NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1 ANTAGONISTS

BACKGROUND

[0001] Several lines of pharmacological and genetic evidence support the role of Melanin Concentrating Hormone Receptor-1 (hereafter "MCHR1") as a modulator of food intake and body weight. Central administration of MCH increases food intake and body weight both rats and mice. Chronic ICV infusion of MCH causes increased food intake and ultimately obesity in mice, while infusion of an MCH peptide antagonist blocks MCH-induced food intake and results in weight loss and decreased feeding in diet-induced obese mice.

[0002] The expression of both the MCH peptide and receptor are modulated by nutritional status. MCH mRNA is upregulated both in hyperphagic obese mice (ob/ob), and fasted animals. Targeted disruption of the gene for MCH peptide results in hypophagia and leanness. Disruption of the MCHR1 gene causes leanness, altered metabolism, and hyperlocomotion accompanied by mild hyperphagia. Conversely, over-expression of MCH peptide results in hyperphagia, obesity and diabetes. Small molecule MCHR1 antagonists have been shown to cause weight loss in rodent weight and feeding models after both oral and intraperitoneal administration; Eur. J. Pharmacol., 438, 129-135, 2002, Nat. Med., 8, 825-830, 2002, Eur. J. Pharmacol., 497, 41-47, 2004.

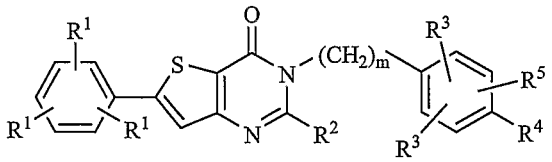
[0003] Numerous non-peptide MCHR1 antagonists have been disclosed. The scope of the genus for each reflects a common perception regarding the criteria required for ligand recognition as MCHR1 agonists. A recent review of MCHR1 patent disclosures emphasized the commonality of these structures by the following description; " Ubiquitous throughout the MCH patent literature are molecules consisting of a central scaffold to which linkers to an aryl or heteroaryl group and a basic amino functionality are attached" (T. J. Kowalski and M. D. MacBriar, Expert Opin. Investig. Drugs 13, 1113 – 1122, 2004). Pharmacophore models of these geni consistently envision a presumed prerequisite electrostatic interaction between a basic amine center of the antagonist ligand and aspartic acid 123 of the receptor which presumably is envisaged to emulate the mandatory interaction between arginine 14 of

MCH peptide agonists with aspartic acid 123 of the MCHR1 receptor. (T. Ulven, J. Med. Chem. 2005, 48, 5684 – 5697) However, incorporation of this basic amine in a MCHR1 antagonist increases substantially the probability of binding to off-target ion-channels and biogenic amine receptors.

[0004] Herein we describe a series of novel high affinity selective MCHR1 antagonists that were obtained by replacement of the basic amine moiety described in WO 03/033476 with non-basic polar functionalities. Moreover, this structural modification results in unexpected ablation of binding to other biogenic amine receptors as well as binding to the HERG receptor in the heart. The reduction/abolition of affinity for the HERG receptor is especially important since ligand occupancy is associated with initiation of fatal arrythmias.

DETAILED DESCRIPTION

[0005] The present application provides compounds, including all stereoisomers, solvates, prodrugs and pharmaceutically acceptable forms thereof according to Formulae I and II. Additionally, the present application provides pharmaceutical compositions containing at least one compound according to Formula I or II and optionally at least one additional therapeutic agent. Finally, the present application provides methods for treating a patient suffering from an MCHR-1 modulated disease or disorder such as, for example, obesity, diabetes, depression or anxiety by administration of a therapeutically effective dose of a compound according to Formula I or II:



I

wherein,

R^1 is independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, aryl, CF_3, CN, NR^7R^7, OR^6 and SR^6;

R^2 is selected from the group consisting of hydrogen and lower alkyl;

R^3 is independently selected from the group consisting of hydrogen, halogen, lower alkyl;

