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(54) Title: SUBSTITUTED-(QUINAZOLINYL)PHENYL THIOPHENYL-SULFONYLUREAS, METHODS FOR MAKING AND INTERMEDIATES THEREOF

(57) Abstract: The present invention provides sulfonylurea compounds of formula (VIII) and pharmaceutically acceptable derivatives thereof and a process for making thereof. The compounds in their various forms are effective platelet ADP receptor inhibitors and may be used in various pharmaceutical compositions, and are particularly effective for the prevention and/or treatment of cardiovascular diseases, particularly those diseases related to thrombosis. The invention also provides intermediate compounds useful in the process, as well as final products produced by the process, and salts or prodrugs thereof. The invention also provides a method for inhibition platelet ADP receptor and preventing or treating thrombosis and thrombosis related conditions in a mammal comprising the step of administering a therapeutically effective amount of a compound of formula (VIII) or a pharmaceutically acceptable salt or forms thereof.

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**SUBSTITUTED-(QUINAZOLINYL)PHENYL THIOPHENYL-
SULFONYLUREAS, METHODS FOR MAKING AND
INTERMEDIATES THEREOF**

CROSS-REFERENCES TO RELATED APPLICATIONS

5 [0001] This application claims the benefit of U.S. Patent Application No. 60/733,650, filed November 3, 2005, the content of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 [0002] Thrombotic complications are a major cause of death in the industrialized world. Examples of these complications include acute myocardial infarction, unstable angina, chronic stable angina, transient ischemic attacks, strokes, peripheral vascular disease, preeclampsia/eclampsia, deep venous thrombosis, embolism, disseminated intravascular
15 coagulation and thrombotic cytopenic purpura. Thrombotic and restenotic complications also occur following invasive procedures, e.g., angioplasty, carotid endarterectomy, post CABG (coronary artery bypass graft) surgery, vascular graft surgery, stent placements and insertion of endovascular devices and prostheses, and hypercoagulable states related to genetic predisposition or cancers. It is generally thought that platelet aggregates play a critical role in
20 these events. Blood platelets, which normally circulate freely in the vasculature, become activated and aggregate to form a thrombus from disturbed blood flow caused by ruptured atherosclerotic lesions or by invasive treatments such as angioplasty, resulting in vascular occlusion. Platelet activation can be initiated by a variety of agents, e.g., exposed subendothelial matrix molecules such as collagen, or by thrombin which is formed in the
25 coagulation cascade.

[0003] An important mediator of platelet activation and aggregation is ADP (adenosine 5'-diphosphate) which is released from blood platelets in the vasculature upon activation by various agents, such as collagen and thrombin, and from damaged blood cells, endothelium or tissues. Activation by ADP results in the recruitment of more platelets and stabilization of
30 existing platelet aggregates. Platelet ADP receptors mediating aggregation are activated by ADP and some of its derivatives and antagonized by ATP (adenosine 5'-triphosphate) and some of its derivatives (Mills, D. C. B. (1996) *Thromb. Hemost.* 76:835-856). Therefore, platelet ADP receptors are members of the family of P2 receptors activated by purine and/or

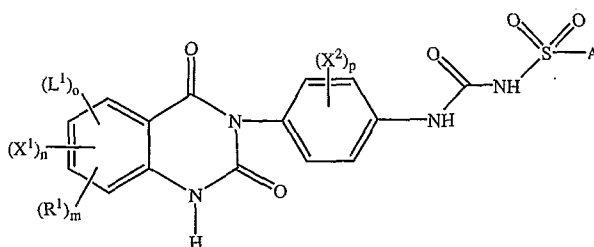
pyrimidine nucleotides (King, B. F., Townsend-Nicholson, A. & Burnstock, G. (1998) *Trends Pharmacol. Sci.* 19:506-514).

[0004] Recent pharmacological data using selective antagonists suggests that ADP-dependent platelet aggregation requires activation of at least two ADP receptors (Kunapuli, S. P. (1998), *Trends Pharmacol Sci.* 19:391-394; Kunapuli, S. P. & Daniel, J. L. (1998) *Biochem. J.* 336:513-523; Jantzen, H. M. *et al.* (1999) *Thromb. Hemost.* 81:111-117). One receptor appears to be identical to the cloned P2Y₁ receptor, mediates phospholipase C activation and intracellular calcium mobilization and is required for platelet shape change. The second platelet ADP receptor important for aggregation mediates inhibition of adenylyl cyclase. Based on its pharmacological and signaling properties this receptor has been provisionally termed P2Y_{ADP} (Fredholm, B. B. *et al.* (1997) *TIPS* 18:79-82), P2T_{AC} (Kunapuli, S. P. (1998), *Trends Pharmacol. Sci.* 19:391-394) or P2Y_{cyc} (Hechler, B. *et al.* (1998) *Blood* 92, 152-159). More recently, molecular cloning of this receptor (Hollopeter, G. *et al.* (2001) *Nature* 409: 202-207) has revealed that it is a new member of the G-protein coupled family and is the target of the thienopyridine drugs ticlopidine and clopidogrel. The nomenclature given to this receptor is P2Y₁₂.

[0005] Various directly or indirectly acting synthetic inhibitors of ADP-dependent platelet aggregation with antithrombotic activity have been reported (*see* 60/733,650 and references cited therein). However, there exists a need for more efficient synthesis of this class of platelet ADP receptor inhibitors. The present invention fulfills the above needs by providing more efficient and cost-effective processes and intermediates for making these compounds.

SUMMARY OF THE INVENTION

[0006] The present invention is directed to inhibitors of ADP-dependent platelet aggregation with antithrombotic activity. One aspect of the present invention relates to a process for making compound of formula VIII:



(VIII)

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

each X^1 is independently selected from the group consisting of:

halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, $-CN$, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$ -alkyl, $-C_{3-8}$ -cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups;

each X^2 is independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

each R^1 is selected from the group consisting of $-OR^3$, $-SR^3$, $-CN$, amino, C_{1-6} -alkylamino and C_{1-6} dialkylamino;

each R^3 and R^4 are independently selected from the group consisting of: hydrogen, halogen, $-CN$, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8} -cycloalkyl, aryl, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyloxy, hydroxy, hydroxy- C_{1-6} -alkyl, -thio and thio- C_{1-6} -alkyl;

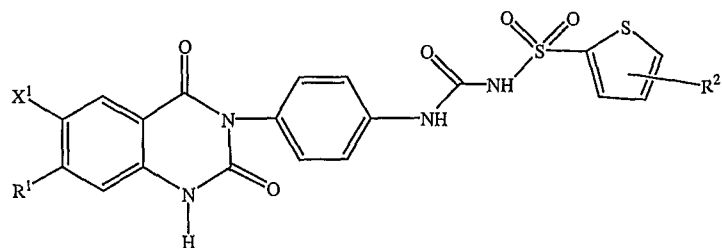
each L^1 is independently a leaving group;

A is thienyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

n is 0, 1, 2, 3 or 4, m is 0, 1, 2 or 3; o is 0, 1, 2, 3 or 4; and the sum of n + m + o is at most 4; and

p is 0, 1, 2, 3 or 4.

[0007] One aspect of the present invention relates to a process for making compound of formula XVIII:

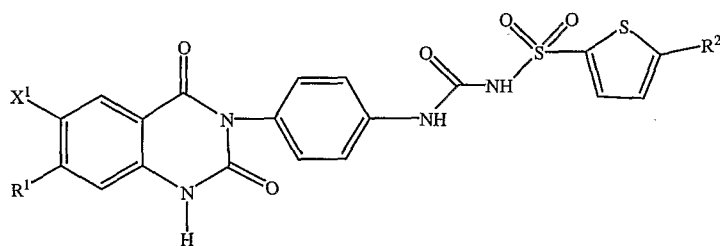


(XVIII)

wherein

R¹ is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl, amino and C₁₋₆-alkylamino; R² is halogen or -O-C₁₋₁₀-alkyl; and X¹ are halogen.

[0008] Another aspect of the present invention relates to a process for making compound of formula XXVIII:

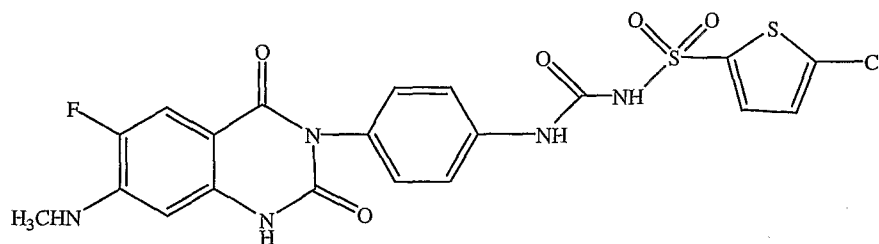


(XXVIII)

wherein

R¹ is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl, amino and C₁₋₆-alkylamino; R² is halogen or -O-C₁₋₁₀-alkyl; and X¹ are halogen.

[0009] Another aspect of the invention relates to a process for making pharmaceutically acceptable salts of the compounds according to formula XXXVIII:

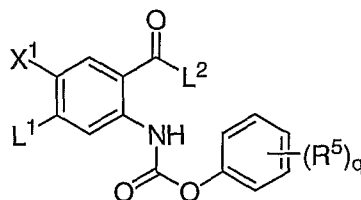


(XXXVIII).

[0010] Another aspect of the present invention relates to a process for making compounds and pharmaceutically acceptable salts thereof which inhibit at least one ADP receptor. Such ADP receptor inhibition can result in antithrombic activity, and thus such compounds are

useful for the prevention or treatment of cardiovascular diseases, particularly those related to thrombosis.

[0011] In another aspect, the present invention provides intermediate compounds of the formula:

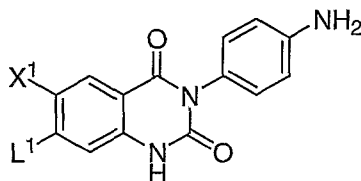


XIII

;

wherein X^1 is halogen; wherein each L^1 and L^2 are independently a leaving group; and each R^5 is an electron withdrawing group and the subscript q is 0, 1, 2, 3, or 4.

[0012] In another aspect, the present invention provides intermediate compounds of the formula:

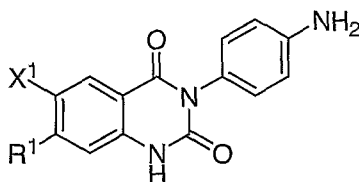


XV

;

wherein X^1 is halogen; and L^1 is a leaving group.

[0013] In another aspect, the present invention provides intermediate compounds of the formula:



XVI

;

wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl, amino and C₁₋₆-alkylamino; and X^1 is halogen.

[0014] Other aspects, objects, features and advantages of the present invention would be apparent to one of ordinary skill in the art from the following detailed description illustrating the preferred embodiments of the invention.

5

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention involves sulfonylurea compounds and their derivatives and their preparation. The compounds of the present invention are useful for the treatment and prevention of undesired thrombosis and thrombosis related conditions in mammals.

10 I. Definitions

[0016] In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[0017] The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such,
15 the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

[0018] The phrase "about" as used herein means variation one might see in measurements taken among different instruments, samples, and sample preparations.

[0019] The term "compound" as used herein is intended to encompass not only the specified molecular entity but also its pharmaceutically acceptable, pharmacologically active
20 derivatives, including, but not limited to, salts, prodrug conjugates such as esters and amides, metabolites, hydrates, solvates and the like.

[0020] The term "solvate" as used herein means a compound of the invention or a salt, thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces in an amount of greater than about 0.3% when
25 prepared according to the invention.

[0021] The term "hydrate" as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular
30 state as H₂O, such combination being able to form one or more hydrate.

[0022] The term "anhydrous" as used herein means a compound of the invention or a salt thereof that contains less than about 3% by weight water or solvent when prepared according to the invention.

[0023] The term "drying" as used herein means a method of removing solvent and/or water from a compound of the invention which, unless otherwise specified, may be done at atmospheric pressure or under reduced pressure and with or without heating until the level of solvent and/or water contained reached an acceptable level.

[0024] The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to about 12 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0025] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. For brevity, the term C₁₋₆alkylamino is meant to include straight chain, branched or cyclic alkyl groups or combinations thereof, such as methyl, ethyl, 2-methylpropyl, cyclobutyl and cyclopropylmethyl. The term "C₁₋₆ alkylamino" or "C₁₋₆ alkylamino" as used herein refers to an amino moiety attached to the remainder of the molecule whereby the nitrogen is substituted with one C₁₋₆ alkyl substituents, as defined above.

[0026] The terms "cycloalkyl" and "cycloalkenyl" refer to a saturated hydrocarbon ring and includes bicyclic and polycyclic rings. Similarly, cycloalkyl and cycloalkenyl groups having a heteroatom (e.g. N, O, S or Si) in place of a carbon ring atom may be referred to as "heterocycloalkyl", "heterocyclyl" and "heterocycloalkylene," respectively. Accordingly, the term "heterocyclyl" includes heteroaryl groups or rings. Examples of cycloalkyl and heterocyclyl groups are, for example, cyclohexyl, norbornyl, adamantyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, pyridinyl, oxadiazolyl, thiadiazolyl, tetrazoyl, thiazoyl and the like. The cycloalkyl and heterocyclyl moieties may also be optionally substituted with halogen atoms, or other groups such as nitro, alkyl, alkylamino, carboxyl, alkoxy, aryloxy and the like. In some embodiments, cycloalkyl and cycloalkenyl moieties are those having 3 to 12 carbon atoms in the ring (e.g., cyclohexyl, cyclooctyl, norbornyl, adamantyl, and the like). In some embodiments, heterocycloalkyl and heterocycloalkylene

moieties are those having 1 to 3 hetero atoms in the ring (e.g., morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperidinyl and the like). Additionally, the term "(cycloalkyl)alkyl" refers to a group having a cycloalkyl moiety attached to an alkyl moiety. Examples are cyclohexylmethyl, cyclohexylethyl and cyclopentylpropyl.

5 [0027] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0028] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Exemplary aryl groups are phenyl (or
10 benzene), naphthyl, biphenyl and the like. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-
15 pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl (or 2-thiophenyl), 3-thienyl (or 3-thiophenyl), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazyl, 4-pyrazyl, 2-pyrimidyl, 4-pyrimidyl, 4-tetrazoyl, 5-tetrazoyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, 1-isoquinolyl, 5-
20 isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0029] The term "substituted" refers to the replacement of an atom or a group of atoms of a compound with another atom or group of atoms. For example, an atom or a group of atoms
25 may be substituted with one or more of the following substituents or groups: halo, nitro, C₁₋₈alkyl, C₁₋₈alkylamino, hydroxyC₁₋₈alkyl, haloC₁₋₈alkyl, carboxyl, hydroxy, C₁₋₈alkoxy, C₁₋₈alkoxyC₁₋₈alkoxy, haloC₁₋₈alkoxy, thioC₁₋₈alkyl, aryl, aryloxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₈alkyl, aryl, heteroaryl, arylC₁₋₈alkyl, heteroarylC₁₋₈alkyl, C₂₋₈alkenyl containing 1 to 2 double bonds, C₂₋₈alkynyl containing 1 to 2 triple bonds, C₂₋₈lk(en)(yn)yl groups, cyano, formyl, oxo, thio, C₁₋₈alkylcarbonyl, arylcarbonyl heteroarylcarbonyl,
30 carboxy, C₁₋₈alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, C₁₋₈alkylaminocarbonyl, C₁₋₈dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylC₁₋

8alkylaminocarbonyl, aryloxy, haloC₁₋₈alkoxy, C₂₋₈alkenyloxy, C₂₋₈alkynyloxy, arylC₁₋₈alkoxy, aminoC₁₋₈alkyl, C₁₋₈alkylaminoC₁₋₈alkyl, C₁₋₈dialkylaminoC₁₋₈alkyl, arylaminoC₁₋₈alkyl, amino, C₁₋₈dialkylamino, arylamino, C₁₋₈alkylarylamino, C₁₋₈alkylcarbonylamino, arylcarbonylamino, azido, mercapto, C₁₋₈alkylthio, arylthio, halo C₁₋₈alkylthio, thiocyano, isothiocyano, C₁₋₈alkylsulfinyl, C₁₋₈alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, C₁₋₈alkylaminosulfonyl, C₁₋₈dialkylaminosulfonyl and arylaminosulfonyl. When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group.

[0030] The term "unsubstituted" refers to a native compound that lacks replacement of an atom or a group of atoms.

[0031] "Acyl" means -CO-R, wherein the group R is variously defined herein.

[0032] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C₁₋₄ haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0033] "Haloalkyl" refers to alkyl group as defined herein in which one or more hydrogen atoms have been replaced with halogens, including perhaloalkyls, such as trifluoromethyl.

[0034] "Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or a group capable of being displaced by a nucleophile and includes halo (such as fluoro, chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (e.g., acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxyamino, and the like.

[0035] "Protecting group" refers to a moiety that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, 1999, and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 (John Wiley and Sons, 1971-1996), which are incorporated herein by reference in their entirety. Representative hydroxy protecting groups include acyl groups, benzyl and trityl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and

allyl ethers. Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), nitro-veratryloxycarbonyl (NVOC), and the like.

5 [0036] The term "electron withdrawing group" refers to a group which reduces the electron density of the atom to which it is attached relative to a hydrogen substituent. Representative electron withdrawing groups include halogen, nitro, cyano, (C₁-C₆)haloalkyl and sulfonyloxy and carboxy. These groups can be introduced into aromatic rings by methods known in the art ("Tetrahedron Organic Chemistry Series", Elsevier, London.; Fieser and
10 Fieser "Reagents for Organic Synthesis", Wiley-Interscience, NY.).

