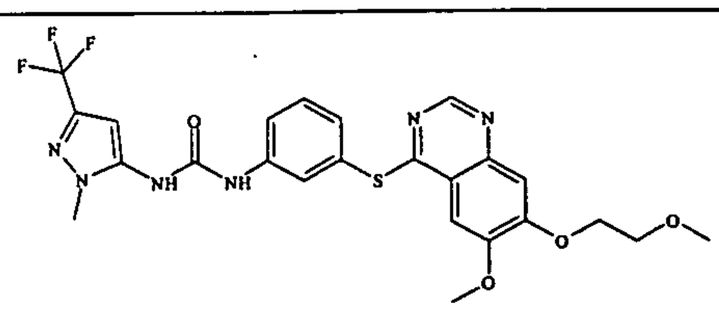
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 210 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	A	ND	D	D	D	D*
	Ex 211 1-(3-(1,1-difluoroethyl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	D	D	B	C	B	C*
	Ex 212 1-[3-(2-ethoxypropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl} urea	C	D	B	D	D	C*
	Ex 213 1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl} urea	A	A	A	B	A	D*
	Ex 214 1-(3-cyclopropylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	D	D	A	A	A	C*

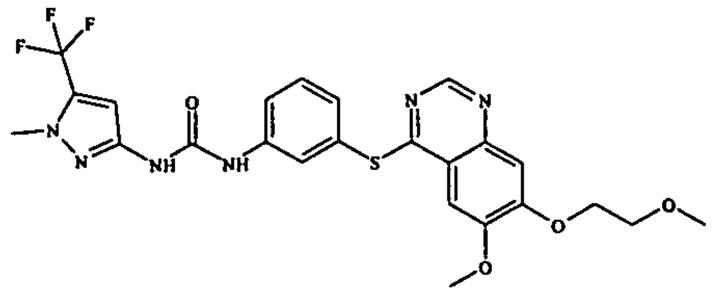
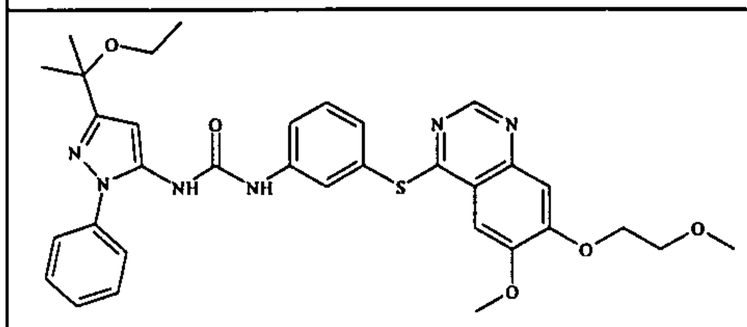
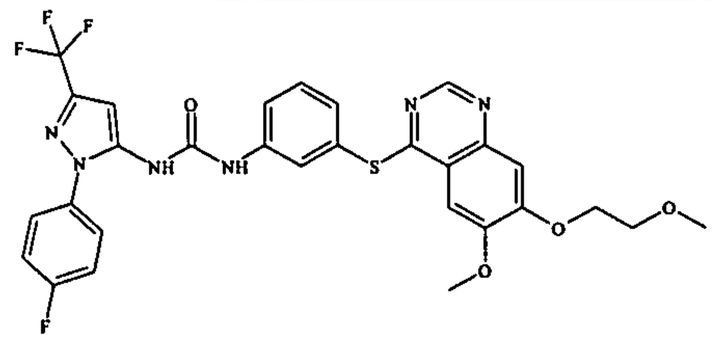
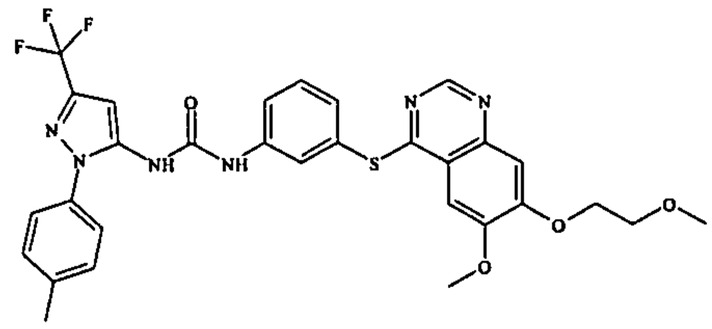
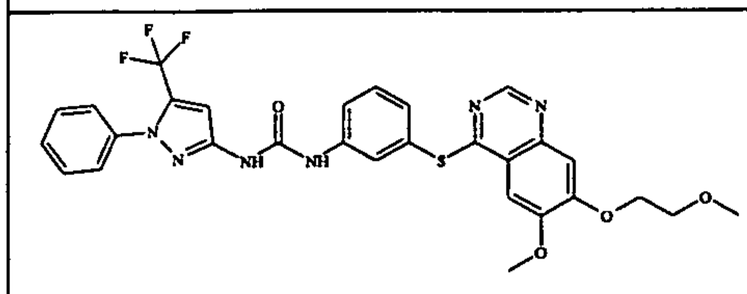
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 215 1-(3-isopropylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	C	D	A	B	B	C*
	Ex 216 1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(tetrahydro-2H-pyran-4-yl)isoxazol-5-yl)urea	D	D	B	D	D	B*
	Ex 217 1-(5-(1-methoxy-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	B	B	C*
	Ex 218 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	B	D	A	B	A	C*
	Ex 219 1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	A	B	A	A	A	C*

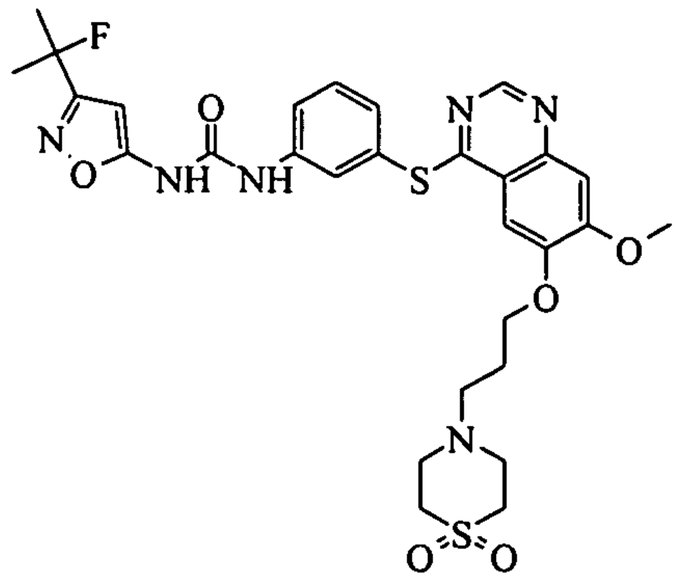
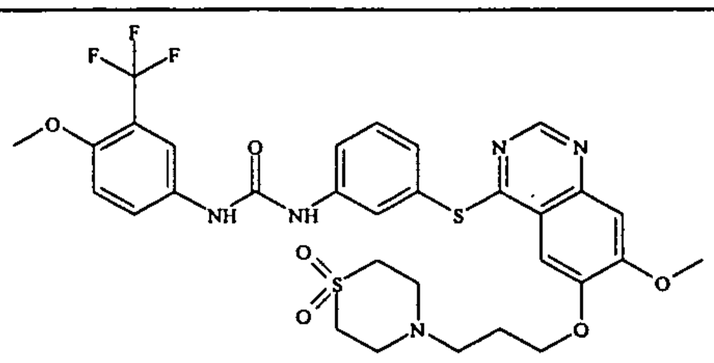
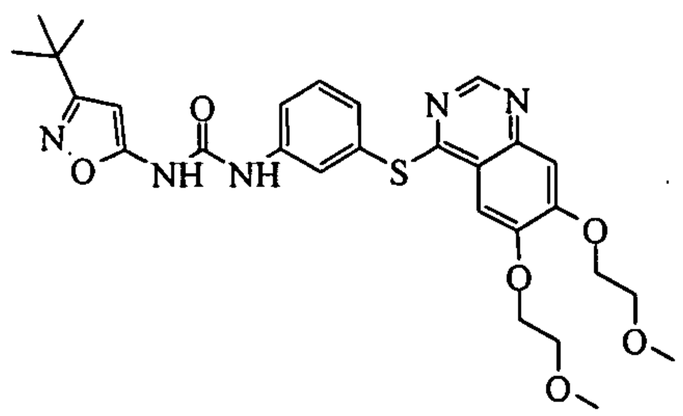
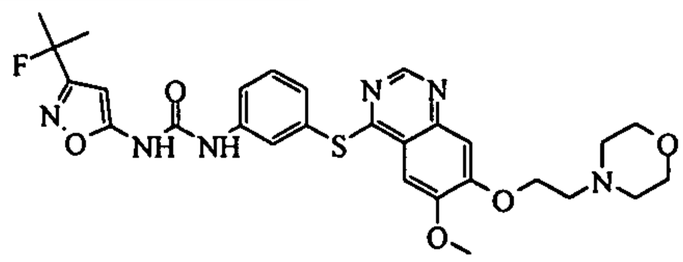
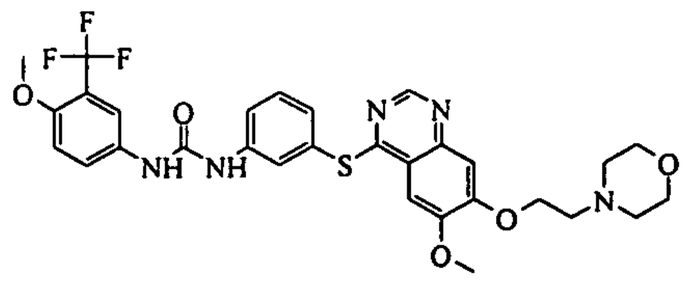
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 220 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	C	D	A	A	A	C*
	Ex 221 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	C	B	D	D	C*
	Ex 222 1-(3-fluoro-4-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	D	D	B	C	B	C*
	Ex 223 1-(3-methoxy-4-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea	D	D	B	D	C	C*
	Ex 224 ethyl 2-[3-*tert*-butyl-5-(3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}ureido)-1*H*-pyrazol-1-yl]acetate hydrochlorid	D	D	D	D	D	A*

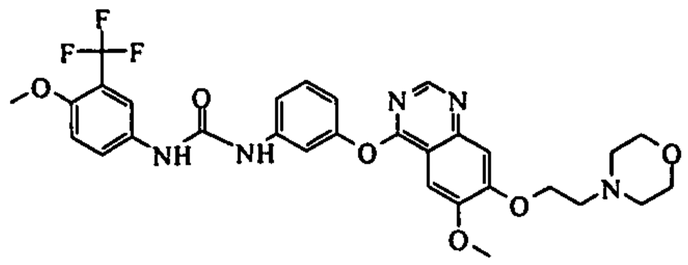
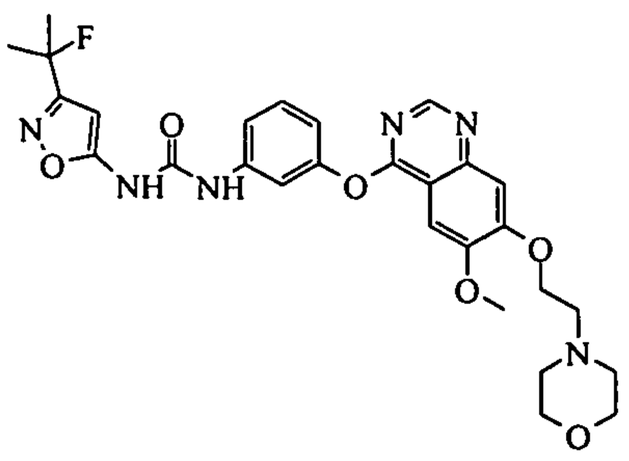
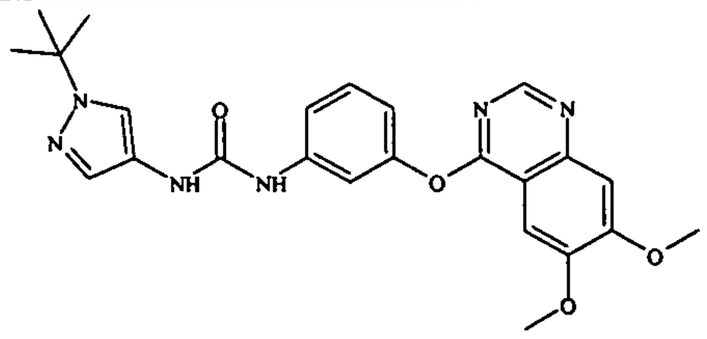
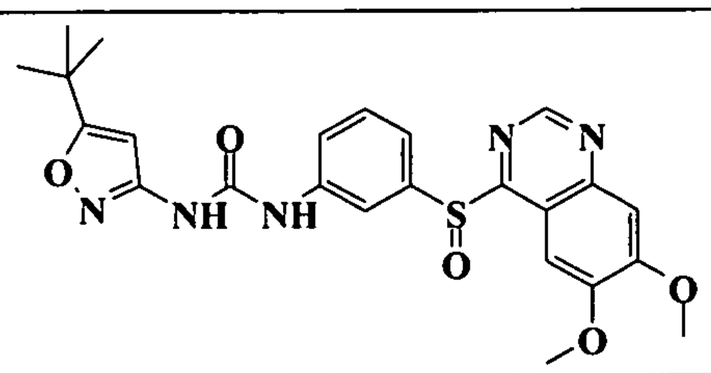
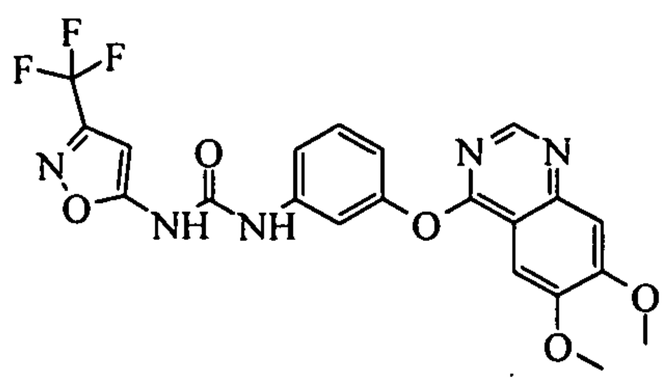
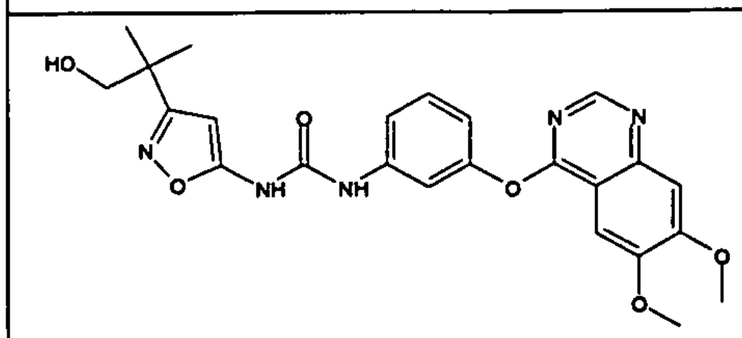
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	e						
	Ex 225 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]urea	C	D	B	D	D	C*
	Ex 226 1-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea	B	D	C	D	D	C*
	Ex 227 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	B	C	D	D	C*
	Ex 228 1-[3-(1,3-difluoro-2-methylpropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl} urea	A	D	C	D	D	D*
	Ex 229 1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea	D	D	A	B	A	C*

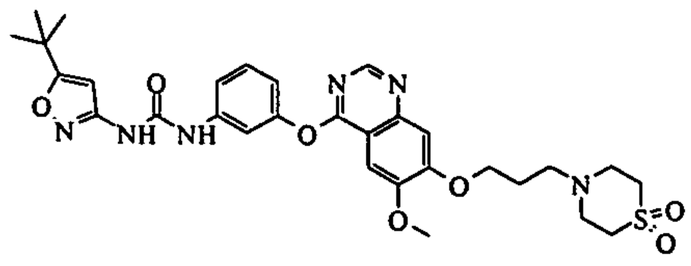
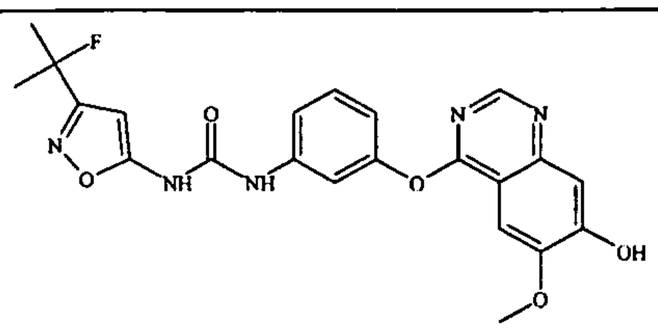
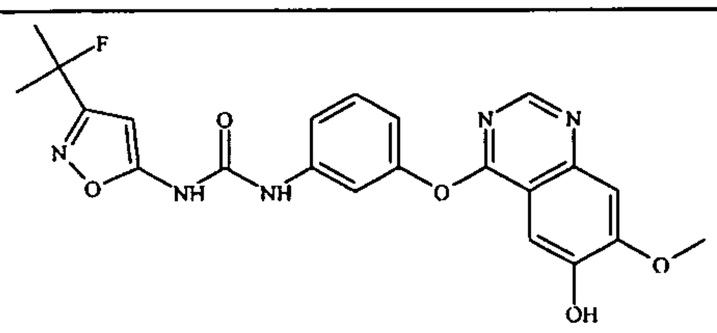
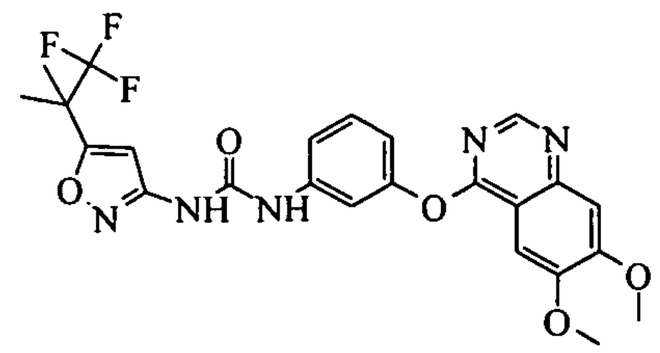
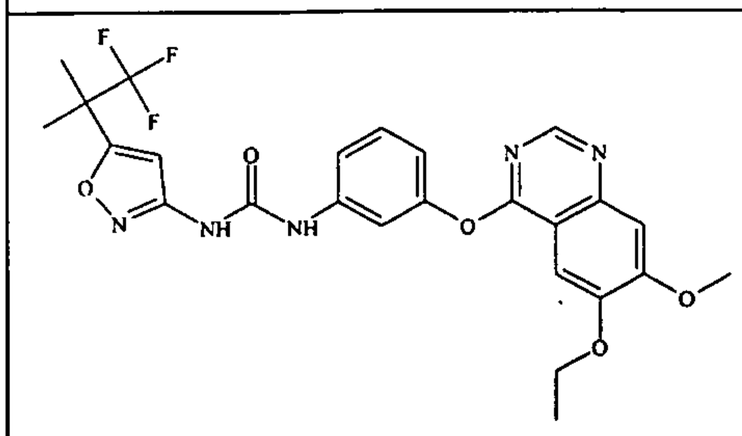
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 230 1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea	A	B	A	C	B	C*
	Ex 231 1-(3-fluoro-4-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	D	D	C	D	D	B*
	Ex 232 1-(5-isopropylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	A	A	A	C*
	Ex 233 1-(3-methoxy-4-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	D	D	C	D	D	C*
	Ex 234 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	A	D	A	B	B	C*

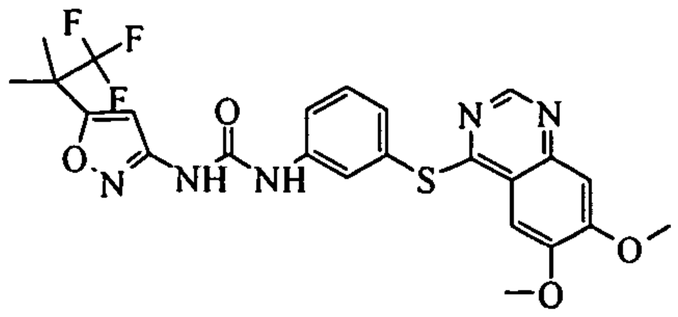
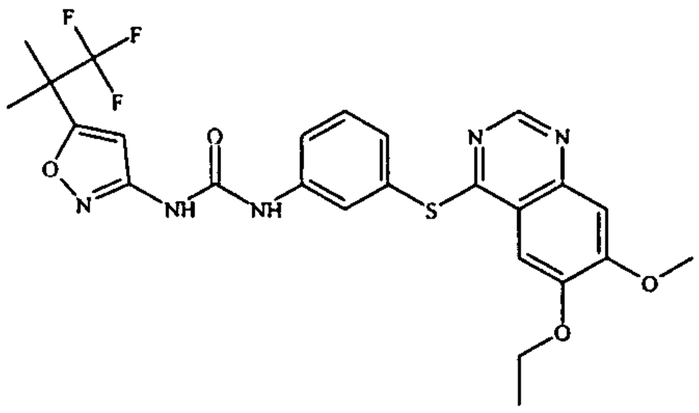
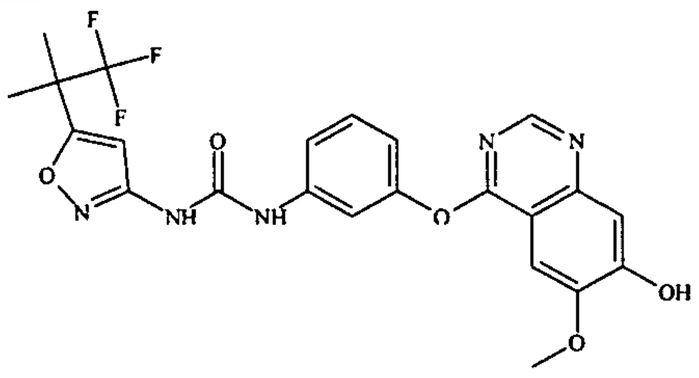
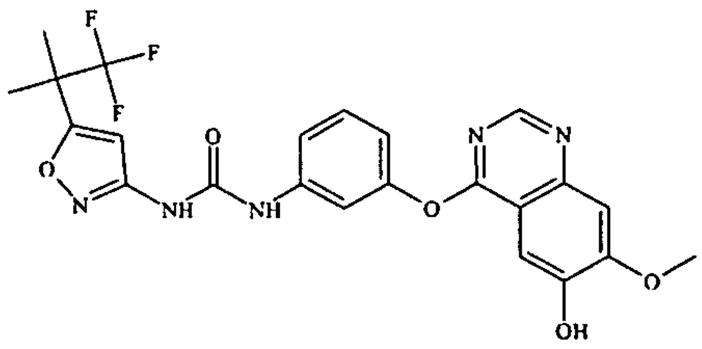
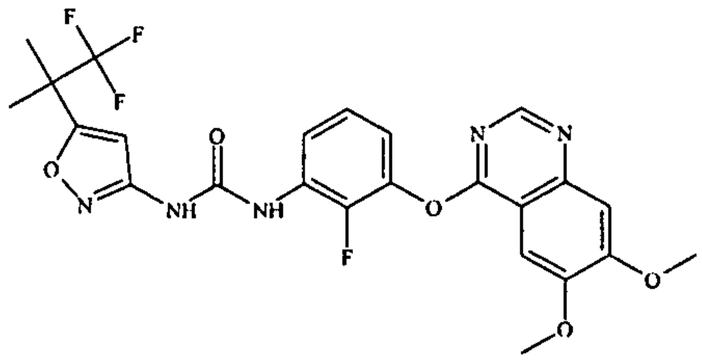
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 235 1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	A	B	A	C*
	Ex 236 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	A	ND	D	D	D	D*
	Ex 237 ethyl 2-[3-*tert*-butyl-5-(3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}ureido)-1*H*-pyrazol-1-yl]acetate	C	D	C	D	D	C*
	Ex 238 1-[3-(1,3-difluoro-2-methylpropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea	A	D	D	D	D	D*
	Ex 239 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-	B	D	A	A	A	D*

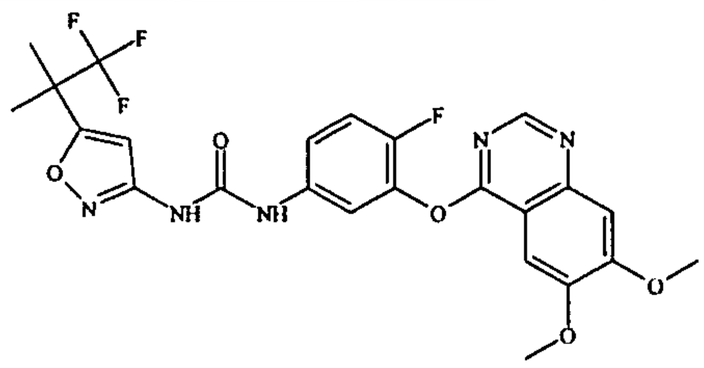
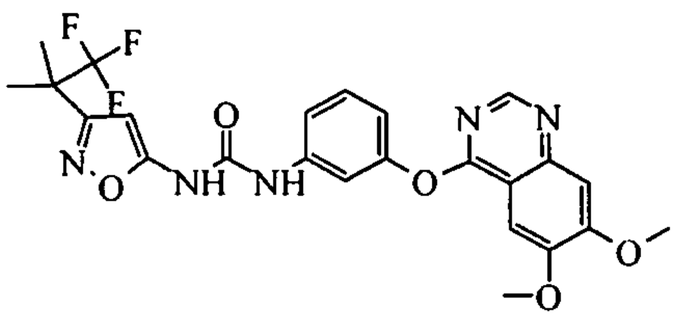
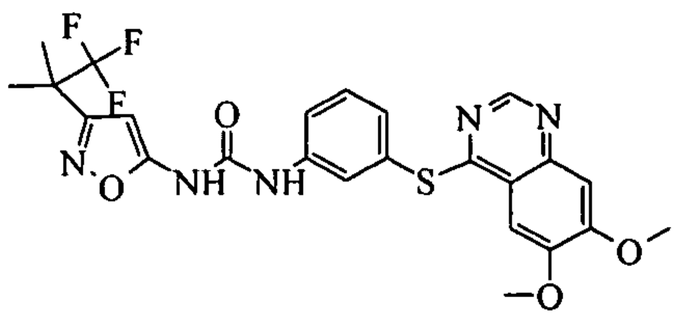
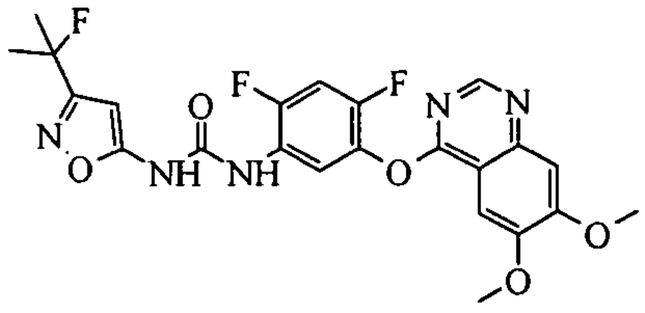
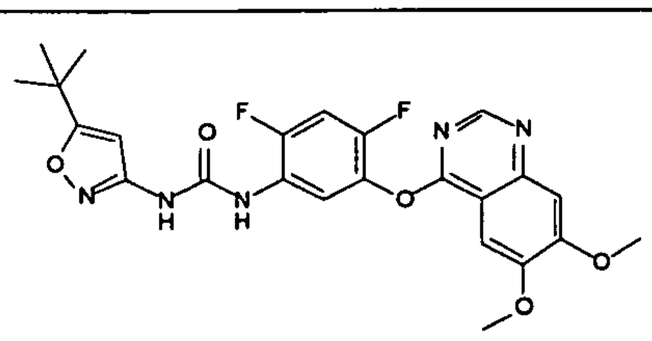
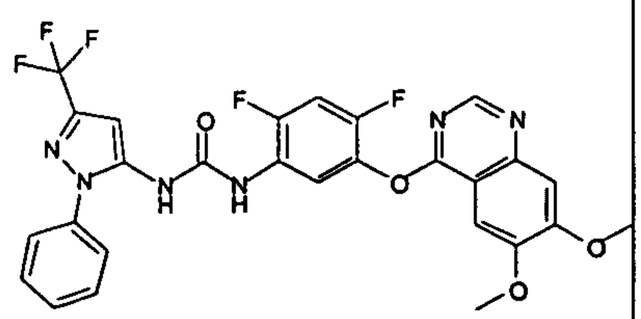
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	yl]urea						
	Ex 240 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	D	A	A	A	C*
	Ex 241 1-[3-(2-ethoxypropan-2-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea	C	D	B	D	D	C*
	Ex 242 1-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea	C	D	D	D	D	C*
	Ex 243 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-[1-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]urea	B	B	D	D	D	C*
	Ex 244 1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-[1-phenyl-5-	D	D	D	D	D	C*

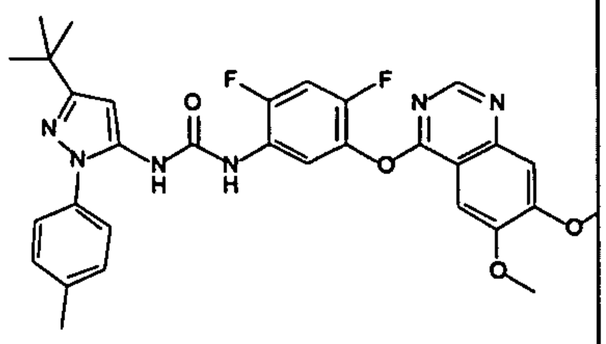
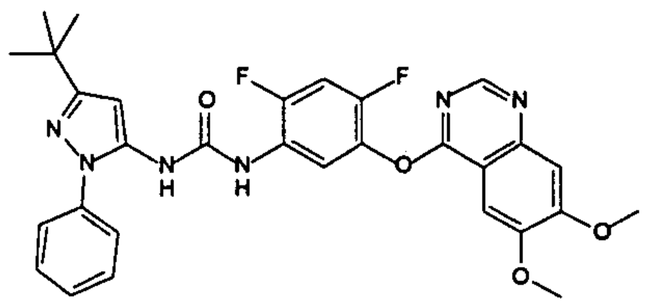
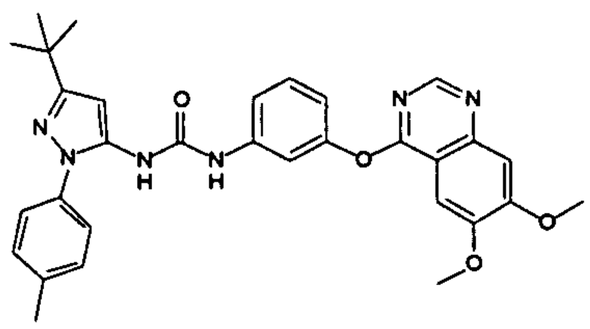
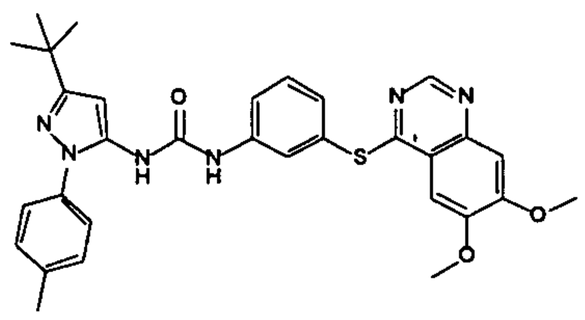
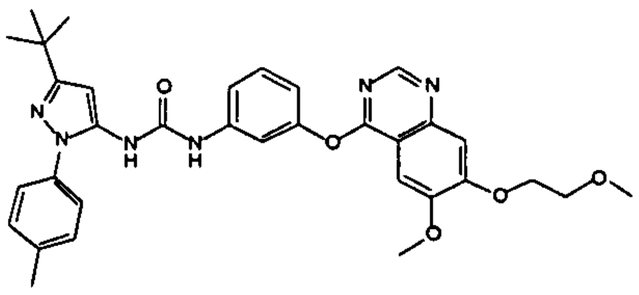
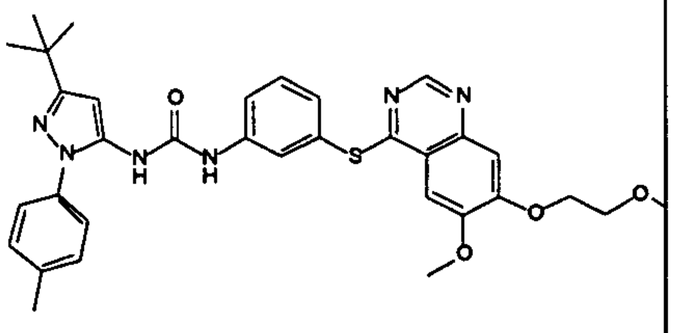
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	(trifluoromethyl)-1H-pyrazol-3-yl]urea						
	Ex 245 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(4,4-dioxo-3-thiomorpholinopropoxy)quinazolin-4-ylthio)phenyl) urea	A	D	A	A	B	C*
	Ex 246 1-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(7-methoxy-6-(3-(4,4-dioxothiomorpholino)propoxy)quinazolin-4-ylthio)phenyl) urea	A	C	A	B	B	C*
	Ex 247 1-(3-(6,7-bis(2-Methoxyethoxy)quinazolin-4-ylthio)phenyl)-3-(3-tert-butylisoxazol-5-yl)urea	A	D	A	B	B	C
	Ex 248 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	A	B	B	C*
	Ex 249 1-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio)phenyl)	C	D	B	C	C	C*

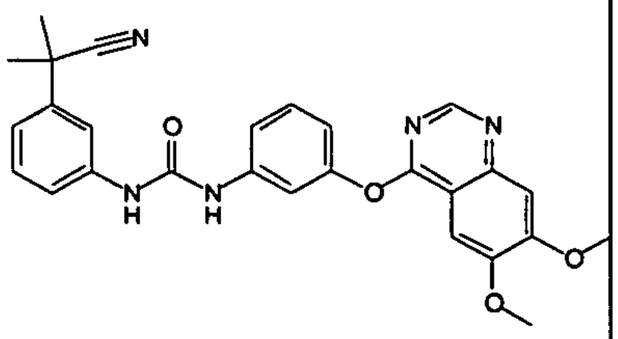
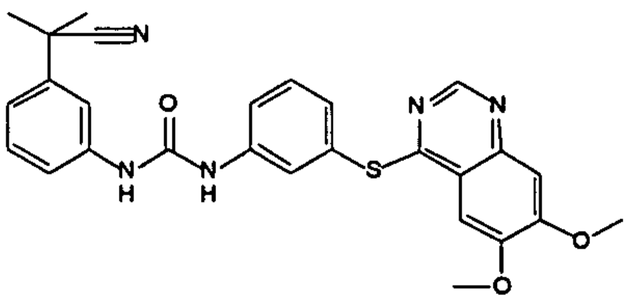
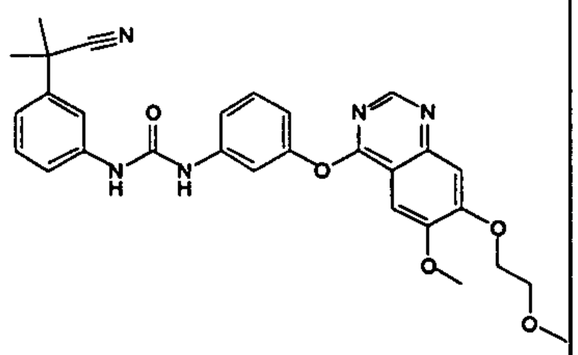
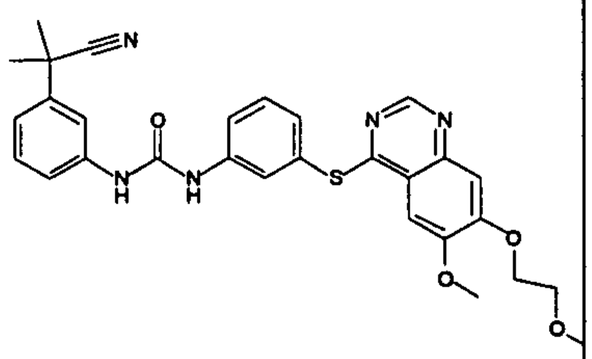
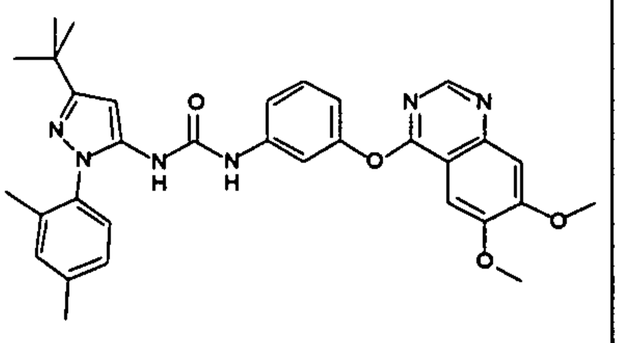
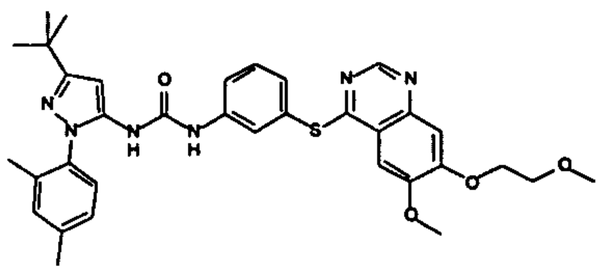
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	urea						
	Ex 250 1-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea	B	D	A	A	A	C*
	Ex 251 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea	B	D	A	A	B	C*
	Ex 252 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	A	B	B	C
	Ex 253 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylsulfinyl)phenyl)urea	C	D	D	D	D	C
	Ex 254 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea	D	D	A	B	A	C*
	Ex 255 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea	D	D	A	B	B	C

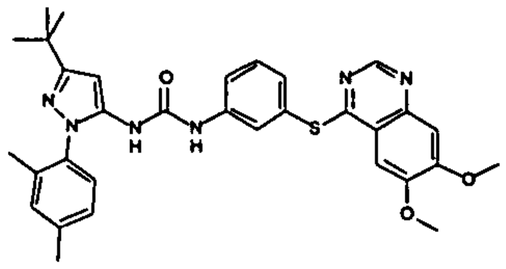
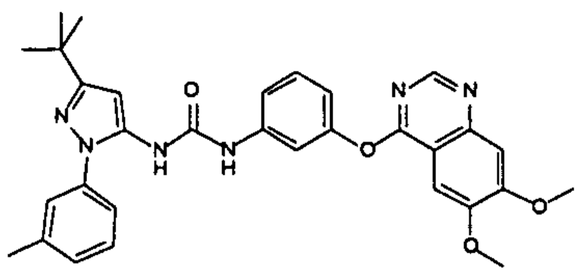
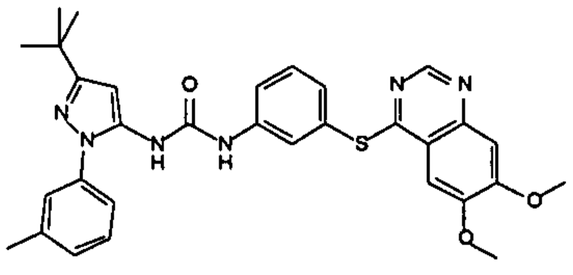
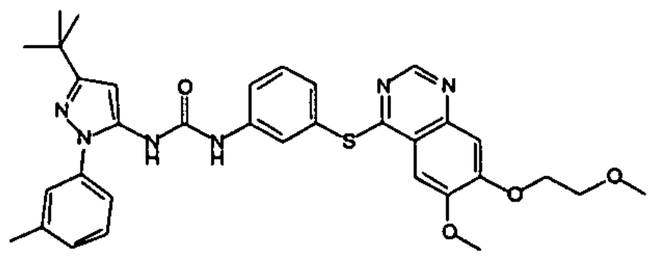
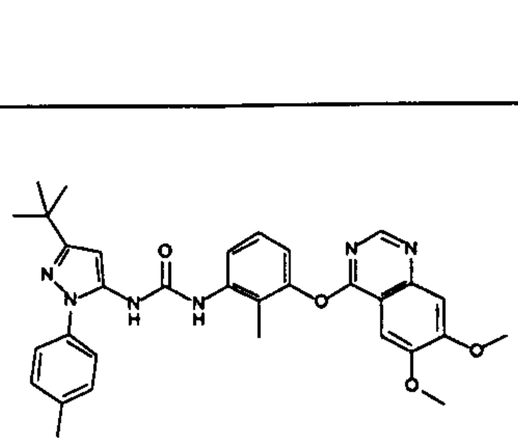
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 256 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea	A	A	A	A	A	D
	Ex 257 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl) urea	B	C	A	A	A	C
	Ex 258 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	B	A	A	A	C
	Ex 259 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	A	A	A	A	C
	Ex 260 1-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	A	A	A	A	C

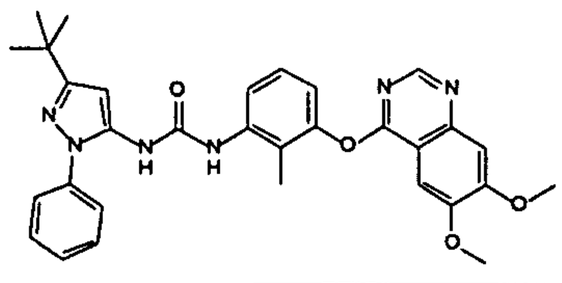
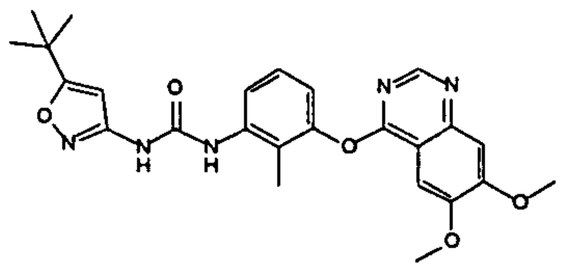
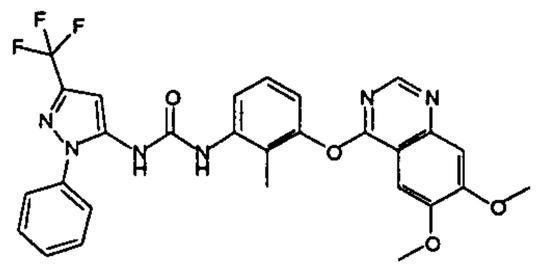
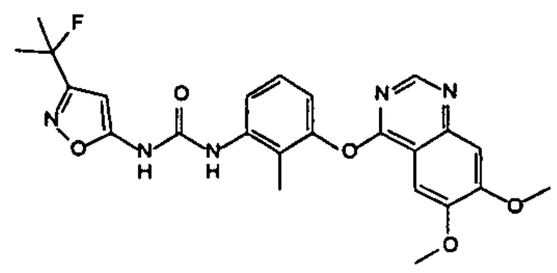
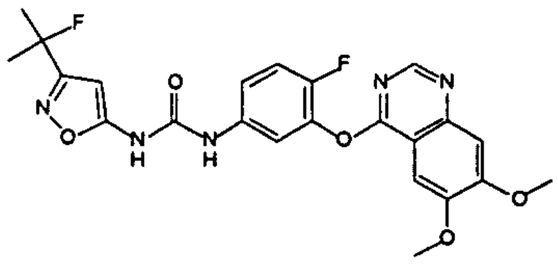
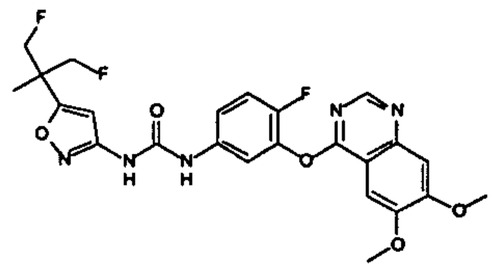
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 261 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	D	A	B	A	ND
	Ex 262 1-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	D	A	A	A	C
	Ex 263 1-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	C	A	A	A	C
	Ex 264 1-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	A	A	A	A	C
	Ex 265 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	B	A	B	A	C

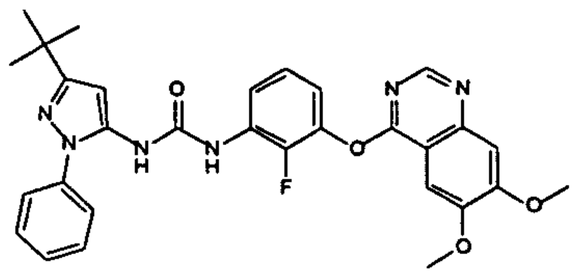
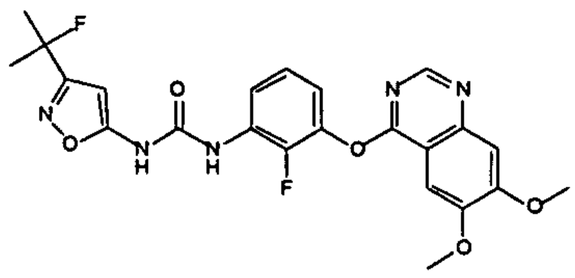
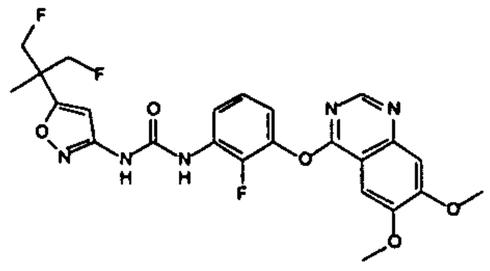
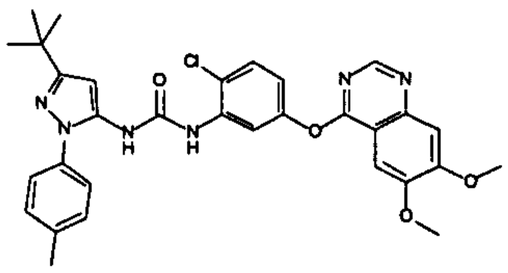
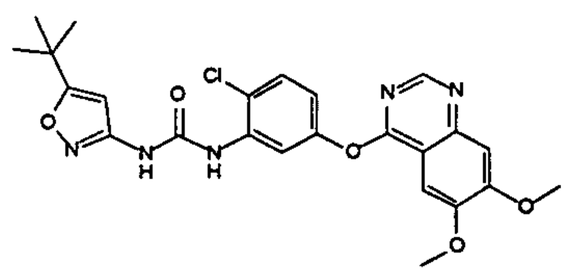
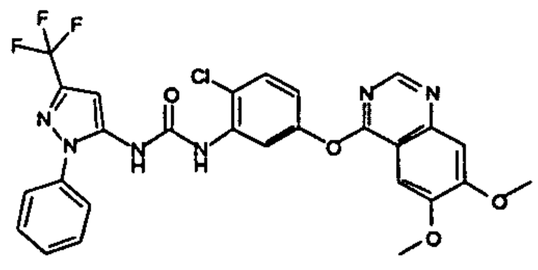
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 266 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea	A	ND	A	A	A	C
	Ex 267 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)urea	A	C	A	A	A	C
	Ex 268 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)urea	A	C	A	A	A	C
	Ex 269 1-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	A	A	A	A	D
	Ex 270 1-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea	A	A	A	A	A	D
	Ex 271 1-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	A	B	B	D	D	D