R^4 is selected from the group consisting of hydroxyl or G-D^2-Z_n, wherein R^4 and R^5 may be taken together to form a ring of 4 to 7 atoms;

R^5 is selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower cycloalkyl, CF_3, SR^6, lower alkoxy, lower cycloalkoxy, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^7SO_2R^6$ and COR^6;

m is an integer from 0 to 1;

n is an integer from 1 to 3;

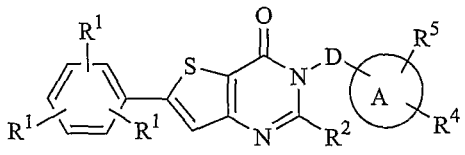
G is selected from the group consisting of a direct bond, O, S and CR^7R^7;

D^2 is selected from the group consisting of a direct bond, lower alkyl, lower cycloalkyl and a 4 to 6-membered non-basic heterocycle;

Z is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkoxy, lower cycloalkyl, lower cycloalkoxy, $OCOR^6$, $OCONR^7R^7$, CN, $CONR^7R^7$, OSO_2R^6, SR^6, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CONR^7R^7$, $NR^7CO_2R^7$, CO_2R^7, heterocycle, heteroaryl, $OPO(OR^6)_2$, $NR^7SO_2R^6$ and COR^6;

R^6 is independently selected from the group consisting of lower alkyl, lower cycloalkyl, heterocycle and heteroaryl; and

R^7 is independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl and heterocycle, wherein two R^7 and the atom to which they are attached may optionally form a ring of 4 to 7 atoms; and



II

wherein,

A is selected from the group consisting of phenyl and a monocyclic heteroaryl;

D is selected from the group consisting of CH_2 and a direct bond;

R^1 is independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, CF_3, OR^6 and SR^6;

R^2 is selected from the group consisting of hydrogen and lower alkyl;

R^4 is selected from the group consisting of hydroxyl or G-D^2-Z_n;

n is an integer from 1 to 3;

R^5 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, CF_3, SR^6, lower alkoxy, lower cycloalkoxy, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^7SO_2R^6$ and COR^6;

G is selected from the group consisting of O, S and CR^7R^7;

D^2 is selected from the group consisting of a direct bond, lower alkyl, lower cycloalkyl and a 4 to 6-membered non-basic heterocycle;

Z is selected from the group consisting of hydrogen, hydroxyl, lower alkoxy, lower cycloalkoxy, $OCONR^7R^7$, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^6SO_2R^6$ and COR^6;

R^6 is independently selected from the group consisting of lower alkyl and lower cycloalkyl; and

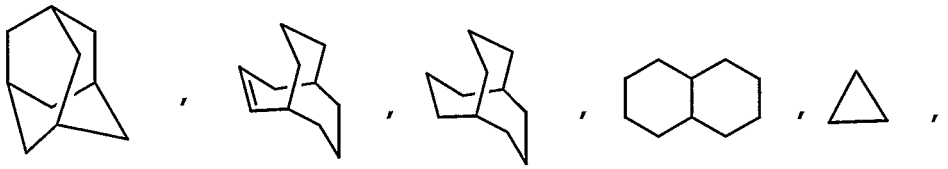
R^7 is independently selected from the group consisting of hydrogen, lower alkyl and lower cycloalkyl, wherein two R^7 and the atom to which they are attached may optionally form a ring of 4 to 7 atoms.

DEFINITIONS

[0006] Unless otherwise indicated, the term "lower alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 8 carbons, and the terms "alkyl" and "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, hydroxy, hydroxyalkyl, acyl, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl,

heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

[0007] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, any one of which may optionally be a spiro substituted cycolalkyl, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

[0008] The term "heterocyclo", "heterocycle", "heterocyclyl" or "heterocyclic ring", as used herein, represents an unsubstituted or substituted stable 4 to 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms, with one to four heteroatoms selected from nitrogen, oxygen or sulfur, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl,

thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl and other heterocycles described in Katritzky, A. R. and Rees, C. W., eds. *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds* 1984, Pergamon Press, New York, NY; and Katritzky, A. R., Rees, C. W., Scriven, E. F., eds. *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995* 1996, Elsevier Science, Inc., Tarrytown, NY; and references therein.

