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(54) Title: INHIBITORS OF PHOSPHATIDYLINOSITOL 3-KINASE

(57) Abstract: The present invention relates to compounds useful as inhibitors of PBK, particularly of PBK γ . The invention also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.



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INHIBITORS OF PHOSPHATIDYLINOSITOL 3-KINASE

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds useful as inhibitors of phosphatidylinositol 3-kinase (PI3K). The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0002] PI3Ks are a family of lipid kinases that catalyze the phosphorylation of the membrane lipid phosphatidylinositol (PI) on the 3'-OH of the inositol ring to produce PI 3-phosphate [PI(3)P, PIP], PI 3,4-bisphosphate [PI(3,4)P₂, PIP₂] and PI 3,4,5-trisphosphate [PI(3,4,5)P₃, PIP₃]. PI(3,4)P₂ and PI(3,4,5)P₃ act as recruitment sites for various intracellular signaling proteins, which in turn form signaling complexes to relay extracellular signals to the cytoplasmic face of the plasma membrane.

[0003] Eight mammalian PI3Ks have been identified so far, including four class I PI3Ks. Class Ia includes PI3K α , PI3K β and PI3K δ . All of the class Ia enzymes are heterodimeric complexes comprising a catalytic subunit (p110 α , p110 β or p110 δ) associated with an SH2 domain-containing p85 adapter subunit. Class Ia PI3Ks are activated through tyrosine kinase signaling and are involved in cell proliferation and survival. PI3K α and PI3K β have also been implicated in tumorigenesis in a variety of human cancers. Thus, pharmacological inhibitors of PI3K α and PI3K β are useful for treating various types of cancer.

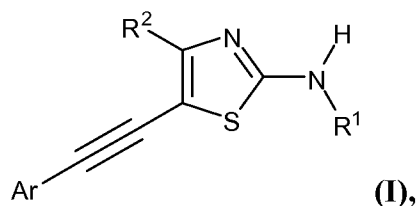
[0004] PI3K γ , the only member of the Class Ib PI3Ks, consists of a catalytic subunit p110 γ , which is associated with a p101 regulatory subunit. PI3K γ is regulated by G protein-coupled receptors (GPCRs) via association with $\beta\gamma$ subunits of heterotrimeric G proteins. PI3K γ is expressed primarily in hematopoietic cells and cardiomyocytes and is involved in

inflammation and mast cell function. Thus, pharmacological inhibitors of PI3K γ are useful for treating a variety of inflammatory diseases, allergies and cardiovascular diseases.

[0005] Although a number of PI3K inhibitors have been developed, there is a need for additional compounds to inhibit PI3Ks for treating various disorders and diseases, especially those affecting the central nervous system (CNS). Accordingly, it would be desirable to develop additional compounds that are useful as inhibitors of PI3K that penetrate the blood-brain barrier (BBB).

SUMMARY OF THE INVENTION

[0006] It has been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of PI3K, particularly PI3K γ . Accordingly, the invention features compounds having the general formula:



or a pharmaceutically acceptable salt thereof, where each of R¹, R², and Ar is as defined herein.

[0007] The invention also provides pharmaceutical compositions that include a compound of formula I and a pharmaceutically acceptable carrier, adjuvant, or vehicle. These compounds and pharmaceutical compositions are useful for treating or lessening the severity of a variety of disorders, including autoimmune diseases and inflammatory diseases of the CNS.

[0008] The compounds and compositions provided by this invention are also useful for the study of PI3K in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Terminology

[0009] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in “Organic Chemistry,” Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry,” 5th Ed., Smith, M.B. and March, J., eds. John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0010] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted,” whether preceded by the term “optionally” or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position.

[0011] As described herein, when the term “optionally substituted” precedes a list, said term refers to all of the subsequent substitutable groups in that list. For example, if X is halogen; optionally substituted C₁₋₃ alkyl or phenyl; X may be either optionally substituted alkyl or optionally substituted phenyl. Likewise, if the term “optionally substituted” follows a list, said term also refers to all of the substitutable groups in the prior list unless otherwise indicated. For example: if X is halogen, C₁₋₃ alkyl, or phenyl, wherein X is optionally substituted by J^X, then both C₁₋₃ alkyl and phenyl may be optionally substituted by J^X. As is apparent to one having ordinary skill in the art, groups such as H, halogen, NO₂, CN, NH₂, OH, or OCF₃ would not be included because they are not substitutable groups. If a

substituent radical or structure is not identified or defined as “optionally substituted,” the substituent radical or structure is unsubstituted.

[0012] Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, preferably, their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0013] The term “aliphatic” or “aliphatic group,” as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. In some embodiments, aliphatic groups contain 1-10 carbon atoms. In other embodiments, aliphatic groups contain 1-8 carbon atoms. In still other embodiments, aliphatic groups contain 1-6 carbon atoms, and in yet other embodiments, aliphatic groups contain 1-4 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Further examples of aliphatic groups include methyl, ethyl, propyl, butyl, isopropyl, isobutyl, vinyl, and sec-butyl. The terms “alkyl” and the prefix “alk-,” as used herein, are inclusive of both straight chain and branched saturated carbon chain. The term “alkylene,” as used herein, represents a saturated divalent straight or branched chain hydrocarbon group and is exemplified by methylene, ethylene, isopropylene and the like. The term “alkylidene,” as used herein, represents a divalent straight chain alkyl linking group. The term “alkenyl,” as used herein, represents monovalent straight or branched chain hydrocarbon group containing one or more carbon-carbon double bonds. The term “alkynyl,” as used herein, represents a monovalent straight or branched chain hydrocarbon group containing one or more carbon-carbon triple bonds.

[0014] The term “cycloaliphatic” (or “carbocycle”) refers to a monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule, and wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable cycloaliphatic groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of aliphatic groups include cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloheptenyl.

[0015] The term “heterocycle,” “heterocyclyl,” “heterocycloaliphatic,” or “heterocyclic” as used herein refers to a monocyclic, bicyclic, or tricyclic ring system in which at least one ring in the system contains one or more heteroatoms, which is the same or different, and that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, and that has a single point of attachment to the rest of the molecule. In some embodiments, the “heterocycle,” “heterocyclyl,” “heterocycloaliphatic,” or “heterocyclic” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 8 ring members.

[0016] Examples of heterocyclic rings include, but are not limited to, the following monocycles: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl; and the following bicycles: 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydroimidazol-2-one.

[0017] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the

quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl).

[0018] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0019] The term “alkoxy,” or “thioalkyl,” as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0020] The terms “haloalkyl,” “haloalkenyl,” and “haloalkoxy” mean alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br, or I.

[0021] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of six to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule, at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” Examples of aryl rings include phenyl, naphthyl, and anthracene.

[0022] The term “heteroaryl,” used alone or as part of a larger moiety as in “heteroaralkyl,” or “heteroarylalkoxy,” refers to a monocyclic, bicyclic, and tricyclic ring system having a total of five to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule, at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms independently selected from nitrogen, oxygen, sulfur or phosphorus, and wherein each ring in the system contains 3 to 7 ring members. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic.”

[0023] Further examples of heteroaryl rings include the following monocycles: 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl,

3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), purinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0024] In some embodiments, an aryl (including aralkyl, aralkoxy, aryloxyalkyl, and the like) or heteroaryl (including heteroaralkyl, heteroarylalkoxy, and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group include: halogen; C₁₋₄aliphatic, -OH; -OR[°]; -SH[°]; -SR[°]; 1,2-methylenedioxy; 1,2-ethylenedioxy; phenyl (Ph); -O(Ph); -(CH₂)₁₋₂(Ph); -CH=CH(Ph); -NO₂; -CN; -NH₂; -NH(R[°]); -N(R[°])₂; -NHC(O)R[°]; -NR[°]C(O)R[°]; -NHC(S)R[°]; -NR[°]C(S)R[°]; -NHC(O)NH₂; -NHC(O)NH(R[°]); -NHC(O)N(R[°])₂; -NR[°]C(O)NH(R[°]); -NR[°]C(O)N(R[°])₂; -NHC(S)NH₂; -NHC(S)N(R[°])₂; -NHC(S)NH(R[°]); -NR[°]C(S)NH(R[°]); -NR[°]C(S)N(R[°])₂; -NHC(O)OR[°]; -NR[°]C(O)OR[°]; -C(O)OH; -C(O)OR[°]; -C(O)R[°]; -C(S)R[°]; -C(O)NH₂; -C(O)NH(R[°]); -C(O)N(R[°])₂; -C(S)NH₂; -C(S)NH(R[°]); -C(S)N(R[°])₂; -OC(O)NH₂; -OC(O)NH(R[°]); -OC(O)N(R[°])₂; -OC(O)R[°]; -C(NOR[°])H; -C(NOR[°])R[°]; -S(O)₂R[°]; -S(O)₃R[°]; -S(O)₃H; -S(O)₂NH₂; -S(O)₂NH(R[°]); -S(O)₂N(R[°])₂; -S(O)R[°]; -NHS(O)₂R[°]; -NR[°]S(O)₂R[°]; -N(OR[°])R[°]; -(CH₂)₀₋₂NHC(O)R[°]; -L-R[°]; -L-N(R[°])₂; -L-SR[°]; -L-OR[°]; -L-(C₃₋₁₀ cycloaliphatic), -L-(C₆₋₁₀ aryl), -L-(5-10 membered heteroaryl), -L-(5-10 membered heterocyclyl), oxo, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, -L-NO₂, -L-CN, -L-OH, -L-CF₃; or two substituents, on the same carbon or on different carbons, together with the carbon or intervening carbons to which they are bound, form a 5-7 membered saturated, unsaturated, or partially saturated ring, wherein L is a C₁₋₆ alkylene group in which up to three methylene units are replaced by -NH-, -NR[°]-, -O-, -S-, -C(O)O-, -OC(O)-, -C(O)CO-, -C(O)-, -C(O)NH-, -C(O)NR[°]-, -C(=N-CN), -NHCO-, -NR[°]CO-, -NHC(O)O-, -NR[°]C(O)O-, -S(O)₂NH-, -S(O)₂NR[°]-, -NHS(O)₂-, -NR[°]S(O)₂-, -NHC(O)NH-, -NR[°]C(O)NH-,

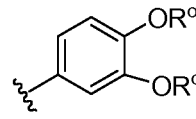
-NHC(O)NR[°]-, -NR[°]C(O)NR[°]-, -OC(O)NH-, -OC(O)NR[°]-, -NHS(O)₂NH-, -NR[°]S(O)₂NH-, -NHS(O)₂NR[°]-, -NR[°]S(O)₂NR[°]-, -S(O)-, or -S(O)₂-, and wherein each occurrence of R[°] is independently selected from optionally substituted C₁₋₆ aliphatic, an unsubstituted 5 to 6 membered heteroaryl or heterocyclic ring, phenyl, or -CH₂(Ph), or, two independent occurrences of R[°], on the same substituent or different substituents, taken together with the atom(s) to which each R[°] group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3- to 8-membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1 to 3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R[°] include -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, halogen, C₁₋₄ aliphatic, -OH, -O(C₁₋₄ aliphatic), -NO₂, -CN, -C(O)OH, -C(O)O(C₁₋₄ aliphatic), -O(haloC₁₋₄ aliphatic), or haloC₁₋₄ aliphatic, wherein each of the foregoing C₁₋₄ aliphatic groups of R[°] is unsubstituted.

[0025] In some embodiments, an aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR^{*}, =NN(R^{*})₂, =NNHC(O)R^{*}, =NNHC(O)O(alkyl), =NNHS(O)₂(alkyl), or =NR^{*}, where each R^{*} is independently selected from hydrogen or an optionally substituted C₁₋₈ aliphatic. Optional substituents on the aliphatic group of R^{*} are selected from -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂, halogen, C₁₋₄ aliphatic, -OH, -O(C₁₋₄ aliphatic), -NO₂, -CN, -C(O)OH, -C(O)O(C₁₋₄ aliphatic), -C(O)NH₂, -C(O)NH(C₁₋₄ aliphatic), -C(O)N(C₁₋₄ aliphatic)₂, -O(halo-C₁₋₄ aliphatic), and halo(C₁₋₄ aliphatic), where each of the foregoing C₁₋₄ aliphatic groups of R^{*} is unsubstituted; or two R^{*} on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

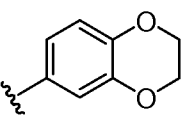
[0026] In some embodiments, optional substituents on the nitrogen of a non-aromatic heterocyclic ring include -R⁺, -N(R⁺)₂, -C(O)R⁺, -C(O)OR⁺, -C(O)C(O)R⁺, -C(O)CH₂C(O)R⁺, -S(O)₂R⁺, -S(O)₂N(R⁺)₂, -C(=S)N(R⁺)₂, -C(=NH)-N(R⁺)₂, or -NR⁺S(O)₂R⁺; wherein R⁺ is

hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted $-O(Ph)$, optionally substituted $-CH_2(Ph)$, optionally substituted $-(CH_2)_{1-2}(Ph)$; optionally substituted $-CH=CH(Ph)$; or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, two independent occurrences of R^+ , on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8 membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from $-NH_2$, $-NH(C_{1-4} \text{ aliphatic})$, $-N(C_{1-4} \text{ aliphatic})_2$, halogen, C_{1-4} aliphatic, $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-NO_2$, $-CN$, $-C(O)OH$, $-C(O)O(C_{1-4} \text{ aliphatic})$, $-O(\text{halo}(C_{1-4} \text{ aliphatic}))$, or $\text{halo}(C_{1-4} \text{ aliphatic})$, wherein each of the foregoing C_{1-4} aliphatic groups of R^+ is unsubstituted.

[0027] As detailed above, in some embodiments, two independent occurrences of R^o (or R^+ , or any other variable similarly defined herein), may be taken together with the atom(s) to which each variable is bound to form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring. Exemplary rings that are formed when two independent occurrences of R^o (or R^+ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+ , or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+ , or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example

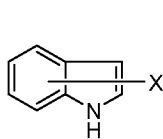


where a phenyl group is substituted with two occurrences of OR^o , these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a

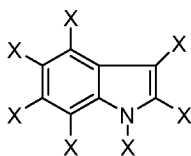
fused 6-membered oxygen containing ring: . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R⁺, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0028] In some embodiments, a methylene unit of the alkyl or aliphatic chain is optionally replaced with another atom or group. Examples of such atoms or groups would include, but are not limited to, -NH-, -NR^o-, -O-, -S-, -C(O)O-, -OC(O)-, -C(O)CO-, -C(O)-, -C(O)NH-, -C(O)NR^o-, -C(=N-CN), -NHCO-, -NR^oCO-, -NHC(O)O-, -NR^oC(O)O-, -S(O)₂NH-, -S(O)₂NR^o-, -NHS(O)₂-, -NR^oS(O)₂-, -NHC(O)NH-, -NR^oC(O)NR^o-, -OC(O)NH-, -OC(O)NR^o-, -NHS(O)₂NH-, -NR^oS(O)₂NR^o-, -S(O)-, or -S(O)₂-, wherein R^o is defined elsewhere herein. Unless otherwise specified, the optional replacements form a chemically stable compound. Optional atom or group replacements can occur both within the chain and at either end of the chain; i.e. both at the point of attachment and/or also at the terminal end. Two optional replacements can also be adjacent to each other within a chain so long as it results in a chemically stable compound. Unless otherwise specified, if the replacement occurs at the terminal end, the replacement atom is bound to an H on the terminal end. For example, if one methylene unit of -CH₂CH₂CH₃ was optionally replaced with -O-, the resulting compound could be -OCH₂CH₃, -CH₂OCH₃, or -CH₂CH₂OH.

[0029] As described herein, a bond drawn from a substituent to the center of one ring within a multiple-ring system (as shown below) represents substitution of the substituent at any substitutable position in any of the rings within the multiple ring system. For example, Structure a represents possible substitution in any of the positions shown in Structure b.

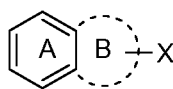


Structure a



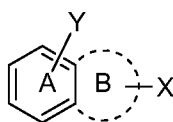
Structure b

[0030] This also applies to multiple ring systems fused to optional ring systems (which would be represented by dotted lines). For example, in Structure c, X is an optional substituent both for ring A and ring B.



Structure c

[0031] If, however, two rings in a multiple ring system each have different substituents drawn from the center of each ring, then, unless otherwise specified, each substituent only represents substitution on the ring to which it is attached. For example, in Structure d, Y is an optionally substituent for ring A only, and X is an optional substituent for ring B only.



Structure d

[0032] The term “protecting group,” as used herein, represent those groups intended to protect a functional group, such as, for example, an alcohol, amine, carboxyl, carbonyl, etc., against undesirable reactions during synthetic procedures. Commonly used protecting groups are disclosed in Greene and Wuts, *Protective Groups In Organic Synthesis*, 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. Examples of nitrogen protecting groups include acyl, aroyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-

methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like, arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

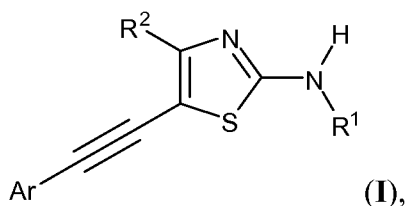
[0033] The term “prodrug,” as used herein, represents a compound that is transformed *in vivo* into a compound of formula **I** or a compound listed in Table 1. Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds of the invention may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C_1 - C_{24}) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound of the invention that contains an OH group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, for example those phosphates resulting from the phosphonation of an OH group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and Judkins *et al.*, *Synthetic Communications* 26(23):4351-4367, 1996, each of which is incorporated herein by reference.

[0034] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

[0035] Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, probes in biological assays, or as PI3K inhibitors with improved therapeutic profile.

Description of Compounds of the Invention

[0036] In one aspect, the invention features compounds having formula **I**:



or a pharmaceutically acceptable salt thereof, wherein:

Ar is a phenyl ring or a 5-10 membered monocyclic or fused bicyclic heteroaryl ring having up to 2 atoms selected from nitrogen, wherein each ring is optionally substituted with up to 3 substituents independently selected from fluoro, chloro, C_{1-4} aliphatic, C_{3-4} cycloaliphatic, $-\text{OC}_{1-4}$ aliphatic, $-\text{OC}_{3-4}$ cycloaliphatic, $-\text{N}(\text{J}^{\text{R}1})\text{C}(\text{O})\text{C}_{1-4}$ aliphatic, or $\text{N}(\text{J}^{\text{R}1})_2$, wherein each of said aliphatic or cycloaliphatic is optionally substituted with up to 3 occurrences of fluoro;

R^1 is selected from $-\text{C}(\text{O})\text{R}^{1a}$, $-\text{C}(\text{O})\text{OR}^{1a}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{1a})(\text{R}^{1b})$, wherein

R^{1a} is C_{1-4} aliphatic, C_{3-6} cycloaliphatic, or C_{5-10} heterocyclic having up to 2 atoms selected from oxygen, sulfur, or nitrogen, wherein R^{1a} is optionally substituted with 1, 2, 3, or 4, occurrences of J^{R} ;

each J^{R} is independently fluoro, oxo, $-\text{C}(\text{O})\text{J}^{\text{R}1}$, $-\text{C}(\text{O})\text{N}(\text{J}^{\text{R}1})_2$, $-\text{C}(\text{O})\text{O}(\text{J}^{\text{R}1})$, $-\text{N}(\text{J}^{\text{R}1})\text{C}(\text{O})\text{J}^{\text{R}1}$, $-\text{OJ}^{\text{R}1}$, $-\text{SJ}^{\text{R}1}$, $-\text{S}(\text{O})\text{J}^{\text{R}1}$, phenyl or a 5-10 membered heteroaryl or heterocyclyl ring having

up to 2 atoms selected from nitrogen, oxygen, or sulfur, wherein said phenyl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 J^{R2} groups;

R^{1b} is, independently, hydrogen, C_{1-4} aliphatic, C_{3-6} cycloaliphatic; or

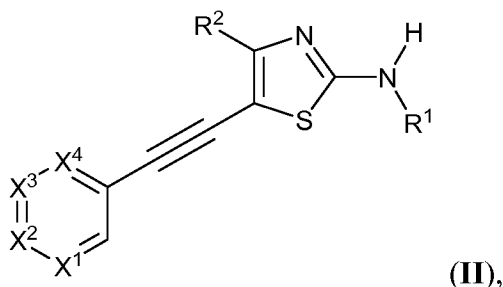
R^{1a} and R^{1b} , together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, wherein said heterocyclic ring optionally comprises one additional heteroatom selected from nitrogen and oxygen, and wherein said heterocyclic ring is optionally substituted with 1 or 2 J^{R2} groups;

R^2 is C_{1-4} aliphatic optionally substituted with 1, 2, or 3 J^{R2} groups;

each J^{R1} is independently selected from hydrogen, C_{1-4} aliphatic, C_{3-6} cycloaliphatic, phenyl, benzyl, or 5-6 membered heteroaryl ring having up to two atom selected from nitrogen, oxygen, or sulfur, wherein each of said C_{1-4} aliphatic, phenyl, benzyl, or heteroaryl is optionally substituted with up to three J^{R2} groups; and

each J^{R2} is, independently, selected from chloro, fluoro, -CN, -NO₂, oxo, C_{1-4} alkyl, C_{3-6} cycloalkyl, -OH, -OC₁₋₄alkyl, -OPhenyl, or -OCH₂Phenyl, wherein each of said alkyl, cycloalkyl or phenyl is optionally substituted with up to 3 fluoro groups.

[0037] In one embodiment, the invention features compounds having formula **II**:



or a pharmaceutically acceptable salt thereof, wherein:

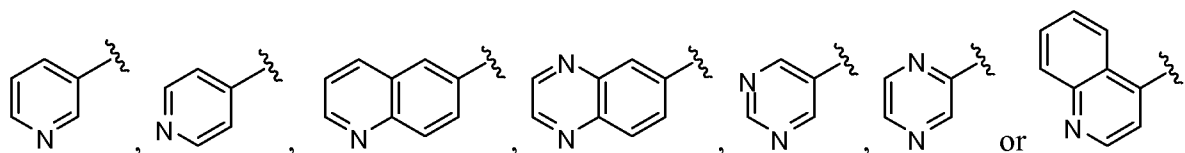
each of X^1 , X^2 , X^3 , and X^4 is N or CR³, where no more than two of X^1 , X^2 , X^3 , and X^4 can be N;

R^1 is selected from -C(O) R^{1a} or -C(O)N(R^{1a})(R^{1b});

R^{1a} is C_{1-4} aliphatic or C_{3-6} cycloaliphatic, wherein R^{1a} is optionally substituted with 1, 2, 3, or 4, occurrences of J^R ; each J^R is independently fluoro, -C(O) J^{R1} , -C(O)N(J^{R1})₂, -C(O)O(J^{R1}), -N(J^{R1})C(O) J^{R1} , -O J^{R1} , -S J^{R1} , phenyl or a 5-6 membered heteroaryl or

heterocyclyl ring having up to 2 atoms selected from nitrogen, oxygen, or sulfur, wherein said phenyl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 J^{R2} groups; each R^{1b} is, independently, hydrogen, C_{1-4} aliphatic, C_{3-6} cycloaliphatic; or R^{1a} and R^{1b} , together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, wherein said heterocyclic ring optionally comprises one additional heteroatom selected from nitrogen and oxygen, and wherein said heterocyclic ring is optionally substituted with 1 or 2 J^{R2} groups; R^2 is C_{1-4} aliphatic or C_{3-4} cycloaliphatic, wherein said aliphatic or cycloaliphatic is optionally substituted with 1, 2, or 3 J^{R2} groups; R^3 is hydrogen, fluoro, chloro, -CN, C_{1-4} aliphatic, C_{3-4} cycloaliphatic, -OC $_{1-4}$ aliphatic, -OC $_{3-4}$ cycloaliphatic, or $N(J^{R1})_2$, wherein each of said C_{1-4} aliphatic, C_{3-4} cycloaliphatic, -OC $_{1-4}$ aliphatic, or -OC $_{3-4}$ cycloaliphatic is optionally substituted with up to 3 occurrences of fluoro; each J^{R1} is independently selected from hydrogen, C_{1-4} aliphatic, C_{3-6} cycloaliphatic, phenyl, benzyl, wherein each of said C_{1-4} aliphatic, phenyl, or benzyl is optionally substituted with up to three J^{R2} groups; and each J^{R2} is, independently, selected from chloro, fluoro, -CN, -NO₂, oxo, C_{1-4} alkyl, C_{3-6} cycloaliphatic, -OH, or -OC $_{1-4}$ alkyl.

[0038] In another embodiment of compounds of formula **I**, Ar is an optionally substituted 5-10 membered heteroaryl ring. In a further embodiment, Ar is an optionally substituted group selected from:



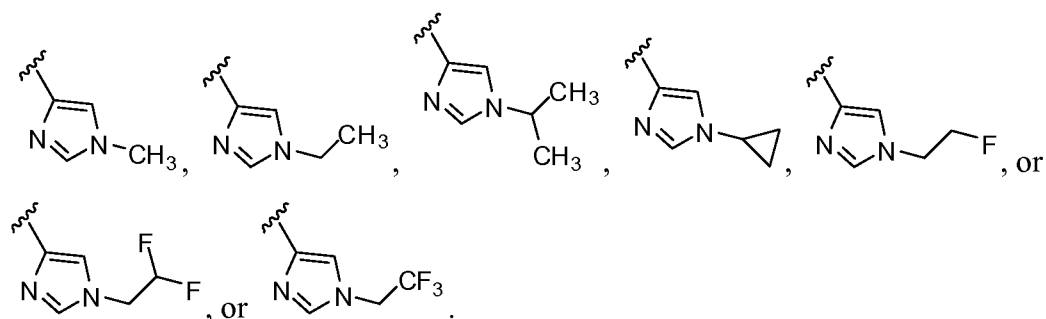
In another further embodiment, Ar is substituted with 1 to 2 groups independently selected from -OCH₃, -OCF₃, -OCHF₂, Cl, F, or CF₃.