[0037] The term "pharmaceutically acceptable salt" or "derivative" is meant to include salts of a compounds which are prepared with acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by
15 contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Certain specific compounds of the present invention contain both basic
20 and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0038] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such
25 as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0039] The term "derivatives" is also meant to include compounds of the present invention which can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be
30 encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical

forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0040] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention.

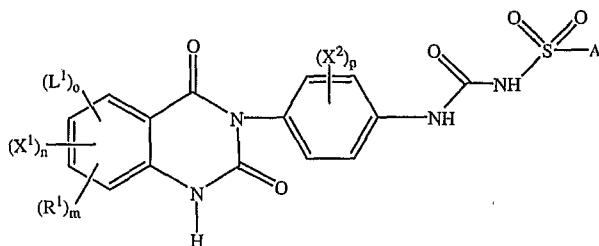
[0041] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0042] In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

[0043] "Optional" or "optionally" in the above definitions means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclo group optionally mono- or di- substituted with an alkyl group means that the alkyl may but need not be present, and the description includes situations where the heterocyclo group is mono- or disubstituted with an alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

II. Compound Embodiments of the Invention

[0044] The present invention relates to a process for making compounds represented by formula VIII as follows: Compounds of formula (VIII) below represent one embodiment of the invention:



(VIII)

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

each X^1 is independently selected from the group consisting of:

halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, $-CN$, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$ -alkyl, $-C_{3-8}$ -cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or disubstituted independently with 0-2 R^4 groups;

each X^2 is independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

each R^1 is selected from the group consisting of $-OR^3$, $-SR^3$, $-CN$, amino, C_{1-6} -alkylamino and C_{1-6} dialkylamino;

each R^3 and R^4 are independently selected from the group consisting of: hydrogen, halogen, $-CN$, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8} -cycloalkyl, aryl, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyloxy, hydroxy, hydroxy- C_{1-6} -alkyl, -thio and thio- C_{1-6} -alkyl;

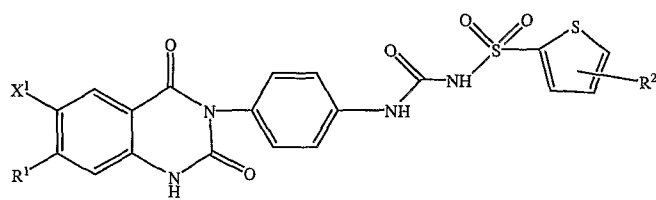
each L^1 is independently a leaving group;

A is thienyl optionally substituted with one, two or three substituents independently selected from the group consisting of C₁₋₆-alkoxy, C₁₋₆-alkyl, C₁₋₆-alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo-C₁₋₆-alkoxy and carboxamide;

n is 0, 1, 2, 3 or 4, m is 0, 1, 2 or 3; o is 0, 1, 2, 3 or 4; and the sum of n + m + o is at most 4; and

p is 0, 1, 2, 3 or 4.

[0045] The present invention also relates to a process for making compounds represented by formula VIII as follows: Compounds of formula (XVIII) below represent one embodiment of the invention:

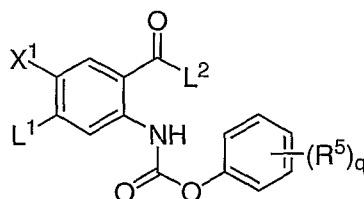


(XVIII)

wherein:

R¹ is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl, amino and C₁₋₆-alkylamino; R² is halogen or -O-C₁₋₁₀-alkyl; and X¹ are halogen.

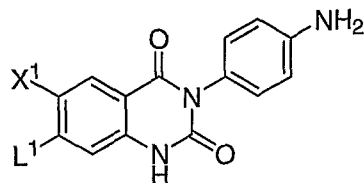
[0046] In one group of embodiments, the present invention relates to intermediate compounds of the formula:



XIII

wherein X¹ is halogen; wherein each L¹ and L² are independently a leaving group; and each R⁵ is an electron withdrawing group and the subscript q is 0, 1, 2, 3, or 4. In another group of embodiments, q is 1.

[0047] In another aspect, the present invention relates to intermediate compounds of the formula:

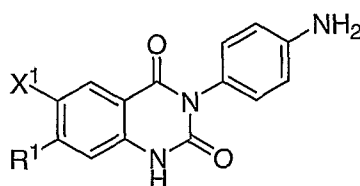


XV

;

wherein X^1 is halogen; and L^1 is a leaving group.

5 [0048] In another aspect, the present invention relates to intermediate compounds of the formula:



XVI

;

wherein R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -alkylamino; and X^1 is halogen.

10 [0049] In another group of embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein X^1 is -F.

[0050] In still another group of embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^1 is a member selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -

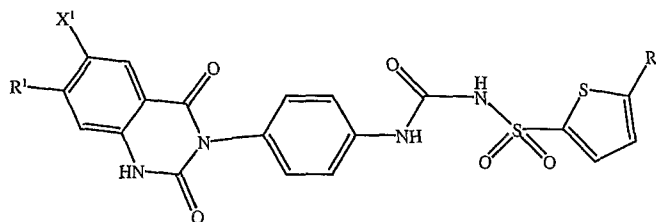
15 alkylamino. In another group of preferred embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^1 is -O- C_{1-10} -alkyl, amino or C_{1-6} -alkylamino. In another group of preferred embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^1 is -OH, C_{1-6} -alkylamino or amino. In another group of preferred

20 embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^1 is NH_2 and -NH(- C_{1-6} alkyl). Another group of embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^1 is -NHCH₃.

[0051] Still another group of embodiments, the invention provides compounds and a process

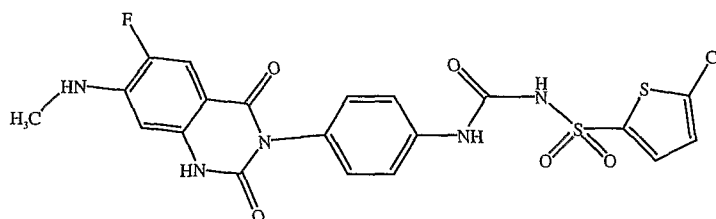
for the production of any of the compounds described herein wherein R^2 is halogen or $-O-C_{1-10}$ -alkyl. another group of embodiments, the invention provides compounds and a process for the production of any of the compounds described herein wherein R^2 is chloro.

[0052] In one embodiment of the invention, compounds of formula (VIII) include the compound having the formula XXVIII:



(XXVIII).

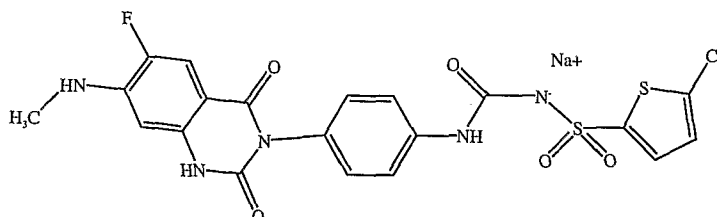
[0053] In one embodiment of the invention, compounds of formula (VIII) include the compound having the formula XXXVIII:



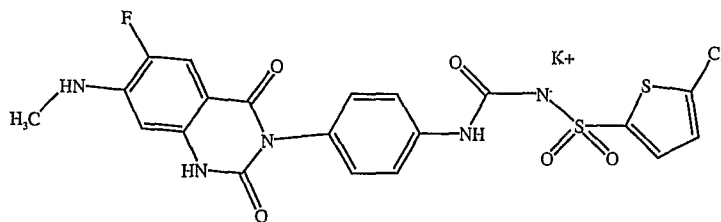
(XXXVIII).

[0054] The invention also covers all typical derivatives of the compounds described herein. Derivative salts can be prepared using at least one inorganic or organic base including, but not limited to potassium hydride, potassium hydroxide, potassium alkoxides, sodium hydride, sodium hydroxide, sodium alkoxides and the like.

[0055] Thus in another group of particularly preferred compounds of the invention have the formula:



and/or

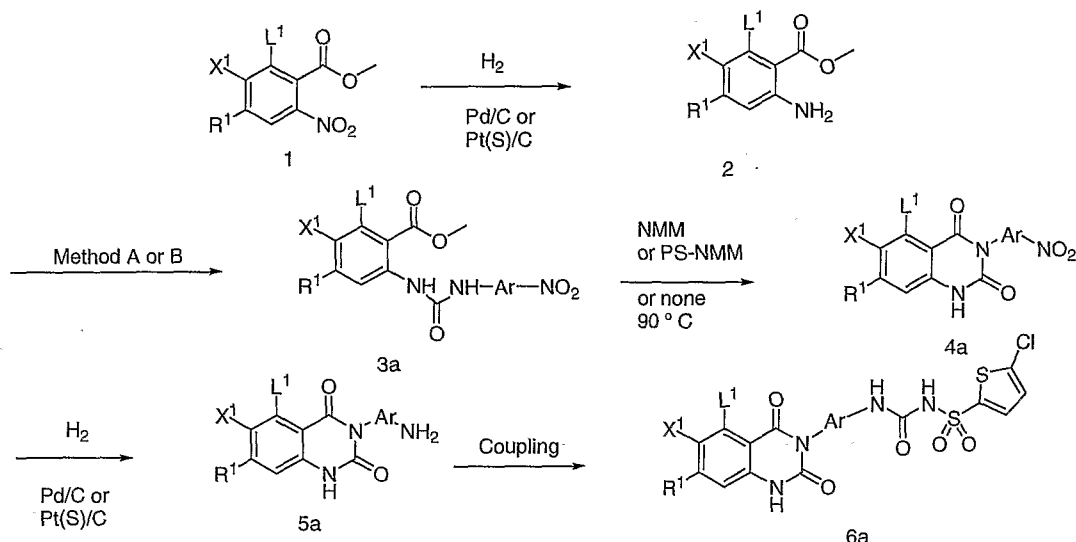


[0056] The present invention process is not limited by the above listed compounds, but includes intermediates for making such compounds or other related compounds.

5 III. Preparation of Compounds of the Invention

[0057] Scheme 1 illustrates a method of preparing certain compounds of formula VIII wherein Ar is phenylene and R^1 , L^1 and X^1 are as described above. The generality of the methods herein is not limited by the substitutions illustrated below.

SCHEME 1



[0058] A compound of formula VIII can be prepared by reducing 2-nitro-benzoic acid methyl ester compound **1** by procedures known to one skilled in the art to yield aniline **2**.

(See also published patent application US 2002/077486). For example, a method of nitro group reduction can be carried out by hydrogenation. The hydrogenation is carried out with a suitable catalyst (e.g., 10% Pd/C or Pt(s)/C) under hydrogen and in an appropriate solvent, typically in an alcohol, preferably ethanol at room temperature. Treating compound **2** with appropriately substituted aryl isocyanate (Method A) provides intermediate urea **3a**.

Alternatively, urea **3a** can be formed by treating compound **2** with triphosgene in the

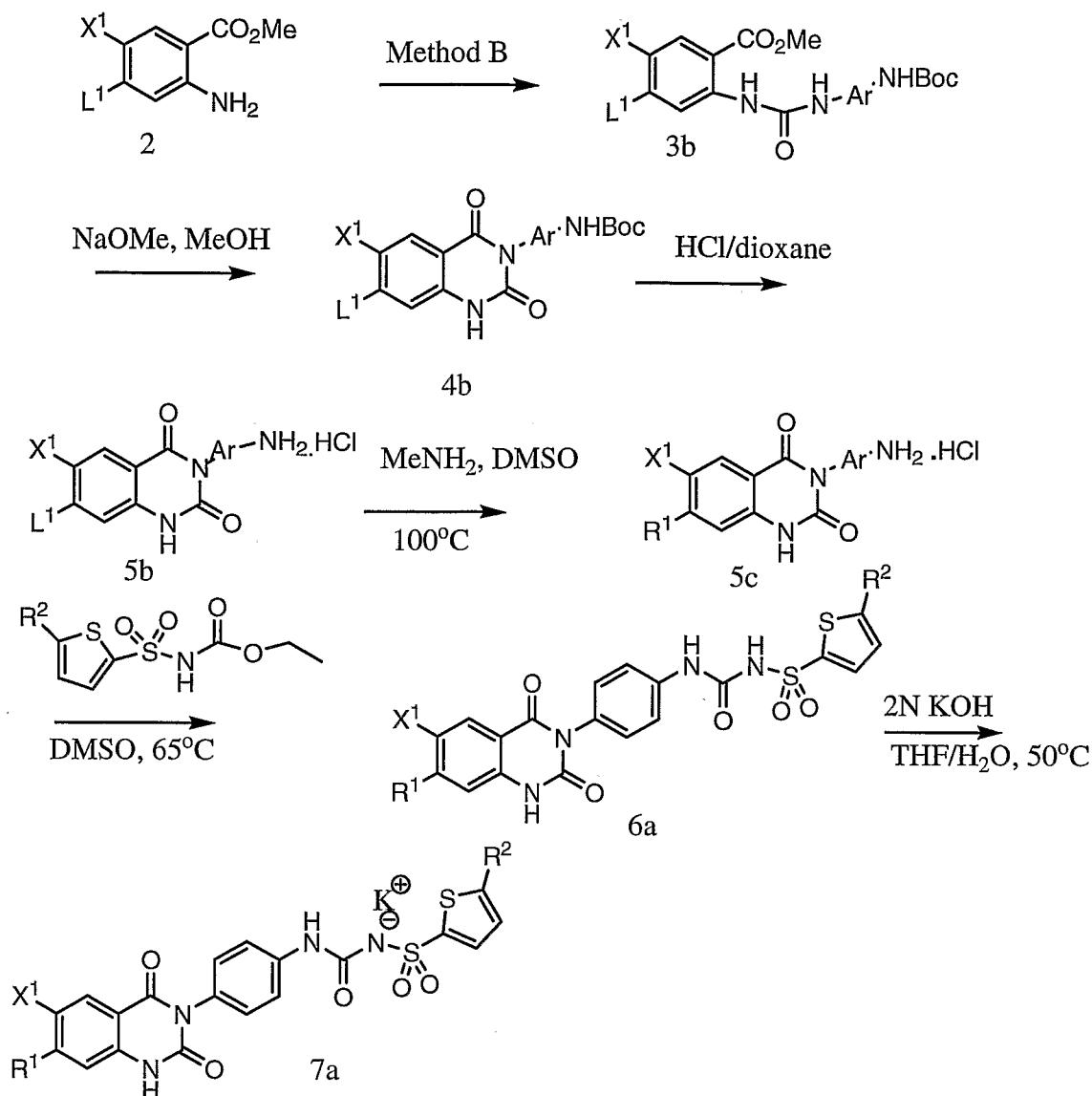
presence of a base such as triethylamine or diisopropylethylamine in an inert solvent such as THF, dichloromethane and MeCN at appropriate temperature, preferably at 20 °C, followed by substituted aniline (Method B). Urea **3a**, prepared by Method A or Method B typically without further purification can be subjected to thermal or base (such as N-methyl

5 morpholine (NMM) or polystyrene-NMM (PS-NMM) induced ring closure to provide quinazolinedione **4a**. The nitro group of compound **4a** can be reduced by procedures known to one skilled in the art to yield free amino group. For example, a method of reduction can be carried out by hydrogenation, with a suitable catalyst (e.g., 10% palladium on carbon) in an appropriate solvent, typically an alcohol. The formation of sulfonylurea linkage can be
10 accomplished by treating the reduced product aniline **5a** with a pre-mixed solution of substituted thiophene-2-sulfonamide, N, N'-disuccinimidyl carbonate and tetramethylguanidine in dichloromethane, followed by treatment with TFA in dichloromethane at room temperature to afford the sulfonylurea of formula I. Alternatively, the sulfonylurea linkage can be formed by reacting the aniline **5a** and 5-Chloro-thiophene-2-
15 sulfonyl ethylcarbamate in suitable solvents, which include, but are not limited to, toluene, acetonitrile, 1,4-dioxane and DMSO.

[0059] Scheme 2 illustrates an alternative method of preparing compounds of Formula VIII wherein R¹ is, for example, alkylamino and L¹ is halogen, alkylsulfonate, haloalkylsulfonate and arylsulfonate.