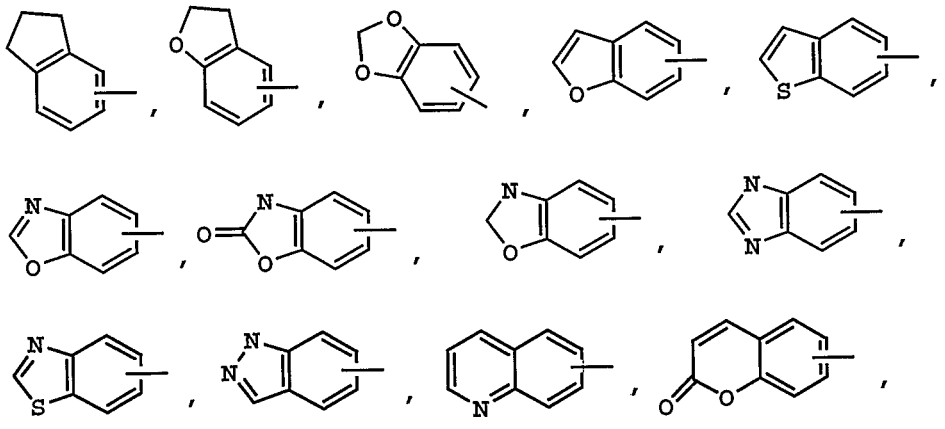
[0009] The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

[0010] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

[0011] The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

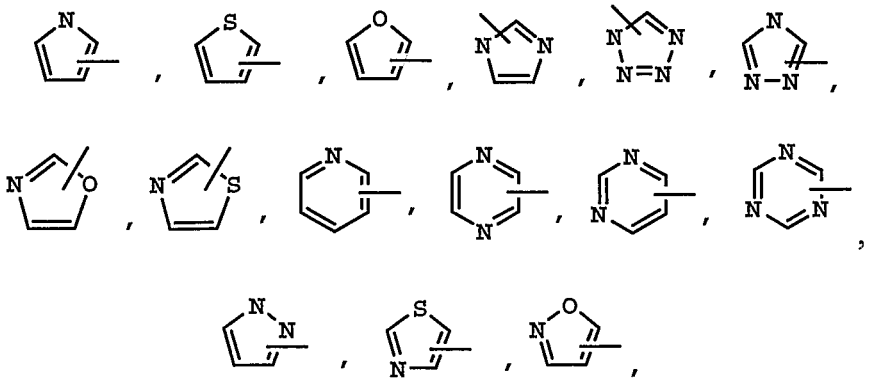
[0012] Unless otherwise indicated, the term "aryl" or "Aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings

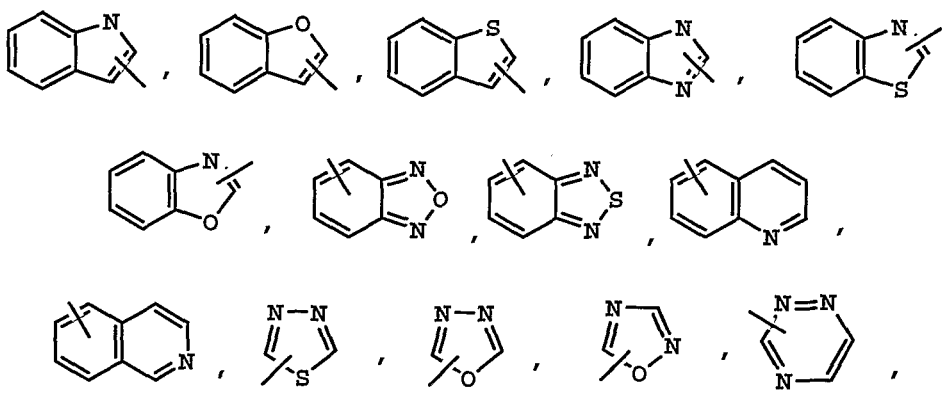
for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino and arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