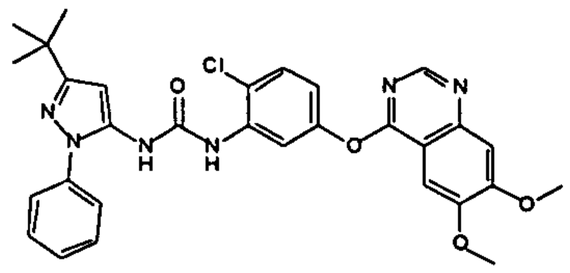
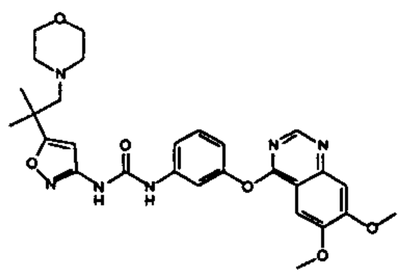
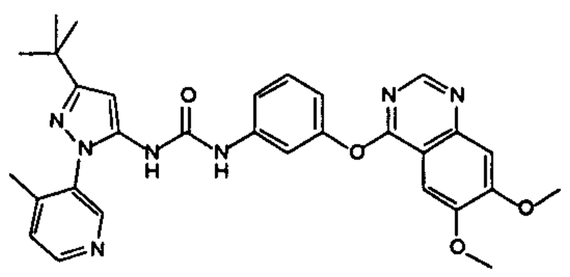
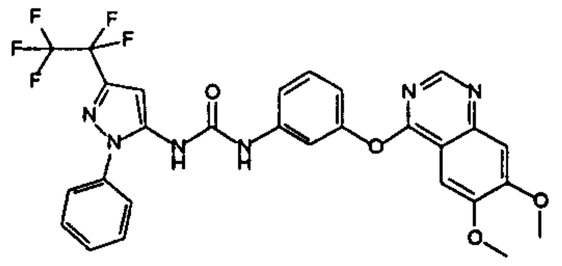
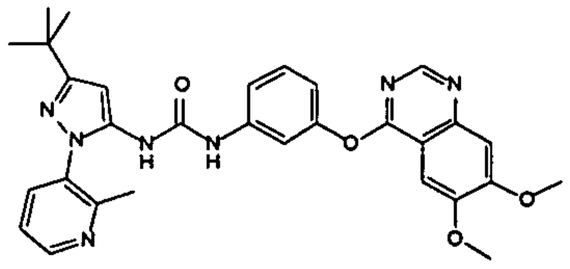
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 272 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea	A	ND	C	D	D	D
	Ex 273 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea	A	ND	C	D	D	D
	Ex 274 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D
	Ex 275 1-(3-tert-Butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	D
	Ex 276 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	A	ND	A	D	D	D
	Ex 277 1-(3-tert-Butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl	A	ND	B	D	D	D

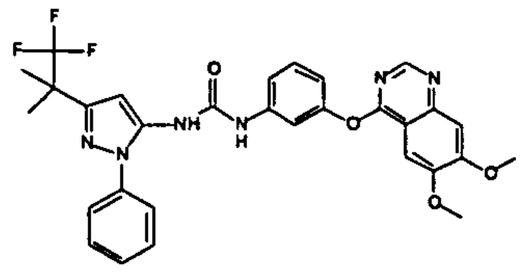
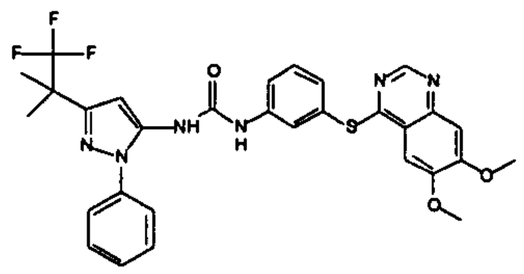
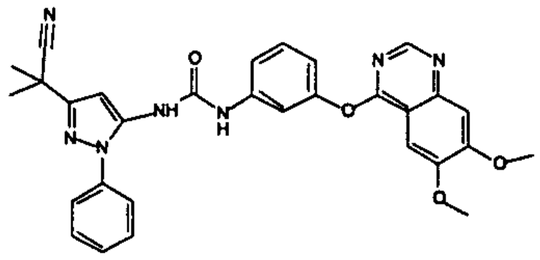
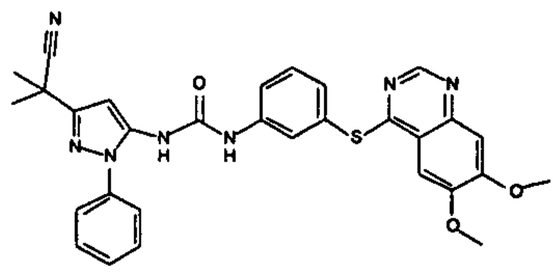
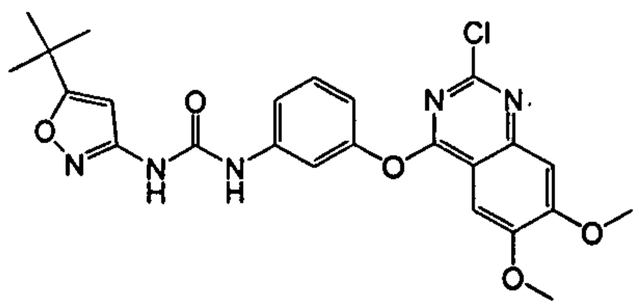
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	)urea						
	Ex 278 1-(3-(2-cyanopropan-2-yl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	C	A	A	A	C
	Ex 279 1-(3-(2-cyanopropan-2-yl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	D	A	A	A	C
	Ex 280 1-(3-(2-cyanopropan-2-yl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea	C	D	A	A	A	ND
	Ex 281 1-(3-(2-cyanopropan-2-yl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	B	D	A	A	A	ND
	Ex 282 1-(3-tert-butyl-1-(2,4-dimethylphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	C	D	D	C
	Ex 283 1-(3-tert-butyl-1-(2,4-dimethylphenyl)-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazoli	A	D	C	D	D	C

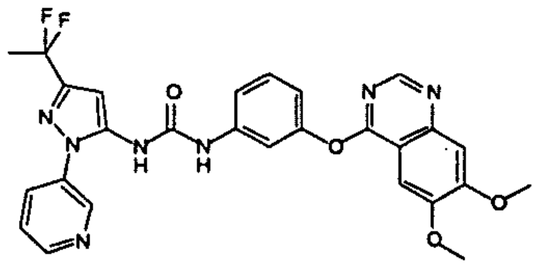
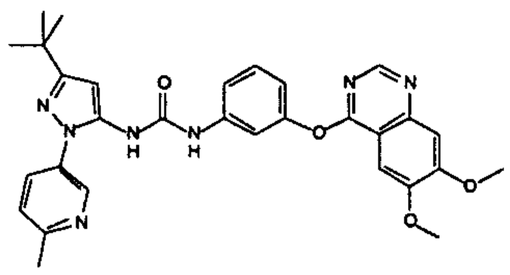
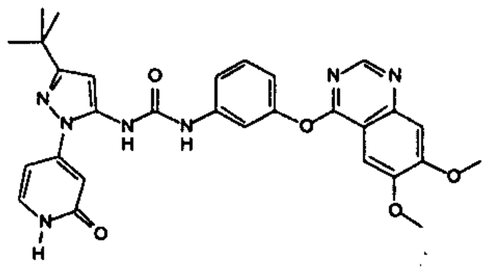
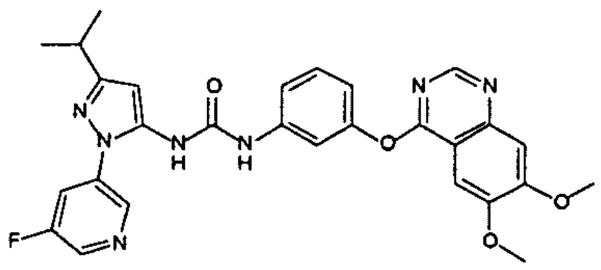
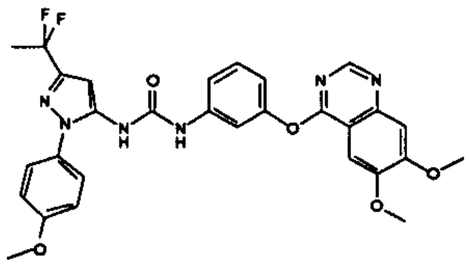
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	n-4-ylthio)phenyl)urea						
	Ex 284 1-(3-tert-butyl-1-(2,4-dimethylphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	D	D	D	D	C
	Ex 285 1-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D
	Ex 286 Preparation of 1-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	D
	Ex 287 1-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea	A	ND	C	D	D	D
	Ex 288 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)urea	A	ND	B	D	D	C
	Ex 289 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyqu	A	C	A	D	C	C

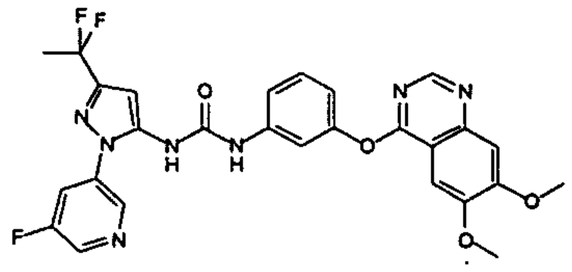
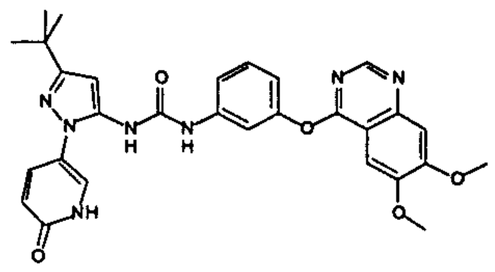
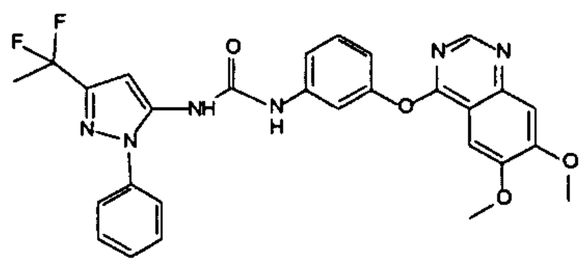
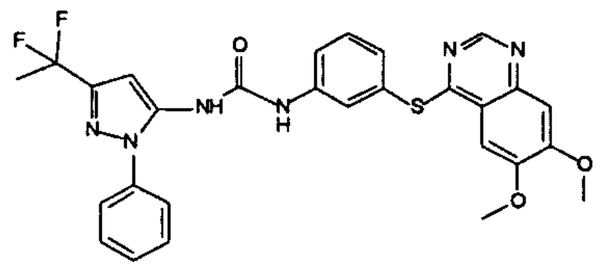
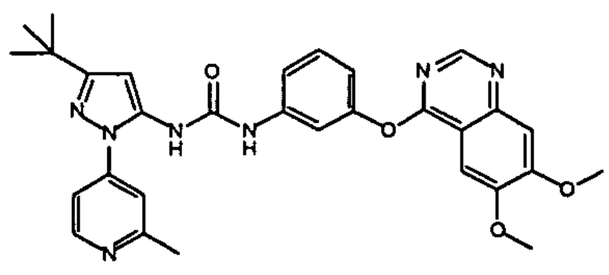
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	inazolin-4-yloxy)-2-methylphenyl)urea						
	Ex290 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)urea	A	B	A	A	A	C
	Ex 291 1-(3-(6,7-Dimethoxyquinazolin-4-yloxy)-2-methylphenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	C	D	A	C	B	B
	Ex292 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-, methylphenyl)-3-(5-(2-fluoropropan-2-yl)isoxazol-3-yl)urea	C	D	A	A	A	C
	Ex293 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	B	A	A	A	C
	Ex 294 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea	A	ND	A	A	A	D

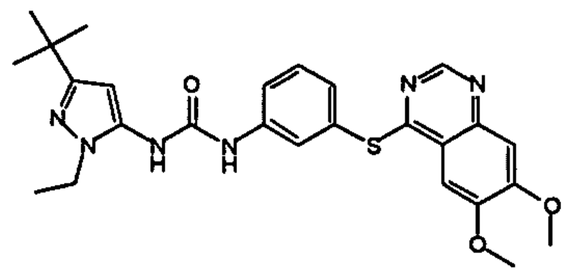
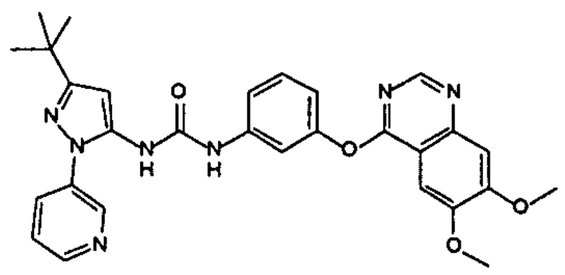
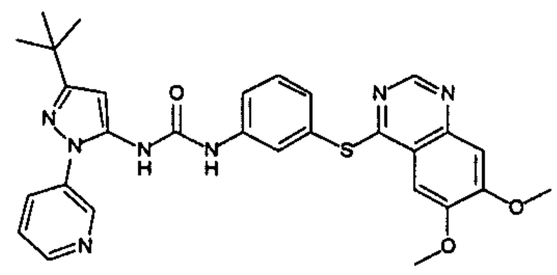
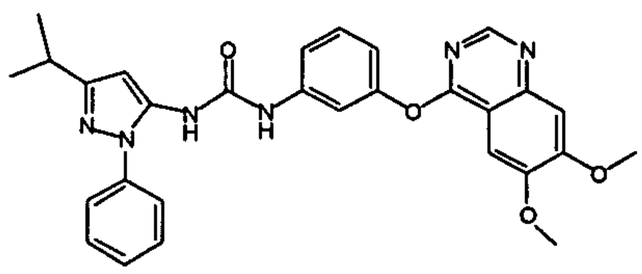
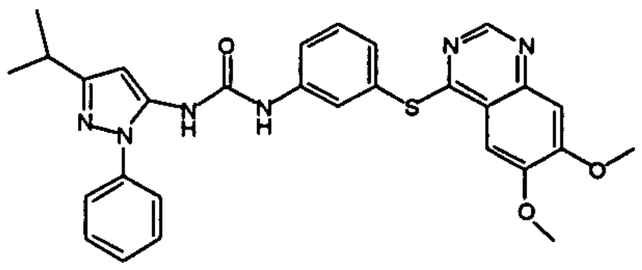
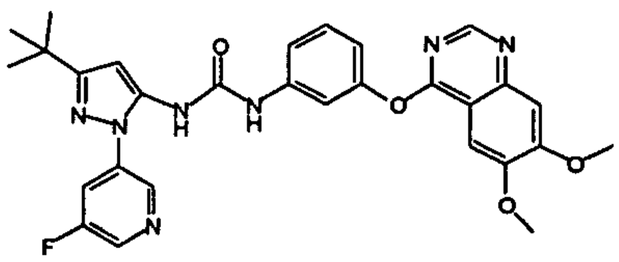
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 295 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea	C	D	A	D	C	C
	Ex 296 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	D	D	A	A	A	B
	Ex 297 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea	B	B	A	A	A	C
	Ex 298 1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	D	D	D	D
	Ex 299 1-(5-tert-butylisoxazol-3-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	B	A	C
	Ex 300 1-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromet	B	D	C	D	D	C

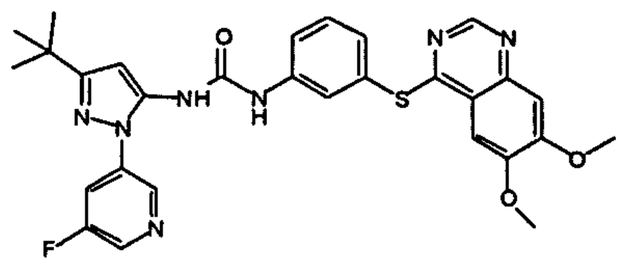
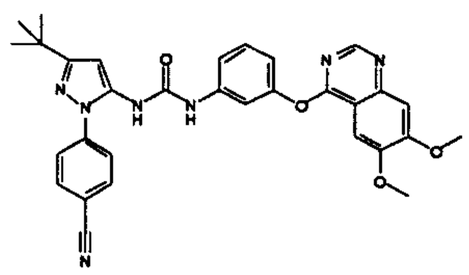
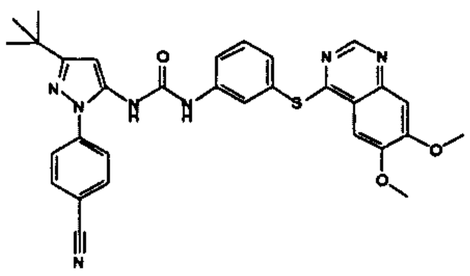
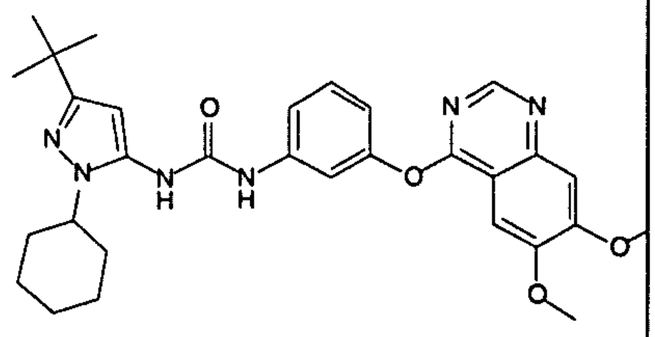
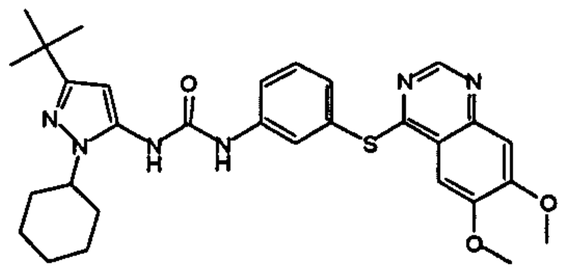
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	hyl)-1H-pyrazol-5-yl)urea						
	Ex 301 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	B	D	D	D	D
	Ex 302 Preparation of 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(2-methyl-1-morpholinopropan-2-yl)isoxazol-3-yl)urea	D	D	B	D	D	B
	Ex 303 1-(3-tert-butyl-1-(4-methylpyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	C	B	D
	Ex 304 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(perfluoroethyl)-1-phenyl-1H-pyrazol-5-yl)urea	B	A	B	D	D	C
	Ex 305 1-(3-tert-butyl-1-(2-methylpyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	C	B	D

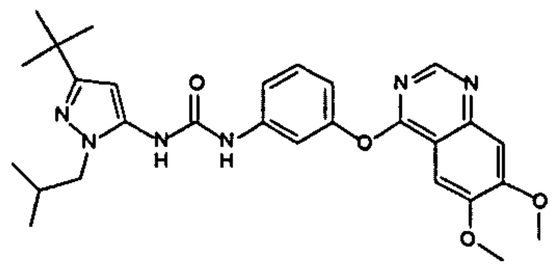
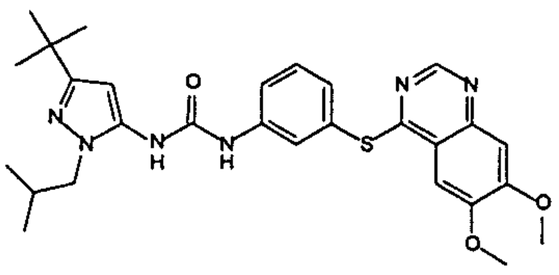
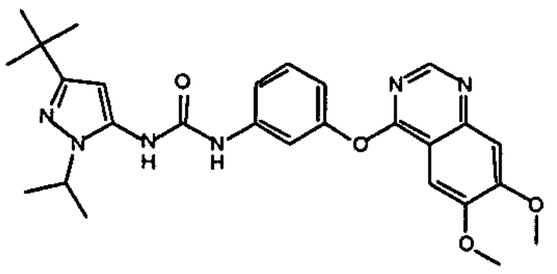
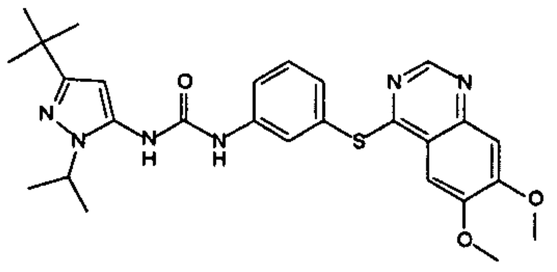
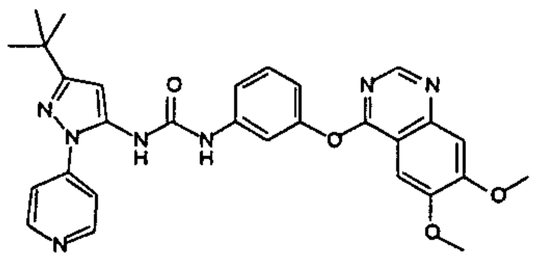
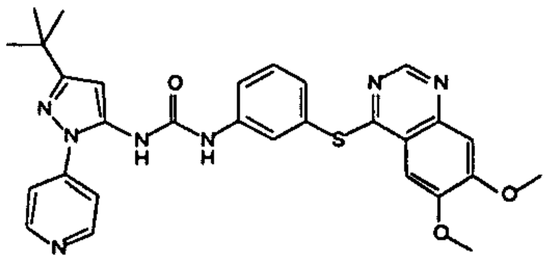
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 306 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-5-yl)urea	A	ND	B	D	D	D
	Ex 307 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-phenyl-3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-5-yl)urea	A	ND	B	D	D	D
	Ex 308 1-(3-(2-cyanopropan-2-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	B	A	B	B	D
	Ex 309 1-(3-(2-cyanopropan-2-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	A	C	C	C
	Ex 310 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	C	D	C	A

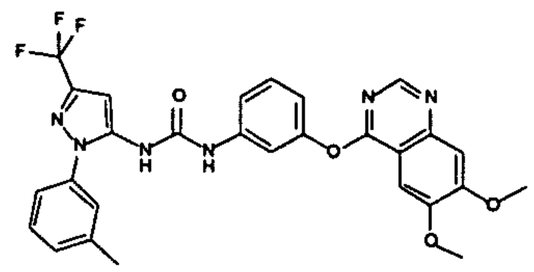
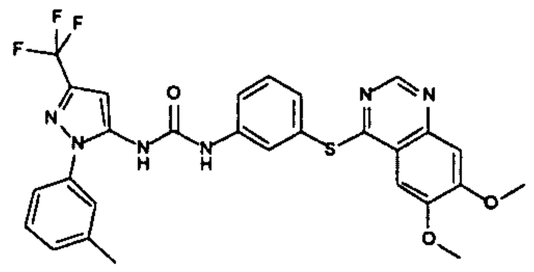
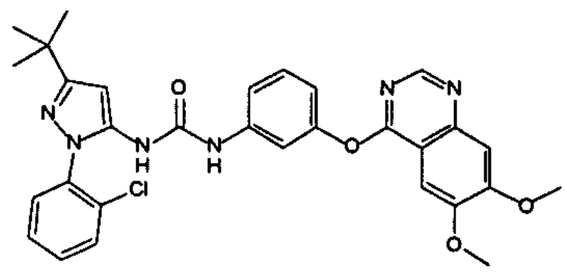
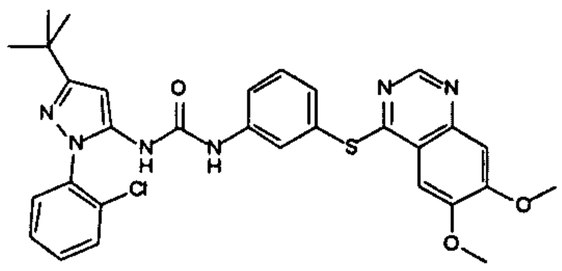
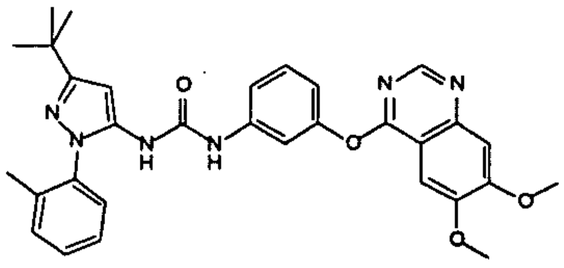
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 311 1-(3-(1,1-difluoroethyl)-1-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	B	A	A	A	C
	Ex 312 1-(3-tert-butyl-1-(6-methylpyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	C	B	D
	Ex 313 Preparation of 1-(3-tert-butyl-1-(2-oxo-1,2-dihydropyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	C	A	B	B	D
	Ex 314 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-(5-fluoropyridin-3-yl)-3-isopropyl-1H-pyrazol-5-yl)urea	B	A	A	C	B	D
	Ex 315 1-(3-(1,1-difluoroethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	D	C	D

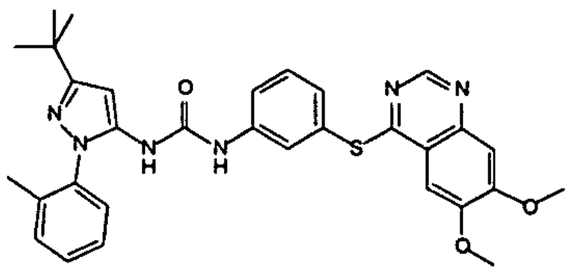
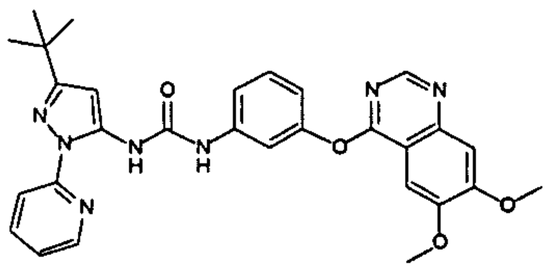
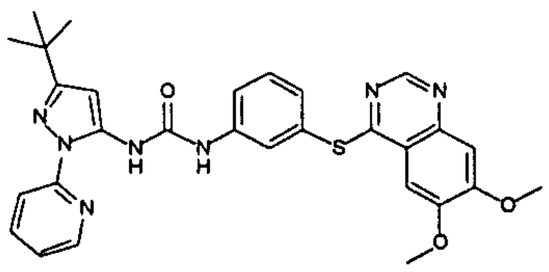
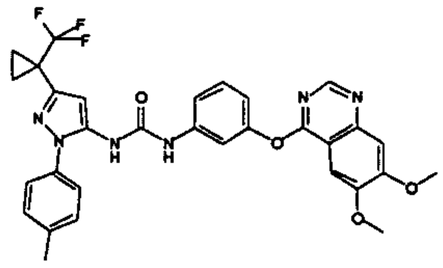
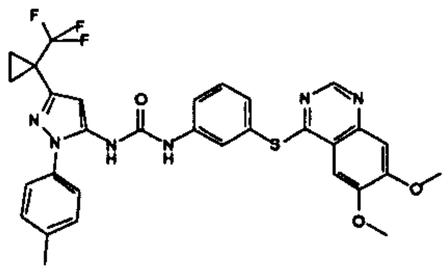
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 316 1-(3-(1,1-difluoroethyl)-1-(5-fluoropyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	C	A	B	A	C
	Ex 317 1-(3-tert-butyl-1-(6-oxo-1,6-dihydropyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	A	D	C	D
	Ex 318 1-(3-(1,1-difluoroethyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	B	B	C
	Ex 319 Preparation of 1-(3-(1,1-difluoroethyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	A	A	C	B	C
	Ex 320 1-(3-tert-butyl-1-(2-methylpyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	D	D	D

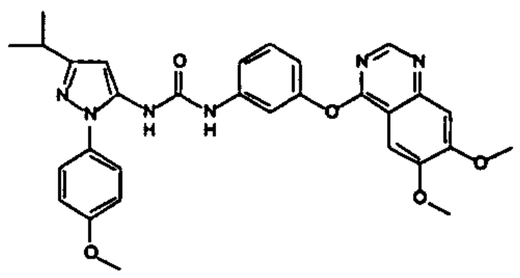
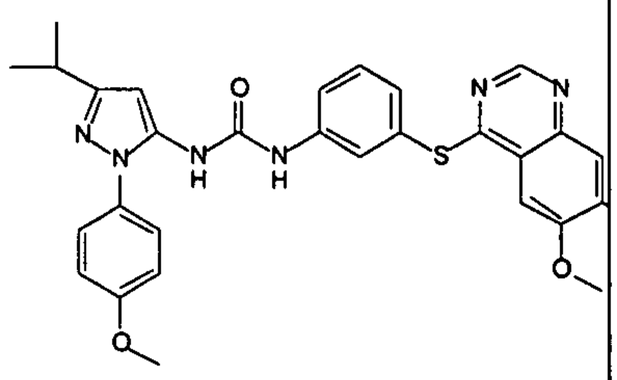
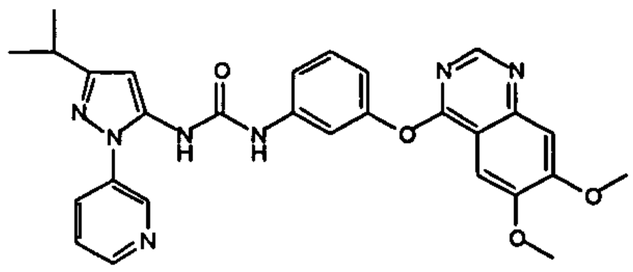
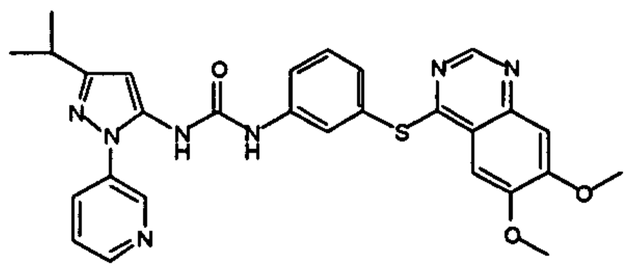
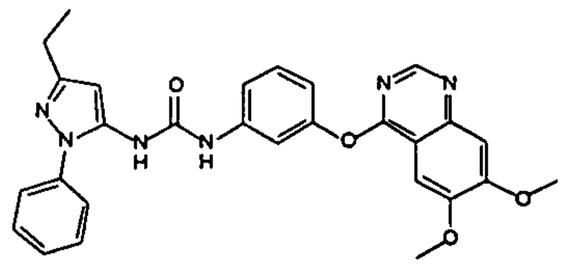
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 321 1-(3-tert-butyl-1-ethyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	C	A	B	A	C
	Ex 322 1-(3-tert-butyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	B	B	D
	Ex 323 1-(3-tert-butyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	B	A	C	C	D
	Ex 324 Preparation of 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea	A	A	A	B	B	D
	Ex 325 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea	A	A	A	B	B	C
	Ex 326 Preparation of 1-(3-tert-butyl-1-(5-fluoropyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyqu	A	ND	A	C	C	D

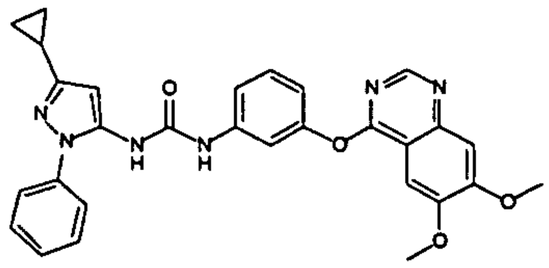
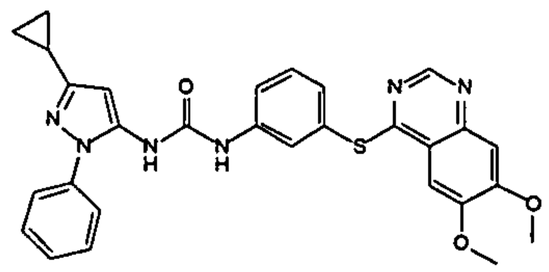
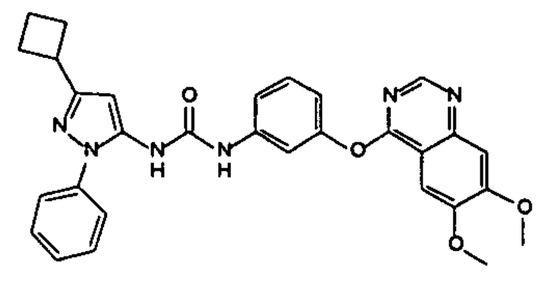
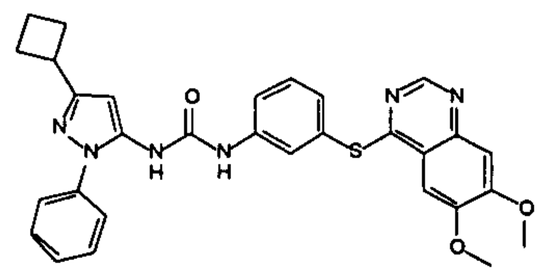
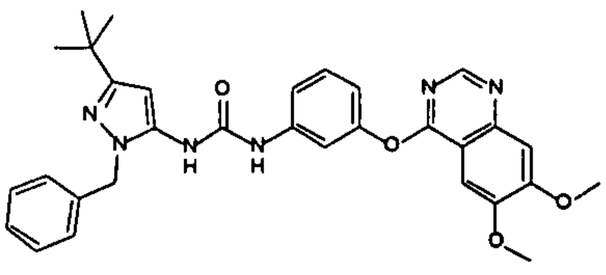
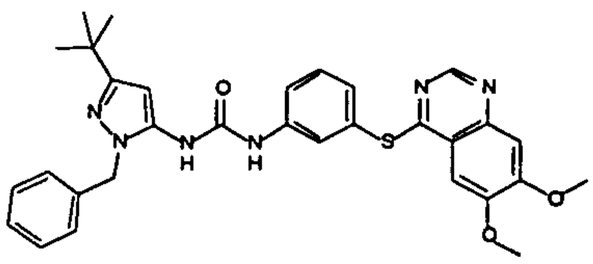
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	inazolin-4-yloxy)phenyl)urea						
	Ex 327 1-(3-tert-butyl-1-(5-fluoropyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	A	C	C	D
	Ex 328 1-(3-tert-butyl-1-(4-cyanophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	B	B	D
	Ex 329 Preparation of 1-(3-tert-butyl-1-(4-cyanophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	B	C	D
	Ex 330 1-(3-tert-butyl-1-cyclohexyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	D	D	A	D	D	C
	Ex 331 1-(3-tert-butyl-1-cyclohexyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	D	B	C	C	B

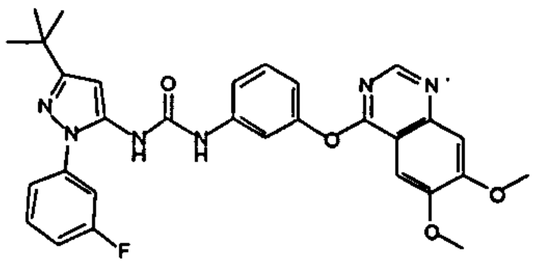
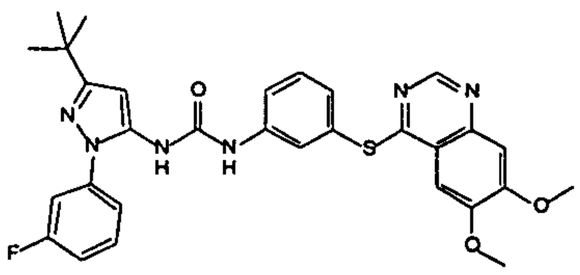
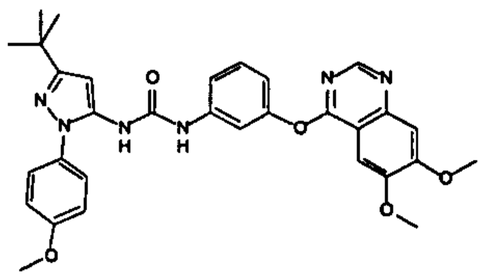
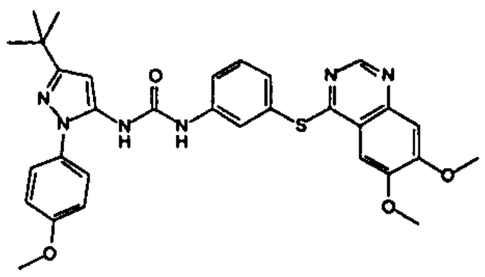
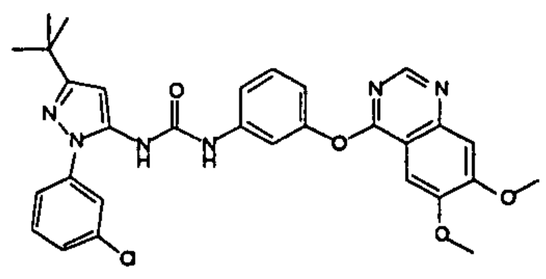
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 332 1-(3-tert-butyl-1-isobutyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	C	D	A	B	B	C
	Ex 333 1-(3-tert-butyl-1-isobutyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	C	ND	A	B	B	C
	Ex 334 1-(3-tert-butyl-1-isopropyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	C	C	A	B	B	C
	Ex 335 1-(3-tert-butyl-1-isopropyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	D	A	B	B	C
	Ex336 1-(3-tert-butyl-1-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	C	C	D
	Ex 337 1-(3-tert-butyl-1-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyqu	A	ND	A	C	C	D

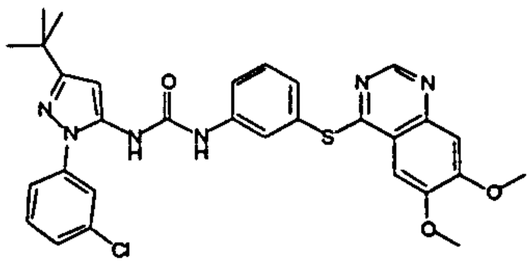
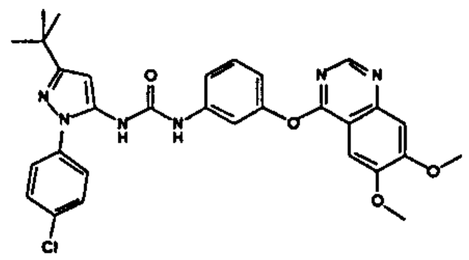
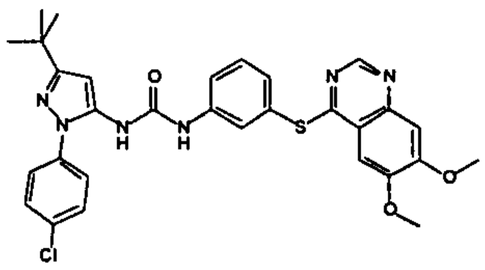
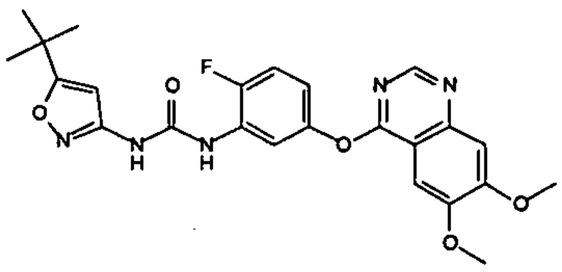
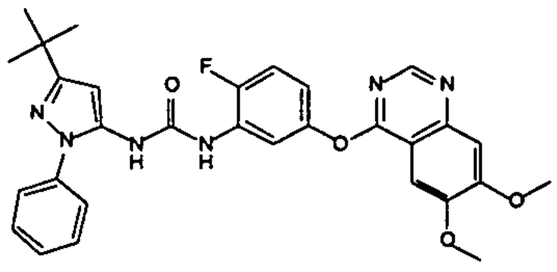
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	inazolin-4-ylthio)phenyl)urea						
	Ex 338 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-m-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	A	A	A	C	B	C
	Ex 339 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-m-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	A	ND	B	D	C	C
	Ex 340 1-(3-tert-butyl-1-(2-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D
	Ex 341 1-(3-tert-butyl-1-(2-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	C
	Ex 342 1-(3-tert-butyl-1-o-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D

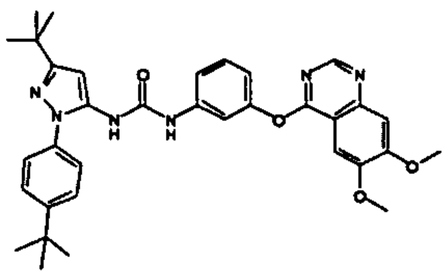
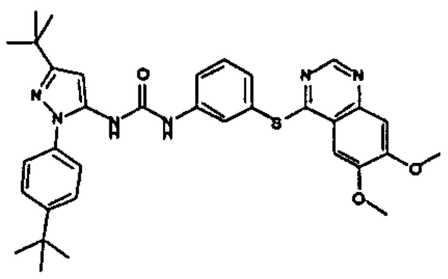
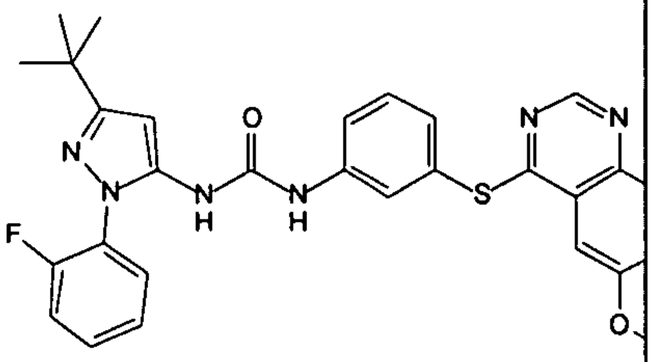
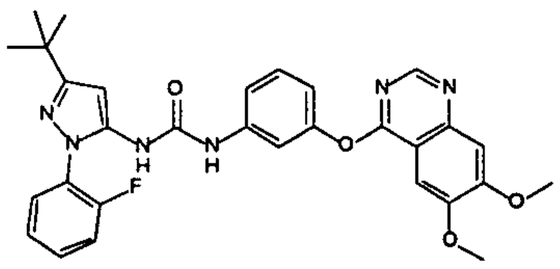
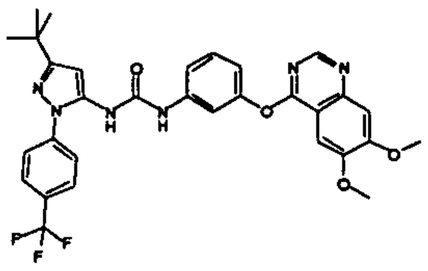
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 343 1-(3-tert-butyl-1-o-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	C
	Ex 344 1-(3-tert-Butyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	C	ND	C	D	D	C
	Ex 345 1-(3-tert-butyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	C	D	D	D	D	B
	Ex 346 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-p-tolyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea	A	ND	A	D	D	D
	Ex 347 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-p-tolyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea	A	ND	B	D	D	D

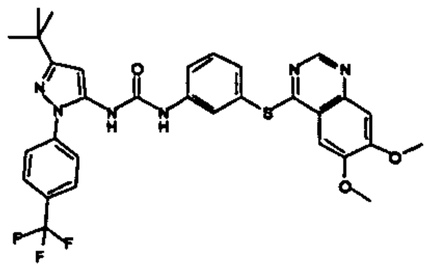
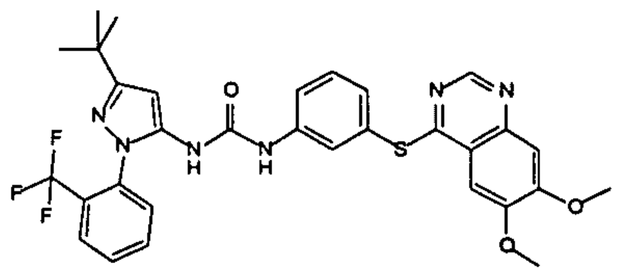
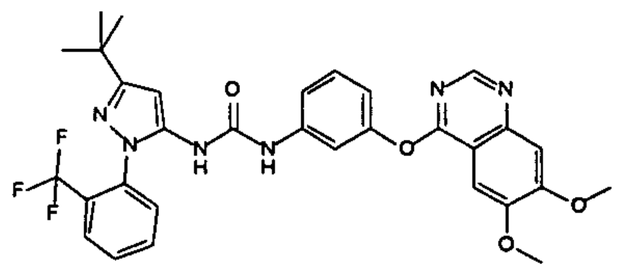
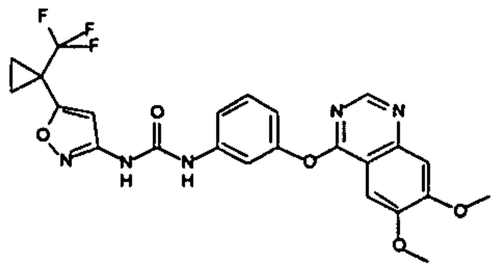
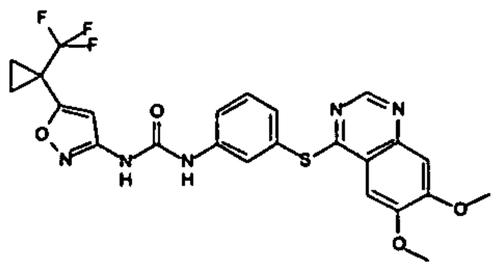
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 348 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)urea	A	A	A	D	C	D
	Ex 349 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)urea	A	A	A	D	C	C
	Ex 350 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)urea	B	B	A	A	A	D
	Ex 351 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-isopropyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)urea	A	B	A	C	A	C
	Ex 352 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-ethyl-1-phenyl-1H-pyrazol-5-yl)urea	C	B	A	A	A	C

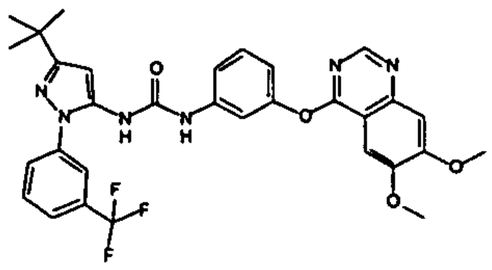
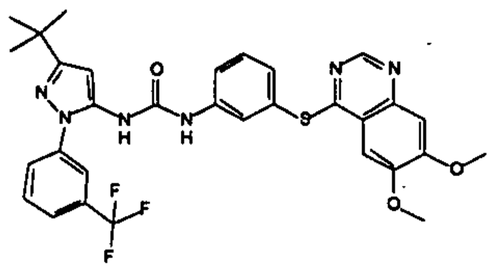
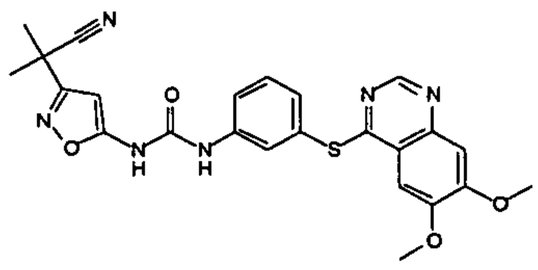
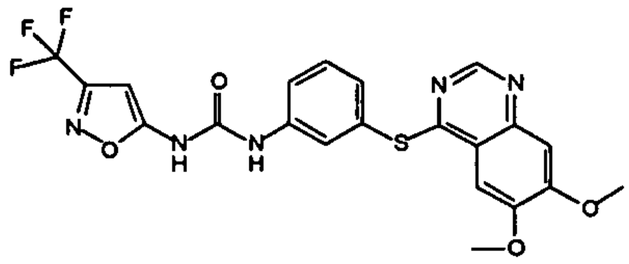
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 353 1-(3-cyclopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	B	A	B	A	C
	Ex 354 1-(3-cyclopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	B	A	A	A	C
	Ex 355 Preparation of 1-(3-cyclobutyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	C	C	C
	Ex 356 1-(3-cyclobutyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	A	A	D	C	C
	Ex 357 1-(1-benzyl-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	B	D	A	C	D	C
	Ex 358 1-(1-benzyl-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	B	ND	A	D	D	C