[0039] In one embodiment, R^2 is methyl.

[0040] In one embodiment, R^1 is -C(O)N(R^{1a})(R^{1b}). In a further embodiment, R^{1b} is hydrogen.

[0041] In one embodiment, R^{1a} is $-\text{CH}_2\text{CH}(\text{R})-\text{J}^{\text{R}}$, wherein R is hydrogen or methyl and J^{R} is $-\text{OJ}^{\text{R}1}$ or a 5-membered heteroaryl ring having 2 nitrogen atoms, said heteroaryl ring substituted with C_{1-3} alkyl or cyclopropyl, each of said alkyl and cyclopropyl optionally substituted with up to 3 fluoro groups.

[0042] In a further embodiment, J^{R} is

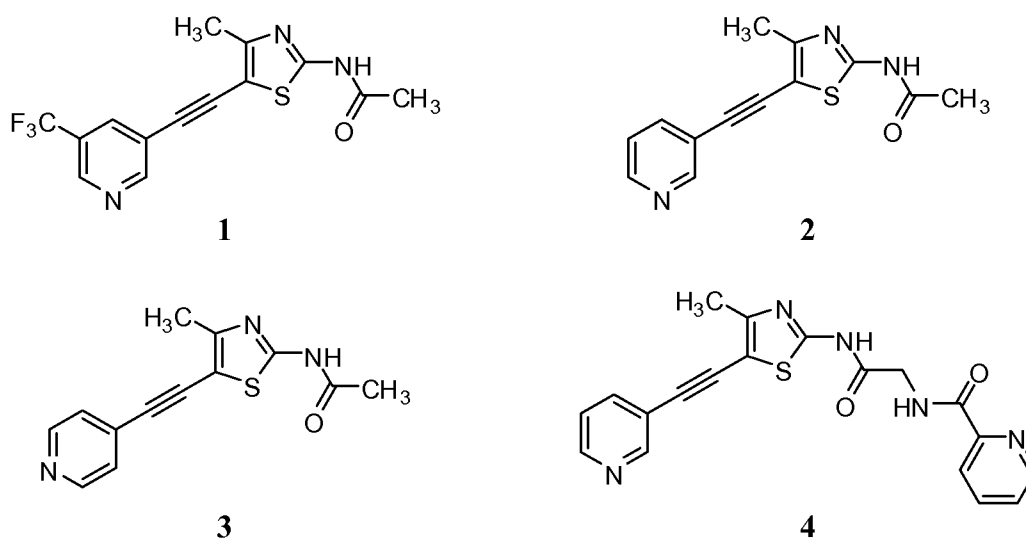


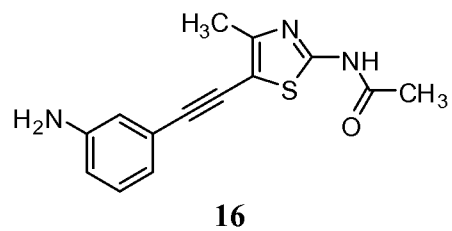
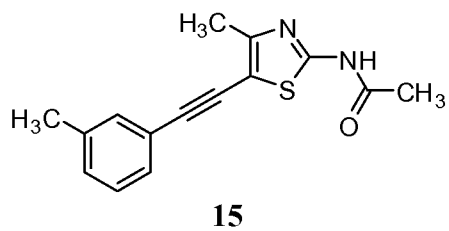
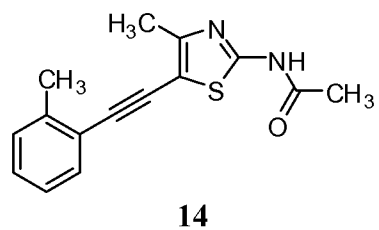
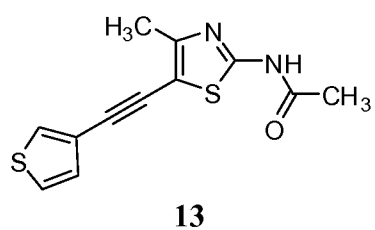
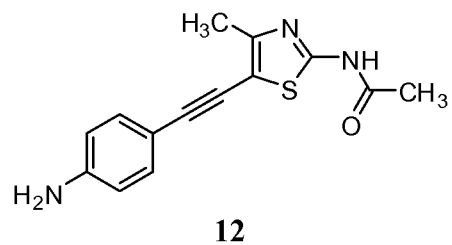
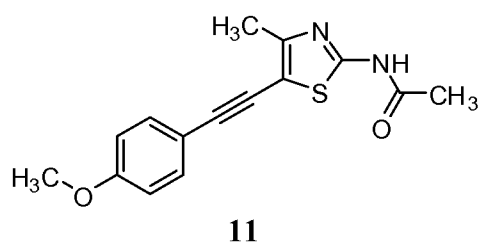
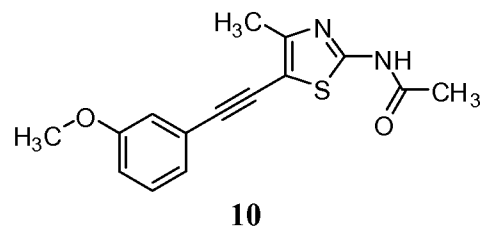
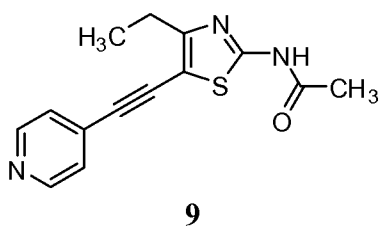
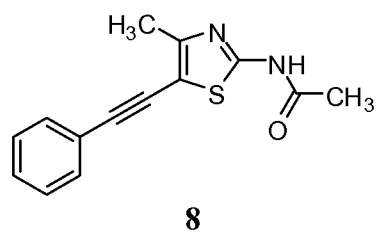
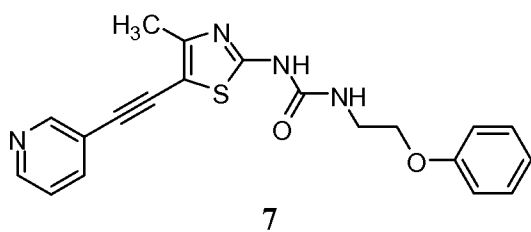
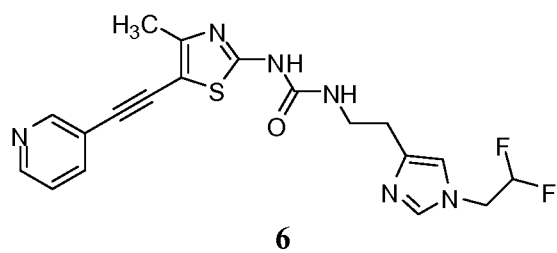
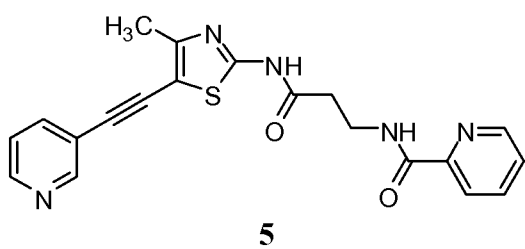
[0043] In another embodiment, J^{R} is $-\text{OJ}^{\text{R}1}$ and $\text{J}^{\text{R}1}$ is C_{1-4} alkyl, optionally substituted with cyclopropyl or up to three fluoro or methyl groups. In a further embodiment, $\text{J}^{\text{R}1}$ is $-\text{CH}_2$ -cyclopropyl.

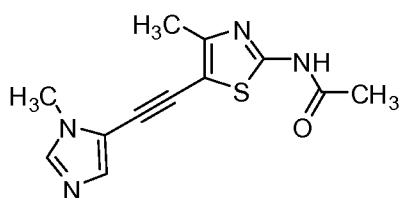
[0044] In another embodiment, J^{R} is $-\text{OJ}^{\text{R}1}$ and $\text{J}^{\text{R}1}$ is phenyl or pyridyl, optionally substituted with up to three fluoro groups.

[0045] In another embodiment, the invention features a compound selected from the group of compounds listed in Table 1.

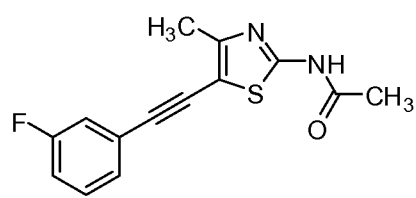
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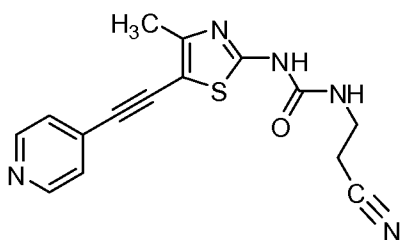




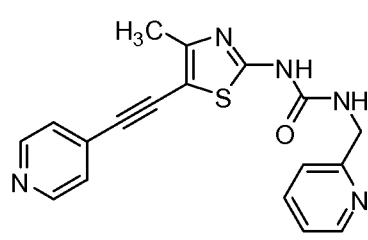
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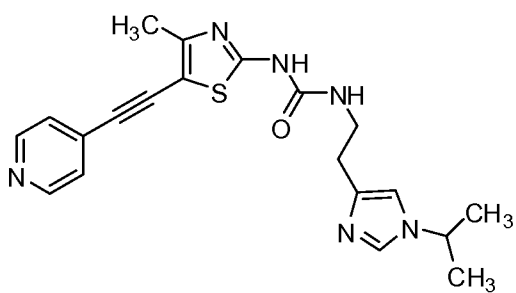
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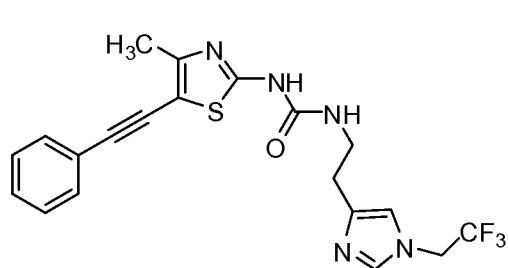
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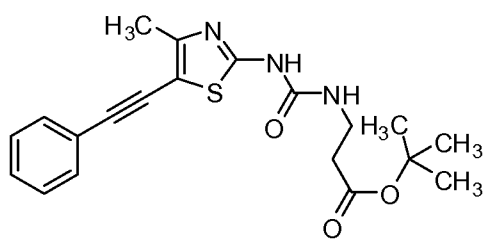
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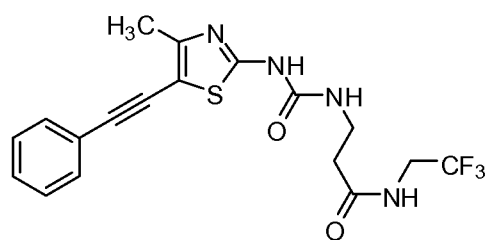
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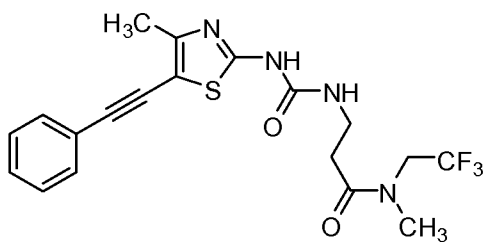
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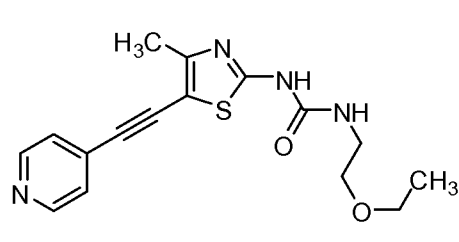
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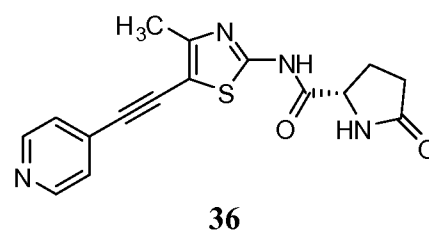
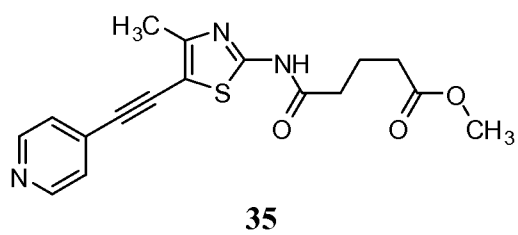
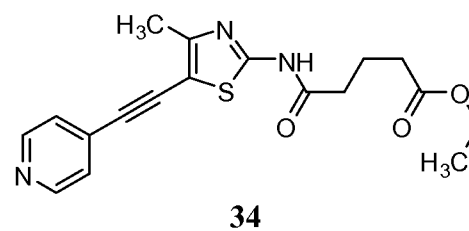
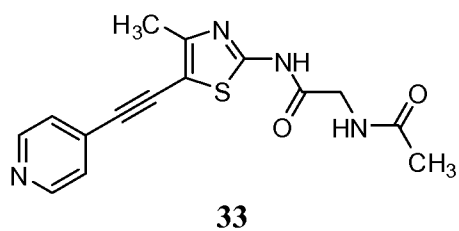
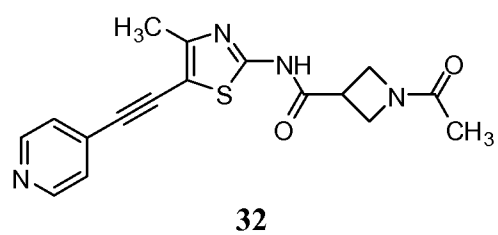
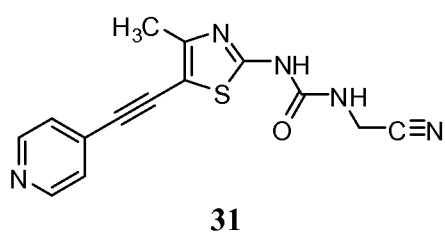
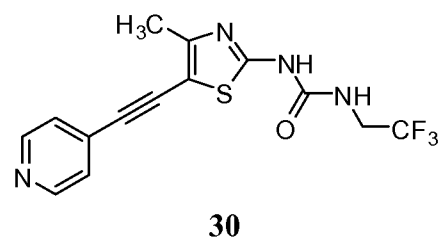
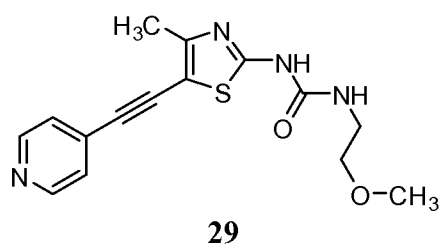
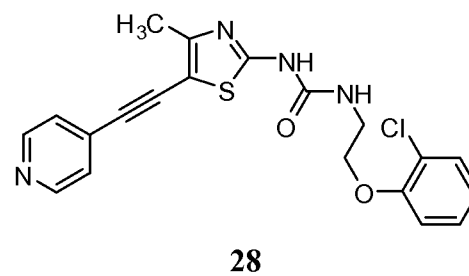
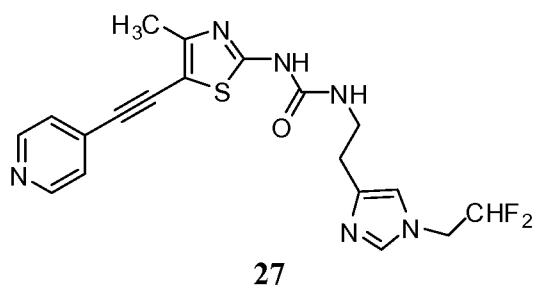
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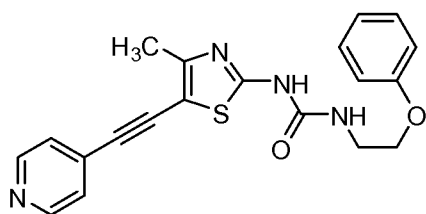


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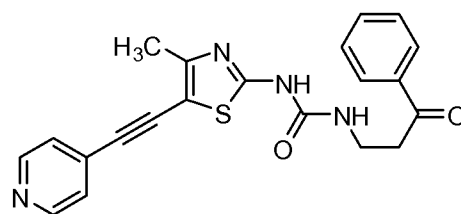


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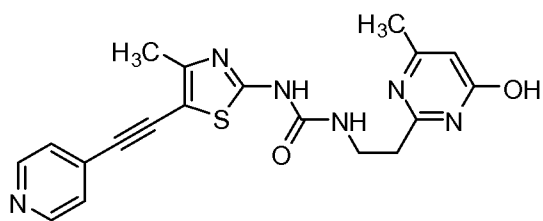