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SCHEME 2



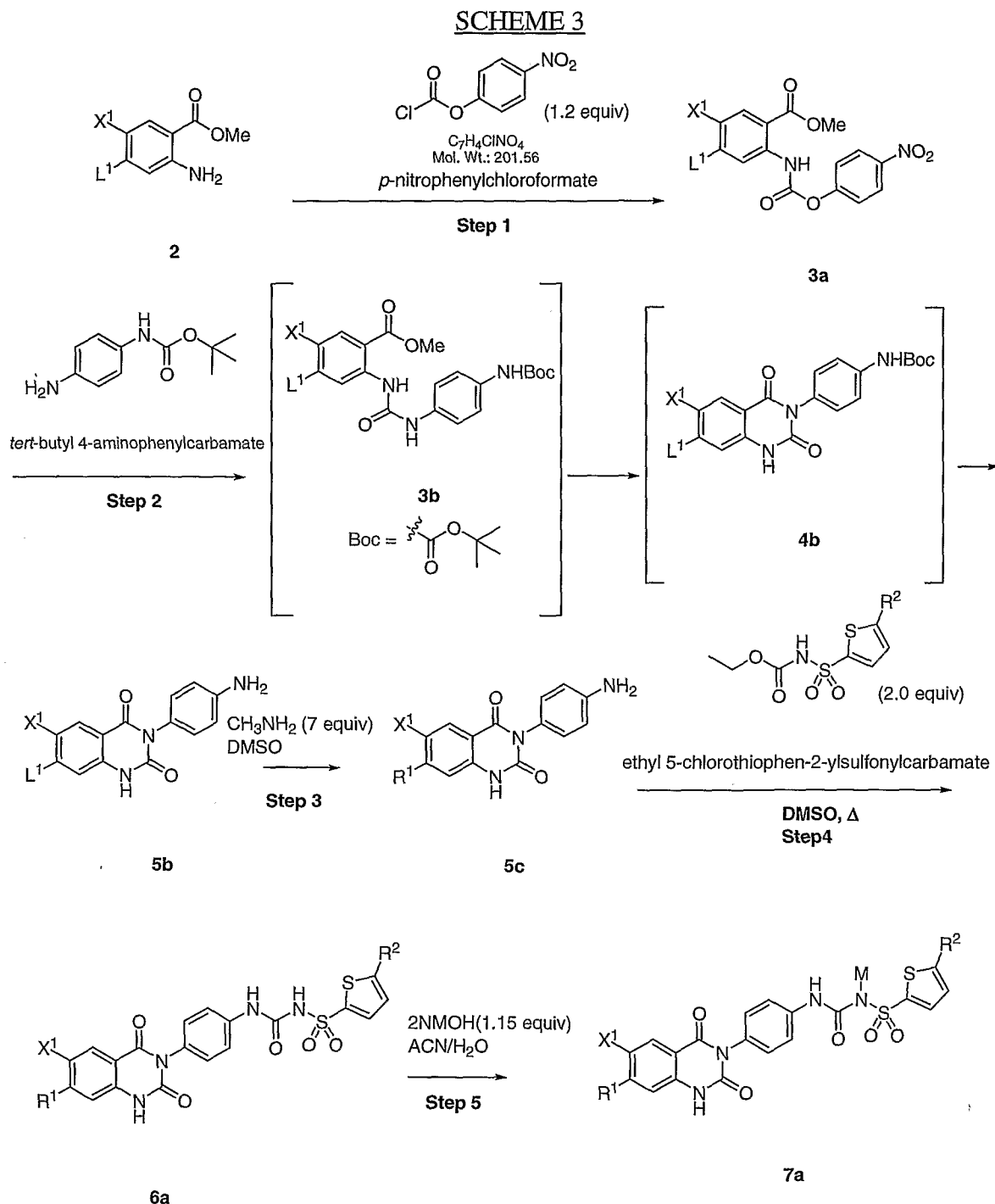
[0060] The urea **3b** can be prepared by treating compound **2** with triphosgene or p-nitrophenyl chloroformate in the presence of a base, such as triethylamine and/or

5 diisopropylethylamine, in an inert solvent, such as THF, dichloromethane and/or MeCN, at an appropriate temperature, typically at about $20^\circ C$, followed by treatment with an appropriately protected aniline (Method B). Urea **3b**, typically without further purification, can be subjected to base induced ring closure to provide intermediate quinazolinone **4b**.

The protecting group of compound **4b** can be removed using standard techniques appropriate
 10 for the protecting group used. For example a BOC protecting group can be removed by treating compound **4b** with 4N HCl in dioxane. The C-7 fluoro of compound **5b** is then displaced by treatment with methylamine in DMSO at about $120^\circ C$ to afford aniline **6a**. The preparation of target sulfonyleurea **7a** can be accomplished by treating aniline **6a** with 5-

chloro-thiophene-2-sulfonyl ethylcarbamate in an appropriate solvent, such as dimethyl sulfoxide, dioxane and/or acetonitrile with heating.

[0061] Scheme 3 illustrates an alternative method of preparing compounds of Formula VIII wherein R¹ is, for example, alkylamino and L¹ is halogen, alkylsulfonate, haloalkylsulfonate and arylsulfonate.



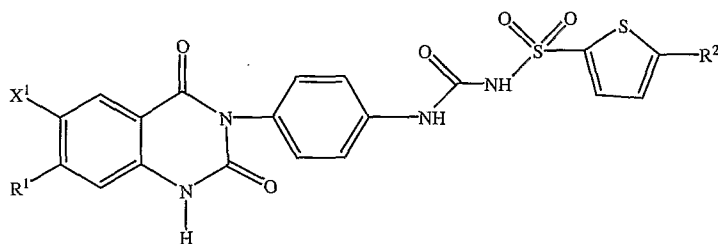
[0062] The urea **3a** can be prepared by treating compound **2** with *p*-nitrophenylchloroformate, in an inert solvent, such as THF, dichloromethane and/or MeCN,

at an appropriate temperature, typically at about 20 °C, followed by treatment with an appropriately protected aniline (Method B). According to the invention, compounds of formula (VIII) may be further treated to form pharmaceutically acceptable salts e.g. **7a**. Treatment of a compound of the invention with an acid or base may form, respectively, a pharmaceutically acceptable acid addition salt and a pharmaceutically acceptable base addition salt, each as defined above. Various inorganic and organic acids and bases known in the art including those defined herein may be used to effect the conversion to the salt.

[0063] Compounds of formula (VIII) may be isolated using typical isolation and purification techniques known in the art, including, for example, chromatographic and recrystallization methods.

[0064] The invention also provides pharmaceutically acceptable hydrates, and solvates of compounds of formula (VIII). Compounds of formula (VIII) may also exist in various isomeric and tautomeric forms including pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers. For example, while some compounds are provided herein as dihydrates having two molecules of water per molecule of the compound of formula (VIII), the present invention also provides compounds that are anhydrous, monohydrates, trihydrates, sesquihydrates, and the like.

[0065] Another embodiment is a process for the production of such compounds wherein a process for making compound of formula XVIII:



(XVIII)

wherein

R¹ is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

X¹ is halogen, and

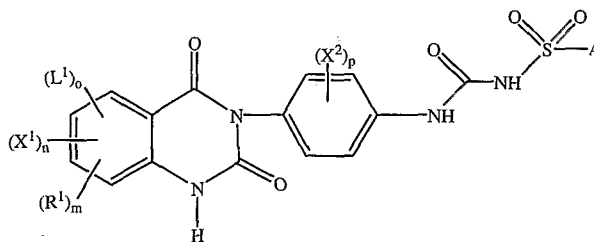
all pharmaceutically acceptable salt, hydrate and solvate derivatives thereof.

5
10

[0067] The pharmaceutically acceptable salts of the compounds according to formula VIII include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, etc.

15

[0069] Therefore in group of embodiments, the present invention is directed to a process for preparing compound of formula VIII:



(VIII)

20 or a pharmaceutically acceptable salt, hydrate or solvate derivative thereof wherein

each X^1 is independently selected from the group consisting of:

25

nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups;

each X^2 is independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy,

5 carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

each R^1 is selected from the group consisting of $-OR^3$, $-SR^3$, $-CN$, amino, C_{1-6} -alkylamino and C_{1-6} dialkylamino;

each R^3 and R^4 are independently selected from the group consisting of:
hydrogen, halogen, $-CN$, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8} -cycloalkyl, aryl, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy- C_{1-6} -alkoxy, hydroxy, hydroxy- C_{1-6} -alkyl, -thio and thio- C_{1-6} -alkyl;

each L^1 is independently a leaving group;

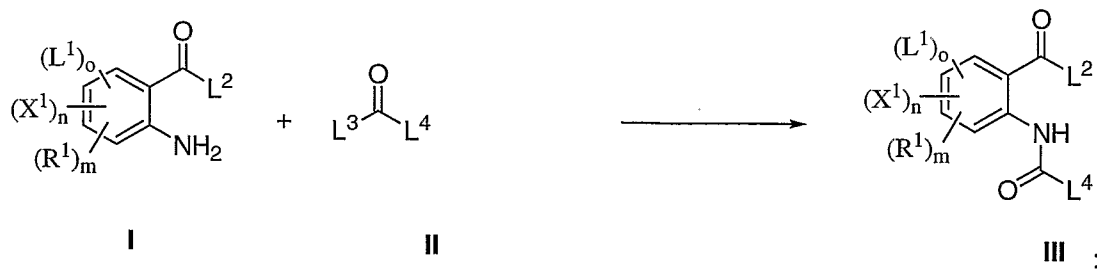
15 A is thienyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

n is 0, 1, 2, 3 or 4, m is 0, 1, 2 or 3; o is 0, 1, 2, 3 or 4; and the sum of $n + m + o$ is at most 4; and

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

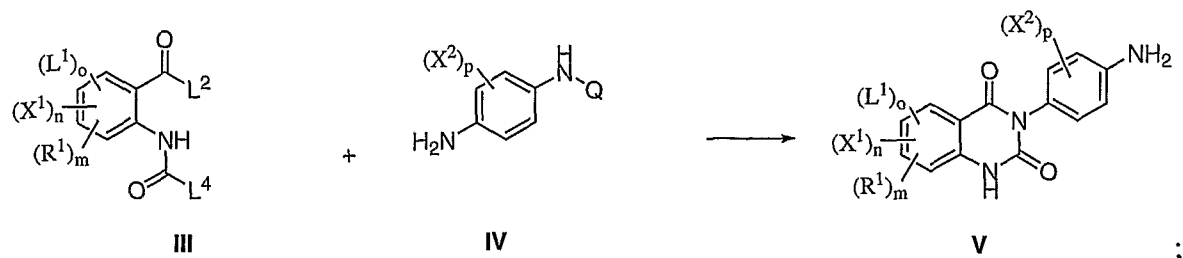
comprising the steps of:

(a) acylating the amino group of a compound of formula I with a compound of formula II to produce a compound of formula III as follows:



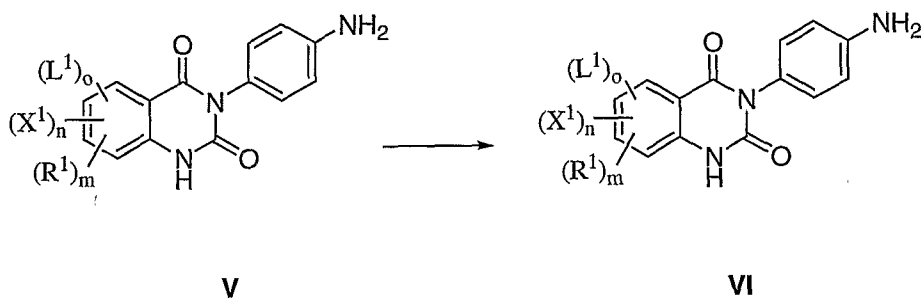
wherein each L^2 , L^3 and L^4 are independently a leaving group;

(b) reacting the compound of formula III, with an amine containing compound IV, to produce a cyclized quinazoline derivative of formula V as follows:



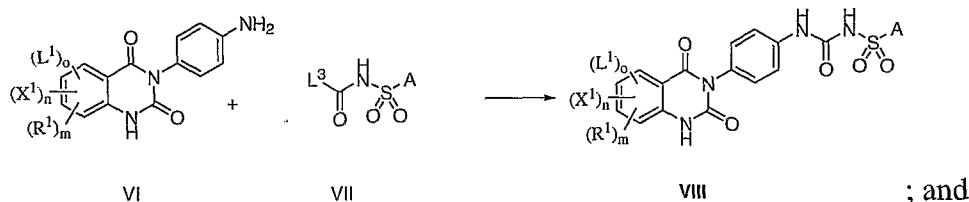
wherein Q is a protecting group;

(c) optionally replacing at least one group L^1 of formula V, with a group R^1 by reacting the compound of formula R^1H to provide a compound of formula VIII as follows:

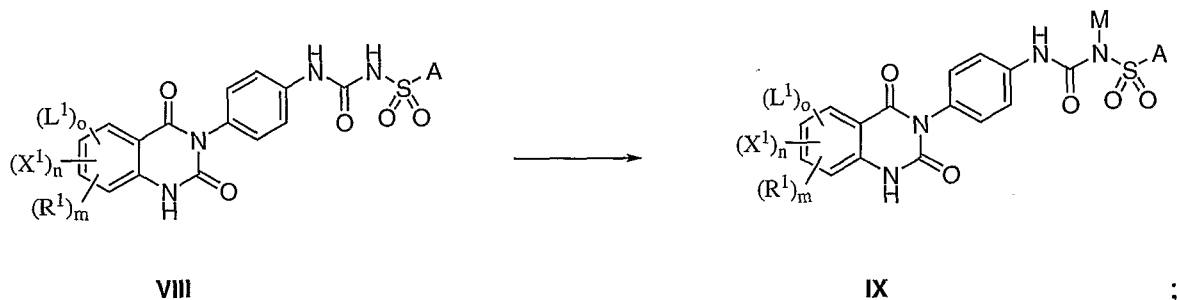


wherein the subscript m is increased and the subscript o is decreased by the number of L^1 groups replaced in VI;

(d) reacting the compound of formula V or VI with a compound of the formula VII to provide a compound of formula VIII, as follows:



(e) optionally, producing a salt, solvate or hydrate of the compound of formula VIII:



wherein M is selected from the group consisting of Na and K.

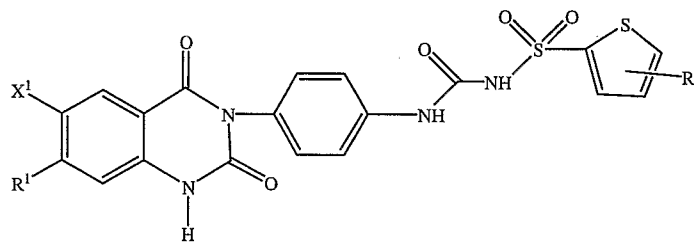
[0070] In one group of embodiments, the present invention provides compounds and methods wherein each L^2 , L^3 and L^4 are independent leaving groups.

In one embodiment the leaving group is selected from the group consisting of halogen, phenoxy, alkoxy, alkylsulfonate, haloalkylsulfonate and arylsulfonate, wherein the alkyl or aryl moiety is optionally substituted with from 1 to 5 electron withdrawing groups..

In one embodiment the leaving group is selected from the group consisting of halogen and phenoxy, optionally substituted with from 1 to 5 electron withdrawing groups. In another group of embodiments, each electron withdrawing group is independently selected from the group consisting of NO₂ and halogen. In another group of embodiments, the electron withdrawing group is F.

[0071] In one group of embodiments, Q is an acyl protecting group. In another group of embodiments, Q is selected from the group consisting of Ac, BOC and CBZ.

[0072] In another group of embodiments, the present invention is directed to a process for preparing compound of formula XVIII:



(XVIII)

wherein

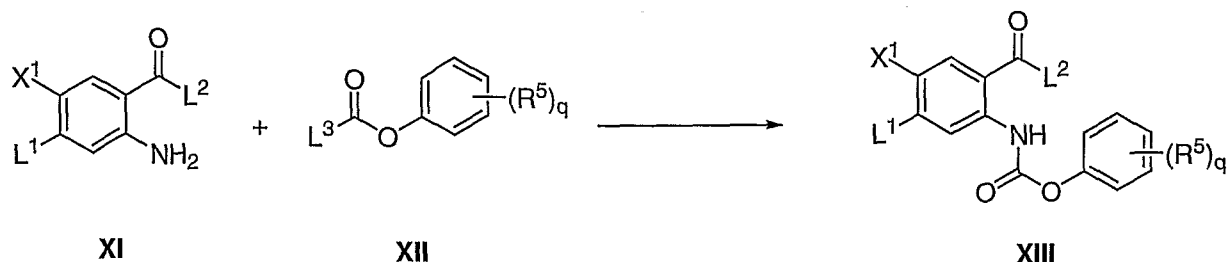
R¹ is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

R² is halogen or -O-C₁₋₁₀-alkyl;

X¹ is halogen:

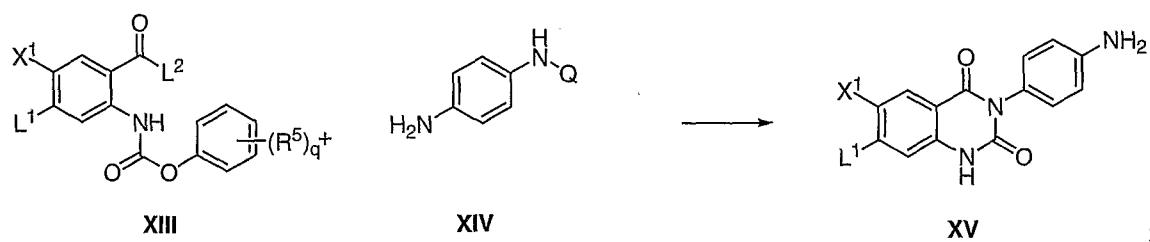
comprising the steps of:

(a) acylating the amino group of a compound of formula XI with a compound of formula XII under basic acylation conditions in the presence of an appropriate solvent to produce a compound of formula XIII as follows:



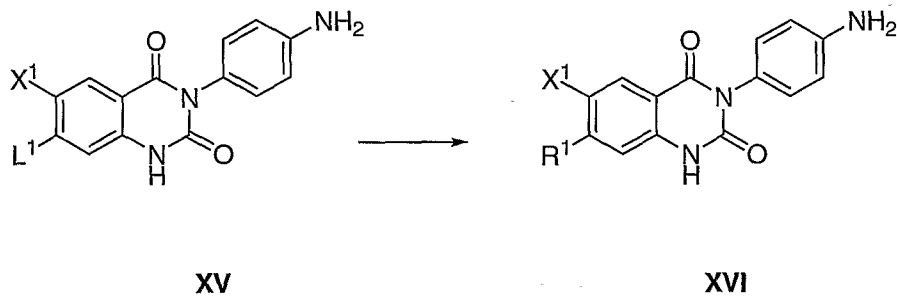
; wherein each L^1 , L^2 and L^3 are independently a leaving group; and each R^5 is an electron withdrawing group and the subscript q is 0, 1, 2, 3, or 4;

- (b) reacting the compound of formula XIII, with an amine containing compound XIV, in the presence of a basic catalyst and a solvent at a suitable temperature to produce a cyclized quinazoline derivative of formula XV, as follows:

