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(54) Title: METHODS FOR TREATING HCV INFECTION

(57) Abstract: The present invention provides methods of treating HCV infection is subjects (e.g., mammals), comprising administering to a subject' in need thereof an effective amount of a RAF kinase inhibitor or a prodrug thereof. The present invention also provides methods of treating IiCV infection, comprising administering to a subject in need thereof an effective amount of a RAF kinase inhibitor conjointly with at least one additional therapeutic agent (eg., an antiviral agent).

METHODS FOR TREATING HCV INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application Serial No. 61/820,479 filed 07 May 2013, which is hereby incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major global health problem with an estimated 150-200 million people having been infected worldwide. According to the World Health Organization, 3 to 4 million new infections occur each year. The onset of HCV infection is often insidious, with anorexia, vague abdominal discomfort, nausea and vomiting, fever and fatigue, progressing to jaundice in about 25% of patients. Of those exposed to HCV, about 40% recover fully whether they develop symptoms or not. However, the majority of HCV-infected individuals develop chronic infection, which often leads to serious liver disease, including fibrosis and steatosis. About 20% of patients with chronic HCV infection develop liver cirrhosis, of which up to 20% develop liver cancer.

Chronic HCV infection is the leading cause for liver transplantations. Unfortunately, liver transplantation is not a cure for hepatitis C; viral recurrence is an invariable problem and leading cause of graft loss. No vaccine protecting against HCV is available to date partially because the virus comes in many forms and constantly mutates leading to "swarms" of closely related viral genomic sequences (often referred to as quasi-species). The rationales for treatment of chronic hepatitis are to reduce inflammation, preventing progression to fibrosis. Current therapies include administration of ribavirin and/or interferon-alpha (IFN-α), two non-specific anti-viral agents. Combination therapy results in better treatment responses than mono therapy. For example, using a combination treatment of pegylated IFN-a and ribavirin, persistent clearance is achieved in about 50% patients with chronic hepatitis C. However, a large number of patients have contraindications to one of the components of the combination, cannot tolerate the treatment, do not respond to IFN therapy at all, or experience a relapse when administration is stopped. In addition to limited efficacy and substantial side effects such as neutropenia, haemolytic anemia and severe depression, current antiviral therapies are also characterized by high cost.

Until recently, the **development** of more effective **therapeutics to** combat HCV infection has been hampered by the lack of a ceil culture system **supporting** HCV **replication.** Robust production of infectious **HCV in** cell culture has now been achieved using a unique HCV **genome** derived from the blood of a Japanese patient with fulminant hepatitis C (JFH-I). The ability of the **JFH-I** sixain of HCV to release infectious particles in cell culture **(HCVce) and** the **development** of retroviral **HCV pseudoparticles** (KCV'pp) have allowed the complete viral life cycle to **be explored.** This, **in tarn,** has led to the development of new **antiviral** agents targeting **HCV** protein processing and **replication.** However, **many** of these agents have proved to be toxic and highly susceptible to the development of viral resistance, **suggesting** that a **different** strategy is needed for the **treatment** of HCV **infection. Moreover, given the health** risks **imposed** on the **public and** the economic harms imposed on society by HCV infection, there is a pressing need for additional methods and agents for **preventing** and treatment of HCV infection and **HCV-**reiated disorders and diseases,

SUMMARY OF THE INVENTION

The present invention relates to **methods** for treating HCV **infection in** a **subject** (e.g., a mammal) in need thereof. According to the present **invention,** there **is** provided a **method of treating** HCV infection comprising the step of administering to a subject **in** need thereof **an** effective amount **of a compound** that inhibits one or more RAF kinases.

In some embodiments, the compound suitable for use in the methods of the present invention is an inhibitor of one or more RAF kinases selected from A-RAF, B-RAF and C-**RAF.** In certain embodiments of the invention, the RAF inhibitor is selected from compounds described and **referred** to in U.S. Patents 7,235,576 **and** 7,351,834, and **International** Patent **Application Publications WO** 02/24680, WO 2006/024834, WO **2008/147782, and WO** 2009/117080 (ail of which are **incorporated herein** by reference for their disclosure of RAF **inhibitors). In** certain embodiments of the **invention,** the RA.F inhibitor is **selected from sorafenib,** CF.P32496, **Raf-265,** regorafentb, SB-590885, **and** AZ-628 **(structures** shown below),

In accordance with another aspect of the present invention, there is provided a method for treating **HCV infection in** a subject in need thereof, the method comprising administering to said subject an RAF inhibitor or a **pharmaceutically** acceptable salt thereof

conjointly with at ieast one additional therapeutic agent. in some embodiments, the additional therapeutic agent is an antiviral agent. in some embodiments, the additional therapeutic agent is a current. Sate stage or marketed direct-acting antiviral (DAA) agent that may be useful in treating HCV infection. Suitable antiviral agents include, but are not limited to, HCV protease inhibitors and HCV polymerase inhibitors (such as NS3/4A protease inhibitors and RNA-dependmt RNA polymerase (NS5B) inhibitors), agents targeting host cell activities involved in HCV replication and inosine monophosphate dehydrogenase (IMPDE) inhibitors. In certain embodiments, the additional therapeutic agent is a DAA selected from Teiaprevir (Vertex), Boceprevir (Merck), TMC435 (Tibotec), Danoprevir (Genentech/Roche), Vaniprevir (Merck), BI201335 (Boe&ringer-ingelheirn), Narlaprevir (Merck), BMS-650032 (Bristol-Myers Squibb), ABT-450 (Abbott), GS-9451 (Gilead), GS-92S6 (Gilead), MK-5172 (Merck), RG7128 (Genenteeh/lRoche), 1DX184 (idciiix), FSi-7977 or GS-7977 (Pharmasset), PSI-938 (Pharma&set), Tegobuvir (Gilead), Filibuvir or FF-00868554 (Pfizer), ANA 598 (Auadys), BI207I27 (Boehringer-Ingelheim), ABT-333 (Abbott), VX-222 (Vertex), BMS-790052, Aiisporivir (Novartis), and SCY-465 (Scyoexis). in certain embodiments, the additional therapeutic agent is GS-7977 or BMS-790052 (structures shown below). in one embodiment, the method of the present disclosure comprises administering to a subject in need thereof a therapeutically effective amount of AZ-628 conjointly with GS-7977 or BMS-790052.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows pan-RAF kinase inhibitors and their potential targets in the Kii/RAF/MEK/BRK pathway. The tested inhibitors are shown in bold.

Figure 2 shows the antiviral -potency of AZ-628 against HCVpp, Genotype lb, a virus-like particle enabling measurement of the ability of a Raf kinase inhibitor to block HCV entry into cultured human hepatoeytes.

Figure 3 shows the antiviral potency of AZ-628 against HCVee, Genotype 2a, a replication competent, fully infections form of hepatitis C virus.

Figure 4 shows synergistic antiviral potency measured with AZ-628 and the direct-acting antiviral GS7977/Sobosuvir, a nucleotide analog that inhibits the viral RNA-dependent RNA polymerase of HCV. The three-dimensional plot displays the synergy volume data at the 95% confidence interval.

Figure 5 shows **synergistic** antiviral potency against measured with **AZ-628** and the direct-acting antiviral **BMS-790052/Daclatasvir,** an inhibitor of the **non-structural** protein NS5a, which plays a vital role **in HCV genomic** replication in the host. The three-dimensional plot displays the synergy volume data at the 95% confidence interval.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise defined herein, **scientific and** technical terms used in this application shall have the **meanings** that are commonly understood by those of ordinary skill in the art **Generally, nomenclature** used in connection with, and **techniques** of, cell and tissue culture, **molecular biology,** cell and cancer biology, **neurobiology,** neinoehemistry, virology, **immunology,** microbiology, **pharmacology,** genetics and protein and **nucleic** acid **chemistry,** described herein, are those well known and commonly used in the art.

The methods and **techniques** of the present **invention** are generally **performed,** unless **otherwise indicated,** according to any suitable method, including conventional methods well known in the art and as described in various general and **more** specific references that are cited and discussed throughout this specification. See, e.g. Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New **York** (2000); Griffiths et **al., "Introduction** to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); **Gilbert** et **al.,** "Developmental Biology, 6th ed.", Sinauer Associates, **Inc.,** Sunderland, **MA (2000).**

Chemistry terms used herein are used according to conventional usage in the art, as exemplified **by** "The McGraw-Hill Dictionary **of Chemical Terms", Parker** S., Ed., **McGraw-Hill, San Francisco,** C.A. (1985).

All of the publications, patents and published patent applications referred to in this application are **specifically incorporated by** reference herein. In case of conflict, **the** present **specification, including** its specific **definitions,** will control.

Throughout this **specification,** the word **"comprise"** or variations such as **"comprises"** or "comprising" will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as weil as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents which are known with respect to structure, and those which are not known with respect to structure. The RAF kinase inhibitory activity of such agents may render them suitable as "therapeutic agents" in the methods of this invention.

A "patient", "subject", or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, poreines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Hepatitis C virus" or "HCV" is a small (55-65 nm in size), enveloped, positive-sense single-stranded RNA virus of the family *Flavivindae*. HCV strains are usually classified into six genotypes and numerous subtypes on the basis of phylogenetic clustering. The methods of the present invention can be used to treat HCV infection and HCV-reiated disorders and diseases caused by any strain of the hepatitis C virus.

"HCV infection" as used herein refers to a process during which HCV particles bind to the cell surfaces of host cells, enter the host cells, proliferate in the host cells, and then are released outside die cells,

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms associated with HCV-iiifcction; delay or slowing of that infection; amelioration, palliation or stabilization of that infection. The present invention provides a method for treating HCV infection by using

RAF kinase inhibitors. In some embodiments, the antiviral activity of such RAF kinase inhibitors is due to their ability to block the HCV viral entry into the host- cells. In some embodiments, the antiviral activity of such RAF kinase inhibitors is due to their ability to inhibit viral propagation, reproduction, and/or replication. In some embodiments, the antiviral activity of such RAF kinase inhibitors is due to their ability to block the viral release.

"Administering" or "administration of a substance, a compound or an agent to a subject can be carried out using any suitable method, such as one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, intravenously, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods. In some aspects, the administration includes both direct administration, including self-administration, and indirect administration, including the act of prescribing a drug. For example, as used herein, a physician who instructs a patient to self-administer a drug, or to have the drug administered by another and/or who provides a patient with a prescription for a drug is administering the drug to the patient.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age of the subject, whether the subject is active or inactive at the time of administering, whether the subject is infected at the time of administering, the extent of the infection, and the chemical and biological properties of the compound or agent (e.g. solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic compounds such that the second

compound is administered while the previousiy administered therapeutic compoitiid is still effective in the body (*e.g.*, the two compounds are simultaneously effective in die patient, which may include synergistic effects of the two compounds). For example, die different: therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. Thus, art individual who receives such treatment can benefit from a combined effect of different therapeutic compounds.

A "therapeutically effective amount" of a drug or agent is art amount ofa drug or an agent that, when administered to a subject will have the intended therapeutic effect, e.g., treating HCV infection. The full therapeutic ef ect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more doses. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, the nature and extent of the infection, and the therapeutics or combination of therapeutics selected for administration, and the mode of administration. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

"RAF family of kinases", "RAF proteins", or "RAF kinases", as used herein interchangeably, include a set of three isozymes, A-RAF, B-RAF, and C-RAF. This family of kinases has emerged in the past several years as a promising target for protein-directed therapies. A-RAF, B-RAF, and C-RAF are protein-serine/ threonine kinases that are related to retroviral oncogenes discovered in 1983. The murine sarcoma virus 361 l enhances fibrosarcoma induction in newborn MSF/N mice, and the name RAF corresponds to rapidly accelerated f bo sarcoma. RAF-1, which was discovered in 1985, is now called C-RAF. A-RAF was discovered in 1986, and B-RAF was discovered in 1988. B-RAF residue numbering changed in 2004 owing to a prior DNA sequencing error. Residues after position 32, in the original version, were one number short of their actual position.

The RAF proteins are central components of the mttogen-aetivated protein kinase (MARK) pathway that regulates cell proliferation. Elimination of RAF function is predicted to be art effective treatment for the many cancers initiating with EGFR and Ras lesions. In particular, the core MAPK pathway is deemed as one of the most common sources of oncogenic lesions in cancer, Overexpression or mutation of members of the epidermal growth factor (EGFR) protein family leads to numerous cancers, including

pancreatic, lung (adenocarcinoma and non-small ceil lung cancer (NSCLC)}, head and neck squamous cell cancer, colorectal, glioblastoma, and (for EGFR2/HER2/NEU/ERB B2) breast cancer, increased expression and/or mutation-based activation of EGFR hyperactivates its downstream effector, Ras. Furthermore, Ras proteins are mutated, resulting in constitutive activation, in a high percentage of pancreatic, colon, and papillary thyroid cancers, and are also found in oilier cancers such as NSCLC and others. These changes *in* EGFR and Ras lead to a greatly enhanced level of Ras-dependent Raf activation, which in turn communicates signals downstream to MEK1/2 and. the MAPKs ERK1 and. ERK2. Although Ras has other important direct effectors in tumor promotion, including phosphoinositoi-3-kinase (PI3K) and RalGDS the Raf > MEK > ERK signaling axis is essential for oncogenesis, based on validation in many systems.

"inhibitor of RAF kinases", "RAF kinase inhibitor" or "RAF inhibitor" refers to any agent, substance or compound that reduces the activities of one or more RAF kinases. A substance, or a compound or an agent is an inhibitor of RAF kinases even if it does not itself bind to a RAF kinase, as long as it causes, or affects the ability of, another compound or agent to bind RAF, and thus, deactivating the RAF kinase. In some embodiments, a RAF inhibitor inhibits only one RAF isozyme, such as A-RAF, B-RAF or C-RA.F. In some embodiments, a RAF inhibitor inhibits more than one RAF isozyme. For instance, it can inhibit two types or even all three types of the isozymes. In some embodiments, a RAF inhibitor inhibits both B-RAF and C-RAF. In some embodiments, the RAF inhibitor is a class I RAF inhibitor, which has cellular selectivity for B-RAF mutations associated with melanoma, such as V600E. Such class I inhibitors bind wild-type B-RAF with equal proficiency to mutant protein in purified form, but selectively target the mutant protein when present inside ceils. Class *I* RAF inhibitors include, but are not limited to, PLX4032 and GSK2118436, in some embodiments, the RAF inhibitor is a class II RAF inhibitor, which does not discriminate mutant B-RAF from their wild-type counterpart. Class II RAF inhibitors include, but are not limited to, sorafemb, RAF-265 and AZ-628. Inhibitors of RAF kinases, as used herein, include pharmaceutically acceptable salts, derivatives, analogs, prodrugs, and polymorphs of the inhibitors thereof.

"Pharmaceutically acceptable salts" is used herein to refer to an agent or a compound according to the invention that is a therapeutically active, non-toxic base and acid salt form of the compounds. The acid addition sail form of a compound that occurs in

its free form as a base can be obtained by treating said free base form: with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric ant! the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maieie, fumaric, malic, tartaric, citric, methanesu!fonic, ethanesitifonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p- aminosalicylic, pamoic and the like. See, e.g., WO 01/062726.

Compounds containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt form, e. g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e. g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e. g. N-methyl-D-glucamine, hydrabarnine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely, said salt forms can be converted into the free forms by treatment with an appropriate base or acid. Compounds and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like. See, e.g., WO 01/062726.

The present invention includes within its scope, prodrugs, analogs, derivatives and polymorphs of the RAF inhibitors of the invention. In general, such prodrugs will be functional derivatives of a compound of the invention which are readily convertible *in vivo* into the compound from which it is notionally derived. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs" Ed. H. Bundgaard, Elsevier, 1985, the contents of which are hereby incorporated by reference herein in their entirety. For example, a common method for making a prodrug is to select moieties which are hydrolyzed or metabolized under physiological conditions to provide the desired compound or agent. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal to an inhibitor of RAF kinases,

"Analog" is used herein to refer to a compound which functionally resembles another chemical entity, but does not share the identical chemical structure. For example, an analog is sufficiently similar to a base or parent compound such that it can substitute for the base compound in therapeutic applications, despite minor structural differences.

"Derivative" is used herein to refer to the chemical modification of a compound. Chemical modifications of a compound can include, for example, replacement of hydrogen by an alkyl, acyi or amino group. Many other modifications are also possible.

As used herein, the term "polymorph" refers to different crystalline forms of the same compound and other solid state molecular forms including pseudo-polymorphs, such as hydrates (e.g., bound water present in the crystalline structure) and solvates (e.g., bound solvents other than water) of the same compound. Different crystalline polymorphs have different crystal structures due to a different packing of the molecules in the lattice. This results in a different crystal symmetry and/or unit cell parameters which directly influences its physical properties such as the X-ray diffraction characteristics of crystals or powders. A different polymorph, for example, will in general diffract at a different set of angles and will give different values for the intensities. Therefore X-ray powder diffraction can be used to identify different polymorphs, or a solid form that comprises more than one polymorph, in a reproducible and reliable way. Crystalline polymorphic forms are of interest to the pharmaceutical industry and especially to those involved in the development of suitable dosage forms. If the polymorphic form is not held constant during clinical or stability studies, the exact dosage form used or studied may not be comparable from one lot to another. It is also desirable to have processes for producing a compound with the selected polymorphic form in high purity when the compound is used in clinical studies or commercial products since impurities present may produce undesired toxicological effects. Certain polymorphic forms may exhibit enhanced thermodynamic stability or may be more readily manufactured in high purity in large quantities, and thus are more suitable for inclusion in pharmaceutical formulations. Certain polymorphs may display other advantageous physical properties such as lack of hygroscopic tendencies, improved solubility, and enhanced rates of dissolution due to different lattice energies.

Many of the compounds useful in the methods of this invention have at least one stereogenic center in their structure. This stcrcogemc center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appi. Chem. (1976), 45, 11-30. The invention also relates to ail stereoisomerie forms such as enantiomeric and diastereoisoraeric forms of the compounds or mixtures thereof (including ail possible mixtures of stereoisomers). See, e.g., WO 01/062726,

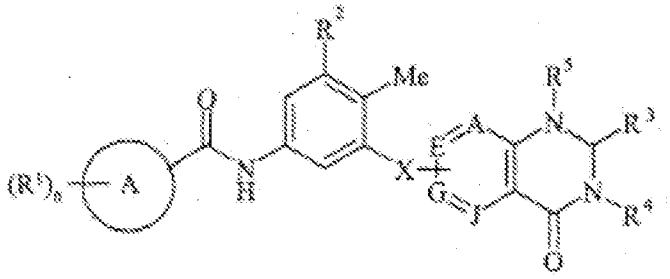
Furthermore, certain **compounds** which contain alkenyi groups may exist as Z **(zusammen)** or E (entgegen) isomers. In each **instance,,** the **invention** includes both mixtures and separated individual isomers. Some of the compounds may also exist in tautomeric **forms.** Such forms although not explicitly indicated in the above **formula** are intended to be included within **the** scope of the present invention. **With** respect to **the** methods and **compositions of the** present invention, reference to a **compound** or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to **specifically.** See, e.g., **WO 01**/062726.

RAF Kinase Inhibitors

Among the RAF inhibitors useful for the methods of this invention are those compounds or agents referred to in:

(i) ***PCI' Application Publication*** *WO 2006/024834, which is incorporated herein by reference:*

A compound of formula A-i:



A-I

wherein:

Ring A is carboeyely l or heterocycly!; wherein if said heterocyeSyi contains an –NH-moiety that nitrogen may he **optionally substituted** by a group selected from R^6;

R^1 is a siibstituent on carbon and is selected from halo, nitre, **cyano,** hydroxy, amino, **carboxy,** carbamoyl **mercapto,** sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, **C½.«aikynyi,** C_1. salkoxy, $C_{1,1}$aikanoy!, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyi)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, ***N*-(Cj.68lkyl)carbamoyl** , *N,N*-(C_{1-6}6alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ **wherein** a is 0 to 2, C_{1-6}alkoxycarbonyl; *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(**Ci.6alkyi)$_2$suiphamoyt**,

N-fC_{1-6}alkoxy)sulphamoyl, *N*-(Ci^aikyl)-.*N*-(C_{1-6}a1koxy)sulphan oy1, C_{1-6}alkylsulphonylamino, carbocyc!yi-R^{7}- or heterocyelyl-R^{8}-; wherein R^{1} may be optionally siibstituicd on carbon by one or more R^{9}; and wherein if said heterocyelyl contains art -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{10};

n is selected from 0-4; wherein the values of R^{1} may be the same or different;

R^{2} is selected from hydrogen, halo, nitro, eyano, hydroxy, amino, carboxy, carbamoyl, mereapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C^alkynyl, C_{2-6}alkoxy, C;i-,,alkaaoy], C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkaiioylamino, *N*-(Cw,aikyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, Ci-salkyiS(0)$_a$ wherein a is 0 to *2*, Ci-,alkoxyearbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$Sulpharaoyk C_{1-6}alkylsulphonylamino, carbocyclyl-R^{11}- or heterocyclyl-R^{12}-; wherein R^{2} may be optionally substituted on carbon by one or more R^{13}; and wherein if said heterocyelyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{14};

X is NR^{f5} or O;

one of A, E, G and J is C which is attached to X of formula A-i; the other three are independently selected from CR^{16} or N;

R^{3} and R^{15} are independently selected from hydrogen, halo, nitro, eyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C^alkyl, CV6alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}a1kanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(Cs-jalkyi)$_2$carbari]ioyl, C_{1-6}alkyiSiO}$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(Cwalkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, Cw;alkylsu!phonyf amino, earbocyclyf-R^{17}- or heterocyelyl -R^{1} wherein R^{3} and R^{16} independently of each other may be optionally substituted on carbon by one or more R^{19}; and wherein if said heterocyelyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20};

R^{4}, R^{5} and R^{15} are independently selected from hydrogen. Chalky!, Ci-salkyisulphonyL C^lkoxycarbonyl, carbamoyl, carbocyclyl, heterocyelyl, *N*-(Ci-$_6$alkyl)carbamoyi and *N;N*-(C$_1$^alkyl)carbamoyl; wherein R^{4}, R^{5} and R^{i5}

independently of each other may be optionally substituted on carbon by one or more R^{21};

the bond "~" between the -NH- and -CR^5- of formula A-I is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

R^9, R^{13}, R^{19} and R^{23} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, Ci-ealkoxycarbonyi, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{22}- or heterocyclyl-R^{25}-; wherein R^9, R^{13}, R^{19} and R^{23} independently of each other may be optionally substituted on carbon by one or more R^{24}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{28};

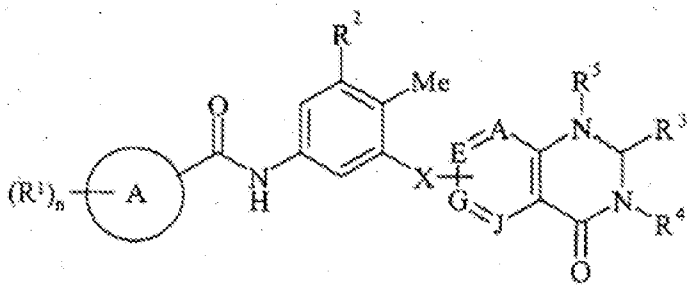
R^7, R^8, R^{12}, R^{17}, R^{18}, R^{22} and R^{23} are independently selected from a direct bond, -G-, -$N(R^{26})$-, -C(O)-, -$N(R^{27})$C(O)-, -C(O)$N(R^{28})$-, -S(O)$_2$-, -S<¾N(R^{29}V or -$N(R^{30})SO_2$-; wherein R^{26}, R^{27}, R^{29}, R^{29} and R^{30} is hydrogen, d-ealkoxycarbonyl or C_{1-6}alkyi and s is 0-2;