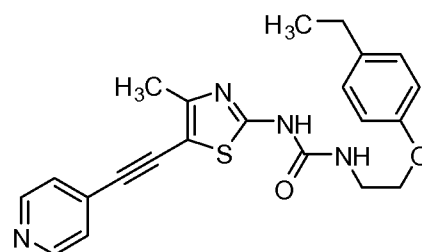
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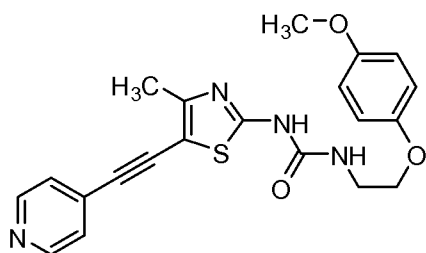
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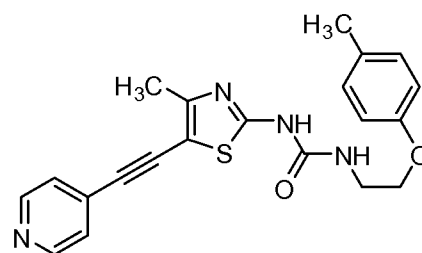
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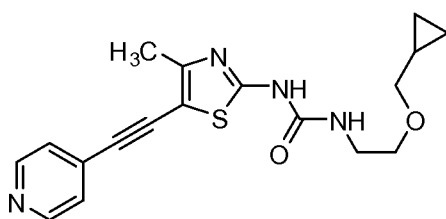
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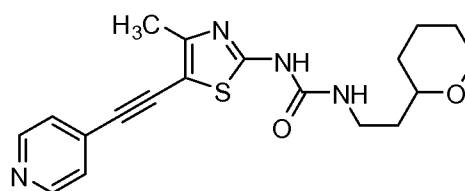
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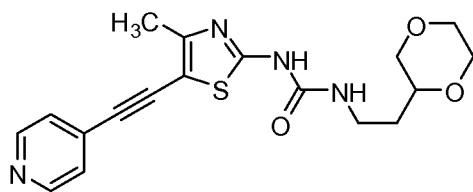
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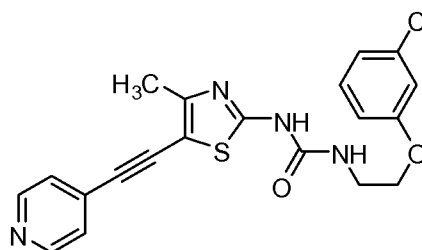
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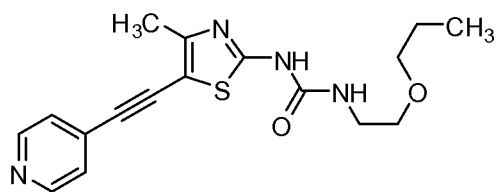
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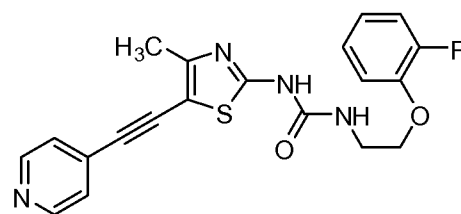
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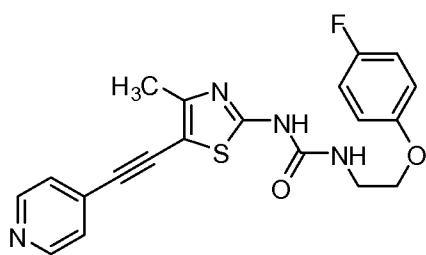
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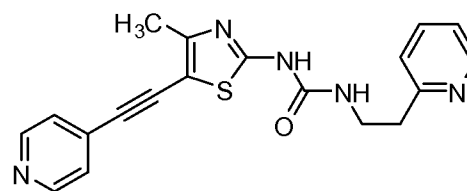
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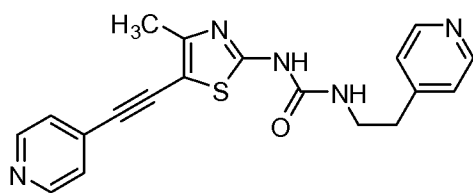
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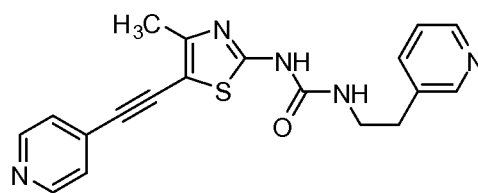
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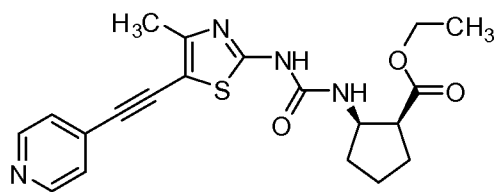
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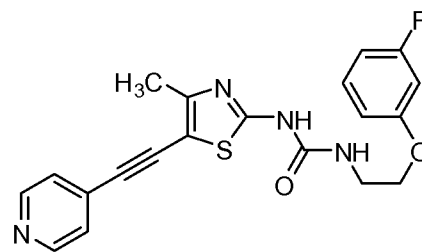
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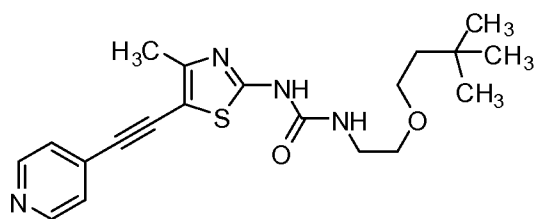
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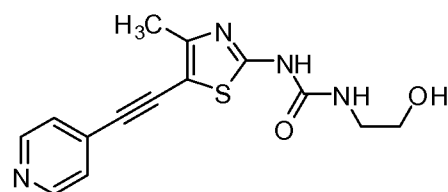
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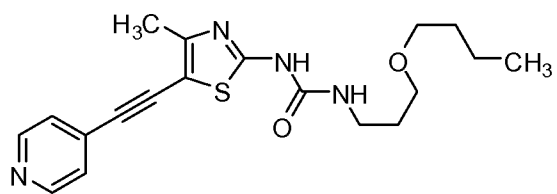
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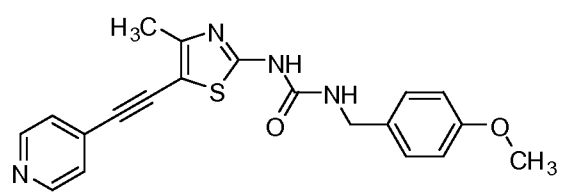
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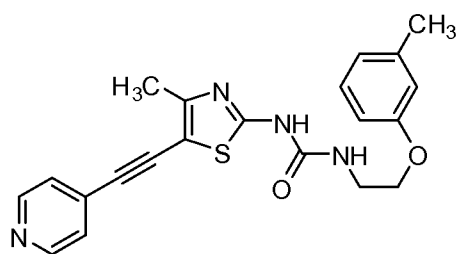
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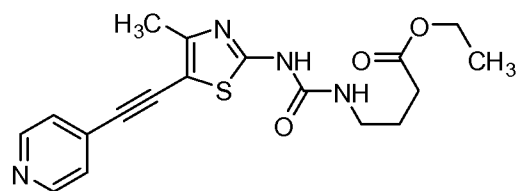
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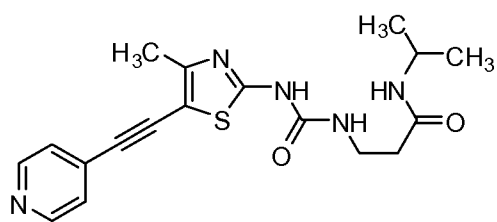
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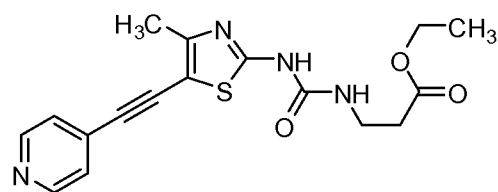
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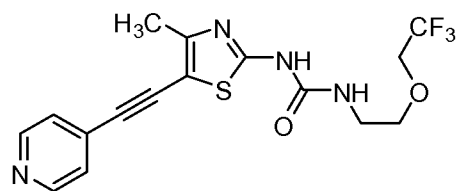
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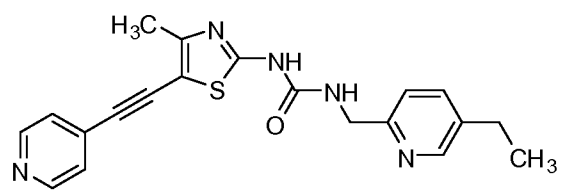
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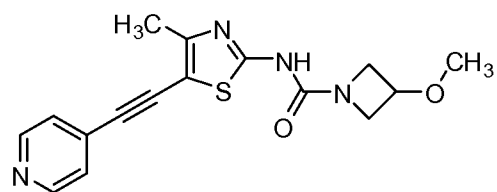
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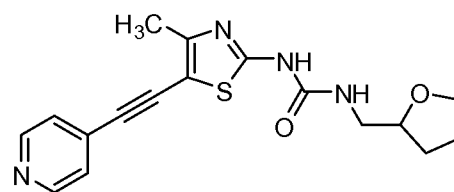
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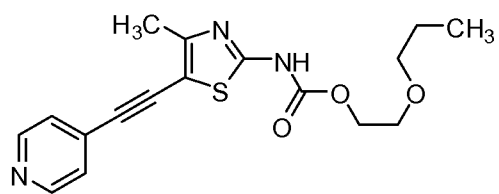
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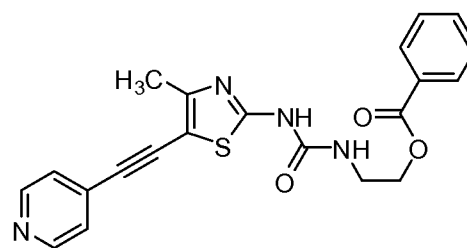
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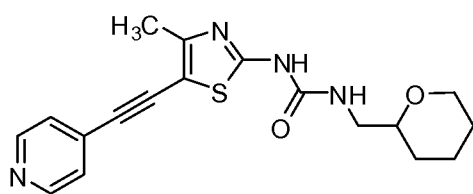
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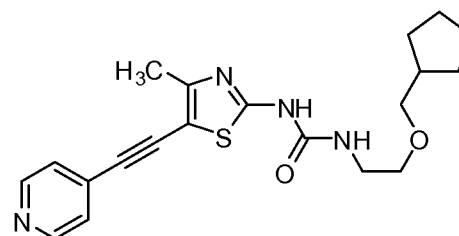
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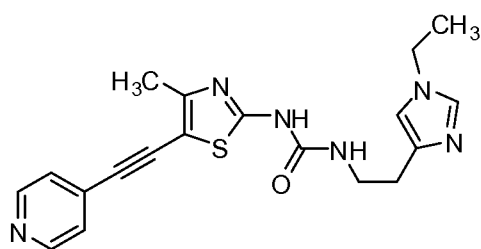
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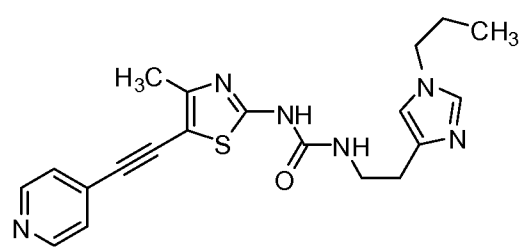
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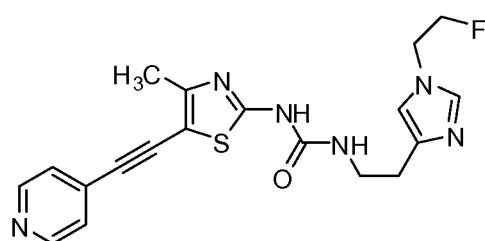
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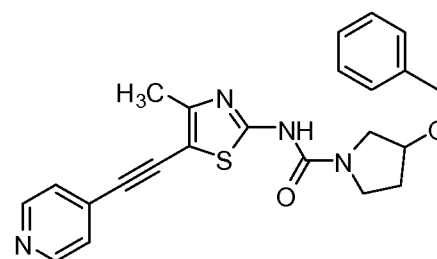
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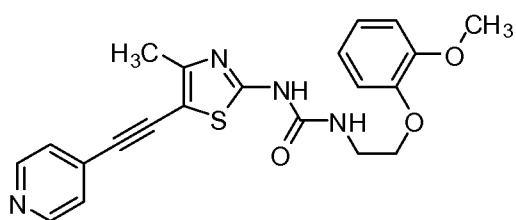
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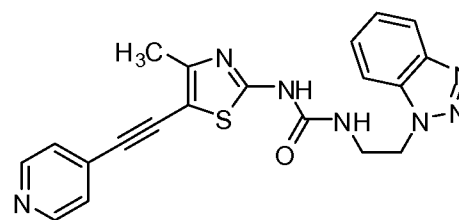
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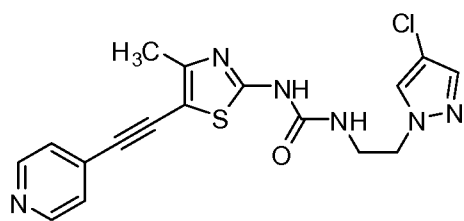
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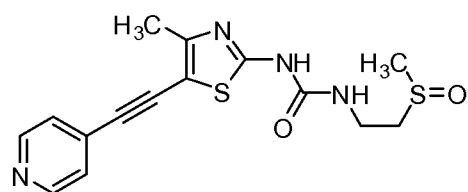
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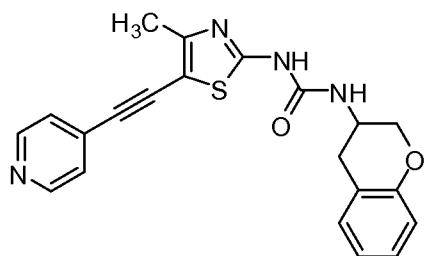
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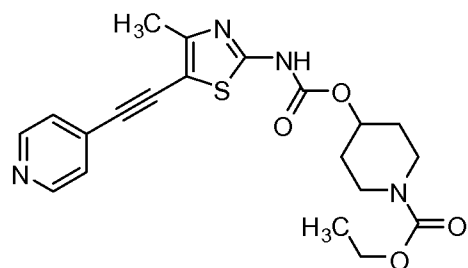
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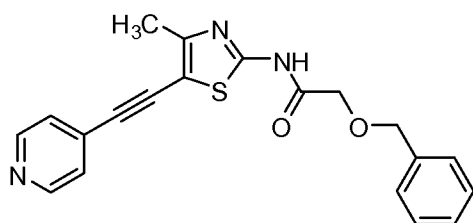
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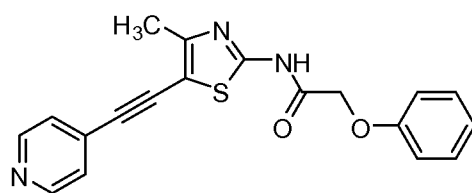
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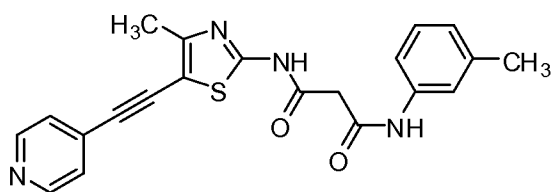
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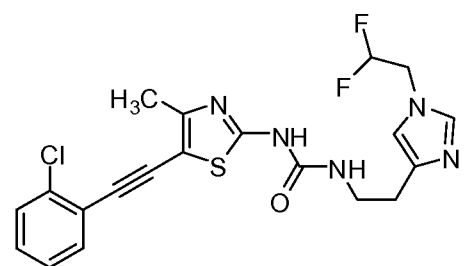
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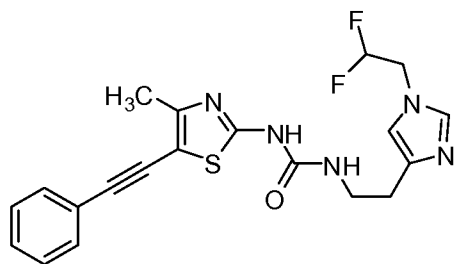
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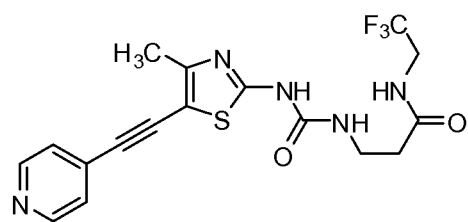
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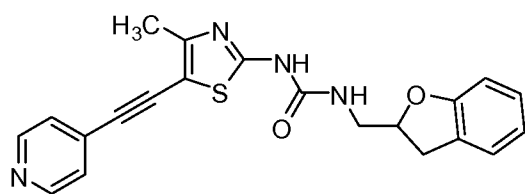
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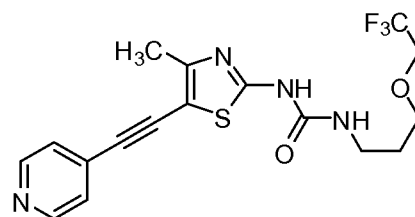
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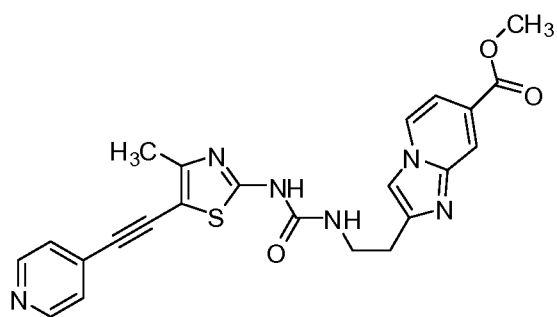
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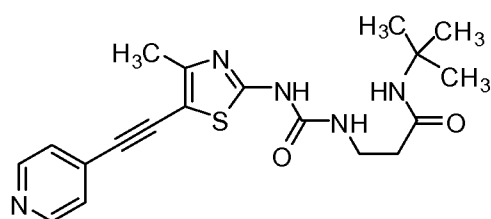
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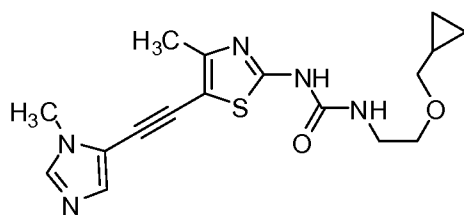
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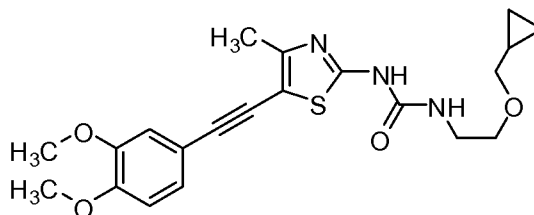
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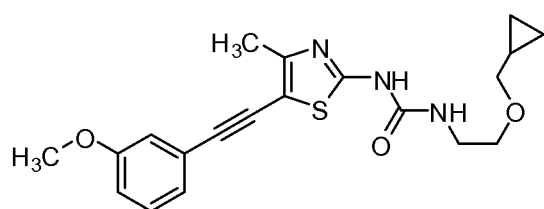
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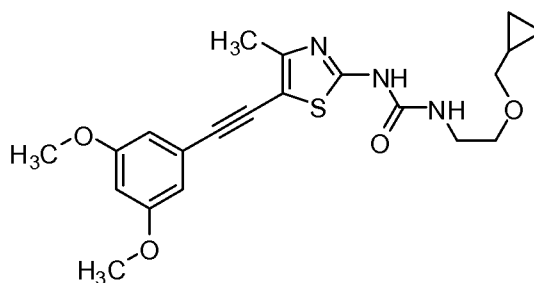
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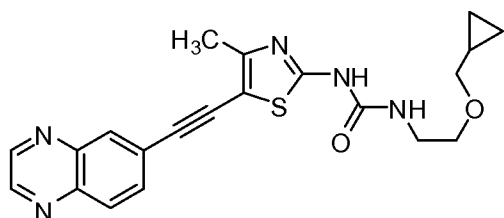
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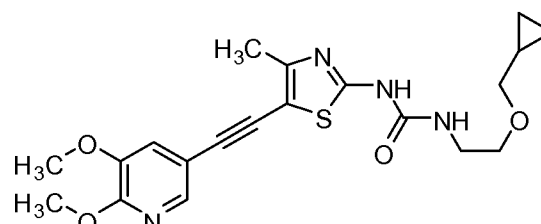
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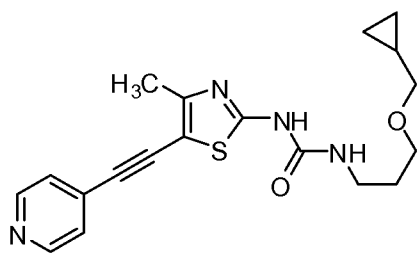
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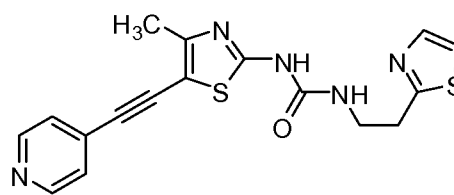
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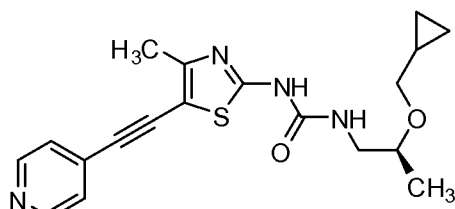
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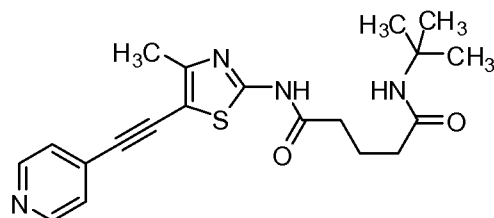
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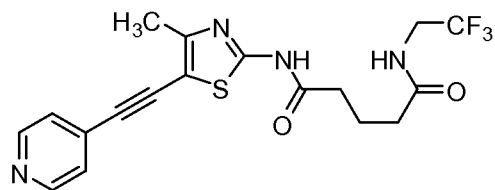
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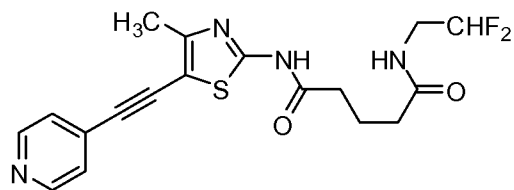
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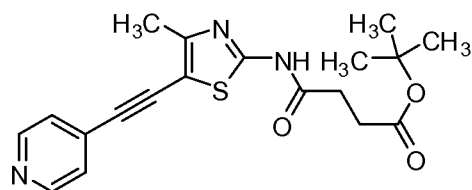
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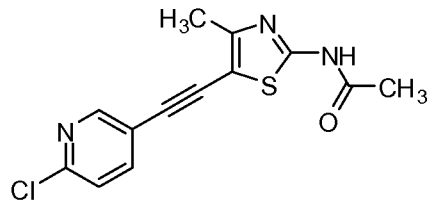
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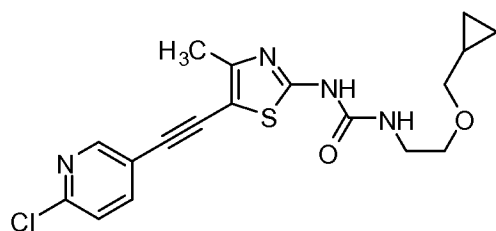
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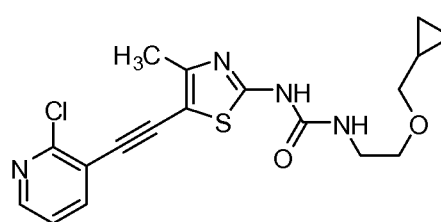
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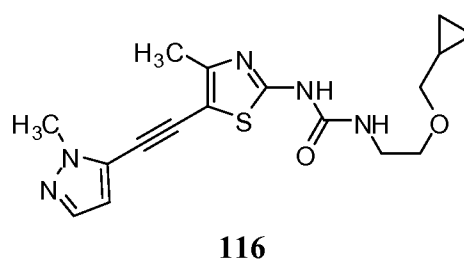
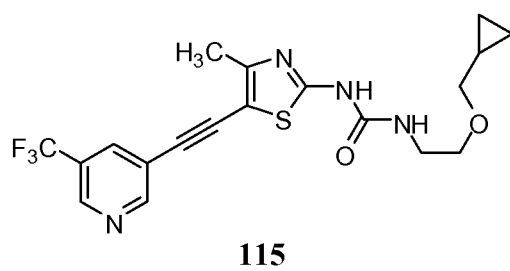
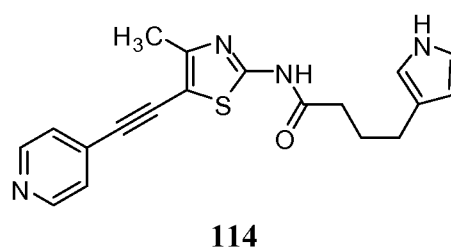
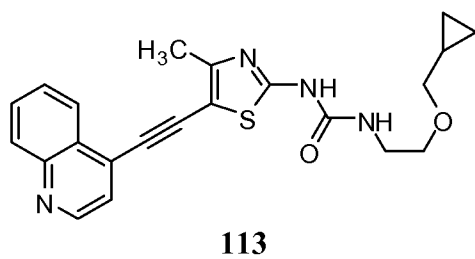
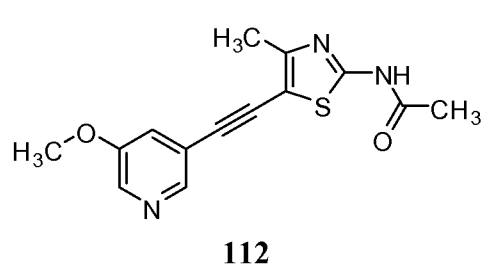
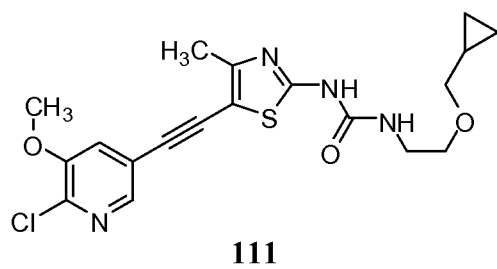
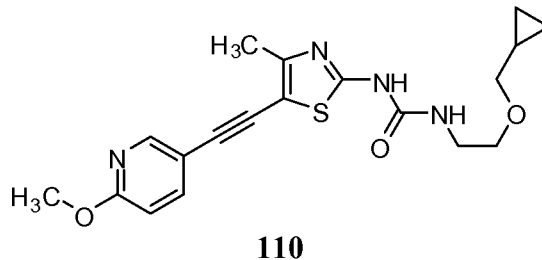
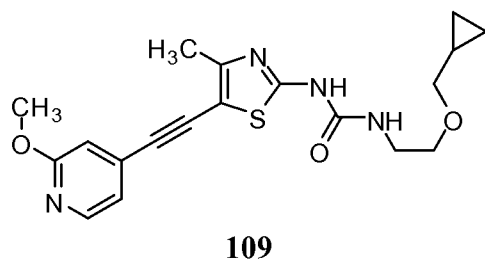
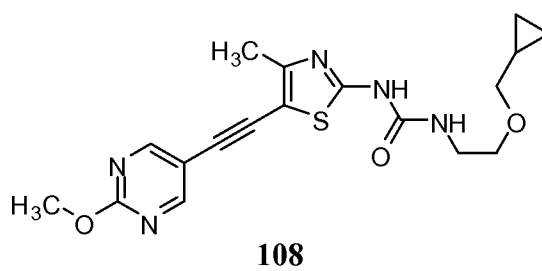
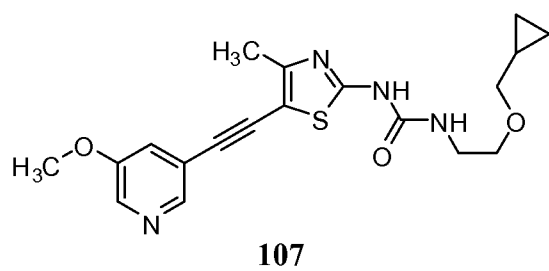
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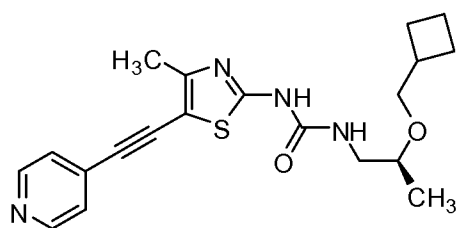


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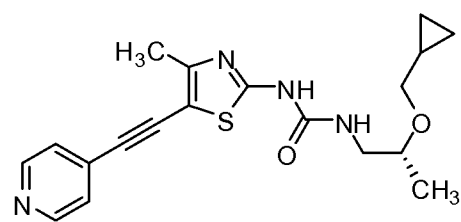


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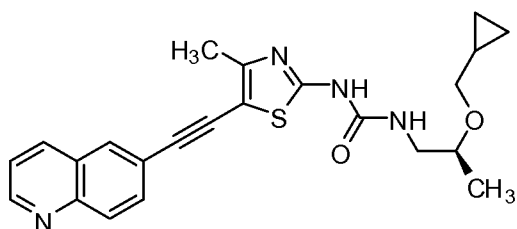