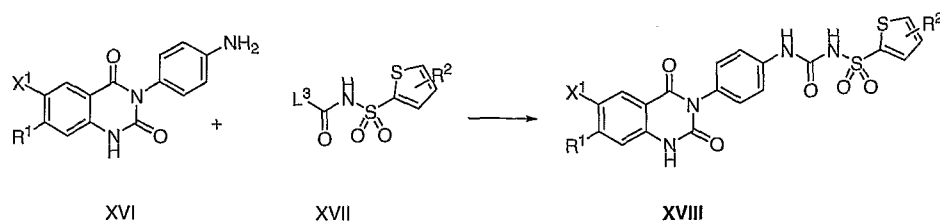


wherein Q is a protecting group;

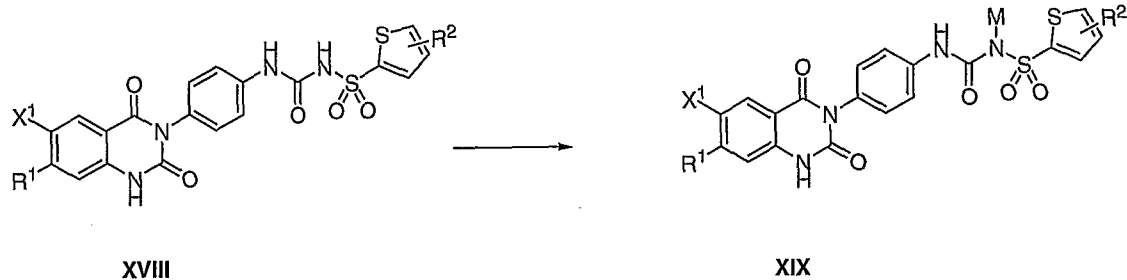
- (c) replacing the leaving group L^1 of the compound of formula XV with R^1 by reacting the compound of formula R^1H to provide a compound of formula XVI as follows:



- (d) reacting the compound of formula XVI with a compound of the formula XVII to provide a compound of formula XVIII as follows:



- (e) and optionally, producing a salt, solvate, or hydrate of the compound of formula XVIII:

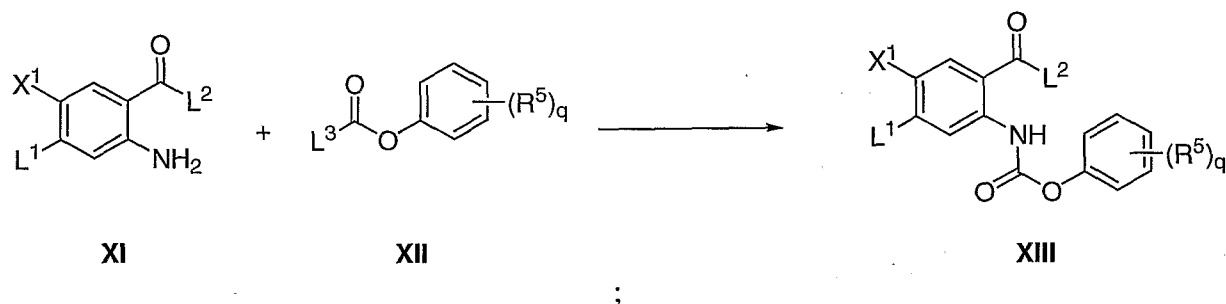


wherein M is Na or K.

[0073] In one group of embodiments, R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl, amino and C₁₋₆-alkylamino.

- 5 [0074] In one group of embodiments, each L^1 and L^3 are independent leaving groups. In another group of embodiments, each L^1 and L^3 are independently selected from the group consisting of halogen, alkylsulfonate, haloalkylsulfonate and arylsulfonate. In one group of embodiments, each L^2 is C₁-C₁₀alkoxy.

- 10 [0075] The invention also provides a process for preparing an intermediate compound having the formula XIII comprising acylating the amino group of a compound of formula XI with a compound of formula XII to produce a compound of formula XIII as follows:

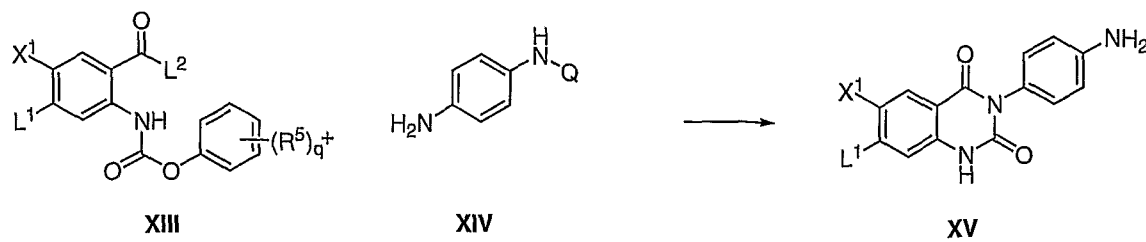


wherein

- 15 X^1 is halogen; and

each L^1 , L^2 and L^3 are independently a leaving group; and each R^5 is an electron withdrawing group and the subscript q is 0, 1, 2, 3, or 4.

- 20 [0076] The invention also provides a process for preparing an intermediate compound having the formula XV comprising reacting the compound of formula XIII, with an amine containing compound XIV, to produce a cyclized quinazoline derivative of formula XV as follows:



wherein

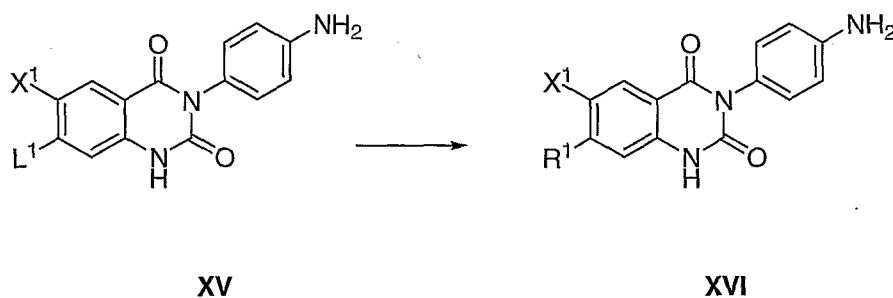
R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

5 X^1 is halogen;

wherein each L^1 and L^2 are independently a leaving group; and each R^5 is independently an electron withdrawing group; and

Q is a protecting group. Within these embodiments, R^5 is independently selected from the group consisting of NO₂ and halogen. In another group of embodiments, R^5 is F.

10 **[0077]** The invention also provides a process for preparing an intermediate compound having the formula XVI comprising replacing the leaving group L^1 of the compound of formula XV with R^1 by reacting the compound of formula R^1H to provide a compound of formula XVI, as follows:



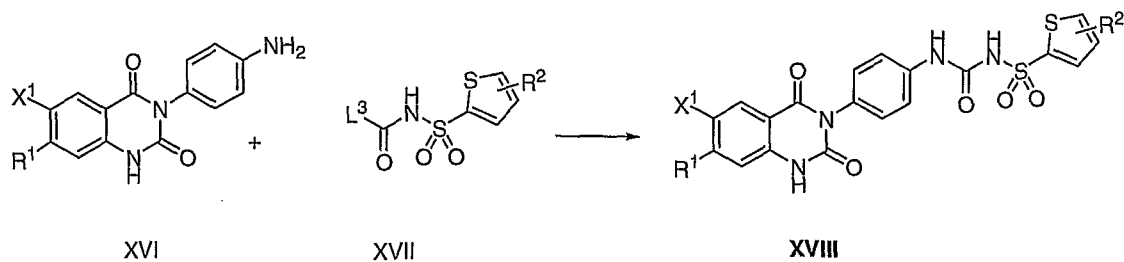
15 wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

X^1 is halogen; and

L^1 is a leaving group.

20 **[0078]** The invention also provides a process for preparing an intermediate compound having the formula XVIII comprising reacting the compound of formula XVI with a compound of the formula XVII to provide a compound of formula XVIII as follows:



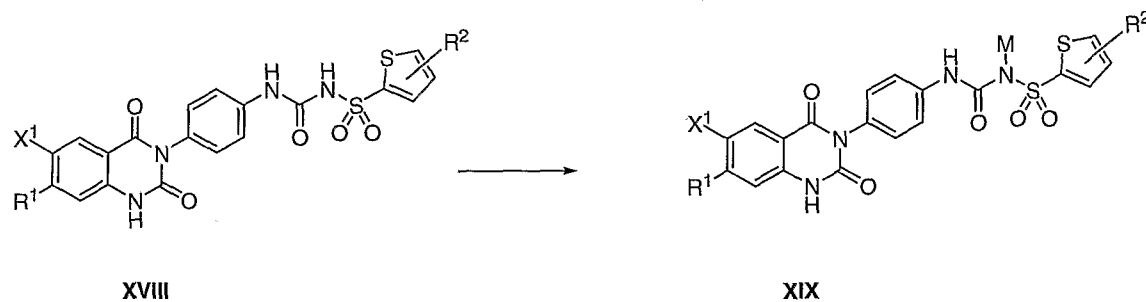
wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -alkylamino;

5 X^1 is halogen; and

wherein L^3 is a leaving group.

[0079] The invention also provides a process for preparing an intermediate compound having the formula A process for preparing compound having the formula XIX comprising producing a salt, solvate, hydrate or prodrug of the compound of formula VIII:



10 XVIII XIX ;

wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -alkylamino;

X^1 is halogen;

15 R^2 is halogen or -O- C_{1-10} -alkyl;

M is selected from the group consisting of Na and K.

[0080] In the above processes, leaving groups such as halogen, phenoxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyloxy, arylsulfonyloxy, etc, may be utilized when necessary except for the reaction point, followed by deprotection. Suitable amino protective groups are, for example, those described in T. W. Greene and P.G.M. Wuts, Protective Groups in Organic
20 Synthesis, John Wiley & Sons Inc. (1999), etc., such as ethoxycarbonyl, t-butoxycarbonyl,

acetyl, benzyl and the like which would be apparent to one of ordinary skill in the art. The protective groups can be introduced and eliminated according to conventional methods used in organic synthetic chemistry.

[0081] Appropriate solvents for particular reaction steps are known to persons of ordinary skill in the art. In one group of embodiments, step (c) may particularly use DMSO as a solvent.

[0082] Examples of base reagents include organic bases, such as triethylamine, diisopropyl ethyl amine, DBU, pyridine, etc., inorganic bases, such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, sodium hydride, etc., metal alkoxides, such as sodium methoxide, potassium tert-butoxide, etc., and the like.

[0083] Appropriate temperatures for conducting particular reaction steps are readily discernable by persons of ordinary skill in the art, for example by monitoring the speed of reaction, solubility of reaction components, and the like. In one group of embodiments, step (c) is conducted at a temperature of about 100 °C to about 120 °C. In one group of embodiments, step (d) is conducted at a temperature of about 55 °C to about 75 °C.

[0084] In such processes, if the defined groups change under the conditions of the working method or are not appropriate for carrying out the method, the desired compound can be obtained by using the methods for introducing and eliminating protective groups which are conventionally used in organic synthetic chemistry. Conversion of functional groups contained in the substituents can be carried out by known methods. See, e.g., R. C. Larock, Comprehensive Organic Transformations, VCH publishers, Inc. (1989), in addition to the above-described processes, and some of the active compounds of formula I may be utilized as intermediates for further synthesizing novel derivatives according to formula VIII.

[0085] The intermediates and the desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, neutralization, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography. The intermediates may be subjected to the subsequent reaction without purification.

[0086] There may be tautomers for some formula VIII, and the present invention covers all possible isomers including tautomers and mixtures thereof, the process of making would be apparent to one of ordinary skill in the art. Where chiral carbons lend themselves to two

different enantiomers, both enantiomers are contemplated as well as procedures for separating the two enantiomers. In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may also exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may

5 employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this

10 invention, may be in one of two configurations (R or S) and both are within the scope of the present invention. In the processes described above, the final products may, in some cases, contain a small amount of diastereomeric or enantiomeric products, however these products do not affect their therapeutic or diagnostic application.

[0087] In the case where a salt of a compound of formula VIII is desired and the compound

15 is produced in the form of the desired salt, it can be subjected to purification as such. In the case where a compound of formula VIII is produced in the free state and its salt is desired, the compound of formula VIII is dissolved or suspended in a suitable organic solvent, followed by addition of an acid or a base to form a salt. Examples of solvents for the recrystallization and salt formation is a lower alcohol, such as methanol or ethanol.

20 [0088] Also, the compounds of formula VIII and pharmaceutically acceptable salts thereof may exist in anhydrous form or in the form of adducts with water (hydrates) or various solvents, which are also within the scope of the present invention.

[0089] It should be understood that the foregoing discussion, embodiments and examples merely present a detailed description of certain preferred embodiments. It will be apparent to

25 those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

[0090] The following non-limiting examples are provided to better illustrate the present invention. The examples are not intended to limit the scope of the present invention and they

30 should not be so interpreted. Amounts are in weight parts or weight percentages unless otherwise indicated. All of the cited patents and publications are incorporated herein by reference. The following specific examples are provided to better assist the reader in the

various aspects of practicing the present invention. As these specific examples are merely illustrative, nothing in the following descriptions should be construed as limiting the invention in any way. Other procedures and adaptations will be apparent to one of ordinary skill in the art upon views these reaction schemes and the structures of the compounds

5 according to the invention. Such procedures are deemed to be within the scope of the present invention.

VIII. Examples

General methods

10 [0091] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, 1967-2004, Volumes 1-22; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, 15 Volumes 1-5 and Supplementals; and *Organic Reactions*, Wiley & Sons: New York, 2005, Volumes 1-65. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

20 [0092] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

25 [0093] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C, and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20 °C to about 75 °C.

30 [0094] Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are well known in the art.

[0095] The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Alliance chromatography system with a 2695 Separation Module (Milford, Mass.). The analytical columns were C-18 SpeedROD RP-18E Columns from Merck KGaA (Darmstadt, Germany). Alternately, characterization was performed using a Waters Unity (UPLC) system with Waters Acquity UPLC BEH C-18 2.1 mm x 15 mm columns. A gradient elution was used, typically starting with 5% acetonitrile/95% water and progressing to 95% acetonitrile over a period of 5 minutes for the Alliance system and 1 minute for the Acquity system. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from EMD Chemicals, Inc. (Gibbstown, NJ). In some instances, purity was assessed by thin layer chromatography (TLC) using glass backed silica gel plates, such as, for example, EMD Silica Gel 60 2.5 cm x 7.5 cm plates. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

[0096] Mass spectrometric analysis was performed on one of two Agilent 1100 series LCMS instruments with acetonitrile / water as the mobile phase. One system using TFA as the modifier and measures in positive ion mode [reported as MH⁺, (M+1) or (M+H)⁺] and the other uses either formic acid or ammonium acetate and measures in both positive [reported as MH⁺, (M+1) or (M+H)⁺] and negative [reported as M⁻, (M-1) or (M-H)⁻] ion modes.

[0097] Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 400 MHz NMR (Palo Alto, Calif.). The spectral reference was either TMS or the known chemical shift of the solvent.

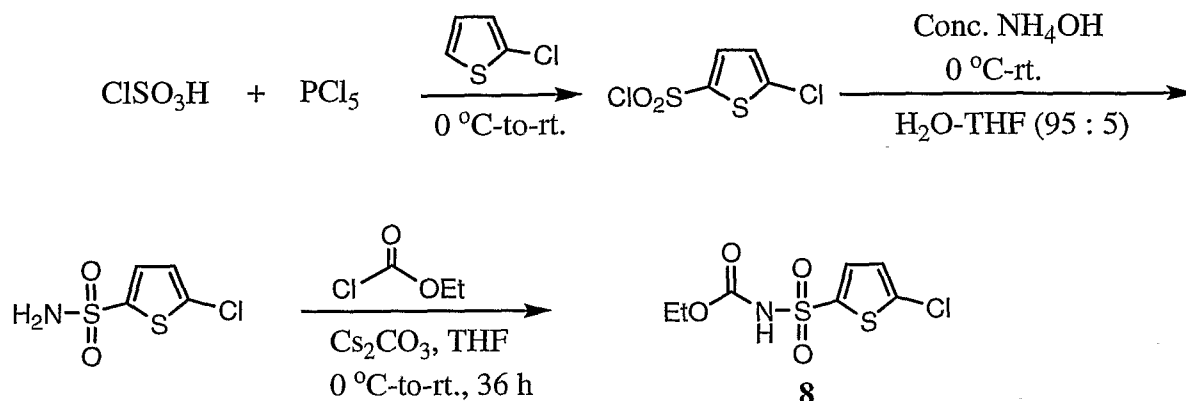
[0098] The purity of some of the invention compounds is assessed by elemental analysis (Robertson Microlit, Madison NJ.).

[0099] Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, Mass.).

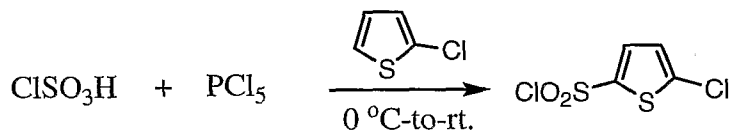
[0100] Preparative separations were carried out using either an Sq16x or an Sg100c chromatography system and prepackaged silica gel columns all purchased from Teledyne Isco, (Lincoln, NE). Alternately, compounds and intermediates were purified by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a C-18 reversed phase column. Typical solvents employed for the Isco systems and flash

column chromatography were dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous hydroxyamine and triethyl amine. Typical solvents employed for the reverse phase HPLC were varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

5 **Example 1: Synthesis of the intermediate sulfonylurea carbamate (8)**



Step 1 - Preparation 5-chlorothiophene-2-sulfonyl chloride:



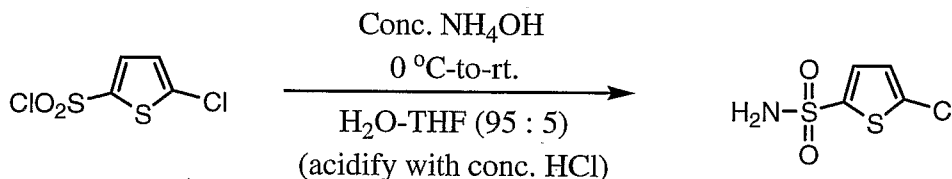
- 10 [0101] The following procedure was adapted from C. A. Hunt, *et al. J. Med. Chem.* **1994**, 37, 240-247. In a three-necked R.B. flask, equipped with a mechanical stirrer, an air condenser, a dropping funnel, and a moisture-guard tube, was placed chlorosulfonic acid (240 mL, 3.594 mol). Under stirring, PCl_5 (300 g, 1.44 mol, 0.40 equiv) was added in portions, over ca. 45 mins. During the addition, a large volume of HCl gas evolved vigorously, but the
- 15 temperature of the mixture did not rise significantly ($<40\text{ }^\circ\text{C}$). By the time all the PCl_5 had been added, an almost clear, pale yellow solution resulted, with only a few solid pieces of PCl_5 floating in the suspension. It was stirred until gas evolution ceased (0.5 h).