R^6, R^{10}, R^{14}, R^{20} and R^{25} arc independently selected from C,.$_6$alkyl, C_{1-6}alkylsulphonyL C_{1-6}alkoxyearbonyl carbamoyl, *N*-(C_1^alkyiearbamoyL *N,*¥-(C_{1-6}aikyl)carbamoyl, benzyl benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{24} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, tr f uoromethyl, amino, earboxy, carbamoyl, mercapto, sulphamoyl, methyl ethyl, methoxy, ethoxy, acetyl acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylearbamoyl, *N*-ethylcarbamoyl, *N*,.V-dimethylcarbamoyl, ,V,iV-dietiiylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methyithio, ethy!thio, methylsuiphinyl, ethylsulphtnyl, mesyl, ethylsuiplionyl methoxycarbonyl ethoxycarbonyl, *N*-methylsuiphamoyl, *N*-ethylsulphamoyl, *N,N*"dvmethylsulphanK>yl, *N,N*-dietfiylsnlphamoyi or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof

in some embodiment, the compound has a structure of formula A~I;



(A-fj

whereia:

Ring A is phenyl, thien~**2**-y.l, thien-3-yl, pyrid~2-yl, pyrid~3~yi, pyrid-4-yl Lthiazol-4-yl, isoxazol-3-yl, l,3-benzodioxo l-5-yl, fur-2-yi, !-methylpyrazol-3-yl, 1-methylpyrazol-5-yl, **1**-i-bitylpyrazot-5-y!, indo 1-5-y!, indo l-6-y!, 2,3-dihydrobe«zofuran~7-yl, imidazo[l,2-a]pyridin-2-yl or pyr midin-4-yl;

R^i is a substituen. on carbon and is selected from fluoro, chloro, bromo, hydroxy, cyano, sulphamoyl, methyl, trifluoromethyi, cyelopropyiamiiioraethyl, meihykhiomethyl, mesylmethyi, dimethylaminomethyl, 1-(cyc!opropyl)- l-hydroxytnethyi, *N*-cycdopropyl-*N*-(*t*-buioxycarbonylamihometbyl, **I**-methylpiperazin -**4**-ylmethyJ, **1**-hydroxy- l-cyclopropylethy!, l-methyl- l-cyanoethyl, **2**-methoxy-l,**1**-dimethylethyl, l-carboxy-i-methylethyl, i,l-difluorocthyi, 2-(djmethylammo)-l,l-ditt»itiiyl-2-oxocihy!, 3-(dimethylamino)propyl, l,l-dimethylpropyl, /f-buty!, methoxy, *N*-methyk arbamoyimethoxy, 2-(diraet-hylamino)edioxy, 2-(py.ox>lidin-l-yl)ethoxy, 2-(mcthoxy)ethoxy , 2~{l-meihylpyrroiidm-2-y!)etboxy, 2-{piperidin- l-yl)ethoxy, 2-(azepan-l-yl}eiboxy, 2~{morpholino)et1oχy, **3**-(!-n¾.thy.lpiperazin-**4**-yl)propoxy, methoxycarbonyl, morphoiinocarbonyl, *N*,*N*-dimethyisulphamoyl, *N*-(2,**3**-dihydroxypropyl)-A[~]-methyIsulphamoyl, *N*-(metJiyl)-iV-(methoxy)sulphamoyi **1**-methy lpiperidin~**4**~yloxy, *N*,**iv**-dimethylcarbamoyl, cyclopropyl, piperidin-l-yf, morpholino, ,-cyclopropyk thenyl, 3-(4~memylpiperazi«~l-yl)prop- l-yn~l-yl, **3**,**3**-dimethylbut-l-yn- i-yi, cyclopropylethynyl, 3-hydroxy-3-methylbut-l-yn-l-yI , l,l-dimctbyiprop-2-yti-i-yi, 3~{dimethy!amino)prop- l-**yn**-**1** -yi, mesyl, cyclopropy!aminosu!phonyl, azetidin-l-yl-sulphonyl, morpholinosuiphonyl,

tetrahydrofur-2-ylmethylaminosulphonyl,

2-(hydroxyethyl)piperidin-1-ylsulphonyl, 3-(hydroxymethyl)piperidin-1-ylsulphonyl or 4-(hydroxymethyl)piperidin-1-ylsulphonyl;

n is selected from 0-2; wherein the values of R^1 may be the same or different;

R^3 is hydrogen;

X is NR^{15} or O;

one of A, E, G and J is C which is attached to X of formula A-I; the other three are all CR^{16} or two are CR^{16} and one is N;

R^5 is selected from hydrogen, methyl *N*-(2-hydroxyethyl)amino, *NN*-dimethylamino or methylthio;

R^4 is selected from hydrogen, methyl, 1-methylpiperidin-3-ylmethyl, cyclopropylmethyl, 2,2-dimethyl-1,3-dioxolan-4-ylmethyl, piperidin-4-ylmethyl, 1-benzyloxycarbonylpiperidin-4-ylmethyl, ethyl, 2-hydroxyethyl, 3-aminopropyl, 3-(t-butoxycarbonylamino)propyl, 3-morpholinopropyl, 2,3-dihydroxypropyl and cyclopropyl;

the bond "---" between the $-NR^5-$ and $-CR^3-$ of formula *A-I* is a double bond wherein R^5 is absent; and

R^{15} is selected from hydrogen, methyl or cyclopropylmethyl;

R^{16} is hydrogen;

or a pharmaceutically acceptable salt thereof,

in some embodiments, the compound is selected from:

3-(1,1-dimethylprop-2-ynyl)-*N*-{4-methyl-3-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino]phenyl}benzamide;

3-(1-cyano-1-methylethyl)-*N*-{4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)aminophenyl}benzamide;

3-(1-cyano-1-methylethyl)-5-fluoro-*N*-{4-methyl-3-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino]phenyl}benzamide;

3-(1-cyano-1-methylethyl)-5-[(dimethylamino)methyl]-*N*-{4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)aminophenyl}benzamide;

4-dimethylaminomethyl-*N*-[4-methyl-3-(3-methyl-4-oxo-3,4-dihydro-quinazolin-6-ylamino)-phenyl]-3-trifluoromethyl-benzamide;

2-(1-cyano-1-methylethyl)-*N*-[4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)aminophenyl]isonicotinamide;

3-(1-cyano-1-methylethyl)-2-fluoro-*N*-{4-methyl-3-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino]phenyl}benzamide;

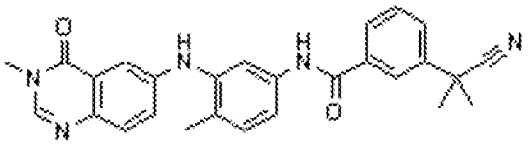
N-(3-{[3-(3-aminopropyl)-4-oxo-3,4-dihydroquinazolin-6-yl]amino}-4-methylphenyl)-3-(1-cyano-1-methylethyl)benzamide;

3-{{methoxy(methyl)amino]sulfonyl}-*N*-[4-methyl-3-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino]phenyl}benzamide; and

3-*tert*-butyl-*N*-{4-methyl-3-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino]phenyl}benzamide;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is AZ-628:



or a pharmaceutically acceptable salt thereof.

(ii) U.S. Patents 7,235,576 and 7,351,834, both of which are incorporated herein by reference:

A compound of formula **B-I:**

A-D-B **(B-I)**

wherein D is --NH--C(O)—NH—,

A is a substituted moiety of up to 40 carbon atoms of the formula: —L— $(M—L^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein B is substituted by at least one substitisent selected from the group consisting of —SO_2R_x, —C(O)R_x and —C(O)NR_yR_z,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms **optionally containing heieroatoms selected** from: N, S and 0 and optionally iialositbstituted, up to per halo,

R_x is hydrogen or a **carbon** based moiety of up o 30 carbon atoms **optionally containing heteroatoms selected** from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents **of up** to 24 carbon atoms, which **optionally** contain heteroatoms selected from N, **S** and O and are **optionally** substituted by halogen;

R_x is R_z or NR_aR_b, where R_a and R_b are

a) independently hydrogen,

a carbon based moiety **of up** to **30** carbon atoms optionally containing heteroatoms selected from N, S and O and optionally **substituted by** halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

—OSi(R_f)$_3$ where **R_f** is hydrogen or **a** carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, **S** and O and **optionally** substituted **by** halogen, hydroxy and carbon based substituents **of up** to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b **together** form a **5-7** member **heterocyclic** structure of 1-**3** heteroatoms selected from N, S and O, or a substituted **5-7** member heterocyclic structure of 1-3 heteroatoms selected from N, S and O **substituted by** halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain **heteroatoms** selected from N, S and **0** and are optionally substituted by **halogen;** or

c) one of R_a or R_b is —C(O)—, a C_1-C_5 divalent **alkylene group** or a **substituted C_1-C_5** divalent alkylene group bound to the moiety **L** to **form** a cyclic structure with **at** least 5 members, wherein the substituents of the substituted **C_{5}-C_5** divalent **alkylene** group **arc** selected **from** the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain **heteroatoms** selected **from N**, S and O and are optionally substituted by halogen;

where **B is** substituted, L is substituted of L^5 is additioiiaily substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected **from the** group consisting **of** —CN, —CO_2R^7, —$C(0)NR^7R^7$, —€ (0)—R^7, —NO_2, —OR^7, —SR^7, —NR^7R^7, —$NR^7C(0)OR^7$, —**-NR⁷C(0)R⁷**, —**Q**—**Ar,** and carbon based moieties of up to 24 carbon atoms, optionally **containing** heteroatoms selected from N, S and O **and** optionally substituted by one or more **substituents** independently selected from the group consisting of —€ N, —$C0_2R^7$, —$C(0)R^7$, —$C(0)NR^7R^7$, —**OR⁷,** —SR^7, —**-NR⁷R⁷,** —NO_2, —$NR^7C(0)R^7$ —$NR^7C(0)OR^7$ and halogen up to per-halo; with each R^7 independently selected from **H** or a carbon based moiety of **up to** 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionaliy substituted by halogen;

wherein **Q** is —O—, —S—, —N(RV —, --$(CH_2)_m$--, --C(0>—, --CH(OH)—, —$(CH_2)_mO$—, —$(CH_2)_mS$—, —$(CH_2)_mN(R^7)$—, ~-$O(CH_2)_m$--€HX ^{a}--, —CX^a_2—, —S—$(CH_2)_m$— and —$N(R^7)(CH_2)_m$—, where m=i-3, **and** X^a **is** halogen; and

Ar **is** a 5- or 6-member **aromatic** structure containing 0-2 members selected **from** the group consisting of nitrogen, oxygen and sulfur, which is optionaliy substituted by halogen, up to **per-halo,** and optionally substituted by Z_{n1}, wherein n1 is 0 **to** 3 and each Z is independently selected **from** the group consisting of **—CN,** —€O_2R^7, —$C(O)R^7$, —$C(O)NR^7R^7$, —NO_2, —OR^7, —SR^7—NR^7R^7, —$NR^7C(O)OR^7$, —$NR^7C(O)R^7$, and a carbon based moiety **of up to** 24 carbon atoms, optionaliy containing heteroatoms selected from N, S and **O** and optionally **substituted** by one or more substituents selected from the group consisting **of** —CN, —€O_2R^7, —COR⁷, —$C(O)NR^7R^7$, —**OR⁷,** —SR⁷, —NO_2, —NR^7R^7, —$NR^7C(O)R^7$, and —$NR^7C(O)OR^7$, with R^7 as defined above.

In formula **B-i,** suitable hctaryl groups include, but are not limited to, 5-12 carbon-atom aromatic rings or ring systems containing 1-3 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms. For **example,** B can be 2- or 3-furyJ, 2- or 3-thienyl, 2- or 4-triazinyJ, 1-, 2- or 3-pyrrolyJ, 1-, 2-, 4- or 5-imidazolyl, 1~, 3-, 4- **or 5-pyrazolyl**, 2-, 4- or 5-oxazolyf 3-, **4, or** 5-isoxazolyl, 2-, 4- or 5-

thiazolyl, 3-, 4- or **5-isothiazolyl,** 2-, 3- **or 4-pyridyl,** 2-, 4-, 5- **or 6-pyriraidmyl, 1,2,3-** triazol-1-, -4- **or** -5-yl, l,2,4-tria2oi-l- , -3- or **-5-yl, .1- or 5-te.razolyl, l,2,3-oxadiazol-4-** or **-5-yl,** l,**2,4-oxadiazQl-3-** or -5-yl, **l,3,4-thiadiazoi-2-** or **-5-yl, l,2,4-oxadiazoi-3- or -5-yl,** l,**3,4-thiadiazol-2-** or -5yi, **l,3,4-thiadiazo1-3-** or **-5-yi,** l,**2,3-thiadiazol-4-** or **-5-yl,** 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, **2-,** 3- or **4-4 H-thiopyranyl,** 3- or **4-pyridazinyl,** pyrazinyl, 2-, **3-,** 4-, 5-, 6- or **7-benzofuryi,** 2-, 3-, **4-,** 5-, 6- or **7-benzothienyi,** 1-, 2-, **3-,** 4-, 5-, 6- or **7-**iadolyl, **1-,** 2-, 4- or **5-bcnzimidazolyl-** !-, 3-, 4-, **5-, 6- or 7-benzopyrazoiyi,** 2-, 4-, 5-, **6- or 7-benzoxazolyl,** 3-, 4-, **5-, 6- or 7-benzisoxazolyl,** 1-, 3-, **4-, 5-,** 6- **or 7-benzothiazoiyJ. 2-,** 4-, **5-,** 6- or **7-benzisothiazolyi,** 2-, 4-, 5-, 6- or **7-benz-l,3-oxadiazolyl,** 2-, **3-,** 4-, 5-, 6-, **7- or 8-quinolinyl,** 1-, 3-, 4-, 5-, 6-, 7-, **8-isoquinolinyi,** 1-, 2-, 3-, 4- or 9-earbazolyl, 1-, 2-, 3-, **4-, 5-,** 6-, **7-, 8- or** 9-**acridiny!, or 2-, 4-,** 5-, 6-, **7- or** 8-quinazolinyl, or **additionally** optionally **substituted phenyl,** 2- **or 3-thienyl,** l,3,4-thiadiazolyi, 3-pyrryl, 3-pyrazolyk 2~ **thiazolyl** or **5-thiazolyl,** etc. For example, **B** can be **4-meihyi-phetiyi, 5-meihyl-2~thtetiyl, 4-methyl-2-thienyl,** 1-methyl-3-pyrryl, **l-methyI-3-pyrazolyl, 5-meihyi-2-thiazo!yl** or **5-** methyl-i,2,4-thiadiazol-2-yL

Suitable alkyl groups and alkyl portions **of groups,** e.g., alkoxy, etc. **throughout include** methyl ethyl, propyl butyl etc., **including** all **straight-chain** and branched isomers such as isopropyl, **isobutyl, sec-butyl, tert-butyl,** etc.

Suitable aryl groups which **do** not **contain heteroatoms** include, for example, phenyl and 1- and **2-naphthyl.**

Suitable halogen groups include F, **Cl, Br, and/or** I, from one to **pcr-substitution** (i.e. **all H** atoms on **a** group replaced by a halogen atom) being possible where an alkyl group is substituted by **halogen,** mixed substitution **of halogen** atom types also being possible on a given moiety.

The methods of the invention relate to **compounds of formula B~l** as well as **pharmaceutically** acceptable salts of formula **B-l. Suitable** pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and orgautc acids, **such** as **hydrochloric acid, hydrobromic** acid, **sulfuric** acid, phosphoric acid, **methanesuiphomc** acid, **trifluoromethane-sulfbnic** acid, bcnzencsulfoutc acid, p- **tolucnesulfonic** acid, **1-naphthalenesuifonk** acid, **2-naphthaienesulfbnic** acid, acetic acid, trifluoroacetie acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, **ftimaric** acid, **maieic** acid, benzoic acid, saiicyitc acid, phenylacetie acid, and mandelic acid. In **addition, pharmaceutically** acceptable salts include acid salts of inorganic bases,

such as salts **containing alkaline** cations (e.g., Li^{+} Na^{+} **or** K^{+}), alkaline earth **cations** (e.g., Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including **aliphatic** aod aromatic substituted **ammonium,** and **quaternary ammonium** cations, **such** as those arising **from** proto-nation or pera!kylation of triethyl amine, N,N-**diethyiamine,** N,N-dicyciohexyiaffline, lysine, pyridine, N,N-dimethylaa inopyr dine (DMAP), 1,4-**diazabiclo**[2.2.2] **octane** (DABCO), l,5-dia2abicyclo[4.3.0jnon-5-ene (DBN) and 1,8-diazabicycio[5.4.0]**undcc-7ene** (DBU),

In some embodiments of the compound **of formula** B-I, the compound is selected **from** the **group** consisting of:

N-(**5**-tert-butyl-**2**~metrioxy phenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl) **phenoxy)** phenyl)urea,

N-(2-methoxy-5-(trifluoromcthyl)phenyl)-N'~(4-(2-(N-methylcarbamoyl)~4-pyridyloxy} phenyl)urea,

N-(4-ehloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy) **phcny!)urca**,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy) pnenyi)urea, or

N-(**2-mcrtioxy-4-chloro-5-(iri.fluoromeihyl)** pheny!)-N'-(**3-(2**-(N-methylcarbant oy!)-4-pyridyioxy) phenyl)urea and their **pharmaceutically** acceptable salts.

[0001] In some embodiments, the compound has a structure of formula B-I:

A—D—B (B-I)

or a **pharmaceutically** acceptable salt thereof, wherein D is —NH—**C(0)** —NH—,

A is substituted moiety of the formula: —L—M—L^{1}

wherein L is phenyl, optionally substituted by halogen, up to **per-halo**, and Wn, where a is 0-3;

wherein each W is independently selected from the group consisting of C_1-C_3 linear or branched alkyl, CVCs **linear** or branched **ha!oa!kyl** up **to pcrha!oa!kyl** and C_3-C_3 alkoxy L^{1} is selected **from** pyridmyJ substituted by —**C(0)R*,** and

optionally substituted with **1**-3 additional substituents independently selected from the group consisting of R^{7} and halogen;

wherein R_x is NR_aR_b, and R_5 and R_6, are

A) independently

a) hydrogen,

b) CrC $_{10}$ alkyi

c) C $_6$ aryl,

d) pyridiiiyi

e) **substituted** C $_{i-10}$ **aikyl,**

f) substituted CV, **aryl,**

g) **substituted pyridiiiyi**

h) -phenylpiperazine(pyrklinyi),

i) -phenylmorpholinyl,

j) -ethy$_{1)}$norpnoiiiiy$_{1,}$

k) -ethylpiperidyi,

$_{1)}$ -methyl pyrrolidinyl,

m) -methyl **tetrahydrofuryl,**

or

j$_{1}$) **—C$_2$H$_4$NH(phcnyi);**

where when R_a and R_{a}, are **a** substituted group, they are substituted by

a) halogen up **to** per halo,

b) hydroxy.

c) -—N**(<¾)?,**

d) C$_t$-C$_3$f alkyl,

e) C$_t$-C$_{10}$ **alkoxy,**

f) halosubstifuted C$_{t-6}$ aikyl, or

g) -OSi(Pr-i)$_3$; or

B) R_a and R_b together form **piperazme** or a substituted piperarine with one or more subsfituenrs selected **from** the group consisting of

a) halogen.

b) hydroxy,

c) C$_t$-C$_{10}$ aikyl,

d) pyridiny!

e) C$_t$-C$_{10}$ alkoxy,

i) C$_6$ aryl,

g) halo **substituted** C $_6$ **aryi,** and

h) N~(4-acetyiphenyl);

M is selected f om the group consisting of oxygen and sulfur;

and

B is phenyl, substituted with 1-3 substituents independently selected from the group consisting of halogen and R^7,

and R^7 is

(a) C_1-C_6 linear or branched alkyl, optionally substituted with 1-3 halogen substituenis; or

(b) C_1-C_6 linear or branched alkoxy.

|0062| In certain embodi ments, the compound has a structure of formula B-1:

A----D----B (B-1)

or a pharmaceutically acceptable salt thereof, wherein

D is ----NH----C(O)----NH----,

A is of the formula: ----L----M----L^1, wherein

L is phenyl, optionally substituted with 1-3 substituenis independently selected from the group consisting of C J-C_5 linear or branched aiky l, C_1-C5 linear or branched haloalky ! up to perhalo, Cr C_3 alkoxy and halogen;

L^1 is pyridinyl, substituted by —C(0)R_x;

wherein R_x is NR_aR_b and R_a and R_b are independently hydrogen,

C_1-C_{10} alkyl,

C_6 aryl,

pyridinyl substituted C_1-C_{10} alkyl

substituted CV. aryl, or

substituted pyridinyl

where R-, and $R_{3/4}$ are a substituted group, they are substituted by halogen up o per halo; and

M is selected from the group consisting of oxygen and sulfur

and

B is phenyl substituted with 1-3 substituents independently selected from the group consisting of R^7 and halogen;

and R^7 is

(a) C_1-C_6 linear or branched alkyl optionally substituted with 1-3 halogen substituents; or

(b) C_t -Cf, linear or branched alkoxy.

[0003] In some embodiments, the compound has the structure of formula B-I;

A—D—B (B-I)

or a pharmaceutically acceptable salt thereof, wherein

D is —NH—C(O)—NH—,

A is of the formula: —L—M—L^1,

L is phenyl,

M is —O—,

L^1 is pyridinyl substituted by —C(O)R_x,

wherein R_x is NR_aR_b and R_a and R_b are independently hydrogen,

C_1-C_{10} alkyl,

C_6 aryl,

pyridinyl,

substituted C_{1-10} alkyl,

substituted C_6 aryl, or

substituted pyridinyl

where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, and

B is a phenyl group substituted by trifluoromethyl or tert-butyl and optionally additional substituents selected from the group consisting of halogen up to per halo, and W_n where n is 0-3, and each w is independently selected from the group consisting of

C_1-C_{10} alkyl,

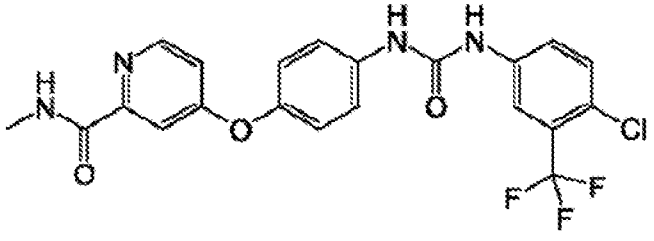
C_1-C_{10} alkoxy,

C_6 aryl,

pyridinyl

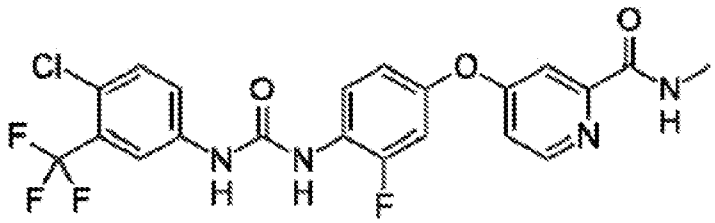
and substituted C_1-C_{10} alkyl, substituted by one or more substituents independently selected from the group consisting of halogen up to per halo.

In some embodiments, the RAF inhibitor is sorafenib:



or a pharmaceutically acceptable sail thereof.

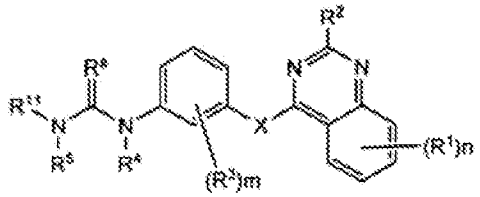
In some embodiments, the RAF inhibitor is regorafenib:



or a pharmaceutically acceptable salt thereof.