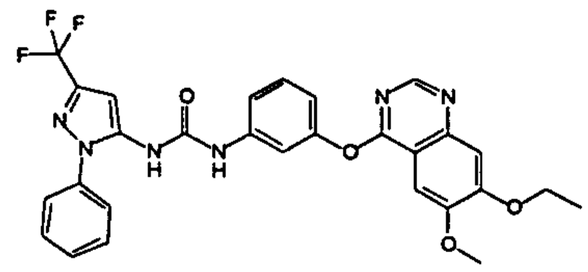
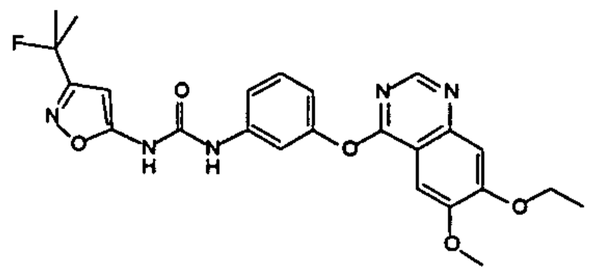
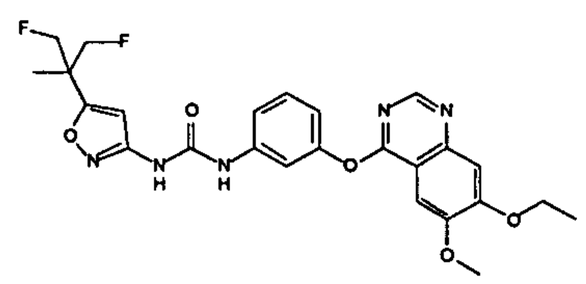
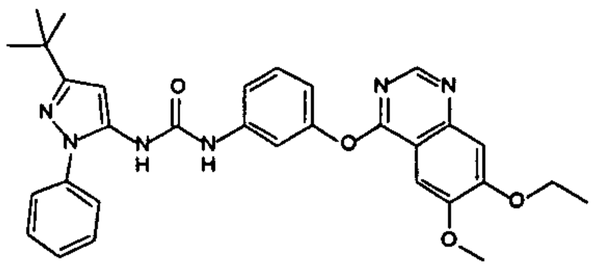
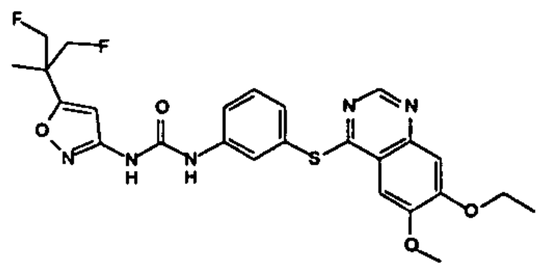
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 359 1-(3-tert-butyl-1-(3-fluorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	D	D	D
	Ex 360 1-(3-tert-butyl-1-(3-fluorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	D
	Ex 361 1-(3-tert-butyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	D	A	B	C	C
	Ex 362 Preparation of 1-(3-tert-butyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	C	D	D	D
	Ex 363 1-(3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	B	D	D

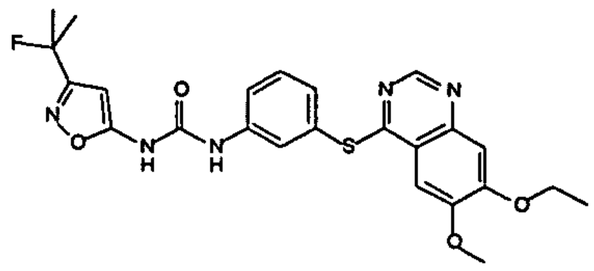
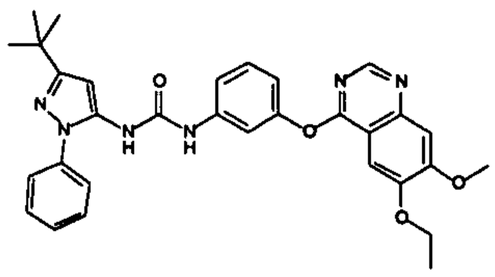
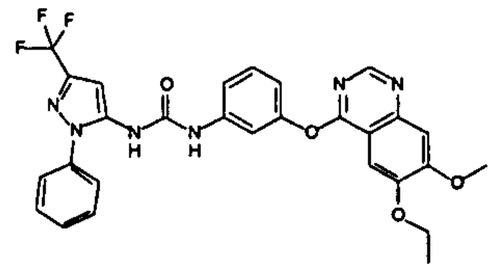
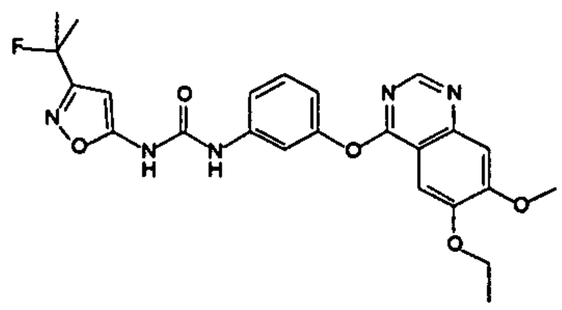
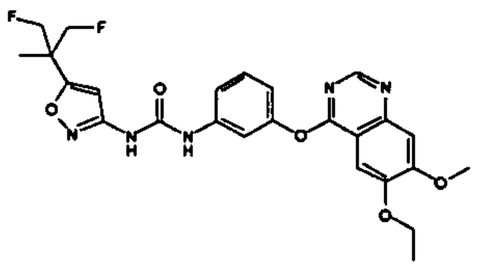
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 364 1-(3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	A	C	D	D
	Ex 365 1-(3-tert-butyl-1-(4-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D
	Ex 366 1-(3-tert-butyl-1-(4-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	D
	Ex 367 1-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea	A	B	A	A	A	D
	Ex 368 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea	A	ND	C	D	D	D

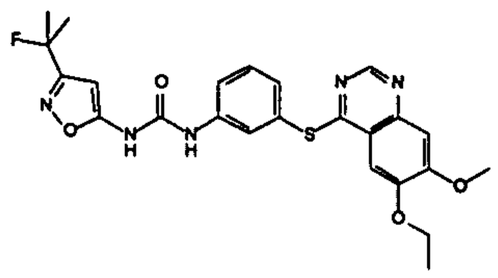
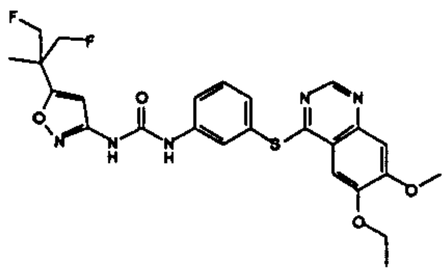
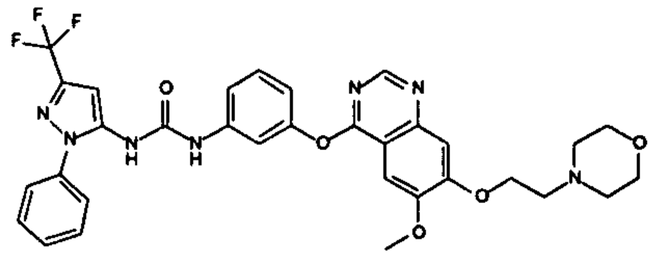
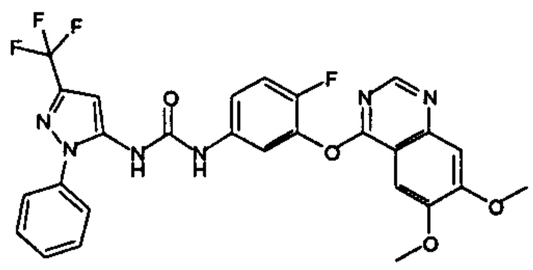
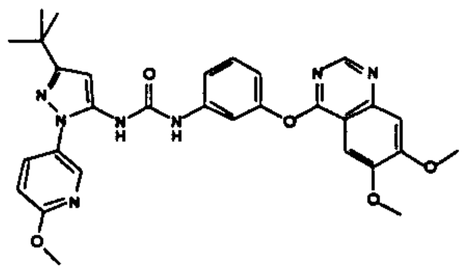
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 369 1-(3-tert-butyl-1-(4-tert-butylphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	D	A	C	D	C
	Ex 370 1-(3-tert-butyl-1-(4-tert-butylphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	A	D	D	D
	Ex 371 1-(3-tert-butyl-1-(2-fluorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	D
	Ex 372 1-(3-tert-butyl-1-(2-fluorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	C	C	D
	Ex 373 1-(3-tert-butyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	C	D	D	C

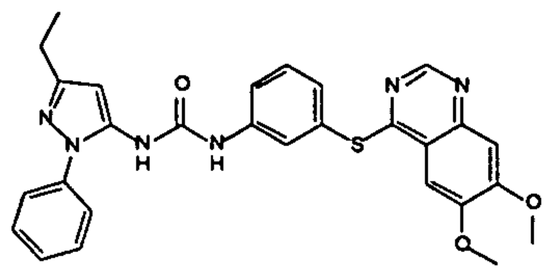
	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	Ex 374 1-(3-tert-butyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	C
	Ex 375 1-(3-tert-butyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	C	D	D	C
	Ex 376 1-(3-tert-butyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	C	D	D	D
	Ex 377 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea	A	A	A	A	A	C
	Ex 378 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea	B	A	A	A	A	C

	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 379 1-(3-tert-butyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	B	D	D	D
	Ex 380 1-(3-tert-butyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	B	D	D	C
	Ex 381 1-(3-(2-cyanopropan-2-yl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea	A	ND	A	A	A	C
	Ex 382 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea	D	D	A	A	A	C
	Ex 383 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-phenyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea	A	ND	B	D	D	C
	Example 384 Preparation of 1-(3-(7-ethoxy-6-	C	B	A	C	B	C

	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF 1 Kd nM	S35
	methoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea						
	Ex 385 1-(3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	B	B	A	A	A	C
	Ex 386 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	A	A	C
	Ex 387 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	C	C	D
	Example 388 Preparation of 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl)urea	B	B	A	A	A	C

	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 389 1-(3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	C	B	A	A	A	C
	Ex 390 1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	B	C	D
	Ex 391 1-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	A	A	A	B	B	C
	Ex 392 1-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	A	A	A	A	C
	Ex 393 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea	A	A	A	A	A	C

	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 394 1-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea	A	B	A	A	A	C
	Ex 395 1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)urea	A	A	A	A	A	C
	Ex 396 (1-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	C	C	A	C	C	C
	Ex 397 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea	A	B	A	D	C	C
	Ex 398 1-(3-tert-butyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea	A	ND	A	C	C	D

	Name	pMEK IC50 (nM)	A375 Viability EC50 (nM)	BRAF V600E Kd (nM)	BRAF WT Kd nM	RAF1 Kd nM	S35
	Ex 399 1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-ethyl-1-phenyl-1H-pyrazol-5-yl)urea	B	B	A	A	A	C

pMEK IC_{50} and A375 Viability EC_{50}: A ≤250, 250<B≤500, 500<C≤1000, D>1000, BRAF V600E Kd, BRAF WT Kd and RAF1 Kd: A ≤250, 250<B≤500, 500<C≤1000, D>1000
S35: A ≤0.10, 0.10<B≤0.20, 0.20<C≤0.40, D>0.40 (Asterisk indicates an S35 score calculated using a panel of 321 distinct kinases, no asterisk indicates an S35 score calculated using a panel of 290 distinct kinases); and
ND= no data.

[00536] Also provided herein are isotopically enriched analogs of the compounds provided herein. Isotopic enrichment (for example, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et. al.*, *Food Cosmet. Toxicol.*, 20: 393 (1982); Lijinsky *et. al.*, *J. Nat. Cancer Inst.*, 69: 1127 (1982); Mangold *et. al.*, *Mutation Res.* 308: 33 (1994); Gordon *et. al.*, *Drug Metab. Dispos.*, 15: 589 (1987); Zello *et. al.*, *Metabolism*, 43: 487 (1994); Gately *et. al.*, *J. Nucl. Med.*, 27: 388 (1986); Wade D, *Chem. Biol. Interact.* 117: 191 (1999).

[00537] Isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[00538] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C–H bond is broken during a rate-determining step in a chemical reaction (*i.e.* the step with the highest transition state

energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (*See, e.g,* Foster *et al.*, Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner *et al.*, Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999)).

[00539] Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S, or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen, will provide a similar kinetic isotope effects.

[00540] In another embodiment, provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates, or hydrates thereof, for the local or systemic treatment or prophylaxis of human and veterinary diseases, disorders and conditions modulated or otherwise affected mediated via RAF kinase, including BRAF kinase, activity.

C. FORMULATION OF PHARMACEUTICAL COMPOSITIONS

[00541] Provided herein are pharmaceutical compositions comprising a compound provided herein, e.g., a compound of Formula I, as an active ingredient, or a pharmaceutically acceptable salt, solvate or hydrate thereof; in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[00542] The compound provided herein may be administered alone, or in combination with one or more other compounds provided herein. The pharmaceutical compositions that comprise a compound provided herein, e.g., a compound of Formula I, can be formulated in various dosage forms for oral, parenteral, and topical

administration. The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2003; Vol. 126).

[00543] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00544] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00545] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvateor hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00546] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.The pharmaceutical compositions provided

herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[00547] In one embodiment, the therapeutically effective dose is from about 0.1 mg to about 2,000 mg per day of a compound provided herein. The pharmaceutical compositions therefore should provide a dosage of from about 0.1 mg to about 2000 mg of the compound. In certain embodiments, pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 20 mg to about 500 mg or from about 25 mg to about 250 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form. In certain embodiments, the pharmaceutical dosage unit forms are prepared to provide about 10 mg, 20 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg or 2000 mg of the essential active ingredient.

Oral Administration

[00548] The pharmaceutical compositions provided herein can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00549] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized

starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[00550] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[00551] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00552] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol;

glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00553] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00554] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00555] The pharmaceutical compositions provided herein can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated

tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00556] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00557] The pharmaceutical compositions provided herein can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00558] The pharmaceutical compositions provided herein can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00559] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00560] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00561] The pharmaceutical compositions provided herein can be provided as non- effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting

agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00562] Coloring and flavoring agents can be used in all of the above dosage forms.

[00563] The pharmaceutical compositions provided herein can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00564] The pharmaceutical compositions provided herein can be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action.

Parenteral Administration

[00565] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00566] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00567] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00568] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00569] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00570] The pharmaceutical compositions provided herein can be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampoule, a vial, or a syringe. The multiple dosage parenteral

formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00571] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00572] The pharmaceutical compositions provided herein can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00573] The pharmaceutical compositions can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00574] Suitable inner matrixes include polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00575] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol

copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

Topical Administration

[00576] The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00577] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00578] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00579] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00580] The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either

water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00581] Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00582] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00583] The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00584] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided

herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00585] The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00586] The pharmaceutical compositions provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00587] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein, a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00588] The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00589] Capsules, blisters and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00590] The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

Modified Release

[00591] The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00592] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945;

5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix Controlled Release Devices

[00593] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz Ed., Wiley, 1999).

[00594] In one embodiment, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00595] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00596] In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or

dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, and ; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate,; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00597] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00598] The pharmaceutical compositions provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00599] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an

aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00600] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00601] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol,; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00602] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic

effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00603] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00604] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00605] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00606] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in

situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00607] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00608] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00609] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00610] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00611] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00612] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about

1 mm in diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00613] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00614] The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

D. EVALUATION OF THE ACTIVITY OF THE COMPOUNDS

[00615] Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity of BRAF kinases, including wild type and mutant BRAF kinases.

[00616] Such assays include, for example, biochemical assays such as binding assays, radioactivity incorporation assays, as well as a variety of cell based assays.

[00617] Exemplary cell based assay methodologies include measurement of MEK phosphorylation inhibition in the A375 human melanoma cell line, inhibition of cell proliferation in the A375 human melanoma cell line.

[00618] .Cells useful in the assays include cells with wildtype or mutated forms. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc.

E. METHODS OF USE OF THE COMPOUNDS AND COMPOSITIONS

[00619] Also provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates, or hydrates thereof, for the treatment, prevention, or amelioration of a disease or disorder that is mediated or otherwise affected via RAF kinase, including BRAF kinase activiy or one or more symptoms of diseases or disorders that are mediated or otherwise affected via RAF kinase, including BRAF kinase, activity. BRAF kinase can be wild type and/or mutant form of BRAF kinase. In one embodiment, provided herein are methods for treatment of diseases or disorders including without limitation: cancers, including melanoma, papillary thyroid carcinoma, colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, Barret's adenocarcinoma, glioma (including ependymoma), lung cancer (including small cell lung cancer and non small cell lung cancer), head and neck cancer, acute lymphoblastic leukemia and non-Hodgkin's lymphoma; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency, immunomodulation, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma and chronic obstructive pulmonary disease (COPD).

[00620] In one embodiment, provided herein are methods for treating cancers including blood borne and solid tunors.

F. COMBINATION THERAPY

[00621] Furthermore, it will be understood by those skilled in the art that compounds provided herein, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, also contemplated herein is the use of compounds and pharmaceutically acceptable salts provided herein in combination with other active pharmaceutical agents for the treatment of the disease/conditions described herein.

[00622] In one embodiment, such additional pharmaceutical agents include without limitation anti-cancer agents, including chemotherapeutic agents and anti-proliferative

agents; anti-inflammatory agents and immunomodulatory agents or immunosuppressive agents.

[00623] In certain embodiments, the anti-cancer agents include anti-metabolites (*e.g.*, 5-fluoro-uracil, methotrexate, fludarabine and others), antimicrotubule agents (*e.g.*, vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel and docetaxel), alkylating agents (*e.g.*, cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosurea and hydroxyurea), platinum agents (*e.g.* cisplatin, carboplatin, oxaliplatin, satraplatin and CI-973), anthracyclines (*e.g.*, doxrubicin and daunorubicin), antitumor antibiotics (*e.g.*, mitomycin, idarubicin, adriamycin and daunomycin), topoisomerase inhibitors (*e.g.*, etoposide and camptothecins), anti-angiogenesis agents (*e.g.* Sutent®, sorafenib and Bevacizumab) or any other cytotoxic agents, (estramustine phosphate, prednimustine), hormones or hormone agonists, antagonists, partial agonists or partial antagonists, kinase inhibitors, and radiation treatment.

[00624] In certain embodiments, the anti-inflammatory agents include matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (*e.g.*, anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (*e.g.*, choline magnesium salicylate and salicylsalicyclic acid), COX-1 or COX-2 inhibitors, or glucocorticoid receptor agonists such as corticosteroids, methylprednisone, prednisone, or cortisone.

[00625] The compounds or compositions provided herein, or pharmaceutically acceptable salta thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents.

[00626] Pharmaceutical compositions containing a compound provided herein or pharmaceutically acceptable salt thereof, and one or more of the above agents are also provided.

[00627] Also provided is a combination therapy that treats or prevents the onset of the symptoms, or associated complications of cancer and related diseases and disorders comprising the administration to a subject in need thereof, of one of the compounds or compositions disclosed herein, or pharmaceutically acceptable salts, solvates, hydrates or clathrates thereof, with one or more anti-cancer agents.

G. PREPARATION OF THE COMPOUNDS

[00628] Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures (*e.g.*, March *Advanced*

Organic Chemistry: Reactions, Mechanisms, and Structure, (1992) 4th Ed.; Wiley Interscience, New York). All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Shimadzu HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% acetic acid). Preparative HPLC was performed using Varian HPLC systems and Phenomenex columns. Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem. 43*:2923).

[00629] It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds under standard conditions.

[00630] It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

[00631] Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1991), 2nd Ed., Wiley-Interscience.

[00632] One of ordinary skill in the art could easily ascertain which choices for each substituent are possible for the reaction conditions of each Scheme. Moreover,

the substituents are selected from components as indicated in the specification heretofore, and may be attached to starting materials, intermediates, and/or final products according to schemes known to those of ordinary skill in the art.

[00633] Also it will be apparent that the compounds provided herein could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers.

[00634] Compounds of formula (I) may be generally prepared as depicted in the following schemes, unless otherwise noted, the various substituents are as defined elsewhere herein.

[00635] Standard abbreviations and acronyms as defined in *J. Org. Chem.* **2007** 72(1): 23A-24A are used herein. Exemplary abbreviations and acronyms used herein are as follows:

DCM - dichloromethane

DIEA - N,N-diisopropylethylamine

EtOAc - ethyl acetate

EDCI - 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide

EtOH - ethanol

FBS - fetal bovine serum

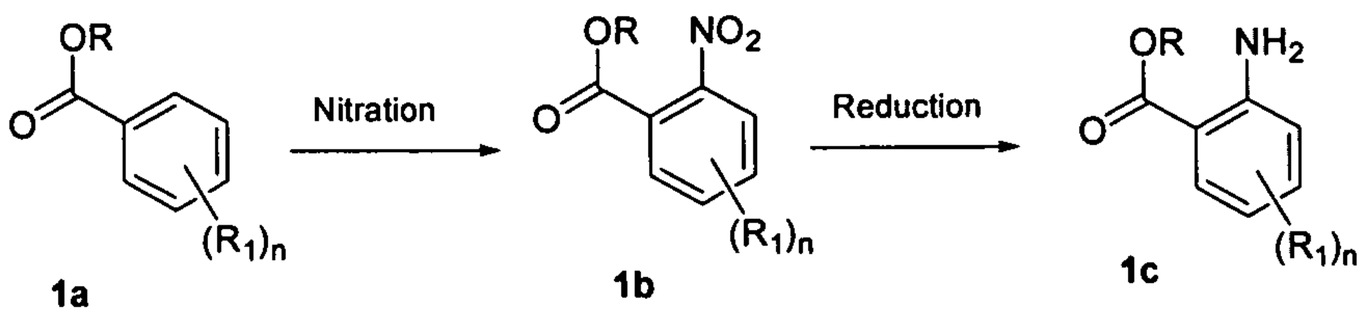
HOAc - acetic acid

MeOH - methanol

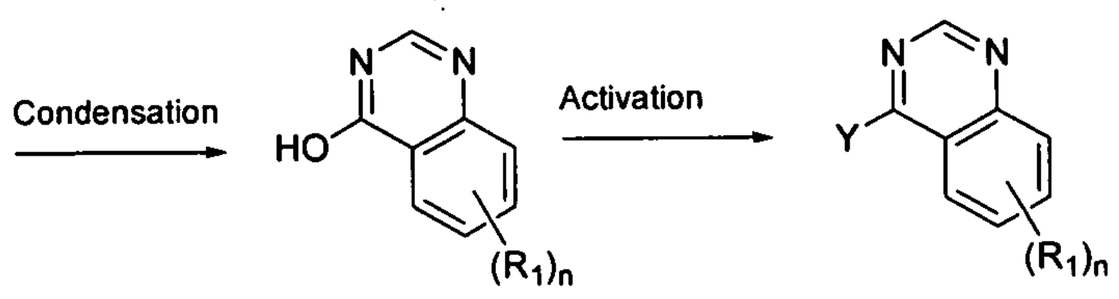
min - minute(s)

[00636] Activated quinazoline derivatives having one or more R^1 substituents (where each R^1 substitutent may or may not differ from the other R^1 substitutent(s)) are either commercially available or may be prepared according to Scheme 1. Activated quinazoline may be synthesized starting from anthranilic esters (**1c,** where R is alkyl) which are either commercially available, or are prepared from benzoic ester derivatives (**1a**, where R is alkyl), which undergoes classical nitration to yield the 2-nitro benzoic ester derivative (**1b**) which is followed by separation from any undesired regioisomers by crystallization or chromatography. For the reduction step, the 2-nitro intermediate in a suitable solvent such as water, $C_1 - C_4$ alcohol, ethyl acetate or *N,N*-dimethylformamide, may be reacted with reducing agents such as hydrogen gas in the presence of noble metal catalyst, sodium dithionite, tin chloride, tin or iron metal in the presence of acid, and the like, to yield the anthranilic ester intermediate (**1c**).

[00637] There are many synthetic routes known to one skilled in the art that may be used to prepare the 4-hydroxy quinazoline derivative (**1d**). One route that may be used is the condensation of a suitable anthranilic ester derivative with formamide or a suitable formamide derivative such as formamidine hydrochloride in a suitable solvent such as ethanol at a temperature from 100 °C to 130 °C, normally in the presence of an acid such as acetic acid (See, for example, Ballard et al. *Bioorganic & Medicinal Chemistry Letters* **2006**, 16, 1633-1637) to yield **1d**. Following isolation, the intermediate 4-hydroxyquinazoline derivative may be treated with an activating agent such as a phosphoric oxytrihalide or an aryl- or alkylsulfonyl halide to produce the activated quinazoline intermediate (**1e**) (See, for example, Takase et al. *J. Med. Chem.* **1994**, *37*, 2106-2111).



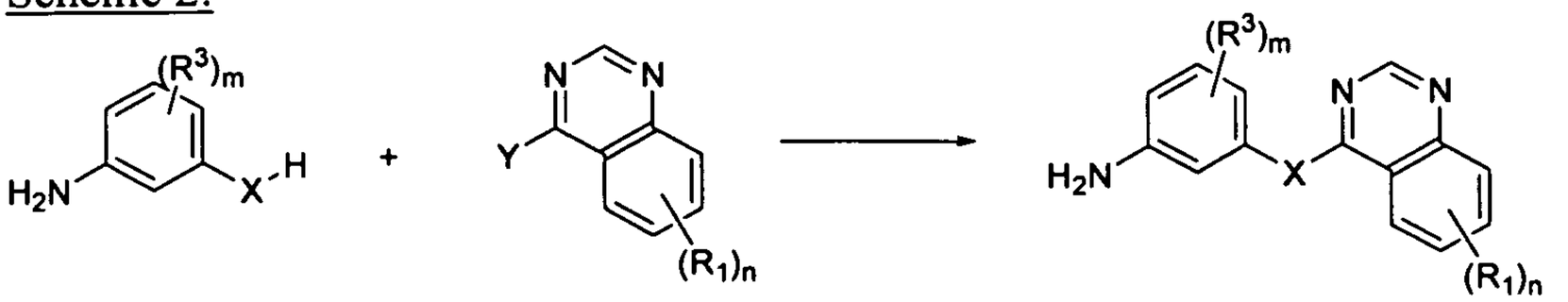
1a 1b 1c



1d 1e

[00638] Phenyleneamine derivatives (**2b**) may be prepared according to Scheme 2 by reaction of corresponding activated quinazoline derivatives (**1e**) with the unprotected *meta*-hydroxy- (X = O) or *meta*-mercapto (X = S) aniline (**2a**) in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide at a temperature from 40 °C to 85 °C, with formation (preferably preformation) of the oxa or sulfa anion with a base such as sodium hydride or cesium carbonate.

Scheme 2:

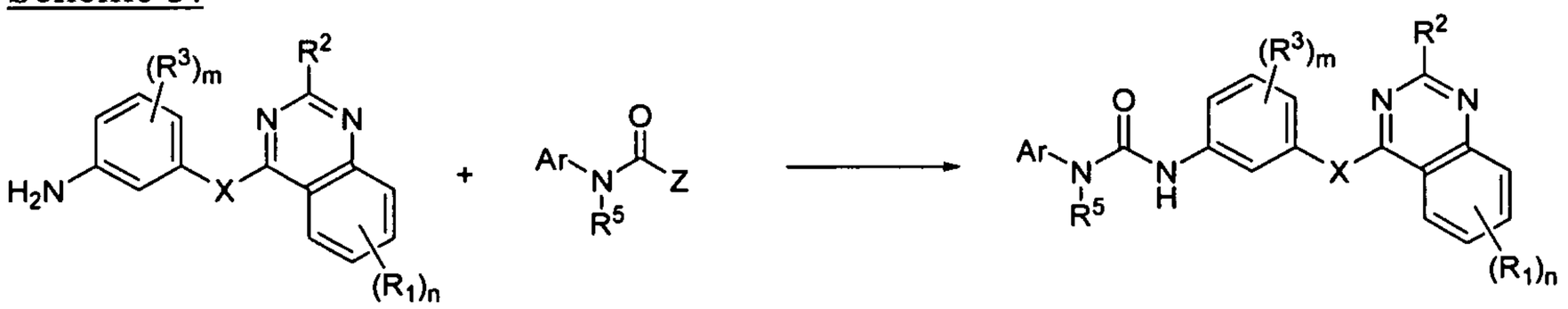


2a **1e** **2b**

[00639] Alternatively, as will be apparent to one skilled in the art, the free amino group of **2a** in Scheme 2 may be introduced in the form of an appropriate precursor, for example nitro or protected amino, followed by liberation of the free amine by nitro reduction or amine deprotection, respectively, to furnish **2b**.

[00640] Diaryl ureas having the Formula **I** may be prepared according to Scheme 3 by the reaction of a phenyleneamine derivative (**2b**) (which may be prepared as described in Scheme 2), with an activated arylcarbamic acid derivative (**3b**, where Ar can be aryl or heteroaryl, which may be prepared as described below), where Z is a leaving group such as halo or optionally substituted phenoxy, for example.

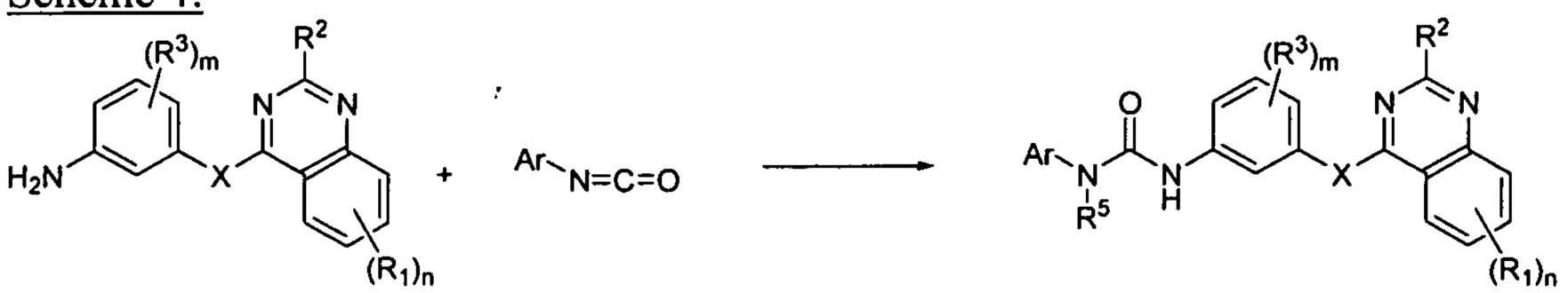
Scheme 3:



2b **3b** **I**

[00641] Alternatively, diaryl ureas having the Formula **I** may be prepared according to Scheme 4 when R^5 = H. Phenyleneamine (**2b**) is treated with an aryl isocyanate (**4b**, where Ar can be aryl or heteroaryl) in a suitable solvent such as tetrahydrofuran at a temperature from 25°C to 60°C, optionally in the presence of a base.

Scheme 4:

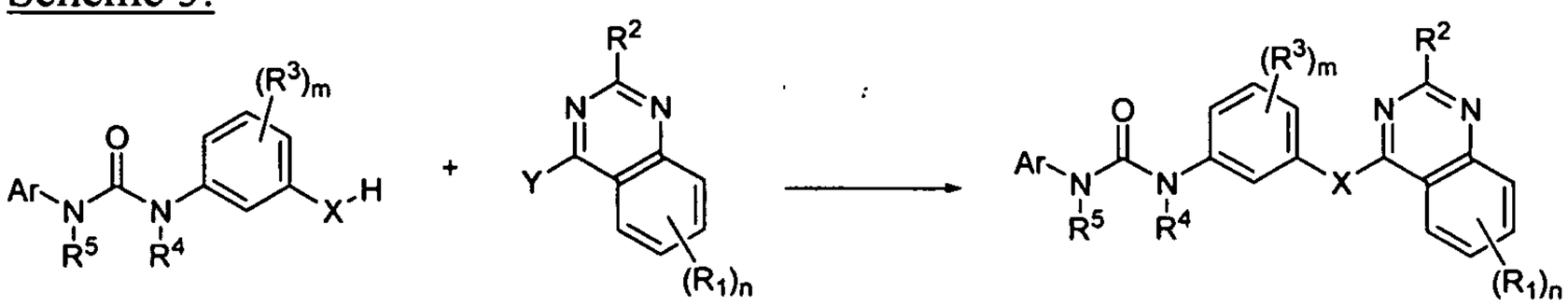


2b **4b** **I**

[00642] Alternatively, compounds having the Formula I may be prepared according to scheme 5 by the reaction of a hydroxy- (X = O) or mercapto- (X = S) substituted diaryl urea (**5a**, where Ar can be aryl or heteroaryl, which may be prepared as described below), with an activated quinazoline derivative (**1e**, where Y is a leaving group such as halo, aryl- or alkylsulfonate, which may be prepared as

described in Scheme 1), in a suitable solvent such as tetrahydrofuran at a temperature from 40 °C to 80°C, normally in the presence of a base such as sodium hydride or cesium carbonate.

Scheme 5:

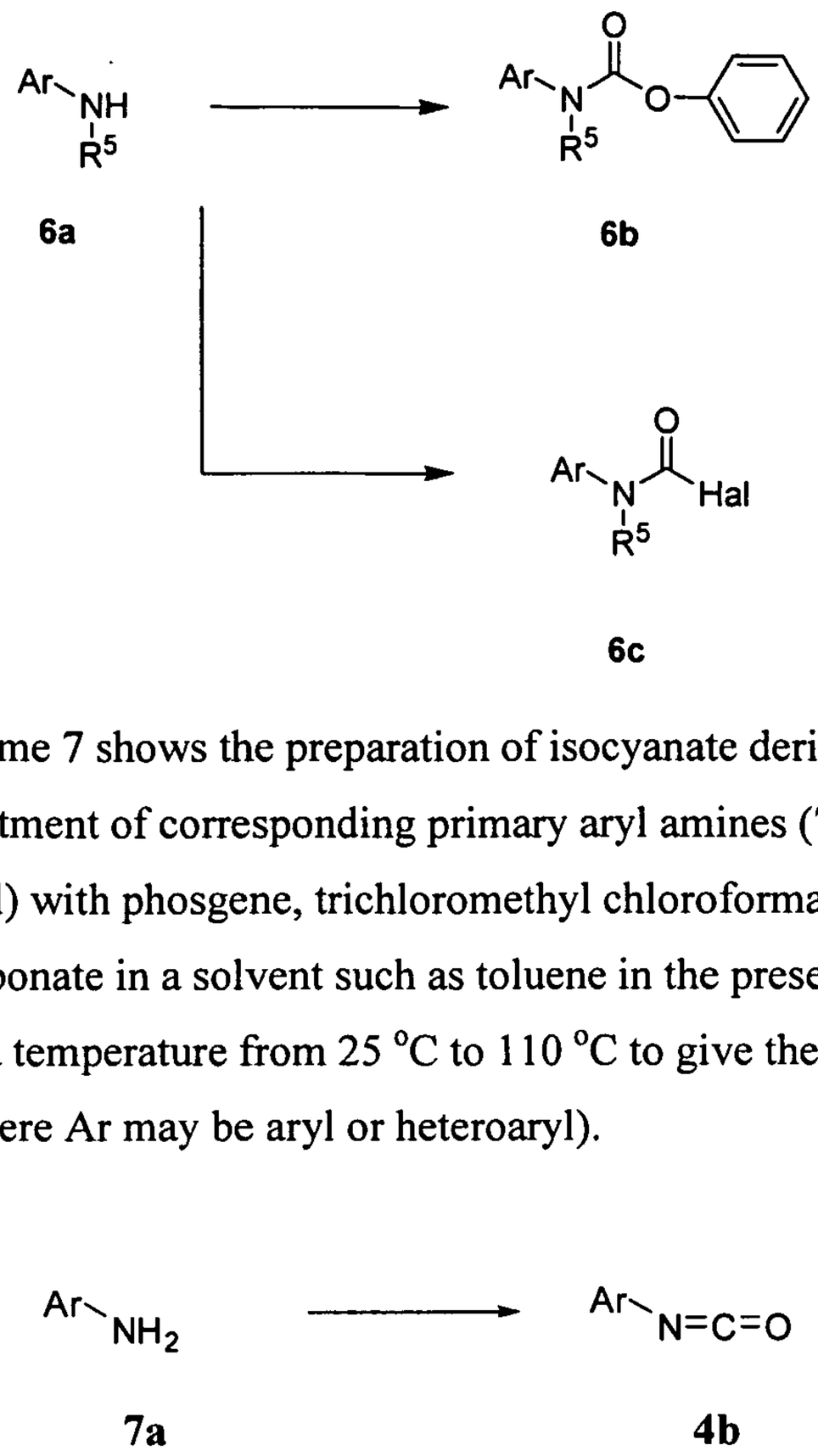


5a **1e** **I**

[00643] In certain embodiments, R^1 substituents of diaryl ureas having the Formula I, prepared as shown in Schemes 3, 4 and 5, may be further modified. For example, R^1 containing a haloalkyl moiety may be transformed to, for example, an aminoalkyl, alkoxyalkyl or thioalkyl, by treatment with, respectively, amines, alkoxides or thiolates. Alternatively, R^1 containing a carboxylic acid or carboxylic ester group may be transformed to the corresponding amides, amidines, alcohol, aldeyhdes, ketones, and aldehyde or ketone derivatives including oximes, hydrazones and the like. Where R^1 contains a hydroxy group, the hydroxy group may be derivatized to form the corresponding ester (by acylation), corresponding carbamate (by carbamylation), corresponding imidate and the like.

[00644] Arylcarbamoyl derivatives may be prepared as in Scheme 6 by treatment of corresponding aryl amines (**6a**, R^5 = H) with a reagent such as an aryl chloroformate in a solvent such as tetrahydrofuran or dichloromethane in the presence of a base such as potassium carbonate at a temperature from 25 °C to 60 °C to give the corresponding aryl carbamate (**6b** or **3b**, where Z may be, for example, phenoxy). When $R^5 \neq$ H, phosgene, trichloromethyl chloroformate, or bis-trichloromethyl carbonate may be used to prepare arylcarbamoyl chloride variants (**6c** where Hal is halogen, or **3b**, where Z may be, for example, halo).

Scheme 6:



6a **6b** **6c**

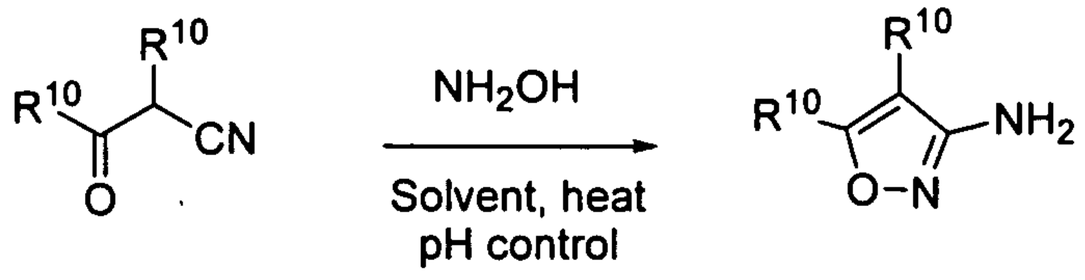
7a **4b**

[00645] Scheme 7 shows the preparation of isocyanate derivatives (**4b**) which are prepared by treatment of corresponding primary aryl amines (**7a**) (where Ar may be aryl or heteroaryl) with phosgene, trichloromethyl chloroformate, or bis-trichloromethyl carbonate in a solvent such as toluene in the presence of a base such as triethylamine at a temperature from 25 °C to 110 °C to give the corresponding isocyanate (**4b**) (where Ar may be aryl or heteroaryl).

Scheme 7:

[00646] Aryl amine derivatives (**7a**), wherein Ar is a 5-membered heteroaromatic ring, may be prepared by condensation of appropriate fragments and precursors by methods well known in the art and described in texts such as Gilchrist, T.L., *Heterocyclic Chemistry* (1992), 2nd Ed., Longman Scientific & Technical and John Wiley & Sons. Scheme 8 shows one example where Ar is 5-substituted-3-aminoisoxazole, whereby an appropriate 3-oxonitrile (**8a**) is treated with hydroxylamine under appropriate conditions of pH and temperature which is described, for example, in Takase et al. *Heterocycles* **1991** *32(6)*, 1153-1158, to afford the desired aryl amine product (**8b**). This method is particularly applicable for cases in which the atom of R^{10} directly attached to the aromatic ring is highly substituted, for example, is an α,α-dialkyl substituent (See Takase et al. *Heterocycles* **1991** *32(6)*, 1153-1158).

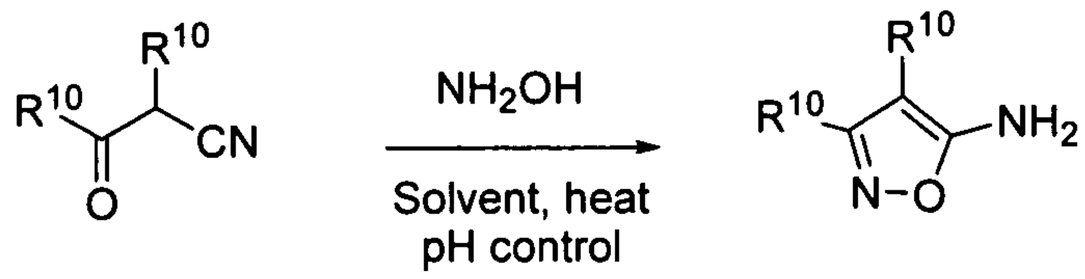
Scheme 8:



8a **8b**

[00647] Scheme 9 shows an example for the case where Ar is 3-substituted-5-aminoisoxazole, whereby an appropriate 3-oxonitrile **9a** is treated with hydroxylamine under appropriate conditions of pH and temperature, as described again in Takase et al. *Heterocycles* **1991** *32(6)*, 1153-1158, to afford the desired aryl amine product (**9b**). This method is particularly applicable for cases in which the atom of R^{10} directly attached to the aromatic ring is not highly substituted, for example, is not an α,α-dialkyl substituent (See Eddington et al. *Eur. J. Med. Chem.* **2002** 37, 635-648), or when R^{10} contains one or more highly electron-withdrawing groups, eg, fluorine, or under special conditions of pH and solvent, such as ethanol and water mixture as described in EP 0220947.

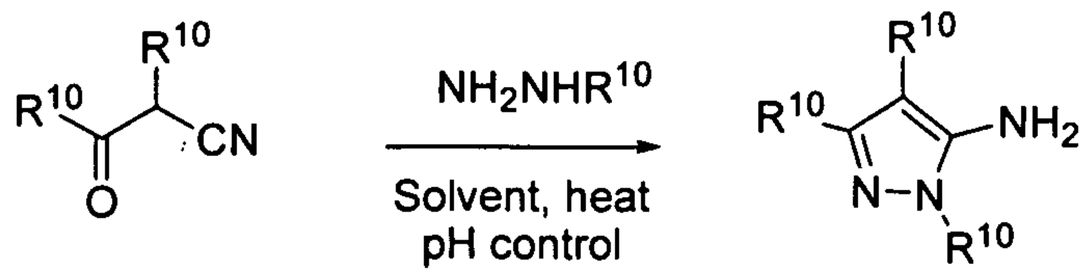
Scheme 9:



9a **9b**

[00648] Scheme 10 shows an example for the case where Ar is a 2,5-disubstituted-3-aminopyrazole, whereby an appropriate 3-oxonitrile (**10a**) is treated with a monosubstituted hydrazine under appropriate conditions of pH and temperature to afford the desired aryl amine product (**10b**).

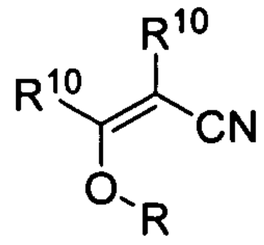
Scheme 10:



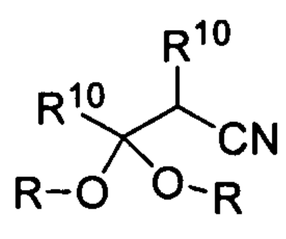
10a **10b**

[00649] Depending on R^{10}, in order to influence the yield and regiochemical outcome of the condensation reaction, 3-oxonitrile (**10a**) may be productively

replaced in the foregoing schemes by oxo-protected derivatives of (**10a**), such as an enol ether derivative (**10c,** R = lower alkyl or substituted silyl) or a ketal derivative (**10d,** R = lower alkyl or taken together, an alkylene derivative to form a ketal ring). These derivatives are prepared from 3-oxonitrile under standard conditions, for example as described in Chan et al. *Synthesis* **1983** 203-205.



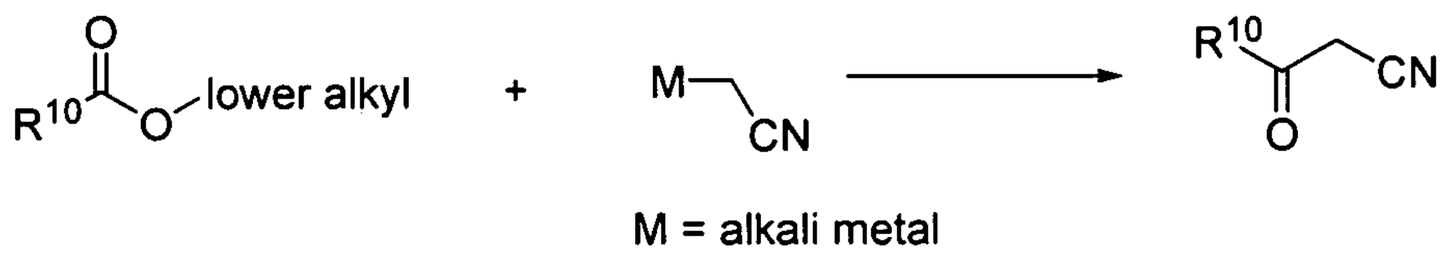
10c



10d

[00650] Scheme 11 illustrates preparation of the requisite 3-oxonitriles (**10a**) by reaction of an R^{10}-containing carboxylic ester (**11a**) with an akali metal salt of acetonitrile (**11b**) (See, for example, US 4,728,743).

Scheme 11:



11a **11b** **10a**

[00651] The subject matter has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Thus, it will be appreciated by those of skill in the art that conditions such as choice of solvent, temperature of reaction, volumes, reaction time may vary while still producing the desired compounds. In addition, one of skill in the art will also appreciate that many of the reagents provided in the following examples may be substituted with other suitable reagents. *See, e.g.,* Smith & March, *Advanced Organic Chemistry*, 5th ed. (2001). Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use provided herein, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

EXAMPLES

[00652] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.

EXAMPLE 1

Preparation Of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea

[00653] Example 1A: preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea: to THF (300 ml, degassed w/ argon) was added 3-aminophenol (4.36 g, 40 mmol) and 5-tert-butyl-3-isocyanatoisoxazole (6.64 g, 40 mmol) and the mixture was heated at 50°C overnight. After cooling to room temperature, the reaction was concentrated *in vacuo*, and the resulting foam purified by column chromatography (25 – 75% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (8.81 g, 32 mmol, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.39 (s, 1h), 9.37 (s, 1h), 8.69 (s, 1h), 7.06 (t, 1h), 7.01 (s, 1h), 6.78 (d, 1h), 6.49 (s, 1h), 6.41 (d, 1h), 1.29 (s, 9h); LC-MS (ESI) *m/z* 275 $(M + H)^+$.