- [0102] Then the reaction vessel was cooled in ice, and 2-chloro-thiophene (66.0 mL, 0.715 mol) was added via the dropping funnel, over 1.0 h. With the addition of the very first few
- 20 drops of 2-Cl-thiophene, the mixture turned dark purple, and by the time all of the thiophene had been added, a dark purple solution resulted. During the addition, HCl gas evolved

continuously, at a slow rate. The reaction mixture was then stirred at room temperature overnight.

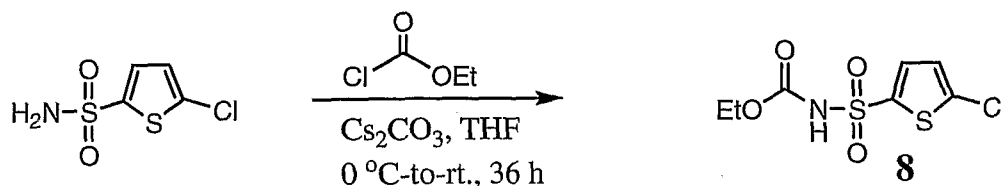
[0103] Then the mixture, dark-purple clear solution, was added dropwise to crushed ice (3 L), over 0.5 h. On addition to ice, the purple color disappeared instantaneously; the colorless thin emulsion was stirred mechanically at room temperature for ca. 15 h. Then the mixture was extracted with CH₂Cl₂ (3 x 300 mL). The combined CH₂Cl₂-extract was washed with water (1x 200 mL), saturated NaHCO₃ (1x 250 mL), brine (1 x 100 mL), dried (Na₂SO₄), and concentrated on a rotary evaporator to yield the crude product as a pale yellow glue, which showed a tendency to solidify, yielding a semi-solid mass. This was then purified by high-vacuum distillation (bp 110-112°/12mm) to yield 135.20 g (88%) of the title compound as a colorless/pale-yellow semi solid.

Step 2 - 5-chlorothiophene-2-sulfonamide:



[0104] The following procedure was adapted from C. A. Hunt, *et al. J. Med. Chem.* **1994**, 37, 240-247. In a three-necked R. B. flask, equipped with a mechanical stirrer, conc. NH₄OH (500 mL, 148.50 g NH₃, 8.735 mol NH₃, 13.07 equiv NH₃) was placed. The flask was cooled in ice and 5-chlorothiophene-2-sulfonyl chloride (145.0 g, 0.668 mol) was added, in portions over 0.5 h (it is a low-melting solid, and it was melted by warming, which was then conveniently added via a wide-bored polyethylene pipette). The sulfonyl chloride immediately solidifies in the reaction flask. After all the sulfonyl chloride had been added, the flask containing it was rinsed with THF (25 mL), and this also was transferred to the reaction vessel. Then the heavy suspension was stirred at room temperature for ca. 20 h. At the end of this time the reaction mixture was still a suspension but of a different texture.

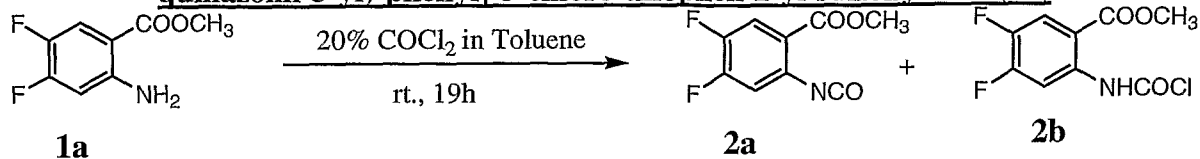
[0105] Then the mixture was cooled in ice, diluted with H₂O (1.5 l), and acidified with conc. HCl to pH ca. 3. The solid product was collected by filtration using a Buchner funnel, rinsed with cold water, and air-dried to afford the title compound as a colorless solid, 103.0 g (78%). MS (M-H): 196.0; 198.0

Step 3 - Ethyl 5-chlorothiophen-2-ylsulfonfylcarbamate:

[0106] A 2-L 3-necked R.B. flask, equipped with a mechanical stirrer and a dropping funnel, was charged with sulfonamide (60.0 g, 303.79 mmol), and Cs_2CO_3 (200g, 613.83 mmol, 2.02 equiv) in THF (900 mL). The clear solution was cooled in ice, and ethyl chloroformate (70.0 mL, 734.70 mmol, 2.418 equiv) was added over ca. 30 mins. The heavy suspension was then stirred at room temperature for ca. 36 h.

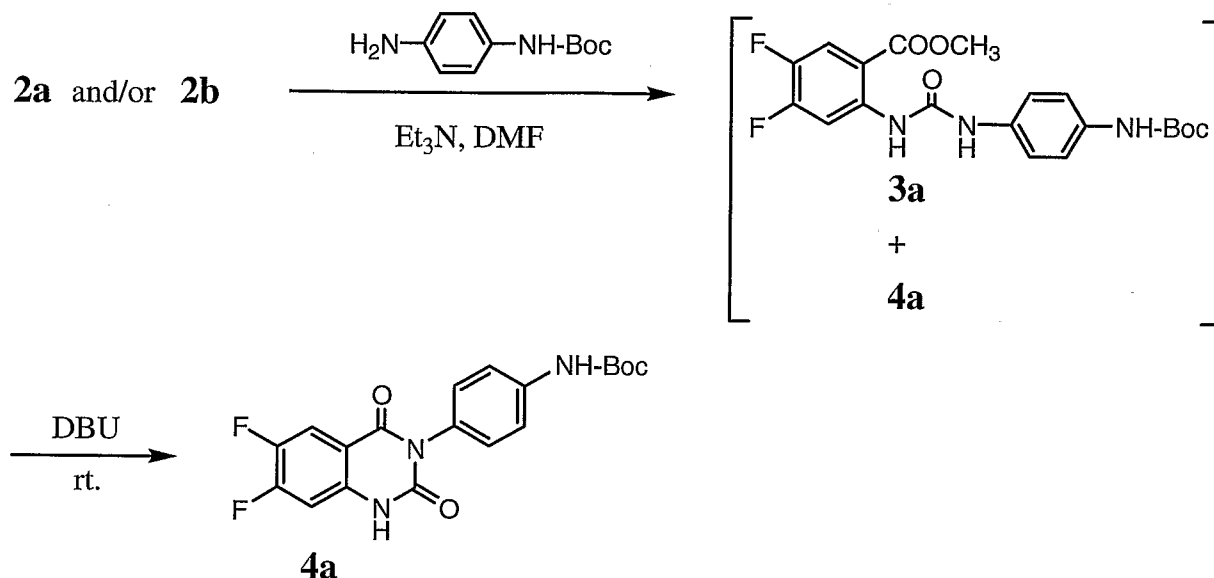
[0107] Then the mixture was diluted with water (200 mL) to yield a clear colorless solution, which was concentrated on rotary evaporator to one-third its volume. This was then diluted with EtOAc (250 mL), cooled in ice, and acidified with 6N HCl to pH ca. 1. The biphasic mixture was transferred to a separatory funnel, layers were separated, and the aqueous layer was again extracted with 2 x 75 mL EtOAc. The combined organic extract was washed with water/brine (2 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4 , and concentrated to yield the title compound as lightly colored oil. This was purified by filtration through a silica-gel plug. The crude product was applied to the silica-gel plug on a sintered funnel in EtOAc, and then was eluted with EtOAc (1 liter). Concentration of the EtOAc filtrate provided the title compound **8** as a colorless solid, 71.28 g (87%). MS (M-H): 268.0; 270.0. ^1H NMR (DMSO): δ 7.62 (d, 1H), 7.25 (d, 1H), 4.10 (q, 2H), 1.16 (t, 3H).

Example 2: Synthesis of [4-(6-fluoro-7-methylamino-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-phenyl]-5-chloro-thiophen-2-yl-sulfonylurea (7a)

*Step 1*

[0108] Aniline **1** (^1H NMR (DMSO): δ 7.58 (dd, 1H), 6.72 (dd, 1H), 3.77 (s, 3H); 6.0 g, 32.085 mmol) was placed in a 500 mL round bottomed flask and 20% phosgene in toluene

(175 mL, 332.50 mmol, 10.36 equiv) was added. The resulting somewhat sticky suspension was then magnetically stirred overnight at room temperature resulting in a clear, colorless solution. An aliquot removed, blown dry with argon, quenched with MeOH, and analyzed by RP-HPLC/MS to show no unreacted aniline **1** and clean formation of the isocyanate **2a** and/or carbamoyl chloride **2b** as analyzed as its methyl-carbamate. The mixture was concentrated first by rotary evaporation and then under high vacuum to yield 6.76g (99% yield) of the isocyanate **2a** and/or carbamoyl chloride **2b** as a free-flowing colorless solid.

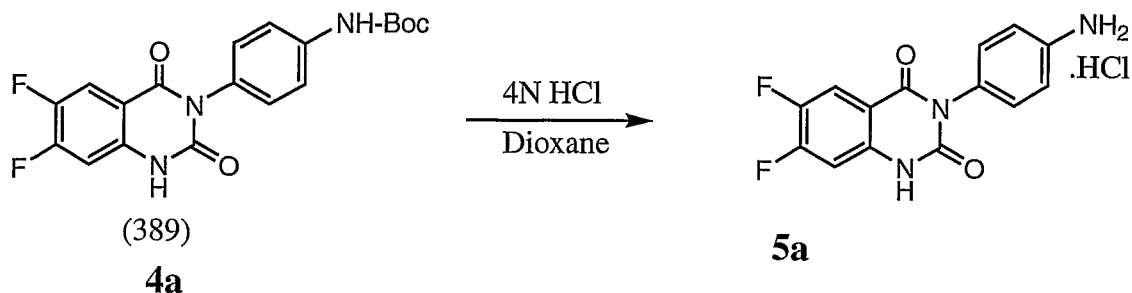


Step 2

[0109] In a 500 mL R. B. flask was placed N-Boc-1, 4-phenylenediamine (6.22 g, 29.866 mmol, 1.20 equiv) in DMF (100 mL). Triethylamine (5.30 mL, 38.025 mmol, 1.52 equiv) was syringed in. Then the clear, dark-brown solution was treated with a solution of the isocyanate **2a** (5.30 g, 24.88 mmol) and/or carbamoyl chloride **2b** in DMF (50 mL), dropwise, over 15 minutes. After the addition was over, a slightly turbid mixture resulted, which was stirred overnight at room-temperature. An aliquot was analyzed, after quenching with MeOH, to show no unreacted isocyanate, and clean formation of the urea, **3a**, and quinazoline-1, 3-dione, **4a**, in a ratio of ca. 2.5: 1. MS (M-H): 388.0.

[0110] DBU (3.75 mL, 25.07 mmol, ca. 1.0 equiv) was then syringed in, dropwise, over 5 minutes, resulting in a clear dark-brown solution. This was stirred at room temperature for 3.0 h resulting in a turbid mixture. HPLC analysis showed no urea **3a** and clean formation of

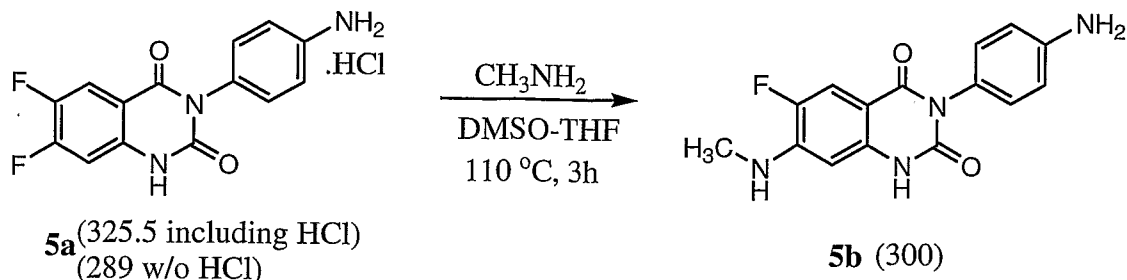
the quinazoline-1,3-dione **4a**. The reaction mixture was concentrated on a rotary evaporator to yield the crude product as a solid. This was dried under high vacuum, and then triturated with CH₂Cl₂/H₂O (5:1) to yield 8.40 g of **4a** as an almost colorless solid (87% yield). ¹H NMR (DMSO): δ 9.39 (s, 1H), 7.68 (dd, 1H), 7.45 (d, 2H), 7.03 (m, 2H), 6.98 (dd, 1H), 1.48 (s, 9H).



Step 3

[0111] The N-Boc-aniline **4a** (4.0g, 10.28 mmol) was placed in a round-bottomed flask and 4N HCl in dioxane (50.0 mL, 200 mmol, 19.40 equiv) was added. The heavy, negligibly solvated suspension was stirred at room temperature for 5.0 h. HPLC showed no starting material and clean formation of the aniline **5a**. The mixture was then concentrated on a rotary evaporator to yield the crude product. The solid thus obtained was triturated with CH₂Cl₂ to yield 3.22g of pure **5a** as an almost colorless solid (96% yield). MS (M-H): 290.3. ¹H NMR (DMSO): δ 11.75 (s, 1H), 7.88 (dd, 1H), 7.32 (m, 4H), 7.21 (dd, 1H).

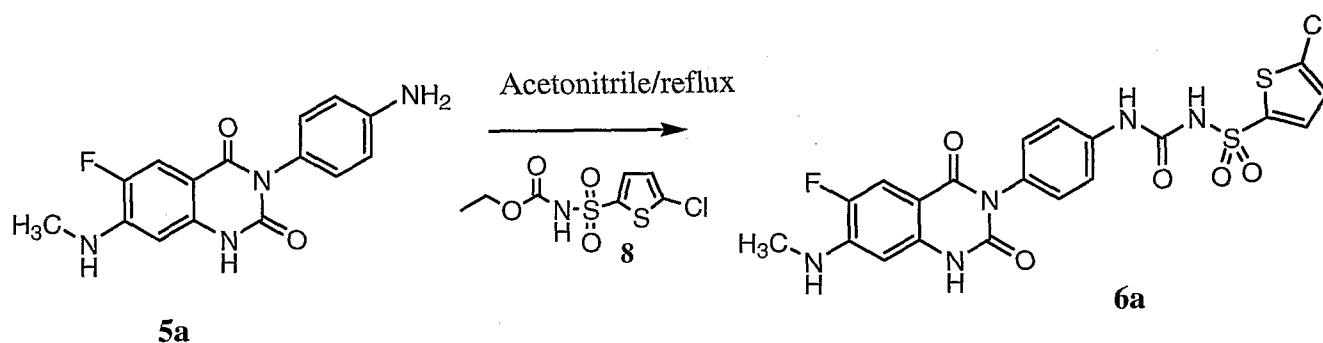
Step 4



[0112] The difluoro-compound, **5a** (1.0g, 3.072 mmol) was placed in a screw-cap sealed tube. DMSO (20 mL) was added, followed by methylamine (2.0M in THF) (15.0 mL, 30 mmol, 9.76 equiv), resulting in a clear solution. This was then heated in an oil bath to 110 °C

for 3h. HPLC showed no unreacted **5a** and clean formation of **5b**. The mixture was then cooled to room temperature, all the MeNH₂ and THF were evaporated, and the residue was diluted with 100 mL water to precipitate **5b**. After stirring for ca. 2 h at room temperature, the colorless solid was collected by filtration through a Buchner funnel and rinsed with H₂O (100 mL), and air-dried. HPLC analysis of this solid showed it to be pure and devoid of any DBU. This solid was further purified by triturating with Et₂O, and then CH₂Cl₂ as in the previous route to this aniline to give 875 mg of the title compound (95% yield). MS (M+1) 301.2. ¹H NMR (DMSO): δ 11.10 (s, 1H), 7.36 (d, 1H), 6.78 (d, 2H), 6.75 (m, 1H), 6.56 (d, 2H), 6.20 (d, 1H), 5.18 (d, 2H), 2.76 (d, 3H).