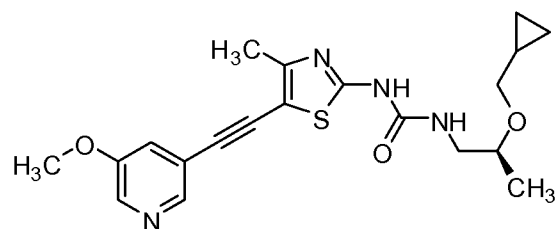
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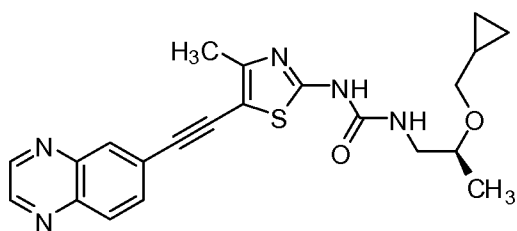
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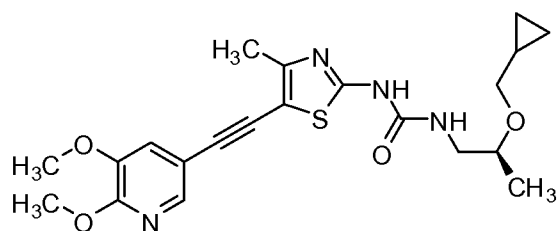
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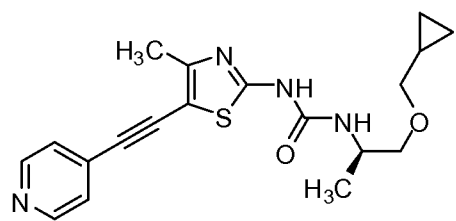
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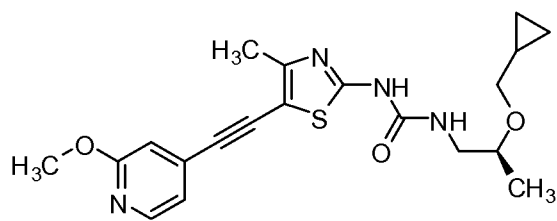
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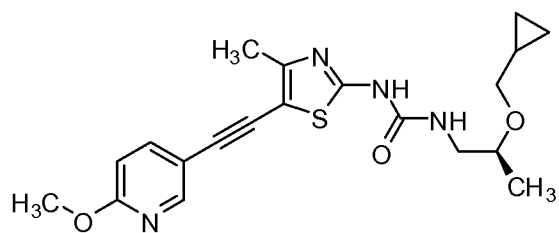
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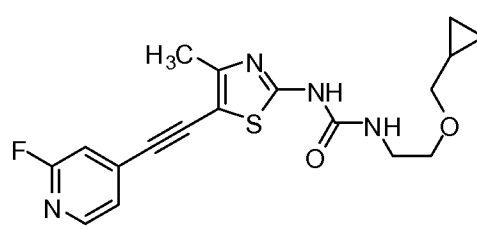
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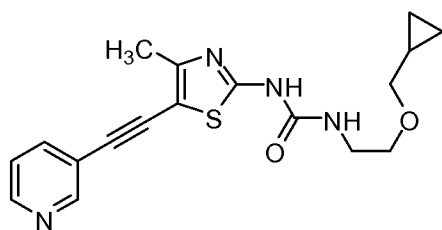
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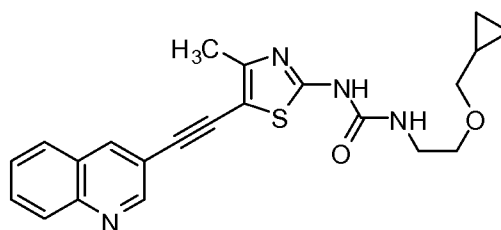
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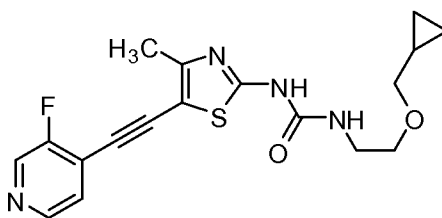
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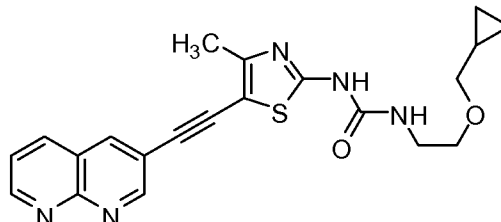
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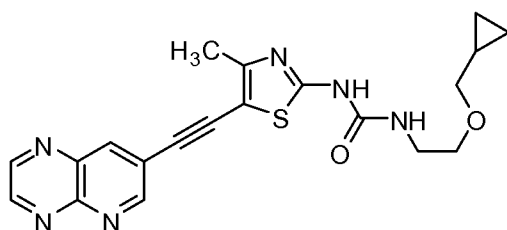
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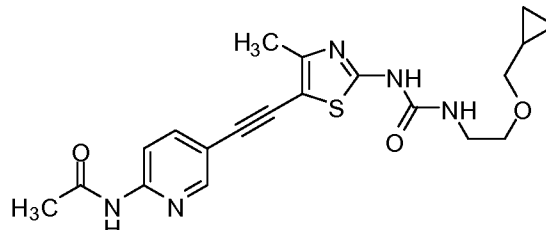
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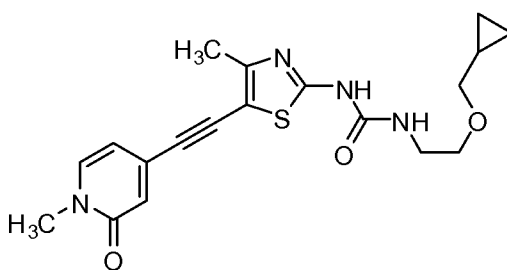
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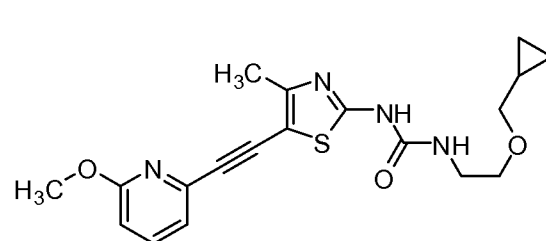
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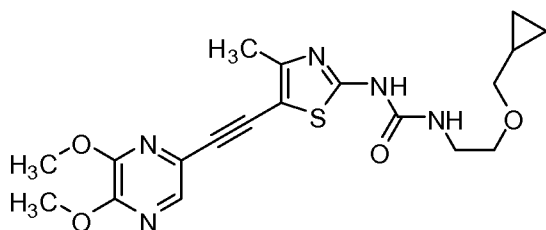
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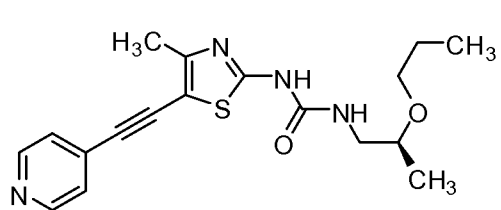
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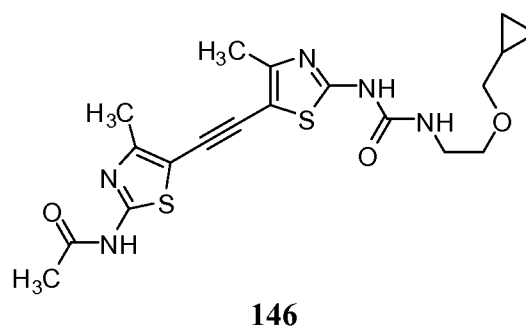
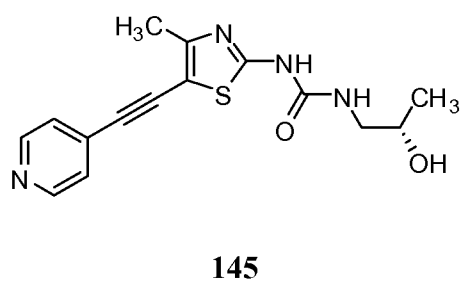
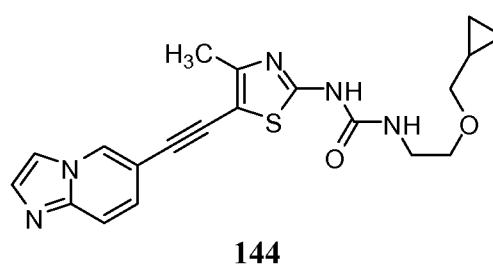
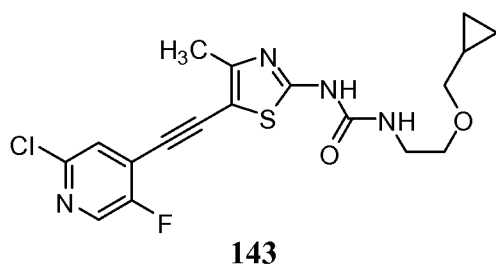
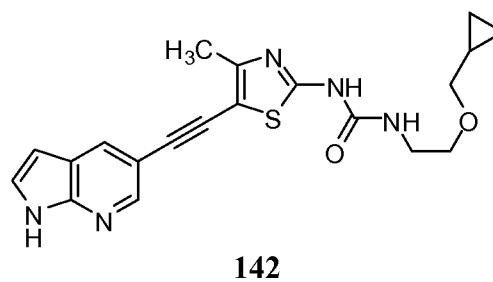
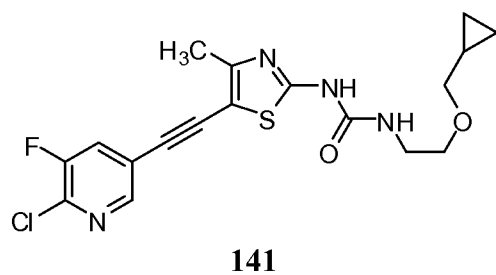
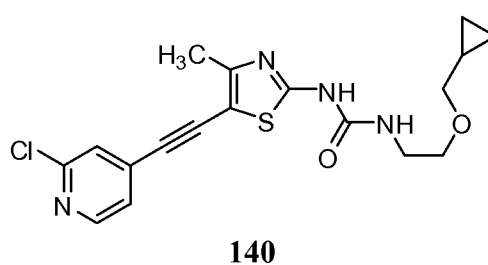
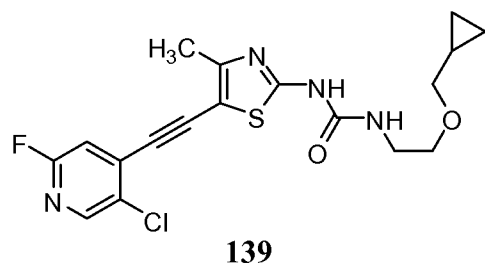
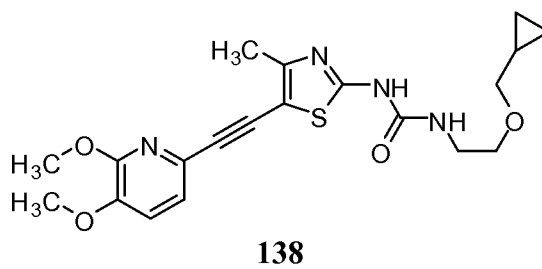
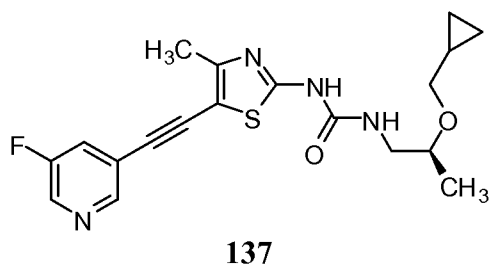
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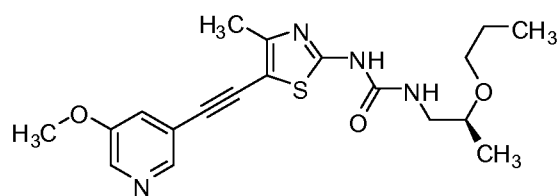


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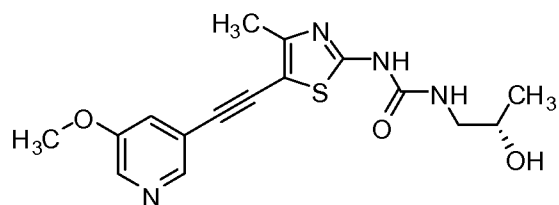


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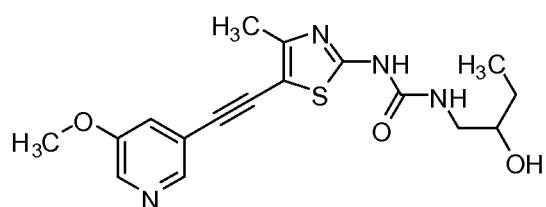




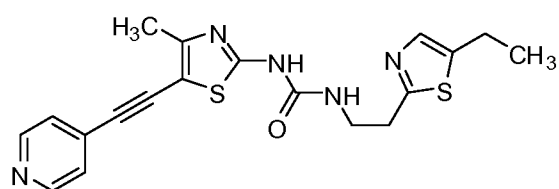
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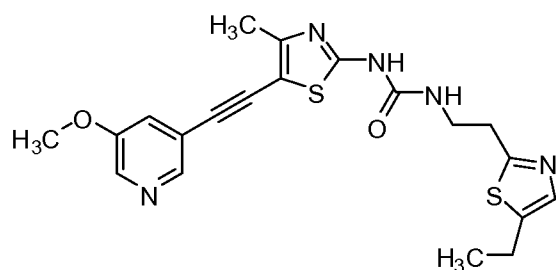
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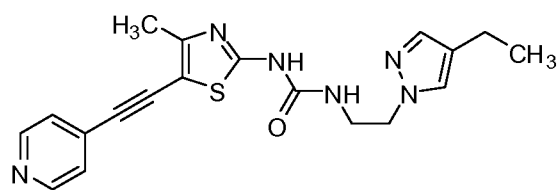
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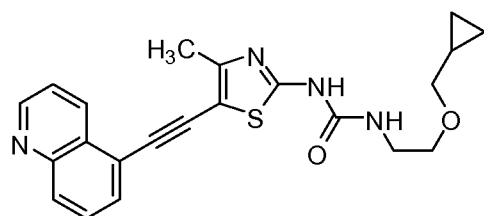
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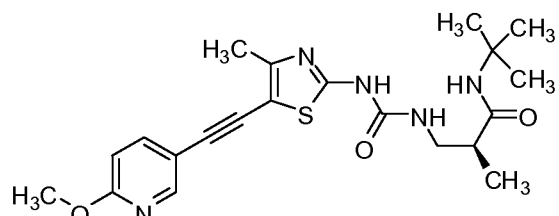
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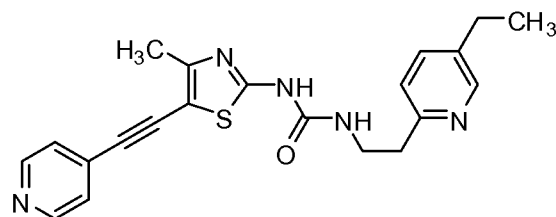
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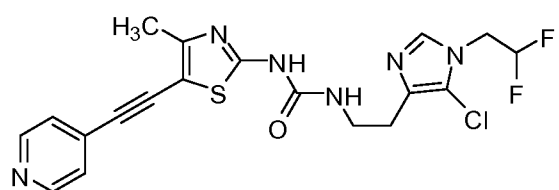
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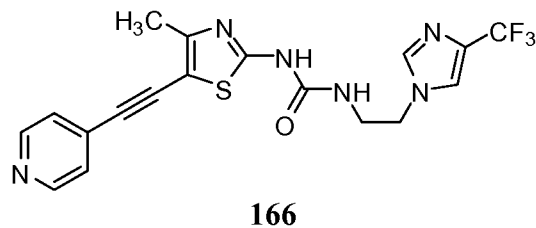
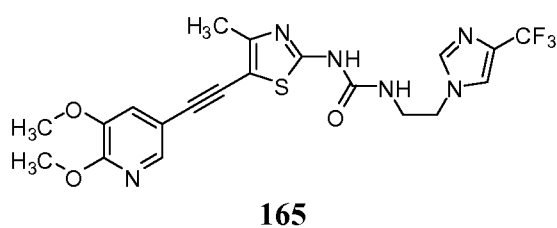
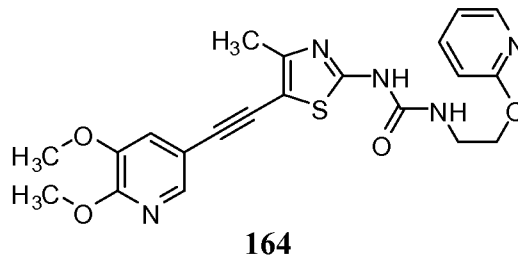
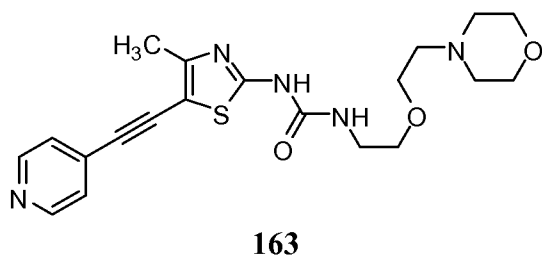
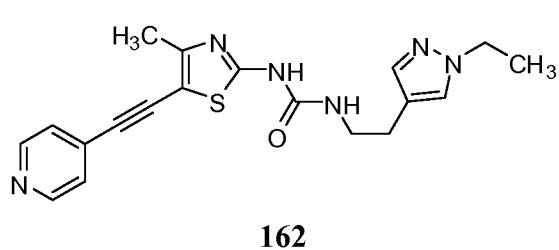
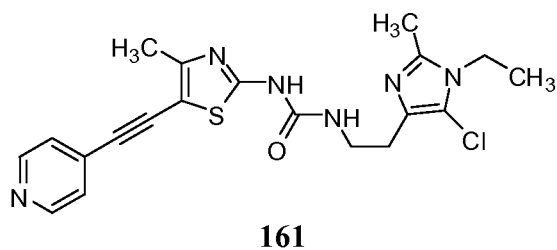
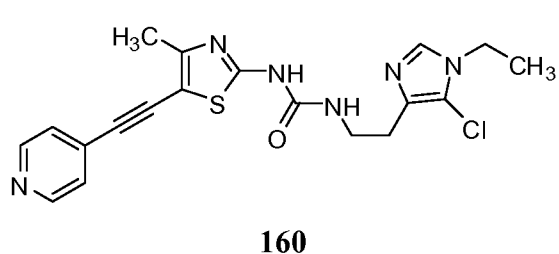
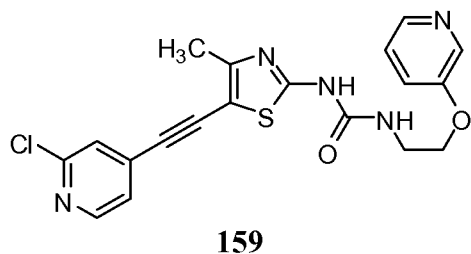
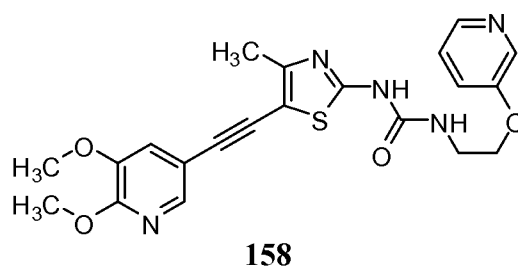
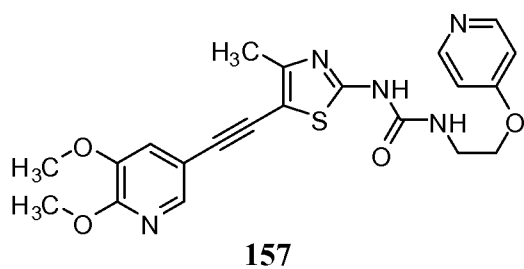
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[0046] The invention also features a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0047] In one embodiment, the composition includes a therapeutic agent selected from an agent for treating multiple sclerosis, an anti-inflammatory agent, an immunomodulatory agent, or an immunosuppressive agent.

[0048] In another embodiment, the invention features a method of treating or lessening the severity of a disease or condition selected from an autoimmune disease or an inflammatory disease of the brain or spinal cord, comprising the step of administering to said patient a compound of the invention or a pharmaceutical composition thereof.

[0049] In a further embodiment, the disease or disorder is multiple sclerosis.

[0050] In another embodiment, the method of treatment includes administering to a patient a compound or composition of the invention and an additional therapeutic agent, wherein the additional therapeutic agent is appropriate for the disease being treated and is administered together with the compound or composition as a single dosage form, or separately as part of a multiple dosage form. Examples of such additional therapeutic agents are those useful for treating multiple sclerosis, such as beta interferon, glatiramer, natalizumab, or mitoxantrone.

[0051] The invention also features a non-therapeutic method of inhibiting PI3K-gamma kinase activity in a biological sample comprising contacting said biological sample with a compound of formula I, or a composition containing said compound.

Compositions, Formulations, and Administration of Compounds of the Invention

[0052] In another embodiment, the invention provides a pharmaceutical composition comprising a compound of any of the formulae or classes described herein. In a further embodiment, the invention provides a pharmaceutical composition comprising a compound of Table 1. In a further embodiment, the composition additionally comprises an additional therapeutic agent.

[0053] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In one embodiment, the amount of compound in a composition of this invention is such that is effective to measurably

inhibit a PI3K, particularly PI3K γ , in a biological sample or in a patient. In another embodiment, the amount of compound in the compositions of this invention is such that is effective to measurably inhibit PI3K α . In one embodiment, the composition of this invention is formulated for administration to a patient in need of such composition. In a further embodiment, the composition of this invention is formulated for oral administration to a patient.

[0054] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0055] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof. As used herein, the term “inhibitory active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of PI3K.

[0056] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like.

[0057] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66:1-19, 1977, which is incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange.

Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate and aryl sulfonate.

[0058] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. In Remington: *The Science and Practice of Pharmacy*, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any

undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[0059] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0060] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraocular, intrahepatic, intralesional, epidural, intraspinal, and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous

or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0061] For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0062] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0063] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature

but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0064] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0065] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0066] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0067] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated, e.g., as micronized suspensions in isotonic, pH adjusted sterile saline or other aqueous solution, or, preferably, as solutions in isotonic, pH adjusted sterile saline or other aqueous solution, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum. The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable

preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0068] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[0069] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0070] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0071] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0072] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, dissolving or suspending the compound in an oil vehicle accomplishes delayed absorption of a parenterally administered compound form. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0073] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0074] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene

glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0075] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0076] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0077] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a

pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0078] The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0079] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0080] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular

disease, or condition, are known as “appropriate for the disease, or condition, being treated.” Examples of additional therapeutic agents are provided *infra*.

[0081] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

Uses of the Compounds and Compositions of the Invention

[0082] In one embodiment, the invention provides a method of inhibiting PI3K activity in the brain or spinal cord of a patient, the method comprising administering to said patient a compound or composition of the invention.

[0083] In another embodiment, the invention comprises a method of treating or lessening the severity of a PI3K-mediated condition or disease in the brain or spinal cord of a patient. The term “PI3K-mediated disease”, as used herein means any disease or other deleterious condition in which a PI3K isoform is known to play a role. In one embodiment, the PI3K isoform is PI3K γ . In another embodiment, the PI3K isoform is PI3K α . In a further embodiment, the invention comprises a method of treating a PI3K-mediated disease of the central nervous system. Such conditions include, without limitation, inflammatory diseases, cancer, and autoimmune-related diseases of the central nervous system. Accordingly, the invention provides a method of treating or lessening the severity of a disease or condition selected from a cancer, an autoimmune disease, or an inflammatory disease of the central nervous system of a patient, comprising administering to said patient a compound or composition of the invention.

[0084] In one embodiment, the invention provides a method of treating or lessening the severity of cancers of the brain and spinal cord. Examples of such cancers include, without limitation, high-grade invasive astrocytomas (e.g. anaplastic astrocytoma, glioblastoma multiforme), high-grade invasive astrocytomas, oligodendrogliomas, ependymomas, brain

metastases, carcinomatous/lymphomatous meningitis, primary CNS lymphoma, and metastatic spinal tumors.

[0085] In another embodiment, the invention provides a method of treating or lessening the severity of an inflammatory or autoimmune disease or disorder of the central nervous system. In another embodiment, the invention provides a method of treating or lessening the severity of a symptom of an inflammatory or autoimmune disease or disorder of the central nervous system. In a further embodiment, the invention provides a method of treating neuroinflammation. Such diseases or disorders include, without limitation, multiple sclerosis, transverse myelitis, progressive multifocal leukoencephalopathy, meningitis, encephalitis, myelitis, encephalomyelitis, intracranial or intraspinal abscess, phlebitis or thrombophlebitis of intracranial venous sinuses, stroke, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, Pick's Disease, amyotrophic lateral sclerosis, HIV type-I dementia, frontotemporal lobe dementia, traumatic brain or spinal cord injury, autism, or a prion disease.

[0086] Compounds or compositions of the invention may be administered with one or more additional therapeutic agents, wherein the additional therapeutic agent is appropriate for the disease being treated and the additional therapeutic agent is administered together with a compound or composition of the invention as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional therapeutic agent may be administered at the same time as a compound of the invention or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[0087] Non-limiting examples of chemotherapeutic agents or other anti-proliferative agents that may be combined with the compounds of this invention include taxanes, aromatase inhibitors, anthracyclines, microtubule targeting drugs, topoisomerase poison drugs, targeted monoclonal or polyclonal antibodies, inhibitors of a molecular target or enzyme (e.g., a kinase inhibitor), or cytidine analogues. In one embodiment, the additional chemotherapeutic agent is amsacrine, anastrozole, asparaginase, Avastin™ (bevacizumab) azathioprine, bicalutamide, bleomycin, camptothecin, carmustine, chlorambucil, cyclophosphamide, cytarabine (araC), daunorubicin, dactinomycin, doxorubicin (adriamycin),

epirubicin, epothilone, etoposide, exemestane, fludarabine, 5-fluorouracil (5-FU), flutamide, Gemzar™ (gemcitabine), Gleevec™ (imatinib), Herceptin™ (trastuzumab), idarubicin, ifosfamide, an interferon, an interleukin, irinotecan, letrozole, leuprolide, lomustine, lovastatin, mechlorethamine, megestrol, melphalan, 6-mercaptopurine, methotrexate (MTX), minosine, mitomycin, mitoxantrone, navelbine, nocodazole, platinum derivatives such as cisplatin, carboplatin and oxaliplatin, raloxifene, tamoxifen, Taxotere™ (docetaxel), Taxol™ (paclitaxel), teniposide, topotecan, tumor necrosis factor (TNF), vinblastin, vincristin, vindesine, vinorelbine, or Zoladex™ (goserelin). Another chemotherapeutic agent can also be a cytokine such as G-CSF (granulocyte colony stimulating factor). In yet another embodiment, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with surgery, radiation therapy, or with standard chemotherapy combinations such as, but not restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, adriamycin and 5-fluorouracil), AC (adriamycin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (adriamycin, cyclophosphamide, and paclitaxel), or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

[0088] Additional therapeutic agents also include those useful for treating multiple sclerosis (MS), such as, for example, beta interferon (e.g., Avonex® and Rebif®), glatiramer (Copaxone®), Tysabri® (natalizumab), Betaseron® (IFN-beta), and mitoxantrone.

[0089] The invention provides a method of inhibiting PI3K kinase activity in a biological sample that includes contacting the biological sample with a compound or composition of the invention. The term “biological sample,” as used herein, means a sample outside a living organism and includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of kinase activity, particularly PI3K kinase activity, in a biological sample is useful for a variety of purposes known to one of skill in the art. Examples of such purposes include, but are not limited to, biological specimen storage

and biological assays. In one embodiment, the method of inhibiting PI3K kinase activity in a biological sample is limited to non-therapeutic methods.