(iii) POT ***Application Publication*** *WO 2009/1 l 7080, which* ***is*** *incorporated* ***herein*** *by* ***reference:***

A compound having formula C-I:



C-I

or a pharmaceutically acceptable sail or prodrug thereof, wherein

X is O or S(0}t;

R3 is O or S;

each R' is independently selected from (i) or (it) below;

(i) each R^1 is independently selected from a group consisting of halo, nitro, alkyl, alkenyl, alkynyl, cycloalkyl, eyeloalkylalkyl, heteroeyclyi, heteroeyelylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^6OR^7$, $-R^6SR^7$, $-R^6S(0)_tR^8$, $-R^6N(R^7)_2$, $-RWOR^7$, $-R^6OR^9SR^7$, $-R^6OR^9S(O)_tR^8$, $-R^6OR^9S(O)_tN(R^7)_2$, $-R^6OR^9N(R^7)_2$, $-R^6OR^9OR^7$, $-R^6SR^9SR^7$, $-R^6SR^9N(R^7)_2$, $-R^6N(R^7)R^9N(R^7)_2$, $-R^6N(R^7)R^9OR^7$, $-R^6N(R^7)R^9SR^7$, $-R^6CN$, $-R^6C(0)R^7$, $-R^6C(0)OR^7$, $-R^6C(O)OR^9OR^7$, $-R^6C(0)N(R^7)_2$, $-R^6C(0)N(R^7)OR^7$, $-R^6C(NR^7)N(R^7)_2$, $-R^6C(0)N(R^7)R^9N(R^7)_2$, $-R^6C(0)N(R^7)R^9OR^7$, $-R^6C(0)N(R^7)R^9SR^7$, $-R^6C(0)SR^8$, $-R^6S(0)_tOR^7$, $-R^6S(0)_tN(R^7)_2$, $-R^6S(0)_tN(R^7)N(R^7)_2$, $-R^6S(O)_tN(R^7)N{=}C(R^7)_2$,

-R⁶S(0)tN(R⁷)C(0)R⁸, -R⁶S(0)tN(R⁷)C(0)N(R¾,
-R⁶S(0)tN(R⁷X(NR⁷)N(R¾, -R⁶N(R⁷)C(0)R⁸, -R⁶N(R⁷)C(0)OR⁸,
-R⁶N(R⁷)C(0)N(R¾, -R⁶N(R⁷)C(NR⁷)N(R⁷)₂, -R⁶N(R⁷)C(S)N(R⁷)₂, and
~R⁶N(R⁷)S(0)tR⁸, or

(ii) any two adjacent R¹ groups together form an alkyieriedioxy group; each R⁶ is independently a direct bond, **aikyleae** chain or aikenylene chain; each R⁷ is independently selected from (i) or (ii) below:

(i) each R⁷ is selected **from** a group **consisting of hydrogen,** alkyl, **alkenyi,** alkynyi, cycioalkyi, cycSoaSkyiaj.kyl, aryl, aralkyk heteroeyciyi, heterocyclyialkyl, heteroaryl and heieroaralkyi, or

(ii) two R⁷ **groups together with the** N **atom to which they** are attached form **a** heteroeyciyi or **heteroaryl;**

each R⁸ is independently selected **from** a group consisting of aikyi, alkenyi, **aikynyi,** cycioalkyi, cycloalkylalkyl, aryl, aralkyl, heteroeyciyi, **heterocyclylalkyl,** heteroaryl and heteroaralkyi;

each R⁹ is independently an alkylene chain or **an** aikenylene chain;

R² is hydrogen, halo, alkyl, amino or alkylamino;

R³ is halo or alky! ;

R⁴ and R⁵ are selected as follows:

a) R⁴ and R⁵ are each independently hydrogen or alkyl, or

b) R⁴ and R⁵, together with the N atom to which they are attached, form an oxo-substituied heteroeyciyi;

R¹¹ **is** aryl, heteroaryl or heteroeyciyi;

m is an integer from 0 to 4;

n is an integer from 0 to 4;

t is an integer from 0 to 2;

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ **and** R¹¹ are optionally substituted **with** one, two or three substituents **independently** selected from Q⁵, **wherein Q**⁵ is tiitro, halo, azido, cyano, oxo, thtoxo, imino, alkyl, alkenyi, alkynyi, **cycioalkyi, cycloaikylalkyl,** aryl aralky!, **heteroaryl,** heteroaralkyi, heteroeyciyi, **heterocyciylalkyi,** -RᵘORˣ, -RᵘOR¾ Rˣ, -RᵘORᵘN(R-XR), -Rᵘ N(Rʸ)(RᶻX
-RᵘSRˣ, -Rᵘ C(J)Rˣ, -RᵘC(J)ORˣ, -RᵘC(i)N(Rʸ)(Rᶻ>, -RᵘC(J)SRˣ, -Rᵘs(O)ᵗRᵂ,
~RᵘOC(J)Rˣ, -RᵘOC◁)ORˣ, -RᵘOC(J>N(RˣXR¾ ~RᵘOC(J)SRˣ,

-R^{u}N(R^{x})C(J)R^{x}, - R"N(R^{x})C(j)OR^{x}, -R^{t}N(R.^{x})C(J)N{R^{j})(R.^{z}),
-R^{u}N(R^{x})C{J)SR^{S}, -R^{u}Si{R^{w})$_{3}$- -R^{u}N{R^{x})S(0) $_{t}$R^{w}, -R^{u}N(R^{x})R^{u}S(O)$_{2}$R^{w},
-R^{u}N(R^{x})S(O)$_{2}$N(R')(r) , -R^{u}S(O)$_{2}$N(R^{y})(R'), -R^{u}P(0)(R^{y})$_{2}$, -R"OP(0)(R^{y})2,
-R^{u}C(J)N(R^{j})S(0)2R^{w}, -R^{u}C(J)N(R^{x})N(R^{x})S{0)2R^{w}, -R^{u}C(R^{x})=N(OR^{x}) and
~R^{u}C(R^{x})~NN(R^{x})(R^{z});

when Q^{1} is alkyi, **alkenyl** or alkynyl, each Q^{i} is **optionally substituted** with halo, **cyano.** hydroxy or aikoxy;

when Q^{1} **is** eyeioalkyl, **cycloalkylalkyl, aryl, aralkyl,** heteroaryl, heteroaraikyl, **heterocyciyi,** or heterocyclylalkyi, each Q^{1} **is** optionally substituted with **halo,** alkyi, haloalkyl, **hydroxyalkyl, alkoxya!kyi, cyanoalkyl, aikoxy** or hydroxy!;

each R^{u} is independently alkyiene or a direct bond;

each **R^{y}** is **independently alkyl**, alkenyl **alkynyl,** cycloalkvi, **cycloalkylalkyl,** heterocyciyi, **heterocyclylalkyi,** aryl **aralkyl, heteroaryl, heteroaraikyl, hydroxy,-OR^{x}** or -N(R¾R $^{?}$);

R^{w} is alkyi, alkenyl, alkynyl, cycloalkvi, cycloalkylalkyl, heterocyciyi, heterocyclylalkyi, aryl, **aralkyl,** heteroaryl, **or heteroaratkyl;**

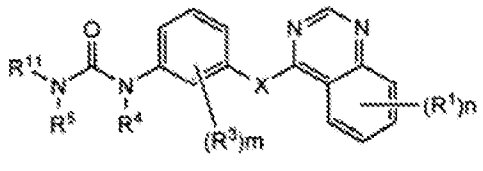
each R^{x} is independently **hydrogen,** alkyi, alkenyl **alkynyl, cycloalkvi, cycloalkylalkyl,** heterocyciyi, heterocyclylalkyi, aryl, **aralkyl,** heteroaryl, or heteroaraikyl;

R^{y} and R' are each **independently** hydrogen, alkyi, **alkenyl** alkynyl, **cycloalkyl, cycloalkylalkyl** heterocyciyi, heterocyclylalkyi, **aryl,** aralkyl, heteroaryl, **or** heteroaraikyl;

R^{y} **and** R^{z}, together with the nitrogen **atom** to which they are attached, form a heterocyciyi or heteroaryl; and

J is O, NR^{x} or S.

In some embodiments, the compound has a structure **of formula €-1**:



C-II

or a pharmaceutically **acceptable** salt **or prodrug** thereof, wherein

X is **0 ,** S, SCO) or SO_{2};

each R' is independently selected **from (i)** or (it) below:

(i) each R^1 is independently selected from the group consisting of halo, alkyl, aikenyl, aikynyl, cycloalkyl, cycloalkylalkyi, heterocyciyi, heteroeyclylalkyl, aryl, araikyl, hcteroaryl, hcteroaralkyl, -R6OR', -R"SR', -R*S(0)tR*, -R6N(R7)2, -R6OR9OR7, -R6GR¾R7, -R6OR9S(O)tR8, -R6OR¾(0)tN(R7)2, -R6OR9N(R7)2, -R-SR¾R7, -R6SR9SR7, -R6SR9N(R7)2, -R6N(R7)R9N(R7)2, -R6N(R7)R9OR7, -R6N(R7)R9SR7, -RiCN, -R*C(0)R7, -R¾(0)0 RW, -R¾(0)N(R7)2, -R6C(0)N(R7)OR7, -RiC(0}N(R7)R¾R7, -R6C(O)N(R7)R9SR7, -R6C(0)SRs, -R6S(O)tOR7, -R6S(OXN(R7)2; or

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

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

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

(i) each R^7 is selected from the group consisting of hydrogen, aikyi, aikenyl, aikynyl, cycloalkyl, cycloalkylalkyi, aryl, araikyl, heteroeyelyl, heterocyciyiaikyi, heteroaryl and heteroaraikyl, or

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

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

R^3 is halo or alkyl;

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

R^{11} is aryl or hctcroaryl;

m is an integer from 0 to 4;

n is an integer from 0 to 4;

R^1, R^2, R^3, R*, R^5, R^6, R^7, R*, R^9 and R^{11} arc optionally substituted with one, two or three substituents independently selected f on Q^1, wherein Q^1 is nitro, halo, azido, cyano, oxo, thioxo, itnino, alkyl, aikenyl aikynyl, cycloalkyl, cycloalkylalkyi, aryl, araikyl, heterocyciyi, heteroeyclylalkyl, heteroaryl, heteroaralkyl, -R"OR^x, -R¾OR"OR^x, -R"OR"N(R^y)(R¾ -R"N(R^x)(R'), -R" SR^x, -Rt C(J)R^x, -R"C(J)OR^x, -R"C(J)N(R^y)(R¾, -R"C(J)$R^x, -R"S(0)tR^w, -R¾ CiJ)R^x, -RtOC(J)OR^x, -R"0 C(J)N(R^yXR*)>-R"OC(J)SR^x, -R¾ (R^x)C(J)R^x, -R"N(R*)C(J)OR*, -R"N(R^x)C(l)N(R^y)(R^z)>-R"N(R^x)C(J)SR^x, -R"Si(R¾)3, -R"N(R^x)S(0)2R^w, -R"N(R^xsR"S(0)jR^w, -R"N(R^x)S(O)2N(R^yXR^z), -

$R^uS(0)_2N(R^xXR^z)$, $-R^uPiO\}(R^y)_2$, $-R^uOW\ )(R^y)_2$, $-R^uC\{J)N(R^x)S(0\ )_{2R^w}$, $-R^{3/4}\ j)N(R^x)N(R^y)S(0\ )_2R^w$, $-R^uC(R^x)=N(OR^i)$ and $-R^uC(R^x)=NN(R^s)(R^z)$;

when Q^1 is **alkyl, alkenyl** or **alkynyl**, each Q^1 is **optionally substituted** with halo, **cyano,** hydroxy or alkoxy;

when Q^1 is **cycloalkyi,** cyeloalkylalkyl aryl, aralkyl **heteroaryl,, heteroaralkyi,** heterocyclyl, or **heterocyclylalkyl, each** Q^1 is **optionally substituted with** halo, **alkyl, haloalkyl,** hydroxyalkyl, alkoxyalkyl, cyanoalkyl, **aikoxy, hydroxyl, oxo or cyano;**

each R^u is **independently alkylene** or **a** direct bond;

each R^v is **independently** alkyl **alkenyl, alkynyl,** cycloalkyi, **cyeloalkylalkyl,** heterocyclyl, heierocyelySaSkyi aryl, **aralkyl, heteroaryl, heteroaralkyi,** hydroxy, $-OR^x$ or $-N(R^y)(R^z)$;

R^w is alkyl, alkenyl, **alkynyl,** cycloalkyi, **cyeloalkylalkyl,** heterocyclyl, **heterocyclylalkyl, aryl, aralkyl, heteroaryl,** or heteroaralkyi;

each R^x is **independently hydrogen,** alkyl, **alkenyl,** alkynyl, cycloalkyi, cyeloalkylalkyl, **heterocyclyl, heterocyclylalkyl,** aryl, aralkyl, heteroaryl, or heteroaralkyi;

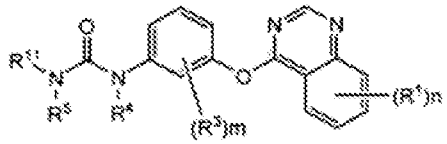
R^y **and** R^z **are** each **independently hydrogen, alkyl, alkenyl, alkynyl,** cycloalkyi, cyeloalkylalkyl heterocyclyl heterocyclylalkyl **aryl,** aralkyl heteroaryl **or heteroaralkyi;**

R^y **and** R^z, together with the **nitroaen** atom to which they are attached, **form** a heierocycle or heteroaryl;

t is **an** integer from 0 to **2;** and

J is O, NR^y or S.

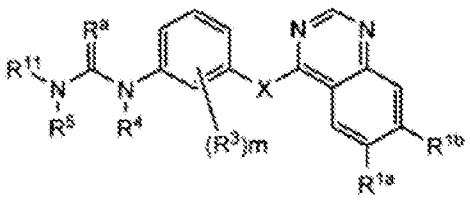
In some of the above embodiments, the compound has a structure of formula C~lli:



C-III

or **a** pharmaceutically **acceptable** salt or prodrug thereof.

In some of **the** above **embodiments,** the compound has a **structure of formula C~XII:**



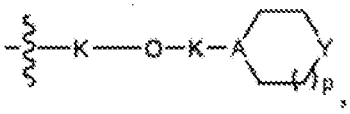
C-XII

or a pharmaceutically **acceptable** salt or prodrug thereof, **wherein** R^9 is **O** or S;

X is O or S;

R^{1a} and R^{1b} are **selected** as follows:

i) **R^{1a}** and R^{1b} are each independently selected **from** hydrogen, halo, amino, alky!. ary!, heteroaryl, alkoxy, hydroxy, alkoxyaSkoxy, cy'cioaikylcarboivylamino and a group of formula:



where each K is **independently a** direct bond or **alkylene;**

A is N or CR^{16};

Y is **-O**, **-S,** -8(0), **-S(0)** 2, -N(R^{14}), -C(H)R^{15}, or -C(0);

p is an integer from 0 to 2;

R^{14} is hydrogen, alkyl, haloalkyi hydroxya!kyl, eycloalky!, heteroaryialkvi arySaikyl, **S(0),R** ^{13} or -C(0)R^{13};

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

R^{16} **is hydrogen** or alkyi;

t is 1 or 2;

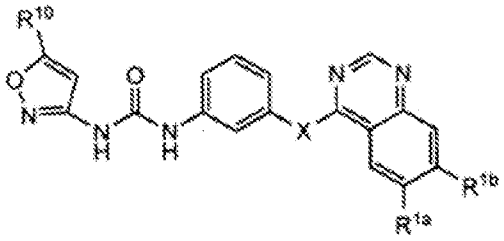
each R^{12} is independently selected from the group consisting of hydrogen and alky!;

R^{13} is alkyl;

each K is **optionally** substituted with one, **two or** three hydroxy or alkyi groups; or

ii) **R^{1a} and** R^{1b} groups together form **an** alky!enedioxy group.

In some of the above **embodiments**, the compound has a **structure** of formula C~XVII:



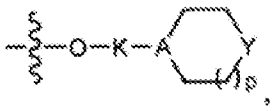
C-XVII

or **a** pharmaceutically acceptable salt or prodrug **thereof,**

wherein X is O or S;

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

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



where K is a direct bond or alkylene, optionally **substituted with** a hydroxy group;

A is N or CH;

Y is -O, **-S(0)** 2, **-N(R**^{14}>or -C(H)R^{15};

p is 0 or I;

R^{14} is hydrogen, alkyl, haloalkyl, hydroxyalkyl or S(0)$_f$R" ;

R^{15} is **hydrogen,** halo, alkyl hydroxyalfcyi. **or -OR**^{13};

f is 1 or 2;

R^{12} is hydrogen or alkyl; **and**

R^{13} is alkyl; **or**

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

R^{10} **is hydrogen,** halo, **alkyl,** aryi. **heterocyclyl, heteroaryl** cycloAlky! or cycloalkylalkyl; where alkyl, **aryl,** heterocyclyl and heteroaryl groups are **optionally** substituted with 1-3 groups selected from halo, **cyano, hydroxyl** and alkoxy.

In some **embodiments, the compound** is selected from;

1-(5-tert-huty lisoxazol-3-yl)-3-(**3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)ui ea;**

l-(5-tert-buty Isoxa¾ol-3~y IW ~(3-(6-methoxyquinazolin-4-yloxyphenyl)urea;

l-(5~tert-buty!:isoxazo!-3~yl}-3~(3-(7-:raet!iOx.yqihiiazolin-4-yloxy)phenyl)urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-difluoroquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(5-methylqumazolm-4-yioxy)phenyi)«rca;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(7-eth^^ y-6-methoxyquinazolin-4-yloxy)phenyl} **urea** hydrochJoride;

l-(5-tert-Buiylisoxazol-3-yl)-3-{3-i6-metlioxy-7-(2-methoxyethoxy)quinazolin-4-yioxy]phenyl}urea hydrochloride;

l-(5-tcrt-biiiylisoxazol-3-yl)-3-(3-(6-nKiliyiq uinazolin-4-yloxy)phenyl)urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-4-fluorophenyl)urea;

l-(5-tert-butylisoxazol-3-yl)-3-(4-chloro-3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

i-(5-tert-butylisoxaz0l-3-yl)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)urea;

l-(3-j6,7-bis(2-methoxyc&oxy)quinaaolin-4-yloxy]phcnyi}-3-(5-tert-butylisoxazoi-3-yl)urea hydrochloride:

l-(5-tert-Butylisoxa2ol-3-yi)-3-[3-(6,7-diethoxyquinazolin-4-yloxy)phenyl]urea hydrochloride;

I-(5-tert-Butylisoxazol-3-yi)-3-[3-(7,8-dihydro-(1,4]dioxinoj2,3-gjquiiiazoiiii-4-yloxy)phenyljurea hydrochloride;

l-(5-iert-biityl)soxazol-3-yf)-3-(3-[7-rriethoxy-6^2-meihoxyethoxy)quh uazolin-4-yloxy]phenyl**}urea** hydrochloride;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-**yl)ethoxy)quinazolin-4-**yioxy)pheiry**i)urca;**

l-(5-ferf-bu ylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydo xymethyl)piperidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

1-(54ert-bufylisoxazol -3-yl)-3-(3-(7-mcthoxy-6-(2-(4-mcAylpiperazm- l-yl)ethoxy)quinazolin-4-yioxy)phenyi)urea;

i-(5-iiTi-biiiylisoxazol-3-yl)-3-(3-(6-(2-(4-(2-hydroxy ethyl)piperazin-1-yl)ethoxy)-7-**rnet¾oxyqainazolm-4-yloxy)phe«yl)va¾a;**

l-(5-iert -butyiisoxazol-3-y1)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(**5-tert-butylisoxazol -3-yl**)-**3-**(**3-**(**7-mcthoxy-6-**(**3-(4-mcthylpipcrazin-** l-**yl)propoxy)quinazolin-4-yIoxy)phenyI)urea;**

i-(5-iert-biity-l)soxazol-3-yi)-3-(3-(7-]«e†boxy-(>-(3-niorpholiaopropoxy)quinazolin-4-yloxy)phenyl)utrea;

l-(i -tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-yioxy)phenyi)urea;

l-(5-tet -butylisoxazol-3-yl)-3-(3-(6-(3-(4-(hydroxymethyl)piperidin-1-yl)propoxy)-7-methoxyquinazoli«-4-yloxy)phenyl)urea;

i-(5~t£rt-butyiisoxazoi-3~yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yi)propoxy)quinazdlin-4-yloxy)phenyl)urea;

I-(5-tert-butyl-isoxazoi-3-y!)-3-(3-{6-{3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy }-7-meth**oxy**-quinazo**!ia-4**-yloxy}-**ph**en**yl**)-urca;

1-(5-tert~butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yioxy)phenyl)urea;

l-(5-ieri-buiylisoxazol-3-yl)-3-{3-(6-mei1ioxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quttias»Utt-4-y!oxy)pheny!)utca;

l-(5~tert-batyl»soxa^l-3~yi)-3-(3-(7-(3-(4-hydroxymethyl) piperidin-1-yljpropoxy)-6-methoxyquinazolin-4-yloxy)phe«yJ)urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(3-(4-(2-hydroxyethyl) piperazin-i-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)u¾a;

1^5-tert-butyl-isoxazoI-3-yl)-3-(3-{7-{ 3-(3-hydroxy-pyrrolidra-1-yljpropoxy]-6-methoxy-quinazolin-4-yloxy}-phenyl)-urea;

l-(5~t£rt-butylisoxazol-3~ylW-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)qinaa _oUa-4-yioxy)phenyi)urca;

(S**)-i** -(54ert-butylisoxazol-3-yl)-3-(3-(7-(3-(3-hydroxypyrroiidm **-l-yi**)propoxy)-6-methoxyqu«aazoIin-4-yloxy)phenyl)urea;

(R)-l-(5-tert-buiylisoxa7,ol-3-yl)-3-(3-(7-(3-(3^ droxypyrrolidin-1-yl)propoxy)-6-methoxyquinazolin-4-yloxy)phenyl)urea;

l-(5-tert -but}lisoxazol-3-yi)-3-(3~(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4-yioxy)phenyi)urea;

l-(5-tert-bulylisoxazol-3-yl)-3-{ 3-(6-methoxy-7-{2-(4-mediyl piperazin-1-**y**l)e.hoxy)quinazolin-4-yloxy)phenyl)uFea;

l-(5-fert-Bu¾l-isoxazol-3-yl)-3-(3-{7-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy}- 6-methoxy-quinazoIi»-4-yloxy}-phenyl)-urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-ethoxy)-6 methoxyquinazolin-4yloxy)phenyl)urea;

1-(5-tert-B«iyl-isoxazo!-3-yl)-3-(3- {7-[2-(l ,1-dioxo-116-ihic>morpholin-4-yl)-e(hoxy]-6-niethoxy-quinazolin-4-yloxy} -phenyl)-urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

l-(5-ieri-Buiyl:boxazo!-3-yl)-3-{3-(7-mei1ioxy-6-{3-(iiieihylsulfonyl)propoxy)quinazolin-4-ylthio)pheiiyl)urea;

1-(3-(2-:fluoropfopaii-2-y!)isoxazoi-5-yl)-3-(3-{7~methoxy-6-(3-(itte(hylsuifonyI)propoxy)qumaz»!m-4-yloxy)phenyl)urea;

l-(5-tert-butylis0xa¾ol-3-yl)-3-(3-(7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl) urea;

l-i5~tert-butylisoxazol-3~yi)-3~(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy)quinazolin-4-ylthio)phenyl)urea;

I-(5-tert-butylisoxazol-3-yS)-3-{3-(7-mcthoxy-6-(2-me&oxycthoxy)quina2olin-4-ylthio)phenyi)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

l-(5-ret ~buiylisoxazol-3-yl)-3-(3-(6,7~dif uoroquinazolin-4-ylthio)phenyl)urea;

l-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxyquinazolin-4-ylthio)phenyf)urea;

l-(5~tert-butylisoxazol-3~yi)-3~(3-(6-meo xyquinazolin-4-ylthio)phenyf)urea;

l-(5-tert-Butylisoxazol-3-yf)-3-[3-(7-ethoxy-6-methoxyquinazolin-4-ylthio)phenyl]urea;

l-(5-tert-butylisoxaz0l~3-yi½ -[3-(6,7-diethoxyquinazolin-4-ylthio)phenyl]urea;

1-(5-tert-butyliSoxazoI-3-y!)-3-{3-[6-metboxy-7-(2-mc{hoxyetboxy)qua azoim-4-ylthio{phenyl} urea hydrochloride;

i-{3-j6,7-bis(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-(5-tert-butylisoxazol-3-yl)urea.hydrochloride;

I-(5-tert-butylisoxazol-3-y!)-3-[3-{7,8-dihydro-(1,4)dioxino{2,3-g]quinazolin-4-ylthio)phenyi]iirea hydrochloride;

1-(5-tet -Butylisoxazol-3-yf)-3-{3-[7-jriethoxy-5-(tetrahydro-2H-pyran-4~ylthio)quinazolin-4-yloxy]pheny!}urea;