Step 5 - Synthesis of 1-(5-chlorothiophen-2-ylsulfonyl)-3-(4-(6-fluoro-7-(methylamino)-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)phenyl)urea (7a):

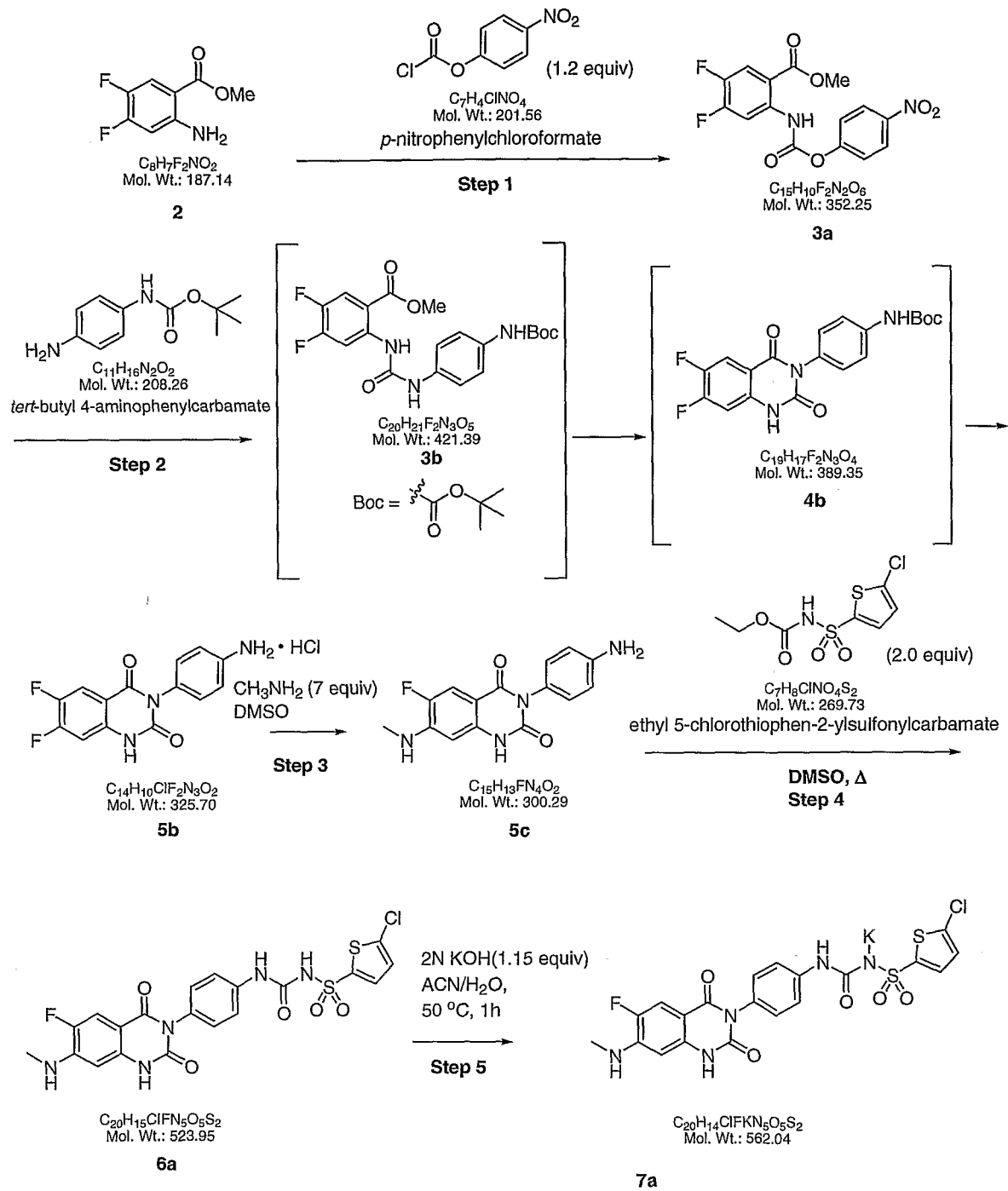


[0113] The reaction mixture comprising of the aniline (16.0 g, 53.33 mmol) and ethylsulfonyl-carbamate (28.77g, 106.66 mmol, 2.0 equiv) in CH₃CN (1300 mL) was heated to reflux for 36h. During this time, the reaction mixture remained as a heavy suspension. HPLC analysis showed a clean reaction, and <1% unreacted aniline. The heavy suspension was cooled to room temperature and filtered through a Buchner funnel. The colorless solid product was further rinsed with CH₃CN (3 x 40 mL). HPLC of the filtrate showed the presence of only a trace amount of the desired product, most of it being the excess carbamate. The crude product was then triturated with CH₂Cl₂ (400 mL), and the almost colorless solid product was collected by filtration through a Buchner funnel: Yield, 25.69g (92%). MS (M+1): 524.0; 526.0. ¹H NMR (DMSO):

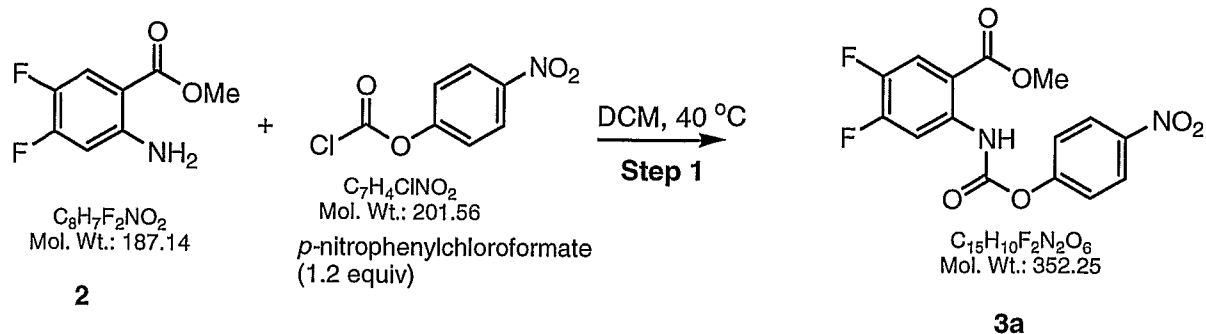
δ 11.20 (s, 1H), 9.15 (s, 1H), 7.68 (d, 1H), 7.42 (d, 2H), 7.36 (d, 1H),

7.26 (m, 1H), 7.16 (d, 2H), 6.78 (m, 1H), 6.24 (d, 1H), 2.78 (d, 3H).

Example 3: Synthesis of [4-(6-fluoro-7-methylamino-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-phenyl]-5-chloro-thiophen-2-yl-sulfonylurea (7a)

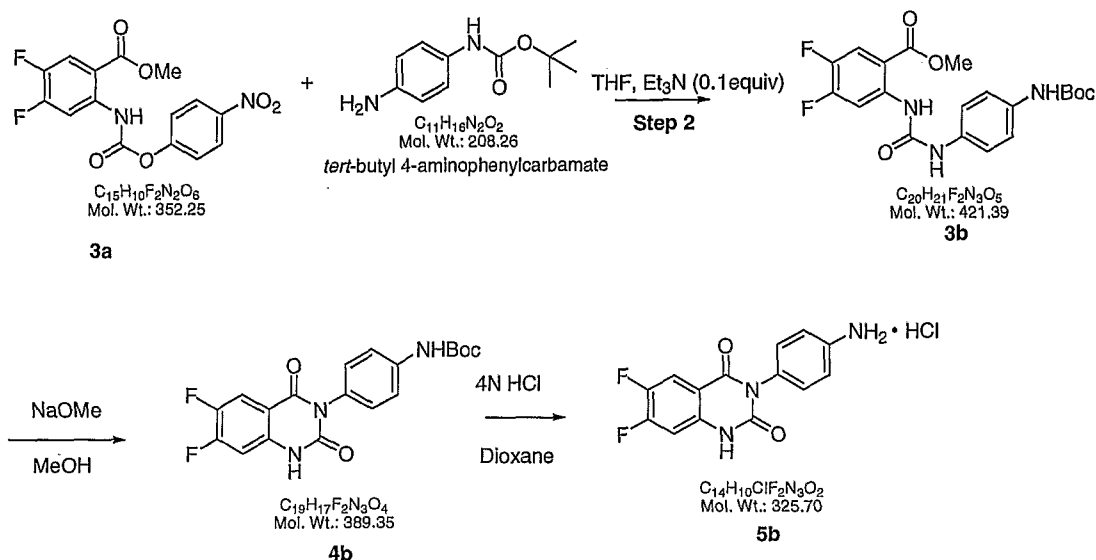


5 Step 1:



[0114] Methyl 2-amino-4,5-difluorobenzoate [**2**] (38 Kg, 1.0 eq) and dichloromethane (560 Kg, 8X, ACS >99.5%) were charged to a PP1-R1000 reactor (2000L GL reactor). The reaction mixture was agitated for 5 mins. 4-Nitrophenylchloroformate(49.1 Kg, 1.2 equiv) was charged into PP1-R2000 reactor (200L) followed by dichloromethane (185Kg) and agitated the contents for 5mins. After pressurizing the 200L reactor the 4-nitrophenylchloroformate solution was transferred into the 2000L reactor containing dichloromethane solution of [**2**]. The reaction mixture was heated to $40 \pm 5^\circ C$ (reflux) under nitrogen gas purge for 3 hrs. The representative TLC analysis confirmed reaction completion (in-process TLC, no compound **2** remaining; 99:1 $CHCl_3$ -MeOH). The solution was cooled to $30^\circ C$ and distilled off 460 Kg of dichloromethane under vacuum. The 2000L reactor was charged with 520 Kg of hexanes and cooled the contents of the reactor to $0 \pm 5^\circ C$ and agitated for 4 hrs. The solid obtained was filtered through GF Nutsche filter lined with a sheet of T-515 LF Typar filter and a sheet of Mel-Tuf 1149-12 filter paper. The filter cake was washed with 20 Kg of hexanes and vacuum dried at $35^\circ C$ until constant weight attained. The dry product was discharged (70.15 Kg) with 98% yield. The product confirmed by ^1H NMR and TLC analysis.

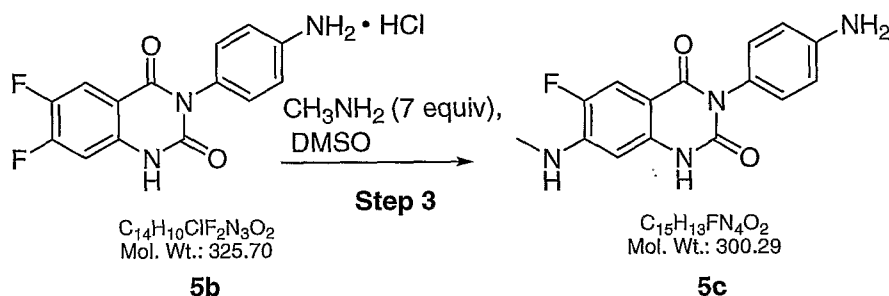
Step 2. Synthesis of 3-(4-aminophenyl)-6,7-difluoroquinazoline-2,4(1H,3H)-dione hydrochloride, compound **5b**



[0115] The PP1-R1000 (2000L GL reactor) reactor was charged with **3a** (64.4 Kg, 1.0 eq), anhydrous tetrahydrofuran (557 Kg) and triethylamine (2.2 Kg, 0.1 equiv). The charging line of 2000L GL reactor was rinsed with tetrahydrofuran (10 Kg). The contents of the reactor were agitated for 25 mins. during that period complete solution was obtained. The PP1-R2000 (200L HP reactor) reactor was charged with N-Boc-p-phenylenediamine (38 Kg, 1.0 equiv), tetrahydrofuran (89 Kg) and agitated for 30 mins. until complete solution obtained. The contents of the 200L HP reactor were transferred to the 2000L GL reactor containing the compound **3a** and then heated at $65 \pm 5^\circ\text{C}$ for 2 hrs. The reaction was deemed complete monitored by HPLC after confirming the disappearance of starting material **3a** (in-process specification < 1%). The contents of 2000L GL reactor were cooled to $20 \pm 5^\circ\text{C}$ and then charged with sodium methoxide (25% solution in methanol, 41.5 Kg, 1.05 equiv.) over 20 mins. maintaining the temperature below 30°C . The charging lines were rinsed with tetrahydrofuran (10 Kg). The contents were agitated at $25 \pm 5^\circ\text{C}$ for 4 hrs. In-process HPLC analysis confirmed the completion of the reaction when the amount of compound **3b** remaining in the reaction mixture is < 1%. To this reaction mixture added filtered process water (500 Kg) and distilled under vacuum the 2000L GL reactor contents into clean 200L GL receiver until 300 Kg of solvent is distilled. The solids obtained were filtered using GL Nutsche filter and washed with process filtered water until the color of the solid the compound **4b** is white to grayish. The 2000L GL reactor is charged with wet compound **4b** filter cake, dioxane (340 Kg) and agitated the contents for 1 hr. The filterable solid obtained were filtered through GL Nutsche filter with a sheet of T-515 LF Typar filter paper. The solid cake was blow dried for 2 hrs and then charged with dioxane (200 Kg) into the 2000L GL reactor. The contents were agitated for 10 min. and then charged with 4 N HCl in

dioxane (914 Kg) over 3 hrs and maintaining the internal temperature below 30 °C. The charging line was rinsed with additional dioxane (10Kg) and the contents of the reactor were agitated for 6 hrs at 25 ± 5 °C. The completion of the reaction is monitored by HPLC (in process control compound 4 is < 1% in the reaction mixture) for the conversion of compound 4b to compound 5b. The contents of the reactor were cooled to 5 ± 5 °C for 2 hr and the solid obtained was filtered through GL Nutsche filter followed by washing with dioxane (50 Kg). The filter cake was blow dried with 8 ± 7 psig of nitrogen for 30 mins. and purity analyzed by HPLC. The filtered solid was dried to constant weight in vacuum oven at 45 °C for 48 hr. The compound 5b (65.8 Kg, actual yield 110.6%) was discharged and analyzed by ¹HNMR and HPLC analysis. ¹H NMR (DMSO): δ 11.75 (s, 1H), 7.88 (dd, 1H), 7.32 (m, 4H), 7.21 (dd, 1H).

Step 3. Synthesis of 3-(4-aminophenyl)-6-fluoro-7-(methylamino)quinazoline-2,4(1H,3H)-dione, Compound 5c



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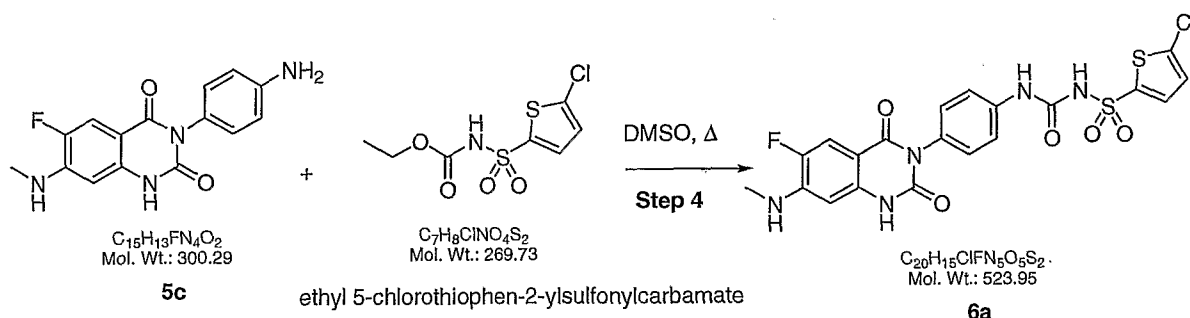
[0116] The PP1-R2000 (200 L HP reactor) was charged with compound 5b (18 Kg, 1.0 eq.) and pressurized with 100 ± 5 psig of nitrogen. Vent the nitrogen from the reactor through the atmospheric vent line then open the condenser valve and then charged dimethyl sulfoxide into the reactor (>99.7%, 105 Kg) under blanket of argon. The reactor contents were agitated at 22 °C (19-25 °C) for 15 mins. and then pulled maximum achievable vacuum on the 200L HP reactor and close all the valves. Using the established vacuum charged to the 200L HP reactor methylamine (33% wt % in absolute ethanol, 37.2 Kg) at a rate that maintains the internal temperature at 25 ± 5 °C and kept a nitrogen blanket on the reagent solution during charging. After rinsing the charging line with dimethyl sulfoxide (5 Kg) closed the 200L HP reactor condenser valve and heated the reactor contents to 110 ± 5 °C. The contents of the reactor were agitated for at least 5 hrs. at 110 ± 5 °C. In-process HPLC taken after 5hr 40 mins. showed compound 5b content of 0.09%, indicating completion of the reaction (in-

20

25

process specification $\leq 1\%$). The contents of 200L HP reactor were cooled to $25 \pm 5^\circ\text{C}$. While the 200L reactor is cooling, closed all the valves of the PP1-R1000 reactor (2000L GL reactor) and charged with process filtered water (550 Kg). The contents of the 200L HP reactor were transferred to the 2000L GL reactor over 15 minutes followed by rinsing the charging line with process filtered water (50 Kg). The contents of the 2000L GL reactor were agitated for 2 hrs at $5 \pm 5^\circ\text{C}$. The filterable solids obtained were filtered onto PPF200 (GL nutsche filter) fitted with Mel-Tuf 1149-12 filter paper under vacuum. The wet filter cake was discharged and transferred into pre-lined vacuum trays with Dupont's fluorocarbon film (Kind 100A). Clamped down the special oven paper (KAVON 992) over the vacuum trays containing the wet compound 6 and transferred to the vacuum oven tray dryer. The oven temperature was set to 55°C and compound 6 dried to a constant weight for 12 hrs. The product 5c was discharged (12.70 Kg) in 76.5% yield (expected 85-95%). HPLC shows 98.96 % purity and ^1H NMR confirmed the structure for compound 5c. ^1H NMR (DMSO): δ 11.10 (s, 1H), 7.36 (d, 1H), 6.78 (d, 2H), 6.75 (m, 1H), 6.56 (d, 2H), 6.20 (d, 1H), 5.18 (d, 2H), 2.76 (d, 3H).