[0013] Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl and include possible N-oxides as described in Katritzky, A. R. and Rees, C. W., eds. *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds* 1984, Pergamon Press, New York, NY; and Katritzky, A. R., Rees, C. W., Scriven, E. F., eds. *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995* 1996, Elsevier Science, Inc., Tarrytown, NY; and references therein. Further, "heteroaryl", as defined herein, may optionally be substituted with one or more substituents such as the substituents included above in the definition of "substituted alkyl" and "substituted aryl". Examples of heteroaryl groups include the following:





and the like.

[0014] Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

[0015] Unless otherwise indicated, the term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

[0016] The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

[0017] The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

[0018] The compounds of formula I of the application can be prepared as shown in the following reaction schemes and description thereof, as well as relevant published literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

ABBREVIATIONS

[0019] The following abbreviations are employed herein:

Ph = phenyl

Bn = benzyl

t-Bu = tertiary butyl

Me = methyl

Et = ethyl

TMS = trimethylsilyl

TBS = tert-butyldimethylsilyl

THF = tetrahydrofuran

Et_2O = diethyl ether

EtOAc = ethyl acetate

DMF = dimethyl formamide

MeOH = methanol

EtOH = ethanol

i-PrOH = isopropanol

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

i-Pr_2NEt = diisopropylethylamine

Et_3N = triethylamine

DMAP = 4-dimethylaminopyridine

$NaBH_4$ = sodium borohydride

n-BuLi = n-butyllithium

Pd/C = palladium on carbon

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

K_2CO_3 = potassium carbonate

$NaHCO_3$ = sodium bicarbonate

Ar = argon

N_2 = nitrogen

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

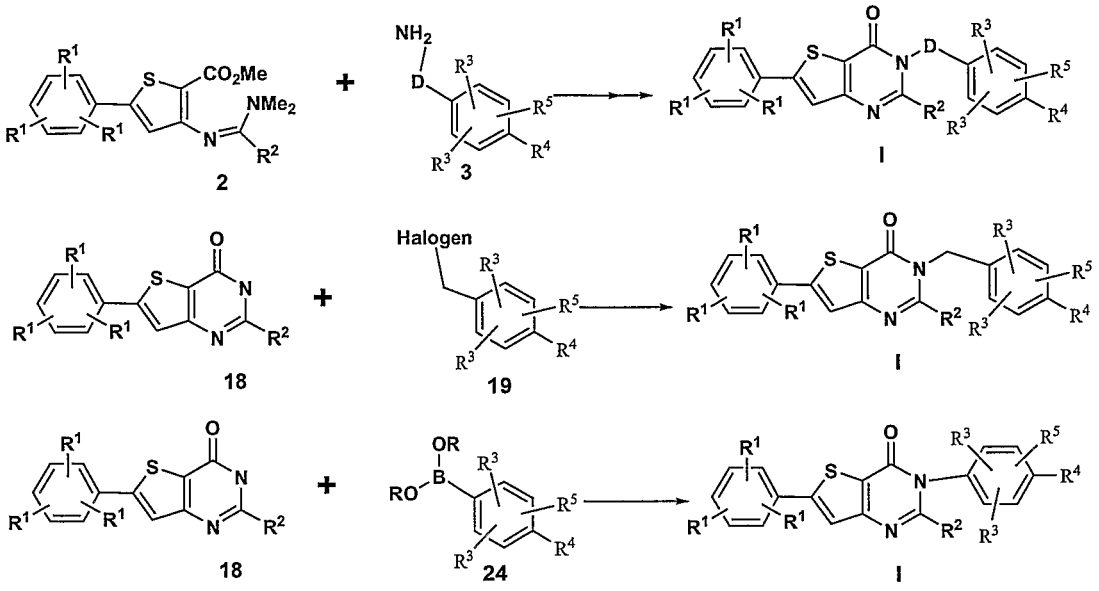
NMR = nuclear magnetic resonance

mp = melting point

METHODS OF PREPARATION

[0020] As summarized in Scheme 1, compounds of formula I may be prepared by either condensing compounds of formula 2 with compounds of formula 3 to generate the thiophenopyrimidone central bicyclic moiety in situ or via alkylation/arylation of compounds of formula 18 with alkylating agents of formula 19 or arylating agents such as borates of formula 24. Depending on the particular molecule of formula I being prepared, R^4 can either be fully completed or elaborated after assemblage of the core structure of formula I.