Preparation of Compounds of the Invention

[0090] As used herein, all abbreviations, symbols and conventions are consistent with those used in the contemporary scientific literature. See, e.g., Janet S. Dodd, ed., *The ACS Style Guide: A Manual for Authors and Editors*, 2nd Ed., Washington, D.C.: American Chemical Society, 1997. The following definitions describe terms and abbreviations used herein:

ATP	adenosine triphosphate
Boc	t-butoxycarbonyl
Brine	a saturated NaCl solution in water
DCM	dichloromethane
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	methylsulfoxide
DTT	dithiothreitol
ESMS	electrospray mass spectrometry
Et ₂ O	ethyl ether
EtOAc	ethyl acetate
EtOH	ethyl alcohol
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
Me	methyl
MeOH	methanol
MTBE	methyl <i>t</i> -butyl ether

MC	methyl cellulose
NIS	N-iodosuccinimide
NMP	N-methylpyrrolidine
PBS	phosphate buffered saline
Ph	phenyl
RT or rt	room temperature
tBu	tertiary butyl
TCA	trichloroacetic acid
THF	tetrahydrofuran
TEA	triethylamine
TFA	trifluoroacetic acid

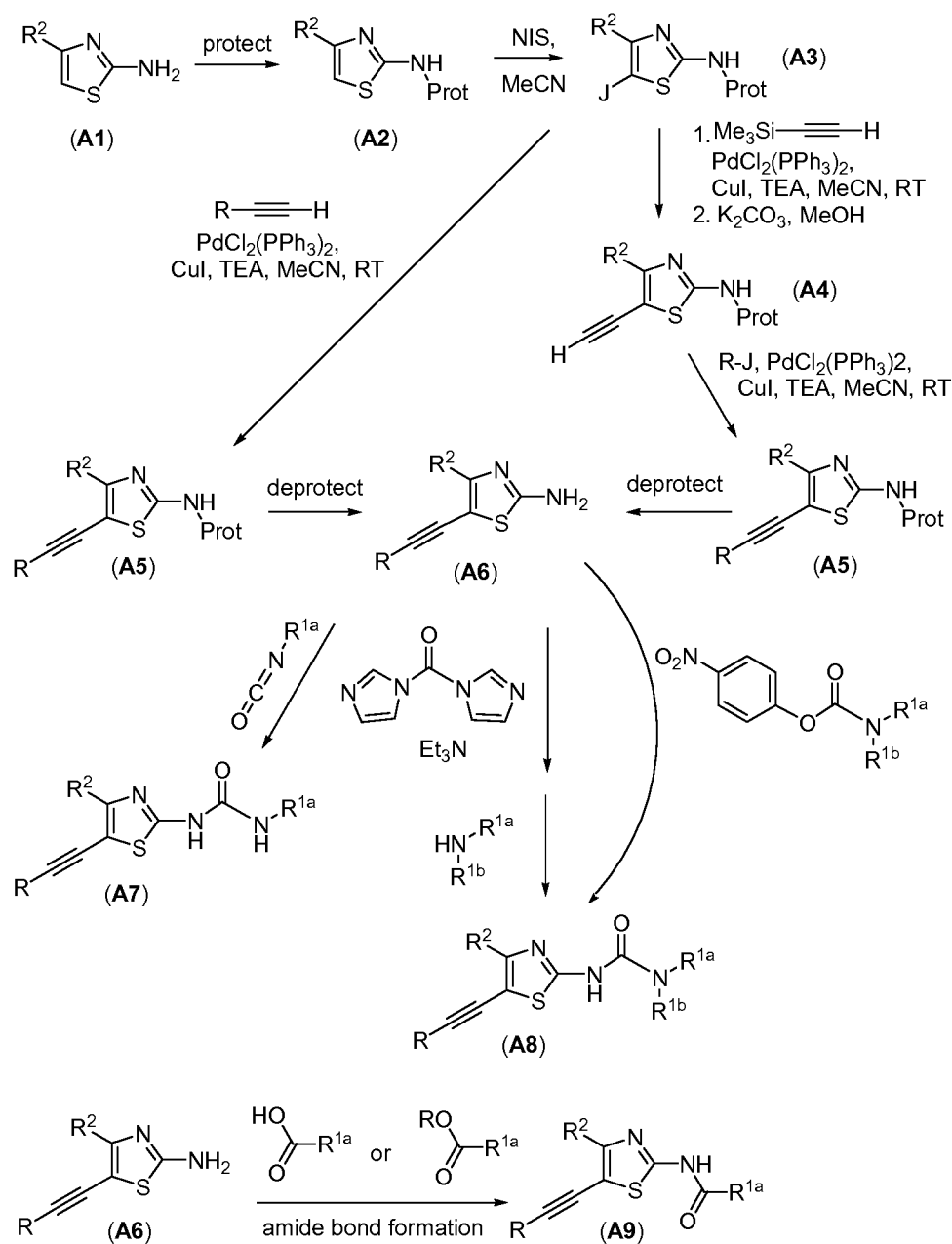
General Synthetic Procedures

[0091] In general, the compounds of this invention may be prepared by methods described herein or by other methods known to those skilled in the art.

Example 1. General preparation of the compounds of formula **I**

[0092] The preparation of compounds of formula **I**, wherein R^1 is $-C(O)R^{1a}$ or $-C(O)N(R^{1a})_2$, is shown in Scheme 1. Accordingly, the amine a compound of formula **A1**, where R^2 is as defined for a compound of formula **I**, is protected to form a compound of formula **A2**. Commonly used protecting groups are disclosed in Greene and Wuts, *Protective Groups In Organic Synthesis, 3rd Edition* (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. Examples of nitrogen protecting groups include acyl, aroyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-

methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like, arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz). Subsequent reaction with N-iodosuccinamide in acetonitrile produces a compound of formula **A3** (where J is iodo). The iodothiazole of formula **A3** can be reacted with an optionally substituted phenyl or heteroaryl acetylene (e.g., R is phenyl or 5-6 membered heteroaryl) under Sonogashira coupling conditions ($\text{PdCl}_2(\text{PPh}_3)_2$ / CuI / triethylamine / acetonitrile) to produce a compound of formula **A5**. See Chinchilla et al., *Chemical Reviews* 107(3): 874, 2007 for a review of the Sonogashira coupling. Compounds of formula **A5** can also be prepared by (i) reacting compounds of formula **A3** with trimethylsilylacetylene under Sonogashira conditions to produce a compound of formula **A4**, (ii) removal of the trimethylsilyl group, and (iii) reacting the resulting terminal alkyne with an aryl or heteroaryl iodide under Sonogashira conditions. Removal of the amine protecting group from a compound of formula **A5** produces a compound of formula **A6**. The primary amine of a compound of formula **A3** can be used to form ureas such as compounds of formulae **A7** and **A8**, wherein R^{1a} and R^{1b} are as defined for a compound of formula **I**. The primary amine of a compound of formula **A6** can also be reacted with esters or carboxylic acids (through their activated esters) by methods known to those skilled in the art to form compounds having the formula **A9**.



Scheme 1

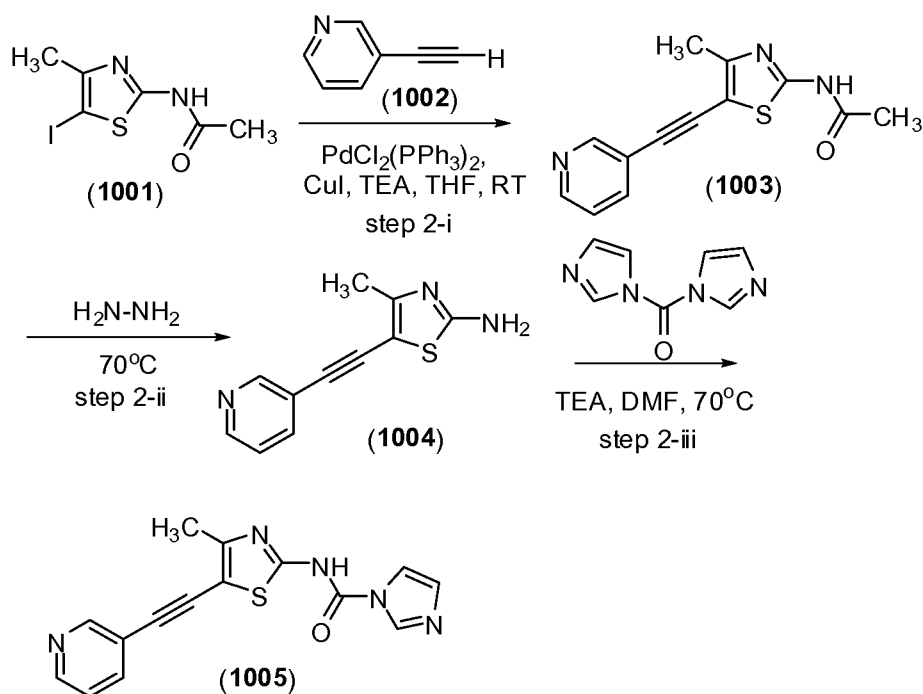
Example 2. Preparation of 3-*N*-(4-methyl-5-(2-(pyridin-3-yl)ethynyl)thiazol-2-yl)-1*H*-imidazole-1-carboxamide (compound **1005**)

[0093] *N*-(5-iodo-4-methylthiazol-2-yl)acetamide (compound **1001**) was prepared according to the procedure of *J. Org. Chem.* 30(4): 1101-1104, 1965. As shown in step 2-i of

Scheme 2, compound **1001** (500 mg, 1.77 mmol) and 3-ethynylpyridine (228 mg, 2.22 mmol) were stirred in 5 mL of THF. After purging the solution with nitrogen gas, CuI (34 mg, 0.177 mmol) and bis(triphenylphosphine)palladium(II) chloride (124 mg, 0.177 mmol) were added, followed by the addition of triethylamine (538 mg, 5.32 mmol). The reaction mixture was stirred at RT for 1.5 hours. The reaction mixture was filtered and the volatiles were removed under reduced pressure to produce *N*-(4-methyl-5-(pyridin-3-ylethynyl)thiazol-2-yl)acetamide (compound **1003**, 300 mg, 77% yield): ¹H-NMR (DMSO-d₆) δ 12.43 (s, 1H), 8.74 (s, 1H), 8.57 (d, J = 2.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 4.8, 7.9 Hz, 1H), 8.57 (d, J = 2.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 4.8, 7.9 Hz, 1H), 2.41 (s, 3H), and 2.16 (s, 3H) ppm.

[0094] As shown in step 2-ii of Scheme 2, compound **1003** (400 mg, 1.56 mmol) was stirred in hydrazine hydrate at 70°C for 20 minutes. Water was added and the resulting precipitate was collected by filtration, washed with water, and dried under high vacuum to produce 4-methyl-5-(pyridin-3-ylethynyl)thiazol-2-amine (compound **1004**), which was used in subsequent reactions as is.

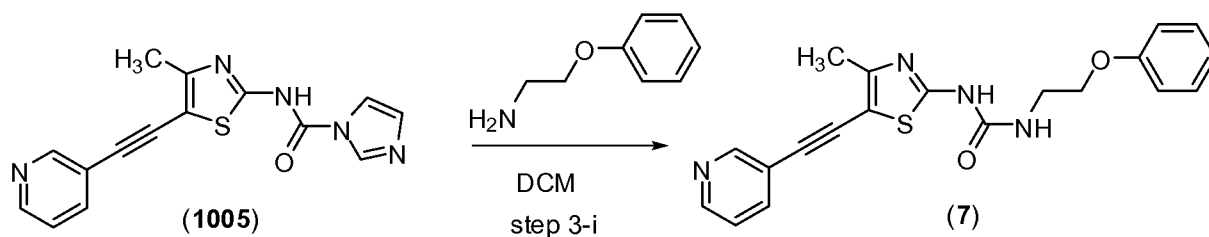
[0095] As shown in step 2-iii of Scheme 2, compound **1004** (91 mg, 0.423 mmol), 1,1'-carbonyldiimidazole (103 mg, 0.634 mmol), and triethylamine (85.6 mg, 0.845 mmol) were stirred in 2.1 mL of DMF at 60°C for 2 hours. After this time, MTBE was added and the resulting precipitate collected by filtration to produce *N*-(4-methyl-5-(pyridin-3-ylethynyl)thiazol-2-yl)-1*H*-imidazole-1-carboxamide (compound **1005**, 120 mg), which was immediately used in subsequent reactions as is.



Scheme 2

Example 3. Preparation of 1-(4-methyl-5-(2-(pyridin-3-yl)ethynyl)thiazol-2-yl)-3-(2-phenoxyethyl)urea (compound **9**)

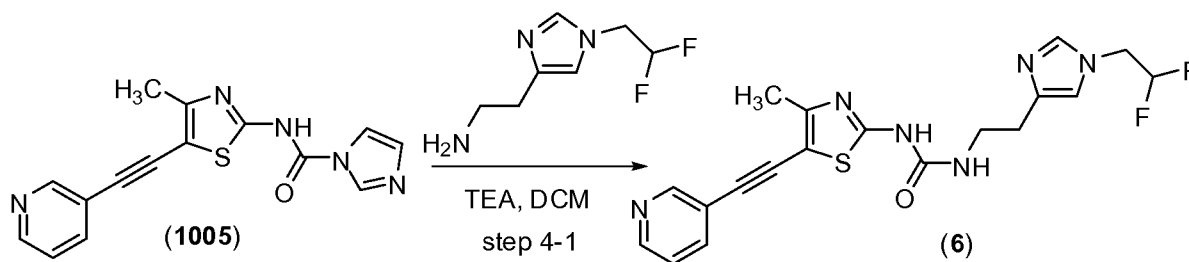
[0096] As shown in step 3-i of Scheme 3, compound **1005** (25 mg, 0.08 mmol) in 0.40 mL of DCM was reacted with 2-phenoxyethylamine (29 mg, 0.32 mmol, Aldrich Chem. Co. cat. no. 44,840-0). After stirring for 20 hours, the mixture purified by medium pressure silica gel chromatography (20-60% EtOAc/hexanes) to provide 1-(4-methyl-5-(2-(pyridin-3-yl)ethynyl)thiazol-2-yl)-3-(2-phenoxyethyl)urea (compound **9**).



Scheme 3

Example 4. Preparation of 1-(2-(1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)ethyl)-3-(4-methyl-5-(2-(pyridin-3-yl)ethynyl)thiazol-2-yl)urea (compound **8**)

[0097] Intermediate 2-heteroarylethanamines can be prepared according to the procedures set forth in International Patent Application Publication Nos. PCT/EP2004/009586 and PCT/EP2008/059298. As shown in step 4-i of Scheme 4, compound **1005** (25 mg, 0.08 mmol) in 0.40 mL of DCM was treated with triethylamine (82 mg, 0.81 mmol) and 2-(1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)ethanamine (80 mg, 0.32 mmol). After stirring for 20 hours, the reaction mixture was filtered, treated with cold methyl t-butylether, and filtered once more. The filtrate was concentrated under reduced pressure and purified by medium pressure silica gel chromatography (0-10% MeOH/DCM) to provide 1-(2-(1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)ethyl)-3-(4-methyl-5-(2-(pyridin-3-yl)ethynyl)thiazol-2-yl)urea (compound **8**).



Scheme 4

[0098] Table 2 provides analytical characterization data for certain compounds of formula I (blank cells indicate that the test was not performed). Compound numbers in Table 2 correspond to those depicted in Table 1.

Table 2.

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
1	326.2	(DMSO-d ₆): 12.48 (s, 1H), 9.03 (s, 1H), 8.96 (s, 1H), 8.46 (s, 1H), 2.44 (s, 3H), 2.17 (s, 3H) and 0.00 (s, H) ppm
2	258.2	(DMSO-d ₆): 12.43 (s, 1H), 8.74 (s, 1H), 8.57 (d, J = 2.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 4.8, 7.9 Hz, 1H), 2.41 (s, 3H) and 2.16 (s, 3H) ppm
3	258.3	(DMSO-d ₆) δ 12.55 (s, 1H), 8.70 (d, J = 6.4 Hz, 2H), 7.80 (d, J = 6.4 Hz, 2H), 2.46 (s, 3H), 2.18 (s, 3H)

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
4	378.5	(DMSO-d ₆): 12.67 (s, 1H), 9.13 (t, J = 5.9 Hz, 1H), 8.83 (s, 1H), 8.70 (d, J = 4.6 Hz, 1H), 8.62 (d, J = 4.4 Hz, 1H), 8.11 - 8.00 (m, 3H), 7.68 - 7.63 (m, 1H), 7.56 (dd, J = 5.0, 8.0 Hz, 1H), 4.25 (d, J = 6.0 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 2H)
5	392.6	(DMSO-d ₆): 12.52 (s, 1H), 8.93 - 8.89 (m, 1H), 8.79 (d, J = 1.5 Hz, 1H), 8.65 - 8.59 (m, 2H), 8.06 - 7.97 (m, 3H), 7.63 - 7.59 (m, 1H), 7.52 (dd, J = 5.0, 7.9 Hz, 1H), 3.63 (dd, J = 6.6, 12.9 Hz, 2H), 2.81 (t, 2H), 2.42 (s, 3H), 2.37 (s, 1.5H)
6	417.6	(DMSO-d ₆): 10.84 (s, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.55 (dd, J = 1.6, 4.9 Hz, 1H), 8.18 (s, 1H), 7.94 (dt, J = 7.9, 2.5 Hz, 1H), 7.44 (dd, J = 4.9, 7.9 Hz, 1H), 7.20 (s, 1H), 6.72 (s, 1H), 6.64 - 6.37 (m, 1H), 4.60 (dt, J = 2.9, 15.9 Hz, 2H), 3.40 (m, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 2H)
7	379.6	(DMSO-d ₆): 10.83 (s, 1H), 8.78 (d, J = 1.8 Hz, 1H), 8.60 (dd, J = 1.5, 5.0 Hz, 1H), 8.04 (dt, J = 8.0, 2.5 Hz, 1H), 7.53 (dd, J = 5.1, 7.9 Hz, 1H), 7.30 (dd, J = 7.2, 8.7 Hz, 2H), 6.98 - 6.86 (m, 4H), 4.24 - 3.99 (m, 2H), 3.56 - 3.43 (m, 2H), 2.42 (s, 3H), 2.36 (s, 5H)
8	257.4	(DMSO-d ₆): 12.38 (s, 1H), 7.52 (m, 2H), 7.46 - 7.39 (m, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H)
9	272.0	(DMSO-d ₆): 12.7(s,1H), 8.82(m,2H), 7.94(d,2H), 2.86(quar,2H), 2.18(s,3H), 1.259(t,3H)
10	287.2	(DMSO-d ₆): 12.35 (s, 1H), 7.32 (m, 1H), 7.11 - 7.07 (m, 2H), 6.99 - 6.96 (m, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 2.14 (s, 3H)
11	287.2	(DMSO-d ₆): 12.30 (s, 1H), 7.49 - 7.44 (m, 2H), 6.99 - 6.96 (m, 2H), 3.79 (s, 3H), 2.38 (s, 3H), 2.15 (s, 3H)
12	272.2	(DMSO-d ₆): 12.26 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H), 2.14 (s, 3H)
13	263.2	(DMSO-d ₆): 12.33 (s, 1H), 7.88 (dd, J = 1.1, 2.9 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.29 - 7.21 (m, 1H), 2.36 (s, 3H), 2.15 (s, 3H)
14	271.2	(DMSO-d ₆): 12.34 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.34 - 7.20 (m, 3H), 2.44 (s, 3H), 2.36 (s, 3H), 2.17 (s, 3H)
15	271.2	
16	272.2	(DMSO-d ₆): 12.36 (s, 1H), 7.32 - 6.99 (m, 6H), 2.38 (s, 3H), 2.15 (s, 3H)
17	261.2	(DMSO-d ₆): 12.51 (s, 1H), 9.00 (s, 1H), 8.00 (s, 1H), 3.86 (s, 3H), 2.41 (s, 3H), 2.18 (s, 3H)
18	275.2	(DMSO-d ₆): 12.38 (s, 1H), 7.50 - 7.36 (m, 3H), 7.29 - 7.22 (m, 1H), 2.37 (s, 3H), 2.17 (s, 3H)
19	312.0	
20	350.0	
21	395.0	

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
22	435.0	
23	387.0	
24	411.7	(DMSO-d ₆): 10.67 (s, 1H), 8.61 - 8.57 (m, 1H), 7.53 - 7.39 (m, 5H), 6.72 - 6.68 (m, 1H), 3.97 - 3.85 (m, 2H), 3.36 (dd, J = 6.4, 12.5 Hz, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.32 (s, 3H)
25	425.7	(DMSO-d ₆): 10.69 (s, 1H), 7.52 - 7.39 (m, 5H), 6.75 - 6.71 (m, 1H), 4.34 - 4.13 (m, 2H), 3.37 (q, J = 6.0 Hz, 2H), 3.07 (s, 3H), 2.62 (m, 2H), 2.61 (s, H), 2.34 (d, J = 12.9 Hz, 3H)
26	331.4	(methanol-d ₄): 8.77 (s, 1H), 8.08(s, 2H), 3.54(m, 4H), 3.44(t, J = 6 Hz, 2H), 2.52(s, 3H), 1.21(s, J=6.0 Hz, 3H)
27	417.5	(methanol-d ₄): 9.00(s, 1H), 8.77(d, J = 5.4 Hz, 2H), 8.06(d, J=5.5 Hz, 2H), 7.53(s, 1H), 6.1(t, J = 5.1 Hz, 1H), 4.73(t, J=15 Hz, 2H), 3.58(m, 2H), 3.00(m, 2H), 2.50(s, 3H)
28	413.4	
29	317.4	
30	341.3	
31	298.0	
32	341.4	(DMSO-d ₆): 12.82 (s, 1H), 8.85 (d, J = 6.7 Hz, 2H), 8.04 (d, J = 6.6 Hz, 2H), 4.27 (dt, J = 14.3, 8.6 Hz, 2H), 3.98 (dt, J = 15.2, 9.4 Hz, 2H), 3.76 - 3.61 (m, 1H), 2.51 (s, 3H), 1.76 (s, 3H)
33	315.4	(DMSO-d ₆): 12.65 (s, 1H), 8.75 (dd, J = 5.1, 1.4 Hz, 2H), 8.31 (t, J = 5.7 Hz, 1H), 7.82 (d, J = 6.5 Hz, 2H), 4.00 (d, J = 5.8 Hz, 2H), 2.47 (s, 3H), 1.87 (s, 3H)
34	358.4	(DMSO-d ₆): 12.48 (s, 1H), 8.65 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 6.0 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.35 (t, J = 7.3 Hz, 2H), 1.85 (p, J = 7.3 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H)
35	344.4	(DMSO-d ₆): 12.54 (s, 1H), 8.76 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 6.2 Hz, 1H), 3.59 (s, 3H), 2.46 (s, 3H), 2.37 (t, J = 7.4 Hz, 2H), 1.96 - 1.80 (m, 2H)
36	327.3	(DMSO-d ₆): 12.74 (s, 1H), 8.68 (d, J = 6.3 Hz, 2H), 7.88 (s, 1H), 7.67 (d, J = 6.1 Hz, 2H), 4.35 (dd, J = 8.4, 4.1 Hz, 2H), 2.71 (d, J = 10.6 Hz, 1H), 2.44 (s, 3H), 2.40 - 1.79 (m, 4H)
37	379.0	
38	391.0	
39	395.0	
40	407.0	
41	409.0	
42	393.0	
43	357.3	
44	371.4	
45	359.3	

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
46	413.3	
47	345.2	
48	397.3	
49	397.3	
50	364.4	
51	350.5	
52	350.4	
53	399.2	
54	397.4	
55	387.5	
56	303.3	
57	373.5	
58	379.5	
59	392.0	
60	372.0	
61	372.0	
62	358.0	
63	384.0	
64	377.0	
65	328.0	
66	342.0	
67	346.4	(methanol-d ₄): 8.74 (d, J = 5.7 Hz, 2H), 8.00(d, J=6.6 Hz, 2H), 4.37(t, J= 3 Hz, 2H), 3.70(t, J= 3.3 Hz, 2H), 3.46(T, J= 6.6 Hz, 2H), 2.49(s, 3H), 1.57(m, 2H), 0.92(t, J=7.5 Hz, 3H)
68	407.5	
69	357.5	
70	385.5	
71	381.0	
72	395.0	
73	399.0	
74	419.0	
76	404.0	
77	387.0	
78	349.3	
79	391.4	
80	415.5	
81	364.4	(methanol-d ₄): 8.75 (d, J = 6.7 Hz, 1H), 7.99 (d, J = 6.7 Hz, 1H), 7.54 - 7.22 (m, 2H), 4.71 (s, 1H), 4.28 (s, 1H), 2.55 (s, 1H)
82	350.4	(methanol-d ₄): 8.77 (d, J = 6.8 Hz, 1H), 8.25 - 7.94 (m, 1H), 7.45 - 7.25 (m, 1H), 7.12 - 6.91 (m, 1H), 4.84 (s, 1H), 2.54 (s, 2H)