1-(5-tert -biitylisoxazol-3-yl)-3-(3-(6-ethoxy-7-m ethoxyquinazolin-4-ylthio)phenyl)urea;

1-(5~tert-butylisoxazol-3~yi)-3-(3-(7-methoxy-6-(3-(piperidin-1-yl)propoxy)quinazolin-4-yithio)pheny l)urea;

l-(5~tert-butylisoxazol-3~yl)-3-(3-(6-i3~(4-^ droxymethyl)piperidin-1-yl)propoxy)-7-niethoxyquinazolin^-ylthio)phenyi)urea;

l-(5-tert-Butylisoxazol-3-yl)-3^3-(7-mcthoxy-6^3-(4-mcihylpipera-dn-l-yi)propoxy)quinazolin-4-yltko)phenyS)urea;

1-(5-ter -butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yJthio)phenyl)u)rea;

1-(5-ter -butylisoxazol-3-yl)-3-(3-(6-(3-(4-(2-hydroxyethyi)piperazin-1-yI)propoxy)-7-methoxyquinazolm-4-ylthio)phenyl)urea;

1-(5~tert-butyl-isoxazol-3-yl)-3~{3-{6-[3-(1,1-dioxo-thiomorpho!in-4~yl)-propoxy j~7-tiK!thoxy-quinazoiin-4-ylsulfanyi} -phenyl}-urea;

1-(5-ter -butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylthioiphenyl)utea;

1-(5-tert-butylisoxazol-3-yi)-3-(3-(7-methoxy-6-(3-(methylsulfonyl)propoxy) quinazolin-4-yithiojpheny Surea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(piperidin-1-yl)ethoxy)quinazolin-4-ylthio)phenyl)urea;

I-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-(4-(hydroxymethyl)piperidin-1-yl)ethoxy)-7-tnc{hoxyq«inazo!in-4-ylIiio)pheny!)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-methylpiperazin-1-yI)ethoxy)quinazolin-4-yitbio)phenyI)urea;

1-(5-tert-butylisoxa?ol-3-yi)-3-(3-(6-(2-(4-(2-hydroxyethyl)piperazin-\-yl)ethoxy)-7-n«itiioxyqumazo!m-4-ylthio)pheny!)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(7-methoxy-6-(2-(4-(methylsulfonyl)piperazin-1-yi)ethoxy)quinazoiin-4-ylthio)phenyi)urea;

1-(5-tet-butylisoxazoi-3-yl)-3-(3-(7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-yithio)phenyi)urea;

1-(5-ter-butyl-isoxazoI-3-yl)-3-(3-{6-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-7-o ethoxy-quinazolin-4-ylsulfanyl}-phenyl)-urea;

1-(5-tert-butylisoxazol-3-yi)-3-(3-(6-meo xy-7-(2-morpholinoethoxy)quinazolin-4-ylthio)pheiyi)urea;

1-(5-tert-butylisoxazol-3-yl)-3K3-(6-mcthoxy-7-(3-(4-mcthylpiperazin-1-yl)propoxy)quinaiolin-4-ylthio)phenyl)urca;

i-(5-tert-butylisoxazol-3-yl)-3-{3-(7-(3-{4-(hydroxylmethyl)piperidin-1-yl)propoxy)-6-metiioxyquinazolin-4-ylthio)phenyi)urca;

1-(5-teit-but>'lisoxa7X>l-3-yi)-3-(3-{7-(3-(4-(2-bydroxyethyI)pipcrazin-\-yl)propoxy)-6-t½tiioxyqua a2olin-4-ylthio)pheny!)urea;

1-(5-tert-butylisoxazol-3-yi)-3-(3-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4-ylthio)quinazolin-4-yl ihio)phenyi)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(3-(4-(methylsulfonyl)piperazin-1-yl)propoxy)quinazolin-4-yIthio)phenyl)urea;

i-(5-tert-buiylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy)quinazolin-4~ylthio)pheny!)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(piperidin~1-yiXnhoxy)qtinazolia-4-ylthio)pheayl)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-tet-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-(4-methylpiperazin-\-yl)ethoxy)quinazolin-4-yithio)phenyl)urea;

1-(5-tet-butylisoxazol-3-yi)-3-(3-(7-(2-(4-(2-hydroxyethyl)piperazin-1-yl)ethoxy)-6-methoxyquina2olin-4-ylthio)phenyl)urea:

l-(5~tert-bu{yiisoxazoi-3~yl)-3-[3-(7-(2~(4-(hydroxymethyl)piperidin~l-yl)ethoxy)-6-nethoxyquinazolin-4-ylthio)phenyl)urea;

I-(5-tert-butylisoxazol-3-y!)-3-(3-(6-(2-niethoxyethoxy)quinazolin-4-ylthio)phenyl)urea;

I-(5-tert -buty lisoxazQl-3-yl)-3-(3-(? -meto xy-6-(2-(methylsulfonyl)ethoxy)quinazolin-4-ylthio)phenyl)urea;

l-(5-rert4butylisoxazGl~3-yl)~3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-ylthio) pha ıy!)urea;

1-(5-tert-Butyl-isoxazol-3-yl)-3-(3-{6-|3-{1,i-dioxo~thiomorphola -4-yj)-propoxy}-quraazolra-4-yls«ifaiiy l}-phenyi)-urea;

l-(5~tert-Buiyl~isoxazo!~3-yl)~3-(3-i6 ~{2-(l, f~dioxo~l 16-thiomorpbolin-4-yl)-ethoxy|-7-medioxy~quina¾olin~4-yloxy}-phe»yl)-urea;

1-(5-tert-butylisoxazol-3-y!.)-3- {3-(6-(5- {j2-(methyisulfonyI}cthylaa ino]mcthyl}furaa-2-yl)qu«iazoiiii-4-yloxy]phenyl}urea;

l.-(5-tert~butylisoxazol-3-yl)-3-{3~j7-methoxy-5-(teto hydro-2H-pyr¾**n-4-yioxy)quin**azolin-4-yloxy jpheny{}urea;

l-(5-tert-butylisoxazol-3-yf)-3-(3-(7-hydroxy-6-methoxyquinazolin-4-yloxy)phenyl) urea;

(S)-1-(5-tert-biitylisoxazoi-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy) quinazolin-4-ySoxy)phenyS)urca;

(S)-1-(5-tert-butylisoxazo!-3-yl)-3-{3-(6-meihoxy-7-(1-methylpyrrolidin-3-yioxy)quinazoii«-4-yloxy)phe5yl);urea mono acetate;

(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-methoxy-7-(pyrrolidin-3-yloxy)quinazolin-4-yloxy)phe«yl)urea;

(R)-1-(5~teri~bulylisoxazoi-3-yl)-3~(3-(6~methoxy~7-(1-methylpyrrolidin-3-yk>xy)qtitnazo!in-4-yloxy)piieiiyf)itrea mono acetate;

(R)-1-(5-tert-busylisoxazoi-3-y!)-3-(3-(7-(2-hydroxy-3-(4-methylpipcrazin-1-yl)propoxy)-**6-mcthoxyquinazolin-4-yIoxy)phenyI)urea;**

1-(3-tert-Butylisoxazol-5-yi)-3-(3-(6-methoxy-7-(piperidin-4-ylmethoxy)quinazolin-4-yloxy)phenyi)urea;

l-(3-ter-buy lisoxazol-5-yl)-3-(3-(f-methoxy-7-((1-methylpiper idin-4-yl)nietiioxy)quinazolin-4-yloxy)phenyI)urea;

(S)-i-(5-tert-btrtyiisoxazol-3-y!)-3-(3 -{7-|i-(2,2-difluorocthyl)pyrTolidin-3-yloxy]-6-methoxyquinazo!in-4-yloxy}phenyi)urea;

(S)-1-(5~tert~Butylisoxazol~3~y])~3~(3-{6~methoxy~7-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yloxy]qiiinazoiitt-4-yloxy}pheny!)ufea;

1-(5~.ert-butylisQxazol-3-yl)-3-(3-{7-[1.-(2,2-dif uoroethyl)piper idin-4-yloxy}-6-medioxyq«inazoiin-4-yloxy}pheny!)orea;

1-(5-tert-butylisoxazol-5-yl)-3-(3-(6-hydroxy-7-methoxyquinazolin-4-yloxy)phenyl) urea;

(S)-tert-butyl 3-(4-(3-(3-(5-tert-butylisoxazole-3-yi)ureido)phenoxy)-7-methoxyquinazolin-6-yloxy)pyrrolidine- 1-carboxy fate;

(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-(4-methylpiperazin-1-yl)propoxy)-7-methoxyquinazolin-4-yloxy)phenyl)urea;

(R)-1-(5-tert-butylisoxazol-3-yl)-3-(3-(6-(2-hydroxy-3-(4-methylpiperazin-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-ylthio)phenyl)-3-(3-methoxy-5-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-methoxy-5-(trifluoromethyl)phenyl)urea;

1-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)phenyl)urea;

1-(3-tert-butylphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butylphenyl)-3-(3-(6,7-diethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butylphenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)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-yi)itrea;

1-(3-cyclopropylisoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(2-cyanopropan-2-yl).isoxazol-5-yi)-3-(3-(6,7-dimethoxyquinazolin-4-yioxy)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-yioxy)phenyl)-3-(5-(1-methylcyclopropyl)isoxazol-3-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)phenyi)urea;

1-(3-(6,7-diethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1-hydroxy-2-methylpropan-2-yi)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-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-methoxy-3-(trifluoromethyl)phenyl)urea;

1-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-chloro-5-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyridin-2-yl)urea;

1-(2-chloro-5-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyrimidin-2-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropylphenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(6-(trifluoromethyl)pyrimidin-4-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(2-methoxyethoxy)-4-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-Dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-methoxyethoxy)-4-**(trifluoromethyl)phenyl)urea**;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(morpholine-4-carbonyl)-5-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(morpholinomethyl)-5-**(trifluoromethyl)phenyl)urea**;

1-(3-(1,1-difluoroethyl)isoxazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-{6,7-di«ethoxyquina-io1in-4-yioxy)phenyl)-3-(3-(I-
(trif uoromethyf)cyclobuty f)isoxazol-5-yl urea;

1-(3-{6,7-din»ethoxyquinazolin-4-ylthio)phenyl)-3-(3-(1-
(e if uorotnethyi)cyclobutyi)isoxazol-5-yl)«rca;

l-(3-tert-butyl-1-methyl-1H-pyra^!-5 -yl)-3-{3-(6,7-dime-hoxyquinazoiin ~4-yithio)phenyl)urea;

1-(3-teit-buiyl-i-methyl- 1H-pyrazoi-5-yi)-3-(3-(6,7-dimethoxyquinazolin-4-yioxy)phenyl)urca;

l-(3-{l,3-Jifluoro-2-methylpropan-2-yl)isoxazol-5-yi}-3-{3-(6,7-dimethoxyquinazolin-4-yioxy}phenyi)urea;

l-{3-(l,3-dif uoro-2-methylpropati-2-yl)isox¾ol-5 -yl}-3-{3-(6,7-dimethoxyquinazolin-4-yithio}plienyl) urea;

1-j3-(6,7-dimethoxyquinazoiin-4-yioxy)phe«ylj-3-| 1-phenyl-3-(triiluoromethyl)-1H-pyrazol-S-yl}urea;

l-{5-(l,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl}-3-{3-(6,7-dimethoxyquinazolin-4-yioxy)phenyi j«rca;

I-(3-cyclopentylisoxazoI-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3^6,7^l½ethoxyquina-iolm-4-yIoxy)pbenyI }-3-[1-meth¾l-3-(trifluoromethyl)-1H-pyrazoi-5-yl jurea;

l-{3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl}-3-[1-methyl-5-(trifluoromethyl)-1W-pyrazoi-3-yi|urea;

ethyl 2-(3-tert-bittyl-5- {3-[3-(6,7-dinKthoxyquina∞lin-4-y1oxy)phenyl]ureido}-1H-pyrazol-1-yl)acetate;

1-[3-{l,3-difluoro~2-methyipropan-2-yi)- 1-phenyl-1H-pyrazol-5-yl]-3-P-(6,7-din:iedioxyqinnazolift-4-yloxy)phenyl]urea;

l-{3-(6,7-dimcthoxyq«in¾olin-4-yioxy)phenyl}-3-{3-(2-ethoxypropan-2-yl)-1-phenyl-1H-pyrazo!-5-yl jurea;

l-j3-(6,7-dimethoxyquinazoii«-4-yloxy)phenyl]-3-[1-phenyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]urea;

1-[3-(6,7-dimethoxyquinazolja-4-ylthio)pheayl}-3-{ 1-phenyl-5-(tr f «oromethyl V1H-pyrazol-3-yl jitrea;

l-(3-{6,7-dimethoxyquinazo1in-4-yloxy)phenyl]-3-[1-(4-fluorophenyl)-3-(trifluoromethyl)-**1H-pyrazo!-5-yl]urea;**

]-[3-{6,7-dimethoxyquinazoiin-**4**-yioxy)phenyl]-3-[1-p-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-y I]urea;

l-(4-tert-butylphenyi)-3-{3-(6 J-dime¾oxyqiH«azoho-4-yloxy)pheriyl)urea;

I-(4-tert-buty lphenyl)-3-(3-{6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(4-chlorophenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(4-(trifluoromethoxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-methoxyphenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-ethoxyphenyl)urea;

1-(3-chloro-4-methoxyphenyl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-phenylurea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(4-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(4-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(trifluoromethyl)phenyl)urea;

1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

1-(3-(6,7-diethoxyquinazolin-4-ylthio)phenyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)urea;

1-(3-(6,7-diethoxyquinazolin-4-ylthio)phenyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)urea;

1-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-(6,7-diethoxyquinazolin-4-ylthio)phenyl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-(6,7-diethoxyquinazolin-4-ylthio)phenyl)-3-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)urea;

ethyl 2-(3-tert-butyl-5-(3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)ureido)-1H-pyrazol-1-yl)acetate;

1-(3-(1,3-difluoro-2-methylpropan-2-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-[3~(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[3-(2-ethoxypropan-2-yl)-1-phenyl-1H-pyrazol-5-yl]urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-[3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl]-3-[1-p-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-methoxyethoxy)-5-(trifluoromethyl)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-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)-3-(3-(morpholine-4-carbonyl)-5-(trifluoromethyl)phenyl)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-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy]phenyl}-3-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]urea;

1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-phenyl-1H-pyrazol-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-[3-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazol-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;

l-(3-(2-fluoropropan-2-yi)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

l-(5-cyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

l-{3-(6-methoxy-7-(2-methoxyethoxy)quinazoiin-4-yloxy]phenyl\-3-j 1-methyS-3-(irifluoromethy!)-lH~pyrazol~5-yljurea;

1-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yioxyjphenyi} -3-j l-phenyl -3-(trifluoronietiiyi)-iH-pyrazo!-5-yijurea;

l-(3~fluoro-4-(trif!uoromethyi)phenyl^ -(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yloxy)phenyl)urea;

H3-.raetlK>xy-4-(tr fluorome hy!)phenyl)-3-(3-(6-.raeihoxy-7-"(2-methoxyethoxy)quinazoiin-4-yloxy)phenyl)urea;

ethyl 2-[3-tert-butyi-5-(3-{3-{6-methoxy-7-(2-methoxyethoxy)quinazoiin-4-yloxy {phenyl}ureido)- lH-pyrazo!-l-yl{acetate hydrochloride;

1-{3-j¾-raethoxy-7-(2-meJhoxyelhoxy)quin.azo!m-4-yloxy jphenyl} -3-[1-pheny l-5-(trifluoroniethylJ-lH-pyrazoi-3-yl]urea;

l-{ l-(4-fluoropheny l)-3-(triil«oronwU)yl)-lH-pyrazol-5-yl j-3-{3-{ 6-tneihoxy-7-(2-methoxy eihoxy)q uinazolin-4-yioxy jpheny l}ue a;

i-{3-f6-methoxy-7-(2-methoxyethoxy)quinazoiin-4-yioxy }phenyi}-3-f i-p-toiyi-3-(tr fluoromethyl)- lH~pyTazo!~5-yl]urea;

1-[3-{1,3-difluoro-2-methylpropan-2-yl)-l -phenyl- lH-pyrazoi-S-yl]-3- (3-[6-n>ethoxy-7-(2-n»xtinoxyethoxy)quinazoiin-4-yloxy]pheny l}urea;

l-(3-i 6-rnethoxy-7-(2-medioxyelhoxy)quinazoiin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)«rea;

l-j5-(l ,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl]-3-{3-[6-methoxy-7-(2-«Kthoxyethc>xy)qumazoHn-4-ylthioj|phenyl} «rea;

l-(3-¾ oro-4-(trifluor<methyl)phenyl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yUhio)phenyi)urea;

l-(5-isopropyiisoxazol-3-yl)-3-(3-(6-meftoxy-7-(2~me^ xyethoxy)quinazolin-4-ylthio)pheayi)urea;

l-(3-raethoxy-4-(trtfiuoromethyl)phenyl)-3-(3-(6 -raefhoxy -7-(2-methoxyef ic»xy)quinazo!m-4-ylthio)pheny!)urea;

i-(3-{2~fluoropropan-2-yi)isoxazoi~5-y l)-3-(3 -{6~methoxy-7-(2-i«ethoxyethoxy)quiriazoiin-4-ylthio)phenyl)urea;

l-(5-eyclopentylisoxazol-3-yl)-3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yithio)pheny i)urea;

1-(3-tert-butyl-1-phenyl- iH-pym2»l-5-yl)-3-< 3-(6-ɐ ef ıoxy-7-(2-nıethoxyethoxy)quinazolin-4-ylthio)phenyl)«rea;

ethyl 2-[3-tet -butyl-5-(3- {3-[6-me&oxy-7-(2-t»ethoxyetiioxy}quinaz»lin-4-ylthiojpheny{}ıreido)-1H-pyrazoi-1-yl]acetate;

1-[3-(1,3-diflu0ro-2-methyipropan-2-yl)-1-phenyl-1H-pyrazol-5-yl]-3-{3-[6-methoxy-7-(2-methoxyethoxy)q«inazolin-4-ylthio]phenyl}urea;

1-p-[{>-nieihoxy-7-(2-]«ethoxyet!ioxy)quffiazoiin-4-yltj¾io]phenyl}-3-[1-methyl-3-(trifluoronictiiyl)-lH-pyrazol-5-yljurca;

1- {3-j6-methoxy-7-(2-methoxyelhoxy)qumazoiin-4-ylihio}phenyi}-3-(l~methyi-3-(irif uoromeihyl)-lH-pyrazoi-5-yl jurea;

1-(3-(2-ethoxypropan-2-yl)-l -pheayl- lH-py.razol-5-y.l]-3-{3-[6-methoxy-?-(2-methoxyethoxy)q«inazolin-4-ylthio]phenyl}urea;

1-[i-(4-fluorophcnyl)-3-(triiluoromethy1)-1H-pyrazo1-5-yi]-3-{3-[6-methoxy-7-(2-methoxyedioxy}quinazolin-4-ylthio]phenyI}urea;

1- {3-j6-methoxy-7-(2-methoxyethoxy)quinazoiiii-4-ylthio]phenyl}-3-{l-p-tolyl-3-(trifluoroniethylJ-lH-pyrazol-5-yl]urea;

l-{3-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio]phenyl}-3-[1-phenyl-5-{trif uoromcthyj)-1H-pyıazol-3-yj]urea;

1-(3-(2-fluoropfopan-2-y!)isoxazol-5-yl)-3-(3-(7-metlioxy-6-(4,4-dioxo-3-ihiomorpholinopropoxy)quinazolin-4-ylthio)phenyl)urea;

l-(4-methoxy-3-(trifluoromethyl)phenyl)-3-(3-(7-methoxy-6-(3-(4,4-dioxothiottıorpholino)pø poxy)quinazolin-4-ylthio)phenyl)urea;

l-(3-(6,7-bis(2-Methoxyethoxy)quinazolin-4-ylthio)phenyl)-3-(3-tert-butylisoxazol-5-yl)urea;

l-(3-(2-fiuoropropan-2-y **!)isoxa2ol** -5-yl)-3-(3-(6-methoxy-7-(2-mo**rpho**iinoeAoxy)quinazolin-4-ylti«o)phenyl)urea;

1-(4-meth0xy-3-(trifluoromethyl)phenyl)-3-(3-(6-methoxy-7-(2-morpholinoethoxy) quin azoln -4-ylthio)phenyl)urea;

l-(4-ɪnethoxy-3-(tr fluoromethyl)pheny!)-3-(3-{6-ɪnethoxy-7-(2-morpholinoethoxy)quinazolin-4-yloxy)phenyl)urea;

l-(3-(2-fiuoropropan-2-y!)isoxazol-5-yl)-3-(3-(6-methoxy-7-(2-morpłwlinocthoxy)q«ɪnazolin-4-yloxy}phcnyl)urea;

1~{\ -tet -butyl-1H-pyrazoi-4-yl }-3-(3-(6J-din^thoxyquinazoHn-4-yloxy)phcnyl)ui¾a;

l-(5-tet -butylisoxazol-3-yi)-3-(3-(6,7-diimethoxyquinazolin-4-ylsulfinyl)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea;

1-(3~(6,7~di«iefhoxyquina-io1ffi-4-yloxy)phe»yr)-3-(3~(1-b.ydfoxy-2-mefhylpropan-2-yl)isoxazol-5-yl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-{3-[7-(3-(1,1-dioxo-thiomorpholin-4-yl)-propoxy]-6-methoxyquinazolin-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-(6,7-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-(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; and

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 or prodrug thereof.