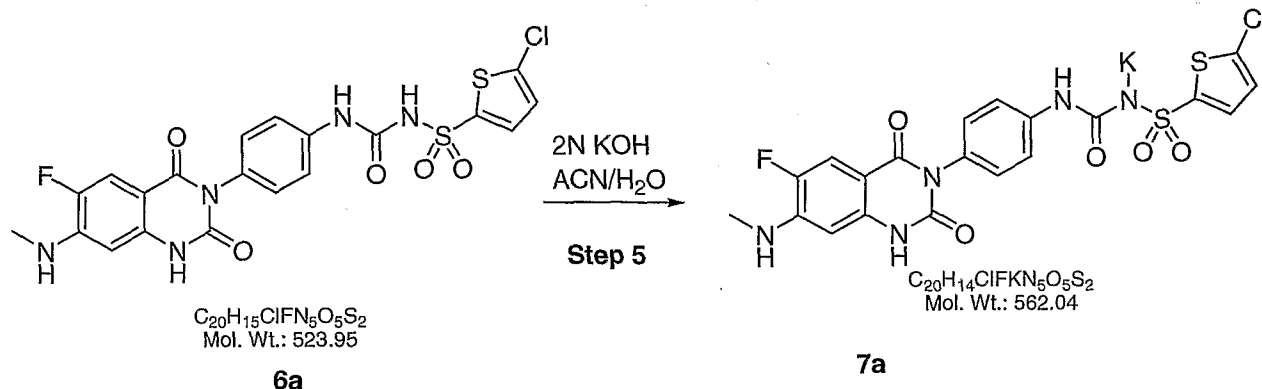
Step 4. 5-Chloro-N-(4-(6-fluoro-7-(methylamino)-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)phenylcarbamoyl)thiophene-2-sulfonamide



[0117] The PP1-R2000 (200L HP reactor) reactor was charged with 6 (20.7Kg, 1.0 equiv), Ethyl 5-chlorothiophene-2-ylsulfonfylcarbamate (37.5 Kg, 2.0 equiv, >95%), dimethyl sulfoxide (>99%, 75 Kg) and agitated for 15 mins. While pulling maximum achievable vacuum, heated the 200L HP reactor Number PP1-R2000 at $65 \pm 5^\circ\text{C}$ for 15 hrs. Took the representative sample from the reactor for HPLC analysis, in-process HPLC indicated <0.9% compound 5c remaining in the reaction mixture (in-process criteria for reaction completion compound 6 < 1%). Charged the 800L reactor number PP5-R1000 with process filtered water (650 Kg) and then transferred the 200L HP contents to the 800 L while maintaining the

internal temperature below 25 °C. The Rinsed the 200L HP reactor with dimethyl sulfoxide (15 Kg) and transfer to the 800L reactor which was then agitated for 2 hrs at 5 ± 5 °C. The solid formed was filtered through filter PP-F2000 to a 200L GL receiver under vacuum and rinsed the filter cake with process filtered water (60 Kg). Took a representative sample of the wet cake and did HPLC analysis, if the purity of compound **6a** is <95% (in-process control < 95% the dichloromethane trituration need). The 800L GL reactor was charged with all the wet compound **6a**, dichloromethane (315 Kg) and agitated the contents for 3 hrs. The solid was filtered through GL nutsche filter lined with 1 sheet of T515 LF TYPAR filter under vacuum. The filter cake was washed with dichloromethane (50Kg) and blow dried the cake with 8 ± 7 psig of nitrogen for 15 mins. Transferred the filter cake into pre-lined vacuum trays with Dupont fluorocarbon film (Kind 100A) and then into the vacuum oven tray dryer set at 60 °C for 12 hrs. The dried compound **6a** was isolated (33.6 Kg, 93% yield) with HPLC purity of 93.5% and 4.3% of sulfonamide. ¹H NMR confirmed the structure for compound **7**. ¹H NMR (DMSO): δ 11.20 (s, 1H), 9.15 (s, 1H), 7.68 (d, 1H), 7.42 (d, 2H), 7.36 (d, 1H), 7.26 (m, 1H), 7.16 (d, 2H), 6.78 (m, 1H), 6.24 (d, 1H), 2.78 (d, 3H).

Step 5. Potassium (5-chlorothiophen-2-ylsulfonyl)(4-(6-fluoro-7-(methylamino)-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)phenylcarbamoyl)amide, 7a

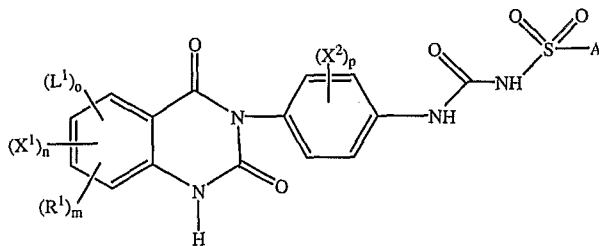


[0118] The 800L GL reactor number PP5-R1000 was charged with acetonitrile (134 Kg), WFI quality water (156 Kg) and agitated the contents for 5 mins. To this then charged compound **6a** (33.6 Kg, 1.0 equiv) and the reaction mixture was a suspension at this point. The suspension was charged with aqueous solution (WFI water, 35 Kg) of potassium hydroxide (4.14 Kg, 1.15 equiv, >85%) at a rate that maintains the internal temperature below 30 °C. The charging lines were rinsed with WFI quality water (2 Kg) followed by heating the 800L GL reactor contents to 50 ± 5 °C for 1 hr. The contents were then filtered hot through a

bag filter, then a seven cartridge 0.2 μ polish filter to clean HDPE drums. The hot filtration system was maintained through out the filtration process so no material crashes out of the solution. Cool the 800L GL reactor jacket to 25 ± 5 °C before proceeding to the reactor rinse. Rinsed the 800L GL reactor with pre-mixed solution of acetonitrile (8.5 Kg) and WFI quality water (10 Kg) through the filter system into the drums labeled as **7a** hot filtration. Using the pressure vessel the 800L GL reactor was rinsed with WFI quality water (20 Kg) followed by acetone (20 Kg) then blow it dry with nitrogen (3+ 2psig). The 800GL reactor bottom valve was closed and pulled 20 + 10 inches Hg of vacuum, then break the vacuum and charge the reactor with the contents of the drums labeled as **7a** hot filtration. Cooled the 800L GL reactor number PP5-R1000 contents to 20 ± 5 °C and then using a polish filter (PP-PF09), charged the reactor with methanol (373 kg, >99%) maintaining the internal temperature below 30°C. The contents of the 800GL reactor number PP5-R1000 were cooled to 15 ± 5 °C followed by agitation of the contents for 12 hrs at this temperature. During this time the filterable solids were filtered through a clean filter apparatus (PP-F1000) into clean 200L GL receiver (PPR-04) followed by pressurizing the reactor, pulled 20 + 10 inches Hg of vacuum on the filter/receiver and filtered the contents. The filter cake was washed with methanol (30 Kg) and blow dried with 8 + 7 psig of nitrogen for 10 mins. The vacuum oven tray dryer temperature was set to 80 °C prior to loading the wet cake of **7a**. Transferred the wet filter cake into the pre-lined vacuum trays with Dupont's fluorocarbon film –Kind 100A and clamped down the special oven paper (Kavon Mel Tuf paper) over the vacuum trays containing the product wet **7a** and transferred to the vacuum oven tray dryer. Set the oven temperature to 80 °C and dry the wet **7a** to a constant weight (constant weight is defined as tray reading at least 1 hr apart having the same weight within + 50 g. The representative sample was analyzed for residual solvents (residual solvent specifications for API) and it met the specifications. The final API was subjected to equilibration with water (5-6%) for 12 hrs with a tray of WFI quality water present, then thoroughly turned and allowed to stand for an additional 12 hrs and finally subjected to KF analysis (5.5% water content). Transferred the **7**-potassium (21.80 Kg, 60.6% yield) to double heavy-duty poly bags and stored in secondary containment. HPLC taken showed purity of 99.7% for **7a** and ^1H NMR confirmed the structure for **7a**. ^1H NMR (DMSO): δ 11.14 (s, 1H), 8.60 (s, 1H), 7.48 (m, 2H), 7.35 (d, 1H), 7.22 (d, 1H), 6.95 (m, 3H), 6.75 (m, 1H), 6.22 (d, 1H), 2.78 (d, 3H).

WHAT IS CLAIMED IS:

1. A process for preparing compound of formula VIII:



(VIII)

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

each X^1 is independently selected from the group consisting of:

halogen, polyhaloalkyl, $-OR^3$, $-SR^3$, $-CN$, $-NO_2$, $-SO_2R^3$, $-C_{1-10}$ -alkyl, $-C_{3-8}$ -cycloalkyl, aryl, aryl-substituted by 1-4 R^3 groups, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, and a 5 to 10 membered fused or non-fused aromatic or nonaromatic heterocyclic ring system, having 1 to 4 heteroatoms independently selected from N, O, and S, with the proviso that the carbon and nitrogen atoms, when present in the heterocyclic ring system, are unsubstituted, mono- or di-substituted independently with 0-2 R^4 groups;

each X^2 is independently selected from the group consisting of C_{1-6} -alkoxy, C_{1-6} -alkyl, C_{1-6} -alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo- C_{1-6} -alkoxy and carboxamide;

each R^1 is selected from the group consisting of $-OR^3$, $-SR^3$, $-CN$, amino, C_{1-6} -alkylamino and C_{1-6} dialkylamino;

each R^3 and R^4 are independently selected from the group consisting of: hydrogen, halogen, $-CN$, $-NO_2$, $-C_{1-10}$ alkyl, C_{3-8} -cycloalkyl, aryl, amino, amino- C_{1-8} -alkyl, C_{1-3} -acylamino, C_{1-3} -acylamino- C_{1-8} -alkyl, C_{1-6} -alkylamino, C_{1-6} -alkylamino C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyl, C_{1-3} -alkoxycarbonyl, C_{1-3} -alkoxycarbonyl- C_{1-6} -alkyl, carboxy- C_{1-6} -alkyloxy, hydroxy, hydroxy- C_{1-6} -alkyl, -thio and thio- C_{1-6} -alkyl;

each L^1 is independently a leaving group;

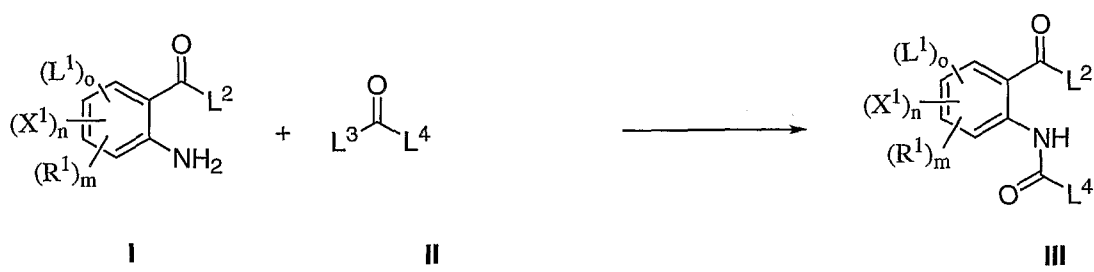
A is thienyl optionally substituted with one, two or three substituents independently selected from the group consisting of C₁₋₆-alkoxy, C₁₋₆-alkyl, C₁₋₆-alkylamino, hydroxy, halogen, cyano, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carbo-C₁₋₆-alkoxy and carboxamide;

n is 0, 1, 2, 3 or 4, m is 0, 1, 2 or 3; o is 0, 1, 2, 3 or 4; and the sum of n + m + o is at most 4; and

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

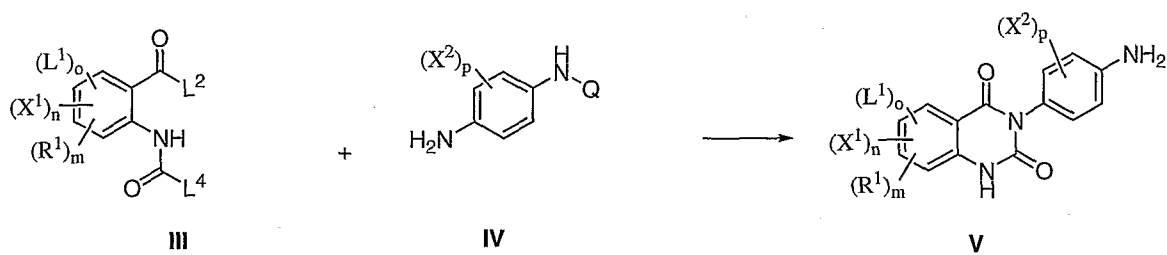
comprising the steps of:

(a) acylating the amino group of a compound of formula I with a compound of formula II to produce a compound of formula III as follows:



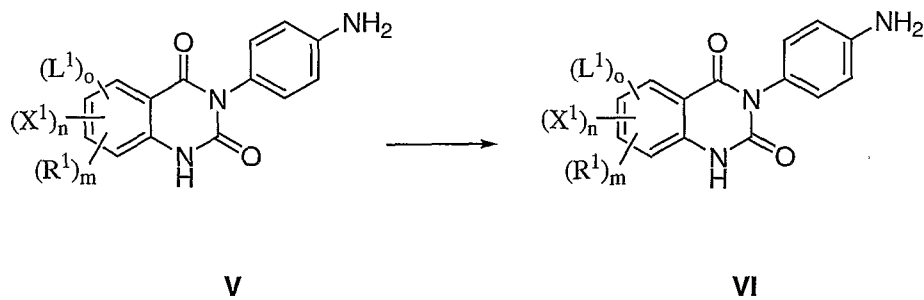
wherein each L², L³ and L⁴ are independently a leaving group;

(b) reacting the compound of formula III, with an amine containing compound IV, to produce a cyclized quinazoline derivative of formula V as follows:



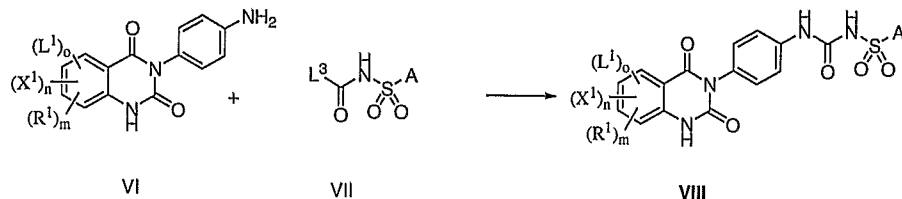
wherein Q is a protecting group;

(c) optionally replacing a group L¹ of formula V, with a group R¹ by reacting the compound of formula R¹H to provide a compound of formula VI as follows:

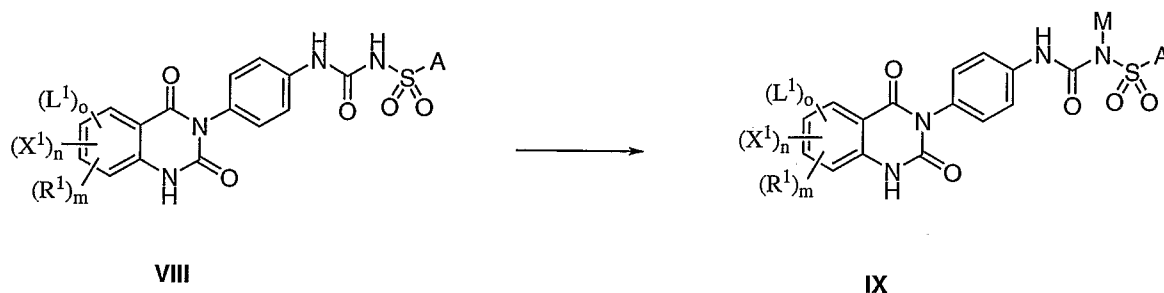


wherein the subscript m is increased and the subscript o is decreased by the number of L^1 groups replaced in VI;

(d) reacting the compound of formula V or VI with a compound of the formula VII to provide a compound of formula VIII, as follows:

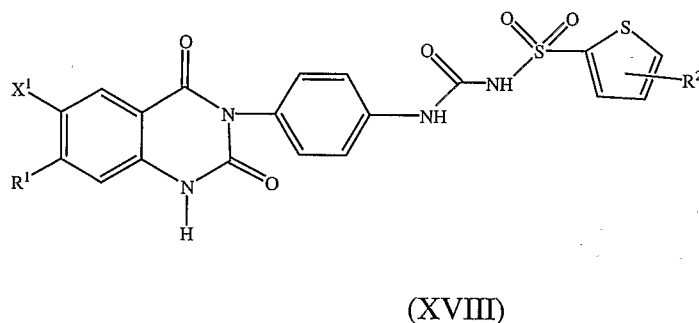


(e) optionally, producing a salt, solvate or hydrate of the compound of formula VIII:



wherein M is selected from the group consisting of Na and K.