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
84	450.8	(DMSO-d ₆): 10.97 (s, 1H), 9.12 (s, 1H), 7.65 - 7.56 (m, 3H), 7.43 - 7.28 (m, 2H), 7.07 - 7.03 (m, 1H), 6.66 - 6.30 (tt, 1H), 4.82 - 4.71 (td, 2H), 3.49 - 3.38 (m, 2H), 2.89 - 2.85 (t, 2H), 2.36 (s, 3H)
85	416.2	(DMSO-d ₆): 10.89 (s, 1H), 9.12 (s, 1H), 7.56 (s, 1H), 7.52 - 7.39 (m, 5H), 7.03 - 6.99 (m, 1H), 6.66 - 6.48 (tt, 1H), 4.81 - 4.71 (td, 2H), 3.43 (m, 2H), 2.89 - 2.85 (m, 2H), 2.33 (s, 3H)
86	412.4	
87	391.5	
88	399.4	
89	461.5	
90	386.00	(DMSO-d ₆): 11.2(m exch,1H), 8.08(d,2H), 7.92(d,2HH), 7.5(s,1H), 5.7(t,1H). 3.3(dt,2H), 2.4(s,3H), 2.25(t,2H), 1.25(s,9H)
91	360.60	(DMSO-d ₆): 10.9(s, 1H), 8.9(s, 1H), 7.9(s, 1H), 6.75(t, 1H), 3.8(s, 3H), 3.4(m, 2H), 3.3(m, 2H), 3.25(d, 2H), 2.3(s, 3H), 1.0(m, 1H), 0.5(m, 2H), 0.2(m, 2H)
92	416.7	(DMSO-d ₆): 10.62 (s, 1H), 7.06 (m, 2H), 6.97 (d, J = 8.1 Hz, 1H), 6.66 (t, J = 5.4 Hz, 1H), 3.78 (s, 6H), 3.45 (d, J = 5.3 Hz, 2H), 3.28 (dd, J = 11.3, 6.2 Hz, 4H), 2.31 (s, 3H), 1.05 - 0.95 (m, 1H), 0.47 (dd, J = 8.1, 1.8 Hz, 2H), 0.18 (dd, J = 4.8, 1.5 Hz, 2H).
93	386.6	(DMSO-d ₆): 10.76 - 10.59 (s, 1H), 7.35 - 7.27 (m, 1H), 7.07 (dd, J = 8.6, 5.1 Hz, 2H), 6.97 (dd, J = 8.3, 2.5 Hz, 1H), 6.69 (t, J = 5.2 Hz, 1H), 3.78 (s, 3H), 3.45 (d, J = 5.3 Hz, 2H), 3.28 (dd, J = 11.3, 6.2 Hz, 4H), 2.33 (s, 3H), 0.98 (m, 1H), 0.53 - 0.40 (m, 2H), 0.22 - 0.13 (m, 2H)
94	416.7	(DMSO-d ₆): 10.66 (s, 1H), 6.66 (m, 3H), 6.52 (t, J = 2.3 Hz, 1H), 3.76 (s, 6H), 3.46 (m, 2H), 3.34 - 3.22 (m, 4H), 2.33 (s, 3H), 0.99 (m, 1H), 0.50 - 0.42 (m, 2H), 0.21 - 0.14 (m, 2H)
95	408.6	(DMSO-d ₆): 10.76 (s, 1H), 8.97 (dd, J = 10.4 Hz, 2H), 8.22 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.93 (dd, J = 8.7, 1.8 Hz, 1H), 6.70 (t, 1H), 3.47 (m, 2H), 3.27 (m, 4H), 2.40 (s, 3H), 1.01 (m, 1H), 0.52 - 0.43 (m, 2H), 0.19 (m, 2H)
96	417.7	(DMSO-d ₆): 10.66 (s, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 6.66 (t, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.46 (t, J = 5.5 Hz, 2H), 3.34 - 3.23 (m, 4H), 2.33 (s, 3H), 2.31 (s, 1.5H), 1.00 (m, 1H), 0.51 - 0.41 (m, 2H), 0.22 - 0.13 (m, 2H)
97	371.5	
98	370.4	
99	371.5	(methanol-d ₄): 8.73(d, J=6.0HZ,2H), 8.03(d,J-6.0Hz,2H), 3.62(m,1H),3.39-3.30(m,3H), 3.15(m,1H), 2.48(s,3H), 1.15(d,J=6.0 HZ,3H), 0.90(m,1H), 0.49(m,2H), 0.01(m,2H)
100	385.8	

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
101	411.6	
102	393.7	
103	372.7	
104	292.3	(DMSO-d ₆): 12.42 (s, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.3, 2.2 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 2.41 (s, 3H), 2.16 (s, 3H)
105	391.4	(methanol-d ₄): 8.49 (d, J = 2.2 Hz, 1H), 7.90 (dd, J = 8.3, 2.3 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 3.58 (t, J = 5.2 Hz, 2H), 3.43 (t, J = 5.2 Hz, 2H), 2.41 (s, 3H), 1.06 (m, 1H), 0.52 (q, J = 5.8 Hz, 2H), 0.22 (q, J = 4.7 Hz, 2H)
106	391.4	(methanol-d ₄): 8.32 (d, J = 3.0 Hz, 1H), 7.98 (dd, J = 7.7, 1.7 Hz, 1H), 7.40 (dd, J = 7.6, 5.0 Hz, 1H), 3.58 (t, J = 5.3 Hz, 2H), 3.44 (t, J = 5.3 Hz, 2H), 3.35 (s, 2H), 2.44 (s, 3H), 1.06 (m, 1H), 0.52 (dd, J = 12.3, 5.9 Hz, 2H), 0.22 (dd, J = 10.7, 4.6 Hz, 2H)
107	387.4	(DMSO-d ₆): 10.79 (br.s, 1H), 8.40 (br. s, 2H), 7.60 (s, 1H), 6.76 (s, 1H), 3.87 (s, 3H), 3.46 (t, J = 5.2 Hz, 2H), 3.30 (q, J = 5.3 Hz, 2H), 3.26 (d, J = 6.7 Hz, 2H), 2.36 (s, 3H), 1.00 (m, 1H), 0.46 (q, J = 7.4 Hz, 2H), 0.18 (q, J = 4.6 Hz, 2H)
108	388.6	(DMSO-d ₆): 10.72(s, 1H), 8.79(s, 2H), 6.69(t, 1H), 3.97(s, 3H), 3.46(t,2H), 3.29(m, 4H), 2.33(s, 3H), 1.00(m,1H), 0.46(m, 2H), 0.18(m, 2H)
109	387.6	(DMSO-d ₆): 10.79(s, 1H), 8.17(d, 1H), 7.05(dd, 1H), 6.91(s, 1H), 6.70(t, 1H), 3.86(s, 3H), 3.46(t,2H), 3.29(m, 4H), 2.35(s, 3H), 0.99(m,1H), 0.46(m, 2H), 0.18(m, 2H)
110	387.6	
111	435.6	(DMSO-d ₆): 10.75(s, 1H), 8.11(d, 1H), 7.70(d, 1H), 6.70(t, 1H), 4.21(q, 2H), 3.46(t, 2H), 3.29(m, 4H), 2.36(s, 3H), 1.37(t, 3H), 0.98(m,1H), 0.46(m, 2H), 0.18(m, 2H)
112	288.3	(DMSO-d ₆): 12.30 (s, 1H), 8.28 (d, J = 2.8 Hz, 1H), 8.25 (d, J = 1.6 Hz, 1H), 7.47 (t, 1H), 3.89 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H)
113	407.5	(DMSO-d ₆): 11.12 (s, 1H), 9.08 (d, J = 5.2 Hz, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.04 (t, J = 7.1 Hz, 1H), 7.96 (d, J = 5.1 Hz, 1H), 7.95 - 7.85 (m, 1H), 6.92 (t, J = 5.4 Hz, 1H), 3.48 (t, J = 5.5 Hz, 2H), 3.33 (dd, J = 11.0, 5.6 Hz, 2H), 3.27 (d, J = 6.8 Hz, 2H), 2.53 (d, J = 4.1 Hz, 2H), 1.08 - 0.91 (m, 1H), 0.52 - 0.37 (m, 2H), 0.25 - 0.12 (m, 2H)
114	351.3	
115	425.4	(DMSO-d ₆): 10.77 (s,1H), 9.01 (s,1H), 8.93 (s,1H), 8.42 (s,1H), 6.68 (t,1H), 3.46 (m,2H), 3.27 (m,4H), 2.38 (s,3H), 1.00 (m,1H), 0.47 (m,2H), 0.19 (m,2H)

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
116	360.4	(DMSO-d ₆): 10.74 (s, 1H), 7.49 (d, 1H), 6.69 (t, 1H), 6.59 (d, 1H), 3.89 (s, 3H), 3.46 (m, 2H), 3.29 (m, 4H), 2.33 (s, 3H), 0.98 (m, 1H), 0.47 (m, 2H), 0.18 (m, 2H)
117	385.4	
118	371.4	
119	421.4	¹ H NMR (300 MHz, CDCl ₃) d 8.95 (s, 1H), 8.36 - 8.09 (m, 2H), 8.01 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 3.82 - 3.45 (m, 3H), 3.44 - 3.16 (m, 3H), 2.50 (s, 3H), 1.37 - 0.91 (m, 4H), 0.55 (dt, J = 5.4, 4.9 Hz, 2H), 0.35 - 0.09 (m, 2H).
120	401.2	(methanol-d ₄): 8.30 (s, 2H), 7.83 - 7.35 (m, 5H), 3.91 (s, 3H), 3.75 - 3.51 (m, 1H), 3.47 - 3.25 (m, 9H), 3.16 (dd, J = 13.8, 6.6 Hz, 1H), 2.39 (s, 3H), 1.15 (d, J = 6.2 Hz, 3H), 1.10 - 0.92 (m, 1H), 0.61 - 0.42 (m, 2H), 0.34 - 0.13 (m, 2H).
121	422.2	(CDCl ₃): 8.85 (dd, J = 13.3, 1.8 Hz, 2H), 8.22 (d, J = 1.6 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.83 (dd, J = 8.7, 1.8 Hz, 1H), 3.67 (ddd, J = 36.5, 19.9, 16.4 Hz, 2H), 3.47 - 3.08 (m, 3H), 2.51 (s, 3H), 1.23 (t, J = 8.9 Hz, 3H), 1.09 (s, 1H), 0.55 (dt, J = 5.6, 5.1 Hz, 2H), 0.35 - 0.06 (m, 2H).
122	431.3	(methanol-d ₄): 7.83 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.71 - 3.53 (m, 1H), 3.47 - 3.26 (m, 14H), 3.23 - 3.03 (m, 1H), 2.37 (s, 3H), 1.15 (d, J = 6.2 Hz, 3H), 1.11 - 0.94 (m, 1H), 0.51 (dd, J = 8.1, 1.6 Hz, 2H), 0.21 (s, 2H).
123	371.4	
124	401.4	(CDCl ₃): 8.13 (d, J = 5.3 Hz, 1H), 6.91 (d, J = 5.3 Hz, 1H), 6.80 (s, 1H), 3.95 (s, 3H), 3.77 - 3.45 (m, 2H), 3.46 - 3.09 (m, 3H), 2.45 (s, 3H), 1.32 - 0.88 (m, 4H), 0.65 - 0.41 (m, 2H), 0.21 (q, J = 4.8 Hz, 2H).
125	401.4	(CDCl ₃): 8.13 (d, J = 5.3 Hz, 1H), 6.91 (d, J = 5.3 Hz, 1H), 6.80 (s, 1H), 3.95 (s, 3H), 3.77 - 3.45 (m, 2H), 3.46 - 3.09 (m, 3H), 2.45 (s, 3H), 1.32 - 0.88 (m, 4H), 0.65 - 0.41 (m, 2H), 0.21 (q, J = 4.8 Hz, 2H).
126	375.4	(DMSO-d ₆): 10.90 (m, 1H), 8.25 (d, J = 5.2 Hz, 1H), 7.44 (d, J = 5.2 Hz, 1H), 7.33 (s, 1H), 6.75 (m, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.30 (t, J = 5.0 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.34 (s, 3H), 1.13 - 0.86 (m, 1H), 0.55 - 0.40 (m, 2H), 0.18 (q, J = 4.9 Hz, 2H).
127	357.3	
128	407.4	(DMSO-d ₆): 10.87 (m, 1H), 9.05 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 12.2, 8.1 Hz, 2H), 7.85 (t, J = 7.1 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 5.4 Hz, 1H), 3.47 (t, J = 5.5 Hz, 2H), 3.40 - 3.29 (m, 2H), 3.27 (d, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.12 - 0.85 (m, 1H), 0.58 - 0.35 (m, 2H), 0.33 - 0.05 (m, 2H).

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
129	375.4	(DMSO-d ₆): 10.91 (s, 1H), 8.73 (s, 2H), 7.7 (m, 2H), 6.76 (m, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.40 - 3.28 (m, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.37 (s, 3H), 0.99 (m, 1H), 0.53 - 0.40 (m, 2H), 0.18 (q, J = 4.9 Hz, 2H).
130	408.4	(DMSO-d ₆): 10.83 (m, 1H), 9.20 (m, 1H), 8.72 (s, 1H), 8.52 (d, J = 8.2 Hz, 1H), 7.76 (m, 1H), 6.78 (t, J = 5.3 Hz, 1H), 3.47 (t, J = 5.5 Hz, 2H), 3.31 (dd, J = 11.1, 5.5 Hz, 2H), 3.27 (d, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.12 - 0.90 (m, 1H), 0.55 - 0.39 (m, 2H), 0.18 (dd, J = 6.1, 4.6 Hz, 2H).
131	409.4	(DMSO-d ₆): 10.74 (m, 1H), 9.0 (m, 2H), 8.52 (s, 1H), 7.79 - 7.25 (m, 2H), 6.64 (s, 1H), 3.34 - 3.25 (m, 2H), 3.14 (dd, J = 10.7, 5.3 Hz, 2H), 3.09 (d, J = 6.8 Hz, 2H), 2.25 (s, 3H), 0.94 - 0.66 (m, 1H), 0.39 - 0.23 (m, 2H), 0.08 - -0.02 (m, 2H).
132	414.4	(DMSO-d ₆): 10.68 (s, 1H), 8.49 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 6.74 (t, J = 5.3 Hz, 1H), 3.46 (t, J = 5.4 Hz, 2H), 3.30 (dd, J = 10.0, 4.4 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.33 (s, 3H), 2.11 (s, 3H), 1.07 - 0.91 (m, 1H), 0.54 - 0.40 (m, 2H), 0.24 - 0.14 (m, 2H).
133	387.4	(DMSO-d ₆): 10.83 (s, 1H), 7.73 (dd, J = 18.1, 7.2 Hz, 1H), 6.48 (d, J = 1.7 Hz, 1H), 6.24 (dt, J = 16.7, 8.3 Hz, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.41 (s, 3H), 3.30 (dd, J = 10.8, 5.4 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.34 (s, 3H), 1.17 - 0.81 (m, 1H), 0.58 - 0.37 (m, 2H), 0.26 - 0.10 (m, 2H).
134	387.3	(DMSO-d ₆): 10.80 (s, 1H), 7.72 (dd, J = 8.3, 7.4 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.83 (t, J = 8.3 Hz, 1H), 3.87 (s, 3H), 3.46 (t, J = 5.5 Hz, 2H), 3.37 - 3.28 (m, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.35 (s, 3H), 1.10 - 0.90 (m, 1H), 0.65 - 0.37 (m, 2H), 0.25 - 0.08 (m, 2H).
135	418.3	(DMSO-d ₆): 10.73 (s, 1H), 7.96 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.46 (t, J = 5.5 Hz, 2H), 3.39 - 3.29 (m, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.33 (s, 3H), 0.97 (m, 1H), 0.54 - 0.37 (m, 2H), 0.24 - 0.10 (m, 2H).
136	359.4	(methanol-d ₄): 8.73 (d, J = 6.0 Hz, 2H), 8.03 (d, J = 6.00 Hz, 2H), 3.50-3.14 (m, 5H), 2.48s, 3H), 1.57 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H), 0.93 (t, J = 6.0 Hz, 3H)
137	389.4	
138	417.5	
139	409.4	(DMSO-d ₆): 10.98 (s, 1H), 8.43 (s, 1H), 7.53 (s, 1H), 6.84 (t, J = 5.1 Hz, 1H), 3.47 (t, J = 5.4 Hz, 2H), 3.32 (t, J = 5.3 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.13 - 0.93 (m, 1H), 0.61 - 0.41 (m, 2H), 0.31 - 0.13 (m, 2H).

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
140	391.4	(DMSO-d ₆): 10.82 (s, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.19 (dd, J = 9.4, 1.9 Hz, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.30 (dd, J = 10.3, 4.8 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.36 (s, 3H), 1.12 - 0.88 (m, 1H), 0.52 - 0.40 (m, 2H), 0.23 - 0.12 (m, 2H).
141	409.4	(DMSO-d ₆): 10.82 (s, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.19 (dd, J = 9.4, 1.9 Hz, 1H), 6.74 (t, J = 5.3 Hz, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.37 - 3.28 (m, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.34 (s, 3H), 1.11 - 0.87 (m, 1H), 0.58 - 0.35 (m, 2H), 0.21 - 0.10 (m, 2H).
142	396.4	(DMSO-d ₆): 11.94 (s, 1H), 8.17 (s, 1H), 7.55 (d, J = 3.3 Hz, 1H), 6.74 (s, 1H), 6.52 (s, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.39 - 3.15 (m, 4H), 2.31 (s, 3H), 0.97 (m, 1H), 0.58 - 0.36 (m, 2H), 0.29 - 0.13 (m, 2H).
143	409.4	(DMSO-d ₆): 10.89 (s, 1H), 8.53 (s, 1H), 7.82 (d, J = 5.2 Hz, 1H), 6.70 (s, 1H), 3.46 (t, J = 5.4 Hz, 2H), 3.31 (m, 2H), 3.26 (d, J = 6.8 Hz, 2H), 2.38 (s, 3H), 1.17 - 0.85 (m, 1H), 0.57 - 0.35 (m, 2H), 0.18 (d, J = 4.9 Hz, 2H).
144	396.4	(DMSO-d ₆): 10.86 (s, 1H), 9.23 (s, 1H), 8.26 (m, 2H), 7.99 (s, 2H), 6.81 (t, J = 5.4 Hz, 1H), 3.46 - 3.11 (m, 6H), 2.32 (s, 3H), 0.97 (dt, J = 14.7, 7.1 Hz, 1H), 0.58 - 0.30 (m, 2H), 0.29 - 0.11 (m, 2H).
145	317.2	
146	434.4	(DMSO-d ₆): 12.34 (s, 1H), 10.72 (m, 1H), 6.75 (t, 1H), 3.46 (t, J = 5.4 Hz, 1H), 3.27 (m, 1H), 3.26 (d, J = 6.8 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 0.97 (dd, J = 11.5, 7.4 Hz, 1H), 0.46 (dt, J = 5.6, 5.1 Hz, 2H), 0.29 - 0.13 (m, 2H).
147	389.4	(methanol-d ₄): 8.41(brs,1H), 8.35(brs,1H), 7.84(d, J= 3.0 HZ,1H), 3.98(s,3H), 3.30-3.60(m,4H), 3.16(m,1H), 2.41(s,3H), 1.60(m,2H), 1.15(d,J=6.0 Hz,3H), 0.94(t,J= 6 HZ,3H).
148	347.2	
149	361.3	(methanol-d ₄): 8.62 (s, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.28 (dd, J = 2.6, 1.4 Hz, 1H), 3.58 (d, J = 4.0 Hz, 1H), 3.41 (dd, J = 13.7, 3.8 Hz, 1H), 3.13 (dd, J = 13.7, 7.4 Hz, 1H), 1.66 - 1.37 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).
150	398.3	(DMSO-d ₆): 7.96(s,2H), 7.46(s,2H), 7.04 (s,1H),3.52(m,2H), 3.14(t,6.2HZ,2H), 2.81(q,J= 7.5 HZ,2H), 2.43(s,3H), 1.22(t, J= 7.5 HZ,3H).
151	428.3	
152	381	
153	407.3	
154	430.3	
155	392	

Compound No.	ESMS (M+H)	¹ H NMR (300 MHz, unless indicated otherwise) NMR peaks given as δ values
156	451.3	(DMSO-d ₆): 8.58 (d, J = 4.9 Hz, 1H), 7.77 (s, 1H), 7.46 (d, J = 6.0 Hz, 1H), 6.77 (s, 1H), 6.33 (m, 1H), 4.48 (dd, J = 16.0, 12.9 Hz, 2H), 3.39 (m, 2H), 2.64 (t, J = 7.0 Hz, 1H), 2.36 (s, 1H).
157	440	
158	440	
159	414	
160	415.3	(CDCl ₃): 8.57 (d, J = 6.0 Hz, 2H), 7.42 (s, 1H), 7.31 (d, J = 6.0 Hz, 2H), 3.94 (q, J = 7.3 Hz, 2H), 3.63 (m, 2H), 2.78 (m, 2H), 2.41 (s, 3H), 1.42 (t, J = 7.3 Hz, 3H).
161	429	(DMSO-d ₆): 8.55 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 5.9 Hz, 1H), 3.86 (q, J = 7.2 Hz, 1H), 2.65 - 2.50 (m, 2H), 2.30 (d, J = 5.0 Hz, 3H), 1.42 - 1.01 (m, 2H).
162	367.5	(methanol-d ₄): 8.52 (dd, J = 4.7, 1.5 Hz, 1H), 7.62 (s, 1H), 7.46 (m, 3H), 4.29 (s, 2H), 4.14 (q, J = 7.3 Hz, 2H), 2.48 (s, 3H), 1.42 (t, J = 7.3 Hz, 2H).
163	416.4	(CDCl ₃): 8.57(d, J = 6.0 Hz,2H), 7.30(d, J= 6.0 Hz,2H), 3.54-3.69 (m,10H), 2.59 (t, J = 6.0 Hz,2H), 2.49 (m,4H), 2.42 (s,3H)
164	440	
165	481	
166	420	

Biological assay of compounds of the invention

Example 28. PI3K Inhibition Assay

[0099] Using a Biomek FX from Beckman Coulter, 1.5 μ L of each of ten 2.5-fold serial dilutions of a compound of the invention in 100% DMSO was added to an individual well (hereafter, “test well”) in a 96 well polystyrene plate [Corning, Costar Item No. 3697]. One test well also contained 1.5 μ L of DMSO with no compound. Another well contained an inhibitor in DMSO at a concentration known to completely inhibit the enzyme, (hereafter “background well”). Using a Titertek Multidrop, 50 μ L of Reaction Mix [100 mM HEPES pH 7.5, 50 mM NaCl, 10 mM DTT, 0.2 mg/mL BSA, 60 μ M phosphatidylinositol(4,5)bisphosphate diC16 (PI(4,5)P₂; Avanti Polar Lipids, Cat. No. 840046P) and PI3K isoform of interest (see Table 3 for isoform concentrations)] was added to each well. To initiate the reaction, 50 μ L of ATP Mix [20 mM MgCl₂, 6 μ M ATP (100

$\mu\text{Ci}/\mu\text{mole } ^{33}\text{P-ATP})$] was added each well, followed by incubating the wells for 30 min. at 25 °C. Final concentrations in each well were 50 mM HEPES 7.5, 10 mM MgCl_2 , 25 mM NaCl, 5 mM DTT, 0.1 mg/mL BSA, 30 μM $\text{PI}(4,5)\text{P}_2$, 3 μM ATP, and the PI3K isoform of interest (see Table 3). Final compound concentrations in each well ranged from 10 μM to 1 nM.

Table 3

PI3K Isoform Concentrations	PI3K- α	PI3K- β	PI3K- γ	PI3K- δ
Enzyme concentration in Reaction Mix	4nM	20nM	4nM	4nM
Final enzyme concentration	2nM	10nM	2nM	2nM

[00100] After incubation, the reactions in each well were quenched by addition of 50 μL of stop solution [30% TCA/Water, 10mM ATP]. Each quenched reaction mixture was then transferred to a 96 well glass fiber filter plate [Corning, Costar Item No. 3511]. The plate was vacuum-filtered and washed three times with 150 μL of 5% TCA/water in a modified Bio-Tek Instruments ELX-405 Auto Plate Washer. 50 μL of scintillation fluid was added to each well and the plate read on a Perkin-Elmer TopCountTM NXT liquid scintillation counter to obtain ^{33}P -counts representing inhibition values.

[00101] The value for the background well was subtracted from the value obtained for each test well and the data were fit to the competitive tight binding K_i equation described by Morrison and Stone, *Comments Mol. Cell Biophys.* 2: 347-368, 1985.

[00102] Each of compounds **1** to **166** had a K_i of less than 0.25 micromolar for the inhibition of PI3K γ . Each of compounds **3-7**, **14**, **19-23**, **26-27**, **29**, **31**, **33**, **37-38**, **41-50**, **52**, **54-62**, **64-73**, **75**, **77-78**, **86-87**, **90**, **92**, **95-96**, **99**, **106-109**, **112-113**, **117**, **119-122**, **124-127**, **129-131**, **135-140**, **142-145**, **147-158**, **160-162**, and **164-165** had a K_i of less than 0.050 micromolar for the inhibition of PI3K γ .