[00654] Example 1B step 1: preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea: to a slurry of potassium *tert*-butoxide (6.73 g, 60 mmol) in THF (300 ml) was added the phenol from example 1a (8.25 g, 30 mmol), and the solution stirred at room temperature for 1 hour, at which point 4-chloro-6,7-dimethoxyquinazoline (6.74 g, 30 mmol) was added, followed by K_2CO_3 (4.1 g, 30 mmol). After stirring at room temperature for 72 hours, the reaction was concentrated in vacuo. The resulting solid was diluted with EtOAc, the organic layer washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (15-100% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea as a white solid.

[00655] Example 1B step 2: the compound was dissolved in EtOAc (50 ml) and 4N HCl in dioxane (5 ml, 20 mmol) was added. The mixture was sonicated,

stirred and concentrated *in vacuo* to give the product (6.23 g, 12.5 mmol, 42%) as the mono-hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1h), 9.44 (s, 1h), 8.73 (s, 1h), 7.65 – 7.60 (m, 2h), 7.45 – 7.38 (m, 2h), 7.29 (d, 1h), 6.98 (d, 1h), 6.48 (s, 1h), 4.02 (s, 3h), 4.00 (s, 3h), 1.28 (s, 9h); LC-MS (ESI) *m/z* 464 $(M + H)^+$.

EXAMPLE 2

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-yloxy)phenyl)urea

[00656] To 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (275 mg, 1 mmol) was added 4-chloro-6-methoxyquinazoline (194 mg, 1 mmol) according to the procedure described in Example 1B Step 1. The resulting compound was dissolved in EtOAc and 4N HCl in dioxane was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-yloxy)phenyl)urea as the mono-hydrochloride (299 mg, 0.64 mmol, 64%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.20 (s, 1H), 8.65 (s, 1H), 7.95 (d, 1H), 7.75 – 7.60 (m, 3H), 7.42 (t, 1H), 7.29 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 3.98 (s, 3H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 434 $(M + H)^+$.

EXAMPLE 3

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-yloxy)phenyl)urea

[00657] To 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (137 mg, 0.5 mmol) was added 4-chloro-7-methoxyquinazoline (97 mg, 0.5 mmol) according to the procedure described in Example 1B. The resulting compound was dissolved in EtOAc (5 mL) and 4N HCl in dioxane (0.2 mL, 0.8 mmol) was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-yloxy)phenyl)urea as the mono-hydrochloride (103 mg, 0.22 mmol, 44%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.63 (s, 1H), 9.15 (s, 1H), 8.69 (s, 1H), 8.28 (d, 1H), 7.58 (s, 1H), 7.45 – 7.35 (m, 3H), 7.27 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 3.98 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 434 $(M + H)^+$.

EXAMPLE 4

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-yloxy)phenyl)urea

[00658] **Example 4A Step 1**: To a stirring mixture of formamide (10 mL) and glacial acetic acid (2.5 mL) was added 2-amino-4,5-difluorobenzoic acid (2.0 g, 11.6 mmol) and the solution stirred at 125°C for 8 hours. After cooling to room temperature , the reaction was diluted with H_2O (100 mL) and the resulting solid filtered and dried under vacuum to give 6,7-difluoro-4-hydroxyquinazoline (1.77 g, 9.7 mmol, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.49 (br s, 1H), 8.15 (s, 1H), 8.04 (dd, 1H), 7.76 (dd, 1H); LC-MS (ESI) *m/z* 183 $(M + H)^+$.

[00659] **Example 4A Step 2:** To $POCl_3$ (15 mL) was added 6,7-difluoro-4-hydroxyquinazoline (910 mg, 5 mmol) followed by triethylamine (700 uL, 5 mmol). The solution was then heated at 100°C for 4 hours and concentrated *in vacuo*. The resulting sludge was triturated with EtOAc (2 x 100 mL), and the combined decanted org layers were flushed through a plug of silica gel to give 4-chloro-6,7-difluoroquinazoline (870 mg, 4.35 mmol, 87%). LC-MS (ESI) *m/z* 201 $(M + H)^+$.

[00660] **Example 4B Step 1**: To the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (110 mg, 0.4 mmol) was added 4-chloro-6,7-difluoroquinazoline from the previous step (80 mg, 0.4 mmol) according to the procedure described in Example 1B Step 1, to afford the title compound.

[00661] **Example 4B Step 2:** The title compound was dissolved in EtOAc and 4N HCl in dioxane was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-yloxy)phenyl)urea as the mono-hydrochloride (88 mg, 0.18 mmol, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.11 (s, 1H), 8.68 (s, 1H), 8.42 (dd, 1H), 8.11 (dd, 1H), 7.60 (s, 1H), 7.42 (t, 1H), 7.30 (d, 1H), 6.98 (d, 1H), 6.49 (s, 1H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 440 $(M + H)^+$.

EXAMPLE 5

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(5-methylquinazolin-4-yloxy)phenyl)urea

[00662] **Example 5A Step 1:** 2-amino-6-methylbenzoic acid (2.0 g, 13.2 mmol) was reacted using the procedure described in Example 4A Step 1 to give 4-hydroxy-5-methylquinazoline (1.6 g, 10.0 mmol, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (br s, 1H), 8.00 (s, 1H), 7.63 (t, 1H), 7.46 (d, 1H), 7.26 (d, 1H), 2.82 (s, 3H); LC-MS (ESI) *m/z* 161 $(M + H)^+$.

[00663] Example 5A Step 2: 4-hydroxy-5-methylquinazoline (600 mg, 3.75 mmol) was reacted using the procedure described in Example 4A Step 2 to give 4-chloro-5-methylquinazoline (585 mg, 3.28 mmol, 87%). LC-MS (ESI) *m/z* 179 $(M + H)^+$.

[00664] Exampe 5B Step 1: To 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (83 mg, 0.3 mmol) was added 4-chloro-5-methylquinazoline from the previous step (53 mg, 0.3 mmol) using the procedure described in Example 1B Step 1, to afford the title compound.

[00665] Example 5B Step 2: Using the procedure described in Example 1B Step 2, the compound from the previous step was dissolved in EtOAc and 4N HCl in dioxane was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(5-methylquinazolin-4-yloxy)phenyl)urea as the mono-hydrochloride (18 mg, 0.04 mmol, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.51 (s, 1H), 8.78 (s, 1H), 7.90 (t, 1H), 7.84 (t, 1H), 7.62 – 7.55 (m, 2H), 7.42 (t, 1H), 7.28 (d, 1H), 6.99 (d, 1H), 6.49 (s, 1H), 2.92 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 418 $(M + H)^+$.

EXAMPLE 6

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl]urea hydrochloride

[00666] Example 6A Step 1: A mixture of methyl vanillate (6.376 g, 35 mmol), bromoethane (4.359 g, 40 mmol), and K_2CO_3 (5.528 g, 40 mmol) in DMF (40 mL) was heated at 70 °C for 2 hours. The reaction mixture was quenched with water, filtered, washed with water, and dried under vacuum with P_2O_5 to give methyl 4-ethoxy-3-methoxybenzoate as white solid (7.123 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, 1H), 7.55 (d, 1H), 6.88 (d, 1H), 4.17 (q, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 1.50 (t, 3H); LC-MS (ESI) *m/z* 211 $(M + H)^+$.

[00667] **Example 6A Step 2:** To a solution of methyl 4-ethoxy-3-methoxybenzoate (7.12 g, 33.9 mmol) and acetic anhydride (40 mL) in acetic acid (40 mL) at room temperature was dropped fume nitric acid (90%, 3.15 g). After stirring at room temperature for 15 minutes, it was heated at 50 °C for 1 hour. The reaction mixture was poured into ice and a solid was formed. It was filtered, washed with water, and dried under vacuum with P_2O_5 to give methyl 4-ethoxy-5-methoxy-2-nitrobenzoate as white solid (8.392 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.07 (s, 1H), 4.19 (q, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 1.52 (t, 3H); LC-MS (ESI) *m/z* 256 $(M + H)^+$.

[00668] **Example 6A Step 3:** A mixture of methyl 4-ethoxy-5-methoxy-2-nitrobenzoate (8.38 g, 32.8 mmol) and Pd/C (10%, 0.85 g) in MeOH (20 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 6 hours. The reaction mixture was filtered with Celite and washed with MeOH. The filtration was concentrated under reduced pressure to give methyl 2-amino-4-ethoxy-5-methoxybenzoate as solid (6.832 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.13 (s, 1H), 5.56 (br, 2H), 4.08 (q, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 1.48 (t, 3H); LC-MS (ESI) *m/z* 226 $(M + H)^+$.

[00669] **Example 6A Step 4:** A mixture of methyl 2-amino-4-ethoxy-5-methoxybenzoate (4.43 g, 19.7 mmol) and formamidine hydrochloride (2.255 g, 28 mmol) in formamide (20 mL) was heated at 130 °C for 8 hours. The reaction mixture was quenched with water, filtered, washed with water, and dried under vacuum with P_2O_5 to give 7-ethoxy-6-methoxyquinazolin-4(3*H*)-one as solid (3.029 g, 70%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (br, 1H), 7.97 (s, 1H), 7.43 (s, 1H), 7.10 (s, 1H), 4.16 (q, 2H), 3.87 (s, 3H), 1.38 (t, 3H); LC-MS (ESI) *m/z* 221 $(M + H)^+$.

[00670] **Example 6A Step 5:** A mixture of 7-ethoxy-6-methoxyquinazolin-4(3*H*)-one (1.20 g, 5.45 mmol) and $POCl_3$ (3 mL), in toluene (10 mL) was heated at 125 °C for 5 hours. It was concentrated under reduced pressure to dryness. To it was added CH_2Cl_2 and it was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to give 4-chloro-7-ethoxy-6-methoxyquinazoline as solid (1.254 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 4.34 (q, 2H), 4.08 (s, 3H), 1.59 (t, 3H).

[00671] **Example 6B Step 1:** A mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (0.2 g 0.73 mmol), 4-chloro-7-ethoxy-6-methoxyquinazoline from the previous step (0.18 g, 0.75 mmol), and potassium *tert*-butoxide (0.252 g, 2.25 mmol) in THF was stirred at room temperature overnight, and then was heated at 60 °C for 5 hours. The reaction was still found to be incomplete and additional 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (0.07 g, 0.025 mmol) was added. The mixture was heated further at 60 °C overnight. The reaction was quenched with water and extracted with EtOAc. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with EtOAc/hexane as eluant to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl]urea as a solid (0.078 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (br and s, 2H), 8.61 (s, 1H), 7.64 (s, 1H), 7.54 (s, 1H), 7.31 (m, 3H), 7.0 (d, 1H), 6.05 (s, 1H), 4.29 (q, 2H), 4.05 (s, 3H), 1.58 (t, 3H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + H)^+$.

[00672] **Example 6B Step 2:** To a solution of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl]urea in MeOH and CH_2Cl_2 was added 1.0 M HCl in ethyl ether (2 equivalents). After solvent was concentrated under reduced pressure, to the residue was added ethyl ether and a white solid was formed. It was filtered, washed with ethyl ether, and dried under vacuum with P_2O_5 to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl]urea hydrochloride as a white solid (0.067 g, 16%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.19 (s, 1H), 8.62 (s, 1H), 7.59 (s, 2H), 7.40 (m, 2H), 7.26 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.27 (q, 2H), 3.99 (s, 3H), 1.44 (t, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + H)^+$.

Example 7

Preparation of 1-(5-*tert*-Butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride

[00673] Example 7A Step 1: A mixture of methyl vanillate (6.376 g, 35 mmol), 1-bromo-2-methoxyethane (5.56 g, 40 mmol), and K_2CO_3 (5.528 g, 40 mmol) in DMF (40 mL) were reacted according to the procedure described in Example 6A Step 1, to afford methyl 3-methoxy-4-(2-methoxyethoxy)benzoate as a solid (8.394 g, 99.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, 1H), 7.54 (d, 1H), 6.92 (d, 1H), 4.23

(q, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.81 (t, 2H), 3.45 (s, 3H); LC-MS (ESI) *m/z* 241 $(M + H)^+$.

[00674] Example 7A Step 2: Using the procedure described in Example 6A Step 2, methyl 3-methoxy-4-(2-methoxyethoxy)benzoate (8.39 g, 34.9 mmol) was reacted with fuming nitric acid (90%, 3.15 g) in AcOH (60 mL) at 50 °C for 8 hours, to afford methyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate as a yellow solid (7.956 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.07 (s, 1H), 4.25 (t, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.82 (t, 2H), 3.46 (s, 3H); LC-MS (ESI) *m/z* 286 $(M + H)^+$.

[00675] Example 7A Step 3: According to the procedure described in Example 6A Step 3, a mixture of methyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate (3.19 g, 11.2 mmol) and Pd/C (10%, 0.3 g) in EtOAc (150 mL) was stirred under 1 atmosphere of hydrogen at room temperature for 6 hours, to afford methyl 2-amino-5-methoxy-4-(2-methoxyethoxy)benzoate as a solid (2.699 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.17 (s, 1H), 5.55 (br, 2H), 4.14 (t, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (t. 2H), 3.44 (s, 3H); LC-MS (ESI) *m/z* 256 $(M + H)^+$.

[00676] Example 7A Step 4: According to the procedure described in Example 6A Step 4, a mixture of methyl 2-amino-5-methoxy-4-(2-methoxyethoxy)benzoate (2.69 g, 10.5 mmol) and formamidine hydrochloride (1.208 g, 15 mmol) in formamide (10 mL) was heated at 140 °C for 8 hours, to afford 6-methoxy-7-(2-methoxyethoxy)quinazolin-4(3*H*)-one as a white solid (1.935 g, 74%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (br, 1H), 7.98 (s, 1H), 7.44 (s, 1H), 7.14 (s, 1H), 4.23 (t, 2H), 3.87 (s, 3H), 3.72 (t, 2H), 3.32 (s, 3H); LC-MS (ESI) *m/z* 251 $(M + H)^+$.

[00677] Example 7A Step 5: According to the procedure described in Example 6A Step 5, a mixture of 6-methoxy-7-(2-methoxyethoxy)quinazolin-4(3*H*)-one (7.83 g, 31.3 mmol) and $POCl_3$ (20 mL) in toluene (50 mL) was heated at 125 °C for 5 hours, to afford 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline as a solid (8.098 g, 96%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 4.36 (t, 2H), 4.01 (s, 3H), 3.76 (t, 2H), 3.34 (s, 3H).

[00678] Example 7B: According to the procedure described in Example 50, a mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (4.405 g, 16 mmol) from Example 1A, 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline from Example 7A (4.837 g, 18 mmol), and Cs_2CO_3 (8.145 g, 16 mmol) in isopropanol (80 mL) was heated at 70 °C for 4 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea as a solid (5.548 g,

68.3%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.57 (s, 1H), 7.58 (m, 2H), 7.41 (m, 2H), 7.25 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.34 (t, 2H), 3.99 (s, 3H), 3.78 (t, 2H), 3.35 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 508 $(M + H)^+$.

[00679] Example 7**C:** The title compound was prepared as described in Example 6B Step 2 using 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea (5.545 g, 10.9 mmol) and 1.0 M HCl/Et_2O solution (1.3 eq.) in CH_2Cl_2 (100 mL) and MeOH (10 mL), to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride as a solid (5.723 g, 96.3%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.68 (s, 1H), 9.28 (s, 1H), 8.65 (s, 1H), 7.60 (m, 2H), 7.41 (m, 2H), 7.27 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.35 (t, 2H), 4.00 (s, 3H), 3.78 (t, 2H), 3.35 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 508 $(M + H)^+$.

Example 8

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methylquinazolin-4-yloxy)phenyl)urea

[00680] Example 8A Step 1: 2-Amino-5-methylbenzoic acid (2.0 g, 13.2 mmol) was reacted according to the procedure described in Example 4A Step 1 to give 4-hydroxy-6-methylquinazoline (1.6 g, 10.0 mmol, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 8.03 (d, 1H), 7.92 (s, 1H), 7.65 (dd, 1H), 7.57 (dd, 1H), 2.45 (s, 3H); LC-MS (ESI) *m/z* 161 $(M + H)^+$.

[00681] Example 8A Step 2: 4-Hydroxy-6-methylquinazoline (500 mg, 3.12 mmol) was reacted according to the procedure described in Example 4A Step 2 to give 4-chloro-6-methylquinazoline (546 mg, 3.05 mmol, 98%). LC-MS (ESI) *m/z* 179 $(M + H)^+$.

[00682] Example 8B Step 1: The title compound was prepared using 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (83 mg, 0.3 mmol) and 4-hydroxy-6-methylquinazoline from the previous step (53 mg, 0.3 mmol) according to the procedure described in Example 1B Step 1 to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methylquinazolin-4-yloxy)phenyl)urea.

[00683] Example 8B Step 2: As in Example 1B Step 2, the product from the previous step was dissolved in EtOAc and 4N HCl in dioxane was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methylquinazolin-4-yloxy)phenyl)urea as the mono-hydrochloride (101 mg, 0.24 mmol, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s,

1H), 9.34 (s, 1H), 8.75 (s, 1H), 8.21 (s, 1H), 7.97 – 7.91 (m, 2H), 7.60 (d, 1H), 7.42 (t, 1H), 7.31 (d, 1H), 6.99 (d, 1H), 6.48 (s, 1H), 2.61 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 418 $(M + H)^+$.

Example 9
Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea

[00684] Example 9A Step 1: To a mixture of 4-fluoro-3-methoxyaniline (2.0 g, 14.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 1.0 M solution of BBr_3 in CH_2Cl_2 (40 mL). It was stirred overnight, at which time the temperature was raised to room temperature. To it was added MeOH and the solvents were removed under reduced pressure. To the residue was added water, basified with saturated $NaHCO_3$, and extracted with EtOAc. Extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford 5-amino-2-fluorophenol as solid (1.3 g, 73%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (s, 1H), 6.81 (dd, 1H), 6.34 (dd, 1H), 6.04 (dd, 1H), 4.63 (br, 2H).

[00685] Example 9A Step 2: A mixture of 5-amino-2-fluorophenol (1.3g, 10.2 mmol) and 5-*tert*-butyl-3-isocyanatoisoxazole (1.7 g, 10.2 mmol) in toluene (60 mL) was heated at 70 °C overnight. The solid was filtered and dried under vacuum to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-(4-fluoro-3-hydroxyphenyl)urea as solid.

[00686] Example 9B. In a sealed reaction vessel the phenol from the previous step (131 mg, 0.45 mmol) was dissolved in dry THF (2 mL). This was added to a suspension of potassium tert-butoxide (55 mg, 0.49 mmol) in THF (5 mL) at 0°C. The reaction was allowed to slowly warm to room temperature. After stirring for 30 minutes, the 4-chloro-6,7-dimethoxyquinazoline was added and the reaction stirred at room temperature for 2 hours, then at 50°C overnight. The reaction was still incomplete, so cesium carbonate (320 mg, 0.98 mmol) and the reaction heated to 80°C for 6 hours. The reaction was partitioned between ethyl acetate and water, and then extracted twice. The extracts were combined, dried over magnesium sulfate, filtered and concentrated. The resulting oil was purified by silica gel chromatography eluting with a gradient of ethyl acetate/dichloromethane 0-25% over 60 minutes. The major peak was collected and concentrated to afford 50 mg of the title compound. This was then dissolved in dry dichloromethane and 1 M HCl in ether (0.5 mL) was added and the solution concentrated to dryness, to give 50 mg of the hydrochloride salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.70 (s, 1H), 8.73 (s, 1H), 7.71

(m, 1H), 7.64 (s, 1H), 7.47 (s, 1H), 7.37 (m, 2H), 6.48 (s, 1H), 4.00 (s, 6H), 1.30 (s, 9H). LC-MS (ESI) m/z 482 $(M+H)^+$.

Example 10

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(4-chloro-3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea

[00687] Example 10A: A mixture of 5-amino-2-chlorophenol (1.0g, 6.97 mmol) and 5-*tert*-butyl-3isocyanatoisoxazole (1.16 g, 6.97 mmol) in toluene (40 mL) was heated at 70 °C overnight. It was purified by silica gel chromatography with 0-25% EtOAc/hexane as eluants to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-(4-chloro-3-hydroxyphenyl)urea as solid.

[00688] Example 10B: In a sealed reaction vessel the phenol from the previous step (138 mg, 0.44 mmol) was dissolved in 4 mL of dry THF, and cesium carbonate (289 mg, 0.89 mmol) was added. To this mixture 4-chloro-6,7-dimethoxyquinazoline (100 mg, 0.44 mmol) was added and the reaction heated to 60°C overnight. The reaction was then partitioned between ethyl acetate and water and extracted twice. The extracts combined, dried over magnesium sulfate, filtered, and concentrated. The resulting concentrate was purified by silica gel chromatography eluting with a gradient of ethyl acetate/dichloromethane 0-25% over 60 minutes. The main peak was collected and concentrated to afford 70 mg of the title compound. The compound was then dissolved in anhydrous dichloromethane and 1 M HCl (0.5 mL) was added and the solution evaporated to dryness to give the hydrochloride salt weighing 67 mg. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.86 (d, 2H), 8.75 (s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.58 (d, 1H), 7.48 (s, 1H), 7.32 (d, 1H), 6.49 (s, 1H), 4.00 (s, 6H), 1.30 (s, 9H). LC-MS (ESI) m/z 498 $(M+H)^+$.

Example 11

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea

[00689] Example 11A Step 1: A mixture of 4,5-dimethoxy-2-nitrobenzoic acid (20.6 g, 90.7 mmol) in 20% KOH solution (136 mL) was heated at 100 °C for 12 hours. After it was cooled with ice, it was acidified with concentrated HCl to pH 2. It was filtered, washed with CH_2Cl_2 and EtOAc, and dried over vacuum to afford 5-hydroxy-4-methoxy-2-nitrobenzoic acid as solid (18.38 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29 (s, 1H), 6.90 (s, 1H), 4.8 (br, 1H), 3.77 (s, 3H).

[00690] Example 11A Step 2: To a suspension of 5-hydroxy-4-methoxy-2-nitrobenzoic acid (8.0 g, 37.5 mmol) in methanol was added concentrated sulfuric acid (3 drops) and it was heated at 80 °C overnight. After solvent was removed under reduced pressure, to it was added water and EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure to afford methyl 5-hydroxy-4-methoxy-2-nitrobenzoate as a solid (3.86 g, 45%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.63 (s, 1H), 7.08 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H).

[00691] Example 11A Step 3: According to the procedure described in Example 6A Step 3, a mixture of methyl 5-hydroxy-4-methoxy-2-nitrobenzoate (3.88 g, 17.1 mmol) and Pd/C in EtOAc (100 mL) was stirred under 1 atmosphere of hydrogen at room temperature overnight, to afford methyl 2-amino-5-hydroxy-4-methoxybenzoate as a solid (3.1 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.08 (s, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H).

[00692] Example 11A Step 4: A mixture of methyl 2-amino-5-hydroxy-4-methoxybenzoate (3.1 g, 15.7 mmol) and AcOH (7.1 mL) in formamide (15.5 mL) was heated at 140 °C overnight. To it was added water (20 mL) and filtered to afford 6-hydroxy-7-methoxyquinazoline-4(3*H*)-one as a solid (2.7 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82 (s, 1H), 7.9 (s, 1H), 7.4 (s, 1H), 7.1 (s, 1H), 3.9 (s, 3H).

[00693] Example 11A Step 5: A mixture of 6-hydroxy-7-methoxyquinazoline-4(3*H*)-one (1.0 g, 5.2 mmol) and Cs_2CO_3 (1.69 g, 5.2 mmol) in H_2O:MeCN:MeOH (10:5:1, 20 mL) was stirred at room temperature for 30 minutes and to it was added bromoethane (0.567 g, 5.2 mmol). Then, it was stirred at 60 °C two days. It was filtered to afford 6-ethoxy-7-methoxyquinazolin-4(3*H*)-one as a solid (0.550 g, 48%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.0 (s, 1H), 7.91 (s, 1H), 7.4 (d, 1H), 7.1 (d, 1H), 4.15 (t, 2H), 3.9 (s, 3H), 1.4 (t, 3H).

[00694] Example 11A Step 6: According to the procedure described in Example 6A Step 5, a mixture of 6-ethoxy-7-methoxyquinazolin-4(3*H*)-one (0.52 g, 2.36 mmol) and $POCl_3$ (1 mL) in toluene (10 mL) was heated at 125 °C for 3.5 hours. The residue was purified by silica gel chromatography with 0-25% EtOAc/hexane as eluants to afford 4-chloro-6-ethoxy-7-methoxyquinazoline as a solid (0.19 g, 34%). ^{1}H

NMR (300 MHz, $CDCl_3$) δ 8.9 (s, 1H), 7.4 (s, 1H), 7.3 (s, 1H), 4.3 (t, 2H), 4.1 (s, 3H), 1.6 (t, 3H).

[00695] Example 11B: The title compound was prepared using the procedure for Example 10B but using the intermediate 4-chloro-6-ethoxy-7-methoxyquinazoline (97 mg, 0.35 mmol) from the previous step and 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (84 mg, 0.35 mmol). To this reaction cesium carbonate (115 mg, 0.35 mmol) was added and the reaction heated to 60 °C overnight. The title compound was purified as above using a gradient of ethyl acetate/ dichloromethane 0-50% over 75 minutes. The corresponding hydrochloride salt was prepared using the procedure described in Example 10B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.69 (s, 1H), 8.84 (s, 1H), 7.64 (m, 2H), 7.43 (m, 2H), 7.29 (m, 1H), 7.01 (m, 1H), 6.49 (s, 1H), 4.30 (m, 2H), 4.04 (s, 3H), 1.46 (m, 3H), 1.16 (s, 9H); LC-MS (ESI) *m/z* 478 $(M+H)^+$.

Example 12

Preparation of 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride

[00696] Example 12A Step 1: According to the procedure described in Example 6A Step 1, a mixture of ethyl 3,4-dihydroxybenzoate (5.465g, 30 mmol), 1-bromo-2-methoxyethane (9.174 g, 66 mmol), and K_2CO_3 (9.122 g, 66 mmol) in DMF (50 mL) was heated at 50 °C for 5 hours, to afford ethyl 3,4-bis(2-methoxyethoxy)benzoate as a solid (7.872 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 1H), 7.59 (d, 1H), 6.91 (d, 1H), 4.35 (q, 2H), 4.22 (m, 4H), 3.80 (m, 4H), 3.46 (s, 6H), 1.38 (t, 3H); LC-MS (ESI) *m/z* 299 $(M + H)^+$.

[00697] Example 12A Step 2: According to the procedure described in Example 6A Step 2, to a solution of ethyl 3,4-bis(2-methoxyethoxy)benzoate (7.87 g, 26.4 mmol) in AcOH (50 mL) was added HNO_3 (90%, 4 mL) and the mixture was heated at 50 °C for 5 hours, to afford ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate as an oil (8.531 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.12 (s, 1H), 4.37 (q, 2H), 4.25 (m, 4H), 3.80 (m, 4H), 3.45 (s, 6H), 1.35 (t, 3H); LC-MS (ESI) *m/z* 344 $(M + H)^+$.

[00698] Example 12A Step 3: According to the procedure described in Example 6A Step 3, a mixture of ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate

(8.53 g, 24.8 mmol) and Pd/C (10%, 0.85 g) in EtOAc (150 mL) was stirred under 1 atmosphere of hydrogen at room temperature overnight, to afford ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate as an oil (7.15 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.15 (s, 1H), 5.60 (br, 2H), 4.30 (q, 2H), 4.13 (t. 2H), 4.08 (t, 2H), 3.78 (t, 2H), 3.73 (t. 2H), 3.45 (s, 6H), 1.36 (t, 3H); LC-MS (ESI) *m/z* 314 $(M + H)^+$.

[00699] Example 12A Step 4: According to the procedure described in Example 6A Step 4, a mixture of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate (7.15 g, 22.8 mmol) and formamidine hydrochloride (2.012 g, 25 mmol) in formamide (20 mL) was heated at 130 °C for 12 hours, to afford 6,7-bis(2-methoxyethoxy)quinazolin-4(3*H*)-one as a solid (3.75 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (br, 1H), 8.00 (s, 1H), 7.62 (s, 1H), 7.16 (s, 1H), 4.29 (t, 4H), 3.86 (t, 4H), 3.48 (s, 6H); LC-MS (ESI) *m/z* 295 $(M + H)^+$.

[00700] Example 12A Step 5: According to the procedure described in Example 6A Step 5, a mixture of 6,7-bis(2-methoxyethoxy)quinazolin-4(3*H*)-one (2.28 g, 7.7 mmol) and $POCl_3$ (10 mL) in toluene (30 mL) was heated at 125 °C for 5 hours, to afford 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline as a solid (2.212 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 4.34 (t, 4H), 3.89 (t, 4H), 3.50 (s, 3H), 3.49 (s, 3H); LC-MS (ESI) *m/z* 313 $(M + H)^+$.

[00701] Example 12B Step 1: According to the procedure described in Example 13B Step 1, a mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (0.688g, 2.5 mmol), 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline from the previous step (0.782 g, 2.5 mmol), and Cs_2CO_3 (0.977 g, 3 mmol) in isopropanol (15 mL) was heated at 70 °C for 7 hours, to afford 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea as solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.98 (s, 1H), 8.55 (s, 1H), 7.58 (m, 2H), 7.42 (s, 1H), 7.40 (t, 1H), 7.25 (d, 1H), 6.97 (d 1H), 6.47 (s, 1H), 4.34 (m, 4H), 3.77 (m, 4H), 3.38 (s, 3H), 3.36 (s, 3H), 1.27 (s, 9H).

[00702] Example 12B Step 2: The title compound was prepared as described in Example 6B Step 2 using 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea and 1.0 M HCl/Et_2O solution (2 eq.) in CH_2Cl_2 and MeOH, to afford 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride as a solid (1.169 g,

85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (s, 1H), 9.39 (s, 1H), 8.70 (s, 1H), 7.66 (s, 1H), 7.60 (m, 1H), 7.46 (s, 1H), 7.44 (t, 1H), 7.28 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.37 (m, 4H), 3.78 (m, 4H), 3.37 (s, 3H), 3.36 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 552 $(M + H)^+$.

Example 13

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea hydrochloride

[00703] Example 13A Step 1: According to the procedure described in Example 6A Step 1, a mixture of ethyl 3,4-dihydroxybenzoate (5.465g, 30 mmol), bromoethane (7.192 g, 66 mmol), and K_2CO_3 (9.122 g, 66 mmol) in DMF (50 mL) was heated at 50 °C for 5 hours, to afford ethyl 3,4-diethoxybenzoate as solid (6.439 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, 1H), 7.55 (d, 1H), 6.87 (d, 1H), 4.35 (q, 2H), 4.15 (q, 4H), 1.48 (m, 6H), 1.38 (t, 3H); LC-MS (ESI) *m/z* 239 $(M + H)^+$.

[00704] Example 13A Step 2: According to the procedure described in Example 6A Step 2, to a solution of ethyl 3,4-diethoxybenzoate (6.43 g, 27 mmol) in AcOH (50 mL) was dropped fuming nitric acid (90%, 6.3 g) and the reaction was heated at 50 °C overnight, to afford ethyl 4,5-diethoxy-2-nitrobenzoate as a solid (7.175 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.05 (s, 1H), 4.37 (q, 2H), 4.18 (m, 4H), 1.50 (m, 6H), 1.35 (t, 3H); LC-MS (ESI) *m/z* 284 $(M + H)^+$.

[00705] Example 13A Step 3: According to the procedure described in Example 6A Step 3, a mixture of ethyl 4,5-diethoxy-2-nitrobenzoate (7.17 g, 25.3 mmol) and Pd/C (10%, 0.7 g) in EtOAc (150 mL) was stirred under 1 atmosphere of hydrogen at room temperature overnight, to afford ethyl 2-amino-4,5-diethoxybenzoate as a solid (6.401 g, 99%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.14 (s, 1H), 5.60 (br, 2H), 4.30 (q, 2H), 4.05 (m, 4H), 1.44 (t, 3H), 1.38 (m, 6H); LC-MS (ESI) *m/z* 254 $(M + H)^+$.

[00706] Example 13A Step 4: According to the procedure described in Example 6A Step 4, a mixture of ethyl 2-amino-4,5-diethoxybenzoate (2.53 g, 10 mmol) and formamidine hydrochloride (0.966 g, 12 mmol) in formamide (10 mL) was heated at 140 °C for 5 hours, to afford 6,7-diethoxyquinazolin-4(3*H*)-one as a white solid (1.702 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (br, 1H), 7.98 (s,

1H), 7.60 (s, 1H), 7.14 (s, 1H), 4.24 (m, 4H), 1.54 (m, 6H); LC-MS (ESI) *m/z* 235 (M + H)$^+$.

[00707] Example 13A Step 5: According to the procedure described in Example 6A Step 5, a mixture of 6,7-diethoxyquinazolin-4(3*H*)-one (1.70 g, 7.3 mmol) and $POCl_3$ (3 mL) in toluene (10 mL) was heated at 120 °C for 5 hours to afford 4-chloro-6,7-diethoxyquinazoline as a solid (1.794 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.45 (s, 1H), 7.39 (s, 1H), 4.31 (m, 4H), 1.58 (m, 6H); LC-MS (ESI) *m/z* 253 (M + H)$^+$.

[00708] Example 13B Step 1: A mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (0.137g, 0.5 mmol), 4-chloro-6,7-diethoxyquinazoline from the previous step (0.126 g, 0.5 mmol), and Cs_2CO_3 (0.326 g, 1 mmol) in isopropanol (6 mL) was heated at 90 °C for 4 hours. The reaction was quenched with water and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography with EtOAc/hexane as eluant to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.03 (s, 1H), 8.56 (s, 1H), 7.57 (m, 1H), 7.55 (s, 1H), 7.40 (t, 1H), 7.37 (s, 1H), 7.25 (d, 1H), 6.96 (dd, 1H), 6.47 (s, 1H), 4.26 (m 4H), 1.43 (m, 6H), 1.27 (s, 9H).

[00709] Example 13C: The title compound was prepared as described in Example 6B Step 2, using 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea and 1.0 M HCl/Et_2O solution (2 eq.) in CH_2Cl_2 and MeOH, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea hydrochloride as a solid (0.053 g, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.27 (s, 1H), 8.66 (s, 1H), 7.68 (m, 2H), 7.40 (m, 2H), 7.26 (d, 1H), 6.97 (d, 1H), 6.48 (s, 1H), 5.78 (br, 1H), 4.28 (m, 4H), 1.43 (m, 6H), 1.27 (s, 9H); LC-MS (ESI) m/z 492 (M + H)$^+$.

Example 14

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-yloxy)phenyl]urea hydrochloride

[00710] Example 14A Step 1: According to the procedure described in Example 6A Step 1, a mixture of ethyl 3,4-dihydroxybenzoate (5.465g, 30 mmol),

1,2-dibromoethane (5.636 g, 30 mmol), and K_2CO_3 (6.219 g, 45 mmol) in DMF (100 mL) was heated at 70 °C overnight. The residue was purified by silica gel chromatography with 20-50% EtOAc/hexane as eluants to afford ethyl 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate as an oil (1.423 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, 1H), 7.56 (dd, 1H), 6.88 (d, 1H), 4.30 (m, 6H), 1.37 (t, 3H); LC-MS (ESI) *m/z* 209 $(M + H)^+$.

[00711] Example 14A Step 2: According to the procedure described in Example 6A Step 2, to a solution of ethyl 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (1.42 g, 6.8 mmol) and Ac_2O (3 mL), in AcOH (15 mL) was dropped fuming nitric acid (1 mL). The reactedion was heated at 50 °C for 2 hours, to afford ethyl 7-nitro-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate as a solid (1.720 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.18 (s, 1H), 4.36 (m, 6H), 1.33 (t, 3H).

[00712] Example 14A Step 3: According to the procedure described in Example 6A Step 3 a mixture of ethyl 7-nitro-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (1.72 g, 6.8 mmol) and Pd/C (10%, 0.2 g) in EtOAc (100 mL) was stirred under 1 atmosphere of hydrogen at room temperature overnight, to afford ethyl 7-amino-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate as a solid (1.459 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.18 (s, 1H), 5.41 (br, 2H), 4.30 (m, 4H), 4.19 (q, 2H), 1.38 (t, 3H); LC-MS (ESI) *m/z* 224 $(M + H)^+$.

[00713] Example 14A Step 4: According to the procedure described in Example 6A Step 4, a mixture of ethyl 7-amino-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (1.45 g, 6.5 mmol) and formamidine hydrochloride (1.208 g, 15 mmol) in formamide (20 mL) was heated at 130 °C for 8 hours, to afford 7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4(3*H*)-one as a solid (1.114 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$ and drops DMSO-d_6) δ 11.80 (br, 1H), 7.88 (s, 1H), 7.63 (s, 1H), 7.13 (s, 1H), 4.36 (m, 4H); LC-MS (ESI) *m/z* 205 $(M + H)^+$.

[00714] Example 14A Step 5: According to the procedure described in Example 6A Step 5, a mixture of 7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4(3*H*)-one (1.114 g, 5.46 mmol) and $POCl_3$ (10 mL) in toluene (10 mL) was heated at 125 °C for 5 hours to afford 4-chloro-7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazoline as a

solid (1.143 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 4.46 (m, 4H).

[00715] Example 14B. According to the procedure described in Example 13B Step 1, a mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (0.138g, 0.5 mmol), 4-chloro-7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazoline from the previous step (0.111 g, 0.5 mmol), and Cs_2CO_3 (0.326 g, 1 mmol) in isopropanol (7 mL) was heated at 70 °C for 13 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4-yloxy]phenyl)urea as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (br, 1H), 9.10 (s, 1H), 8.59 (s, 1H), 7.72 (s, 1H), 7.60 (m, 1H), 7.42 (s, 1H), 7.31 (m, 2H), 6.95 (d, 1H), 6.02 (s, 1H), 4.41 (m 4H), 1.30 (s, 9H).

[00716] Example 14C. According to the procedure described in Example 6B Step 2, to a solution of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4-yloxy)phenyl]urea in CH_2Cl_2 and MeOH was added 1.0 M HCl/Et_2O solution to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4-yloxy)phenyl]urea hydrochloride as a solid (0.086 g, 35%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.28 (s, 1H), 8.63 (s, 1H), 7.72 (s, 1H), 7.57 (m, 1H), 7.43 (s, 1H), 7.40 (t, 1H), 7.28 (d, 1H), 6.96 (d, 1H), 6.48 (s, 1H), 5.43 (br, 1H), 4.47 (m, 4H), 1.28 (s, 9H); LC-MS (ESI) m/z 462 $(M + H)^+$.

Example 15

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride

[00717] Example 15A Step 1: According to the procedure described in Example 6A Step 1, a mixture of methyl 3-hydroxy-4-methoxybenzoate (5.00 g, 27.4 mmol), 1-bromo-2-methoxyethane (4.96 g, 35.7 mmol), and K_2CO_3 (4.6 g, 32.9 mmol) in DMF (20 mL) was heated at 90 °C overnight, to afford methyl 4-methoxy-3-(2-methoxyethoxy)benzoate as a solid (5.6 g, 85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (dd, 1H), 7.46 (d, 1H), 7.09 (d, 1H), 4.12 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.67 (m, 2H), 3.33 (s, 3H).

[00718] Example 15A Step 2. According to the procedure described in Example 6A Step 2, to a solution of methyl 4-methoxy-3-(2-methoxyethoxy)benzoate (5.6 g, 23.3 mmol) and Ac_2O (12 mL) in AcOH (60 mL) was dropped fuming nitric acid (90%, 4 mL). The reaction was heated at 50 °C for 3 hours, and the residue was

purified by silica gel chromatography with 0-15% EtOAc/hexane as eluants to afford methyl 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoate as a solid (3.67 g, 56%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 (s, 1H), 7.34 (s, 1H), 4.26 (m, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.68 (m, 2H), 3.33 (s, 3H).

[00719] Example 15A Step 3. According to the procedure described in Example 6A Step 3, a mixture of methyl 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoate (3.67 g, 12.9 mmol) and Pd/C (10%, 0.4 g) in EtOAc (60 mL) was stirred under 1 atmosphere of hydrogen at room temperature overnight, to afford methyl 2-amino-4-methoxy-5-(2-methoxyethoxy)benzoate as a solid (3.05 g, 93%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (s, 1H), 6.46 (s, 2H), 6.36 (s, 1H), 3.91 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.59 (m. 2H), 3.32 (s, 3H).

[00720] Example 15A Step 4. According to the procedure described in Example 6A Step 4, a mixture of methyl 2-amino-4-methoxy-5-(2-methoxyethoxy)benzoate (3.05 g, 11.9 mmol) and AcOH (5.4 mL) in formamide (15.25 mL) was heated at at 140 °C overnight, to afford 7-methoxy-6-(2-methoxyethoxy)quinazolin-4(3*H*)-one as a solid (2.07 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.0 (br, 1H), 7.99 (s, 1H), 7.45 (s, 1H), 7.14 (s, 1H), 4.19 (t, 2H), 3.91 (s, 3H), 3.71 (t, 2H), 3.32 (s, 3H).

[00721] Example 15A Step 5. According to the procedure described in Example 6A Step 5, a mixture of 7-methoxy-6-(2-methoxyethoxy)quinazolin-4(3*H*)-one (0.6 g, 2.4mmol) and $POCl_3$ (1 mL) in toluene (10 mL) was heated at 125 °C for 2 hours, to afford 4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline as solid (0.445 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 7.45 (s, 1H), 7.41 (s, 1H), 4.33 (t, 2H), 4.03 (s, 3H), 3.77 (t, 2H), 3.33 (s, 3H).

[00722] Example 15B. According to the procedure described in Example 50, a mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (0.201 g, 0.73 mmol) from Example 1A, 4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline (0.195 g, 0.73 mmol) from the previous step, and Cs_2CO_3 (0.261 g, 0.8 mmol) in isopropanol (10 mL) was heated at 70 °C for 7 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (br and s, 2H), 8.61 (s, 1H), 7.62 (s, 1H), 7.55 (s, 1H), 7.31 (m, 3H), 6.97 (dd, 1H), 6.08 (s, 1H), 4.34 (t, 2H), 4.11 (s, 3H), 3.89 (t, 2H), 3.49 (s, 3H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 508 (M + H)$^+$.

[00723] Example 15C. The title compound was prepared as described in Example 6B Step 2 using 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea and 1.0 M HCl in Et_2O solution (1 mL) in CH_2Cl_2 and MeOH, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride as a solid (0.211 g, 53%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.33 (s, 1H), 8.68 (s, 1H), 7.63 (s, 1H), 7.60 (d, 1H), 7.43 (s, 1H), 7.41 (t, 1H), 7.27 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 5.36 (br, 1H), 4.34 (m, 2H), 4.02 (s, 3H), 3.77 (m, 2H), 3.34 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 508 $(M + H)^+$.

Example 16

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea

[00724] Example 16A Step 1: To DMF (40mL) was added potassium carbonate (9.1 g, 65.9 mmol) and methyl 3-hydroxy-4-methoxybenzoate (10.0 g, 54.9 mmol) and the mixture stirred 30 minutes at room temperature 1-bromo-2-chloroethane (11.0 g, 76.8 mmol) was added and the mixture was heated at 60°C overnight at which point excess 1-bromo-2-chloroethane (5.5 g, 38.4 mmol) was added and heating continued for 8 hours. After cooling to room temperature , the mixture was diluted with H_2O, filtered, and the solid washed with EtOAc to give methyl 3-(2-chloroethoxy)-4-methoxybenzoate (4.04 g, 16.6 mmol, 30%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.63 (d, 1H), 7.47 (s, 1H), 7.11 (d, 1H), 4.29 (t, 2H), 3.95 (t, 2H), 3.86 (s, 3H), 3.81 (s, 3H); LC-MS (ESI) *m/z* 245 $(M + H)^+$.

[00725] Example 16A Step 2: To acetic acid (42 mL) and acetic anhydride (8.5 mL) was added methyl 3-(2-chloroethoxy)-4-methoxybenzoate (4.0 g, 16.3 mmol) followed by 70% nitric acid (2.8 mL) and the mixture heated at 50°C for 1 hour. The mixture was poured into H_2O, filtered, and washed with H_2O to give methyl 5-(2-chloroethoxy)-4-methoxy-2-nitrobenzoate (4.08 g, 14.1 mmol, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.38 (s, 1H), 4.43 (t, 2H), 3.99 (t, 2H), 3.94 (s, 3H), 3.85 (s, 3H).

[00726] Example 16A Step 3: To methyl 5-(2-chloroethoxy)-4-methoxy-2-nitrobenzoate (4.07 g, 14.1 mmol) under argon was added 10% palladium on carbon and in EtOAc (150mL) and MeOH (50 mL). The flask was flushed with H_2 (g) and

stirred under H_2 (1 atm) for 30 minutes. The mixture was filtered through Celite and concentrated *in vacuo* to give methyl 2-amino-5-(2-chloroethoxy)-4-methoxybenzoate (3.61 g, 13.9 mmol, 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (s, 1H), 6.52 (br s, 2H), 6.38 (s, 1H), 4.07 (t, 2H), 3.85 (t, 2H), 3.77 (s, 3H), 3.75 (s, 3H); LC-MS (ESI) *m/z* 260 $(M + H)^+$.

[00727] Example 16A Step 4: To a solution of methyl 2-amino-5-(2-chloroethoxy)-4-methoxybenzoate (3.61 g, 13.9 mmol) in ethanol was added formamidine hydrochloride and the mixture heated in a sealed tube at 130°C overnight. The reaction was cooled to room temperature and filtered to give 6-(2-chloroethoxy)-4-hydroxy-7-methoxyquinazoline (3.05 g, 12.0 mmol, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 8.00 (s, 1H), 7.47 (s, 1H), 7.16 (s, 1H), 4.36 (t, 2H), 4.00 (t, 2H), 3.92 (s, 3H); LC-MS (ESI) *m/z* 255 $(M + H)^+$.

[00728] Example 16B: The intermediate 6-(2-chloroethoxy)-4-hydroxy-7-methoxyquinazoline from the previous step (5.0 g, 19.6 mmol) was reacted according to the procedure described in Example 4A Step 2 to give 4-chloro-6-(2-chloroethoxy)-7-methoxyquinazoline (4.3 g, 15.8 mmol, 80%). LC-MS (ESI) *m/z* 273 $(M + H)^+$.

[00729] Example 16C: To a slurry of cesium carbonate in THF was added 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (2.02 g, 7.3 mmol). After stirring for about 15 minutes at room temperature, the chloride intermediate (2.0 g, 7.3 mmol) from the previous step was added and the reaction mixture was heated at 50°C overnight. The mixture was diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (10-50% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (2.15 g, 4.2 mmol, 58%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.58 (s, 1H), 7.61 (s, 2H), 7.48 – 7.37 (m, 2H), 7.26 (d, 1H), 6.98 (d, 1H), 6.49 (s, 1H), 4.53 – 4.47 (m, 2H), 4.12 – 4.00 (m, 5H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 512 $(M + H)^+$.