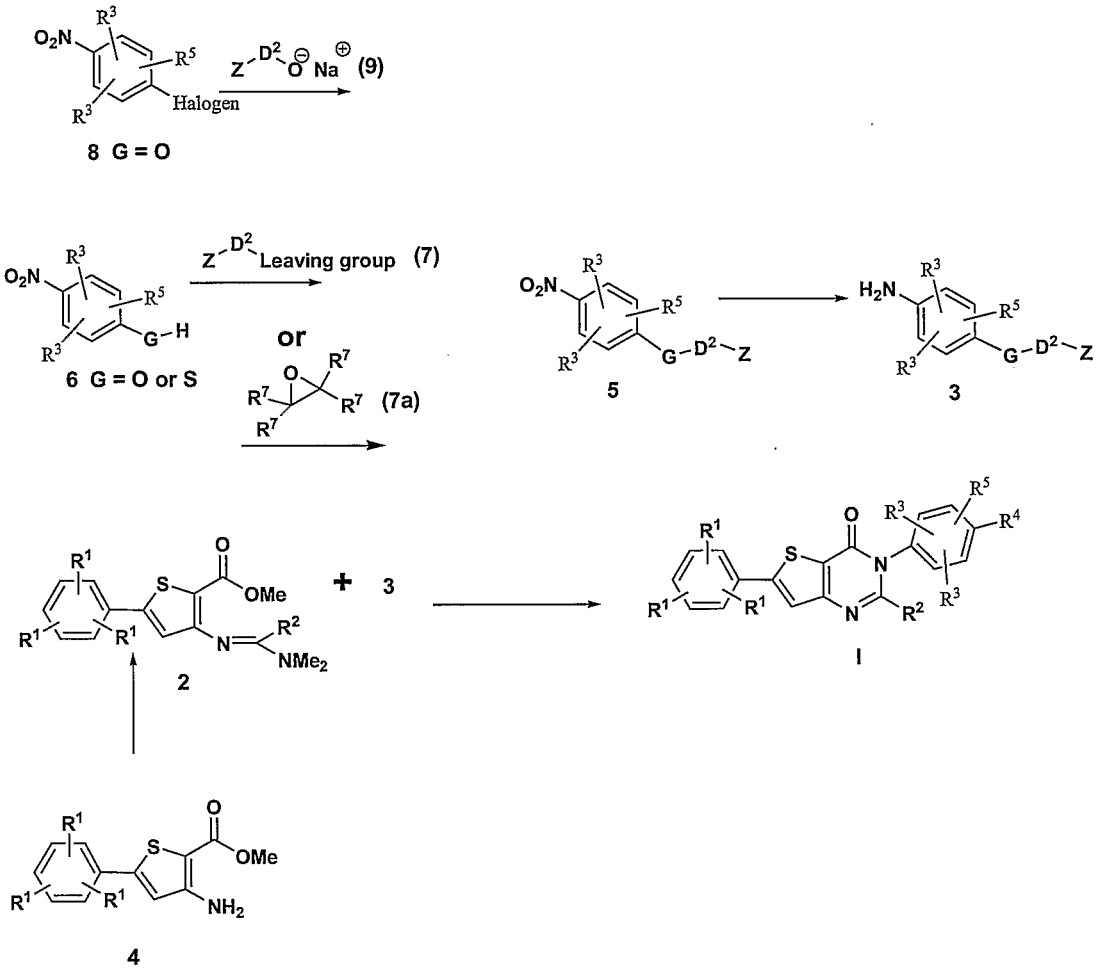
SCHEME 1



[0021] Specifically, compounds of formula I may be prepared by condensing compounds of formula 2 with compounds of formula 3 in a solvent such as hot EtOH (Scheme 2). Compounds of formula 2 can be prepared as described in WO2003/033476 by heating compounds of formula 4 with dimethylformamide dimethyl acetal. Preparation of compounds of formula 4 is described in WO1998/49899. Amines of formula 3 for which D is a bond may be prepared by reduction of nitro aromatics of formula 5 either by catalytic hydrogenation using a catalyst such as Pd/C in a solvent such as EtOH or by reduction with $SnCl_2$ in a solvent such EtOAc. Compounds of formula 5 where G = O or S and D is a bond can be prepared by alkylation of the corresponding phenol or thiophenol of formula 6 with an appropriate alkylating agent of formula 7 in the presence of a base such as Cs_2CO_3 or K_2CO_3 in a solvent such as DMF by employing procedures readily known to those skilled in the art. Alternatively compounds of formula 5 can be prepared by heating alkali metal salts of compounds of formula 6 with epoxides of formula 7a thermally or preferably by