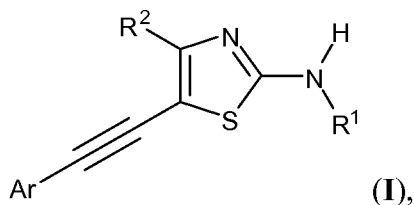
[00103] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes

and modifications may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

What is claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar is a phenyl ring or a 5-10 membered monocyclic or fused bicyclic heteroaryl ring having up to 2 atoms selected from nitrogen, wherein each ring is optionally substituted with up to 3 substituents independently selected from fluoro, chloro, C₁₋₄aliphatic, C₃₋₆cycloaliphatic, -OC₁₋₄aliphatic, -OC₃₋₄cycloaliphatic, -N(J^{R1})C(O)C₁₋₄aliphatic, or N(J^{R1})₂, wherein each of said aliphatic or cycloaliphatic is optionally substituted with up to 3 occurrences of fluoro;

R¹ is selected from -C(O)R^{1a}, -C(O)OR^{1a}, or -C(O)N(R^{1a})(R^{1b}), wherein

R^{1a} is C₁₋₄ aliphatic, C₃₋₆ cycloaliphatic, or C₅₋₁₀ heterocyclic having up to 2 atoms selected from oxygen, sulfur, or nitrogen, wherein R^{1a} is optionally substituted with 1, 2, 3, or 4, occurrences of J^R;

each J^R is independently fluoro, oxo, -C(O)J^{R1}, -C(O)N(J^{R1})₂, -C(O)O(J^{R1}), -N(J^{R1})C(O)J^{R1}, -OJ^{R1}, -SJ^{R1}, -S(O)J^{R1}, phenyl or a 5-10 membered heteroaryl or heterocyclyl ring having up to 2 atoms selected from nitrogen, oxygen, or sulfur, wherein said phenyl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 J^{R2} groups;

R^{1b} is, independently, hydrogen, C₁₋₄aliphatic, C₃₋₆cycloaliphatic; or

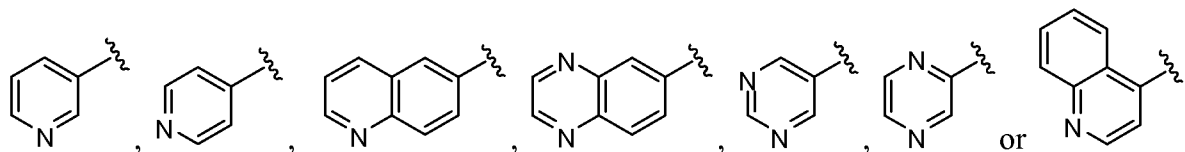
R^{1a} and R^{1b}, together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, wherein said heterocyclic ring optionally comprises one additional heteroatom selected from nitrogen and oxygen, and wherein said heterocyclic ring is optionally substituted with 1 or 2 J^{R2} groups;

R² is C₁₋₄aliphatic optionally substituted with 1, 2, or 3 J^{R2} groups;

each J^{R1} is independently selected from hydrogen, C_{1-4} aliphatic, C_{3-6} cycloaliphatic, phenyl, benzyl, or 5-6 membered heteroaryl ring having up to two atom selected from nitrogen, oxygen, or sulfur, wherein each of said C_{1-4} aliphatic, phenyl, benzyl, or heteroaryl is optionally substituted with up to three J^{R2} groups; and
 each J^{R2} is, independently, selected from chloro, fluoro, -CN, -NO₂, oxo, C_{1-4} alkyl, C_{3-6} cycloalkyl, -OH, -OC₁₋₄alkyl, -OPhenyl, or -OCH₂Phenyl, wherein each of said alkyl, cycloalkyl or phenyl is optionall substituted with up to 3 fluoro groups.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar is an optionally substituted 5-10 membered heteroaryl ring.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein Ar is an optionally substituted group selected from:



4. The compound according to claim 3, wherein Ar is substituted with 1 to 2 groups independently selected from -OCH₃, -OCF₃, -OCHF₂, Cl, F, or CF₃.

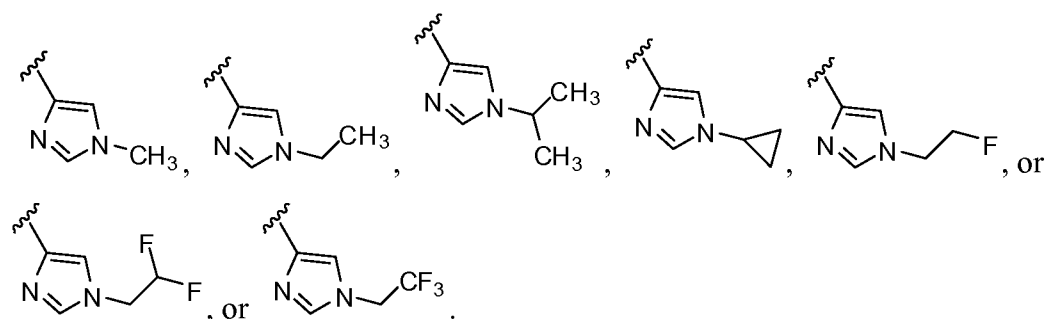
5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is CH₃.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is -C(O)N(R^{1a})(R^{1b}).

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is hydrogen.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-\text{CH}_2\text{CH}(\text{R})-\text{J}^{\text{R}}$, wherein R is hydrogen or methyl and J^{R} is $-\text{OJ}^{\text{R}1}$ or a 5-membered heteroaryl having 2 nitrogen atoms and substituted with C_{1-3} alkyl or cyclopropyl, each optionally substituted with up to 3 fluoro groups.

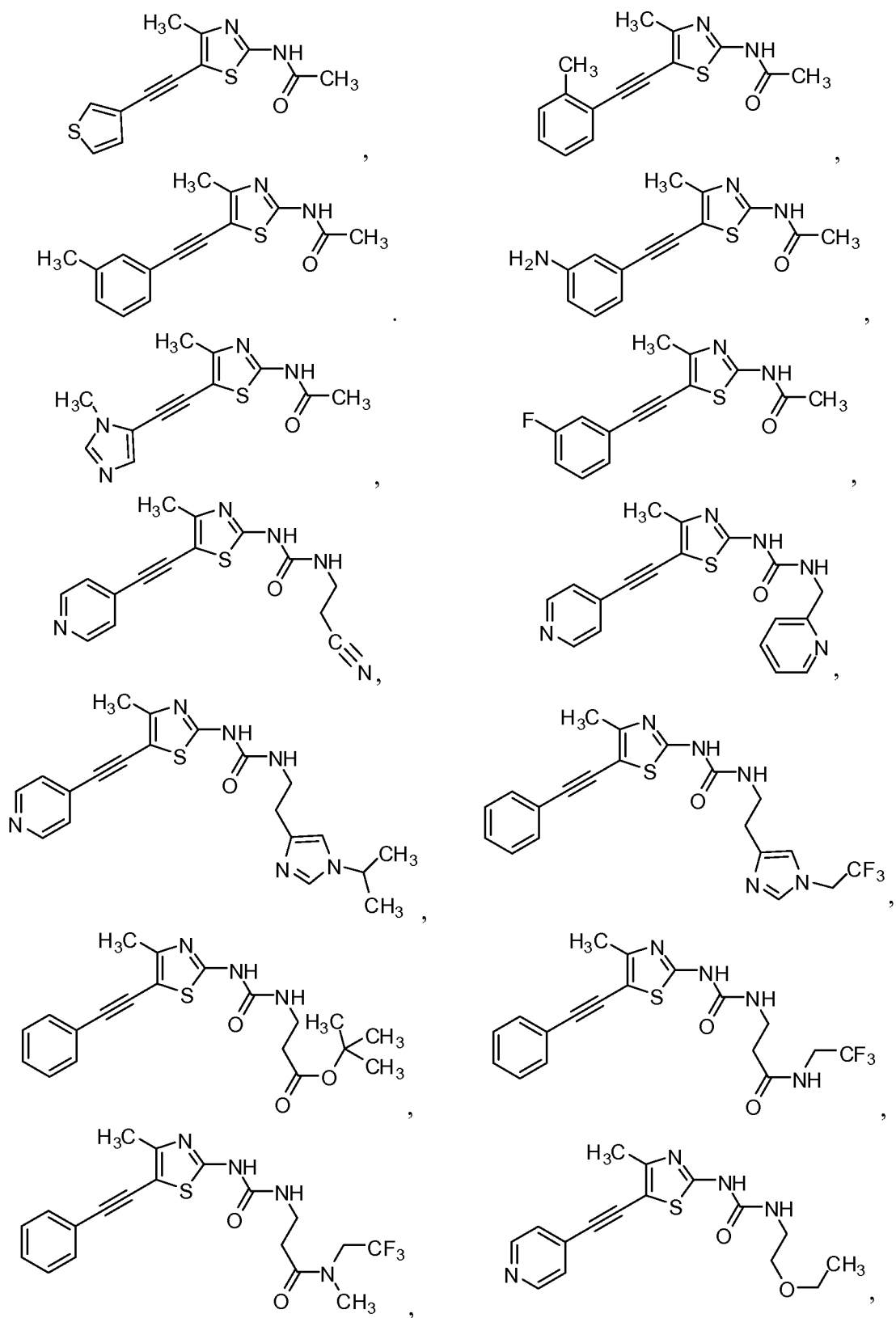
9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein J^{R} is

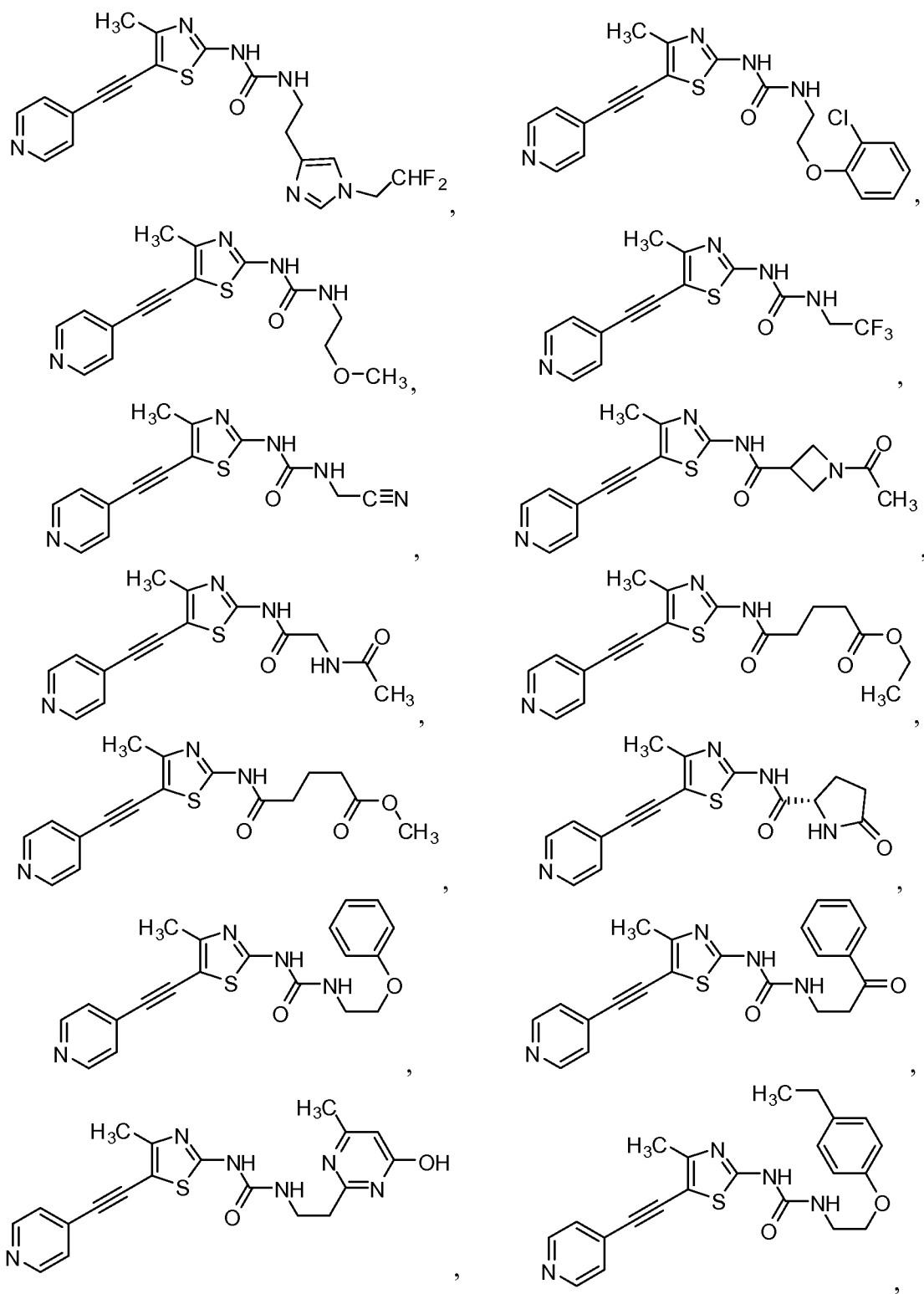


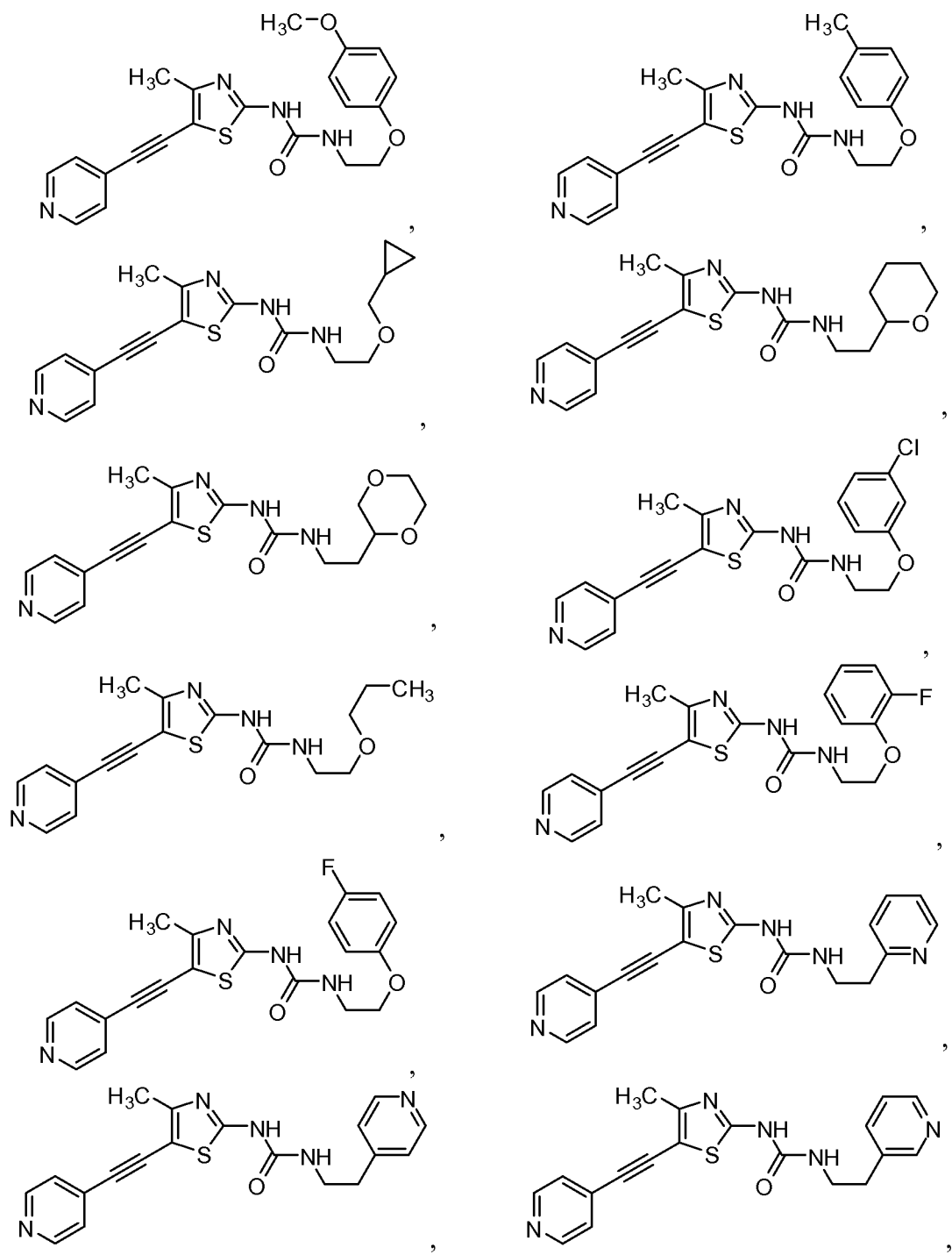
10. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein J^{R} is $-\text{OJ}^{\text{R}1}$ and $\text{J}^{\text{R}1}$ is C_{1-4} alkyl, optionally substituted with cyclopropyl or up to three fluoro or methyl groups.

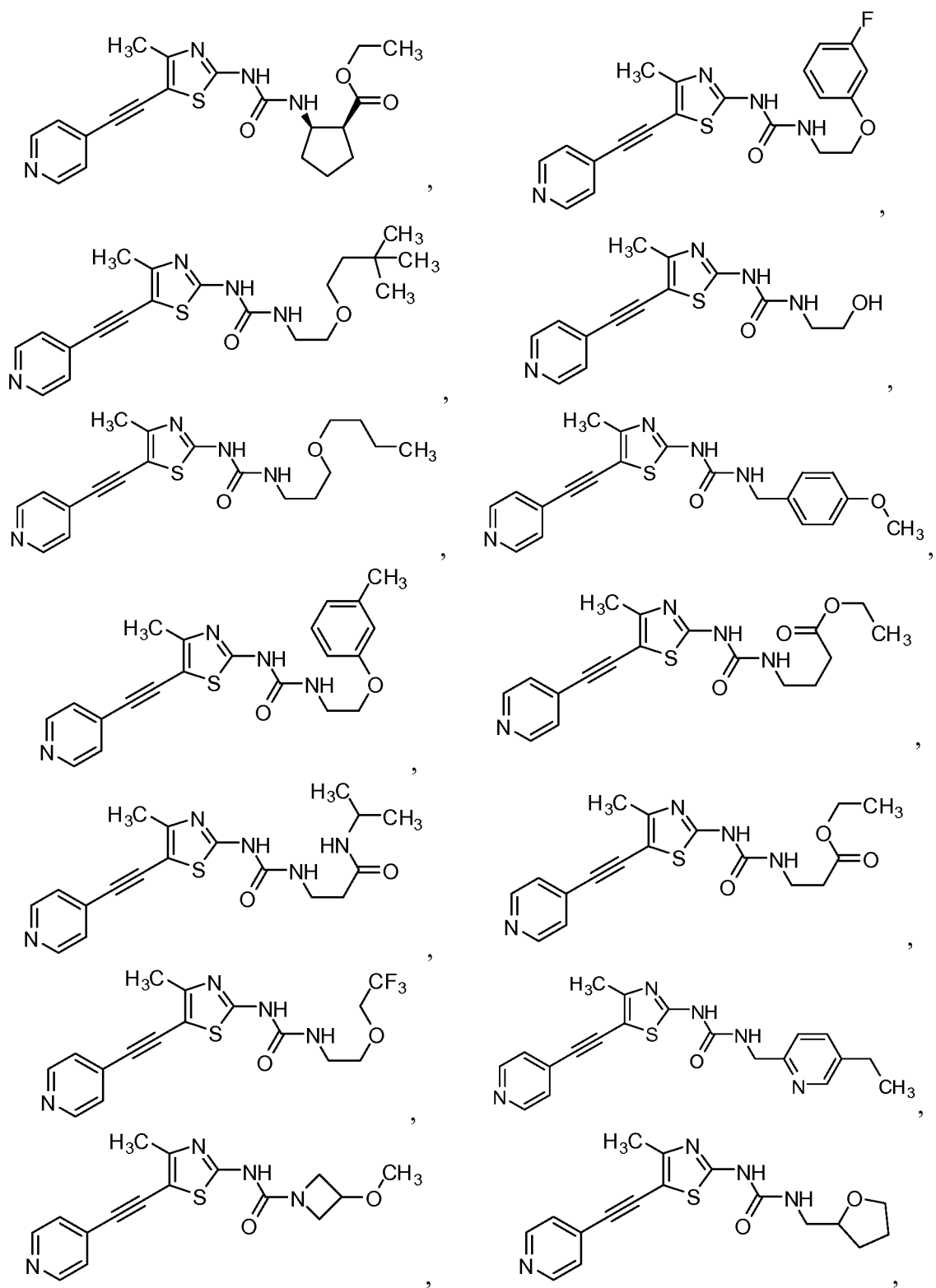
11. The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein $\text{J}^{\text{R}1}$ is $-\text{CH}_2$ -cyclopropyl.

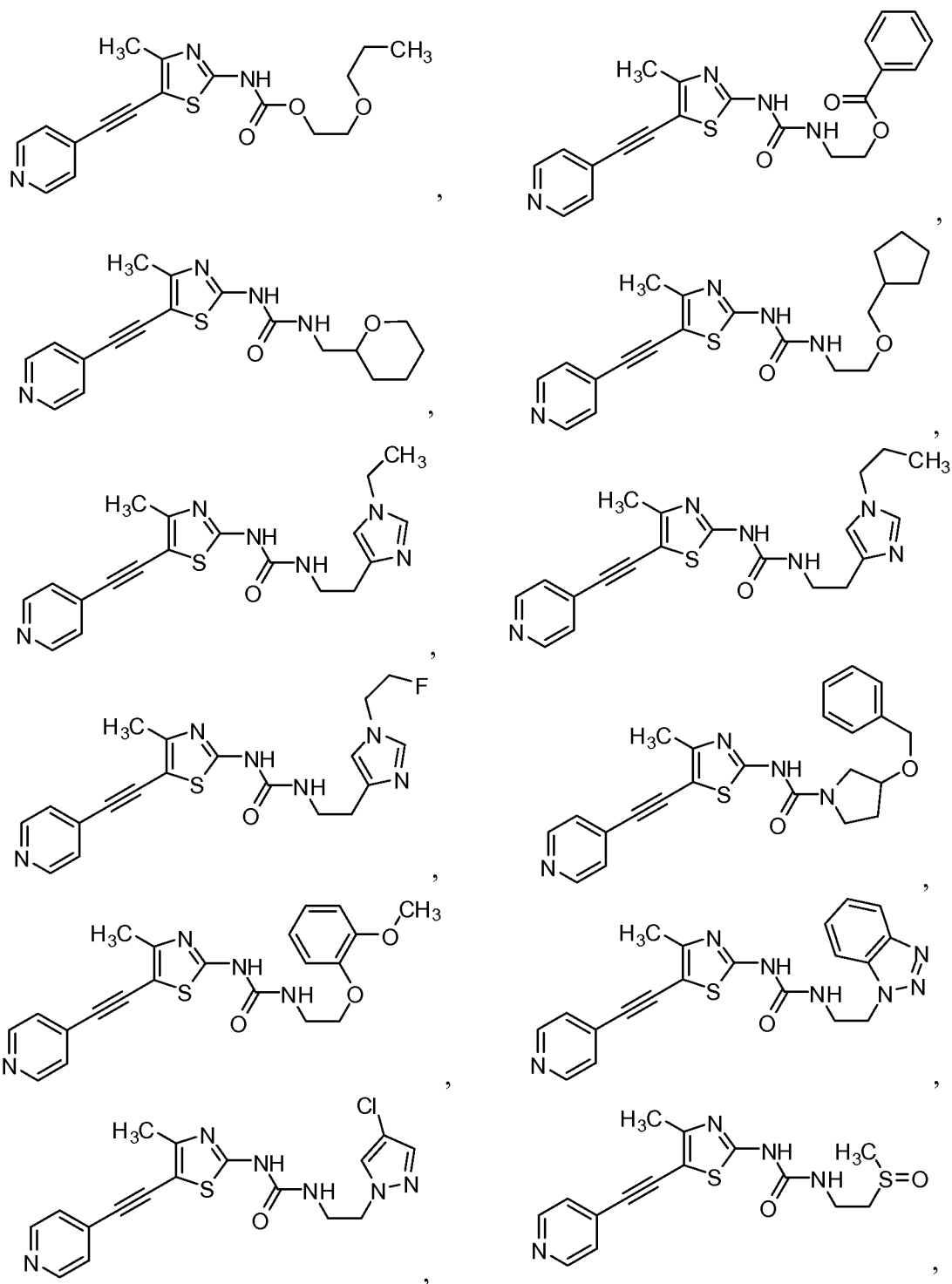
12. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein J^{R} is $-\text{OJ}^{\text{R}1}$ and $\text{J}^{\text{R}1}$ is phenyl or pyridyl, optionally substituted with up to three fluoro groups.