[0004] In some embodiments, the compound is selected *from:*

1-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea;

1-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea;

l-(3-.ert-butyl-l-phenyl-iH-pyra^ -5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2,4-difluorophenyl)urea;

I-(3-tert-butyl-l-p-tolyl-lB-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phcny\)urea;

l.-(3-tert-butyl-.l-p-tolyl-i H-pyrazoi-5-yl)-3-(3~(6J~diraeilioxyquina?.o!in--4--yithio)phenyl)urea;

1-(3-teit-butyl-l-p-toly!-lH-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-n«t»oxyc»oxy)quina2oli»-4-yloxy)phcnyl)urea;

1-(3-fert-*Butyl*-l-p-toly 1-l Ii-pyrazol-5-y l)~3-(3-(6-methoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio)phenyl)urea;

l-(3-(2~cyario»ropan-2-yl}phenyl)~3-(3-(6,7-dimethoxyquinazolin-4-yloxy)pheijy l)urea;

!-(3-(2-cyanGpropan-2-yl)phenyI)-3-(3-(6J -dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-i3~{2-cyanopropan-2-yl)phenyl)-3-i3~(6-meihoxy-7-i2~me-hoxyeihoxy)qumazolm-4-yloxy)phenyl)urea;

]-(3-(2~cyanopropaii-2-yl)plieny1)~3-(3-(^ ıethoxy-7-(2-methoxyethoxy)quinazolin-4-ylthio»pheny!)utea;

1-(3-ieri-biityi-l-(2,4-dimeihyiphenyl)-l H-pyrazoi-5-yl)-3-(3-{6 ,7-din efhoxyquitıazolin-4-ySoxy)phenyS)urca;

l-(3-tert-butyl-l-(2,4-dimethylphenyl)-lH-pyrazol-5-yl)-3-(3-(6-methoxy-7-(2-nethoxyc»oxy)quinazolin-4-ylthio)pheny!)«rea;

1-(3-tert-buty 1- i-(2,4-diracthy lphenyl)-lH-pyrazol-5-yl)-3-(3-(6;7-d«iJc&oxyquma5i-olm-4-ylihio)phenyl)utrea;

l-(3-tert-butyl-l-m-tolyl-lH-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yioxy)phenyi)urea;

1-(3-tert-butyl-l-m-tolyl-lH-pyrazoi-5-yl)-3-(3-(6,7-dimethoxyquinazoliin-4-ylthio)phcnyI)«rea;

l-(3-iert-buiyl-l-m-tolyl-lii-pyi^ol-5-yl)-3-(3-(6-n)eihoxy-7-(2-methoxyethoxy)quinazolin-4-yltbio)phenyl)urea;

l-(3-fert-butyl-l-p-toiyl-lH-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methyl»henyl)urea;

1-(3-tert-butyl-l-phenyl-lH-pyraxoJ-5-yi)-3-(3-(6 ,7-dimethoxyquinazolin-4-yloxy)-2-methyiphenyi)urea;

l-(5~tert-buiyiis0xazoi~3~ylM ~(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)urea;

1-(3-(6,7-Dimcthoxyquinazoiin-4-yioxy)-2-nietinylphenyl)-3-(1-phenyi-3-(trifluororacthyl)-1H-pyrazol-5-yl)urea;

i-(3-{6,7-dimethoxyquinazolin-4-yloxy)-2-methylphenyl)-3-(5-(2-fluoropropan-2-yl)isoxazoi-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-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)-2-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-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(2-Chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(2-chloro-5-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(2-ethyl-1-morpholinopropan-2-yl)isoxazol-3-yl)urea;

1-(3-tert-butyl-1-(4-methylpyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-(perfluoroethyl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-(2-methylpyridin-3-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

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;

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;

1-(3-(2-cyanopropan-2-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-(2-cyanopropan-2-yl)-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(5-tert-butylisoxazol-3-yl)-3-(3-(2-chloro-6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

l-(3-(1,1-difluoroethyl)-1-(pyridin-3-y!)-1H-**pyrazol-5-yl**)-3-(3-(6,7-di**m ef**oxyquina2» 1in-**4-yloxy)pheny**l)u**rea;**

I-(3-tert-butyl-1-{6-methylpyridin-3-y i)-1*E* **-pyrazol-5-yl**)-3-(3-(6,7-dime&oxyquinazolin-**4-yloxy)pheayl)urea;**

l.-(**3-tert~butyl-.l**-(2-QXO-1,**2-djhydropyridin-4-yl)** - 1H-**pyrazol**-5-**yl**)-3-(3-(6,7-dimethoxyquinazoiin-4-yloxy)phenyl)urea;

l-(3-{6,7-dimethoxyquinazolin-4-Yioxy)phenYl)-3-(1-(5-fluoropyridin-3-yl)-3-isopropyl-1H-**pyrazoI-5-yl)urca;**

l-(3~{1,1-difluoroethyl)-1-(4-methoxyphenyl)-iH-pyrazoi-5-yI)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

l-(3-(i,1-difluoroethyl)~l-(5-fluoropyr din~3-y!)~1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazoiin-4-yloxy)phenyl)urea;

1-(3-tet -butyl-1-(6-oxo-1,6-dihydropyridin-3-yl)-1H-pyraxol-5-yl)-3-(3-(6,7-dimedioxyquinazolin-4-yloxy)pheriyl)urea;

1-(3~{**1,l~difluoroethyl**)-**l**-phenyl-1H-pyrazoI-5-yl)-3-(3-(6,7-dimethcxyquinazoin -4-yioxy)phenyi)«rca;

1-(3-(1,1-**difluoroeihyl**)- l-phenyl-1**H-pyrazol-5-yl**)-3-(**3**-(6,**7-dimethoxyquinazol**in-**4-**ylthio)phenyl)urea;

]-(3-tert-butyl-1-(2~methyipyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-**teit-bu**tyl-1-ethyl-1H-pyTazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yithio)plieny!)urea;

l-(3-tert-butyl-l-(pyridm-3-yi)-iH-p%'^ ol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phe«yl)urea;

1-(3-tert-butyl-1-(pyridin-3-yl)-1**H-pyrazol-5-yl**)-3-(**3**-(**6**,**7-dimethoxyquina2o!in-4-**ylthio)phenyi)urea;

l-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yS)urea;

1-(3-(6,7-**di«ethoxyquinazolin-4-yithio)phenyl**)-3-(**3-isopropyl-.l** -**phenyl-1H-pyrazo**!-**5-**yi)urca;

S-(3-tcit-butyl-1-(5-fluoropyridiii-3-yl)-l H-pyrazol-5-yl)-3-(3-(f,7-dimethoxyquinazolin-4-**yloxy)phenyl)urea;**

1-(**3-tert-butyl**-1-(**5-fluompyridin -3-yl)-l H-pyrazol-5-yi**)-3-(3-(**6**,**7-dimethoxyquinazol**in-**4-**ysthio)phenyi)urea;

1-(3-tert-butyl-1-(4-cyaaopheny 1)-1 H-pyrazoi-5-yl)-3-(3-(6 ,7-dnttefhoxj·qujnazolja-4-yi**oxy)phenyl**)urea;

1-(3-tert-butyl-1-(4-cyanophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-cyclohexyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-cyclohexyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-isobutyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-isobutyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-isopropyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-isopropyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-p-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(1-m-tolyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-(2-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-(2-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-o-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-o-tolyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-tert-butyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(1-p-tolyl-3-(1-(trifluoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea;

1-(3-(6,7-di«ethoxyquinazo1in-4-ylthio)pheny!)-3-(l-p-to!yl-3-(1-
(trif uoromethyf)cyc o propy!)-1H-pyrazof-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(3-iSopropyl-1-(4-a%ethoxyphenyl)-1H-pyrazoi-5-yl)urea;

1-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazoi-5-yl)urea;

1-(3-{6,7-dimethoxyquinazolin-4-yioxy)phenyl}-3-(3-isopropyl-1-(pyridin-3-yl)-1H-pyra2oi-5-yl)urca;

1-(3-(6,7-dimethoxyquinazoiin-4-ylthio)phenyl)-3-(3-isopropyl-1-(pyridin-3-yl)-1H-pyrazo!-5-y])urea;

1-(3-(6 ,7-dimethoxyquinazolin-4-y!oxy)phe«yl)-3-(3-ethyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-cyclopiOpyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)urea;

1-(3-cyclopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yidnio**)pheny**l)urea;

1-(3-cyclobuty!-1 -phenyl- lH-pyrazol-5-yI>3-(3-(6,7-dmiethoxyquinazolin-4-y!oxy)pheny1)urea;

1-(3-cyclobuiy l-1-pSteayi-1H-**p**>^azol-5-yl)-3-(3-(6 ,7-dimethoxyquinazolin-4 -yithio)phenyl)urea;

1-(!-benzyl-3-tert-butyi-1H-pyrazoi-5-yl)-3-(3-{6,7-dimethoxyquinazolin-4-yioxy)pheny 1)urea;

1-(1-benzyl-3-tert-butyl-1H-pyr.azol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio**)phejayi**)urea;

1-(3-tert-b«iyl-l-(3-fluoropheny!)- 1i:l-pyrazof-5-yi}-3-(3-(6,7-dif ethoxyqui«azoli«-4-yioxy)phenyi)urea;

1-**(3-tert-butyl-i**-(3-fluorophenyi)-1**H-pyrazoi-5-yi)-3-(3-(6,7-dimethoxyquma2X>lm-4-**ylthio)phenyl)urea;

1-(3-tert-butyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyi)urea;

1-(3-tert-buty1- \-(4-meihoxyphenyl}-1H-pyrazol-5-yI)-3-(3-(6,7-dimcihoxyquinaii:olin-4-**ylthio)pheayl)urea;**

1-(3-tert-buty1- i-(3-chiorophenyl)- 1**H-pyrazoi-5-yl**)-**3-(3**-(6,7-dimethoxyquinazoi***in***-4-yloxy)phenyl)urea;**

1-(3-tert -butyl-1-(3-chIorophenyl)-l H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

1-t3-ieit-bittyl- l-(4-chk>ropheriyl)-IH -pyrazol-5-yl)-3-(3-t6,7-dimethoxyquiinazolin-4-yioxy)phenyi)urea;

l-(3-.ert-butyl-l-(4-chlorophenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)urea;

I-(5-tert-butylisoxazol-3-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2-fluorophenyl)urea;

l-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(5-(6,7-dimethoxyquinazolin-4-yloxy)-2-fuorophenyl)urea;

1-(3-tert-butyl- l-{4~tert-butylphenyl)-lH-pyrazol-5-yi)-3 -{3~(6,7-diinethoxyquinazolin-4-yioxy)pheny l)urea;

1-(3-ter -butyl-l-(4-ter -bisty Sphenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-dit ½tinoxyquinaZolin-4-yithio)pheny l)urea;

l-(3~tert-butyl-l~(2-fluorophenyl)~1H-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl}urea;

l-(3-tcrt-butyl-l-(2-fluorophcnyi)- lH-pyTazol-5-yl)-3-(3-(6,7-din ethoxyqui«azolin-4-yloxy)phenyl)urea;

1-(3-tert-butyl-l-{4-(trifluoromethyl)phenyi)-l H-py razol-5-yi)-3~(3-(6,7-dimethoxyquinazolin~4-yloxy)phenyl)urea;

H3-tert-b«tyl-l-(4^ ir f uoromethyl)phenyl)-1H-pyrazol-5-yl)-3-(3-(6,7-diine‡hoxyquinazoIin-4-ylthio)pbenyI)urea;

l-(3-tert-buty 1-l-(2-(tr fluoromethyi)pheny!)-1H-pyrazol-5-y!)-3-(3-(6,?-dimeihoxyquinazoiin-4-ylthio)phenyi)urea;

]-(3-tcrt-butyl- !-(2~(trifluoromethyi)phcnyl)-1H~pyrazol-5-y i)-3-{3-(6,7-dimethoxyquinazoiin-4-yloxy)phenyl)urea;

l.-(3-(6J-dimethoxyqujnazolin-4-yloxy)pheKyl)-3-(5-(l-(trifhiororaethyl)cyclopropyl)isa>xazol-3-yl)urea;

1-(3~(6,7-dimethoxyquinazolin-4~ylthio)phenyi)~3-(S-(1-(trifluoromethyljcyclopropy!)isoxazol-3-y!)urea;

1-(3-tert-buty 1-l-(3-(trifluoromethyl)pheny!)-1H-pyraeol-5-y()-3-(3-(6,?-dimethoxyquinazolin-4-yloxy)phejiyl)urea;

l-(3-tert-butyl- 1-(3-(tri fluoromethy !)phenyi)- 1H-pyrazol-5-yl)-3 ~(3-(6;7-dimethoxyqutinazolin-4-ylthio)phenyl)urea;

l-(3-(2-cyw}Opropan-2->4)isoxazol-5-yl)-3-(3-(6,?-diraeti}OxyquraazoHn-4-yiihio)phetiyi)urea;

l-(3-(6,7-dimethoxyquinazolf -4-yithio)phenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea;

l-(3-(6,7-dimethoxyquinazolin-4-ylthio)phenyl)-3-(.l~phenyl-3-(i~(tr f uoromethyl)cyclopropyl)-1H-pyrazol-5-yl)urea;

1-(3-(7-edioxy-6-metk>xyquinazolin-4-yloxy)pheKyl)-3-(.l -phenyl-3-(triflaQromethyl)-1H-pyrazo!-5-yl)urea;

l-(3~{7-ethoxy~6-methoxyquinazolin~4-yloxy)phenyl)~3~(3-(2~fluoropropan~2~yl)isoxazol-5~yl)urea;

1-(5-(!,3-dif]uoro-2-i»ethylpropa»-2-yl)i½xazol-3-yl)-3-(3-(7-ethoxy-6-tnethoxyq«inazo!ift-4-yloxy)phe3}yl)ufea;

l.-(3-tert~butyl~l-pheny!~1H-pyrazo^~5~yl)-3-(3-(7~ethoxy-6-methoxyquinazolin-4-yioxy)pheny 1)urea;

1-(5-(!,3Hjifluoro-2-nK!thylpropan-2-yl)isoxazol-3-yI)-3-(3-(7-e{feoxy-6-n«itiioxyqumazo!m-4-ylth.io)pheny!)utca;

l-(3~(7~ethoxy~6~methoxyquinazoiin~4~ylthio)phenyl)~3~(3-(2~fluoropropan~2~yl)isoxazol-5~y])urea;

H3-tert-butyl-.l-phenyl- lH-pyrazo.l-5-y1)-3-(3-(6-ethoxy-7-methoxyquinazolin-4-' yioxy)phenyi)urea;

l-(3-(6-ethoxy-7-methoxyquinazolin-4-yloxy)phenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazoi-5-yl)urea;

i~(3-(6-ethoxy~7~medioxyquinazolin~4~yloxy)phenyl)~3~(3-(2~fluoropropan~2~yl)isoxazol-5-yi)itrea;

l-(5-(l **3**-dif uoro-2-metiylpropan-2-yl)isoxazol-3-yl)-3-(3-(6-ethoxy-7-methoxyqu«azoIin-4-yloxy)phenyl)urea;

l-(3-(6-ethoxy-7-methoxyquinazolin-4-ylthio)phenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea;

l-(5-{!,3-difluoro-2-methylpropan-2-yi)isoxazol-3-yl)-3-(3--{6-ethoxy-7-tt½tiioxyquraa25o!m-4-ylth.io)pheny!)ufea;

(1-(3-(6-methoxy- 7-(2-morpho!inoeihoxy}qu»nazolin-4-y loxy)pheHyl)-3-(l-pheiiyi-3-(trifluoromethy!)-1H-pyrazol-5-yi)urea;

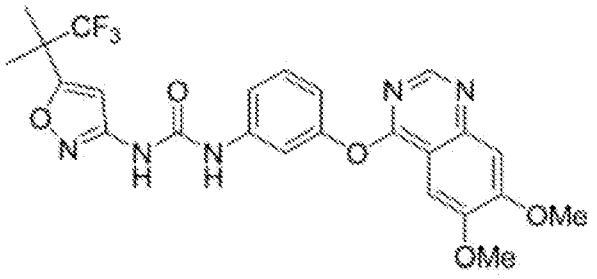
l-(3-(6,7-Dimethoxyquinazolin-4-yioxy)-4-flu3rophenyl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-y l)urea;

l-(3-tert-butyl-1-(4-methoxyphenyl)-iH-pyrazol-5-yl)-3-(3-(6,7-dimethoxyquinazolin-4-ySoxy)phenyS)urea; and

1-(3-(6,7-di«ethoxyquinazolin-4-ylthio)phenyl)-3-(3-ethyl-1-phenyl- \H-pyrazol-5-yl)urea;

or a **pharmaceutically acceptable** salt or prodrug thereof.

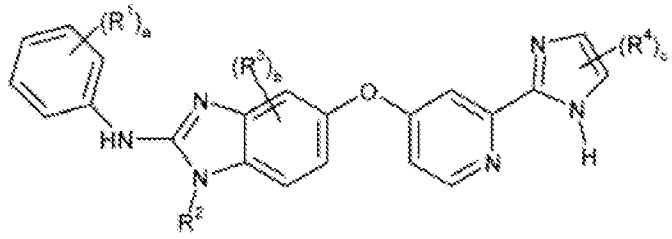
In some embodiments, the RAF **inhibitor** is **CEP32496:**



or a pharmaceutically **acceptable salt thereof.**

(iy) PCTApplication ***Publication WO 2008/147782,*** *which* ***is incorporated herein*** *by reference:*

Substituted benzimidazoie compounds having the following formula D-1:



D-I,

wherein each R^1 is **independently** seiected **from hydroxy,** halo, C_{1-6}alkyl, C_{1-6}**aikoxy,** $(C_{1-6}$alkyl)**sulfanyl, (C|^alkyl)su.lfonyl, cycloalkyl, heterocycloalkyl, phenyl and heieroary!;**

R^2 is C_{1-6}alkyl or halo(C_{1-6}alkyl);

each R^3 is **independently selected from halo,** C_{1-6}**alkyl** and **Cs^alkoxy;**

each R^4 **is independently selected** from **hydroxy,** C_{1-6}alkyl, C_{1-6}alkoxy**, halo,** heterocycioaiky icarboiry l, earboxy 1, (C_{1-6}**alkoxy**)carbonyl**, aminocarbonyl, C1^alkylaminocarbonyl, carbonitriie,** cycloalkyl, **he.erocyeloaIkyl,** phenyl and heteroaryi;

wherein R^1, R^2, R^3 **and** R^4 may be **optionally** substituted with one or more **substituents independently** seiected from hydroxy, halo, C_{1-6}alkyl, !ialo(Ci. ;alkyl), C_{1-6}**alkoxy** and haio(C_{1-6}aikoxy):

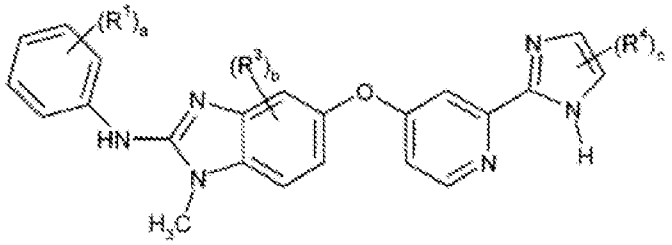
a is l**, 2, 3,4 or 5;**

b is **0**, Ï**, *2* or 3;** and

c is 1 **or** 2;

or a tautomer, stereoisomer, ester, or prodrug thereof or a pharmaceuticaUy acceptabie salt of the compound, tautomer, stereoisomer, ester, or prodrug.

In some **embodiments**, the compound has a structure of **formula** D-II;



D-II

wherein each R^1 is independently selected **from** C_{1-6}alkyl, **C_{1-6}alkoxy**, hydroxy, halo, **(C_{1-6}alkyl)sulfanyl, (Ci.*alkyI)sulfonyl, cycloalkyi,** heterocyeloalkyi, phenyl **and** fieteroaryi;

each R^2 is **independently selected** from **halo,** C_{1-6}alkyl **and** C^alkoxy;

each R^4 is **independently** selected from hydroxy, **C_{1-6}alkyl**, C_{1-6}alkoxy, halo, earboxyl, **(Ci.«,a!koxy)carbonyl, aminocarbonyl,** carboniiriie, eycloalkyi, heterocyeloalkyL **heterocycloalkylcarbonyl,** phenyl and heteroaryl;

wherein R^1, R^2, R^3 and R^4 may be **optionally substituted** with one **or** more **substituents** independently **selected from hydroxy, halo, C_{1-6}alkyl and C_{1-6}alkoxy**;

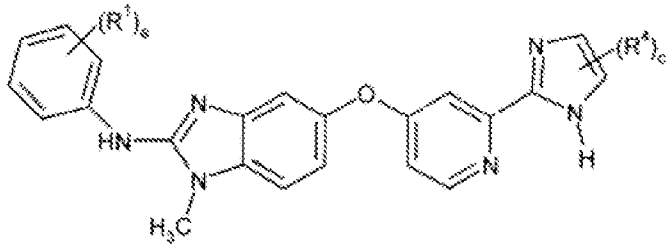
a is 1, 2, 3, 4 or 5;

b is 0, 1, 2 or 3; and

c is I or 2;

or a tautomer, **stereoisomer,** ester, or prodrug thereof or a **pharmaceutically** acceptable salt of the compound, tautomer, stereoisomer, ester, or prodrug.

hi some embodiments, die compound has a structure of formula D-III:



D-III

wherein each R^1 is **independently selected** from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, halo, (C_{1-6}alkyl)**sulfanyl,** (C_{1-6} aikyl)sulfoiiyi, **eycloalkyi, heterocyeloalkyL, phenyl and** heteroaryl;

each R* is independently selected from hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, *halo,* earboxyl, (C_{1-6}a-koxy)carbQnyl, arainocarbonyl, carbonitrile, cyeloalkyl, heterocycloalkyl, heierocycloalkyicarbonyi, phenyl and heteroaryl;

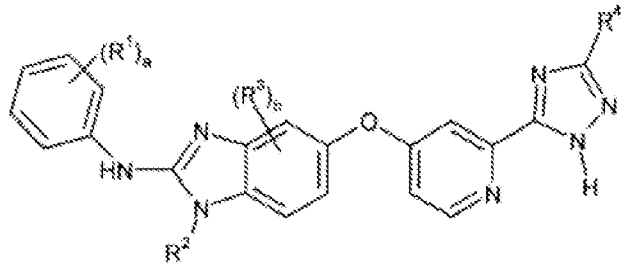
wherein R^1 and R^4 may be optionally substituted with one or more substituents independently selected from hydroxy, halo. C_{1-6}alkyl and C_{1-6}alkoxy;

a is 1, 2, 3, 4 or 5; and

c is 1 or 2;

or a tautomer, stereoisomer, ester, or prodrug thereof or a pharmaceutically acceptable salt of the compound, tautomer, stereoisomer, ester, or prodrug.

Also disclosed are compounds of the following formula D-IV:



D-IV

wherein each R' is independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy; halo, (C_{1-6}alkyl)sulfanyl, (C_{1-6}alkyl)sulfonyl, cyeloalkyl, heterocyeloalkyl, phenyl and heieroary!;

R^2 is C_{1-6}alkyl or halo(C_{1-6}salkyl);

each R^5 is independently selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy;

each R^4 is independently selected from hydroxy, C_{1-6}alkyl, C;-$_f$alkoxy, halo, earboxyl, (C_{1-6}alkoxy)c-arbonyi, aminocarbonyl, C^alkylaminocarbonyl, carbonitrile, carbonitrile(C_{1-*}alkyl), cyeloalkyl, heterocyeloalkyl, heterocycloalkyl(C_{j-6}alkyl), heterocycloalkylcarbonyl, phenyl and heteroaryl;

wherein R^1, R^2, R^3 and R* may be optionally substituted with one or more substituents independently selected from hydroxy, halo, C_{1-6}alkyl and C_{1-6}alkoxy;

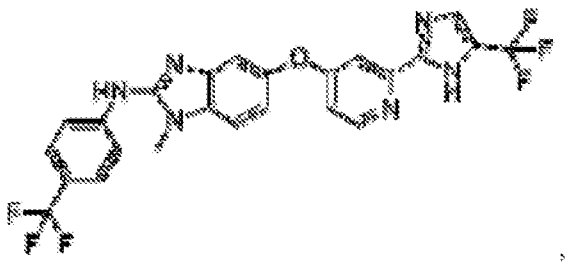
a is I, 2, 3, 4 or 5; and

b is 0, i, 2 or 3;

or a tautomer, stereoisomer, ester, or prodrug thereof or a pharmaceutically acceptable salt of the compound, tautomer, stereoisomer, ester, or prodrug.

in other **embodiments, new substituted** benzirnidazole compounds are provided of **formulae D-I** through **D-IV** set forth above, wherein each R^1 is independently selected from **the group consisting of hydroxy, chloro, fluoro, bromo, methyl, ethyl, propyl, butyl,** methoxy, **ethoxy, propoxy,** butoxy, **trifluoromethyi, trifluoroethyl,** trifiuororoethoxy, **trifluoroethoxy,** trifluoromethylsulfanyl, piperidinyl, C_{1-6}alkylpiperidinyl, **piperazinyl, C_{1-6}alkylpiperaziny!, ierrahydrofuranyl, pyridmyi** and **pyrimidmyi.** la other embodiments, new substituted benzimidazole **compounds** are provided of formulae D-I through D-IV, wherein a is **1** or **2,** and **at** least one R^1 is halo(C_{1-6}alkyl), such as trifluoromethyi. In oilier **embodiments,** new substituted **benzimidazoie** compounds are provided of formulae **D-1** and **D-1Y,** wherein R^2 is **C1-$alkyi,** such **as, e.g.,** methyl or ethyl In further **embodiments, new substituted** benzimidazoie compounds are provided of formulae D-I, D-II and ***D~W,*** wherein b is 0, and thus R^3 is **not** present. In **alternate** embodiments, new substituted **benzimidazoie compounds** are provided of **formulae** D-I through D-IV, **wherein b** is **1, and** R^3 is **C_{1-6}alkoxy, such** as, **e.g.,** methoxy. In yet further embodiments, new **substituted** benzimidazoie **compounds** are provided **of formulae D-1.** through **D-lli,** wherein e is **1** or 2, and **at least** one **R^4 is** liaIo(C_{1-6}alkyl), such **as,** e.g., **trifluoromethyi.**

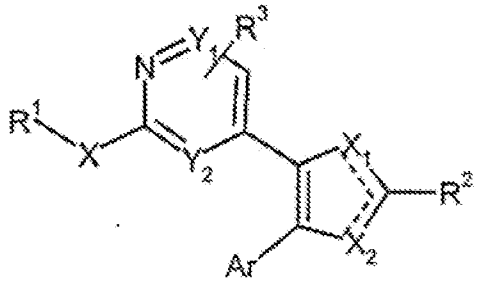
In some embodiments, the compound is Raf-265 :



or a pharmaceutically acceptable salt thereof.