[00730] Example 16D. 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.39 mmol) from the previous step was treated with piperidine (0.116 mL, 1.17 mmol), tetrabutylammonium iodide (0.39 mmol) and N,N'-diisopropylethylamine (0.78 mmol) in N,N'-dimethylformamide. The mixture was heated to 60 °C for 56h and cooled to room

temperature. Water was added and the solid filtered off and dried. The crude solid was purified by preparative HPLC (phenylhexyl reverse phase column) and the obtained solid triturated with water (10 mL) and drops of methanol, then filtered off and dried under high vacuum to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea as a colorless solid (29 mg, 13%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (brs, 1H), 9.10 (brs, 1H), 8.55 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.37-7.42 (m, 2H), 7.26 (m, 1H), 6.96 (m, 1H), 6.48 (s, 1H), 4.26-4.30 (m, 2H), 3.99 (s, 3H), 2.72-2.76 (m, 2H), 2.40-2.50 (m, 4H), 1.48-1.52 (m, 4H), 1.37-1.39 (m, 2H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 561 $(M + H)^+$.

Example 17

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea

[00731] 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.39 mmol) from Example 16C was reacted with 4-piperidinemethanol (135 mg, 1.17 mmol) according to the procedure described in Example 16D to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea as a colorless solid (36 mg, 16%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (brs, 1H), 9.10 (brs, 1H), 8.55 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.37-7.43 (m, 2H), 7.27 (m, 1H), 6.97 (m, 1H), 6.48 (s, 1H), 4.20-4.50 (m, 3H), 3.99 (s, 3H), 3.23 (m, 2H), 2.96-3.00 (m, 2H), 2.74-2.78 (m, 2H), 2.01-2.05 (m, 2H), 1.61-1.65 (m, 2H), 1.27 (s, 9H), 1.00-1.15 (m, 2H); LC-MS (ESI) *m/z* 591 $(M + H)^+$.

Example 18

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea

[00732] 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.39 mmol) from Example 16C was reacted with *N*-methyl piperazine (0.130 mL, 1.17 mmol) according to the procedure described for Example 16D to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea as a colorless solid (18 mg, 8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 9.00 (brs, 1H), 8.55 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.37-7.42 (m, 2H), 7.25 (m, 1H),

6.96 (m, 1H), 6.47 (s, 1H), 4.26-4.30 (m, 2H), 3.99 (s, 3H), 2.75-2.79 (m, 2H), 2.20-2.50 (m, 8H), 2.13 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 576 $(M + H)^+$.

Example 19

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea

[00733] Prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.39 mmol) from Example 16C (200 mg, 0.39 mmol) and 1-(2-hydroxyethyl)piperazine (0.144 mL, 1.17 mmol) according to the procedure described for Example 16D to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea as a colorless solid (28 mg, 12%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (brs, 1H), 9.01 (brs, 1H), 8.55 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.37-7.42 (m, 2H), 7.26 (m, 1H), 6.96 (m, 1H), 6.47 (s, 1H), 4.26-4.35 (m, 3H), 3.99 (s, 3H), 3.40-3.50 (m, 2H), 2.75-2.79 (m, 2H), 2.30-2.50 (m, 9H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 606 $(M + H)^+$.

Example 20

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea

[00734] Prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.39 mmol) from Example 16C (200 mg, 0.39 mmol) and morpholine (0.102 mL, 1.17 mmol) according to the procedure described for Example 16D to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea as a colorless solid (28 mg, 13%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (brs, 1H), 9.08 (brs, 1H), 8.56 (s, 1H), 7.58-7.65 (m, 2H), 7.38-7.43 (m, 2H), 7.25 (m, 1H), 6.97 (m, 1H), 6.48 (s, 1H), 4.30-4.32 (m, 2H), 4.00 (s, 3H), 3.60-3.62 (m, 4H), 2.80 (m, 2H), 2.49-2.52 (m, 4H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 563 $(M + H)^+$.

Example 21

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00735] Example 21A Step 1: To DMF (80mL) was added potassium carbonate (5.7 g, 41.1 mmol) and methyl 3-hydroxy-4-methoxybenzoate (5.0 g, 27.4 mmol). The mixture was cooled to 0°C and 1-bromo-3-chloropropane (8.64 g, 57.9 mmol) in DMF (10 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to r.t overnight. After removing most of the DMF *in vacuo*, the remaining oil was diluted with H_2O and filtered to give methyl 3-(3-chloropropoxy)-4-methoxybenzoate (6.65 g, 25.8 mmol, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 (d, 1H), 7.47 (s, 1H), 7.09 (d, 1H), 4.12 (t, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (t, 2H), 2.23 – 2.15 (m, 2H); LC-MS (ESI) *m/z* 259 $(M + H)^+$.

[00736] Example 21A Step 2: Methyl 3-(3-chloropropoxy)-4-methoxybenzoate (6.65 g, 25.7 mmol) was reacted with nitric acid as described in Example 16A Step 2 to give methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate (6.70 g, 22.1 mmol, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.37 (s, 1H), 4.26 (t, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 (t, 2H), 2.26 – 2.18 (m, 2H).

[00737] Example 21A Step 3: Methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate (6.70 g, 22.1 mmol) in EtOAc (100mL) was reacted with H_2 in the presence of 10% palladium on carbon in the manner described in Example 16A Step 3 to give methyl 2-amino-5-(3-chloropropoxy)-4-methoxybenzoate (6.0 g, 22.0 mmol, 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18 (s, 1H), 6.49 (br s, 2H), 6.37 (s, 1H), 3.93 (t, 2H), 3.82 – 3.71 (m, 8H), 2.14 – 2.06 (m, 2H); LC-MS (ESI) *m/z* 274 $(M + H)^+$.

[00738] Example 21A Step 4: Methyl 2-amino-5-(3-chloropropoxy)-4-methoxybenzoate (6.0 g, 21.9 mmol) in EtOAc was reacted with formamidine hydrochloride in the manner described in Example 16A Step 4 to give 6-(3-chloropropoxy)-4-hydroxy-7-methoxyquinazoline (4.48 g, 16.7 mmol, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 8.00 (s, 1H), 7.47 (s, 1H), 7.15 (s, 1H), 4.19 (t, 2H), 3.97 (s, 3H), 3.81 (t, 2H), 2.27 – 2.19 (m, 2H); LC-MS (ESI) *m/z* 269 $(M + H)^+$.

[00739] Example 21A Step 5: The intermediate 6-(3-chloropropoxy)-4-hydroxy-7-methoxyquinazoline (3.5 g, 13.0 mmol) was reacted with $POCl_3$ in the manner described in Example 4A Step 2 to give 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline (3.2 g, 11.2 mmol, 86%). LC-MS (ESI) *m/z* 287 $(M + H)^+$.

[00740] Example 21B: 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (1.92 g, 6.97 mmol) and 4-chloro-6-(3-chloropropoxy)-7-

methoxyquinazoline from the previous step (2.0 g, 6.97 mmol) were reacted in the manner described in Example 16C to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (2.00 g, 3.8 mmol, 55%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.98 (s, 1H), 8.54 (s, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.38 (t, 1H), 7.33 (s, 1H), 7.26 (d, 1H), 6.96 (d, 1H), 6.47 (s, 1H), 4.27 (t, 2H), 3.98 (s, 3H), 3.82 (t, 2H), 2.30 – 2.24 (m, 2H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 526 $(M + H)^+$.

[00741] Example 21C: In a sealed reaction flask 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.38 mmol) was dissolved in 3 mL of anhydrous DMF, to this solution tetrabutylammonium iodide (140mg, 0.38 mmol) was added followed by N-methylpiperazine (0.127 mL, 1.14 mmol) and the reaction heated at 60°C for 56 hours. At the end of this time 10 mL of water was added and the resulting solid removed by filtration. The solid was purified by reversed phase HPLC using a phenyl-hexyl reverse phase column with a 30-50% ACN/H_2O gradient over 60 minutes. The appropriate peak was concentrated, basified with saturated sodium bicarbonate and extracted twice with ethyl acetate. The extracts were dried with magnesium sulfate, filtered and concentrated to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea as a solid weighing 15.75 mg. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.55 (s, 1H), 7.58 (d, 2H), 7.4 (m, 2H), 7.26 (m, 1H), 6.98 (m, 1H), 6.47 (s, 1H), 4.2 (m, 2H), 3.99 (s, 3H), 2.5-2.2 (m, 9H), 2.11 (s, 3H), 1.99 (m, 2H), 1.27 (s, 9H). LC-MS (ESI) m/z 590 $(M+H)^+$.

Example 22

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yloxy)phenyl)urea

[00742] In the manner described in Example 21C, 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.38 mmol) from Example 21B was reacted with morpholine (99 μL, 1.14 mmol), diisopropylethyl amine (199 μL, 1.14 mmol), and tetrabutyl ammonium iodide (140 mg, 0.38 mmol). After heating at 60°C overnight the reaction was cooled to room temperature, and 10 mL of water added. The resulting precipitate was collected by

filtration and purified by HPLC on a phenyl-hexyl reverse phase column eluting with an acetonitrile/water gradient 35-55% over 60 minutes. The major peak was collected, neutralized to pH-8 with saturated sodium bicarbonate and extracted twice with ethyl acetate. The extracts were combined, dried with magnesium sulfate, and concentrated to a solid. The solid was triturated with 20:1 methanol water and the solid removed by filtration and dried to give 72 mg of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.99 (s, 1H), 8.55 (s, 1H), 7.58 (m, 2H), 7.39 (m, 2H), 7.26 (m, 1H), 6.99 (m, 1H), 6.47 (s, 1H), 4.25 (m, 2H), 3.99 (s, 3H), 3.58 (m, 4H), 2.5-2.35 (m, 6H), 1.97 (m, 2H), 1.30 (s, 9H). LC-MS (ESI) m/z 577 $(M+H)^+$.

Example 23

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00743] The title compound was prepared using the procedure for Example 21C, substituting piperidine (0.113 mL, 1.14 mmol) for the N-methylpiperazine. The title compound (38.76 mg) was isolated. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.07 (s, 1H), 8.55 (s, 1H), 7.58 (d, 2H), 7.40 (m, 2H), 7.25 (m, 1H), 6.98 (m, 1H), 6.48 (s, 1H), 4.23 (m, 2H), 4.00 (s, 3H), 2.4-2.2 (m, 6H), 2.0 (m, 2H), 1.5(m, 4H), 1.3 (m, 11H). LC-MS (ESI) m/z 575 $(M+H)^+$.

Example 24

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea

[00744] The title compound was prepared using the procedure for Example 21C substituting 4-piperidinemethanol (131 mg, 1.14 mmol) for the N-methyl piperazine. Purification was carried out under identical conditions. The title compound (27.3 mg) was isolated. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.55 (s, 1H), 7.57 (d, 2H), 7.38 (m, 2H), 7.27 (m, 1H), 6.95 (m, 1H), 6.47 (s, 1H), 4.39 (m, 1H), 4.2 (m, 2H), 3.95 (s, 3H), 3.20 (m, 2H), 2.90 (m, 2H), 2.49 (m, 2H), 2.1-1.8 (m, 4H), 1.6 (m, 2H), 1.3 (s, 9H), 1.2 (m, 2H); LC-MS (ESI) m/z 605 $(M+H)^+$.

Example 25

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00745] The title compound was prepared using the procedure for Example 21C, substituting 1-methylsulfonyl piperazine (182 mg, 1.14 mmol) for the N-methyl piperazine. Purification was carried out under identical conditions. The title compound (52.69 mg) was isolated. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.7 (s, 1H), 9.1 (s, 1H), 8.55 (s, 1H), 7.58 (d, 2H), 7.37 (m, 2H), 7.23 (m, 1H), 6.97 (m, 1H), 6.47 (s, 1H), 4.23 (m, 2H), 4.00 (s, 3H), 3.10 (m, 4H), 2.82 (s, 3H), 2.00 (m, 2H), 1.37 (s, 9H). LC-MS (ESI) m/z 654 $(M+H)^+$.

Example 26

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea

[00746] The intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea (200 mg, 0.38 mmol) from Example 21B was treated with thiomorpholine-1,1-dioxide (154 mg, 1.14 mmol), tetrabutylammonium iodide (140 mg, 0.38 mmol) and N,N'-diisopropylethylamine (135 μL, 0.76 mmol) in N,N'-dimethylformamide (2 mL). The mixture was heated to 60 °C for 56h and cooled to room temperature. Water was added and the solid filtered off and dried. The crude solid was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) and the obtained solid triturated with water and drops of methanol, then filtered off and dried under high vacuum to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea (46.40 mg, 20%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (bs, 1H), 9.04 (bs, 1H), 8.56 (s, 1H), 7.57 (d, 2H), 7.40-7.37 (m, 2H), 7.25 (d, 1H), 6.97 (d, 1H), 6.47 (s, 1H), 4.25-4.21 (m, 2H), 4.00 (s, 3H), 3.34 (bs, 4H), 2.93 (bs, 4H), 2.68-2.64 (m, 2H), 1.99-1.96 (m, 2H), 1.18 (s, 9H); LC-MS (ESI) *m/z* 625 $(M + H)^+$.

Example 27

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yloxy)phenyl)urea

[00747] Example 27A Step 1: To a solution of 4-(3-chloro-propoxy)-3-methoxy-benzoic acid methyl ester (12 g, 65.8 mmol) and potassium carbonate (36.3

g, 263 mmol) in DMF (100 mL) was added 1-bromo-3-chloro-propane (32.5 mL, 329 mmol). The mixture was stirred at ambient temperature for 15 hours. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate and the ethyl acetate layer was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated to afford 4-(3-chloropropoxy)-3-methoxy-benzoic acid methyl ester (15 g, 88%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.52 (s, 1H), 6.88 (d, 1H), 4.20 (t, 2H), 3.90 (s, 6H), 3.75 (t, 2H), 2.30 (q, 2H).

[00748] Example 27A Step 2: The intermediate from Step 1 (26.4 g, 102 mmol) was taken in acetic acid (185 mL) and acetic anhydride (15 mL) was added. The solution was cooled to 0°C and 90% nitric acid (15 mL) was added. The reaction mixture was stirred for 10-15 minutes at ambient temperature, then heated to 50^0C for 3 hours. Completion of the reaction was monitored by LCMS. The reaction mixture was cooled and was diluted with ethyl acetate. The ethyl acetate layer was washed with aq. sodium bicarbonate, and concentrated to afford the pure compound 4-(3-chloro-propoxy)-5-methoxy-2-nitro-benzoic acid methyl ester (29.14 g, 94%) yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (s, 1H), 7.33 (s, 1H), 4.24 (t, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.77 (t, 2H), 2.21 (q, 2H).

[00749] Example 27A Step 3: To a solution of the intermediate from Step 2 (29.14 g, 95.8 mmol) in ethyl acetate: methanol (3:1, 1L) was added 10% Pd/C (3 g). The mixture was stirred under H_2 for 12 hours. Completion of the reaction was monitored by LCMS. The reaction mixture was filtered using a celite pad and washed with excess ethyl acetate. The filtrate was evaporated to dryness to afford the pure 2-amino-4-(3-chloro-propoxy)-5-methoxy-benzoic acid methyl ester (24.2g, 94%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.13 (s, 1H), 6.43 (s, 2H), 6.39 (s, 1H), 4.04 (t, 2H), 3.80 (t, 2H), 3.74 s, 3H), 3.65 (s, 3H), 2.19 (m, 2H), LC-MS (ESI)m/z 274 $(M+H)^+$.

[00750] Example 27A Step 4: To a solution of the intermediate from Step 3 (4.2 g, 15.35 mmol) in ethanol was added formamidine hydrochloride (2.97 g, 36.96 mmol). The mixture was heated at 140°C in sealed tube for 12h. Completion of the reaction was monitored by LCMS. The precipitate formed was filtered and washed with ethanol and dried to afford the pure compound 7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ol (2.32 g, 56%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ

11.93 (brs, 1H), 7.99 (s, 1H), 7.45 (s, 1H), 7.16 (s, 1H), 4.23 (t, 2H), 3.88 (s, 3H), 3.80 (t, 2H), 2.23 (t, 2H), LC-MS (ESI)m/z 269 $(M+H)^+$.

[00751] Example 27A Step 5: To a solution of the intermediate from Step 4 (3.00 g, 11.16 mmol) in toluene (30 mL) in a pressure vessel was added phosphorous oxychloride (8 mL). The mixture was heated to 125°C for 5 hours. Completion of the reaction was monitored by LCMS. The mixture was concentrated to dryness and excess ethyl acetate was added. The solution was washed with water and brine and was dried (Na_2SO_4) and concentrated to afford the pure compound 4-chloro-7-(3-chloro-propoxy)-6-methoxy-quinazoline (2.51 g, 78 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 4.35 (t, 2H), 4.00 (s, 3H), 3.75 (t, 2H), 2.25 (q, 2H). LC-MS (ESI)m/z 287 $(M+H)^+$.

[00752] Example 27B: To a solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-(3-hydroxy-phenyl)-urea, 300 mg, 1.089 mmol) from Example 1A and (4-chloro-7-(3-chloro-propoxy)-6-methoxy-quinazoline (343.96 mg, 1.119 mmol), from the previous step in THF, was added Cs_2CO_3 (532.2 mg, 1.63 mmol) and the mixture was heated at 50°C for 12 hours. Completion of the reaction was monitored by LCMS. The reaction mixture was diluted with ethyl acetate and the ethyl acetate layer was washed with water and brine successively. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude compound was purified by column chromatography to afford the pure compound 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea, (310 mg, 61%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1H), 9.00 (s, 1H), 8.55 (s, 1H), 7.55 (m, 2H), 7.40 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.35 (t, 2H), 4.00 (s, 3H), 3.85 (2, 2H), 1.30 (s, 9H); LC-MS (ESI)m/z 526 $(M+H)^+$.

[00753] Example 27C: In a sealed reactor (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from the previous step (300 mg, 0.57 mmol) was dissolved in 10 mL of dry DMF. To this solution was added diisopropylethyl amine (220 mg, 1.7 mmol), tetrabutylammonium iodide (210 mg, 0.57 mmol) and morpholine (149 mg, 1.7 mmol). The reaction was heated to 60°C for 48 hours. The solution was then poured into 100 mL of water and extracted three times with ethyl acetate, the extracts combined, washed with brine, dried with magnesium sulfate, filtered and concentrated. The resulting oil was purified using silica gel chromatography eluting with a methanol/dichloromethane

gradient 1-12% over 18 column volumes. The appropriate peak was concentrated, then dissolved in 13 mL of dichloromethane. To this was added 3 mL of 1M HCl in ether and the solution concentrated to a solid. The solid was dissolved in a minimal amount of methanol and the salt precipitated by adding ether. The resulting precipitate was collected by vacuum filtration to afford the title compound (264 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.7 (s, 1H), 9.76 (s, 1H), 9.56 (s, 1H), 8.66 (s, 1H), 7.62 (m, 2H), 7.5-7.3 (m, 2H), 7.28 (m, 1H), 6.95 (m, 1H), 6.48 (s, 1H), 4.36 (m, 2H), 4.04 (s, 6H), 3.54 (m, 4H), 3.30 (m, 3H), 3.2 (m, 2H), 2.3 (m, 3H), 1.30 (s, 9H). LCMS (ESI) m/z 577 (M+H)

Example 28

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00754] To a solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea (225 mg, 0.427 mmol) from Example 27B in DMF (3 mL) was added N-methyl piperazine (0.142 mL, 1.281 mmol) followed by diisopropyl ethylamine (0.223 mL, 1.281 mmol) and tetrabutyl ammonium iodide (157.72 mg, 0.427 mmol). The reaction mixture was heated at 60^{0}C for 15 h. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using a phenyl-hexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN). The appropriate fractions were concentrated followed by trituration with ether to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea (46 mg, 18%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.25 (s, 1H), 8.55 (s, 1H), 7.60 (d, 2H), 7.40 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.50 (s, 1H), 4.25 (m, 2H), 3.98 (s, 3H), 2.55-2.30 (m, 10H), 2.15 (s, 3H), 1.98 (m,2H), 1.28 (s, 9H); LC-MS (ESI)m/z 590 $(M+H)^+$.

Example 29

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-hydroxymethyl) piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00755] In the manner described in Example 28 (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea (225 mg, 0.427 mmol) from Example 27B was reacted with piperidin-4-yl-methanol (147 mg,

1.281 mmol) to yield 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-hydroxymethyl) piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea (86 mg, 33%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.55 (s, 1H), 7.55 (d, 2H), 7.35 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.40 (m, 1H), 4.22 (m, 2H), 4.00 (s, 3H), 3.22 (m, 2H), 2.80 (d, 2H), 2.45 (m, 2H), 2.10-1.85 (m, 4H), 1.65 (d, 2H), 1.30 (s, 10H), 1.15 (m 2H); LC-MS (ESI)m/z 605 $(M+H)^+$.

Example 30

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00756] To a solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 27B (225 mg, 0.427 mmol) in DMF (3 mL) was added 2-piperazin-1-yl-ethanol (0.157 mL, 1.281 mmol) followed by diisopropylethylamine (0.223 mL, 1.281 mmol) and tetrabutylammonium iodide (157.72 mg, 0.427 mmol). The reaction mixture was heated at 60°C for 2 days. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using phenyl-hexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea (68 mg, 26%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.45 (brs, 2H), 8.55 (s, 1H), 7.55 (d, 2H), 7.35 (d, 2H), 7.25 (d, 1H), 6.85 (d, 1H), 6.45 (s, 1H), 4.20 (m, 2H), 3.88 (s, 3H), 3.45 (m, 2H), 2.50-2.25 (m, 12H), 2.00 (m,2H), 1.25 (s, 9H); LC-MS (ESI)m/z 620 $(M+H)^+$.

Example 31

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(3-hydroxy-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea

[00757] In the manner described in Example 28 (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea (225 mg, 0.427 mmol) from Example 27B was reacted with pyrrolidin-3-ol (0.103 mL, 1.281 mmol) to yield 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(3-hydroxy-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea (16 mg, 4%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1H), 9.28 (s, 1H), 8.52 (s, 1H), 7.55 (d, 2H), 7.35 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.70 (brs, 1H), 4.25 (m, 3H), 3.95 (s, 3H), 2.80-2.30 (m, 6H),1.95 (m, 2H), 1.55 (m, 2H), 1.30 (s, 9H); LC-MS (ESI) m/z 577 $(M+H)^+$.

Example 32

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00758] In the manner described in Example 30 (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 27B (225 mg, 0.427 mmol) was reacted with 1-methanesulfonyl-piperazine (140.2 mg, 0.854 mmol) to yield 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methyl sulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea (51mg, 18%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1H), 9.05 (s, 1H), 8.55 (s, 1H), 7.58 (d, 2H), 7.35 (m, 2H), 7.22 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.25 (m, 2H), 3.98 (s, 3H), 3.15 (m, 5H), 2.88 (s, 4H), 2.55 (m, 4H), 2.00 (m, 2H), 1.25 (s, 9H); LC-MS (ESI) m/z 654 $(M+H)^+$.

Example 33

Preparation of (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00759] A stirred solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 27B (102 mg, 0.194 mmol), (S)-3-pyrrolidinol (51 mg, 0.582 mmol), *N*, *N*-diisopropylethylamine (75 mg, 0.582 mmol) and tetrabutylammonium iodide (71 mg, 0.194 mmol) in dry *N*, *N*-dimethylformamide (5 mL) was heated at 60 °C for 20 h. After cooling to room temperature, the reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL) and the organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative HPLC (using a phenyl-hexyl reverse phase column, eluted with gradient of solvent B = 0.05% HOAC/CH_3CN and solvent A = 0.05% HOAc/H_2O). The combined fractions were washed with saturated aqueous $NaHCO_3$ and the aqueous

layer extracted with a mixture of 20% methanol in dichloromethane (2 x 50 mL). Concentration under reduced pressure afforded (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea as a colorless solid (16 mg, 14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (brs, 1H), 7.68 (brs, 1H), 7.52-7.55 (m, 2H), 7.26-7.35 (m, 4H), 6.95 (m, 1H), 6.11 (s, 1H), 4.34-4.40 (m, 3H), 4.04 (s, 3H), 3.00-3.20 (m, 2H), 2.84 (m, 1H), 2.67-2.68 (m, 2H), 2.50 (m, 1H), 2.10-2.30 (m, 3H), 1.80 (m, 1H), 1.51 (m, 1H), 1.26 (s, 9H); LC-MS (ESI) *m/z* 577 $(M + H)^+$.

Example 34

Preparation of (R)-1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00760] (1-(5-Tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea (210 mg, 0.4 mmol) from Example 27B was treated with (*R*)-(+)-3-pyrrolidinol (65 μL, 0.8 mmol), tetrabutylammonium iodide (148 mg, 0.4 mmol) and N,N'-diisopropylethylamine (69 μL, 0.4 mmol) in N,N'-dimethylformamide (4 mL). The mixture was stirred at 50°C for 5h. After cooling to room temperature water (4 mL) was added and the precipitating solid filtered off and dried. The solid residue was purified by preparative HPLC (phenylhexyl reverse phase column). The obtained solid was triturated with water to give (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea (37.76 mg, 16%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.10 (s, 1H), 8.55 (s, 1H), 7.58-7.56 (m, 2H), 7.40-7.38 (m, 2H), 7.25 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.70 (s, 1H), 4.31-4.20 (m, 3H), 3.99 (s, 3H), 3.32 (s, 1H), 2.81-2.69 (m, 2H), 2.40-2.19 (m, 3H), 2.10-1.98 (m, 3H), 1.67-1.4 (m, 1H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 577 $(M + H)^+$.

Example 35

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea

[00761] Example 35A Step 1: To a solution of 4-hydroxy-3-methoxy-benzoic acid methyl ester (10 g, 54.8 mmol) and potassium carbonate (22.75 g, 164.4 mmol) in DMF (100 mL) was added 1-bromo-2-chloro-ethane (22.7 mL, 274 mmol). The

mixture was heated at 70°C for 3h and monitored by TLC. The reaction mixture was diluted with ethyl acetate and washed the ethyl acetate layer with water and brine. The organic layer was dried (Na_2SO_4) and concentrated to afford 4-(2-chloro-ethoxy)-3-methoxy-benzoic acid methyl ester (13.1 gm, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H), 7.55 (s, 1H), 6.90 (d, 1H), 4.35 (t, 2H), 3.90 (m, 8H).

[00762] Example 35A Step 2: The intermediate 4-(2-chloro-ethoxy)-3-methoxy-benzoic acid methyl ester (2.7 g, 11.03 mmol) was taken in acetic acid (30 mL) and acetic anhydride (6 mL) was added. The solution was cooled to 0^0C and 90% nitric acid (2 mL) was added. The reaction mixture was stirred for 10-15 minutes at ambient temperature, then heated to 50°C for 2h. Completion of the reaction was monitored by TLC. The reaction mixture was cooled and was poured on to crushed ice. The precipitate formed was filtered and was dried to afford the pure 4-(2-chloro-ethoxy)-5-methoxy-2-nitro-benzoic acid methyl ester (2.73 g, 85 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (s, 1H), 7.35 (s, 1H), 4.42 (t, 2H), 4.10-3.90 (m, 5H), 3.80 (m, 3H).

[00763] Example 35A Step 3: To a solution of 4-(2-chloro-ethoxy)-5-methoxy-2-nitro-benzoic acid methyl ester (2.7 g, 9.32 mmol) in ethyl acetate (30 mL) was added 10% Pd/C (405 mg) and the mixture was stirred under H_2 for 12 h. Completion of the reaction was monitored by LCMS. The reaction mixture was filtered using a celite pad and was washed with excess ethyl acetate and evaporated to dryness to afford the pure 2-amino-4-(2-chloro-ethoxy)-5-methoxy-benzoic acid methyl ester (2.40g, 99%)' as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (s, 1H), 6.40 (s, 2H), 6.35 (s, 1H), 4.18 (t, 2H), 3.95 (t, 2H), 3.70 s, 3H), 3.65 (s, 3H), LC-MS (ESI) *m/z* 260 $(M+H)^+$.

[00764] Example 35A Step 4: To a solution of 2-amino-4-(2-chloro-ethoxy)-5-methoxy-benzoic acid methyl ester (2.4 g, 9.24 mmol) in ethanol was added formamidine hydrochloride (2.97 g, 36.96 mmol). The mixture was heated at 130°C in sealed tube for 8 h. The precipitate formed was filterd and washed with ethanol and dried to afford the pure compound 7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ol (2.25 g, 96%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.45 (s, 2H), 7.15 (s, 1H), 4.40 (t, 2H), 4.00 (t, 2H), 3.88 (s, 3H), LC-MS (ESI) *m/z* 255 $(M+H)^+$.

[00765] Example 35A Step 5: To a solution of 4-chloro-7-(2-chloro-ethoxy)-6-methoxy-quinazoline 4-chloro-7-(2-chloro-ethoxy)-6-methoxy-quinazoline (3.00 g,

11.77 mmol) in toluene (25 mL) in a pressure vessel was added phosphorous oxychloride (5 mL) and the mixture was heated to 125°C for 5h. Completion of the reaction was monitored by LCMS. The mixture was evaporated to dryness, then excess ethyl acetate was added. The solution was washed with water and brine, and dried (Na_2SO_4) then concentrated to afford the pure compound 4-chloro-7-(2-chloro-ethoxy)-6-methoxy-quinazoline (2.5 g, 78 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 7.45 (s, 1H), 7.35 (s, 1H), 4.50 (t, 2H), 4.05 (t, 2H), 3.95 (s, 3H). LC-MS (ESI) *m/z* 273 $(M+H)^+$.

[00766] Example 35B: To a solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-(3-hydroxy-phenyl)-urea, 300.13 mg, 1.098 mmol) from Example 1A and (4-chloro-7-(2-chloro-ethoxy)-6-methoxy-quinazoline from the previous step (300 mg, 1.098 mmol) in THF was added Cs_2CO_3 (532.7 mg, 1.64 mmol), and the mixture was heated at 50°C for 12 h. Completion of the reaction was monitored by LCMS. The reaction mixture was diluted with ethyl acetate and the solution was washed with water and brine successively. The organic layer was dried (Na_2SO_4) and concentrated to dryness to afford the pure compound 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea (525 mg, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.55 (s, 1H), 7.57 (s, 2H), 7.40 (m, 2H), 7.22 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.50 (m, 2H), 4.00 (m, 5H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 512 $(M+H)^+$.

[00767] Example 35C: To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 35B (225 mg, 0.439 mmol) in DMF (3 mL) was added morpholine (114.86 mg, 1.318 mmol) followed by diisopropylethylamine (0.229 mL, 1.318 mmol) and tetrabutylammonium iodide (162.3 mg, 0.439 mmol). The reaction mixture was heated at 60^{0}C for 3 days. Formation of product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea (51 mg, 21 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.55 (s, 1H), 7.60-7.35 (m, 4H), 7.25 (m, 1H), 6.95 (m, 1H), 6.45 (s,1H), 4.32 (m, 2H), 3.95 (s, 3H), 3.62 (m, 4H), 2.85 (m, 2H), 2.65-2.45 (m, 4H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 563 $(M+H)^+$.

Example 36

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea

To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 35B (225 mg, 0.439 mmol) in DMF (3 mL) was added N-methyl piperazine (0.146 mL, 1.317 mmol) followed by diisopropyl ethylamine (0.229 mL, 1.317 mmol) and tetrabutyl ammonium iodide (162.15 mg, 0.439 mmol). The reaction mixture was heated at 60^0C for 2 days. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea (21mg, 8%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.32 (s, 1H), 8.55 (s, 1H), 7.55 (d, 2H), 7.40 (m, 2H), 7.25 (s, 1H), 6.98 (m, 1H), 6.48 (s, 1H), 4.30 (m, 2H), 4.00 (s, 3H), 2.82-2.25 (m, 10H), 2.15 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 576 $(M+H)^+$.

Example 37

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea

1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 35B (225 mg, 0.427 mmol) and piperidin-4-yl-methanol (0.103 mL, 1.281 mmol) were reacted in the manner described in Example 36 to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea (41 mg, 16%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.15 (s, 1H), 8.55 (s, 1H), 7.55 (d, 2H), 7.38 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.45 (brs, 1H), 4.30 (m, 2H), 3.98 (s, 3H), 3.25 (m, 2H), 3.00 (m, 2H), 2.75 (m, 2H), 2.00 (m, 2H), 1.65 (d, 2H), 1.25 (s, 10H), 1.15 (m, 2H); LC-MS (ESI) m/z 591 $(M+H)^+$.

Example 38

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00768] 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 35B (225 mg, 0.427 mmol) and 2-piperazin-1-yl-ethanol (0.161 mL, 1.317 mmol) were reacted in the manner described in Example 36. 1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea (33 mg, 13%) was isolated as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (brs, 1H), 9.25 (brs, 1H), 8.52 (s, 1H), 7.55 (s, 2H), 7.35 (m, 2H), 7.25 (m, 1H), 6.95 (d, 1H), 6.45 (s, 1H), 4.40 (s, 1H), 4.30 (m, 2H), 3.95 (s, 3H), 3.45 (m, 2H), 2.85-2.30 (m, 12H), 1.25 (m, 9H); LC-MS (ESI) *m/z* 606 $(M+H)^+$.

Example 39

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea

[00769] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-yloxy]-phenyl}-urea from Example 35B (225 mg, 0.439 mmol) in DMF (3 mL) was added thiomorpholine-1,1-dioxide (178 mg, 1.317 mmol) followed by diisopropylethylamine (0.229 mL, 1.317 mmol) and tetrabutylammonium iodide (162.15 mg, 0.439 mmol). The reaction mixture was heated at 60°C for 5 days. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using phenyl-hexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea (29 mg, 11%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80-9.15 (brs, 2H), 8.52 (s, 1H), 7.55 (d, 2H), 7.35 (m, 2H), 7.25 (d, 1H), 6.92 (d, 1H), 6.45 (s, 1H), 4.30 (m, 2H), 3.95 (s, 3H), 3.20-3.00 (m, 8H), 2.60 (m, 2H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 611 $(M+H)^+$.

Example 40

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea

[00770] Example 40A Step 1: To 5-hydroxy-2-nitrobenzaldehyde (1.0 g , 6.0 mmol) in 2.5M NaOH(aq) (10 mL) at 100°C was added 35% H_2O_2 (12 mL) dropwise over 10 minutes and the mixture heated at reflux overnight. The solution was

acidified with 10% H_2SO_4, extracted with EtOAc (2 x 100 mL), and the combined organic layers washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 5-hydroxy-2-nitrobenzoic acid (1.03 g, 5.63 mmol, 94%). LC-MS (ESI) *m/z* 182 $(M - H)^+$.

[00771] Example 40A Step 2: To MeOH (125 mL) was added 5-hydroxy-2-nitrobenzoic acid (1.02 g, 5.6 mmol) followed by dropwise addition of thionyl chloride (~4 mL) and the mixture heated at reflux overnight. The solution was cooled to room temperature, concentrated *in vacuo*, reconcentrated twice from MeOH, dissolved in EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give methyl 5-hydroxy-2-nitrobenzoate (1.09 g, 5.5 mmol, 98%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.05 (d, 1H), 7.03 (d, 1H), 7.01 (s, 1H), 3.82 (s, 3H); LC-MS (ESI) *m/z* 196 $(M - H)^+$.

[00772] Example 40A Step 3: To methyl 5-hydroxy-2-nitrobenzoate (1.08 g, 5.5 mmol) in DMF (50 mL) was added potassium carbonate (1.52 g, 11 mmol) followed by 1-bromo-2-methoxyethane (1.55 mL, 16.4 mmol) and the mixture heated at 60°C overnight. After cooling to room temperature, the reaction was diluted with H_2O, extracted with EtOAc, and the organic layer washed with H_2O and brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (12-100% EtOAc/hexanes) to give methyl 5-(2-methoxyethoxy)-2-nitrobenzoate (1.08 g, 4.2 mmol, 77%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (d, 1H), 7.31 (s, 1H), 7.29 (d, 1H), 4.29 (dd, 2H), 3.86 (s, 3H), 3.68 (dd, 2H), 3.31 (s, 3H); LC-MS (ESI) *m/z* 256 $(M + H)^+$.

[00773] Example 40A Step 4: To methyl 5-(2-methoxyethoxy)-2-nitrobenzoate (1.08 g, 4.2 mmol) under argon was added 10% Palladium on carbon and MeOH (20 mL). The flask was flushed with H_2(g) and stirred under H_2 (1 atm) for 30 minutes. The mixture was filtered through Celite and concentrated *in vacuo* to give methyl 2-amino-5-(2-methoxyethoxy)benzoate (964 mg, 4.2 mmol, 100%). LC-MS (ESI) *m/z* 226 $(M + H)^+$.

[00774] Example 40A Step 5: To methyl 2-amino-5-(2-methoxyethoxy)benzoate (964 mg, 4.2 mmol) in absolute EtOH (25 mL) was added formamidine hydrochloride (1.4 g, 17.2 mmol) and the mixture heated in a sealed tube at 130°C overnight. The mixture was cooled to room temperature and filtered to give 4-hydroxy-6-(2-methoxyethoxy)quinazoline (871 mg, 4.0 mmol, 95%). ^1H NMR (300

MHz, DMSO-d_6) δ 8.42 (br s, 1H), 7.99 (s, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.43 (dd, 1H), 4.21 (dd, 2H), 3.70 (dd, 2H), 3.32 (s, 3H); LC-MS (ESI) *m/z* 221 $(M + H)^+$.

[00775] Example 40A Step 6: 4-hydroxy-6-(2-methoxyethoxy)quinazoline (870 mg, 3.9 mmol) was reacted with $POCl_3$ as described in Example 4A Step 2 to give 4-chloro-6-(2-methoxyethoxy)quinazoline (662 mg, 2.8 mmol, 71%). LC-MS (ESI) *m/z* 239 $(M + H)^+$.

[00776] Example 40B: The title compound was prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea from Example 1A (138 mg, 0.5 mmol) and 4-chloro-6-(2-methoxyethoxy)quinazoline from Example 40A Step 5 (119 mg, 0.5 mmol) using the procedure of Example 16C. The crude product was purified by column chromatography (25-100% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea (45 mg, 0.094 mmol, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.62 (s, 1H), 7.94 (d, 1H), 7.74 – 7.64 (m, 3H), 7.60 (s, 1H), 7.42 (t, 1H), 7.27 (d, 1H), 6.99 (d, 1H), 6.48 (s, 1H), 4.37 – 4.31 (m, 2H), 3.78 – 3.71 (m, 2H), 3.34 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + H)^+$.

Example 41

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00777] Example 41A Step 1: To DMF (80 mL) was added potassium carbonate (5.7 g, 41.1 mmol) and methyl 3-hydroxy-4-methoxybenzoate (5.0 g, 27.4 mmol). The mixture was cooled to 0°C and 1-bromo-3-chloropropane (8.64 g, 57.9 mmol) in DMF (10 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to room temperature overnight. After removing most of the DMF *in vacuo*, the remaining oil was diluted with H_2O and filtered to give methyl 3-(3-chloropropoxy)-4-methoxybenzoate (6.65 g, 25.8 mmol, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 (d, 1H), 7.47 (s, 1H), 7.09 (d, 1H), 4.12 (t, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (t, 2H), 2.23 – 2.15 (m, 2H); LC-MS (ESI) *m/z* 259 $(M + H)^+$.

[00778] Example 41A Step 2: In the manner described in Example 16A Step 2 methyl 3-(3-chloropropoxy)-4-methoxybenzoate (6.65 g, 25.7 mmol) was reacted with nitric acid to give methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate (6.70 g, 22.1 mmol, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.37 (s, 1H), 4.26 (t, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 (t, 2H), 2.26 – 2.18 (m, 2H).

[00779] Example 41A Step 3: In the manner described in Example 16A Step 3, methyl 5-(3-chloropropoxy)-4-methoxy-2-nitrobenzoate (6.70 g, 22.1 mmol) in EtOAc (100mL) was reacted with 10% palladium on carbon as described in Example 16A Step 3 to give methyl 2-amino-5-(3-chloropropoxy)-4-methoxybenzoate (6.0 g, 22.0 mmol, 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18 (s, 1H), 6.49 (br s, 2H), 6.37 (s, 1H), 3.93 (t, 2H), 3.82 – 3.71 (m, 8H), 2.14 – 2.06 (m, 2H); LC-MS (ESI) *m/z* 274 $(M + H)^+$.

[00780] Example 41A Step 4: In the manner described in Example 16A Step 4, methyl 2-amino-5-(3-chloropropoxy)-4-methoxybenzoate (6.0 g, 21.9 mmol) in EtOAc from the previous step was reacted with formamidine hydrochloride as in Example 16A Step 4 to give 6-(3-chloropropoxy)-4-hydroxy-7-methoxyquinazoline (4.48 g, 16.7 mmol, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 8.00 (s, 1H), 7.47 (s, 1H), 7.15 (s, 1H), 4.19 (t, 2H), 3.97 (s, 3H), 3.81 (t, 2H), 2.27 – 2.19 (m, 2H); LC-MS (ESI) *m/z* 269 $(M + H)^+$.

[00781] Example 41B Step 1: To N,N-dimethylformamide (40 mL, purged with argon) was added cesium carbonate (1.43 g, 4.4 mmol) and 6-(3-chloropropoxy)-4-hydroxy-7-methoxyquinazoline from the previous step (1.08 g, 4.0 mmol), at which point methanethiol (g) was bubbled into the reaction for 10 minutes. The mixture was stirred at room temperature for an additional 60 minutes, poured into H_2O and filtered to give 4-hydroxy-7-methoxy-6-(3-(methylthio)propoxy)quinazoline (877 mg, 3.13 mmol, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 7.99 (s, 1H), 7.45 (s, 1H), 7.13 (s, 1H), 4.14 (t, 2H), 3.91 (s, 3H), 2.64 (t, 2H), 2.05 (s, 3H), 2.04 – 1.97 (m, 2H); LC-MS (ESI) *m/z* 281 $(M + H)^+$.

[00782] Example 41B Step 2: To dichloromethane (20 mL) at 0°C was added 4-hydroxy-7-methoxy-6-(3-(methylthio)propoxy)quinazoline (870 mg, 3.1 mmol) followed by 3-chloroperbenzoic acid (2.7 g, 15.7 mmol). The solution was stirred for10 minutes, diluted with DCM, and filtered to give 4-hydroxy-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline (710 mg, 2.28 mmol, 73%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 8.00 (s, 1H), 7.45 (s, 1H), 7.15 (s, 1H), 4.19 (t, 2H), 3.91 (s, 3H), 3.30 (t, 2H), 3.05 (s, 3H), 2.26 – 2.15 (m, 2H); LC-MS (ESI) *m/z* 313 $(M + H)^+$.

[00783] Example 41B Step 3: The intermediate 4-hydroxy-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline (700 mg, 2.24 mmol) from the previous step was reacted with $POCl_3$ in the manner described in Example 4A Step 2 to give 4-

chloro-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline (480 mg, 1.45 mmol, 65%). LC-MS (ESI) *m/z* 331 $(M + H)^+$.

[00784] Example 41C: 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (124 mg, 0.45 mmol) from Example 1A was treated with cesium carbonate (294 mg, 0.90 mmol) in anhydrous tetrahydrofuran (2.5 mL). The mixture was stirred at room temperature for 30 minutes. 4-chloro-7-methoxy-6-(3-(methylsulfonyl)propoxy) quinazoline from the previous step (149 mg, 0.45 mmol) was then added to the suspension and the mixture heated to 60°C for 2h. After cooling to room temperature the crude mixture was taken in ethyl acetate/water and extracted. The organic fractions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative HPLC (phenylhexyl reverse phase column) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy) quinazolin-4-ylthio)phenyl)urea (10.3 mg, 4%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.08 (s, 1H), 8.57 (s, 1H), 7.58 (s, 2H), 7.43-7.38 (m, 2H), 7.27 (d, 1H), 6.97 (d, 1H), 6.48 (s, 1H), 4.34-4.32 (m, 2H), 4.02 (s, 3H), 3.33-3.30 (m, 2H), 3.06 (s, 3H), 3.29-3.27 (m, 2H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 570 $(M + H)^+$.

[00785]

Example 42

Preparation of 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-yloxy)phenyl)urea

[00786] Example 42A Step 1: Prepared from ethyl 2-isobutyrate (10g, 74.62 mmol) according to the method described for 4-methyl-3-oxopentanenitrile in Example 122A Step 1, to afford 4-fluoro-4-methyl-3-oxopentanenitrile as a yellow oil (8 g, 83%) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 2H), 1.54 (d, J = 21 Hz, 6H).

[00787] Example 42A Step 2: Prepared from 4-fluoro-4-methyl-3-oxopentanenitrile (6 g, 47 mmol) according to the method described for 3-isopropylisoxazol-5-amine in Example 122A Step 2, to afford 3-(2-fluoropropan-2-yl)isoxazol-5-amine as a light yellow solid (4.83 g, 71%) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.48 (brs, 2H), 1.68 (d, J = 21 Hz, 6H); LC-MS (ESI) *m/z* 145 $(M + H)^+$.

[00788] Example 42A Step 3: Prepared from 3-(2-fluoropropan-2-yl)isoxazol-5-amine (4.83 g, 33.54 mmol) according to the method described for phenyl 3-

isopropylisoxazol-5-ylcarbamate in Example 122A Step 3, to afford phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate as a colorless solid (6.04 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (brs, 1H), 7.39-7.45 (m, 2H), 7.18-7.32 (m, 3H), 6.27 (s, 1H), 1.74 (d, J = 21 Hz, 6H); LC-MS (ESI) *m/z* 265 $(M + H)^+$.

[00789] Example 42B: To THF (10 mL) was added phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate from the previous step (500 mg, 1.9 mmol), 3-aminophenol (207 mg, 1.9 mmol) and dimethylaminopyridine (60 mg, 0.5 mmol) and the mixture stirred overnight at room temperature. The mixture was concentrated *in vacuo* and purified by chromatography on silica gel (10 – 50% EtOAc/hexanes) to afford 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-hydroxyphenyl)urea (390 mg, 1.4 mmol, 74%). LC-MS (ESI) *m/z* 280 $(M + H)^+$.

[00790] Example 42C: The title compound was prepared from 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-hydroxyphenyl)urea (84 mg, 0.3 mmol) and 4-chloro-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline from Example 41B Step 1 (76 mg, 0.23 mmol) using the procedure described in Example 16C. The crude product was purified by chromatography on silica gel (25 – 100% EtOAc/hexanes) to afford 1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-yloxy)phenyl)urea (81 mg, 0.14 mmol, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (br s, 1H), 9.11 (s, 1H), 8.57 (s, 1H), 7.63 – 7.58 (m, 2H), 7.47 – 7.40 (m, 2H), 7.32 (d, 1H), 7.00 (d, 1H), 6.15 (s, 1H), 4.32 (t, 2H), 4.02 (s, 3H), 3.41 – 3.29 (m, 2H), 3.06 (s, 3H), 2.31 – 2.22 (m, 2H), 1.66 (d, 6H); LC-MS (ESI) *m/z* 574 $(M + H)^+$.

Example 43

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea

[00791] Example 43A: 7-(Benzyloxy)quinazolin-4(3H)-one (5 g, 19.8 mmol) was treated with thionyl chloride (50 mL) and anhydrous N,N'-dimethylformamide (0.5 mL) and heated to 80 °C for 1.5h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane, cooled to 0 °C and the pH adjusted to basic (pH = 8) with a saturated solution of sodium bicarbonate. The organic layer was separated, the water extracted with ethyl acetate and the organics combined, dried ($MgSO_4$) and concentrated under reduced pressure to give 7-

(benzyloxy)-4-chloroquinazoline (4.75 g, 89%), which was used directly in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.18 (d, 1H), 7.97-7.46 (m, 4H), 7.46-7.35 (m, 4H), 5.35 (s, 2H); LC-MS (ESI) *m/z* 271 (M + H)$^+$.