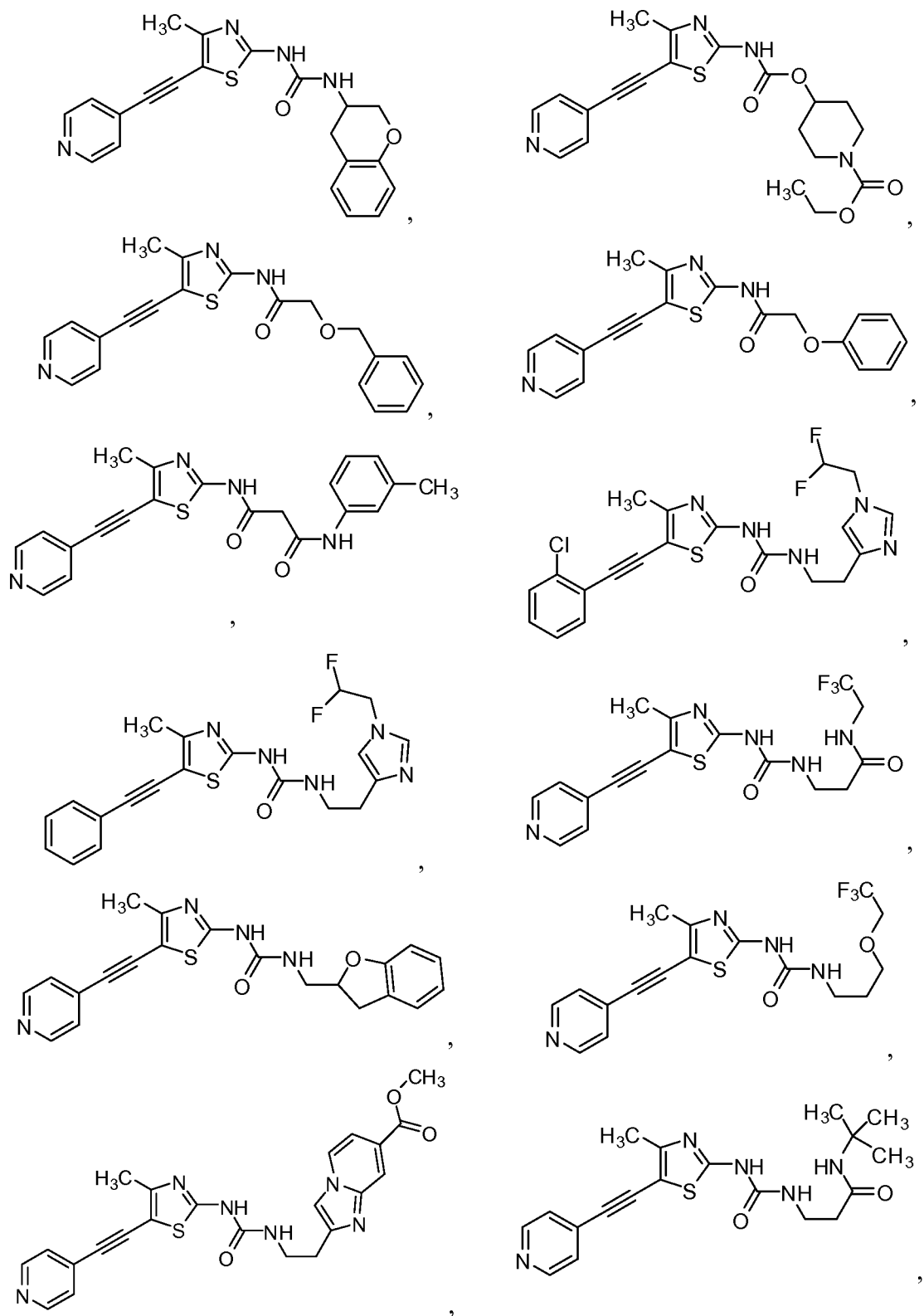


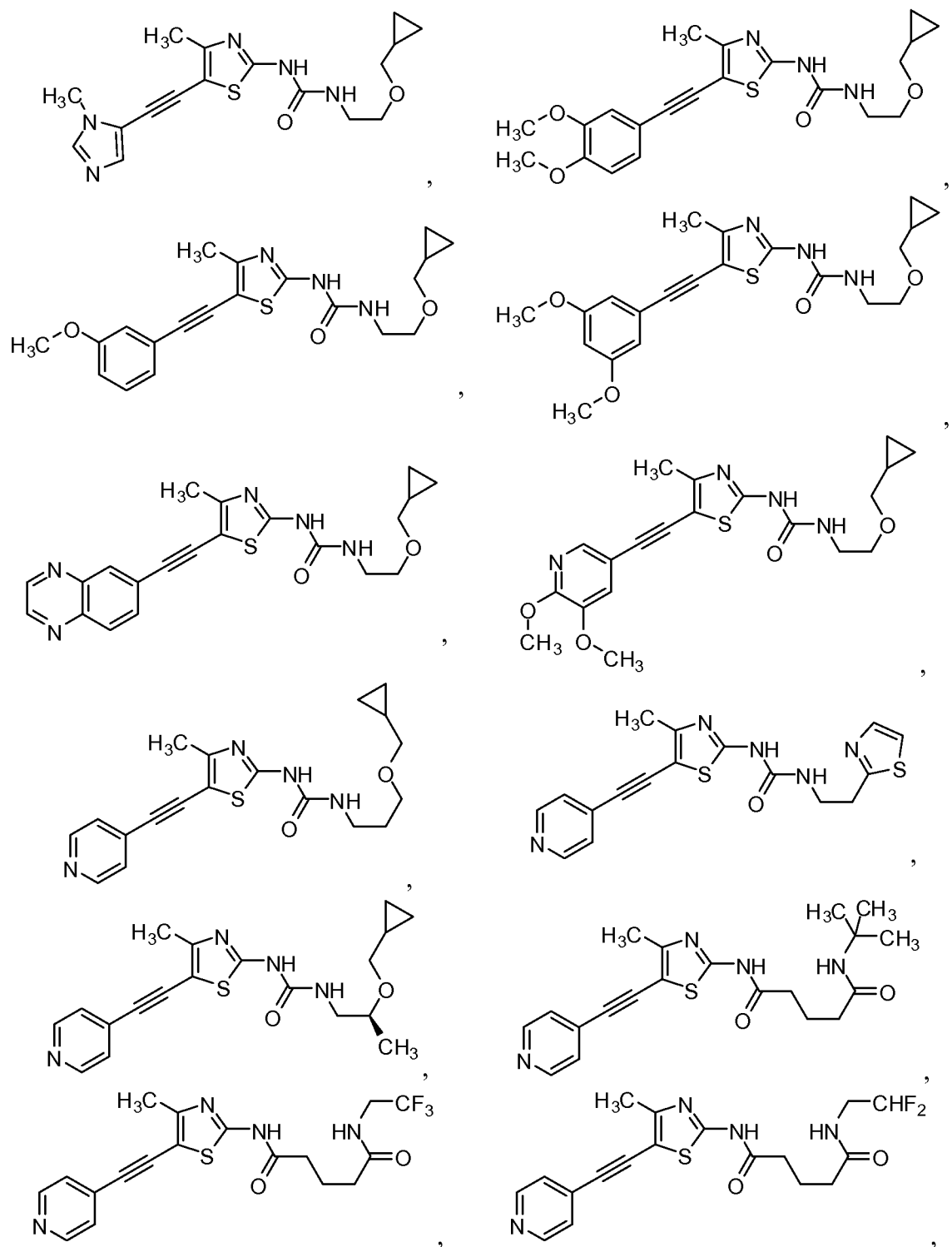


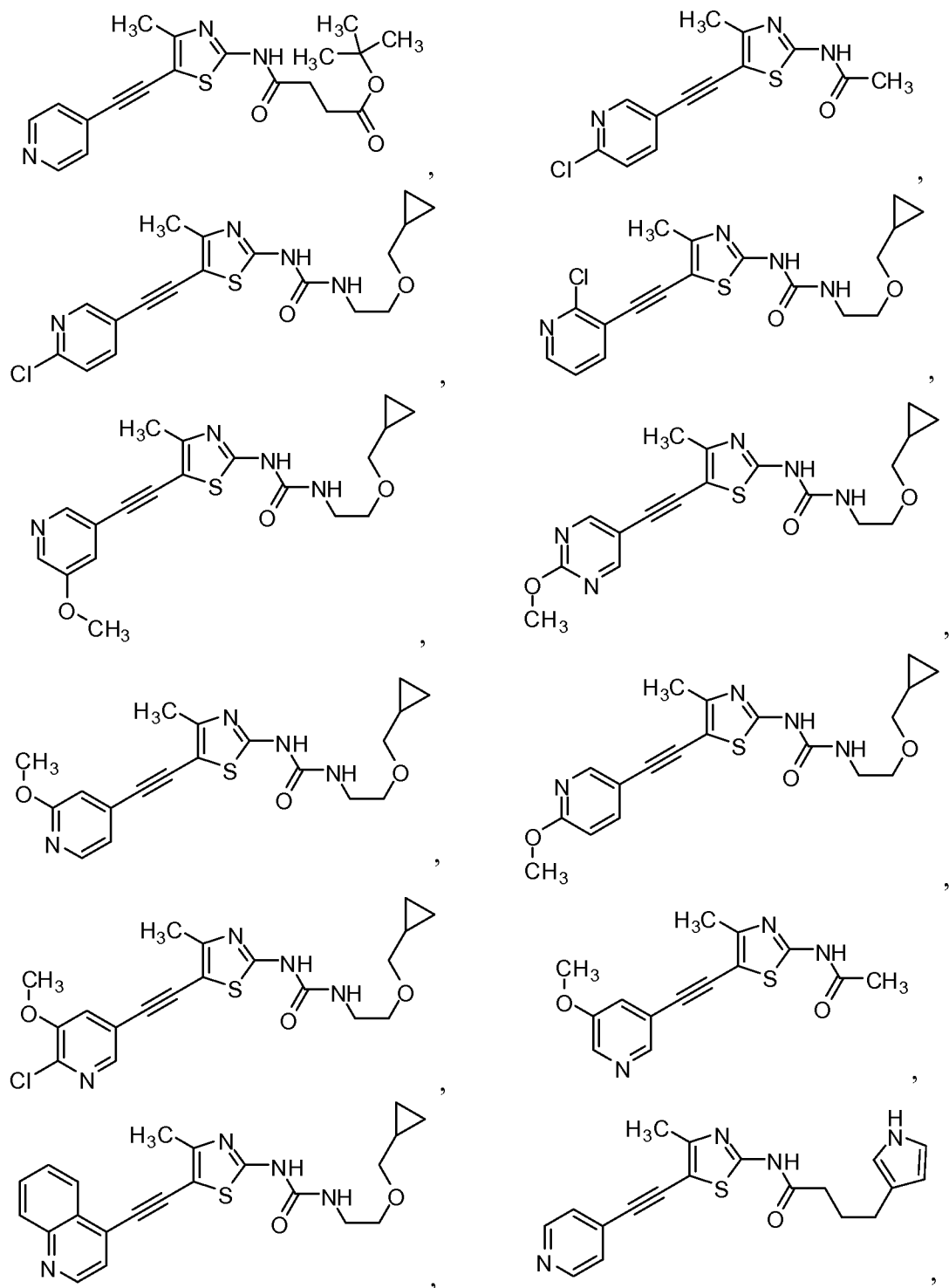


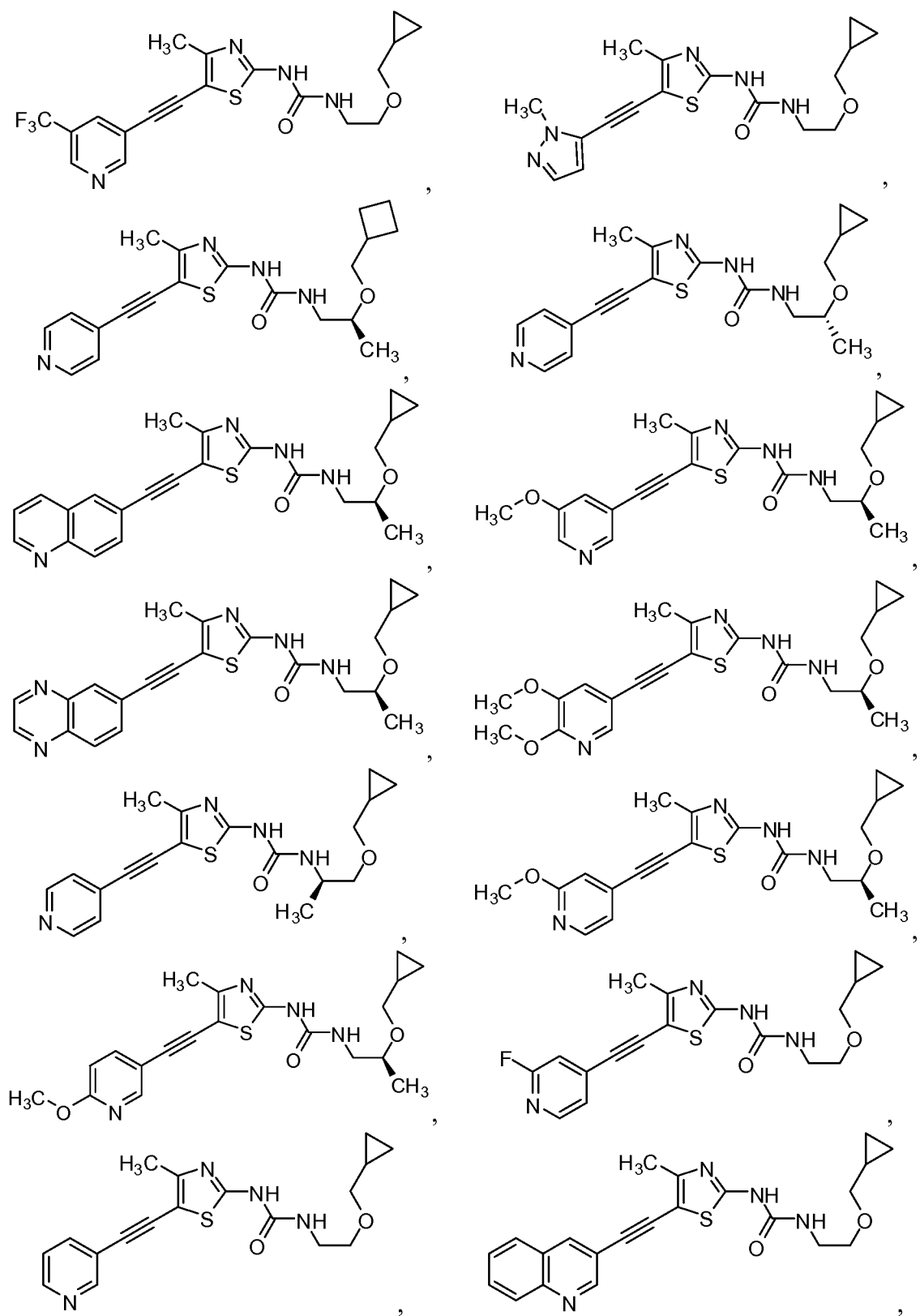


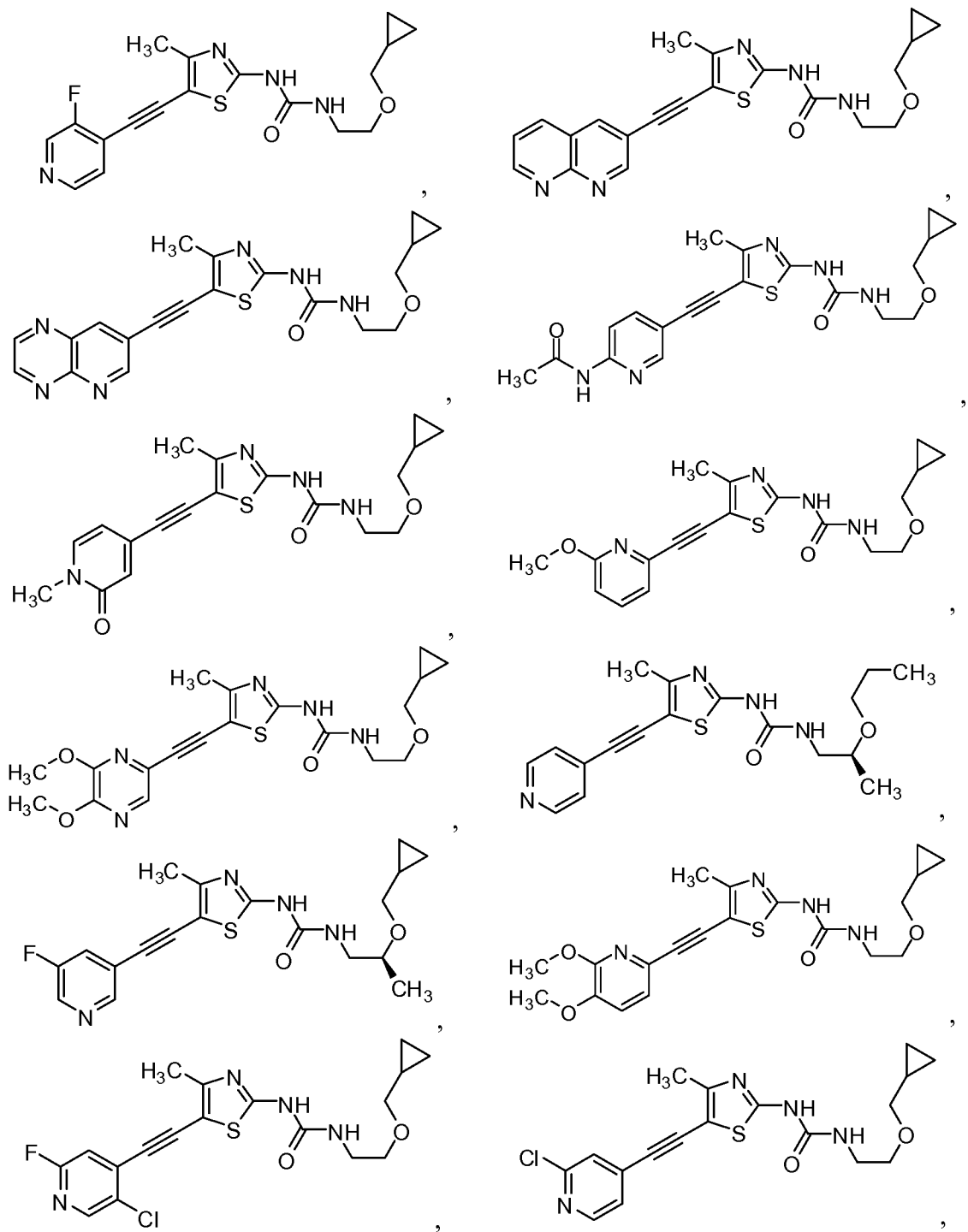


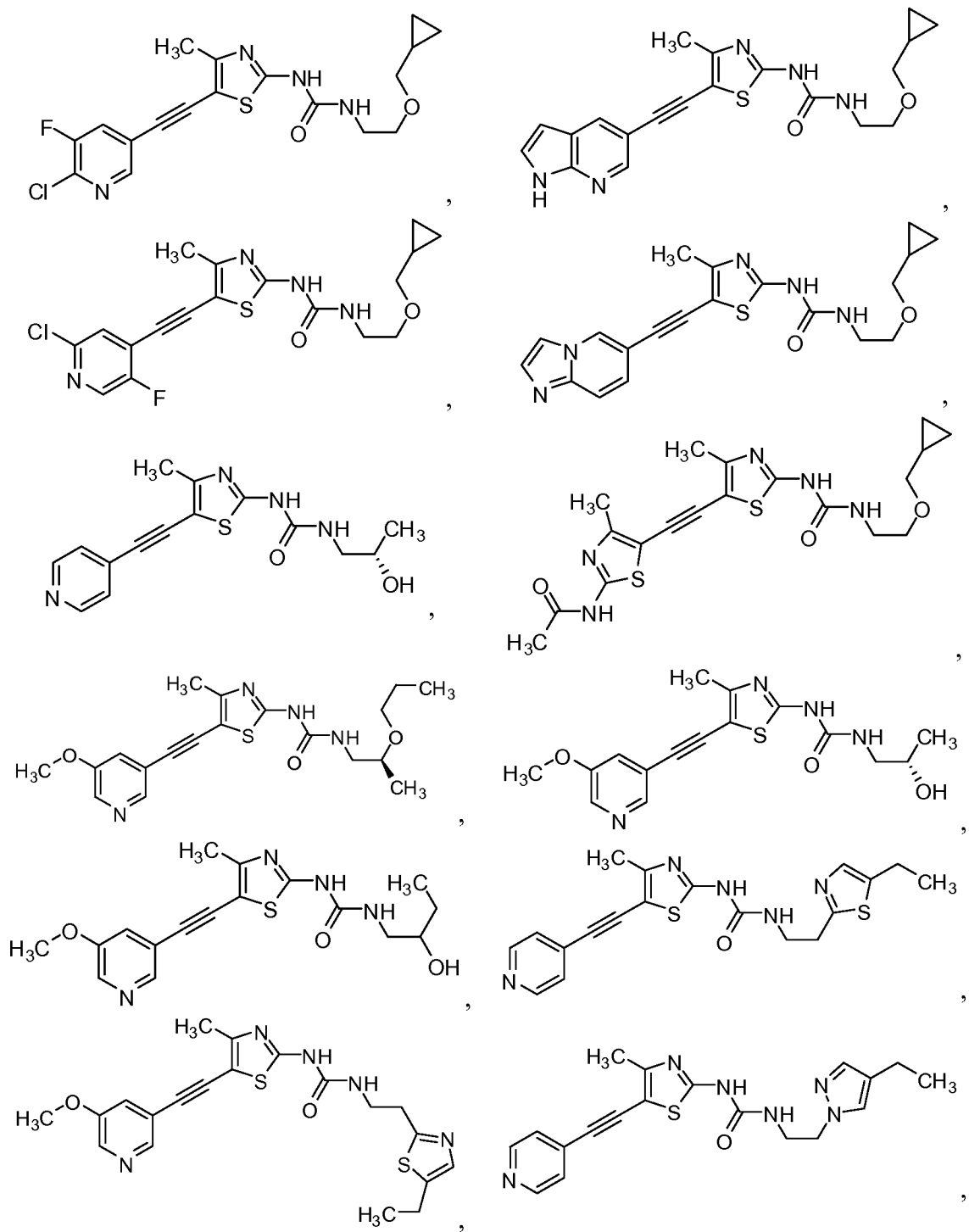


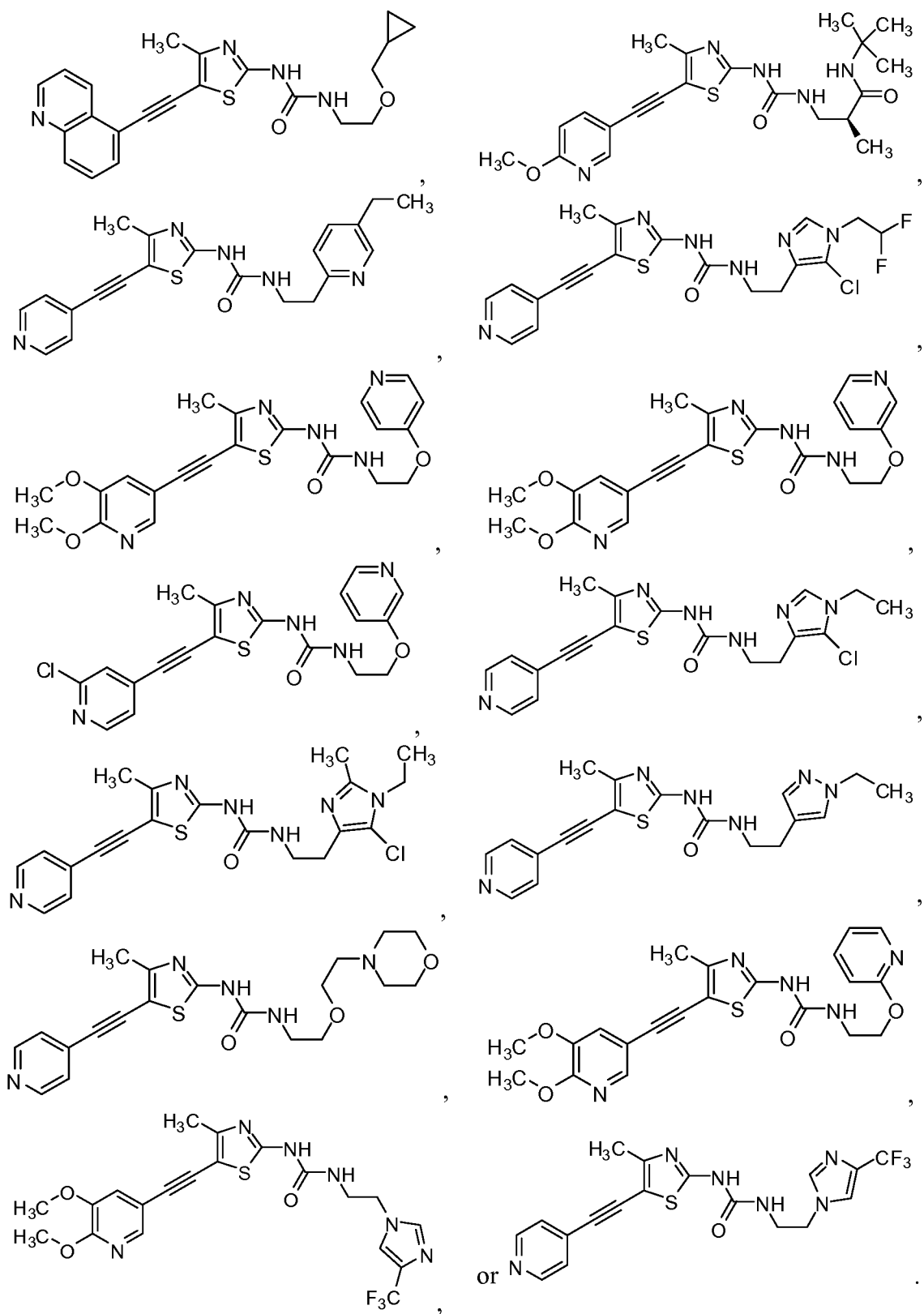












14. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

15. The composition according to claim 14, additionally comprising a therapeutic agent selected from an agent for treating multiple sclerosis, an anti-inflammatory agent, an immunomodulatory agent, or an immunosuppressive agent.

16. The composition according to claim 15, wherein said therapeutic agent is beta interferon, glatiramer, natalizumab, or mitoxantrone.

17. A method of treating or lessening the severity of a disease or condition selected from an autoimmune disease or an inflammatory disease of the brain or spinal cord, comprising the step of administering to said patient a compound or salt thereof according to claim 1, or a pharmaceutical composition thereof.

18. The method according to claim 17, wherein said disease or disorder is multiple sclerosis.

19. A method of inhibiting PI3K-gamma kinase activity in a biological sample comprising contacting said biological sample with a compound according to claim 1 or a composition according to claim 14.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/037865

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/06 A61K31/427 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/027584 A2 (VERTEX PHARMA [US]; WANG TIANSHENG [US]; GREEN JEREMY [US]; CORNEBISE) 6 March 2008 (2008-03-06) See the examples. -----	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

2 September 2010

Date of mailing of the international search report

13/09/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/037865

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008027584 A2	06-03-2008	AU 2007290359 A1	06-03-2008
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		EP 2061787 A2	27-05-2009
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		US 2010144721 A1	10-06-2010