2. The process of claim 1 for preparing compound of formula XVIII:



wherein

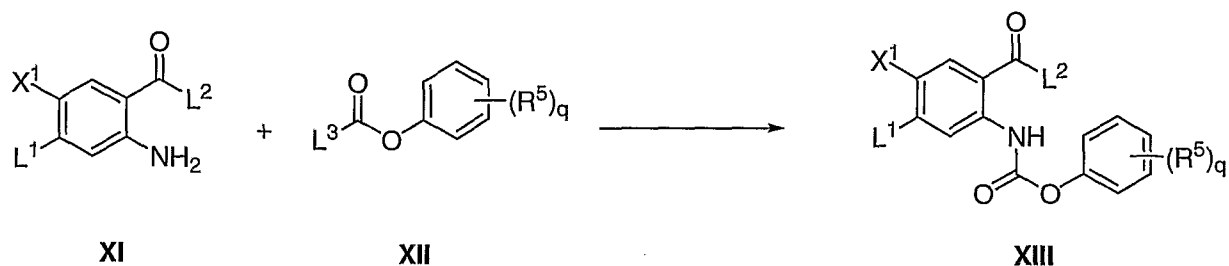
R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -alkylamino;

R^2 is halogen or -O- C_{1-10} -alkyl;

X^1 is halogen, and

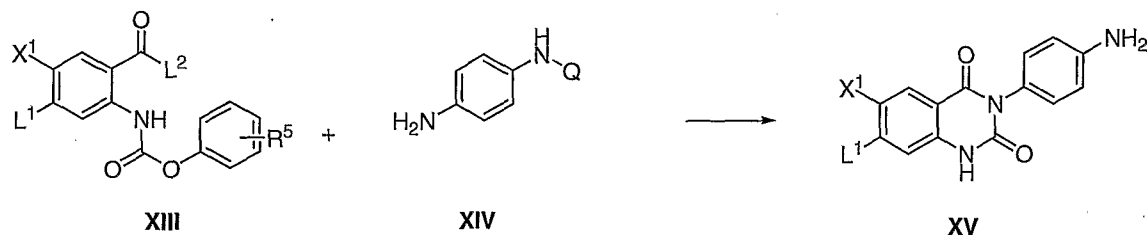
all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof, comprising the steps of:

11 (a) acylating the amino group of a compound of formula XI with a compound of
 12 formula XII under basic acylation conditions in the presence of an appropriate solvent to
 13 produce a compound of formula XIII as follows:



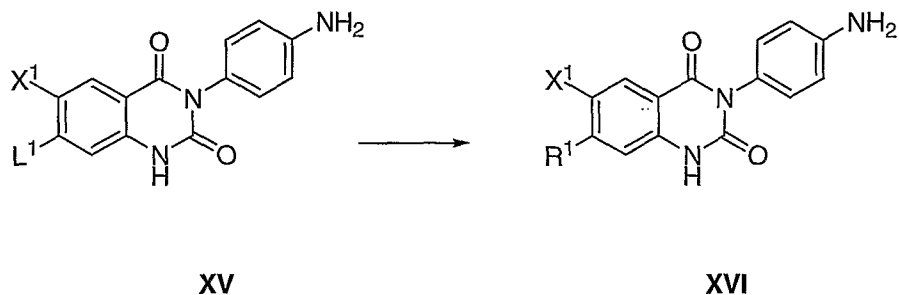
14 **XI** **XII** **XIII**
 15 ; wherein each L^1 , L^2 and L^3 are independently a leaving group; and each R^5 is an electron
 16 withdrawing group and the subscript q is 0, 1, 2, 3, or 4;

17 (b) reacting the compound of formula XIII, with an amine containing compound
 18 XIV, in the presence of a basic catalyst and a solvent at a suitable temperature to produce a
 19 cyclized quinazoline derivative of formula XV, as follows:

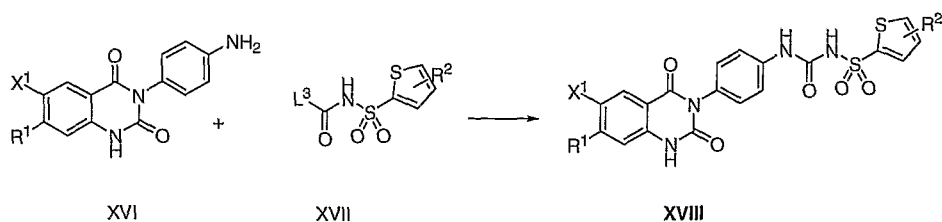


20 **XIII** **XIV** **XV** ;
 21 wherein Q is a protecting group;

22 (c) replacing the leaving group L^1 of the compound of formula XV with R^1 by
 23 reacting the compound of formula R^1H to provide a compound of formula XVI as follows:

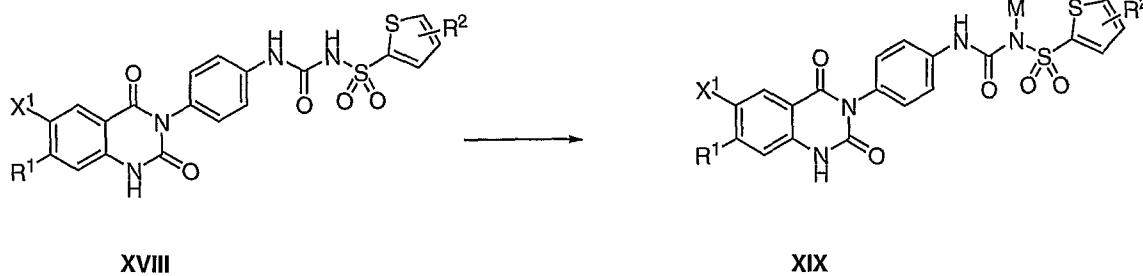


24 **XV** **XVI** ;
 25 (d) reacting the compound of formula XVI with a compound of the formula XVII
 26 to provide a compound of formula XVIII as follows:



27 **XVI** **XVII** **XVIII** ;

28 (e) and optionally, producing a salt, solvate, or hydrate of the compound of
 29 formula XVIII:



31 wherein M is Na or K.

1 3. The process according to claim 2 wherein the amine compound in step
 2 (b) is 4-nitro-aniline.

1 4. The process according to claim 2 wherein the protecting group Q is
 2 selected from the group consisting of Ac, t-BOC and CBZ

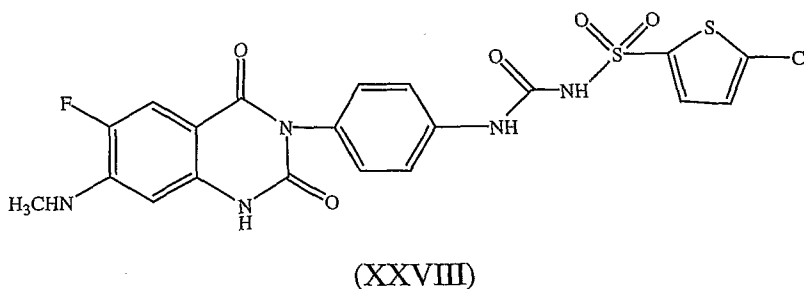
1 5. The process according to claim 2 wherein step (e) is done with a base
 2 selected from the group consisting of potassium carbonate, sodium carbonate, potassium
 3 hydroxide and sodium hydroxide.

1 6. The process according to claim 2 wherein step (c) further comprises
 2 DMSO as a solvent.

1 7. The process according to claim 2 wherein step (c) is conducted at a
 2 temperature of about 100 °C to about 120 °C.

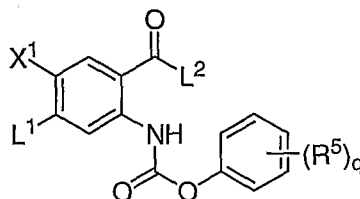
1 8. The process according to claim 2 wherein step (d) is conducted at a
 2 temperature of about 55 °C to about 75 °C.

1 9. The process according to claim 2 which is a process for making a
 2 compound according to formula XXVIII :



and all pharmaceutically acceptable salt, hydrate and solvate derivatives thereof.

10. A compound of the formula:



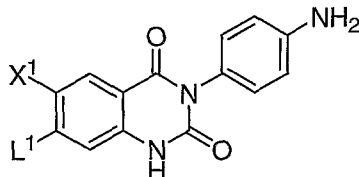
XIII

wherein

X¹ is halogen;

wherein each L¹ and L² are independently a leaving group; and each R⁵ is an electron withdrawing group and the subscript q is 0, 1, 2, 3, or 4.

11. A compound having the formula:



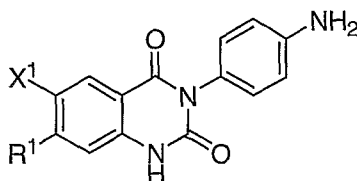
XV

wherein

X¹ is halogen; and

L¹ is a leaving group.

12. A compound having the formula:

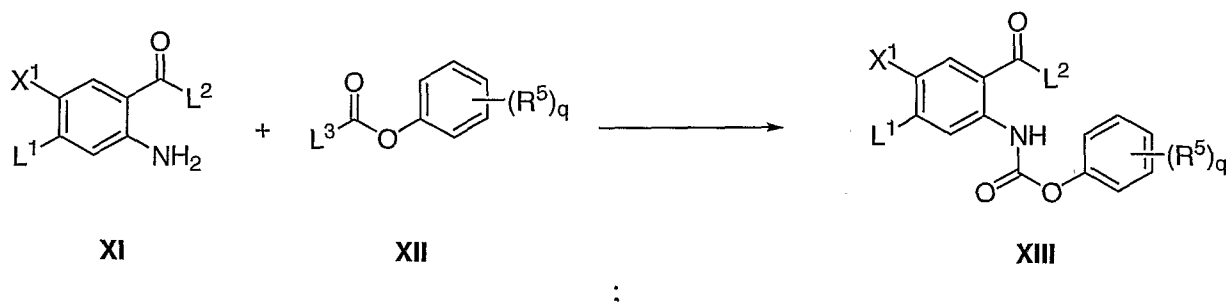


XVI

wherein

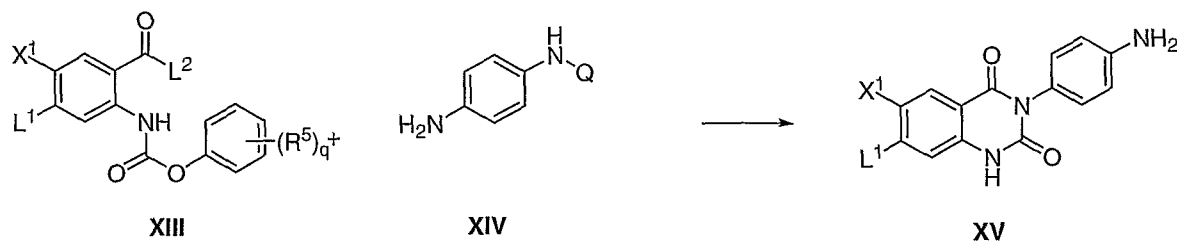
- 4 R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-
 5 alkylamino; and
 6 X^1 is halogen.

1 13. A process for preparing compound of formula XIII comprising
 2 acylating the amino group of a compound of formula XI with a compound of formula XII
 3 under basic acylation conditions in the presence of an appropriate solvent to produce a
 4 compound of formula XIII as follows:



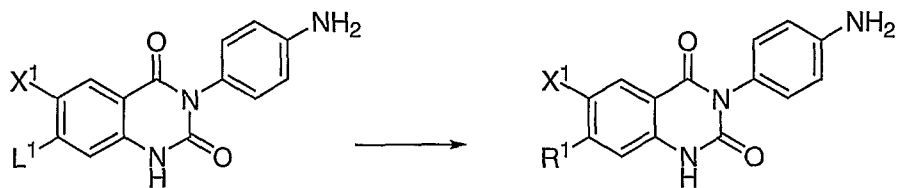
- 7 wherein
 8 X^1 is halogen;
 9 wherein each L^1 , L^2 and L^3 are independently a leaving group; and each R^5 is an electron
 10 withdrawing group and the subscript q is 0, 1, 2, 3, or 4.

1 14. A process for preparing compound of formula XV comprising reacting
 2 the compound of formula XIII, with an amine containing compound XIV, to produce a
 3 cyclized quinazoline derivative of formula XV as follows:



- 5 wherein
 6 X^1 is halogen;
 7 wherein each L^1 and L^2 are independently a leaving group; and each R^5 is an electron
 8 withdrawing group and the subscript q is 0, 1, 2, 3, or 4; and
 9 Q is a protecting group.

15. A process for preparing compound of formula XVI comprising replacing the leaving group L^1 of the compound of formula XV with R^1 by reacting the compound of formula R^1H to provide a compound of formula XVIII, as follows:



XV

XVI

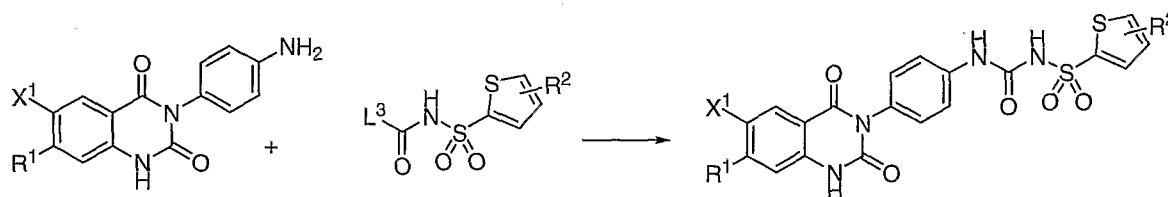
wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl, amino and C_{1-6} -alkylamino;

X^1 is halogen; and

L^1 is a leaving group.

16. A process for preparing compound of formula XVIII comprising reacting the compound of formula XVI with a compound of the formula XVII to provide a compound of formula XVIII as follows:



XVI

XVII

XVIII

wherein

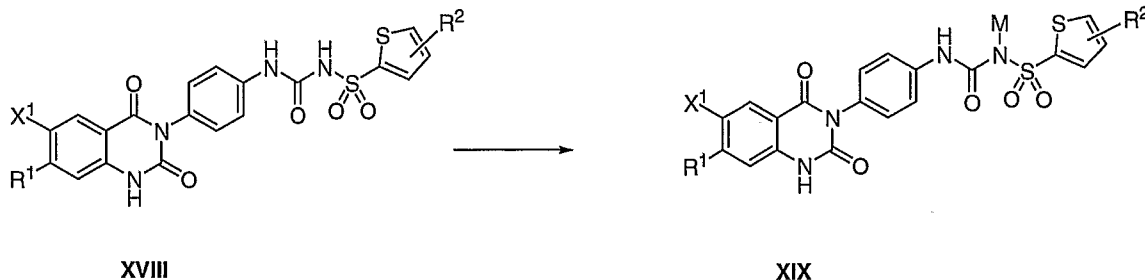
R^1 is selected from the group consisting of H, halogen, -OH, -O- C_{1-10} -alkyl and C_{1-6} -alkylamino;

X^1 is halogen;

wherein L^3 is a leaving group; and

R^2 is halogen or -O- C_{1-10} -alkyl.

17. A process for preparing compound having the formula XIX comprising producing a salt, solvate, hydrate or prodrug of the compound of formula XVIII:



wherein

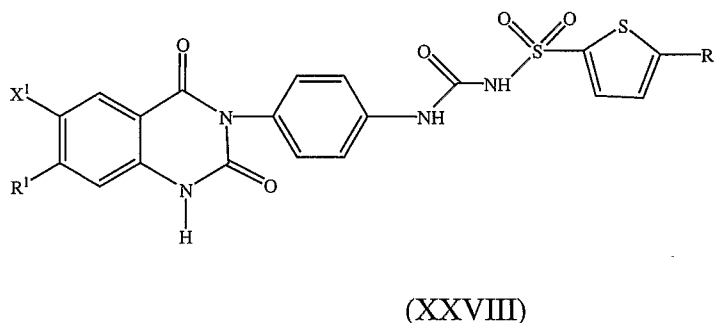
R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

X^1 is halogen;

R^2 is halogen or -O-C₁₋₁₀-alkyl;

M is selected from the group consisting of Na and K.

18. The process according to any one of claims 1 to 9 and 16 to 17 which is a process for making a compound of formula XXVIII:



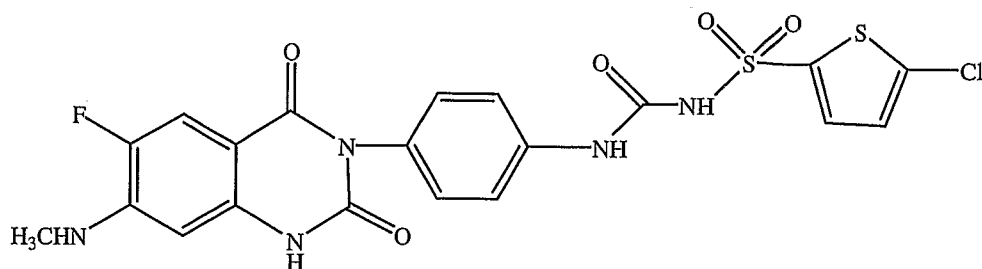
wherein

R^1 is selected from the group consisting of H, halogen, -OH, -O-C₁₋₁₀-alkyl and C₁₋₆-alkylamino;

R^2 is halogen or -O-C₁₋₁₀-alkyl; and

X^1 is halogen

19. The process according to any one of claims 1 to 9 and 16 to 17 which is a process for making a compound of formula XXXVIII :



(XXXVIII).

20. The process according to any one of claims 1 to 9 and 14 to 17 wherein X¹ is -F.

21. The process according to any one of claims 1 to 9 and 14 to 17 wherein R¹ is a member selected from the group consisting of -OH, NH₂ and -NH(-C₁₋₆alkyl).

22. The process according to any one of claims 1 to 9 and 14 to 17 wherein R¹ is -NHCH₃.

23. The process according to any one of claims 1 to 9 and 14 to 17 wherein R² is chloro.

24. The process according to any one of claims 1 to 9 and 14 to 17 wherein each leaving group L¹ and L³ are independently selected from the group consisting of halogen, alkylsulfonate, haloalkylsulfonate and arylsulfonate.

25. The process according to any one of claims 1 to 9 and 14 to 17 wherein each R⁵ is independently NO₂ or halogen.

26. The process according to any one of claims 1 to 9 and 14 to 17 wherein the leaving group L² is C₁-C₁₀alkoxy.

27. The compound according to any one of claims 10 to 12 wherein X¹ is -F.

28. The compound according to any one of claims 10 to 12 and 27 wherein R¹ is a member selected from the group consisting of -OH, NH₂ and -NH(-C₁₋₆alkyl).

29. The compound according to any one of claims 10 to 12 and 27 to 28 wherein R¹ is -NHCH₃.

1 30. The compound according to claim 10 to 12 and 27 to 29 wherein each
2 leaving group L^1 is selected from the group consisting of halogen, alkylsulfonate,
3 haloalkylsulfonate and arylsulfonate.

1 31. The compound according to claim 10 wherein each R^5 is selected from
2 the group consisting of NO_2 and halogen.

1 32. The compound according to claim 10 wherein the leaving group L^2 is
2 C_1 - C_{10} alkoxy.