(v) PCT Application ***Publication*** *WO* ***02/24680, which*** *is incorporated herein by reference:*

A compound of formula E-I:



E-I

wherein

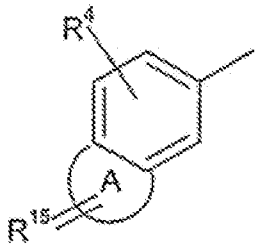
X is O, C¾, CO, S or NH, or the moiety **X-R'** is hydrogen;

Y_1 and Y_2 are **independently** N or CH;

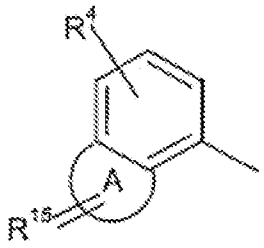
R^* **is hydrogen,** C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, or heteroarylC_{1-6}alkyl, any **of which** may be **optionally** substituted; in **addition** when **X** is ¾ **then** R^1 may be **hydroxy! or** C_{1-6}alkoxy which may be **optionally substituted;**

R^2 is H, C_{1-6}alkyl, **C^alkenyl,** C^eycloaSkyi CV?cycIoaIkeiiyi, heterocyclyl, **aryl** or **heteroaryl,** any of which may **be** optionally substituted;

Ar is a group of the formula a) or b):



a)



b)

wherein **A** represents a **fused 5- to** ?~membered **ring optionally containing** up **to two** heteroatoffis **selected from O,** S **and** NR^5, **wherein** R^5 **is** hydrogen **orCj.¾a.lkyk** which ring **is optionally** substituted by up to 2 substituents selected from halogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or keto;

R^3 **and** R^4 are independently seiected from hydrogen, halogen. C_{1-6}alkyl, aryl, aryl C_{1-6}**alkyl**, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, **halo** C_{1-6}**alkyl,** arylC_{1-6}alkoxy, **hydroxy.**

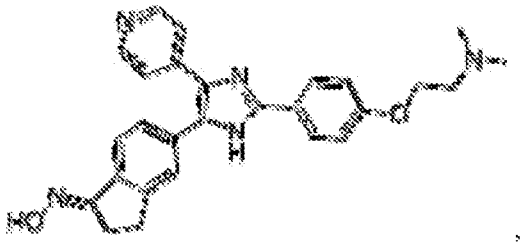
nitro, cyano, azido, amino, mono- and di-N-C_{1-6}-saikylamino, acyiamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- ant! di-N-C_{1-6}alkylcarbamoyl, CV_6alkoxycarbonyl, aryloxycarbonyl, ureido, guanidino-C_{1-6}alkylguanidino, amidino, C_{1-6}alkylamidino, sulphonylamino, arninositlphonyi, C{.$aikylthio, C_{1-6}alkylsulphinyl or C_{1-6}alkylsulphonyl;

R^{15} is O or N-QH;

one of X_1 and X_2 is N and the other is NR^6 wherein R^6 is hydrogen or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is SB-590885:



or a pharmaceutically acceptable sail thereof.

Method of Treating HCV-infection with the Administration of a RAF Inhibitor or a Pharmaceutically Acceptable Salt Thereof

la one aspect, the invention provides methods for treating HCV-infection in a subject in need thereof by administering a RAF kinase inhibitor or a pharmaceutically acceptable salt thereof. The RAF kinase inhibitor suitable for the method of this invention may be selected from any of those as described above. In some embodiments, the compound suitable for use in the methods of the present invention is an iiihibitor of one or more RAF kinases selected from A-RAF, B-RAF, and C-RAF. In some embodiments, the RAF inhibitor is selected from the group of compounds referred to in U.S. Patents 7,235,576 and 73 51,834, and Internationa! Patent Application Publications WO 02/24680, WO 2006/024834, WO 2008/147782, and WO 2009/117080 (each of the U.S. Patent or PCX publication is incorporated herein in its entirety by reference for their disclosure of RAF inhibitors). In certain embodiments of the invention, the RAF inhibitor is selected from sorafenib, CEP32496, Raf-265, regorafenib, SB-590885, AZ-628, or prodrugs or pharmaceutically acceptable salts thereof. In some embodiments, the RAF inhibitor is

selected from **sorafenib,** Raf-265, **and** AZ-628.

In accordance with this **invention,** the **RAF** inhibitors and **pharmaceutically acceptable** salts **thereof can** be **administered** to a subject via any **suitable route or** routes. In some **embodiments,** the drugs are **administered orally;** however, **administration intravenously, subcutaneously,** intra-arterially, **intramuscularly, mtraspinally, reetally,** intrathoracically, **inttaperitoneaHy, intraventricular!}',** or **transdermally,** topically, **or by inhalation is** also **contemplated. The** agents can be administered orally, for example, in the form **of tablets,** troches, capsules, elixirs, suspensions, **syrups,** wafers, or the like, prepared by art recognized procedures.

In some **embodiments,** the administration is a slow or extended release. The term **"extended release"** is **widely** recognized **in** the **art** of pharmaceutical **sciences** and **is used herein** to **refer** to a contcoiied release of an active compound or agent **from** a dosage **form o an** enviroiunent over **(throughout** or **during)** an extended **period of time,** e.g. greater than **or** equal to one **hour. An** extended release dosage form will release drug at **substantially** constant rate over an extended period **of** time or a **substantially** constant amount **of drug** will be released **Incrementally** over an extended period of time. The term "extended release" used herein includes the terms "controlled release," "prolonged release," **"sustained** release," **"delayed release,"** or "slow release" **as these** terms are **used in the** pharmaceutical sciences. In some **embodiments,** the extended release dosage is administered in the form of a patch or a pump.

When a solid **carrier** is used for administration, the preparation may **be in** a tablet, placed **in** a hard gelatin capsule **in powder** or pellet form, or it **may** be in the **form** of a troche or lozenge. If a liquid carrier **is** used, the preparation may be in the forms of a syrup, **emulsion,** soft gelatin capsule, **or** sterile injectable liquid such as **an** aqueous **or** non¬aqueous liquid suspension or solution.

Dosage schedules **of the** agents and compositions according to the **methods of the** invention will **vary** according to the **particular compound or compositions** selected, the route of administration, the nature of the condition being treated, the age, and condition **of** the patient, the course, or stage **of** treatment, and will **ultimately** be at the discretion of the attending physician. It will be understood **that the** amount of the RAF inhibitor and **their** pharmaceuticaliy acceptable salts thereof administered will **be amounts** effective to produce

a desired **biological** effect, such as beneficial results, including **clinical** results. It will be understood that an effective amount can be administered in more than one dose and over a course of treatment.

Desired duration of **administration of the** RAF inhibitor and their pharmaceutically acceptable salts thereof can be determined by **routine** experimentation **by** one skilled in the art. For **example,** the RAF inhibitor and/or its pharmaceutically acceptable salts may be administered for a period of 1-4 weeks, **1-3** months, 3-6 months, 6-12 months, 1-2 years, or more, up to the lifetime of the patient. In some embodiments, the RAF inhibitor and/or its **pharmaceutically** acceptable salts may be administered for **a** period of **1** week to 48 weeks. In some **embodiments,** the RAF **inhibitor** and their **pharmaceutically acceptable** salts may be administered for a period of 12 weeks or 24 weeks.

It is known **in** the art that normalization **to** body surface area **is an** appropriate method for extrapolating doses between species. The human equivalent dose (HED) **for** this dosage can be estimated using the following **formula** that accounts for differences in body surface area (see Estimating the Safe Starting Dose in Clinical Triais for Therapeutics in **Adult Healthy** Volunteers, December 2002, Center for Biologies Evaluation and Research):

HED = animal dose X (Km animal / ***Km*** human)

where the ***Km*** .factor is body weight divided by body **surface** area (Km rat has been **determined** as 6, and ***Km*** human is 37; see Reagan-Saw, Nihal, Ahmad, 2007). Thus, a dosage of **1.0 mg/kg** in rats is equivalent to 1.6 mg/kg in **humans** (10 mg/kg X (6 / 37) = 1.6 mg/kg). For human subjects, to calculate a dose in rag **from** the dose in mg/kg, the dose in mg/kg is multiplied by a typical adult weight of **70** kg,

In certain embodiments of the invention, the dose of the RAF inhibitor or its pharmaceutically **acceptable** salt is 0,01 **to 10 mg/kg/day (which,** given a typical human subject of 70 kg, is 0,7 to 700 mg/day).

In accordance **with** another aspect of the present invention, there is provided a method for treating HCV infection in a subject in need thereof, the method comprising the step of administering to said subject an RAF inhibitor or **a pharmaceutically acceptable** salt thereof in combination with at least one additional **therapeutic** agent. in some

embodiments, the additional tlierapeutdc agent is an antiviral agent. In some embodiments, the additional therapeutic agent is a current, late stage or marketed **DAA** agent. Suitable antiviral **agents include,** but are not limited to, HCV protease and polymerase inhibitors **(such as** NS3/4A protease inhibitors and RNA-dependent **UNA** polymerase (NS5B) inhibitors), agents targeting host ceil activities involved **in** HCV **replication** and inosine monophosphate **dehydrogenase** (IMPDH) inhibitors.

Examples of therapeutic agents that may be present **in** a combination include ribavirin, ievovirin, vifamidine, thymosin **alpha-1,** interferon-}! **intef eron-α, pegylated** mferferon **-a** (pegmferferon-a), a combination of inferferon- α and ribavirin, a combination of peginterf ron-«.arid **ribavirin,** a **combination of interferon-a** and Ievovirin, and a combination of peginterferon-a and Ievovirin. **Interferon-a** includes recombinant interferon-α2a (such as ROFERON interferon available **from Hoffmann-LaRoche, Nutley,** NJ), pegylated interferon-«2a **(PEGASYS),** interferon~a2b (such as **INTRON-A** interferon available from Schering Corp., Kenilworth, NJ), pegylated intcrferon-«2b (PEGINTRON), a recombinant consensus interferon *(such* **as** interferon aiphacon-3), and a purified interferon **-a** product, Amgeu's recombinant consensus interferon has the brand name **INFERGEN.** Levovirin is the L-enantiomer of ribavirin which has shown **immunomodulatory** activity similar **to** ribavirin. Yuaniidine represents **an** analog **of** ribavirin disclosed in WO 01/60379. The **individual components** of the **combination** can be administered separately at different times during the course of therapy or concurrently in divided or single **combination** forms.

Ribavirin, Ievovirin, and viramidine may exert their anti-HCV effects by modulating intracellular poofs of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting **enzyme** on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily **phosphorylated** intraccllulariy and **the** monophosphate derivati ve is an inhibitor of IMPDH. **Thus,** inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the **compounds** of the present invention may also be **administered** in combination with an inhibitor **of IMPDH,** such as VX-497, which is disclosed in International Patent Application Publications WO 97/41211 and WO 01/00622; another IMPDH inhibitor, such as that disclosed in WO 00/25780; or mycophenolate **mofetil.** *See* A.C. Allison and **E.M.** Eugui 44 (Suppl.) Agents Action 165 (1993).

Macrocyclic compounds useful as HCV protease inhibitors are described in WO 06/1.19061, WO 7/015785, WO 7/016441, WO 07/148135, WO 08/051475, WO 08/05 1477, WO 08/05 1514, WO OS/057209. Sonic HCV NS3 protease inhibitors are disclosed in International Patent Application Publications WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888. WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, WO 02/48116, WO 02/48172, British Patent No. GB 2 337 262, and U.S. Patent No. 6,323,180,

Hepatitis C NS3/4A protease inhibitor may be employed in the present disclosure as the additional therapeutic agent. A compound may be assayed for its ability to inhibit Hepatitis C protease by methods known in the art and/or by methods provided herein. Examples of such inhibitors include, but are not limited to, compounds identified as inhibitors in such assays and the inhibitors of WO 03/087092, WO 03/006490, WO 03/064456, WO 03/064416, WO 03/035060, WO 02/060926, WO 02/079234, WO 02/481 16, WO 02/48157, WO 00/31 129, WO 02/18369. WO 02/08256, WO 02/08244, WO 02/08198, WO 02/08187, WO 01/81325, WO 01/771 13, WO 01/74768, WO 01/64678, WO 01/07407, WO 00759929, WO 00/09588, WO 00/09543, WO 99/64442, WO 99/50230, WO 99/38888, WO 99/07734, WO 99/07733, WO 98/46630. WO 98/46630, WO 98/22496, WO 98/17679, WO 97/43310, 086,018,020, US5,990,276, US5,866,684, US2O030008828, US20020 177725, US200200 16442, US200200 16294, M. Liinas-Dnmet et at., Bioorg. Med. Chem. Lett, 8, pp. 1713-18 (1998); W..Han et aL Bioorg. Med. Chem. Lett., 10, 711-13 (2000); R. Dunsdon et aL Bioorg. Med. Chem. Lett, 10, pp. 1571-79 (2000); M. Llinas-Srunet et al., Bioorg Med. Chem. Lett, 10, pp. 2267-70 (2000); and S. LaPiante et ai., Bioorg. Med. Chem. Lett., 10, pp. 2271-74 (2000)] (which are incorporated herein by reference).

HCV NS5B polymerase inhibitors that may be used in combination with the RAF inhibitors in the present disclosure include, but are not limited to, those disclosed in International Patent Application Publications WO 02/057287, WO 02/057425, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; U.S. Patent No, 6,777,392 and U.S. Patent Application Publication US2004/0067901 ; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, vafopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine *(see also* WO 2005/003147). In some embodiments, nucleoside HCV

NS5B polymerase inhibitors that are used in combination with the present-RAF inhibitors are selected from the following compounds:

4-ammo-7-(2-C-methyl -β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(2-C-methyi-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-methylamino-7-(2-t'-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-dimethyiamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7*H*-pyrrolop,3-*d*]pyrimidine;

4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-araino-5-ineth}d-7-(2-C-]neihyi-p-D-ribofkranosy!)-7 *H*-pyrrolo[2,3-*d*]pyrimidine;

4-amin0-7-(2-C-f ethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid:

4-an]ino-5-bromo-7-(2-C-mei hy!-p-D-riboftirai»syl}-7 Hpyrrolo[2,3-*d*]pyrimidine;

4-amino-5-chloro-7-(2-C-methyl-**p-D**-ribafuranosyl)-7H-pyrrolo[2,3-*d*]pyrimidine;

4-amino-5-fluoro-7-(2-C-mcthyi-β-D-ribofuranosyl)-7Hpyrrolo[2,3-*d*]pyrimidine;

2,4-diamino-7-(2-C-a ethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-*d*]pyrimidine;

2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

2-amino-4-cyelopropylamino-7-{2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

2-aniino-7-(2-C-mcihyi-p-D-ribof»nitiosyJ)-7 *H* pyrrolo[2,3-*d*]pyrimidin-4(3H)-oi-e;

4-amino-7-(2-C-eiky!-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(2-C,2-0-dimethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

7-(2-C-methyI-**p**-D-ribofuranosyi)-7H-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one;

2-amino-5-methyi-7-(2-C, **2-0**-dimedyl-β-**D**-ribofuranosyl)-7***H*-pyrrolo[2,3-*d*]pyrimidin-**4(3H)-one;

4-amino-7-(3-deoxy-2-**C**-methyl-**p**-**D**-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amiino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7*H* pyrrolo[2,3-*d*]pyrimidine;

4-amino-2-fluoro-7-(2-C-mcthyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

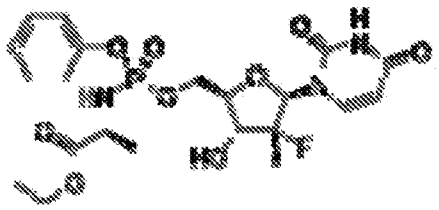
4-amino-7-(3-C-methyl-p-D-ribofuranosy!)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

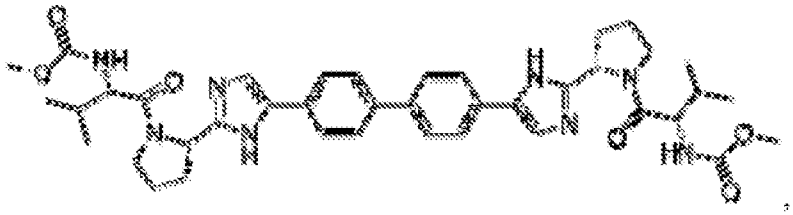
4-amino-7-(2,4-di-C-methyi-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine;

4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; and the corresponding 5'-**triphosphates;** or a pharmaceutically acceptable **salt** thereof.

In certain embodiments, the additional **therapeutic** agent **is** GS-797? **(an** nucleotide HCV NS5**B** polymerase inhibitor.):



or pharmaceutically acceptable salts thereof In certain embodiments, the additional therapeutic agent is BMS-790052 (aNS5A inhibitor):



or a pharmaceutically **acceptable** salt thereof. **In certain embodiments, the** method of the present disclosure comprises administering to a **subject in** need **thereof a therapeutically** effective amount of AZ-62S **conjointly with** GS-7977 or BMS-790052.

In some embodiments of the invention, the RAF inhibitor and the additional therapeutic agent are administered **simultaneously,** or **sequentially, or** in a single **formulation** or in separate **formulations** packaged **together.** In other embodiments, the **RAF** inhibitor and the additional **therapeutic** agent are administered via different routes. As **used** herein, "combination" includes **administration** by any of these **formulations** or routes of administration.

It will **be** understood by one of ordinary skill **in** the art that the methods described herein may be adapted and modified as is appropriate for **the** application being addressed and that the **methods** described herein may be employed in other suitable applications, and **that such** other additions and **modifications will** not depart from the scope hereof.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the embodiments which follow thereafter.

EXAMPLES

Example 1: RAF inhibitors

To identity potential compounds that could be advanced as part of a comprehensive antt-HCY therapy, a series of compounds that inhibit one or more RAF isoforms were evaluated. The tested inhibitors are shown in bold in Figure 1.

The intrinsic ability of these RAF inhibitors to block one or more RAF isoforms is characterized in Table 1.

Table 1: Kinase Profile of RAF inhibitors to be evaluated as antiviral agents

Drug Substance	Class[a]	IC50 C-Raf (nmol/L)	IC50 B-Raf (wt) (nmol/L)	IC50 VEGFR2 (nmol/L)	IC50 c-Kit (nmol/L)	IC50 FLT3 (nmol/L)
sorafenib	II	6	22	90	68	58
Raf265	II	5[b]	70[b]	70[b]	20[b]	NA[b]
Zelboraf/PLX4032	I	1.72	0.16	-[c]	-[c]	-[c]
AZ-628	II	29	100	-[b]	-[b]	-[b]
GSK2118436/dabrafinib	I	48	100	-[c]	-[c]	-[c]

*Class I inhibitors have eellnlar selectivity for B-Raf mutations associated with melanoma, such as V600E; such inhibitors bind wildtype B-Raf with equal proficiency to mutant protein in purified form, but selectively target the mutant protein when present inside cells. Class 11 inhibitors do not discriminate mutant B-Raf from their wiidtype counterpart. "Not available. [c]No meaningful inhibition.

Example 2; Antiviral potency of Raf inhibitors against HCVpp

Overview of experimental design

The initial screen for anti-HCV activity utilized HCV pseudoparticks (HCVpp), the equivalent of an HCV-VLP, to evaluate the effect of Eaf inhibition on viral entry. The HCV entry inhibitor assay uses Huh 7.5 cells and HIV-1 virus which has been pseudotyped with the HCV (GT1a or GT1b) E.1./E2. Briefly, cells are plated one day prior to assay. On the day of assay, media is aspirated and 50ul of 2X compound and 50µ1of pretitered virus are added to each well. Toxicity plates receive only the test compound in tissue culture

medium. On day 5, the medium is removed from **all wells** of the **efficacy** plates, **followed** by **one** wash with medium and addition of 10Oμl **of .firefly** lucifcrase reagent and subsequent lucifcrase **detection** is **carried** out using **a** Microbeta detector (Wailac). For toxicity plates, 10μl of MIS reagent is added to **all** wells and incubated until cell control optical density values are between 1 and 2. Compound cytotoxicity is assessed by MTS (CellTiter¾)96 **Reagent, Promega,** Madison **Wi)** dye reduction. The % reduction in viral entry is determined and reported). Each assay **includes** 1μMg/rril cyanovirin **and /or** 10μg/mi **antibody** CD81 as a positive **control.**

Cell Preparation

Huh 7.5 cells (**human hepatocyte** cell line) were obtained from **APath** LLC and were grown in Dulbecco's Modified Eagle's **Medium** (DMEM) supplemented with. 5% fetal bovine serum **(FBS),** 2.0 raM L-Giutaraine, 100 **units/ml** Penicillin and 100 μg/a i Streptomycin, and 0.1 **mM non-essential** amino acids ("growth **medium"). Cells** were sub-cultured twice **a** week at a split ratio of **1:15** using standard cell culture **techniques.** Total cell number and percent viability determinations were performed using a hemacytometer and **trypan** blue exclusion. **Cell** viability must be greater than **95%** for the cells to **be** utilized in the assay. The cells are seeded in **96-well** tissue culture plates the day **before** the **assay** at a **concentration** of 8-10 x 10^3 **cells/well.**

Virus Preparation

The virus used for this assay is HIV-1 where the HIV envelope is knocked out and then **pseudotyped** with the HCV **(GTa** or GTib) E1/E2. This virus also has a **lucifcrase** reporter gene. For each assay, a pre-tiiered **aliquot** of virus is removed **from** the freezer (-80°**C)** and aiknved to thaw slowly **to** room temperature in a biological safety cabinet.. The virus is resuspended and diluted into tissue **culture** medium such that the amount of virus added to each well is at a MOI {multiplicity of infection) of 1.

Plate Format

The **format** of the test plate has been standardized. Each efficacy plate contains cell control wells (cells only), virus **control** wells **(cells** plus virus), and experimental wells

(drug plus ceils plus virus). Toxicity plate **wells contain** cell control **wells** (ceils only) **and** experimental wells (cells plus **drug in the** absence of virus). Samples were **evaluated** for antiviral efficacy with tfiplicate mcasurcmcois using *6* concentrations at half-log **(or** other) dilutions (12 concentrations can also be **performed)** in order to determine EC_{50} values and cellular cytotoxicity, if detectable. Compounds were tested at 6 concentrations using a **representative** high-test concentration of 100 μM,

Results of the viral inhibitory assay

The results of the anti-HCV assay using **HCVpp** constructed from **genotype 1b** (GTlb) are shown in Tabic 2. A graphical representation of the dose response of compound AZ-628 on HCVpp **viral** entry into cultured **human** hepatoeytes is shown in Figure 2.

Table 2: Antiviral potency against HCV entry using virus-like particles in Huh 7.5.1

Drug	Genotype	EC50 (μM)[1]	TI[2]	Class[3]
Sorafenib	1b	1.81	>2.8 (5μM)	II
Raf-265	1b	0.89	>5.6 (5μM)	II
AZ-628	1b	0.42	>49 (20μM)	II
Zelboraf/PLX4032	1b	>5	1 (5μM)	I
Dabrafenib/GSK2118436	1b	>5	1 (5μM)	I

[1]Measured by luciferase tagged HCV GT-1b pseudotyped virus in ≥80% confluent cells at **MOI 0.02.** [2]Ratio **of** EC_{50} **and** CC_{50}, where EC_{50} **is** the **concentration** necessary **to** inhibit viral **reproduction by** 50% and CC¾ is the **intrinsic** drag cytotoxicity **measured** in the absence of virus. **Number** in parentheses **indicates the** highest **concentration** tested in **the experiment** > sign indicates **that** concentration range tested was too low to fully evaluate the TL so the lower limit is specified. [3]**Defined** by the specificity **of the** inhibitor to a RAF isoforro.

The data suggest a potent entry blockage for Class II **Raf** inhibitors. Class I inhibitors show little or no antiviral activity.