[00792] Example 43B Step 1: Following to the procedure described in Example 41C, 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (1.02 g, 3.7 mmol) from Example 1A was reacted with 7-(benzyloxy)-4-chloroquinazoline (1 g, 3.7 mmol) and cesium carbonate (24 g, 7.4 mmol) in anhydrous tetrahydrofuran (10 mL) and the mixture was heated at 50 °C overnight. The crude product was triturated with dichloromethane to give 1-(3-(7-(benzyloxy)quinazolin-4-yloxy)phenyl)-3-(5-tert-butylisoxazol-3-yl)urea (725 mg, 38%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.65 (s, 1H), 8.29 (d, 1H), 7.57-7.38 (m, 9H), 7.28 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 5.37 (s, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 510 (M + H)$^+$.

[00793] Example 43B Step 2: 1-(3-(7-(Benzyloxy)quinazolin-4-yloxy)phenyl)-3-(5-tert-butylisoxazol-3-yl)urea (725 mg, 1.42 mmol) was treated with trifluoroacetic acid (7 mL) and heated at 85 °C for 3h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate/water. The solution was neutralized with saturated sodium bicarbonate (pH = 8) and the organic layer separated. After extraction of the aqueous phase with ethyl acetate, the organic fractions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The solid was triturated with ethyl acetate to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxyquinazolin-4-yloxy)phenyl)urea (358 mg, 60%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 9.64 (s, 1H), 9.07 (s, 1H), 8.58 (s, 1H), 8.24 (d, 1H), 7.57 (s, 1H), 7.41 (t, 1H), 7.30 (d, 2H), 7.20 (s, 1H), 6.97 (d, 1H) 6.49 (s, 1H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 420 (M + H)$^+$.

[00794] Example 43B Step 3: 1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-hydroxyquinazolin-4-yloxy)phenyl)urea (126 mg, 0.3 mmol) was treated with cesium carbonate (117 mg, 0.36 mmol) in anhydrous N,N'-dimethylformamide (3 mL) and stirred at room temperature for 30 minutes. 2-Bromoethylmethyl ether (50 mg, 0.36 mmol) was added and the mixture was stirred at 50 °C overnight. Cesium carbonate was filtered off and the residue purified by preparative HPLC (phenylhexyl reverse phase column) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-

methoxyethoxy)quinazolin-4-yloxy)phenyl)urea (21.16mg, 15%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (bs, 1H), 9.00 (bs, 1H), 8.65 (s, 1H), 8.27 (d, 1H), 7.57 (s, 1H), 7.41-7.38 (m, 3H), 7.28 (d, 1H), 6.98 (d, 1H), 6.48 (s, 1H), 4.34 (bs, 2H), 3.76 (bs, 2H), 3.35 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + H)^+$.

Example 44

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00795] Example 44A Step 1: To DMSO (2.75 mL, 38.3 mmol) was added 3-aminothiophenol (4.07 mL, 38.3 mmol) and the mixture was heated at 90°C for 4 hours and then poured into 6N HCl (40 mL). The yellow solid was filtered and dried under vacuum to give 3,3'-disulfanediyldianiline-xHCl (6.7 g, 17-23 mmol). LC-MS (ESI) *m/z* 249 $(M + H)^+$.

[00796] Example 44A Step 2: To DMF (50 mL) was added triethylamine (10 mL), 3,3'-disulfanediyldianiline-xHCl (1.98 g) and 5-tert-butyl-3-isocyanatoisoxazole (1.81 g, 11 mmol), and the mixture heated at 50°C overnight. After cooling to room temperature , the reaction was poured into H_2O, extracted with EtOAc (2 x 250 mL), and the combined org layers were washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (25 – 100% EtOAc/hexanes) to give 1,1'-(3,3'-disulfanediylbis(3,1-phenylene))bis(3-(5-tert-butylisoxazol-3-yl)urea) (2.2 g, 3.8 mmol). LC-MS (ESI) *m/z* 581 $(M + H)^+$.

[00797] Example 44A Step 3: To glacial acetic acid (40 mL) was added 1,1'-(3,3'-disulfanediylbis(3,1-phenylene))bis(3-(5-tert-butylisoxazol-3-yl)urea) (2.2 g, 3.8 mmol) and Zinc dust (1.24 g, 19 mmol). The mixture was heated at 50°C overnight, cooled to r.t, and the AcOH decanted and concentrated. The crude solid was sonicated in 1N aqueous $NaHSO_4$, extracted with EtOAc, the organic layer dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (15 – 50% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea (1.08 g, 3.7 mmol, 49%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.79 (s, 1H), 7.50 (s, 1H), 7.20 – 7.09 (m, 2H), 6.91 (d, 1H), 6.50 (s, 1H), 5.50 (br s, 1H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 291 $(M + H)^+$.

[00798] Example 44B: To a suspension of sodium hydride (11mg, 0.44 mmol) in anhydrous tetrahydrofuran (2 mL) cooled to 0 °C, was added 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea from the previous step (117 mg, 0.40 mmol) as a solution in tetrahydrofuran (1 mL) and the mixture stirred at 0 °C for 30 minutes. To this suspension 4-chloro-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline from Example 41B Step 1 (133 mg, 0.40 mmol) was added and the resulting mixture was stirred at 0 °C and slowly allowed to reach room temperature. After stirring for additional 1h, the mixture was taken up in ethyl acetate/water and extracted. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea (10.30 mg, 4%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.73 (bs, 1H), 9.19 (bs, 1H), 8.70 (s, 1H), 7.85 (s, 1H), 7.53-7.27 (m, 5H), 6.49 (s, 1H), 4.32 (bs, 2H), 4.01 (s, 3H), 3.35 (2H), 3.07 (s, 3H), 2.28 (bs, 2H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 586 $(M + H)^+$.

Example 45

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea

[00799] 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (223 mg, 0.83 mmol) was treated with cesium carbonate (325 mg, 1.0 mmol) in anhydrous tetrahydrofuran (8 mL). The mixture was stirred at room temperature for 30 minutes. 4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline (149 mg, 0.45 mmol) from Example 15A was added to the suspension and the mixture heated to 50 °C overnight. After cooling to room temperature the mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography (ethyl acetate/dichloromethane 1:1) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea (218 mg, 50%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.52-7.27 (m, 5H), 6.49 (s, 1H), 4.32 (bs, 2H), 4.00 (s, 3H), 3.77 (bs, 2H), 3.36 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 524 $(M + H)^+$.

Example 46

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea

[00800] To a slurry of sodium hydride (53 mg, 2.2 mmol) in THF (20 mL) was added the thiol described in Example 44A (582 mg, 2.0 mmol), prepared as described previously, and the solution stirred at r.t until gas evolution ceased. After an additional 30 minutes of stirring, 4-chloro-6,7-dimethoxyquinazoline (448 mg, 2.0 mmol) was added. After stirring at r.t for 4 hours, the reaction was concentrated in vacuo. The resulting solid was diluted with EtOAc, the organic layer washed with aqueous sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (25-100% EtOAc/hexanes) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea as a white solid. The compound was dissolved in EtOAc (5 mL) and 4N HCl in dioxane (0.2 mL, 0.8 mmol) was added. The mixture was sonicated, stirred and concentrated *in vacuo* to give the product (300 mg, 0.58 mmol, 29%) as the mono-hydrochloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.50 (s, 1H), 8.79 (s, 1H), 7.86 (s, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.38 (s, 2H), 7.30 (d, 1H), 6.50 (s, 1H), 4.00 (s, 6H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 480 $(M + H)^+$.

Example 47

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-ylthio)phenyl)urea

[00801] The title compound was prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (87 mg, 0.3 mmol) and 4-chloro-6,7-difluoroquinazoline (60 mg, 0.3 mmol) from Example 4A Step 2 as described in Example 46 to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-ylthio)phenyl)urea (50 mg, 0.11 mmol, 37%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.05 (s, 1H), 8.88 (s, 1H), 8.34 (dd, 1H), 8.09 (dd, 1H), 7.88 (s, 1H), 7.53 (d, 1H), 7.47 (t, 1H), 7.30 (d, 1H), 6.49 (s, 1H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + Na)^+$.

Example 48

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-ylthio)phenyl)urea

[00802] The title compound was prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (116 mg, 0.4 mmol) and 4-chloro-7-methoxyquinazoline (78 mg, 0.4 mmol) as described in Example 46 and its corresponding hydrochloride salt was prepared as described in Example X4 Step 2 to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-ylthio)phenyl)urea as the mono-hydrochloride (143 mg, 0.30 mmol, 75%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.55 (s, 1H), 8.85 (s, 1H), 8.20 (d, 1H), 7.87 (s, 1H), 7.55 (d, 1H), 7.48 – 7.42 (m, 2H), 7.38 (s, 1H), 7.29 (d, 1H), 6.50 (s, 1H), 3.99 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 450 $(M + H)^+$.

Example 49

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-ylthio)phenyl)urea

[00803] The title compound was prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (87 mg, 0.3 mmol) and 4-chloro-6-methoxyquinazoline (59 mg, 0.3 mmol) as described in Example 46 and its corresponding hydrochloride salt was prepared as described in Example 4B Step 2 to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-ylthio)phenyl)urea as the mono-hydrochloride (76 mg, 0.15 mmol, 50%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.49 (s, 1H), 8.80 (s, 1H), 7.95 (d, 1H), 7.87 (s, 1H), 7.71 (dd, 1H), 7.55 (d, 1H), 7.49 – 7.42 (m, 2H), 7.29 (d, 1H), 6.50 (s, 1H), 4.00 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 450 $(M + H)^+$.

Example 50

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl]urea

[00804] A mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.146 g 0.5 mmol), 4-chloro-7-ethoxy-6-methoxyquinazoline from Example 6B Step 1 (0.12 g, 0.5 mmol), and Cs_2CO_3 (0.161 mg, 0.5 mmol) in isopropanol (10 mL) was heated at 70 °C for 7 hours. It was quenched with water and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with EtOAc/hexane as eluant to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-

methoxyquinazolin-4-ylthio)phenyl]urea as solid (0.118 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (br, 1H), 8.74 (s, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.62 (d, 1H), 7.37 (m, 3H), 7.25 (1H), 5.91 (s, 1H), 4.29 (q, 2H), 4.06 (s, 3H), 1.58 (t, 3H), 1.32 (s, 9H); LC-MS (ESI) *m/z* 494 $(M + H)^+$.

Example 51

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-ylthio)phenyl]urea

[00805] As described in Example 50 the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.117g, 0.4 mmol) was reacted with 4-chloro-6,7-diethoxyquinazoline (0.101 g, 0.4 mmol) from Example 13A, and Cs_2CO_3 (0.130 g, 0.4 mmol) in isopropanol (10 mL) at 70 °C for 4 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-ylthio)phenyl]urea as solid (0.131 g, 65%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.03 (s, 1H), 8.68 (s, 1H), 7.84 (s, 1H), 7.50 (d, 1H), 7.44 (t, 1H), 7.33 (m, 2H), 7.29 (d, 1H), 6.49 (s, 1H), 4.26 (m 4H), 1.45 (m, 6H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 508 $(M + H)^+$.

Example 52

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea hydrochloride

[00806] Example 52A: As described in Example 50 the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.105 g, 0.36 mmol) was reacted with 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinazoline from Example 7A (0.134 g, 0.5 mmol), and Cs_2CO_3 (0.325 g, 1 mmol) in isopropanol (8 mL) at 70 °C for 4 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea as solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.69 (s, 1H), 7.84 (m, 1H), 7.51 (m, 1H), 7.44 (t, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 7.28 (m 1H), 6.49 (s, 1H), 4.33 (t, 2H), 4.00 (s, 3H), 3.76 (t, 2H), 3.34 (s, 3H), 1.28 (s, 9H).

[00807] Example 52B: To 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea was added 1.0 M HCl in Et_2O solution (2 eq.) in the manner described in Example 6B Step 2 to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-

ylthio]phenyl}urea hydrochloride as solid (0.16 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.23 (s, 1H), 8.72 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H), 7.44 (t, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.28 (d, 1H), 6.49 (s, 1H), 4.34 (t, 2H), 4.01 (s, 3H), 3.76 (t, 2H), 3.34 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 524 $(M + H)^+$.

Example 53

Preparation of 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride

[00808] Example 53A: As described in Example 50, a mixture of the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.117g, 0.4 mmol), 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (0.125 g, 0.4 mmol) from Example 12A, and Cs_2CO_3 (0.20 g, 0.6 mmol) in isopropanol (5 mL) was heated at 90 °C overnight, to afford 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea. as solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.99 (s, 1H), 8.68 (s, 1H), 7.84 (m, 1H), 7.51 (m, 1H), 7.46 (t, 1H), 7.39 (s, 1H), 7.38 (s, 1H), 7.28 (dd 1H), 6.49 (s, 1H), 4.34 (m 4H), 3.78 (m, 4H), 3.37 (s, 3H), 3.35 (s, 3H), 1.28 (s, 9H).

[00809] Example 53B: As described in Example 6B Step 2, to a solution of 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea in CH_2Cl_2 and MeOH was added 1.0 M HCl/Et_2O solution (2 eq.), to afford 1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-*tert*-butylisoxazol-3-yl)urea hydrochloride as solid (0.098 g, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.23 (s, 1H), 8.72 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H), 7.44 (t, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 7.28 (d, 1H), 6.49 (s, 1H), 4.35 (m, 4H), 3.78 (m, 4H), 3.37 (s, 3H), 3.35 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 568 $(M + H)^+$.

Example 54

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-ylthio)phenyl]urea hydrochloride

[00810] Example 54A: According to the procedure described in Example 50, a mixture of the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.105g, 0.36 mmol), 4-chloro-7,8-dihydro-

[1,4]dioxino[2,3-*g*]quinazoline described in Example 14A (0.111 g, 0.5 mmol), and Cs_2CO_3 (0.326 g, 1 mmol) in isopropanol (7 mL) was heated at 60 °C for 2 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4-ylthio]phenyl)urea as solid.

[00811] Example 54B: According to the procedure described in Example 6B Step 2, to a solution of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin -4-ylthio)phenyl]urea in CH_2Cl_2 and MeOH was added 1.0 M HCl/Et_2O solution, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-*g*]quinazolin-4-ylthio)phenyl]urea hydrochloride as solid (0.113 g, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.23 (s, 1H), 8.69 (s, 1H), 7.83 (m, 1H), 7.56 (s, 1H), 7.51 (d, 1H), 7.44 (t, 1H), 7.38 (s, 1H), 7.27 (d, 1H), 6.49 (s, 1H), 4.47 (m, 4H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 478 $(M + H)^+$.

Example 55

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-ylthio)quinazolin-4-yloxy]phenyl}urea

[00812] According to the procedure described in Example 50, a mixture of the intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (0.204 g, 0.7 mmol), 4-chloro-7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazoline from Example 94A (0.212 g, 0.72 mmol), and Cs_2CO_3 (0.326 g, 1 mmol) in isopropanol (10 mL) was heated at 60 °C for 4 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-ylthio]phenyl}urea as solid (0.086 g, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.60 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.65 (d, 1H), 7.41 (t, 1H), 7.33 (d, 1H), 6.86 (d, 1H), 6.54 (d, 1H), 5.90 (s, 1H), 4.78 (m 1H), 4.18 (m, 2H), 3.94 (s, 3H), 3.69 (m, 2H), 2.19 (m, 2H), 2.11 (m, 2H), 1.33 (s, 9H); LC-MS (ESI) *m/z* 550 $(M + H)^+$.

Example 56

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)urea

[00813] In a sealed reaction vessel 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (333 mg, 1.14 mmol) was dissolved in 11 mL of THF. To this solution was added cesium carbonate (447 mg, 1.37 mmol), and the solution stirred for 30 minutes. At the end of this time 4-chloro-6-ethoxy-7-

methoxyquinazoline (273 mg, 1.14 mmol) from Example 10A and the reaction heated to 50°C for 48 hours. The reaction was concentrated and purified by silica gel chromatography eluting with an ethyl acetate/dichloromethane gradient 0-50% over 75 minutes. Concentration of the main peak gave the title compound (374 mg, 66.5% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.48 (s, 1H), 7.55-7.25 (m, 5H), 6.49 (s, 1H), 4.25 (m, 2H), 3.99 (s, 3H), 1.47 (m, 3H), 1.32 (s, 9H). LCMS (ESI) m/z 494 (M+H)

Example 57

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00814] Example 57A: The intermediate 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (1.01g, 3.5 mmol) was reacted with 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline (1.0 g, 3.5 mmol) from Example 21 A Step 5 as described in Example 46 to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea (1.69 g, 3.12 mmol, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.70 (s, 1H), 7.85 (s, 1H), 7.51 (d, 1H), 7.44 (t, 1H), 7.36 (s, 2H), 7.28 (d, 1H), 6.49 (s, 1H), 4.31 (t, 2H), 4.00 (s, 3H), 3.85 (t, 2H), 2.37 – 2.25 (m, 2H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 542 $(M + H)^+$.

[00815] Example 57B: The urea from the previous step (200 mg, 0.37 mmol) was treated with piperidine (109 μL, 1.11 mmol), tetrabutylammonium iodide (136 mg, 0.37 mmol) and N,N'-diisopropylethylamine (129 μL, 0.74 mmol) in N,N'-dimethylformamide (3 mL). The mixture was heated to 60 °C for 56h and cooled to room temperature. Water (10 mL) was added and the solid filtered off and dried. The crude solid was purified by preparative HPLC (phenylhexyl reverse phase column) and the obtained solid triturated with water (10 mL) and drops of methanol, then filtered off and dried under high vacuum to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (24.05 mg, 11%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.52-7.41 (m, 2H), 7.35-7.26 (m, 3H), 6.49 (s, 1H), 4.22-4.18 (m, 2H), 3.99 (s, 3H), 2.51-2.36 (m, 6H), 1.99-1.95 (m, 2H), 1.51-1.49 (m, 4H), 1.39-1.38 (m, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 591 $(M + H)^+$.

Example 58

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea

[00816] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) and 4-piperidinemethanol (127 mg, 1.11 mmol) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea (35.75 mg, 58%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.02 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.53-7.43 (m, 2H), 7.34-7.26 (m, 3H), 6.49 (s, 1H), 4.42-4.40 (m, 1H), 4.22-4.18 (m, 2H), 4.18 (s, 3H), 3.25-3.21 (m, 2H), 2.91 (d, 2H), 2.50-2.47 (m, 2H), 2.00-1.88 (m, 4H), 1.64 (d, 2H), 1.27 (s, 9H), 1.16-1.12 (m, 2H); LC-MS (ESI) *m/z* 621 $(M + H)^+$.

Example 59

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00817] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) and N-methyl piperazine (123 μL, 1.11 mmol) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (15.75 mg, 7%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.52-7.43 (m, 2H), 7.34-7.26 (m, 3H), 6.49 (s, 1H), 4.20 (bs, 2H), 3.99 (s, 3H), 2.46-2.34 (m, 10H), 2.14 (s, 3H), 1.99-1.97 (m, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 606 $(M + H)^+$.

Example 60

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00818] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) and N-methylsulfonyl-piperazine (182 mg, 1.11 mmol) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (54.17 mg, 22%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.00 (s, 1H), 9.69 (s, 1H), 7.85 (s, 1H), 7.51-7.26 (m, 5H), 6.49 (s, 1H), 4.22 (bs, 2H), 3.99 (s, 3H), 3.14 (s, 4H), 2.86 (s, 3H), 2.20-1.90 (m, 2H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 670 $(M + H)^+$.

Example 61

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea

[00819] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) and 1-(2-hydroxyethyl)piperazine (136 μL, 1.11 mmol) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea (17.86 mg, 7%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (bs, 1H), 9.05 (bs, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.65-7.36 (m, 5H), 6.49 (s, 1H), 4.21 (bs, 2H), 3.99 (s, 3H), 3.70-3.19 (m,6H), 2.50-2.29 (m, 8H), 1,98 (bs, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 636 $(M + H)^+$.

Example 62

1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea

[00820] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) and thiomorpholine 1,1-dioxide (150 mg, 1.11 mmol) to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea (54.51 mg, 23%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.52-7.27 (m, 5H), 6.49 (s, 1H), 4.25-

4.21 (m, 2H), 3.99 (s, 3H), 3.11 (bs, 4H), 2.95 (bs, 4H), 2.70-2.65 (m, 2H), 2.01-1.97 (m, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 641 $(M + H)^+$.

Example 63

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylthio)phenyl)urea

[00821] In the manner described in Example 21C 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 57B (200 mg, 0.37 mmol) was reacted with morpholine (96 μL, 1.11 mmol), diisopropylethyl amine (193 μL, 1.11 mmol), and tetrabutyl ammonium iodide (136 mg, 0.37 mmol). The purification and isolation steps afforded 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylthio)phenyl)urea (49 mg, 22% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.48 (s, 1H), 7.55-7.25 (m, 5H), 6.47 (s, 1H), 4.25 (m, 2H), 3.99 (s, 3H), 3.59 (m, 4H), 2.5-2.35 (m, 6H), 2.01 (m, 2H), 1.37 (s, 9H); LCMS (ESI) *m/z* 593 (M+H).

Example 64

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00822] To a suspension of sodium hydride (11mg, 0.44 mmol) in anhydrous tetrahydrofuran (2 mL) cooled to 0 °C, was added compound 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (117 mg, 0.40 mmol) as a solution in tetrahydrofuran (1 mL) and the mixture stirred at 0 °C for 30 minutes. To this suspension 4-chloro-7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazoline from Example 41B Step 1 (133 mg, 0.40 mmol) was added and the resulting mixture was stirred at 0 °C and slowly allowed to reach room temperature. After stirring for additional 1h, the mixture was taken up in ethyl acetate/water and extracted. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea (10.30 mg, 4%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.73 (bs, 1H), 9.19 (bs, 1H), 8.70 (s, 1H), 7.85 (s, 1H), 7.53-7.27 (m, 5H), 6.49 (s, 1H), 4.32 (bs, 2H), 4.01 (s, 3H), 3.35 (2H), 3.07 (s, 3H), 2.28 (bs, 2H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 586 $(M + H)^+$.

Example 65

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00823] Example 65A: To 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (1.07 g, 3.70 mmol) was added 4-chloro-6-(2-chloroethoxy)-7-methoxyquinazoline (1.0 g, 3.70 mmol) from Example 16B according to the procedure described in Example 46 to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea (1.54 g, 2.92 mmol, 79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.02 (s, 1H), 8.71 (s, 1H), 7.85 (s, 1H), 7.51 (d, 1H), 7.44 (t, 1H), 7.38 (s, 2H), 7.28 (d, 1H), 6.49 (s, 1H), 4.50 (t, 2H), 4.07 (t, 2H), 4.01 (s, 3H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 528 $(M + H)^+$.

[00824] Example 65B: The urea intermediate from the previous step (200 mg, 0.38 mmol) and piperidine (0.112 mL, 1.14 mmol) were reacted as described in Example 57B to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea as a colorless solid (28 mg, 13%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (brs, 1H), 9.01 (brs, 1H), 8.69 (s, 1H), 7.86 (s, 1H), 7.25-7.53 (m, 5H), 6.49 (s, 1H), 4.25-4.29 (m, 2H), 3.99 (s, 3H), 2.73-2.77 (m, 2H), 1.50-1.54 (m, 8H), 1.38-1.40 (m, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 577 $(M + H)^+$.

Example 66

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea

[00825] The urea intermediate from Example 65A (200 mg, 0.38 mmol) and 4-piperidinemethanol (131 mg, 1.14 mmol) were reacted as described in Example 16D to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea as a colorless solid (28 mg, 12%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (brs, 1H), 9.04 (brs, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.26-7.52 (m, 5H), 6.49 (s, 1H), 4.41 (m, 1H), 4.27 (m, 2H), 3.99 (s, 3H), 3.24 (m, 2H), 2.96-3.00 (m, 2H), 2.74-2.78 (m, 2H), 1.99-2.06 (m, 2H), 1.61-1.65 (m, 2H), 1.27 (s, 9H), 1.00-1.15 (m, 2H); LC-MS (ESI) *m/z* 607 $(M + H)^+$.

Example 67

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00826] The urea intermediate from Example 65A (200 mg, 0.38 mmol) and *N*-methyl piperazine (0.126 mL, 1.14 mmol) were reacted as described in Example 57B to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea as a colorless solid (49 mg, 22%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 9.00 (brs, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.26-7.49 (m, 5H), 6.49 (s, 1H), 4.25-4.29 (m, 2H), 3.98 (s, 3H), 2.75-2.79 (m, 2H), 2.20-2.60 (m, 8H), 2.15 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 592 $(M + H)^+$.

Example 68

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea

[00827] The urea intermediate from Example 65A (200 mg, 0.38 mmol) and 1-(2-hydroxyethyl)piperazine (0.139 mL, 1.14 mmol) in the manner described in Example 57B to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea as a colorless solid (32 mg, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 9.00 (brs, 1H), 8.69 (s, 1H), 7.84 (s, 1H), 7.26-7.49 (m, 5H), 6.49 (s, 1H), 4.26-4.37 (m, 3H), 3.99 (s, 3H), 3.40-3.50 (m, 2H), 2.75-2.79 (m, 2H), 2.30-2.50 (m, 9H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 622 $(M + H)^+$.

Example 69

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00828] The urea intermediate from Example 65A (200 mg, 0.38 mmol) and 1-methylsulfonyl-piperazine (187 mg, 1.14 mmol) in the manner described in Example 57B to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea as a colorless solid (53 mg, 21%).^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 8.99 (brs, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.29-7.51 (m, 5H), 6.48 (s, 1H), 4.30-4.32 (m, 2H), 3.99 (s,

3H), 3.14-3.15 (m, 4H), 2.86-2.87 (m, 5H), 2.66-2.67 (m, 4H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 656 $(M + H)^+$.

Example 70

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea

[00829] The urea intermediate from Example 65A (200 mg, 0.38 mmol) and morpholine (0.099 mL, 1.14 mmol) in the manner described in Example 57B to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea as a colorless solid (29 mg, 13%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 9.02 (brs, 1H), 8.69 (s, 1H), 7.84 (s, 1H), 7.26-7.49 (m, 5H), 6.48 (s, 1H), 4.30-4.32 (m, 2H), 3.99 (s, 3H), 3.60-3.62 (m, 4H), 2.80 (m, 2H), 2.49-2.52 (m, 4H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 579 $(M + H)^+$.

Example 71

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea

[00830] The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from Example 65A (200 mg, 0.38 mmol), thiomorpholine 1,1-dioxide (154 mg, 1.14 mmol), tetrabutylammonium iodide (140 mg, 0.38 mmol) and N,N'-diisopropylethylamine (135 µL, 0.76 mmol) in N,N'-dimethylformamide (2 mL) to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea (56.27 mg, 24%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 7.85 (s, 1H), 7.52-7.27 (m, 5H), 6.49 (s, 1H), 4.30 (bs, 2H), 3.99 (s, 3H), 3.12-3.04 (m, 10H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 627 $(M + H)^+$.

Example 72

Preparation of (1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl) urea)

[00831] Example 72A: To a solution of (1-(5-tert-butyl-isoxazol-3-yl)-3-(3-mercapto-phenyl)-urea described in Example 44A (303.02 mg, 1.04 mmol) in THF:

DMF (2:1, 6 mL) was added NaH (95%, 28.9 mg, 1.144 mmol), stirred for 5-10 min at ambient temperature. Then (4-chloro-7-(3-chloro-propoxy)-6-methoxy-quinazoline, (300 mg, 1.04 mmol) described in Example 27A was added as solution in DMF:THF (2:1). The reaction mixture was then stirred overnight. Completion of the reaction was monitored by LCMS. The reaction mixture was diluted with ethyl acetate and washed the ethyl acetate layer with water and brine successively. The organic layer was dried (Na_2SO_4) concentrated to dryness to afford the pure 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea (480 mg, 85%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.68 (s, 1H), 7.85 (s, 1H), 7.60-7.28(m, 5H), 6.50 (s, 1H), 4.35 (t, 2H), 4.05 (s, 3H), 3.82 (t, 2H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 542 $(M+H)^+$.

[00832]

[00833] Example 72B: To a solution of urea from the previous step (250mg, 0.461 mmol) in DMF (3 mL) was added morpholine (120.5 mg, 1.383 mmol) followed by diisopropyl ethylamine (0.241 mL, 1.383 mmol) and tetrabutyl ammonium iodide (170.35 mg, 0.461 mmol). The reaction mixture was heated at 60^0C for 15 h. Formation of product was determined by LCMS. The crude reaction was diluted with ethyl acetate (50 mL), washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (DCM/MeOH) to afford (1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl) urea) (40 mg, 15%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.12 (s, 1H), 8.72 (s, 1H), 7.85 (s, 1H), 7.61-7.21 (m, 5H), 6.45 (s, 1H), 3.95 (s, 3H), 3.62 (s, 3H), 2.75 - 2.25 (m, 6H), 2.01 (m, 2H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 593 $(M+H)^+$.

Example 73

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00834] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) in DMF (3 mL) was added N-methyl piperazine (0.122 mL, 1.104 mmol) followed by diisopropyl ethylamine (0.192 mL, 1.104 mmol) and tetrabutyl ammonium iodide (136.2 mg, 0.368 mmol). The reaction mixture was heated at 60^0C for 24 h. Formation of the product was determined by LCMS. The crude reaction

mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (72mg, 32%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.00 (s, 1H), 8.68 (s, 1H), 7.85 (s, 1H), 7.60-7.20 (m, 5H), 6.45 (s, 1H), 4.25 (m, 2H), 3.88 (s, 3H), 2.50-2.25 (m, 10H), 2.15 (s, 3H), 1.95 (m,2H), 1.23 (s, 9H); LC-MS (ESI) *m/z* 606 $(M+H)^+$.

Example 74

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea

[00835] 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) and piperidin-4-yl-methanol (127 mg, 1.104 mmol) were reacted as described in Example 73. Isolated yield of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea (47mg, 21%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.70 (s, 1H), 7.60-7.20 (m, 5H), 6.45 (s, 1H), 4.40 (m, 1H), 4.20 (m, 2H), 3.98 (s, 3H), 3.25 (m, 2H), 2.87 (d, 2H), 2.45 (m,2H), 2.10-1.80 (m, 4H), 1.65 (d, 2H), 1.30 (s, 10H), 1.15 (m,2H); LC-MS (ESI) *m/z* 621 $(M+H)^+$.

Example 75

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea

[00836] 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) and 2-piperazin-1-yl-ethanol (135 mL, 1.104 mmol) were reacted as described in Example 73. Isolated yield of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea (75mg, 32%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.55 (s, 1H), 8.65 (s, 1H), 7.85 (s,1H), 7.60-7.25 (m, 5H), 6.50 (s, 1H), 4.40 (s, 1H), 4.25 (m, 2H), 4.00 (s, 3H), 3.45 (m,2H), 2.50-2.25 (m, 12H), 1.95 (m, 2H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 636 $(M+H)^+$.

Example 76

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00837] 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) and piperidine (0.109 mL, 1.104 mmol) were reacted as described in Example 73. Isolated yield of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (57mg, 26%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.65 (s, 1H), 7.85 (s,1H), 7.60-7.20 (m, 5H), 6.45 (s, 1H), 4.20 (m, 2H), 4.00 (s, 3H), 2.50-2.25 (m, 6H), 1.95 (m, 2H), 1.60-1.30 (m, 6H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 591 $(M+H)^+$.

Example 77

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00838] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) in DMF (3 mL) was added 1-methane sulfonyl piperazine (181 mg, 1.104 mmol) followed by diisopropyl ethylamine (0.192 mL, 1.104 mmol) and tetrabutyl ammonium iodide (136.2 mg, 0.368 mmol). The reaction mixture was heated at 60^{0}C for 2 days. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (85 mg, 35 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.70 (s, 1H), 7.85 (s, 1H), 7.55-7.20 (m, 5H), 6.50 (s, 1H), 4.25 (m, 1H), 3.95 (s, 3H), 3.15 (m,4H), 2.55 (m, 6H), 2.00 (m, 2H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 670 $(M+H)^+$.

Example 78

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea

[00839] 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(3-chloro-propoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 72A (200 mg, 0.368 mmol) and pyrrolidine (91 µL 1.104 mmol) were reacted in the manner described in Example 73 to yield 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea (12 mg, 6%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.85 (s, 1H), 8.30 (s, 1H), 7.25 (m, 2H), 7.35-7.00 (m, 4H), 6.45 (s, 1H), 4.20 (m, 2H), 3.85 (m, 7H), 3.15 (m, 2H), 2.20-1.85 (m, 6H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 577 $(M+H)^+$.

Example 79

Preparation of (1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl)urea)

[00840] Example 79A: To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-mercapto-phenyl)-urea (319 mg, 1.098 mmol) described in Example 44A in THF: DMF (2:1, 6 mL) was added NaH (95%, 30.5 mg, 1.207 mmol), stirred for 5-10 min at ambient temperature. Then 4-chloro-7-(2-chloro-ethoxy)-6-methoxy-quinazoline from Example 35A (300 mg, 1.098 mmol) was added as a solution in DMF:THF (2:1). The reaction mixture was then stirred overnight. Completion of the reaction was monitored by LCMS. The reaction mixture was diluted with ethyl acetate and washed the ethyl acetate layer with water and brine successively. The organic layer was dried (Na_2SO_4) concentrated to dryness to get the pure compound 1-(5-tert-Butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea (550 mg, 95%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.68 (s, 1H), 7.85 (s, 1H), 7.55-7.25 (m, 5H), 6.45 (s, 1H), 4.50 (m, 2H), 4.05 (m, 5H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 528 $(M+H)^+$.

[00841] Example 79B: To a solution of the urea from the previous step (100 mg, 0.189 mmol) in DMF (2 mL) was added morpholine (49.3 mg, 0.567 mmol) followed by diisopropyl ethylamine (98.7 µL, 0.567 mmol) and tetrabutyl ammonium iodide (69.8 mg, 0.189 mmol). The reaction mixture was heated at 60^{0}C for 3 days. Formation of product was determined by LCMS. The crude reaction mixture was

purified by preparative HPLC (using phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford (1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl)urea) (23 mg, 23 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.70 (s, 1H), 8.70 (s, 1H), 7.85 (s, 1H), 7.70-7.25 (m, 5H), 6.50 (s, 1H), 4.40 (s, 2H), 4.05 (s, 3H), 3.85 (m, 4H), 2.75-2.35 (m, 6H), 1.35 (s, 9H); LC-MS (ESI) *m/z* 579 $(M+H)^+$.

Example 80

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00842] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 79A (225 mg, 0.426 mmol) in DMF (3 mL) was added piperidine (0.126 mL, 1.278 mmol) followed by diisopropyl ethylamine (0.222 mL, 1.278 mmol) and tetrabutyl ammonium iodide (157.35 mg, 0.426 mmol). The reaction mixture was heated at 60^{0}C for 2 days. Formation of product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea (42mg, 17 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.20 (s, 1H), 8.65 (s, 1H), 7.85 (s, 1H), 7.60-7.22 (m, 5H), 6.45 (s, 1H), 4.30 (m, 2H), 3.95 (s, 3H), 2.85-2.30 (m, 6H), 1.70-1.30 (m, 6H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 577 $(M+H)^+$.

Example 81

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea.

[00843] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 79A (225 mg, 0.426 mmol) in DMF (3 mL) was added 1-methane sulfonyl pyperazine (139.9 mg, 0.852 mmol) followed by diisopropyl ethylamine (0.222 mL, 1.278 mmol) and tetrabutyl ammonium iodide (157.35 mg, 0.426 mmol). The reaction mixture was

heated at 60°C for 3 days. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (phenomenex phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea (47mg, 17 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.65 (s, 1H), 7.85 (s, 1H), 7.62-7.25 (m, 5H), 6.45 (s, 1H), 4.30 (m, 2H), 3.15 (m, 4H), 2.85 (m, 5H), 2.60 (m,4H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 656 $(M+H)^+$.

Example 82

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(3-hydroxypyrrolidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea

[00844] The intermediate 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 79A and pyrrolidin-3-ol were reacted as described in Example 80 to yield 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(3-hydroxypyrrolidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea (59mg, 24 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.85 (s, 1H), 8.30 (s, 1H), 7.65-7.50 (m, 2H), 7.35-7.05 (m, 4H), 6.50 (s, 1H), 5.05 (s, 1H), 4.45-4.25 (m, 3H), 4.15-3.85 (m,6H), 3.75-3.65 (d, 1H), 3.45 (m, 2H), 2.00 (m, 2H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 579 $(M+H)^+$.

Example 83

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00845] To a solution of 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea from Example 79A (225 mg, 0.426 mmol) in DMF (3 mL) was added N-methyl piperazine (0.141 mL, 1.278 mmol) followed by diisopropyl ethylamine (0.222 mL, 1.278 mmol) and tetrabutyl ammonium iodide (157.35 mg, 0.426 mmol). The reaction mixture was heated at 60°C for 24 h. Formation of the product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using phenylhexyl reverse phase

column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea (21mg, 8.3 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.65 (s, 1H), 7.85 (s, 1H), 7.60-7.25 (m, 5H), 6.45 (s, 1H), 4.35 (m, 2H), 4.00 (m, 3H), 2.80-2.25 (m, 10H), 2.15 (s, 3H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 592 $(M+H)^+$.

Example 84

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea

[00846] To the intermediate 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea (225 mg, 0.426 mmol) from Example 79A was added 2-piperazin-1-yl-ethanol (0.157 mL, 1.278 mmol) followed by diisopropyl ethylamine (1.3 mmol) and tetrabutyl ammonium iodide (0.43 mmol). The reaction mixture was heated at 60°C for 3 days. Formation of product was determined by LCMS. The crude reaction mixture was purified by preparative HPLC (using phenylhexyl reverse phase column eluted with gradient of solvent A = 0.05% HOAc/H_2O and solvent B = 0.05% HOAc/CH_3CN) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea (34mg, 13%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.05 (s, 1H), 8.65 (s, 1H), 7.85 (s, 1H), 7.60-7.20 (m, 5H), 6.45 (s, 1H), 4.45-4.25 (m, 3H), 4.00 (s, 3H), 3.45 (m, 2H), 2.80-2.30 (m, 12H), 1.25 (s, 9H); LC-MS (ESI)m/z 622 $(M+H)^+$.

Example 85

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00847] To the intermediate 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea (225 mg, 0.426 mmol) from Example 79A was added pyrrolidine (0.105 mL, 1.278 mmol) in the manner described in Example 80 to yield 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea (41mg, 18%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.85 (s, 1H), 8.30 (s, 1H),

7.65-7.50 (m, 2H), 7.35-7.05 (m, 4H), 6.50 (s, 1H), 4.30 (m, 2H), 4.00-3.75 (m, 7H), 2.55 (m, 2H), 1.98 (m, 4H), 1.30 (s, 9H); LC-MS (ESI)m/z 563 $(M+H)^+$.

Example 86

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea

[00848] The intermediate 1-(5-tert-butyl-isoxazol-3-yl)-3-{3-[7-(2-chloro-ethoxy)-6-methoxy-quinazolin-4-ylsulfanyl]-phenyl}-urea (225 mg, 0.426 mmol) from Example 79A and piperidin-4-yl-methanol (147 mg, 1.278 mmol) were reacted using the procedure described in Example 80 to yield of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea (61mg, 24%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.55-10.05 (m, 2H), 8.68 (s, 1H), 7.85 (s, 1H), 7.65-7.20 (m, 5H), 6.50 (s, 1H), 4.50 (s, 1H), 4.30 (s, 2H), 4.02 (s, 3H), 3.25 (m, 2H), 3.00 (m, 2H), 2.80-2.65 (m, 4H), 2.05 (m, 2H), 1.70-1.50 (m,2H), 1.30 (s, 10H); LC-MS (ESI)m/z 607 $(M+H)^+$.

Example 87

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea

[00849] The title compound was prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (146 mg, 0.5 mmol) and 4-chloro-6-(2-methoxyethoxy)quinazoline from Example 40A (119 mg, 0.5 mmol) using the procedure described in Example 46 to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea (160 mg, 0.32 mmol, 64%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.03 (s, 1H), 8.76 (s, 1H), 7.96 – 7.85 (m, 2H), 7.70 (dd, 1H), 7.58 – 7.42 (m, 3H), 7.30 (d, 1H), 6.50 (s, 1H), 4.37 – 4.30 (m, 2H), 3.79 – 3.74 (m, 2H), 3.38 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 494 $(M + H)^+$.

Example 88

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazolin-4-ylthio)phenyl)urea

[00850] Example 88A Step 1: 6-(2-Chloroethoxy)-4-hydroxy-7-methoxyquinazoline (1.12 g, 4.4mmol) from Example 16A was reacted using the procedure described in Example 41B Step 1 to give 4-hydroxy-7-methoxy-6-(2-(methylthio)ethoxy)quinazoline (1.02 g, 3.83 mmol, 87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 7.99 (s, 1H), 7.46 (s, 1H), 7.14 (s, 1H), 4.24 (t, 2H), 3.91 (s, 3H), 3.89 (t, 2H), 2.20 (s, 3H); LC-MS (ESI) *m/z* 267 $(M + H)^+$.

[00851] Example 88A Step 2: 4-Hydroxy-7-methoxy-6-(2-(methylthio)ethoxy)quinazoline (800 mg, 3.0 mmol) was reacted using the procedure described in Example 41B Step 2 to give 4-hydroxy-7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazoline (880 mg, 2.95 mmol, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 8.02 (s, 1H), 7.51 (s, 1H), 7.18 (s, 1H), 4.43 (t, 2H), 3.92 (s, 3H), 3.68 (t, 2H), 3.17 (s, 3H); LC-MS (ESI) *m/z* 299 $(M + H)^+$.

[00852] Example 88A Step 3: 4-Hydroxy-7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazoline (880 mg, 2.95 mmol) was reacted using the procedure described in Example 41B Step 3, to give 4-chloro-7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazoline (405 mg, 1.28 mmol, 43%). LC-MS (ESI) *m/z* 317 $(M + H)^+$.

[00853] Example 88B: 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (92 mg, 0.32 mmol) was treated with cesium carbonate (113 mg, 0.35 mmol) in anhydrous tetrahydrofuran (2 mL) and the suspension stirred at 40°C for 20 minutes. 4-Chloro-7-methoxy-6-(2-(methylsulfonyl)ethoxy) quinazoline from the previous step (100 mg, 0.32 mmol) was carefully added in portions and the resulting mixture heated at 40 °C for 2h. Cesium carbonate was filtered off, the filtrate concentrated under reduced pressure and the residue purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazolin-4-ylthio)phenyl)urea (36.88 mg, 20%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.01 (s, 1H), 8.72 (s, 1H), 7.85 (s, 1H), 7.53-7.40 (m, 4H), 7.30-7.28 (d, 1H), 6.49 (s, 1H), 4.59-4.56 (m, 2H), 4.00 (s, 3H), 3.78-3.74 (m, 2H), 3.20 (s, 3H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 572 $(M + H)^+$.

Example 89

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio) phenyl)urea

[00854] To a slurry of sodium hydride (7.5 mg, 0.3 mmol) in DMF (3 mL) was added 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (90 mg, 0.3 mmol), and the solution stirred at room temperature When gas evolution ceased, 2,4-dichloro-6,7-dimethoxyquinazoline (78 mg, 0.3 mmol) was added and the solution heated at 50°C overnight, cooled to room temperature, and diluted with H_2O. The mixture was extracted with EtOAc, the organic layer washed with aqueous sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was purified by HPLC to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea (20 mg, 0.04 mmol, 13%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.53 (s, 1H), 7.90 (s, 1H), 7.62 (d, 1H), 7.44 (t, 1H), 7.36 (s, 2H), 7.27 (d, 1H), 6.49 (s, 1H), 4.00 (s, 6H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 514 $(M + H)^+$.

Example 90

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo--thiomorpholin-4-yl)-propoxy]-quinazolin-4-ylsulfanyl}-phenyl)-urea

[00855] Example 90A Step 1: Methyl 5-hydroxy-2-nitrobenzoate (4.37 g, 22.17 mmol, prepared as previously described), and 1-bromo-3-chloropropane (6.58 mL, 66.5 mmol) were reacted using the procedure described in Example 40A Step 3 to give methyl 5-(3-chloropropoxy)-2-nitrobenzoate (5.70 g, 20.8 mmol, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (d, 1H), 7.33 (d, 1H), 7.30 (dd, 1H), 4.27 (dt, 2H), 3.86 (s, 3H), 3.68 (t, 2H), 2.21 (t, 2H); LC-MS (ESI) *m/z* 274 $(M + H)^+$.

[00856] Example 90A Step 2: Methyl 5-(3-chloropropoxy)-2-nitrobenzoate (5.7 g, 20.8 mmol) was reacted using the procedure described in Example 40A Step 4 to give methyl 2-amino-5-(3-chloropropoxy)benzoate (4.83 mg, 19.8 mmol, 95%). LC-MS (ESI) *m/z* 244 $(M + H)^+$.

[00857] Example 90A Step 3: Methyl 2-amino-5-(3-chloropropoxy)benzoate (4.83 g, 19.8 mmol) was reacted using the procedure described in Example 40A Step 5. The product was purified by column chromatography (25-100% EtOAc/hexanes) to give 6-(3-chloropropoxy)-4-hydroxyquinazoline (1.04 g, 4.3 mmol, 22%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 7.99 (s, 1H), 7.62 (d, 1H), 7.52 (d, 1H),

7.44 (dd, 1H), 4.17 (dt, 2H), 3.82 (t, 2H), 2.22 (t, 2H); LC-MS (ESI) *m/z* 239 (M + H)$^+$.

[00858] Example 90A Step 4: 6-(3-chloropropoxy)-4-hydroxyquinazoline (540 mg, 2.26 mmol) was reacted using the procedure described in Example 40A Step 6 to give 4-chloro-6-(3-chloropropoxy)quinazoline (485 mg, 1.9 mmol, 83%). LC-MS (ESI) *m/z* 258 (M + H)$^+$.

[00859] Example 90B: Using the procedure described in Example 46, 1-(5-tert-butylisoxazol-3-yl)-3-(3-mercaptophenyl)urea described in Example 44A (181 mg, 0.62 mmol) was reacted with 4-chloro-6-(3-chloropropoxy)-quinazoline from the previous step (160 mg, 0.62 mmol) to give 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea (230 mg, 0.45 mmol, 72%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.02 (s, 1H), 8.76 (s, 1H), 7.94 (d, 1H), 7.86 (s, 1H), 7.72 (d, 1H), 7.58 – 7.42 (m, 3H), 7.30 (d, 1H), 6.49 (s, 1H), 4.33 (t, 2H), 3.87 (t, 2H), 2.32 – 2.25 (m, 2H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 512 (M + H)$^+$.

[00860] Example 90C: The title compound was prepared as described in Example 57B by using 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-chloropropoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea from the previous step (230 mg, 0.45 mmol), thiomorpholine 1,1-dioxide (182 mg, 1.35 mmol), tetrabutylammonium iodide (166 mg, 0.45 mmol) and N,N'-diisopropylethylamine (160 μL, 0.89 mmol) in N,N'-dimethylformamide (3 mL) to afford 1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo--thiomorpholin-4-yl)-propoxy]-quinazolin-4-ylsulfanyl}-phenyl)-urea (117 mg, 43%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.03 (s, 1H), 8.75 (s, 1H), 7.94-7.86 (m, 2H), 7.68 (d, 1H), 7.51-7.41 (m, 3H), 7.30 (d, 1H), 6.49 (s, 1H), 4.26-4.23 (m, 2H), 3.11 (bs, 4H), 2.95 (bs, 4H), 2.71-2.67 (m, 2H), 2.00-1.96 (m, 2H), 1.27 (s,m 9H); LC-MS (ESI) *m/z* 611 (M + H)$^+$.