Example J: Antiviral potency of RAF inhibitors against: HCVcc

Overview of experimental design

The secondary screen for aad-HCV activity utilized HCVcc, a lab-adapted M l infection cycle virus, to evaluate the effect of Raf inhibition on viral entry. The HCVcc inhibitor assay uses Huh 7.5 cells and HCVcc containing the luciferase gene generated from pJ6/JFHl-p7Rluc. Briefly cells are plated one day prior to assay. On the day of assay, media is aspirated. The cells are pre-treated with 10oμl of 1X compound. After 1h pretreatan ent, compound containing media is aspirated, HCVcc diluted 1x compound is added o each well. Toxicity plates receive only the test compound in tissue culture medium. The medium is removed from all wells of the efficacy plate 72h post-infection, followed one wash with IxPBS and addition of 30μl of Renilla hieiferase reagent and subsequent iuciferase detection using a Microbeta detector (Waliac). For toxicity plates, 1oμl of MTS reagent is added to ail wells and incubated until cell control optical density values arc between: 1 and 2. Compound cytotoxicity is assessed by MTS (CellTiter€:96 Reagent, Promega, Madison WI) dye reduction. The % reduction in viral entry is determined and reported. Each assay includes anti-CD81 as a positive control.

Cell Preparation

Huh 7.5 ceils (human hepatocyte cell line) were obtained from APath LLC and were grown in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (PBS), 100 units/mi Penicillin and 100 μg/ml Streptomycin, 1% Non¬essential amino aeids(NLAA) in a 5% C0¾ incubator at 37°C, Cells were sub-cultured twice a week at a split ratio of 1:10 using standard cell culture techniques. Total cell number and percent viability determinations were performed using a hemacytometer and trypan blue exclusion. Cell viability must be greater than 95% for the cells to be utilized in the assay. The ceils were seeded in 96-weli tissue culture plates the day before the assay at a concentration of 1×10^4 cells/well.

Generation of viral stocks and HCVcc titration

Theplasmids carrying HCV J6/JFH1 genome, or chimeric mCon1/JFH1 or mH77/JFHi genome and Riue reporter gene were kindly provided by Dr. Charles Rice at

Rockefeller University. HCV **RNA** was produced by ***in vitro*** transcription using **a** RiboMaxTM Large scale RNA production system (Promega) according to manufacturer 's **instructions.** HCV RNA was delivered to **Huh?.5J** cells by **using** TransIT mRNA transfection kit **(Minis).** The infectious supernatants were **harvested** from 72h- 192h post-transfecdon and filtered through a **0.22um membrane.** The cleared supernatant (HCVcc) was aliquoted and frozen at **-80°C** or used freshly. HCVcc infectivity was **determined** by $TCID_{50}$ assay. Briefly, infectious **supernatant** was series **diluted** and **inoculated** onto **Huh7.5** cells in a 96-well piate at 37°C. At **72h** post-infection, ceils were fixed and **immunostamed. with the** anii-NS5A **MAb.** The number of HCV positive cells **was counted.** The $TCID_{50}$ was **calculated** according to the Reed and **Muench** method.

Plate Formal

The **format** of the test plate has been standardized by SOUTHERN. Each efficacy plate contains cell control wells (ceils only), virus control wells (ceils plus virus), and **experimental wells** (drug plus ceils plus virus). Toxicity plate **wells contain cell** control wells (cells only) **and experimental** wells (cells plus **drug** in the absence of virus). Samples were evaluated for antiviral **efficacy** with triplicate **measurements** using 6 concentrations at half-log (or other) **dilutions** in order to determine EC_{50} values and **cellular** cytotoxicity, if **detectable.** Compounds were tested at 6 **concentrations** using a representati ve high-test concentration of 100 μM.

Results of the viral inhibitory assay

Table 4 illustrates the potency of antiviral inhibition against **HCVcc.** A graphical representation of the dose response of compound AZ-628 on HCVcc viral entry into **cultured human** hepatocytes is **shown** in Figure 3.

Table 3: Antiviral potency against HCVcc in Huh 7.5.1

Drug	Genotype	EC50 (μM)[1]	TI[2]	Class[3]
Raf-265	2a	1.05	>3.7 (5μM)	II
AZ-628	2a	0.12	>3.S (5μM)	II

[1]Measured **by luciferase** tagged **HCV GT-2a** cell culture derived virus in 50% **confluent cells** at MOI **0.02.** [2]Ratio of EC_{50} and CC_{50}, where EC_{50} **is** the concentration necessary **to** inhibit viral reproduction by 50% and CC_{50} is the intrinsic **drug** cytotoxicity measured in the absence of virus. Number in parentheses indicates the Iighest **concentration** tested in the experiment. > sign indicates that concentration range tested was too low to **fully** evaluate

the Ti, so the lower limit is specified. [3] **Defined by** the **specificity** of the **inhibitor to** a RAF **isoform**

Example 4; Synergistic antiviral potency against HCVcc

The tested RAF **inhibitors** were **evaluated** for an **ability** to **syncrgize** with **other current,** late **stage** or marketed **direct-acting antivirals** (DAAs). Synergistic **antiviral** potency was measured with AZ-628 **and the direct-acting antiviral** GS7977/Sobasuvir, a nucleotide analog that inhibits the viral **RNA-dependcnt RNA polymerase ofHCV** or with AZ-628 and the direct-acting **antiviral BMS-790052/Daclatasvir,** an **inhibitor** of the **non-structural protein NS5a,** which plays a vital role in **HCV** genomic replication in the host. The top panels of Tables 4 and 5 show the % antiviral inhibition as a **function** of concentration of both drugs. The bottom panels of Tables 4 and 5 show the synergy volume calculated from the top table at the 95% confidence interval. The three-dimensional plots **of Figures** 4 and 5 display the synergy **volume** data at the 95% confidence interval for AZ-628 in combination with GS797? and BMS-790052, respectively. Table 6 compares the single drag and synergy drug EC_{50} values tested in HCVcc GT2a. The results of these tests indicate that DAAs that are in late stage **development synergize** well with **AZ-628** and this may have further applications in a combination therapy for treating HCV infection.

Table 4: Synergistic antiviral potency measured with AZ-628 and GS7977

		GS-7977 (nM)								
	[DRUG]	0	1.563	3.125	6.25	12.5	25	50	100	200
AZ-628 (nM)	400	73.43	73.89	74.28	81.68	81.78	84.14	83.25	84.96	86.2
	200	8.48	8.88	4.46	24.83	27.78	37.33	47.26	48.43	63.86
	100	0	0	0	0	0	5.88	13.51	26.5	80.66
	50	0	0	0	0	0	1.62	11.55	22.74	47.13
	25	0	0	0	0	0	2.29	9.57	22.42	45.09
	0	0	0	0	0	0	2.68	11.54	21.51	44.74

		GS-7977 (nM)								
	[DRUG]	0	1.563	3.125	6.25	12.5	25	50	100	200
AZ-628 (nM)	400	0	0	0	5.987	5.234	5.541	0.488	4.085	2.587
	200	0	0	0	13.35	12.09	25.67	24.71	12.88	13.09
	100	0	0	0	0	0	0	0	3.05	0
	50	0	0	0	0	0	0	0	0	0
	25	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0

Antiviral Potency

SYNERGY PLOT (95%)

SYNERGY VOLUME
128.71

ANTAGONISM VOLUME
0

Table 5: **Synergistic** antiviral poteiicv **measured with AZ-628** and the direct-acting **antiviral BMS-790052**

		BMS-790052 (nM)									Antiviral Potency
	[DRUG]	0	0.781	1.563	3.125	6.25	12.5	25	50	100	
AZ-628 (nM)	400	74.25	77.01	75.45	80.19	81.83	83.5	83.44	87.37	91.74	
	200	17.39	21.84	18.29	34.05	36.01	44.17	47.45	51.76	73.6	
	100	0	0	0	0.89	9.67	9.33	15.83	33.9	63.67	
	50	0	0	0	0	6.13	7.23	30.08	32.34	63.34	
	25	3.83	0	0	4.97	2.98	9.29	19.07	28.92	61.71	
	0	0	0	0	8.7	8.72	17.27	19.84	33.86	59.54	

		BMS-790052 (nM)									SYNERGY PLOT (95%)
	[DRUG]	0	0.781	1.563	3.125	6.25	12.5	25	50	100	
AZ-628 (nM)	400	0	0	0	0	3.884	0.194	0	0.696	0.827	SYNERGY VOLUME 37.13
	200	0	1.532	0	0	4.011	6.414	10.94	4.288	3.648	
	100	0	0	0	0	0	-2.766	0	0	0	ANTAGONISM VOLUME -6.69
	50	0	0	0	0	0	0	0	0	0	
	25	0	0	0	-0.43	-3.488	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	

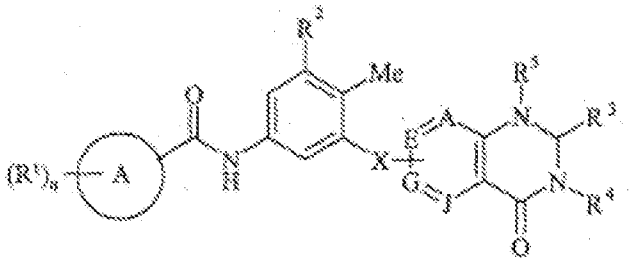
Table 6: Synergistic antiviral potency against HCVcc of AZ-628 and DAAs

Drug	**Genotype**	**ECS© alone**	**EC50 AZ-628 -s- sob sbuvir**	**EC50 AZ-628 + daelatasvir**	Fold **Synergy**
Sofosbuvir (GS-7977) (NSSb inhibitor, 'nuc')	2a	250 nM	so nM	-	5
Dadatasvir (BMS-790052 (NS5a inhibitor)	2a	0.1 nM	--	0.033 nM	3
AZ-628	2a	300 nM	200 nM	200 nM	---

What is claimed is:

1. A method of treating a viral infection, such as an HCV infection, in a subject iu need thereof, comprising sdmioistcring to the- subject an effective amount of a RAF kinase inhibitor or a prodrug thereof.

2. The method of claim 1, wherein the RAF kinase inhibitor is a compound having a structure of formula:



wherein:

Ring A is carbocyclyl or heterocyc!yl; wherein -if said hetetocyclyl contains an - NH-moiety that nitrogen may be optionally substituted by a group selected from R^6;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, eyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulpbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, Cj^aikanoyloxy. *N*-(C_{1-6}alky!)amino, *N,N*-(C_{1-6}a.ikyl hatnitio, Ci-ealkanoylaraino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}6alkyl)$_2$carhanioyl, C_{1-6}alkylS(0)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl; *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, *N*-(C_{1-6}alkoxy)suiphamoyi, *N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)sulphamoyl, C_{1-6}alkylsulphonylamino, earbocyclyl-R^7- or heterocyelyl-R^8-; wherein R^3 may be- optionally substituted on carbon by one or more R^9; and wherein if said heterocyciyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{10};

n is selected from 0-4; wherein the values of R^1 may be the same or different;

$\mathbf{R^2}$ is selected from hydrogen, halo, nitro, eyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sidphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{2-6}alkoxy, C_{1-6}aikanoyl, CV6alkanoySoxy, *N*-(C_{1-6}alkyl)amino,

N,iV-(C{-6alkyl)2amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$sulphamoyl, Ci-$_6$alkylsulphonylamino, carbocycly1-R^{11}- or heterocyelyl-R^{12}-; wherein R^2 may be optionally substituted on carbon by one or more R^{13}; and wherein if said heteroeyclyl contains an -NH- motery that nitrogen may be optionally substituted by a group selected from R^{14};

X is NR'^5 or O;

one of A, E, *G* and J *is* C which is attached to X of the formula; the other three are independently selected from CR^{16} or N;

R^3 and R^{16} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, Cvalkanoyloxy, A-(Ci .6a!kyl)amino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, C1^alkanoyl amino, A-(Ci.¾alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbarmoyl, C_{1-6}afkyiS(0)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulpharnoyk *N*,*N*-(C_{1-6}alkyl)$_2$suipharaoyL C_{1-6}alkyisulphonylamino, carbocyclyl-R^{17}- or heterocyclyl-R^{1} wherein R^3 and R^{tft} independently of each other may be optionally substititted oa carboa by one or more R^{19}; and wherein if said heteroeyclyl contains an ~NH~ moiety that nitrogen may be optionally substituted by a group selected from R^{20};

R^4, R^5 and R^{15} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, carbocyeiyf heteroeyclyl, *N*~(C_{1-f}alkyi)carbamoyi and *N*,*A*-(C_{1-6}alkyl)carbamoyl; wherein R^4, R^5 and R^{15} independently of each other may be optionally substituted on carbon by one or more R^{21};

the bond " ^"between the -NR^5- and -CR'- of the formula is either (i) a single bond wherein R^5 is as defined above, or {ii) a double bond wherein $R^{"}$ is absent;

R^9, R^{13}, $R^{1;}$ and R^{21} arc independently selected from halo, nitre, cyano, hydroxy, amino, carboxy, carbamoyl mereapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, Ci^alkanoylamvno, *N*-(C_{1-6}alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(0)$_a$ wherein a is 0 to 2, C^aikoxycarbonyi C^alkoxycarbonylamino,

N-(Cwlky1)sulphamoyl , *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{22}- or heterocyclyl-R^{23}-; wherein R^9, R^{13}, R^{19} and R^{21} independent{y of each other may be optionally substituted on carbon by one or more R^{24}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{25};

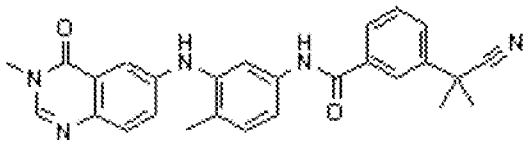
R^7, R^8, R", R^{17}-R^{18}, R^{22} and R^{23} are independently selected from a direct bond, -0-, -N(R^{26})-, -C(O)-, -N(R^{27})C(0)-, -C(0)N(R^{28})-, -S(0)$_s$-, -$(¾NΩR^{28}*)$- or -N(R^{30})SOr ; wherein R^{26}, R^{27}, R^{28}, R^{29} and $R^{¾}$ is hydrogen, Ci-6alkoxycarbxa y! or Ci^alkyl and s is 0-2;

$R^{(}$, R^{10}, R^{14}, R^{20} and R^{25} are independently selected from C_{1-6}aiky!, C_{1-6}alkylsulphonyl, €$_{1-6}$alkoxycarbonyk carbamoyl, *N*-(C_{1-6}alkypearbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenyisu!phonyl;

R^{24} is selected from halo, nitro, cyano, hydroxy, trifliioromethoxy, tr fluoromethyJ, amino, carboxy, carbamoyl, mereapto, suiphamoyi, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-cthyiainirio, acety{amino, A¾ieroykarbamoyI, *N*-ethylcarbamoyl, *N,N*-dimethy{caroamoyl ,.*N;N*-diethylcarbamoy{, *N*-methyl-A-etliy!carbamoyi. methylthio, ethyUhio, methyisulphinyi, ethylsulphinyi, mesyi, ethylsulphonyl, methoxycarbonyl, etlioxycarbonyl, *N*-methylsu!phaa oyl, *N*-@hylsulphamoyl, *N,N*-dimethylsulphamoyl, A *N*-diethylsulphamoyl or *N*-methyl-*N*-ethyisulphamoyl;

or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the RAF inhibitor is AZ-628:



or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the RAF kinase inhibitor is a compound having a structure of formula:

A-D-B

wherein;

D is —NR—C(O)—NH—,

A is a substituted moiety of up to 40 carbon atoms of the formula: —L—(M—L')$_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L' comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L' is substituted by at least one substituent selected from the group consisting of —SO_2R_x, —C(O)R_x and —C(NR$_y$)R$_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing lieteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionaily substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionaily substituted by halogen, or

—OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionaily substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and 0, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon

based substituents of up to 24 carbon atoms, which optionally contain heieroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is -----C(0) -----, a C_1-C_5 divalent alkylenc group or a substituted C1-Cj divalent alkyiene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the sitbstituted C_1-C$ divalent aikylene group are selected from the group consisting of halogen, hydroxy1, and carbon based substituents of op to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted of L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-haio, and Wn, where n is 0-3;

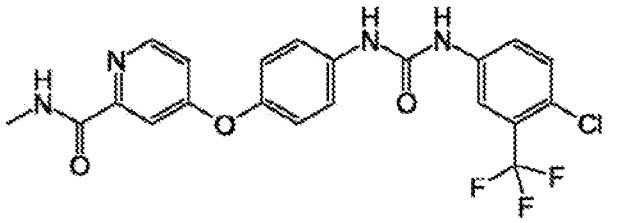
wherein each W is independently selected from the group consisting of —€ N, -----C0 $_2R^7$, - - C(O)NR¾ ^{7}, --C(OV--R ^{7}, -----N0 $_2$, —OR^7, —SR^7, -----N R^{7}R^7, ----- NR^{7}G'O)OR^7, —NR'C(0)R'^{7}, —Q—Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally sitbstituted by one or more substituents independently selected from the group consisting of -----CN, -----CO$_2$R^7, -----C(0)R^7, ~~C(0)NR ^{7}R.^{7}, -----OR^7, —SR.^{7}, -----NR^{7}R.^{7}, -----NO$_2$, ~~NR^{7}C(0)R ^{7}, -----N R^{7}C{0) OR^7 and halogen up to per-haio; with each R^7 independently selected from H or a carbon based moiety of up to 24 atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -----O-----, -----S-----, -----N(R^7)-----, ~~(CH$_2$)$_m$~~, —C(0)— , —€ H(OH>----, -----(CH$_2$)$_m$O-----, -----(CH$_2$)$_m$S-----, -----(C¾) $_m$N(R^7)-----, -----Q(C¾)$_m$-----CHX^a-----, -----CX$^a_2$-----, -----S—(CH$_2$)$_m$-~- and —N(R^{7}XCH$_2$)$_m$-----, where m~1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-haio, and optionally sitbstituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of —CN, —COaR', —C(O)R^7, —C(O)NR^{7}R^7, —NO$_2$, -----OR^7, -----SR^7-----NR^{7}R^7, -----NR^{7}Ct(O)OR^7, -----NR^{7}C(0)R ^{7}, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the

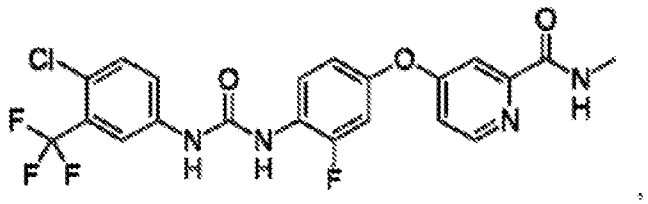
group consisting of —CN, —CO_2R^7, —COR^7, —$C(O)NR^7R^7$, —OR^7, —SR^7, —NO2, —NR^7R^7, —$NR^7C(O)R^7$, and —$NR^7C(O)OR^7$, with R^7 as defined above.

5. The method of claim 4, wherein the RAF inhibitor is sorafenib:



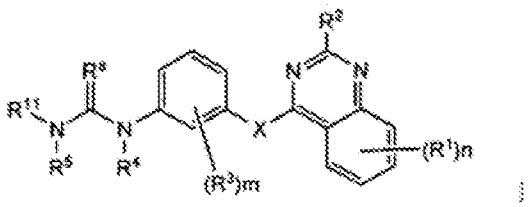
or a pharmaceutically acceptable salt thereof.

6. The method of claim 4, wherein the RAF inhibitor is regorafenib:



or a pharmaceutically acceptable salt thereof.

7. The method of claim 1, wherein the RAF kinase inhibitor is a compound having a structure of formula:



or a pharmaceutically acceptable salt or prodrug thereof, wherein

X is O or S(O)$_k$;

R^3 is O or S;

each R^1 is independently selected from (i) or (ii) below;

(0 **each** R^1 **is independently** selected from a **group** consisting of halo, iiitro, **alkyl**, alkenyl, **alkynyl**, **cycioaikyl, cycioaikylalkyl, heterocyeiyl,** heterocyelylalkyi, aryl, aralkyl **heteroaryi, heteioamlkyi,** **-R*QR^7, -R^{6}SR^7,** **-R^{6}S(OXR^8, -R^{6}N(R^7)$_2$, -R^{6}OR^{9}OR^7, -R^{6}OR^{9}SR', -R¾ R^{9}S(O)$_1$R^8,** **-R^{6}OR^{9}S(O)$_1$N{R^7)$_2$, -R^{6}OR^{9}N(R^7)$_2$,** ~R¾R^{9}GR^7, **-R^{6}SR¾R ^{7},** -R^{6}SR^{9}N(R¾ , -R^{1}N(R^7)R^{9}N(R^{7}fc, **-R^{6}N(R^7)R^{9}OR^7, -R^{6}N(R ^{7})R^{9}SR^7,** -R^{5}CN, -R^{1}C(O)R^7, -R¾(Q)QR ^{7}, -R^{6}C(O)OR^{9}OR^7, -R^{6}C(O)N(R^7)$_2$, -R¾ (O)N(R^7)OR^7, -R^{6}C(NR^7)N(R^7)$_2$, -R¾(0)N(R ^{7})R^{9}N(R^{7}¾, -R¾ (O)N(R^7)R^{9}OR^7, -R^{6}C(O)N(R^7)R^{9}SR^7, **-R*C(G)SR ^{8}, -R*S(0) $_1$OR^7,** **-R^{6}S(0) $_1$N(R^7)$_2$, -R^{6}S(0)tN{R^7)N(R^7)$_2$, -R^{6}S(0)$_1$N(R^7)N=C(R^7}$_3$,** -R^{6}S{0)$_1$N(R}^{7})C(0)R ^{8}, -R^{6}S(0) $_1$N(R^7)C(0)N(R ^{7}}$_2$, -R^{6}S(0}$_1$N(R^7)C(NR^7)N(R^7)$_2$, **-R^{1}N(R^7)C(0)R*,** -R^{6}N(R^7)QO)OR ^{8}, **-R^{6}N(R^7)CX0)N(R^7)$_2$, -R^{6}N(R')C(NR^7)N(R^7)$_2$, -R^{6}NCR^7)C($)N(R¾ , and** ~R^{6}N(R^7)S(0) $_1$R^8, or

(ii) **any two** adjacent R^1 groups together form **an aikylenedioxy group;** each R^6 **is independently** a direct bond, **alkyiene chain** or **alkenylene chain;** each R^7 is **independently** selected from (i) or (ii) below:

(i) each R^7 is selected from **a** group **consisting** of hydrogen, **alkyi, alkenyl,** alkynyl, cycioaikyl, **cycioaikylalkyl, aryl,** aralkyl, **heterocyeiyl,** heterocyelylalkyi, heteroaryi and **heteroaraikyi,** or

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

each **R*** is independently selected from a group consisting of alkyi, aikenyl, alkynyl, **cycioaikyl,** cycioaikylalkyl, **aryl, aralkyl,** heterocyeiyl, **heterocyelylalkyi,** heteroaryi and heteroaraikyi;

each R^9 is **independently an alkyiene** chain or an **alkenylene** chain;

R^2 is **hydrogen, halo, alkyi,** amino **or aikylamino;**

R^3 is halo or **aikyl;**

R^4 and R^5 are selected **as follows:**

a) R^4 and R^5 are each independently hydrogen or alkyi, or

b) R^4 and R^5, together with the **N** atom to which they are attached, form **an** oxo-substituted hefetOcyely1;

R^{11} is **aryl,** heteroaryi or **heterocyeiyl;**

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 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, $-R^aOR^x$, $-R^aOR^bOR^x$, $-R^aOR^bN(R^y)(R^z)$, $-R^aN(R^y)(R^z)$, $-R^aSR^x$, $-R^aC(O)R^x$, $-R^aC(O)OR^x$, $-R^aC(O)N(R^y)(R^z)$, $-R^aC(O)SR^x$, $-R^aS(O)_tR^w$, $-R^aOC(O)R^x$, $-R^aOC(O)OR^x$, $-R^aOC(O)N(R^y)(R^z)$, $-R^aOC(O)SR^x$, $-R^aN(R^x)C(O)R^x$, $-R^aN(R^x)C(O)OR^x$, $-R^aN(R^x)C(O)N(R^y)(R^z)$, $-R^aN(R^x)C(O)SR^x$, $-R^aSi(R^w)_3$, $-R^aN(R^x)S(O)_tR^w$, $-R^aN(R^x)S(O)_tOR^w$, $-R^aN(R^x)S(O)_2N(R^y)(R^z)$, $-R^aS(O)_2N(R^y)(R^z)$, $-R^aP(O)(R^v)_2$, $-R^aOP(O)(R^v)_2$, $-R^aC(O)N(R^x)S(O)_2R^w$, $-R^aC(O)N(R^x)N(R^x)S(O)_2R^w$, $-R^aC(R^x)=NOR^x$ and $-R^aC(R^x)=NN(R^y)(R^z)$;

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 or hydroxy;

each R^a 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* or $-N(R^y)(R^z)$;

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

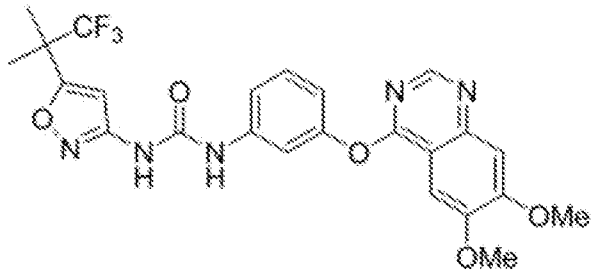
each R^x is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl;

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

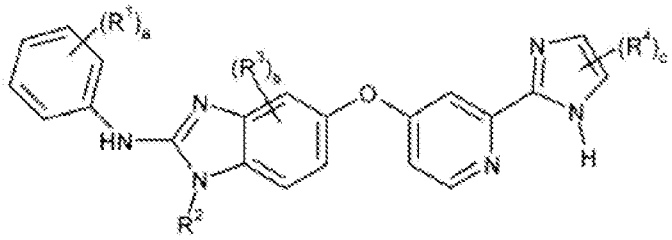
J is C, NR^X or S.

8. The **method of claim** 7, **wherein** the RAF kinase inhibitor is CEP32496;



or a pharmaceutically acceptable salt thereof.

9. The **method of claim** 1, **wherein** the RAF kinase inhibitor is a compound having **a** structure of formula:



(I)

wherein each R^1 is independently selected from hydroxy, **halo, C\$.gaikyl,** C_{1-6}alkoxy, (C_{1-6}alkyl)suifanyl, iC1-ialkyi)sul6 inyi, cyeloalkyl, heterocyeloalkyl, phenyl and heteroaryl:

R^2 **is** C_{1-6}alkyl or **halo(C_{1-6}alkyl);**

each R^3 is independently selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy;

each R4 is independently selected **from** hydroxy, C_{1-6}alkyl, **C_{1-6}alkoxy,** halo, **heterocycloalkylcarbonyl,** carboxyl, (C_{1-6}alkoxy)carbonyl, **aminocarbonyl,** C_{1-6}alkylaminocarbonyl, earbonitrile, cyeloalkyl, heterocycloalky!, phenyl and heteroaryl:

wherein R^1, R^2, R^3 **and R* may be** optionally **substituted** with one or more substituents **independently selected from** hydroxy, halo, C_{1-6}alkyl, **halo(C_{1-6}alkyl).** C_{1-6}alkoxy and **halo(C_{1}^aikoxy);**

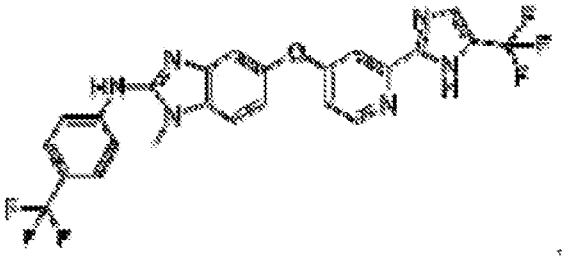
a is 1, 2, 3, 4 or 5;

b is 0, 1, 2 or 3; and

c is 1 or 2;

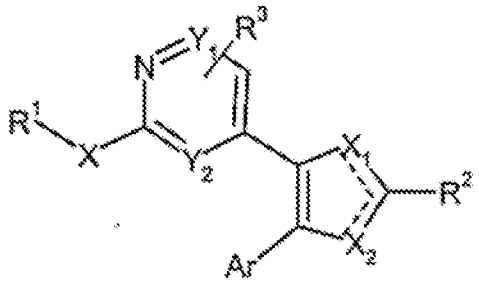
or a taittomer, stereoisomer, polymorph, ester, metabolite, or prodrug thereof or a pharmaceutically acceptable salt of the compound, tautomer, **stereoisomer,** polymorph, ester, metabolite or prodrug.

10, The **method of claim** 9, wherein the RAF inhibitor is Raf-265:



or a **pharmaceutically** acceptable salt **thereof.**

11. The method of claim I, wherctn the RAF kinase inhibitor is a **compound** having a **structure** of **formula;**



wherein

X is CX C¾, CO, S or NH, **or the** moiety **X-R'** is hydrogen;

Y_1 **and** Y_2 are independently N or CH;

R^1 **is hydrogen,** C_{1-6}alkyl, $C_{3-?}$**cycloalkyl,** aryl, arylC_{1-6}alkyl, **heterocyclyl,** heterocyclylC_{1-6}alkyl, heteroaryl, or heteroarylC_{1-6}alkyl, any **of which may be** optionally substituted; **in addition when X is** CH? then R^1 *may* **be hydroxy! or** C_{1-6}alkoxy which may be optionally **substituted;**

R^2 **is** H, C_{1-6}**alkyl,** $C_{2-¾}$alkenyl, $C_{3-?}$**cycioalky! , C_{5-7}cyc!oa!keny!,** heterocyciyl, aryl or heteroaryl., any of which may be **optionally** substituted;

Ar is a group of the formula a) or **b):**



a) b)

wherein A represents a fused 5~ o 7~membered ring **optionally containing** up **to two heteroatoms** selected **frora** O, S and **NR*, wherein R**^{5} **is hydrogen** or C_{1-6}alky1, which ring is optionally substituted by up to 2 substttuents selected **from halogen,** C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or keto;

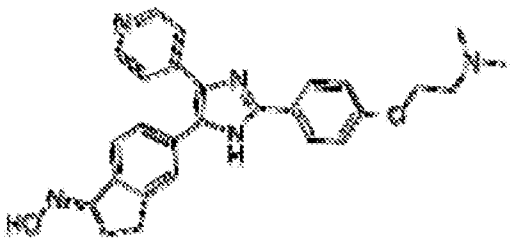
R^3 **and R**^{4} are independently selected from hydrogen, halogen, C_{1-6}alky!, aryl, aryl C_1. falkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, haloC_{1-6}alkyl, arylC_{1-6}alkoxy, hydroxy, **nttto, cyano,** azido, amino, **mono- and** di-*N*-C_{1-6}alkylamino, **acylamino, arylcarbonylamino, acyloxy,** carboxy, carboxy salts, **carboxy** esters, **carbamoyl, mono-** and **di-*N*-C_{1-6}alkylearbamoyl,** C_{1-6}alkoxycarbonyl, aryioxycarbonyl, ureido, guanidino, **d-ealkylguanidino,** amidino, **C^lky!amidino., sulphonylamino, aminosulphonyk** Ci-ealkylthio, **C**$_{1-6}$alky**Isulphinyl or** C_{1-6}alkylsulphonyl;

R^{15} is O or N-OH;

one of X_1 and X_2 is N and the other is NR^6 wherein R^6 is hydrogen or C_{1-6}alkyl;

or a pharmaceutically **acceptable** salt thereof.

12. The compound of claim 1 !, wherein the RAF kinase **inhibitor** is **SB-590885:**

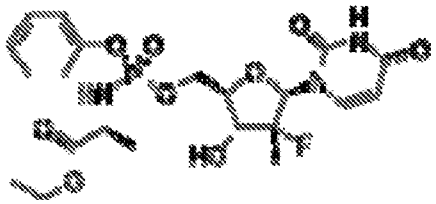


or a pharmaceutically **acceptable salt** .hereof.

13. The method of any one of claims .1-12, wherein the RAF inhibior is administered conjointly with at least one additional therapeutic agent.

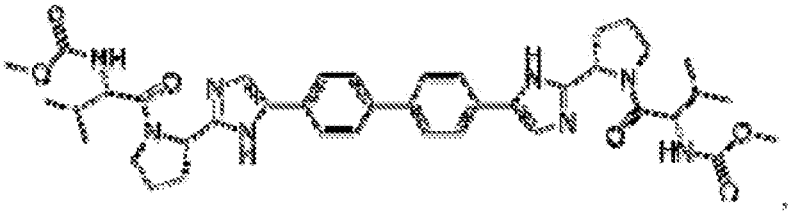
14. The method of claim 13, wherein said at least one additional therapeutic agent is a« antivai agent selected from HCV protease- inhibitors, HCV polymerase inhibitors, agents targeting host cell activities itivolved in HCV replication and inositie monophosphate dehydrogenase (IMPDH) inhibitors.

15. The method of claim 14, wherein the at least one additional iherapeutic agent is GS-7977:



or a pharmaceutically acceptable salt thereof.

16. The method of claim 14, wherein the at least one additional therapeutic agent is BMS-790052:



or a pharmaceutically acceptable salt thereof.

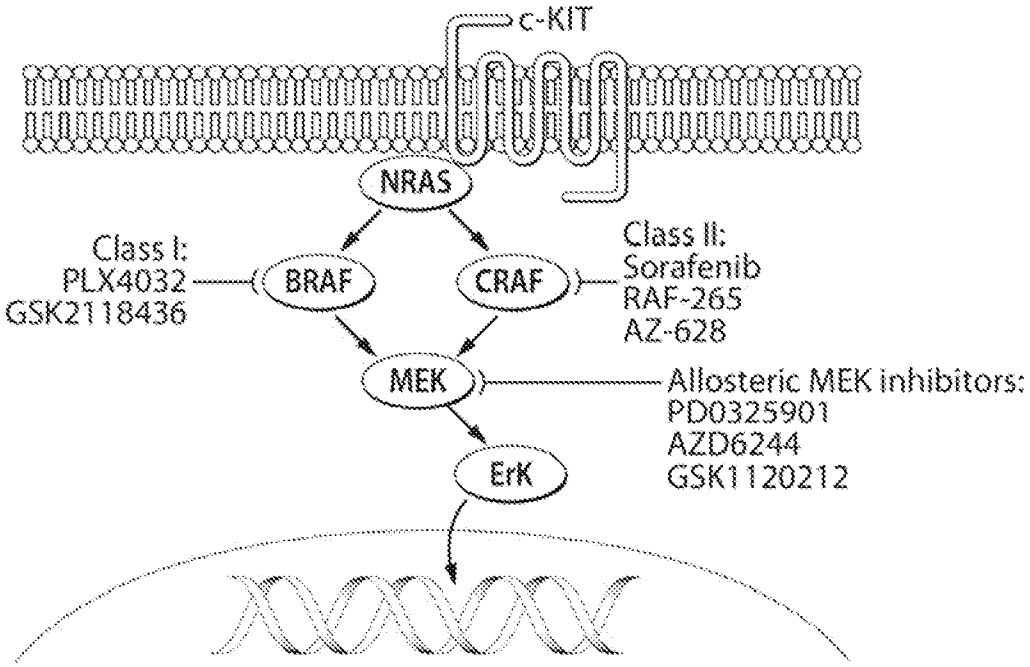

c-KIT
NRAS
Class I:
PLX4032
GSK2118436
BRAF
CRAF
Class II:
Sorafenib
RAF-265
AZ-628
MEK
Allosteric MEK inhibitors:
PD0325901
AZD6244
GSK1120212
ErK

Fig. 1

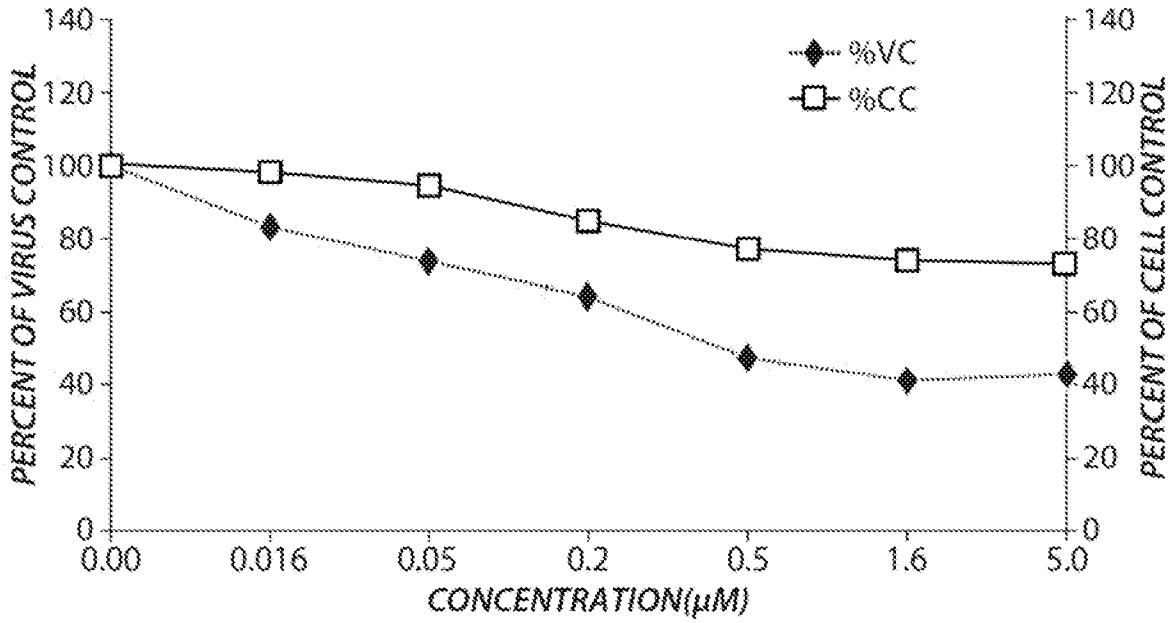

%VC
%CC
PERCENT OF VIRUS CONTROL
PERCENT OF CELL CONTROL
140
120
100
80
60
40
20
0
0.00
0.016
0.05
0.2
0.5
1.6
5.0
CONCENTRATION(μM)

Fig. 2

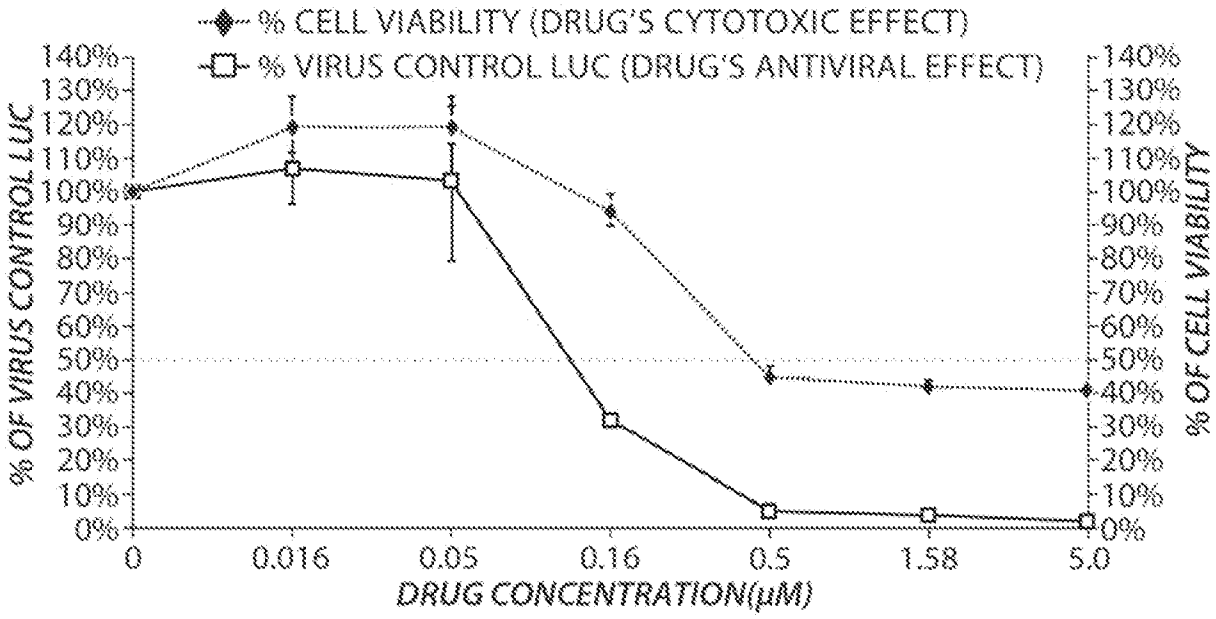

% CELL VIABILITY (DRUG'S CYTOTOXIC EFFECT)
% VIRUS CONTROL LUC (DRUG'S ANTIVIRAL EFFECT)
% OF VIRUS CONTROL LUC
% OF CELL VIABILITY
140%
130%
120%
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
0.016
0.05
0.16
0.5
1.58
5.0
DRUG CONCENTRATION(μM)

Fig. 3

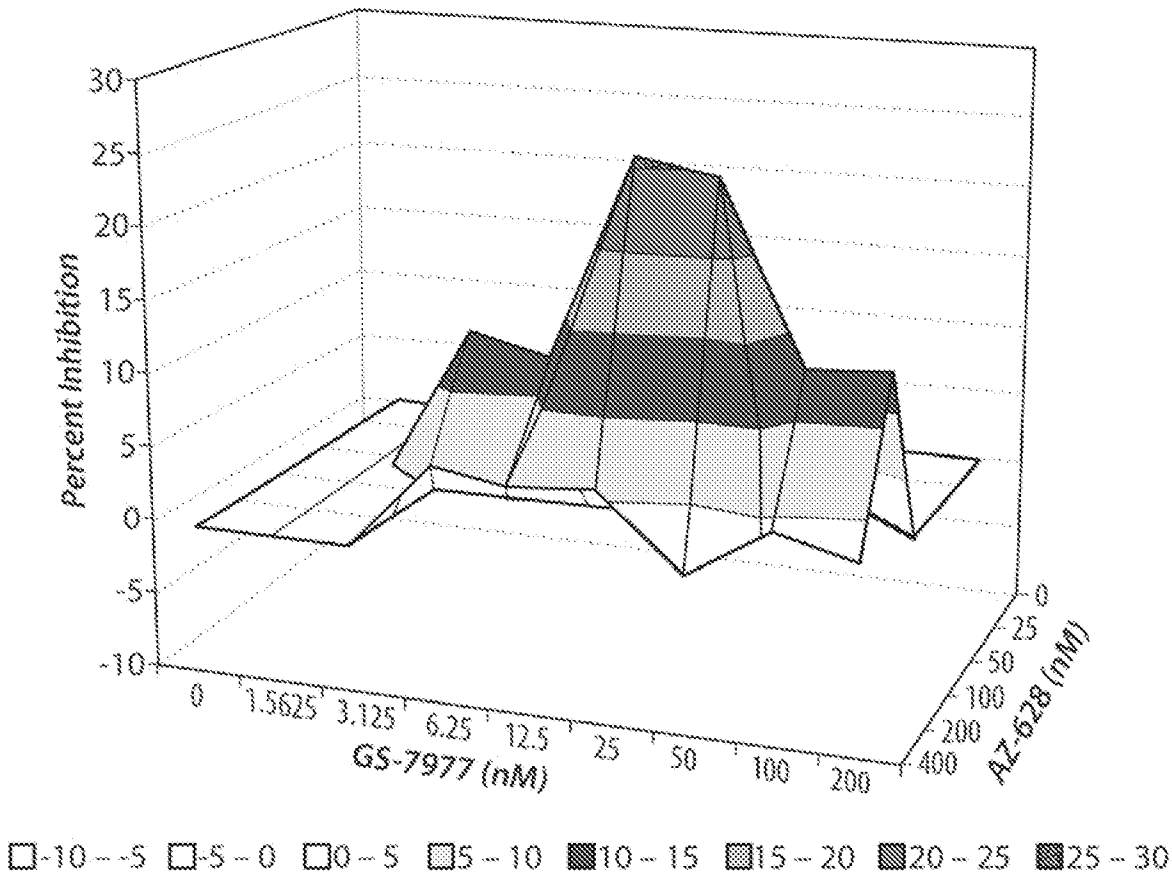

Percent Inhibition
30
25
20
15
10
5
0
-5
-10
0
1.5625
3.125
6.25
12.5
25
50
100
200
GS-7977 (nM)
0
25
50
100
200
400
AZ-628 (nM)
-10 – -5
-5 – 0
0 – 5
5 – 10
10 – 15
15 – 20
20 – 25
25 – 30

Fig. 4

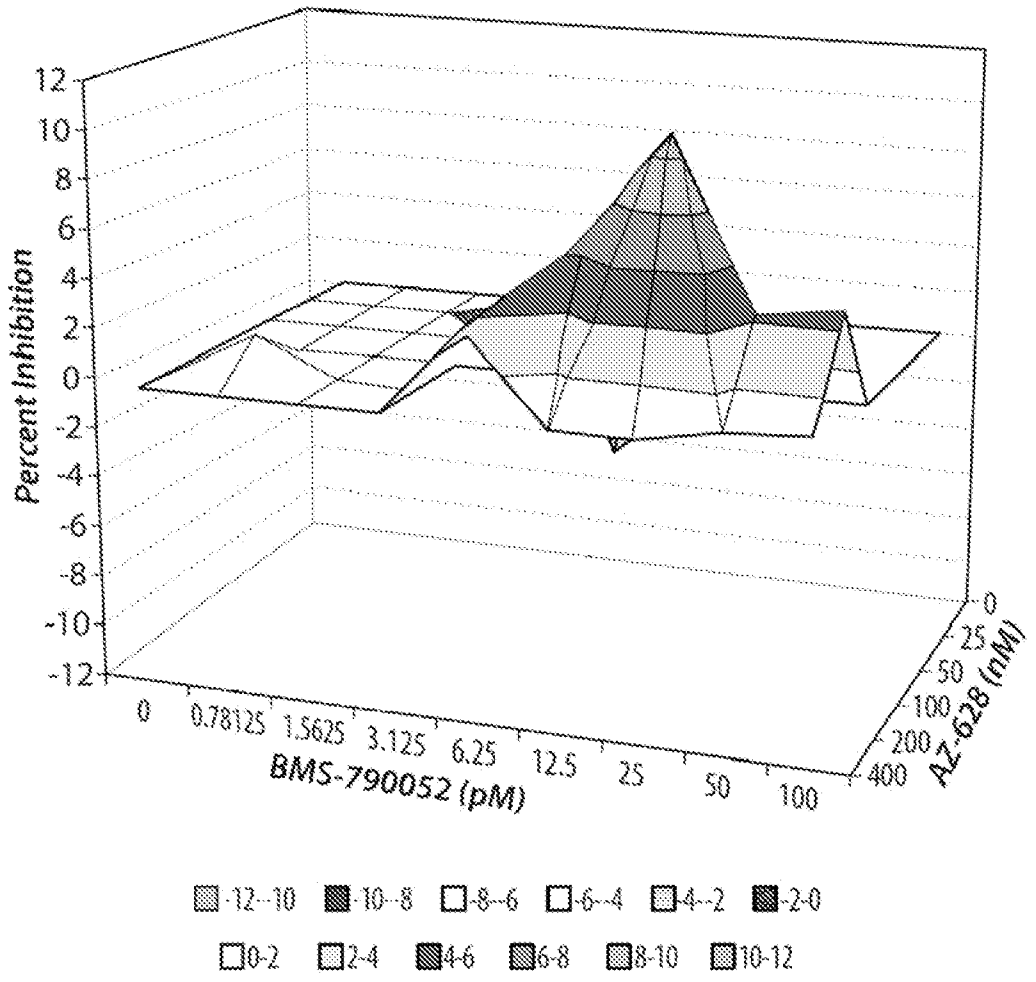

Percent Inhibition
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
0
0.78125
1.5625
3.125
6.25
12.5
25
50
100
BMS-790052 (pM)
0
25
50
100
200
400
AZ-628 (nM)
-12--10
-10--8
-8--6
-6--4
-4--2
-2-0
0-2
2-4
4-6
6-8
8-10
10-12

Fig. 5