Example 91

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea

[00861] The title compound was prepared as described in Example 57B by using compound 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-chloroethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea from Example 16C (200 mg, 0.39 mmol), thiomorpholine 1,1-dioxide (158 mg, 1.17 mmol), tetrabutylammonium iodide (144 mg, 0.39 mmol) and N,N'-diisopropylethylamine (139 μL, 0.78 mmol) in N,N'-dimethylformamide (2 mL) to afford 1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea (52.75 mg, 23%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.00 (s, 1H), 8.56 (s, 1H), 7.61 (d, 2H), 7.40-7.37 (m, 2H), 7.25 (d, 1H), 6.97 (d, 1H), 6.47 (s, 1H), 4.31 (m, 2H), 4.00 (s, 3H), 3.10-3.03 (m, 10H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 611 $(M + H)^+$.

Example 92

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-(5-{[2-(methylsulfonyl)ethylamino]methyl}furan-2-yl)quinazolin-4-yloxy]phenyl}urea

[00862] Example 92A Step 1: A mixture of 2-amino-5-iodobenzoic acid (9.00 g, 34.2 mmol) and formamidine acetate (18.00 g, 173mmol) in acetic acid (50 mL) was heated at 130 °C for 3 hours. After it was cooled down to room temperature, it was quenched with water, filtered, washed with water, and dried under vacuum with P_2O_5 to afford 6-iodoquinazolin-4(3*H*)-one as solid (9.289 g, 99.8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, 1H), 8.13 (s, 1H), 8.09 (dd, 1H), 7.46 (d, 1H); LC-MS (ESI) *m/z* 273 $(M + H)^+$.

[00863] Example 92A Step 2: To a mixture of 6-iodoquinazolin-4(3*H*)-one (1.70 g, 6.25 mmol) in $SOCl_2$ (10 mL) was dropped a few drops of DMF, and then it was heated at 90 °C for 5 hours. After excess $SOCl_2$ was removed under reduced pressure, to it was added CH_2Cl_2 and water, and neutralized with saturated $NaHCO_3$ solution. The aqueous was extracted with CH_2Cl_2 three times. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 4-chloro-6-iodoquinazoline as solid (1.266 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.67 (d, 1H), 8.22 (dd, 1H), 7.81 (d, 1H).

[00864] Example 92A Step 3: A mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (0.413 g, 1.5 mmol) from Example 1A, 4-chloro-6-

iodoquinazoline (0.436 g, 1.5 mmol), and Cs_2CO_3 (0.489 g, 1.5 mmol) in isopropanol (10 mL) was heated at 50 °C for 2 hours. It was quenched with water and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with EtOAc/hexane as eluant to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6-iodoquinazolin-4-yloxy)phenyl]urea as solid (0.551 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.08 (s, 1H), 8.84 (s, 1H), 8.78 (m, 1H), 8.40 (dd, 1H), 7.87 (d, 1H), 7.67 (d, 1H), 7.49 (t, 1H), 7.38 (d, 1H), 7.09 (d, 1H), 6.55 (s, 1H), 1.35 (s, 9H); LC-MS (ESI) *m/z* 530 $(M + H)^+$.

[00865] Example 92B. A mixture of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6-iodoquinazolin-4-yloxy)phenyl]urea from the previous step (0.21 g, 0.4 mmol), 5-formylfuran-2-ylboronic acid (0.07 g, 0.51 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.035 g, 0.05 mmol), and 1.0 M Na_2CO_3 solution (3 mL) in EtOH (2 mL) and 1,2-dimethoxyethane (3 mL) was heated at 55 °C for 1 hour. It was quenched with water and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with 30-60% EtOAc/hexane as eluants to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-(5-formylfuran-2-yl)quinazolin-4-yloxy]phenyl}urea as solid (0.172 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 9.53 (br, 1H), 8.80 (d, 1H), 8.78 (s, 1H), 7.32 (dd, 1H), 8.07 (d, 1H), 7.67 (m, 2H), 7.34-7.54 (m, 3H), 7.07 (d, 1H), 7.01 (d, 1H), 5.94 (s, 1H), 1.32 (s, 9H); LC-MS (ESI) m/z 498 $(M + H)^+$.

[00866] Example 92C Step 1. To a 1.0 M solution of BH_3·THF in THF (40 mL) at –40°C was added 2-(methylsulfonyl)acetonitrile (2.383 g, 20 mmol) in several small portions. After addition it was stirred at room temperature overnight. It was poured into MeOH (40 mL) and concentrated under reduced pressure. To the residue was added MeOH (60 mL) and 1.0 M HCl/Et_2O solution (30 mL), and then it was heated to reflux for 1 hour. After it was concentrated under reduced pressure to about 40 mL, to it was added a 7 N NH_3/MeOH solution until it was basic. It was concentrated under reduced pressure to dryness and dried under vacuum, to afford 2-(methylsulfonyl)ethanamine as solid (2.41 g). It was used in next step without further purification.

[00867] Example 92C Step 2. To a mixture of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-(5-formylfuran-2-yl)quinazolin-4-yloxy]phenyl}urea (0.17 g. 0.34 mmol), 2-(methylsulfonyl)ethanamine (0.15 g. 1.2 mmol), and $MgSO_4$ in CH_2Cl_2 was added

acetic acid (4 drops), followed by MeOH (1 mL). After the mixture was stirred at room temperature for 1 hour, $NaBH(OAc)_3$ (0.212 g, 1 mmol) was added. After stirring the mixture at room temperature for more 2 hours, more $NaBH(OAc)_3$ (0.212 g, 1 mmol) was added and stirred at room temperature overnight. The reaction was quenched with water, basified with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography with 2-6% MeOH/EtOAc as eluants to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-(5-{[2-(methylsulfonyl)ethylamino]methyl}furan-2-yl)quinazolin-4-yloxy]phenyl}urea as solid (0.052 g, 25%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.02 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.38 (d, 1H), 8.03 (d, 1H), 7.61 (s, 1H), 7.43 (t, 1H), 7.31 (d, 1H), 7.23 (d, 1H), 7.03 (d, 1H), 6.48 (m, 2H), 3.83 (br, 2H), 3.24 (t, 2H), 3.02 (s, 3H), 2.97 (br, 2H), 1.27 (s, 9H); LC-MS (ESI) m/z 605 $(M + H)^+$.

Example 93

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6-morpholinoquinazolin-4-yloxy)phenyl]urea

[00868] A mixture of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6-iodoquinazolin-4-yloxy)phenyl]urea from Example 92A (0.225 g, 0.425 mmol), morpholine (0.5 mL), xamtphhos (0.087 g, 0.15 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.046 g, 0.05 mmol), and Cs_2CO_3 (0.489 g, 1.5 mmol) in 1,2-dimethoxyethane (8 mL) was heated at 70 °C for 4 hours. It was quenched with water and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatophraphy with 30-100% EtOAc/hexane and 5% MeOH/EtOAc as eluants, and by preparative HPLC (C_{18}) with 60-80% CH_3CN/H_2O (0.05% AcOH) to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(6-morpholinoquinazolin-4-yloxy)phenyl]urea as a solid (0.007 g, 3.4%). ^{1}H NMR (300 MHz, CD_3CN) δ 9.48 (br, 1H), 8.39 (s, 1H), 7.78 (m, 4H), 7.67 (dd, 1H), 7.44 (m, 3H), 7.03 (d, 1H), 3.76 (t, 4H), 3.23 (t, 4H), 1.11 (s, 9H); LC-MS (ESI) m/z 489 $(M + H)^+$.

Example 94

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-yloxy]phenyl}urea

[00869] Example 94A Step 1: To a solution of 3,5-dimethoxyaniline (15.00 g, 97.9 mmol) in diethyl ether (300 mL) was added 1.0 M HCl solution in diethyl ether (100 mL). A white solid was formed, filtered, washed with Et_2O, and dried under vacuum. The solid was mixed with oxalyl chloride (30 mL) and it was heated at 165 °C for 30 minutes to form a green solid. The excess oxalyl chloride was evaporated under reduced pressure. To the solid was added MeOH (150 mL) and heated to reflux. After it was cooled down to room temperature, it was filtered, washed with MeOH, and dried under vacuum, to afford 4,6-dimethoxyindoline-2,3-dione as a solid (20.285 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 6.17 (d, 1H), 6.01 (d, 1H), 3.88 (s, 3H), 3.86 (s, 3H); LC-MS (ESI) *m/z* 208 $(M + H)^+$.

[00870] Example 94A Step 2: To a mixture of 4,6-dimethoxyindoline-2,3-dione (20.28 g, 97.9 mmol) in 30% NaOH solution (100 mL) at 100 °C was carefully dropped a 50% H_2O_2 solution. It was heated at 100 °C for 20 minutes. It was cooled down and neutralized by concentrated HCl to pH 8, followed by acetic acid to pH 5 to form a solid. It was filtered, washed with water, and dried under vacuum with P_2O_5 to afford 2-amino-4,6-dimethoxybenzoic acid as a yellow solid (15.034 g, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.00 (d, 1H), 5.85 (d, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.41 (br, 2H); LC-MS (ESI) *m/z* 198 $(M + H)^+$.

[00871] Example 94A Step 3: To a mixture of 2-amino-4,6-dimethoxybenzoic acid (7.888 g, 40 mmol) in MeOH (40 mL) and THF (40 mL) at room temperature was dropped 2.0 M solution of (trimethylsilyl)diazomethane in diethyl ether. The mixture was stirred at room temperature overnight. After the solvent was evaporated under reduced pressure, water and EtOAc was added to the residue. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography with 20-40% EtOAc/hexane as eluants to afford methyl 2-amino-4,6-dimethoxybenzoate as a solid (6.462 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, 1H), 5.78 (d, 1H), 5.53 (br, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H); LC-MS (ESI) *m/z* 212 $(M + H)^+$.

[00872] Example 94A Step 4: A mixture of methyl 2-amino-4,6-dimethoxybenzoate (6.46 g, 30.6 mmol), formamidine acetate (15.92 g, 153 mmol) in 2-methoxyethanol (50 mL) was heated at 130 °C for 4 hours. After the solvent was removed under reduced pressure, the reaction was quenched with water, filtered, washed with water, and dried under vacuum with P_2O_5 to afford 5,7-dimethoxyquinazolin-4(3*H*)-one as a solid (4.805 g, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.7 (br, 1H), 7.98 (s, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 3.92 (s, 3H), 3.88 (s, 3H); LC-MS (ESI) *m/z* 207 $(M + H)^+$.

[00873] Example 94A Step 5: To a mixture of 5,7-dimethoxyquinazolin-4(3*H*)-one (4.80 g, 23.3 mmol) in pyridine (50 mL) at room temperature was slowly added $MgBr_2$ (4.29 g, 23.3 mmol). It was heated to reflux for 1.5 hour. After solvent was evaporated under reduced pressure, to the residue was added a solution of AcOH (10 mL) in water (50 mL). A solid was precipitated. It was filtered, washed with water, and dried under vacuum with P_2O_5 to afford 5-hydroxy-7-methoxyquinazolin-4(3*H*)-one as solid (4.398 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (br, 1H), 8.08 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 3.85 (s, 3H); LC-MS (ESI) *m/z* 193 $(M + H)^+$.

[00874] Example 94A Step 6: To a suspension of 5-hydroxy-7-methoxyquinazolin-4(3*H*)-one (4.395 g, 22.9 mmol) in DMF (50 mL) at 0 °C was added 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (55 mL, 55 mmol). After it was stirred at room temperature for 1 hour, it was cooled again with an ice-water bath and to it was added chloromethyl pivalate (4.14 g, 27.5 mmol). After it was stirred at room temperature for another hour, it was quenched with a solution of AcOH (10 mL) in water (150 mL) and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated to afford the (5-hydroxy-7-methoxy-4-oxoquinazolin-3(4*H*)-yl)methyl pivalate solid (5.674 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.36 (s, 1H), 8.16 (s, 1H), 6.69 (d, 1H), 6.51 (d, 1H), 5.88 (s, 2H), 3.89 (s, 3H), 1.21 (s, 9H); LC-MS (ESI) *m/z* 307 $(M + H)^+$.

[00875] Example 94A Step 7: To a solution of (5-hydroxy-7-methoxy-4-oxoquinazolin-3(4*H*)-yl)methyl pivalate (2.50 g, 8.16 mmol), tetrahydro-4H-pyran-4-ol (1.02 g, 10 mmol), and Ph_3P (3.41 g, 13 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added di t-butyl azodicarboxylate (3.993 g, 13 mmol). It was stirred at room temperature for 2 hour. After solvent was evaporated under reduced pressure, to the residue was added 7 N NH_3/MeOH (80 mL) and stirred at room temperature

overnight. A solid was precipitated. It was filtered, washed with MeOH, and dried under vacuum to afford 7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4(3*H*)-one as solid (1.091 g, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.6 (br, 1H), 7.98 (s, 1H), 6.74 (d, 1H), 6.69 (d, 1H), 4.79 (m, 1H), 3.97 (m, 2H), 3.91 (s, 3H), 3.57 (m, 2H), 1.98 (m, 2H), 1.74 (m, 2H); LC-MS (ESI) *m/z* 277 $(M + H)^+$.

[00876] Example 94A Step 8: A mixture of 7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4(3*H*)-one (0.60 g, 2.17 mmol), $POCl_3$ (0.5 mL), and *N*,*N*-diisopropylethylamine (1.5 mL) in $ClCH_2CH_2Cl$ (6 mL) was heated at 100°C for 4 hours. After the solvent and reagents were evaporated under reduced pressure, toluene was added to the residue, and the solution was evaporated under reduced pressure. The residue was dried under vacuum to afford 4-chloro-7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazoline as a brown solid. LC-MS (ESI) *m/z* 295 $(M + H)^+$.

[00877] Example 94B. Using the procedure described in Example 92A Step 3, using 1-(5-tert-butylisoxazol-3-yl)-3-(3-hydroxyphenyl)urea (0.193 g, 0.7 mmol) from Example 1A, 4-chloro-7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazoline from the previous step (0.212 g, 0.72 mmol), and Cs_2CO_3 (0.326 g, 1 mmol) in isopropanol (10 mL) at 60 °C for 4 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4-yloxy]phenyl}urea as solid (0.104 g, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.58 (s, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.37 (d and s, 2H), 6.95 (d and s, 2H), 6.59 (s, 1H), 5.89 (s, 1H), 4.76 (m 1H), 3.99 (m, 2H), 3.96 (s, 3H), 3.66 (m, 2H), 2.06 (m, 2H), 1.95 (m, 2H), 1.33 (s, 9H); LC-MS (ESI) m/z 534 $(M + H)^+$.

Example 95

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00878] Example 95A Step 1: A stirred mixture of 7-(benzyloxy)-6-methoxyquinazolin-4-ol (5.10 g, 18.09 mmol) and phosphorous oxychloride (10 mL, 109 mmol) in dry toluene (30 mL), was heated to 120 °C for 2 h. After cooling to room temperature the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with sat aqueous $NaHCO_3$ solution (2 x 100 mL). The organic layer was separated and dried over $MgSO_4$ then concentrated under reduced pressure to afford 7-(benzyloxy)-4-chloro-6-

methoxyquinazoline as a cream solid (3.89 g, 72%) which was taken into the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.49 (m, 2H), 7.33-7.43 (m, 5H), 5.33 (s, 2H), 4.07 (s, 3H); LC-MS (ESI) *m/z* 301 $(M + H)^+$.

[00879] Example 95A Step 2: To a stirred solution of 3-aminophenol (1.41 g, 12.93 mmol) in dry tetrahydrofuran (70 mL) at room temperature, was added cesium carbonate (6.32 g, 19.39 mmol). After stirring for a further 75 mins, added 7-(benzyloxy)-4-chloro-6-methoxyquinazoline from the previous step (3.89 g, 12.93 mmol) in one portion and the reaction mixture was heated at 75 °C for 24 h. After cooling to room temperature the mixture was concentrated under reduced pressure. The residue was partitioned between water (200 mL) and a mixture of dichloromethane (160 mL) and 2-propanol (60 mL). The mixture was filtered through a celite plug and the organic layer was separated and dried over $MgSO_4$ and concentrated under reduced pressure. Trituration with diethyl ether, followed by filtration and drying under reduced pressure, afforded 3-(7-(benzyloxy)-6-methoxyquinazolin-4-yloxy)aniline as a cream solid (3.57 g, 74%) which was taken into the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.21-7.55 (m, 8H), 6.57-6.63 (m, 3H), 5.33 (s, 2H), 4.03 (s, 3H), 3.73 (brs, 2H); LC-MS (ESI) *m/z* 374 $(M + H)^+$.

[00880] Example 95A Step 3: A stirred mixture of 3-(7-(benzyloxy)-6-methoxyquinazolin-4-yloxy)aniline from the previous step (2.52 g, 6.76 mmol) and palladium (10% wt on activated carbon) (200 mg) in ethanol (100 mL), under 1 atmosphere of hydrogen gas, was heated at 50 °C for 45 mins. The reaction mixture was filtered through a celite plug and concentrated under reduced pressure. The residue was purified via silica gel chromatography eluting with 1% to 10% methanol in dichloromethane to afford 4-(3-aminophenoxy)-6-methoxyquinazolin-7-ol as a colorless solid (840 mg, 44%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (brs, 1H), 8.47 (s, 1H), 7.50 (s, 1H), 7.21 (s, 1H), 7.08 (m, 1H), 6.35-6.50 (m, 3H), 5.28 (brs, 2H), 3.97 (s, 3H); LC-MS (ESI) *m/z* 284 $(M + H)^+$.

[00881] Example 95B: A stirred mixture of 4-(3-aminophenoxy)-6-methoxyquinazolin-7-ol from the previous step (500 mg, 1.77 mmol) and phenyl 5-tert-butylisoxazol-3-ylcarbamate (460 mg, 1.77 mmol) in dry *N*, *N*-dimethylformamide (10 mL) was heated at 60 °C for 5 h. After cooling to room temperature the mixture was concentrated under reduced pressure. The residue was triturated with diethyl ether and filtered and dried under reduced pressure to afford 1-

(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea as a cream solid (650 mg, 82%) which did not require further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (brs, 1H), 9.58 (brs, 1H), 9.00 (brs, 1H), 8.48 (s, 1H), 7.55-7.57 (m, 2H), 7.40 (m, 1H), 7.24-7.26 (m, 2H), 6.97 (m, 1H), 6.48 (s, 1H), 3.99 (s, 3H), 1.28 (s, 9H); LC-MS (ESI) *m/z* 450 $(M + H)^+$.

Example 96

Preparation of (S)-1-(5-tert-Butyl-isoxazol-3-yl)-3-{3-[6-methoxy-7-(pyrrolidin-3-yloxy)-quinazolin-4-yloxy]-phenyl}-urea (S)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate

[00882] Example 96A: A solution of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea from Example 95B (50 mg, 0.111 mmol), (R)-3-hydroxy-1-tert-butoxycarbonylpyrrolidine (31 mg, 0.167 mmol), triphenylphosphine (44 mg, 0.167 mmol) and diisopropylazodicarboxylate (34 mg, 0.167 mmol) in dry tetrahydrofuran (1 mL) was stirred at room temperature for 15 h. The reaction mixture was partitioned between aqueous 1M sodium hydroxide solution (20 mL) and 10% methanol in dichloromethane (50 mL) and the organic layer was separated and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified via silica gel chromatography eluting with 100% dichloromethane to 10% methanol in dichloromethane to afford (S)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate as a colorless oil (35 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (brs, 1H), 8.62 (s, 1H), 8.30 (brs, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 7.26-7.39 (m, 2H), 7.00 (m, 1H), 5.95 (s, 1H), 5.12 (s, 1H), 4.02 (s, 3H), 3.50-3.80 (m, 5H), 2.20-2.40 (m, 2H), 1.50 (s, 9H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 619 $(M + H)^+$.

[00883] Example 96B: A solution of (S)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate from the previous step (35 mg, 0.0566 mmol) and hydrochloric acid (0.1 mL of a 4N solution in 1,4-dioxane, 0.40 mmol) in dry dichloromethane (.01 mL) was stirred at room temperature for 2 h. Concentrated under reduced pressure to afford (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea dihydrochloride as a colorless solid (22 mg, 67%), which did not

require further purification. ^{1}H NMR (300 MHz, MeOH-d_4) δ 9.02 (brs, 1H), 7.82 (s, 1H), 7.73 (brs, 1H), 7.54 (s, 1H), 7.41 (m, 1H), 7.29 (m, 1H), 7.06 (m, 1H), 6.32 (s, 1H) 5.56 (brs, 1H), 4.04 (s, 3H), 3.50-3.85 (m, 5H), 2.50-2.60 (m, 2H), 1.35 (s, 9H); LC-MS (ESI) *m/z* 519 $(M + H)^+$.

Example 97

Preparation of (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea mono acetate

[00884] A solution of (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea dihydrochloride from Example 96B (100 mg, 0.193 mmol) and formaldehyde (0.08 mL of a 37 wt % solution in water, 0.987 mmol) in a mixture of dry 1,2-dichloroethane (1.5 mL) and dry *N*, *N*-dimethylformamide (0.8 mL) was stirred at room temperature for 20 mins. Sodium triacetoxyborohydride (135 mg, 0.640 mmol) was added in one portion and stirring continued for a further 45 mins. The reaction mixture was partitioned between aqueous 1M sodium hydroxide solution (20 mL) and 10% methanol in dichloromethane (50 mL) and the organic layer was separated and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative HPLC (using phenylhexyl reverse phase column, eluted with gradient of solvent B = 0.05% HOAc/CH_3CN and solvent A = 0.05% HOAc/H_2O) to afford (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea mono acetate as a colorless solid (29 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (brs, 1H), 9.00 (brs, 1H), 8.60 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.30-7.40 (m, 2H), 7.22 (s, 1H), 6.99 (m, 1H), 6.05 (s, 1H), 5.10 (s, 1H), 4.01 (s, 3H), 3.37 (m, 1H), 2.96-3.12 (m, 3H), 2.59 (s, 3H), 2.50 (m, 1H), 2.25 (m, 1H), 2.10 (s, 3H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 533 $(M + H)^+$.

Example 98

Preparation of (R)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate

[00885] Example 98A: Prepared from 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea from Example 95B (350 mg, 0.780 mmol) and (S)-3-hydroxy-1-tert-butoxycarbonylpyrrolidine (219 mg, 1.17 mmol) according to the procedure described for (S)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate in Example 96A to afford (R)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate as a colorless oil (109 mg, 23%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (brs, 1H), 9.00 (brs, 1H), 8.57 (s, 1H), 7.50-7.70 (m, 2H), 7.40-7.50 (m, 2H), 7.30 (m, 1H), 7.00 (m, 1H), 6.48 (s, 1H), 5.30 (brs, 1H), 4.00 (s, 3H), 3.70 (m, 1H), 3.40-3.50 (m, 2H), 3.25 (m, 1H), 2.20-2.40 (m, 2H), 1.40 (s, 9H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 619 (M + H)$^+$.

[00886] Example 98B: Prepared from (R)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazol-3-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate from the previous step (109 mg, 0.176 mmol) according to the procedure described for (S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea dihydrochloride in Example 96B to afford (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea dihydrochloride as a colorless solid (42 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (brs, 1H), 8.61 (brs, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.20-7.40 (m, 4H), 6.99 (m, 1H), 6.02 (s, 1H), 5.05 (m, 1H), 4.01 (s, 3H), 3.10-3.40 (m, 2H), 3.00 (m, 1H), 2.00-2.40 (m, 4H), 1.40 (s, 9H); LC-MS (ESI) *m/z* 519 (M + H)$^+$.

Example 99

Preparation of (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea mono acetate

[00887] A solution of (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea dihydrochloride from Example 98B (110 mg, 0.212 mmol) and formaldehyde (0.08 mL of a 37 wt % solution in water, 0.987 mmol) in a mixture of dry 1,2-dichloroethane (1.5 mL) and dry *N*, *N*-dimethylformamide (0.8 mL) was stirred at room temperature for 20 mins. Sodium triacetoxyborohydride (135 mg, 0.640 mmol) was added in one portion and stirring continued for a further 45 mins. The reaction mixture was partitioned between aqueous 1M sodium hydroxide solution (20 mL) and 10% methanol in

dichloromethane (50 mL) and the organic layer was separated and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column, eluted with gradient of solvent B = 0.05% HOAc/CH_3CN and solvent A = 0.05% HOAc/H_2O) to afford (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea mono acetate as a colorless solid (48 mg, 38%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (brs, 1H), 9.00 (brs, 1H), 8.60 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.30-7.40 (m, 2H), 7.22 (s, 1H), 6.99 (m, 1H), 6.05 (s, 1H), 5.11 (s, 1H), 4.01 (s, 3H), 3.49 (s, 3H), 3.38 (m, 1H), 2.97-3.06 (m, 3H), 2.59 (s, 3H), 2.50 (m, 1H), 2.20 (m, 1H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 533 $(M + H)^+$.

Example 100

Preparation of (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea

[00888] Example 100 Step 1: A stirred mixture of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea from Example 95B (160 mg, 0.356 mmol), (R)-(-)-epichlorohydrin (65 mg, 0.702 mmol), cesium carbonate (120 mg, 0.356 mmol) and potassium iodide (40 mg, 0.241 mmol) in dry *N*, *N*-dimethylformamide (4 mL) was heated in a sealed vial at 80 °C in a Biotage microwave synthesizer for 90 mins. After cooling to room temperature, the mixture was partitioned between water (50 mL) and a mixture of ethyl acetate (40 mL) and tetrahydrofuran (10 mL). The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification via silica gel chromatography eluting with 100% dichloromethane to 5% methanol in dichloromethane to afford (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(oxiran-2-ylmethoxy)quinazolin-4-yloxy)phenyl)urea as a colorless solid (27 mg, 15%). LC-MS (ESI) *m/z* 506 $(M + H)^+$.

[00889] Example 100 Step 2: A stirred solution of (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(oxiran-2-ylmethoxy)quinazolin-4-yloxy)phenyl)urea from the previous step (25 mg, 0.0495 mmol) and *N*-methylpiperazine (10 mg, 0.0998 mmol) in dry *N*, *N*-dimethylformamide (1 mL) was heated at 70 °C for 15 h. Concentration under reduced pressure gave a residue that was triturated with diethyl ether and further purified via silica gel chromatography eluting with 10% methanol in

dichloromethane to afford (R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea as a colorless solid (5 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (brs, 1H), 8.62 (s, 1H), 8.30 (brs, 1H), 7.64 (s, 1H), 7.52 (s, 1H), 7.27-7.39 (m, 3H), 7.00 (m, 1H), 5.96 (s, 1H), 4.20-4.28 (m, 3H), 4.02 (s, 3H), 2.00-2.80 (m, 14H), 1.29 (s, 9H); LC-MS (ESI) *m/z* 606 $(M + H)^+$.

Example 101

Preparation of 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyl)urea

[00890] Example 101A: The intermediate from Example 95B (102 mg, 0.23 mmol) was treated with cesium carbonate (89 mg, 0.27 mmol) in N,N'-dimethylformamide (4 mL) and stirred at room temperature for 30 minutes. tert-Butyl 4-(tosyloxymethyl)piperidine-1-carboxylate (84.3 mg, 0.23 mmol) was added and the mixture stirred at 70 °C for 17h. After cooling to room temperature the solid was filtered off and washed with diethyl ether. The filtrate was concentrated under reduced pressure and the resulting residue purified by silica gel chromatography (dichloromethane/methanol 9:1) to afford 4-((4-(3-(3-(3-tert-butylisoxazol-5-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)methyl)piperidine-1-carboxylate (71 mg, 48%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.2 (bs, 1H), 8.80 (bs, 1H), 8.62 (s, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 7.37-7.27 (m, 3H), 6.98 (d, 1H), 6.04 (s, 1H), 4.30-4.05 (m, 2H), 4.05 (s, 5H), 2.79 (t, 3H), 2.25-2.05 (m, 1H), 1.99-1.89 (m, 3H), 1.46 (s, 9H), 1.28 (2, 9H); LC-MS (ESI) *m/z* 647 $(M + H)^+$.

[00891] Example 101B. To a solution of 4-((4-(3-(3-(3-tert-butylisoxazol-5-yl)ureido)phenoxy)-6-methoxyquinazolin-7-yloxy)methyl)piperidine-1-carboxylate (49 mg, 0.062 mmol) in dichloromethane (0.31 mL) was added hydrochloric acid (0.31 mL, 4M in dioxane) and the mixture stirred at room temperature for 30 minutes. The solid was filtered off, dissolved in methanol and concentrated under reduced pressure. The residue was taken in ethyl acetate and a saturated solution of sodium bicarbonate was added until the solution became basic. The solid was filtered off, washed thoroughly with water and dried to afford 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyl)urea as a white

solid (23.31 mg, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.10 (bs, 1H), 9.65 (bs, 1H), 8.56 (s, 1H), 7.61-7.21 (m, 5H), 6.95 (d, 1H), 6.56 (s, 1H), 4.25-3.90 (m, 6H), 3.00 (d, 2H), 2.45 (d, 2H), 2.20-1.79 (m, 1H), 1.78-1.51 (m, 4H), 1.25 (s, 9H); LC-MS (ESI) *m/z* 547 $(M + H)^+$.

Example 102

Preparation of 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yloxy)phenyl)urea

[00892] To a solution of 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyl)urea (82.5 mg, 0.15 mmol) in 1,2-dichloroethane/N,N'-dimethylacetamide (1.3 mL, 3:1) was added 37% formaldehyde (24 mL, 0.3 mmol) and acetic acid (10 μL, 0.18 mmol). The mixture was stirred at room temperature for 20 minutes. Sodium triacetoxyborohydride (48 mg, 0.23 mmol) was added in portions and the resulting mixture stirred at room temperature for 2h. Ethyl acetate and 1N sodium hydroxide were added to the mixture, the organic layer was separated and the water phase extracted three times. The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by preparative HPLC (Phenomenex phenylhexyl reverse phase column) to afford 1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yloxy)phenyl)urea (57 mg, 68%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (bs, 1H), 9.21 (bs, 1H), 8.55 (s, 1H), 7.57 (d, 2H), 7.37-7.26 (m, 3H), 6.96 (d, 1H), 6.47 (s, 1H), 4.07-3.99 (m, 5H), 2.83-2.79 (m. 2H), 2.17 (s, 3H), 1.93-1.76 (m, 5H), 1.39-1.35 (m, 2H), 1.27 (s, 9H); LC-MS (ESI) *m/z* 561 $(M + H)^+$.

Example 103

Preparation of (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)pyrrolidin-3-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea

[00893] Example 103A: To a suspension of 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl]urea from Example 95B (0.45 g, 1 mmol), (*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (0.225 g, 1.2 mmol), and Ph_3P (0.393 g, 1.5 mmol) in THF (10 mL) was added di *t*-butyl azodicarboxylate

(0.345 g, 1.5 mmol). After it was stirred at room temperature overnight, it was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with 70-90% EtOAc/hexane as eluants to afford (*S*)-*tert*-butyl 3-(4-{3-[3-(5-*tert*-Butylisoxazol-3-yl)ureido]phenoxy}-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate as solid (0.609 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.8 (s, 1H), 8.61 (s, 1H), 7.67 (m, 1H), 7.50 (m, 2H), 7.34 (t, 1H), 7.31 (m, 1H), 6.96 (d, 1H), 6.13 (s, 1H), 5.12 (m, 1H), 4.06 (s, 3H), 3.61-3.80 (m, 4H), 2.34 (m, 2H), 1.47 (s, 9H), 1.31 (s, 9H); LC-MS (ESI) m/z 619 $(M + H)^+$.

[00894] Example 103B: To a solution of (*S*)-*tert*-butyl 3-(4-{3-[3-(5-*tert*-butylisoxazol-3-yl)ureido]phenoxy}-6-methoxyquinazolin-7-yloxy)pyrrolidine-1-carboxylate (0.609 g, 0.98 mmol) in CH_2Cl_2 (10 mL) was dropped 4.0 M solution of HCl in 1,4-dioxane (2 mL) and it was stirred at room temperature for 4 hours. After solvents were concentrated under reduced pressure, it was dissolved in CH_2Cl_2 with a few milliliters of MeOH and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure to afford (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy]phenyl}urea as a white solid (0.396 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.61 (s, 1H), 8.5 (s, 1H), 7.67 (m, 2H), 7.49 (m, 2H), 7.38 (t, 1H), 6.99 (d, 1H), 5.99 (s, 1H), 5.05 (m, 1H), 4.01 (s, 3H), 3.40 (m, 1H), 3.21 (m, 2H), 3.0 (m, 1H), 2.3 (m, 1H), 2.1 (m, 2H), 1.32 (s, 9H); LC-MS (ESI) m/z 519 $(M + H)^+$.

[00895] Example 103C: To a solution of (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy]phenyl}urea (0.198 g, 0.38 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL) in CH_2Cl_2 (10 mL) was added 2,2-difluoroethyl trifluoromethanesulfonate (0.128 g. 0.6 mmol) and it was stirred at 40 °C for 1 hour. It was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Extracts were dried over $MgSO_4$ and concentrated under reduced pressure. It was purified by silica gel chromatography with 70-85% EtOAc/hexane as eluants to afford (*S*)-1-(5-*tert*-Butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)pyrrolidin-3-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea as solid (0.098 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.62 (s, 1H), 7.81 (s, 1H), 7.65 (t, 1H), 7.54 (s, 1H), 7.40 (t, 1H), 7.33 (m, 1H), 7.19 (s, 1H), 7.00 (d, 1H), 5.93 (tt, 1H), 5.87 (s, 1H), 5.05 (m,

1H), 4.03 (s, 3H), 3.20 (m, 1H), 3.89-3.09 (m, 4H), 2.8 (m, 1H), 2.5 (m, 1H), 2.15 (m, 1H), 1.33 (s, 9H); LC-MS (ESI) *m/z* 583 $(M + H)^+$.

Example 104

Preparation of (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yloxy]quinazolin-4-yloxy}phenyl)urea

[00896] The title compound was prepared as described in Example 103C using (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy]phenyl}urea (0.198 g, 0.38 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.139 g, 0.6 mmol), and *N*,*N*-diisopropylethylamine (0.5 mL) in CH_2Cl_2 (10 mL) at 40 °C for 3 hours, which was purified by silica gel chromatography with 70-85% EtOAc/hexane as eluants to afford (*S*)-1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yloxy]quinazolin-4-yloxy}phenyl)urea as solid (0.108 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.62 (s, 1H), 7.93 (s, 1H), 7.65 (t, 1H), 7.54 (s, 1H), 7.39 (t, 1H), 7.32 (m, 1H), 7.20 (s, 1H), 7.01 (d, 1H), 5.89 (s, 1H), 5.06 (m, 1H), 4.03 (s, 3H), 3.41 (m, 1H), 3.18 (q, 2H), 2.9-3.08 (m, 3H), 2.44 (m, 1H), 2.2 (m, 1H), 1.33 (s, 9H); LC-MS (ESI) *m/z* 601 $(M + H)^+$.

Example 105

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)piperidin-4-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea

[00897] Example 105A: Using the procedure described in Example 103A, 1-(5-*tert*-butylisoxazol-3-yl)-3-[3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl]urea from Example 95B (0.45 g, 1 mmol) was reacted with *tert*-butyl 4-hydroxypiperidine-1-carboxylate (0.242 g, 1.2 mmol) in the presence of Ph_3P (0.393 g, 1.5 mmol), and di *t*-butyl azodicarboxylate (0.345 g, 1.5 mmol) in THF (10 mL) at room temperature overnight, to afford *tert*-butyl 4-(4-{3-[3-(5-*tert*-butylisoxazol-3-yl)ureido]phenoxy}-6-methoxyquinazolin-7-yloxy)piperidine-1-carboxylate as a crude product. LC-MS (ESI) *m/z* 633 $(M + H)^+$.

[00898] Example 105B: Using the procedure described in Example 103B,tert-butyl 4-(4-{3-[3-(5-*tert*-butylisoxazol-3-yl)ureido]phenoxy}-6-methoxyquinazolin-7-yloxy)piperidine-1-carboxylate was reacted with 4.0 M HCl/1,4-dioxane at room temperature for 6 hours, to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-yloxy]phenyl}urea as a crude product. LC-MS (ESI) *m/z* 533 $(M + H)^+$.

[00899] Example 105C: The title compound was prepared as described in Example 103C, using 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-yloxy]phenyl}urea (0.213 g, 0.4 mmol), 2,2-difluoroethyl trifluoromethanesulfonate (0.128 g. 0.6 mmol), and *N*,*N*-diisopropylethylamine (0.5 mL) in CH_2Cl_2 (10 mL) at room temperature for 4 hours, which was purified by silica gel chromatography with EtOAc/hexane as eluants to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)piperidin-4-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea as a solid (0.011 g, 4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.61 (s, 1H), 7.66 (t, 1H), 7.55 (s, 1H); 7.31-7.44 (m, 4H), 7.01 (d, 1H), 5.90 (tt, 1H), 5.81 (s, 1H), 4.58 (m, 1H), 4.04 (s, 3H), 2.93 (m, 2H), 2.80 (td, 2H), 2.53 (m, 2H), 2.15 (m, 2H), 2.00 (m, 2H), 1.33 (s, 9H); LC-MS (ESI) *m/z* 597 $(M + H)^+$.

Example 106

Preparation of 1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)piperidin-4-yloxy]quinazolin-4-yloxy}phenyl)urea

[00900] The title compound was prepared as described in Example 103C, using 1-(5-*tert*-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(piperidin-4-yloxy)quinazolin-4-yloxy]phenyl}urea (0.213 g, 0.4 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.139 g, 0.6 mmol), and *N*,*N*-diisopropylethylamine (0.5 mL) in CH_2Cl_2 (10 mL) at room temperature for 4 hours, which was purified by silica gel chromatography with EtOAc/hexane as eluants and preparative HPLC (C_{18} column and 60-90% MeCN/H_2O with 0.05% AcOH) to afford 1-(5-*tert*-butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)piperidin-4-yloxy]quinazolin-4-yloxy}phenyl)urea as a solid (0.027 g, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.61 (s, 1H), 7.66 (t, 1H), 7.59 (m, 1H), 7.55 (s, 1H), 7.40 (t, 1H), 7.31 (m, 2H), 7.02 (d, 1H), 5.83 (s, 1H), 4.60 (m, 1H), 4.04 (s, 3H), 3.04 (q, 2H), 3.00 (m, 2H), 2.67 (m, 2H), 2.15 (m, 2H), 2.02 (m, 2H), 1.33 (s, 9H); LC-MS (ESI) *m/z* 615 $(M + H)^+$.

Example 107

Preparation of 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea

[00901] Example 107A Step 1: A suspension of 5,4-dimethoxy-2-nitrobenzoic acid (15.0 g, 0.066 mol) in 20% potassium hydroxide solution (99 mL) was heated at 100°C for 12 h. The reaction mixture was cooled down to 0°C and 6N HCl was added to bring the solution to pH 3. The yellow solid was filtered and the cake washed with cold water. LC/MS: M-1: 212. The solid was dissolved in MeOH (400 mL) and HCl gas was bubbled for 2-3 min. After stirring at 65°C for 16 h, the solvent was evaporated under vacuum. The solid was taken up in ethyl acetate and washed with sat'd $NaHCO_3$ solution. The organic phase was washed with brine and dried over $MgSO_4$ to yield methyl 5-hydroxy-4-methoxy-2-nitrobenzoate (13.01 g , 87% yield). LC-MS (ESI) *m/z* 228 $(M + H)^+$.

[00902] Example 107A Step 2: To solution of methyl 5-hydroxy-4-methoxy-2-nitrobenzoate (13.0 g, 0.0572 mol) in DMF (120 mL) and benzyl chloride (7.23 ml, 0.0629 mol), K_2CO_3 (8.69 g, 0.0629 mol) and potassium iodide (0.949 g, 0.0057 mol) were added. The reaction mixture was heated at 90-95°C overnight. The solvent was evaporated under vacuum and the residue was taken in ethyl acetate and washed with water and brine. After drying over $MgSO_4$, the solution was concentrated ad purified on silica gel column to yield methyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate (13.99 g, 77% yield). ^{1}HNMR (DMSO-d_6): δ 7.66 (1H, s), 7.40 (6H, m), 5.27 (2H, s), 3.83 (3H, s), 3.80 (3H, s). LC-MS (ESI) *m/z* 318 $(M + H)^+$.

[00903] Example 107A Step 3: To a solution of methyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate (13.48 g, 0.0425 mol) in MeOH (700 mL) at 55°C, a concentrated solution of $Na_2S_2O_4$ in water was added slowly until no more starting material was observed on TLC. The heterogeneous solution was concentrated under vacuum. The residue was treated with water (100 ml) and the mixture extracted with ethyl acetate (2x200 mL) . The combined organic layers were washed with water and brine. After drying over $MgSO_4$, the solvent was evaporated and the residue was purified on silica gel column, using ethyl acetate/DCM (1/9) as eluent to yield methyl 2-amino-5-(benzyloxy)-4-methoxybenzoate. Yield: 7.36 g (60%). ^{1}HNMR (DMSO-

d_6): δ 7.34 (5H, m), 7.25 (1H, s), 6.48 (2H, s), 6.39 (1H, s), 4.91 (2H, s), 3.80 (3H, s), 3.73 (3H, s). LC-MS (ESI) *m/z* 288 $(M + H)^+$.

[00904] Example 107A Step 4: A mixture of methyl 2-amino-5-(benzyloxy)-4-methoxybenzoate (7.36 g, 0.025 mol), formamide (25 mL) and acetic acid (6.25 mL) was heated at 130°C for 24 hr. After letting cooling down to room temperature, water was added and the resulting solid was filtered and washed with plenty of cold water. The solid was dried under vacuum at 120°C for 3 hr to yield 6-(benzyloxy)-7-methoxyquinazolin-4(3H)-one. Yield: 7.45 g (100%). ^{1}HNMR (DMSO-d_6): δ 12.15 (1H, s), 8.05 (1H, s), 7.66 (1H, s), 7.44 (5H, m), 7.23 (1H, s), 5.28 (2H, s), 3.92 (3H, s). LC-MS (ESI) *m/z* 207 $(M + H)^+$.

[00905] Example 107A Step 5: A solution of 6-(benzyloxy)-7-methoxyquinazolin-4(3H)-one (7.45 g, 0.026 mol) was heated at 4 hr under argon. The reaction mixture was concentrated to dryness, the residue taken in toluene (150 mL) and evaporated to dryness again. The solid was taken in ethyl acetate and washed with cold sat'd solution of $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. After solvent evaporation the titled compound was obtained 6-(benzyloxy)-4-chloro-7-methoxyquinazoline as a light yellow solid. Yield: 6.34 g (79.8%). ^{1}HNMR (DMSO-d_6): δ 8.89 (s, 1H), 7.40 (m, 7H), 5.34 (s, 2H), 4.00 (s, 3H).

[00906] Example 107A Step 6: To a solution of 6-(benzyloxy)-4-chloro-7-methoxyquinazoline (3.3 g, 0.01097 mol) and 3-aminophenol (1.2 g, 0.01097 mol) in THF (70 mL), Cs_2CO_3 (5.36 g, 0.0164 mol) was added at room temperature. The reaction mixture was stirred at 75°C for 25 hr. The mixture was filtered and the solid was washed with ethyl acetate (100 mL). The organic phase was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated under vacuum and the solid was triturated with ethyl ether (20 mL). The solid was filtered and washed with ethyl ether to afford 3-(6-(benzyloxy)-7-methoxyquinazolin-4-yloxy)aniline (3.72 g, 90% yield). ^{1}HNMR (DMSO-d_6): δ 8.55 (s,1H), 7.66 (s, 1H,), 7.46 (m, 8H), 7.08 (t, 1H), 6.49 (d, 1H), 6.40 (m, 2H), 5.30 (s, 2H), 4.02 (s, 3H). LC-MS (ESI) *m/z* 508 $(M + H)^+$.

[00907] Example 107A Step 7: A mixture of 3-(6-(benzyloxy)-7-methoxyquinazolin-4-yloxy)aniline (3.64 g, 0.00974 mol) and Pd/C (10 %) in ethanol/THF (400 mL, 3/1) was hydrogenated at 1 atm. of H_2, at 50-55°C for 3 h. The mixture was filtered through Celite and the filtrate was concentrated to about 100 mL. The crude was left in the fridge overnight. The solid was filtered and washed with small portion of cold ethanol to afford 4-(3-aminophenoxy)-7-methoxyquinazolin-6-ol (2.05 g, 74.3% yield). ^{1}HNMR (DMSO-d_6): δ 10.30 (1H, s), 8.49 (1H, s), 7.46 (1H, s), 7.34 (1H, s), 7.07 (1H, m), 6.48 (1H, m), 6.40 (2H, m), 5.29 (2H, s), 3.90 (3H, s). LC-MS (ESI) *m/z* 284 $(M + H)^+$.

[00908] Example 107B: To a solution of 4-(3-aminophenoxy)-7-methoxyquinazolin-6-ol (2.0 g, ~ 0.0070 mol) in DMF (10 mL), phenyl 5-tert-butylisoxazol-3-ylcarbamate (1.74 g, 0.0067 mol) was added. The reaction mixture was stirred at 60°C, overnight. The solvent was evaporated under vacuum and the residue was sonicated in the presence of ethyl ether (60 mL). The solid was filtered and washed with ethyl ether to afford 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea (2.75 g, 87.5% yield). ^{1}HNMR (DMSO-d_6): δ 10.53 (s, 1H), 9.57 (s, 1H), 8.99 (s,1H), 8.50 (s, 1H), 7.52 (d, 2H), 7.37 (m, 2H), 7.25 (d, 1H), 6.95 (d, 1H), 6.18 (s, 1H), 4.00 (s, 3H), 1.30 (s, 9H); LC-MS (ESI) *m/z* 450 $(M + H)^+$.

Example 108

Preparation of (S)-*tert*-butyl 3-(4-(3-(3-(5-*tert*-butylisoxazole-3-yl)ureido)phenoxy)-7-methoxyquinazolin-6-yloxy)pyrrolidine-1-carboxylate

[00909] To a stirred solution of diisopropylazodicarboxylate (155 µL, 0.80 mmol) in THF (5 mL) under argon, triphenylphosphine (209 mg, 0.80 mmol) was added. After stirring 15 at room temperature, a solution of (R)-tert-butyl pyrrolidinol carboxylate (150 mg, 0.80 mmol) 1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea (300 mg, 0.668 mmol) in THF (3 mL) was added. Reaction mixture was left stirring at room temperature overnight. The solvent was evaporated and the residue was purified on silica gel column, using ethyl acetate/hexane as eluent. The titled compound was obtained as a foam. Yield: 330 mg (80%). ^{1}HNMR (dmso-d6): δ 9.58 (1H, s), 9.00 (1H, s), 8.57 (1H, s), 7,60 (2H, m),

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

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THIS IS VOLUME __1___ OF __2___

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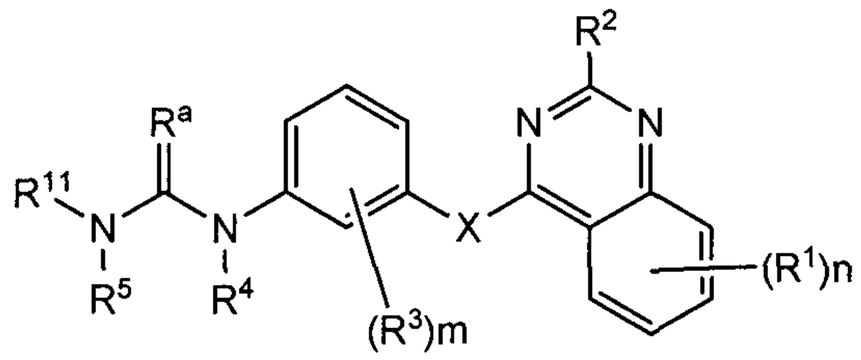
1. A compound having formula (I):



I

or a pharmaceutically acceptable salt, solvate, clathrate or hydrate thereof, wherein

X is O or $S(O)_t$;

R^a is O or S;

each R^1 is independently halo, nitro, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(NR^7)N(R^7)_2$, $-R^6C(O)N(R^7)R^9N(R^7)_2$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$, $-R^6S(O)_tN(R^7)_2$, $-R^6S(O)_tN(R^7)N(R^7)_2$, $-R^6S(O)_tN(R^7)N{=}C(R^7)_2$, $-R^6S(O)_tN(R^7)C(O)R^8$, $-R^6S(O)_tN(R^7)C(O)N(R^7)_2$, $-R^6S(O)_tN(R^7)C(NR^7)N(R^7)_2$, $-R^6N(R^7)C(O)R^8$, $-R^6N(R^7)C(O)OR^8$, $-R^6N(R^7)C(O)N(R^7)_2$, $-R^6N(R^7)C(NR^7)N(R^7)_2$, $-R^6N(R^7)C(S)N(R^7)_2$, or $-R^6N(R^7)S(O)_tR^8$; or any two adjacent R^1 groups together form an alkylenedioxy group;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaralkyl, or two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

each R^8 is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaralkyl;

each R^9 is independently an alkylene chain or an alkenylene chain;

R^2 is hydrogen, halo, alkyl, amino or alkylamino;

R^3 is halo or alkyl;

R^4 and R^5 are each independently hydrogen or alkyl, or

R^4 and R^5, together with the N atom to which they are attached, form an oxo-substituted heterocyclyl;

R^{11} is isoxazolyl;

m is an integer from 0 to 4;

n is an integer from 0 to 4;

t is an integer from 0 to 2;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally substituted with one, two or three Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^uN(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^uN(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_tR^w$, $-R^uN(R^x)R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ or $-R^uC(R^x)=NN(R^y)(R^z)$;

when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy;

when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy, hydroxyl, oxo or cyano;

each R^u is independently alkylene or a direct bond;

each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$;

R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

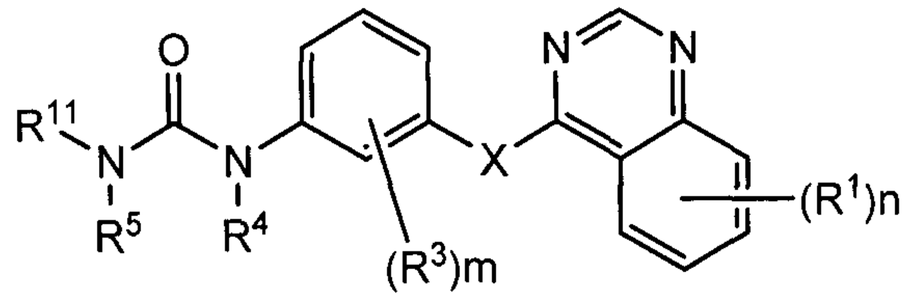
each R^x is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl; and

J is O, NR^x or S.

2. The compound of claim 1 having formula (II):



II

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

X is O, S, S(O) or SO_2;

each R^1 is independently halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(O)_tR^8$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$, $-R^6C(O)N(R^7)OR^7$, $-R^6C(O)N(R^7)R^9OR^7$, $-R^6C(O)N(R^7)R^9SR^7$, $-R^6C(O)SR^8$, $-R^6S(O)_tOR^7$, or $-R^6S(O)_tN(R^7)_2$; or any two adjacent R^1 groups together form an alkylenedioxy group;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaralkyl, or two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl;

each R^9 is independently an alkylene chain or an alkenylene chain;

R^3 is halo or alkyl;

R^4 and R^5 are each independently hydrogen or alkyl;

R11 is isoxazolyl;

m is an integer from 0 to 4;

n is an integer from 0 to 4,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{11} are optionally substituted with one, two or three Q^1 substituents which are independently nitro, halo, azido, cyano, oxo, thioxo, imino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,

heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-R^uOR^x$, $-R^uOR^uOR^x$, $-R^uOR^uN(R^y)(R^z)$, $-R^u N(R^y)(R^z)$, $-R^u SR^x$, $-R^u C(J)R^x$, $-R^uC(J)OR^x$, $-R^uC(J)N(R^y)(R^z)$, $-R^uC(J)SR^x$, $-R^uS(O)_tR^w$, $-R^uOC(J)R^x$, $-R^uOC(J)OR^x$, $-R^uOC(J)N(R^y)(R^z)$, $-R^uOC(J)SR^x$, $-R^u N(R^x)C(J)R^x$, $-R^uN(R^x)C(J)OR^x$, $-R^uN(R^x)C(J)N(R^y)(R^z)$, $-R^uN(R^x)C(J)SR^x$, $-R^uSi(R^w)_3$, $-R^uN(R^x)S(O)_2R^w$, $-R^uN(R^x)R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2N(R^y)(R^z)$, $-R^uS(O)_2N(R^y)(R^z)$, $-R^uP(O)(R^v)_2$, $-R^uOP(O)(R^v)_2$, $-R^uC(J)N(R^x)S(O)_2R^w$, $-R^uC(J)N(R^x)N(R^x)S(O)_2R^w$, $-R^uC(R^x)=N(OR^x)$ or $-R^uC(R^x)=NN(R^y)(R^z)$;

when Q^1 is alkyl, alkenyl or alkynyl, each Q^1 is optionally substituted with halo, cyano, hydroxy or alkoxy;

when Q^1 is cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl, each Q^1 is optionally substituted with halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, alkoxy, hydroxyl, oxo or cyano;

each R^u is independently alkylene or a direct bond;

each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$;

R^w is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

each R^x is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocycle or heteroaryl;

t is an integer from 0 to 2; and

J is O, NR^x or S.

3. The compound of claim 1 or 2, wherein the compound is a pharmaceutically acceptable salt of the compound of formula (I) or formula (II).

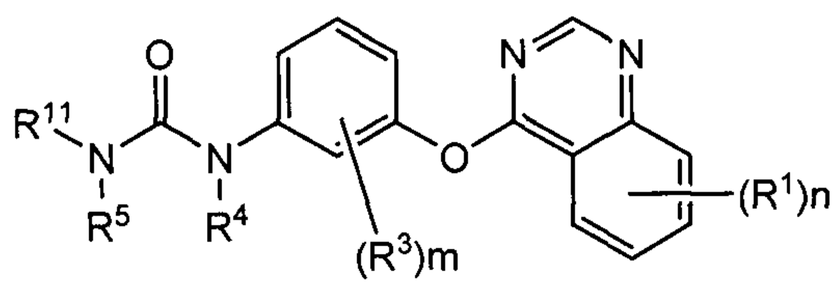
4. The compound of claim 1 or 2, wherein the compound is a solvate of the compound of formula (I) or formula (II).

5. The compound of claim 1 or 2, wherein the compound is a hydrate of the compound of formula (I) or formula (II).

6. The compound of any one of claims 1 to 5, wherein X is O, S or S(O).

7. The compound of any one of claims 1 to 6, wherein R^3 is methyl, chloro or fluoro.

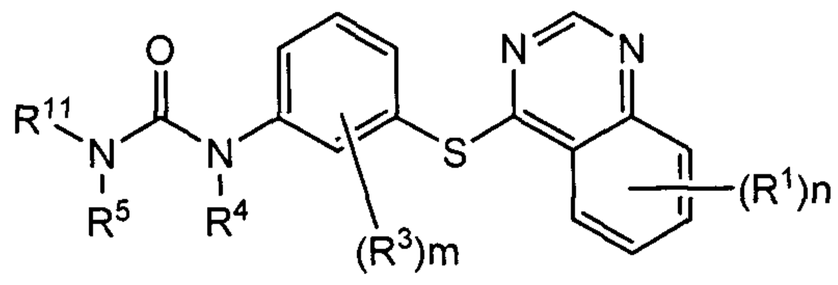
8. The compound of claim 1, wherein the compound has formula III:



III,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

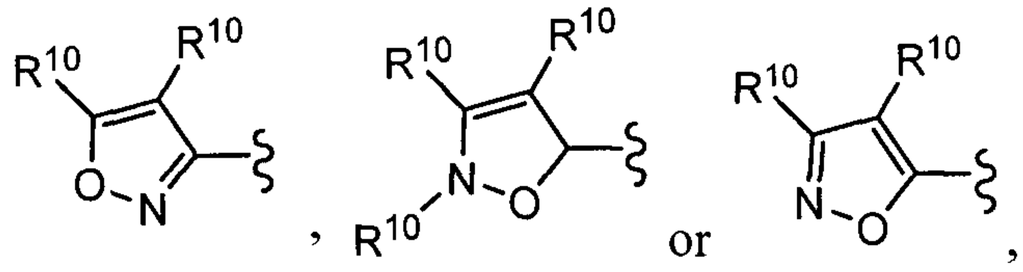
9. The compound of claim 1, wherein the compound has formula IV:



IV,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

10. The compound of any one of claims 1 to 9, wherein R^{11} is:

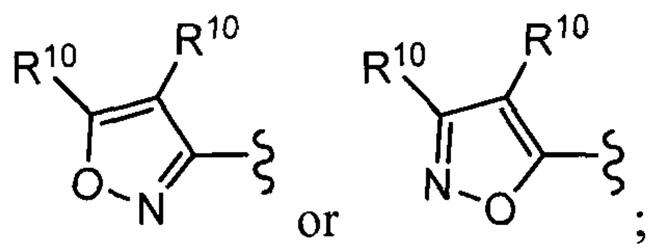


wherein each R^{10} is independently hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, alkoxyalkoxy, aryl, heterocyclyl, heterocyclylcarbonyl, alkoxycarbonyl or heteroaryl, wherein the alkyl, aryl, heteroaryl and heterocyclyl

groups are optionally substituted with 1 to 5 halo, cyano, hydroxy, alkoxy, cycloalkyl, heterocyclyl, alkylcarbonyl or alkoxycarbonyl groups.

11. The compound of any one of claims 1 to 10, wherein

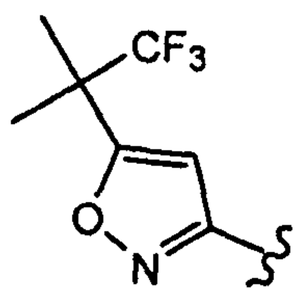
R^{11} is



;

wherein each R^{10} is independently hydrogen, alkyl, hydroxyalkyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, alkoxyalkyl, aryl or heteroaryl.

12. The compound of any one of claims 1 to 10, wherein R^{11} is



13. The compound of any of one of claims 1 to 12, wherein

each R^1 is independently hydrogen, halo, nitro, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6OR^9SR^7$, $-R^6SR^9OR^7$, $-R^6SR^9SR^7$, $-R^6OR^9N(R^7)_2$, $-R^6SR^9N(R^7)_2$, $-R^6CN$, $-R^6C(O)R^7$, $-R^6C(O)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(O)N(R^7)_2$ or $-R^6N(R^7)C(O)R^8$, or any two adjacent R^1 groups together form an alkylenedioxy group;

each R^6 is independently a direct bond, alkylene chain or alkenylene chain;

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaralkyl, or two R^7 groups together with the N atom to which they are attached form a heterocyclyl or heteroaryl; and

each R^9 is independently an alkylene chain or an alkenylene chain,

wherein R^1, R^6, R^7 and R^9 groups are optionally substituted with one, two or three Q^1 groups, wherein each Q^1 is independently haloalkyl, alkyl, $-R^uOR^x$, $-R^uC(J)OR^x$, $-R^uS(O)_2R^w$, $-R^uN(R^x)S(O)_2R^w$ or $-R^uN(R^x)\ R^uS(O)_2R^w$; wherein

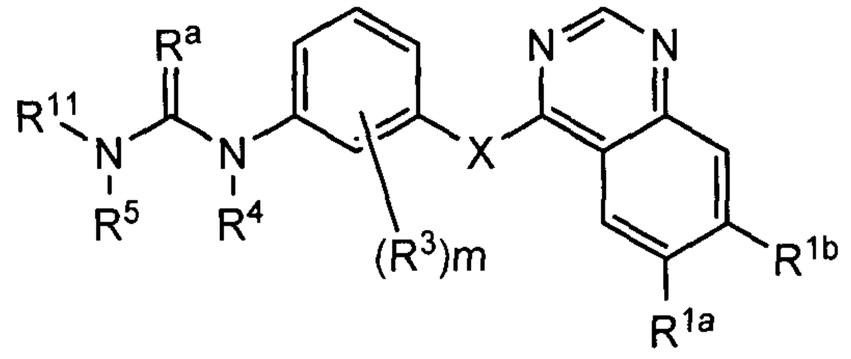
R^u is direct bond or alkylene;

R^x is hydrogen or alkyl;

R^w is alkyl; and

J is O, S or NR^x, such that at least one R^1 is other than hydrogen.

14. The compound of any one of claims 1 to 7, having formula XII:



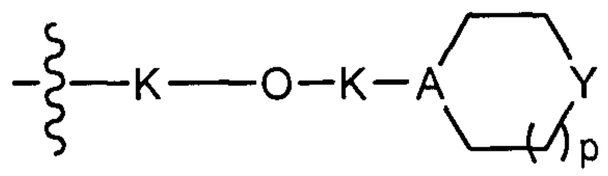
XII

or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R^a is O or S;

X is O or S;

R^{1a} and R^{1b} groups together form an alkylenedioxy group; or R^{1a} and R^{1b} are each independently hydrogen, halo, amino, alkyl, aryl, heteroaryl, alkoxy, hydroxy, alkoxyalkoxy, cycloalkylcarbonylamino or a group of formula:



,

wherein

each K is independently a direct bond or alkylene and is optionally substituted with one, two or three hydroxy or alkyl groups;

A is N or CR^{16};

Y is –O, -S, -S(O), $-S(O)_2$, $-N(R^{14})$, $-C(H)R^{15}$, or -C(O);

p is an integer from 0 to 2;

R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heteroarylalkyl, arylalkyl, $S(O)_tR^{13}$ or $-C(O)R^{12}$;

R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

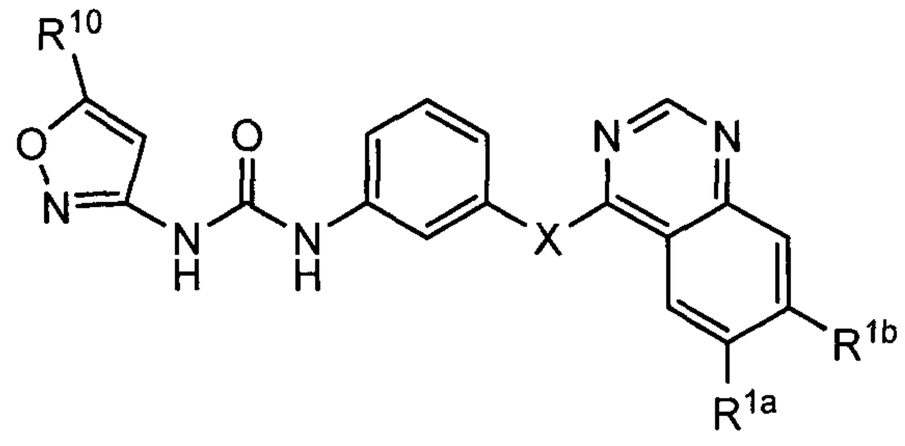
R^{16} is hydrogen or alkyl;

t is 1 or 2;

each R^{12} is independently hydrogen or alkyl; and

R^{13} is alkyl.

15. The compound of claim 1, having formula XVII:

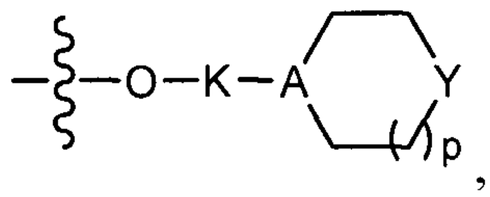


XVII,

or a pharmaceutically acceptable salt, solvate or hydrate thereof,

wherein X is O or S;

R^{1a} and R^{1b} groups together form an alkylenedioxy group; or R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy, alkylsulfonylalkoxy or a group of formula:



,

wherein

K is a direct bond or alkylene, optionally substituted with a hydroxy group;

A is N or CH;

Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

p is 0 or 1;

R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl or $S(O)_tR^{13}$;

R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or $-OR^{12}$;

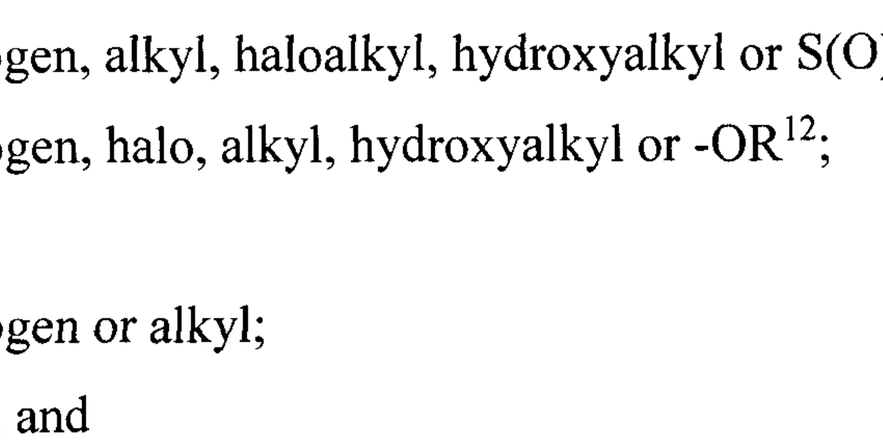
t is 1 or 2;

R^{12} is hydrogen or alkyl;

R^{13} is alkyl; and

R^{10} is hydrogen, halo, alkyl, aryl, heterocyclyl, heteroaryl, cycloalkyl or cycloalkylalkyl; wherein alkyl, aryl, heterocyclyl and heteroaryl groups are optionally substituted with 1-3 halo, cyano, hydroxyl or alkoxy groups.

16. The compound of claim 1, having formula XIX:



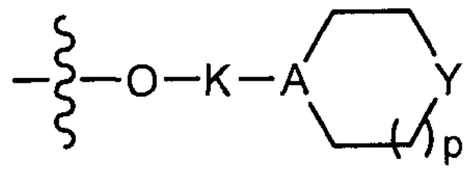
XIX

or a pharmaceutically acceptable salt, solvate or hydrate thereof,

wherein

X is O or S;

R^{1a} and R^{1b} groups together with the carbon atoms on which they are substituted form an ethylenedioxy group; or R^{1a} and R^{1b} are each independently methoxy, methoxyethoxy, methylsulfonylpropyloxy, or a group of formula:



,

wherein K is ethylene or propylene, optionally substituted with a hydroxy group;

A is N or CH;

Y is –O, $-S(O)_2$, $-N(R^{14})$ or $-C(H)R^{15}$;

p is 1;

R^{14} is hydrogen, methyl, hydroxyethyl, or methylsulfonyl;

R^{15} is hydrogen, hydroxymethyl, hydroxyethyl or hydroxy;

and

R^{10} is hydrogen, halo, alkyl, aryl, heterocyclyl, heteroaryl, cycloalkyl or cycloalkylalkyl; wherein alkyl, aryl, heterocyclyl and heteroaryl groups are optionally substituted with 1-3 halo, cyano, hydroxyl or alkoxy groups.

17. The compound of claim 1, that is:

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-yloxyphenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(5-methylquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl] urea hydrochloride;

1-(5-tert-Butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methylquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(4-chloro-3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-(5-tert-butylisoxazol-3-yl)urea hydrochloride;

1-(5-tert-Butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea hydrochloride;

1-(5-tert-Butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-yloxy)phenyl]urea hydrochloride;

1-(5-tert-butylisoxazol-3-yl)-3-{3-[7-methoxy-6-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea hydrochloride;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-hydroxymethyl) piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(3-hydroxy-pyrrolidin-1-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yloxy)phenyl)urea;
(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;
(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-yloxy)phenyl)urea;
1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{7-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl) ethoxy)-6 methoxyquinazolin-4yloxy)phenyl)urea;
1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{7-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea
1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-yloxy)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-Butylisoxazol-3-yl)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl]urea;
1-(5-tert-butylisoxazol-3-yl)-3-[3-(6,7-diethoxyquinazolin-4-ylthio)phenyl]urea;
1-(5-tert-butylisoxazol-3-yl)-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea hydrochloride;
1-{3-[6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-tert-butylisoxazol-3-yl)urea hydrochloride;
1-(5-tert-butylisoxazol-3-yl)-3-[3-(7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-ylthio)phenyl]urea hydrochloride;
1-(5-tert-Butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2H-pyran-4-ylthio)quinazolin-4-yloxy]phenyl}urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-Butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-7-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl) urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(hydroxylmethyl)piperidin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quinazolin-4-ylthio) phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(methylsulfonyl)ethoxy)quinazolin-4-ylthio)phenylurea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio) phenyl)urea;
1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-[3-(1,1-dioxo--thiomorpholin-4-yl)-propoxy]-quinazolin-4-ylsulfanyl}-phenyl)-urea;
1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethoxy]-7-methoxy-quinazolin-4-yloxy}-phenyl)-urea;
1-(5-tert-butylisoxazol-3-yl)-3-{3-[6-(5-{[2-(methylsulfonyl)ethylamino]methyl}furan-2-yl)quinazolin-4-yloxy]phenyl}urea;
1-(5-tert-butylisoxazol-3-yl)-3-{3-[7-methoxy-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-yloxy]phenyl}urea;
1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea;
(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea;
(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl) urea mono acetate;
(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea;
(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(1-methylpyrrolidin-3-yloxy) quinazolin-4-yloxy)phenyl)urea mono acetate;
(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-Butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yloxy)phenyl)urea;

(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)pyrrolidin-3-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea;

(S)-1-(5-tert-Butylisoxazol-3-yl)-3-(3-{6-methoxy-7-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yloxy]quinazolin-4-yloxy}phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-{7-[1-(2,2-difluoroethyl)piperidin-4-yloxy]-6-methoxyquinazolin-4-yloxy}phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea;

(S)-tert-butyl-3-(4-(3-(3-(5-tert-butylisoxazole-3-yl)ureido)phenoxy)-7-methoxyquinazolin-6-yloxy)pyrrolidine-1-carboxylate;

(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(1-methylpyrrolidin-3-yloxy)quinazolin-4-yloxy)phenyl)urea;

(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

(S)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-hydroxy-3-(4methylpiperazin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-hydroxy-3-(4methylpiperazin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-phenylisoxazol-3-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropylisoxazol-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(tetrahydro-2H-pyran-4-yl)isoxazol-5-yl)urea;

1-(3-cyclopropylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(2-cyanopropan-2-yl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-methylcyclopropyl)isoxazol-3-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-hydroxy-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-tert-butylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-isopropylisoxazol-3-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-isopropylisoxazol-3-yl)urea;
1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(2-fluoropropan-2-yl)isoxazol-3-yl)urea;
1-(3-(1,1-difluoroethyl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1-(trifluoromethyl)cyclobutyl)isoxazol-5-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(1-(trifluoromethyl)cyclobutyl)isoxazol-5-yl)urea;
1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;
1-[3-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-yloxy]phenyl)urea;
1-[3-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-5-yl]-3-[3-(6,7-dimethoxyquinazolin-4-ylthio]phenyl)urea;
1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-[3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]urea;
1-(3-cyclopentylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;
1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]urea;
1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;
1-(3-tert-butylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;
1-(3-(6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(5-phenylisoxazol-3-yl)urea;
1-(5-isopropylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-cyclopentylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-(1,1-difluoroethyl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}urea;

1-(3-cyclopropylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-isopropylisoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(tetrahydro-2H-pyran-4-yl)isoxazol-5-yl)urea;

1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea;

1-[5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}urea;

1-(5-isopropylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxy ethoxy)quinazolin-4-ylthio)phenyl)urea;

1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea;

1-(5-cyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea;

1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-methoxy-6-(4,4-dioxo-3-thiomorpholinopropoxy)quinazolin-4-ylthio)phenyl)urea;

1-(3-(6,7-bis(2-Methoxyethoxy)quinazolin-4-ylthio)phenyl)-3-(3-tert-butylisoxazol-5-yl)urea;

1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-ylthio)phenyl)urea;

1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylsulfinyl)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea;
1-(5-tert-butyl-isoxazol-3-yl)-3-(3-{7-[3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea;
1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)urea;
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)urea; or
1-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea,
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

18. The compound of claim 1, that is:

1-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea ;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)-3-(5-(2-fluoropropan-2-yl)isoxazol-3-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(2-methyl-1-morpholinopropan-2-yl)isoxazol-3-yl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea;

1-(3-(2-cyanopropan-2-yl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

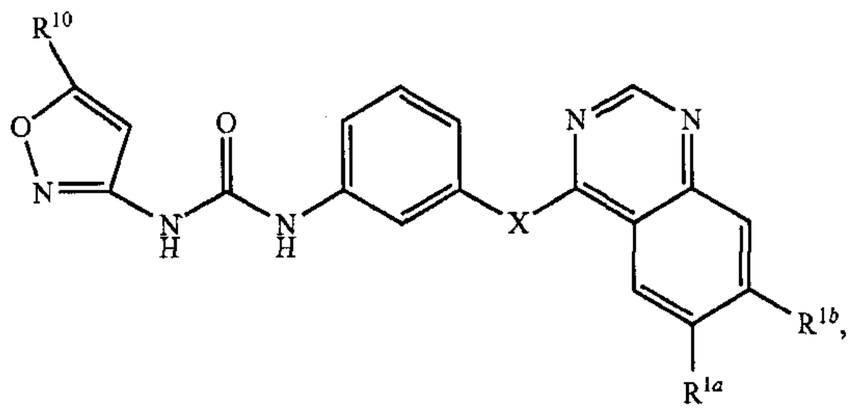
1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea;

1-(3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(7-ethoxy-6-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl)urea;
1-(3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;
1-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;
1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea;
1-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea; or
1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)urea;
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

19. A compound having formula XVII:

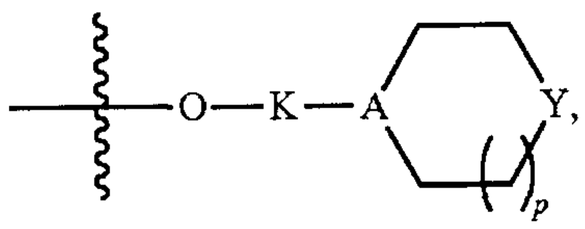
XVII



or a pharmaceutically acceptable salt thereof,

wherein X is O or S;

R^{1a} and R^{1b} groups together form an alkylenedioxy group; or R^{1a} and R^{1b} are each independently alkoxy, alkoxyalkoxy, alkylsulfonylalkoxy or a group of formula:



wherein K is a direct bond or alkylene, optionally substituted with a hydroxy group;

A is N or CH;

Y is —O, —$S(O)_2$, —$N(R^{14})$ or —$C(H)R^{15}$;

p is 0 or 1;

R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl or $S(O)_tR^{13}$;

R^{15} is hydrogen, halo, alkyl, hydroxyalkyl or —OR^{12};

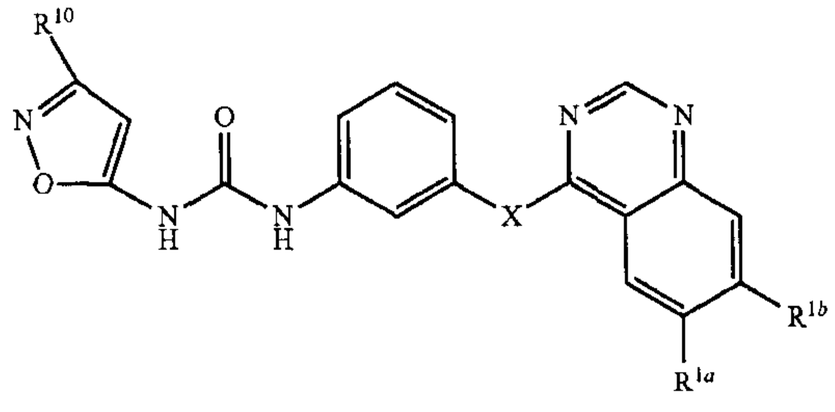
t is 1 or 2;

R^{12} is hydrogen or alkyl;

R^{13} is alkyl; and

R^{10} is hydrogen, halo, alkyl, aryl, heterocyclyl, heteroaryl, cycloalkyl or cycloalkylalkyl; wherein alkyl, aryl, heterocyclyl and heteroaryl groups are optionally substituted with 1-3 halo, cyano, hydroxyl or alkoxy groups.

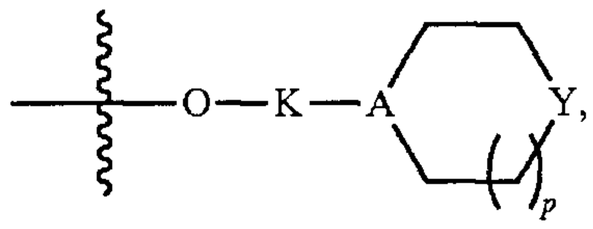
20. The compound of claim 19, having formula XIX:



or a pharmaceutically acceptable salt thereof,

wherein X is O or S;

R^{1a} and R^{1b} groups together with the carbon atoms on which they are substituted form an ethylenedioxy group; or R^{1a} and R^{1b} are each independently methoxy, methoxyethoxy, methylsulfonylpropyloxy, or a group of formula:



wherein K is ethylene or propylene, optionally substituted with a hydroxy group;

A is N or CH;

Y is —O, —$S(O)_2$, —$N(R^{14})$ or —$C(H)R^{15}$;

p is 1;

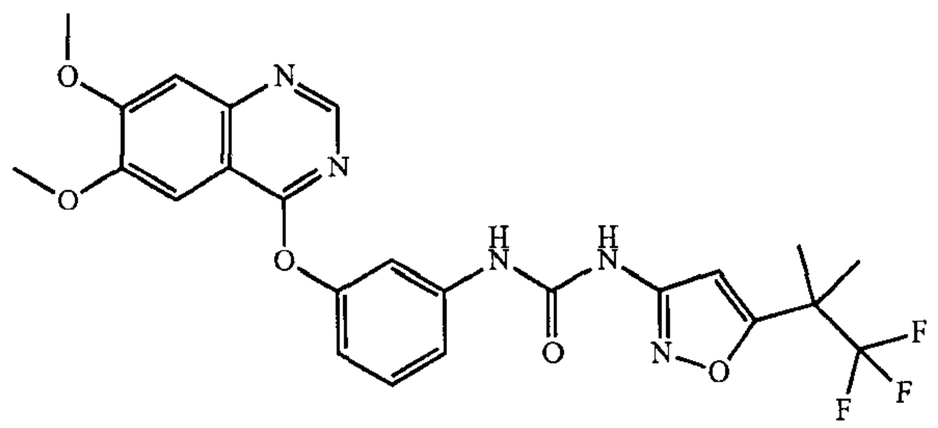
R^{14} is hydrogen, methyl, hydroxyethyl, or methylsulfonyl;

R^{15} is hydrogen, hydroxymethyl, hydroxyethyl or hydroxy; and

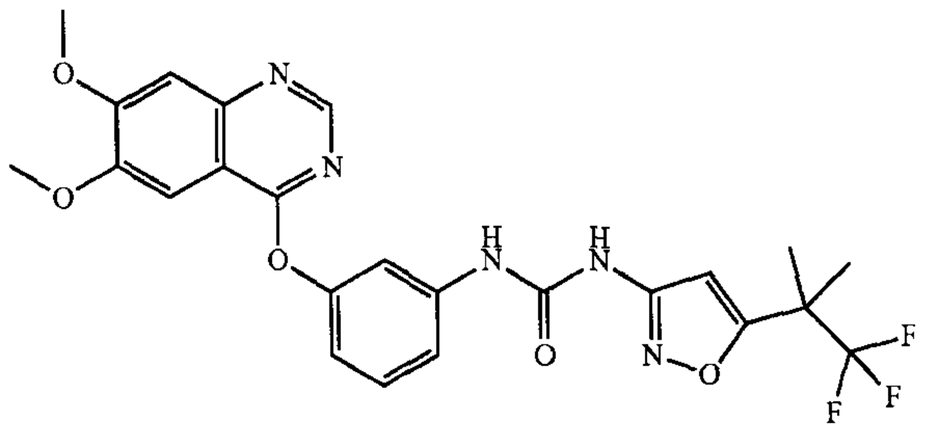
R^{10} is hydrogen, halo, alkyl, aryl, heterocyclyl, heteroaryl, cycloalkyl or cycloalkylalkyl; wherein alkyl, aryl, heterocyclyl and heteroaryl groups are optionally substituted with 1-3 halo, cyano, hydroxyl or alkoxy groups.

21. The compound of claim 19, that is 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea or a pharmaceutically acceptable salt thereof.

22. A compound that is



23. A pharmaceutically acceptable salt of compound

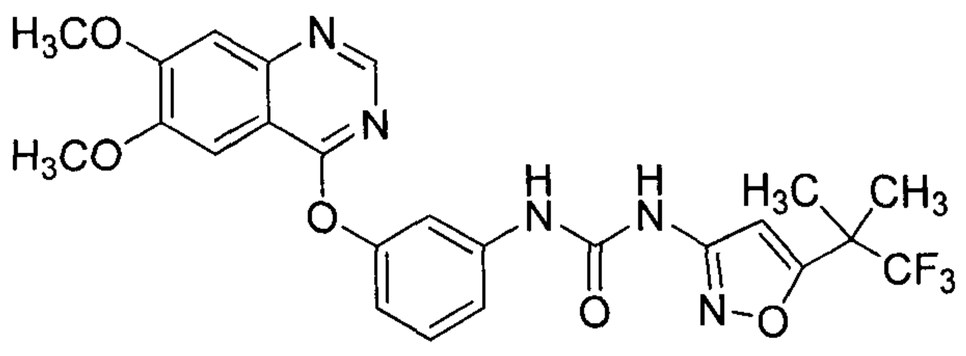


24. A pharmaceutical composition comprising the compound defined in any one of claims 1 to 22, or of the salt defined in claim 23, and a pharmaceutically acceptable carrier, excipient or diluent.

25. The pharmaceutical composition of claim 24, further comprising a second therapeutic agent that is a chemotherapeutic agent, an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent or an immunosuppressive agent.

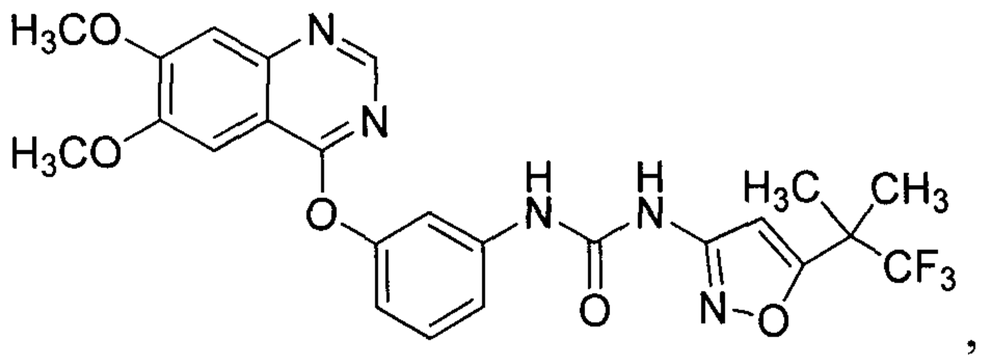
26. A pharmaceutical composition comprising 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.

27. A pharmaceutical composition, comprising from about 1 mg to about 2000 mg of a compound that is



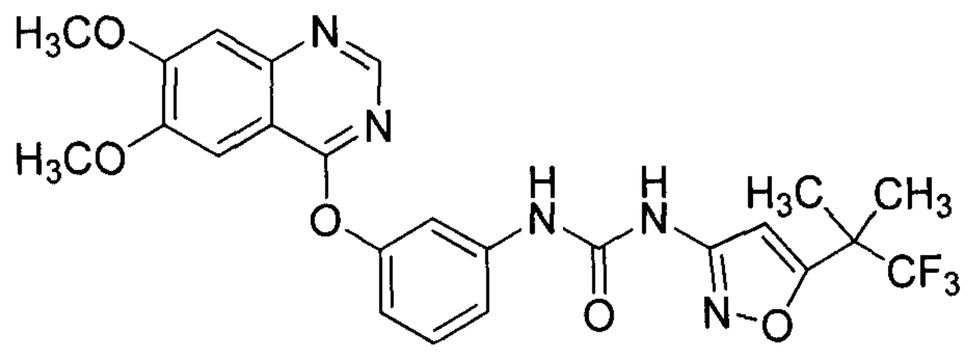
or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient or diluent.

28. The pharmaceutical composition of claim 27, comprising from about 10 mg to about 1000 mg of a compound that is



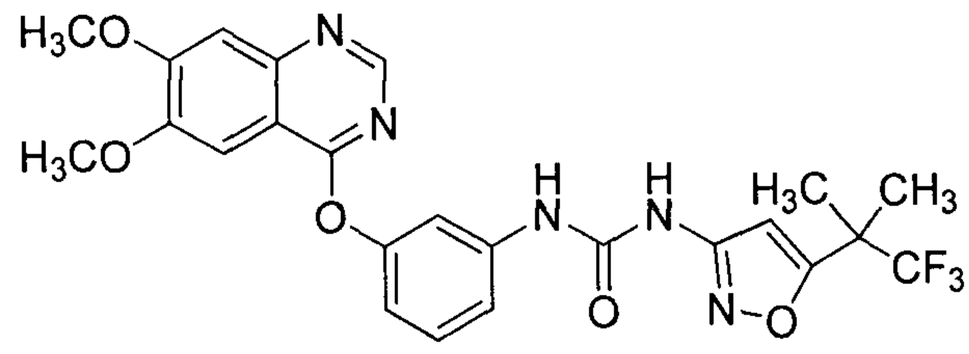
or a pharmaceutically acceptable salt thereof.

29. The pharmaceutical composition of claim 27, comprising from about 20 mg to about 500 mg of a compound that is



or a pharmaceutically acceptable salt thereof.

30. The pharmaceutical composition of claim 27, comprising from about 25 mg to about 250 mg of a compound that is



or a pharmaceutically acceptable salt thereof.

31. The pharmaceutical composition of any one of claims 24 to 30, wherein said pharmaceutical composition is in a dosage form suitable for oral administration to a patient.

32. The pharmaceutical composition of claim 31, wherein said dosage form is a tablet, capsule, troche, lozenge, pastille, cachet, pellet, gum, bulk powder, effervescent powder, non-effervescent powder, solution, emulsion, suspension, wafer, sprinkle, elixir, or syrup.

33. The pharmaceutical composition of claim 32, wherein said dosage form is a tablet, capsule, cachet, effervescent powder, non-effervescent powder, solution, emulsion, suspension, or syrup.

34. The pharmaceutical composition of claim 33, wherein said dosage form is a tablet, capsule, solution, emulsion, suspension, or syrup.

35. The pharmaceutical composition of claim 34, wherein said dosage form is a tablet or capsule.

36. The pharmaceutical composition of claim 35, wherein said dosage form is a tablet.

37. The pharmaceutical composition of claim 35, wherein said dosage form is a capsule.

38. Use of the compound defined in any one of claims 1 to 22, of the salt defined in claim 23, or of the pharmaceutical composition defined in any one of claims 24 to 37, for the treatment of cancer, wherein the cancer is melanoma, papillary thyroid carcinoma, colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, Barret's adenocarcinoma, glioma, small cell lung cancer, non-small cell lung cancer, head and neck cancer, acute lymphoblastic leukemia or non-Hodgkin's lymphoma.

39. Use of the compound defined in any one of claims 1to 22, of the salt defined in claim 23, or of the pharmaceutical composition defined in any one of claims 24 to 37, for the treatment of an inflammatory disease, wherein the inflammatory disease is immune dysfunction, immunodeficiency, immunomodulation, autoimmune disease, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, allergic rhinitis, inflammatory bowel disease, systemic lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma or chronic obstructive pulmonary disease.

40. Use of the compound defined in any one of claims 1 to 22, or of the salt defined in claim 23, for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, papillary thyroid carcinoma, colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, Barret's adenocarcinoma, glioma, small cell lung cancer, non-small cell lung cancer, head and neck cancer, acute lymphoblastic leukemia or non-Hodgkin's lymphoma.

41. Use of the compound defined in any one of claims 1 to 22, or of the salt defined in claim 23, for the manufacture of a medicament for the treatment of an inflammatory disease, wherein the inflammatory disease is immune dysfunction, immunodeficiency, immunomodulation, autoimmune disease, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, allergic rhinitis, inflammatory bowel disease, systemic lupus erythematosis, arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma or chronic obstructive pulmonary disease.

42. The use of claim 38 or 40, further comprising a second therapeutic agent that is a chemotherapeutic agent, an anti-proliferative agent, an antiintlammatory agent, an immunomodulatory agent or an immunosuppressive agent.

43. The use of claim 42, wherein the second therapeutic agent is an antimetabolite, a topoisomerase inhibitor or a platinum agent.

44. The use of claim 42, wherein the second therapeutic agent is 5-fluorouraci1, methotrexate, fludarabine, vincristine, vinblastine, paclitaxel, docetaxel, cyclophosphamide, melphalan, caimustine, bischloroethylnitrosurea, hydroxyurea, cisplatin, carboplatin, oxaliplatin, satraplatin, CI-973, doxorubicin, daunorubicin, mitomycin, idarubicin, adriamycin, daunomycin, etoposide, camptothecins, sorafenib, bevacizumab, estramustine phosphate or prednimustine.

45. The use of claim 38 or 40, wherein the cancer is papillary thyroid carcinoma.

46. Use of 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea or a pharmaceutically acceptable salt thereof for treating a cancer associated with activated BRAF kinase.

47. The use of claim 46, wherein the cancer is melanoma.

48. The use of claim 46, wherein the cancer is thyroid cancer.

49. The use of claim 46, wherein the cancer is colorectal cancer.

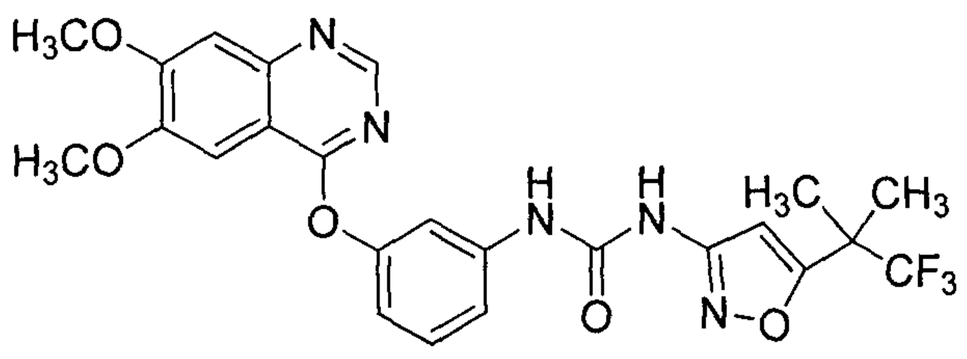
50. The use of claim 46, wherein the cancer is non-small cell lung cancer.

51. Use of 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea or a pharmaceutically acceptable salt thereof for inhibiting the activity of a mutated form of BRAF kinase.

52. The use of claim 51, wherein the mutated form is a V600 mutant.

53. The use of claim 52, wherein the V600 mutant is V600E.

54. Use of a compound which is



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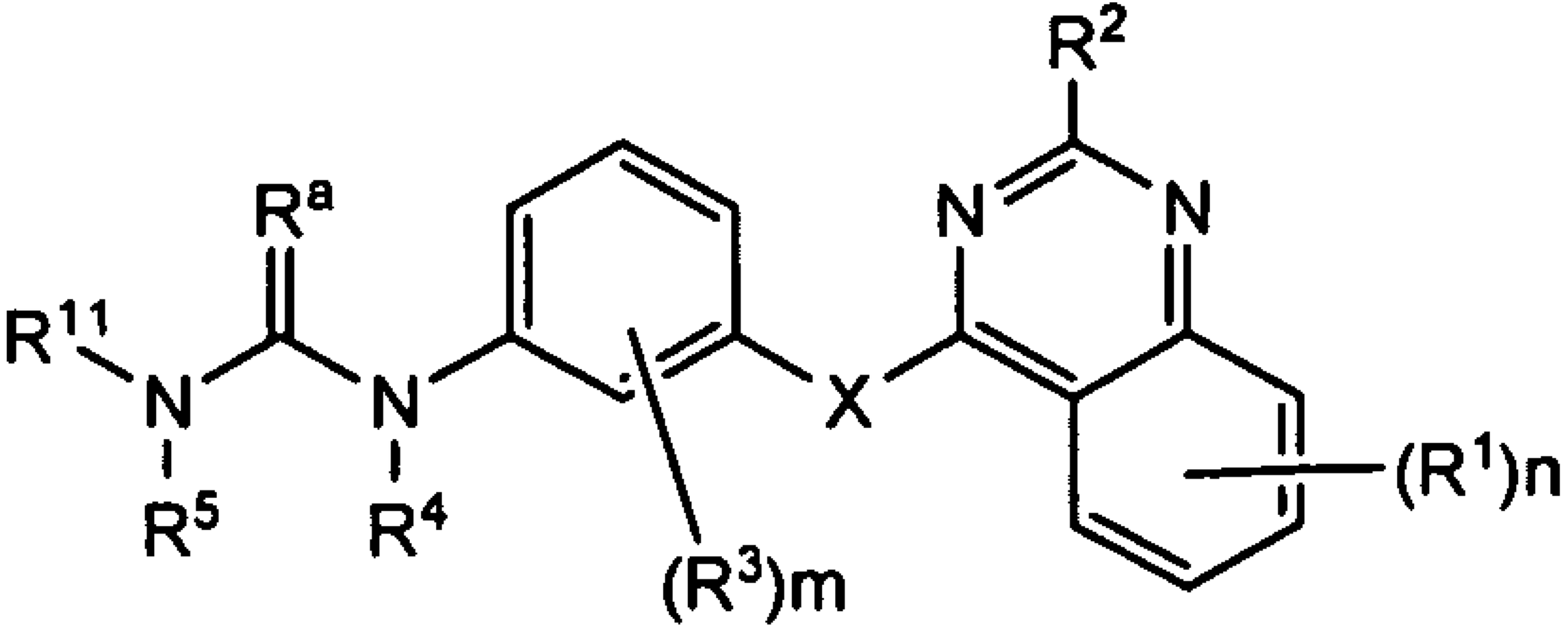
or a pharmaceutically acceptable salt thereof, for treating cancer, wherein said cancer has a BRAF V600E mutation.

55. The use of claim 54, wherein said cancer is colorectal cancer or melanoma.

56. The use of claim 55, wherein said cancer is colorectal cancer.

57. The use of claim 55, wherein said cancer is melanoma.



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