microwave in a solvent such as 15% H_2O/MeCN containing NaH_2PO_4. Compounds of formula 5 can be also prepared by heating compounds of formula 8 with preformed sodium salts of compounds of formula 9 in a solvent such as DMF. Compounds of formula 6 and 8 are either commercially available or can be readily prepared in the case of formula 6 from the corresponding un-nitrated phenol by

sequential acylation, nitration or sulfonalation using methods known to those skilled in the arts.

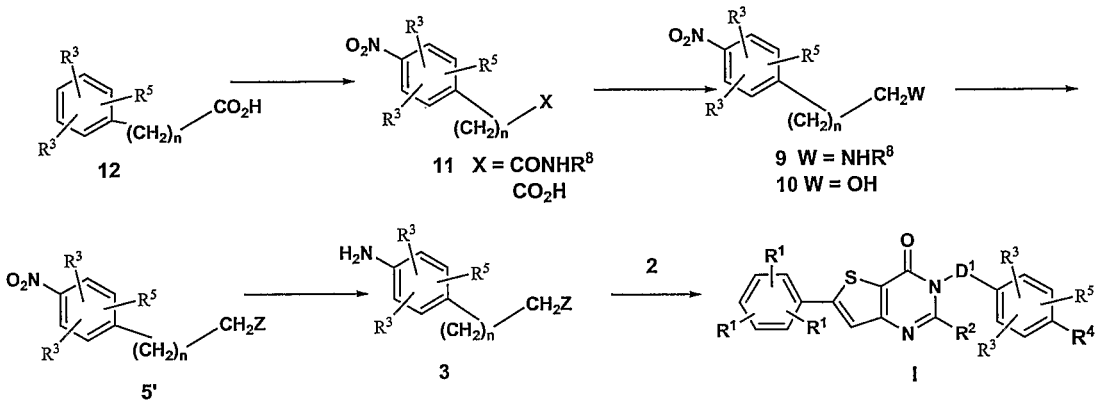
SCHEME 2



[0022] Compounds of formula I where G = alkylidine and D is a bond (Scheme 3) can be prepared by condensation of compounds of formula 2 with compounds of formula 3 which had been prepared as previously described by reduction of compounds of formula 5'. Compounds of formula 5' can be prepared by derivitization of amines of formula 9 or alcohols of formula 10 employing procedures readily known to those skilled in the art. Amines of formula 9 and alcohols of formula 10 can be prepared by BH_3 mediated reduction of amides and acids respectively of formula 11 in a solvent such as THF. Compounds of formula 11 can be prepared by nitration

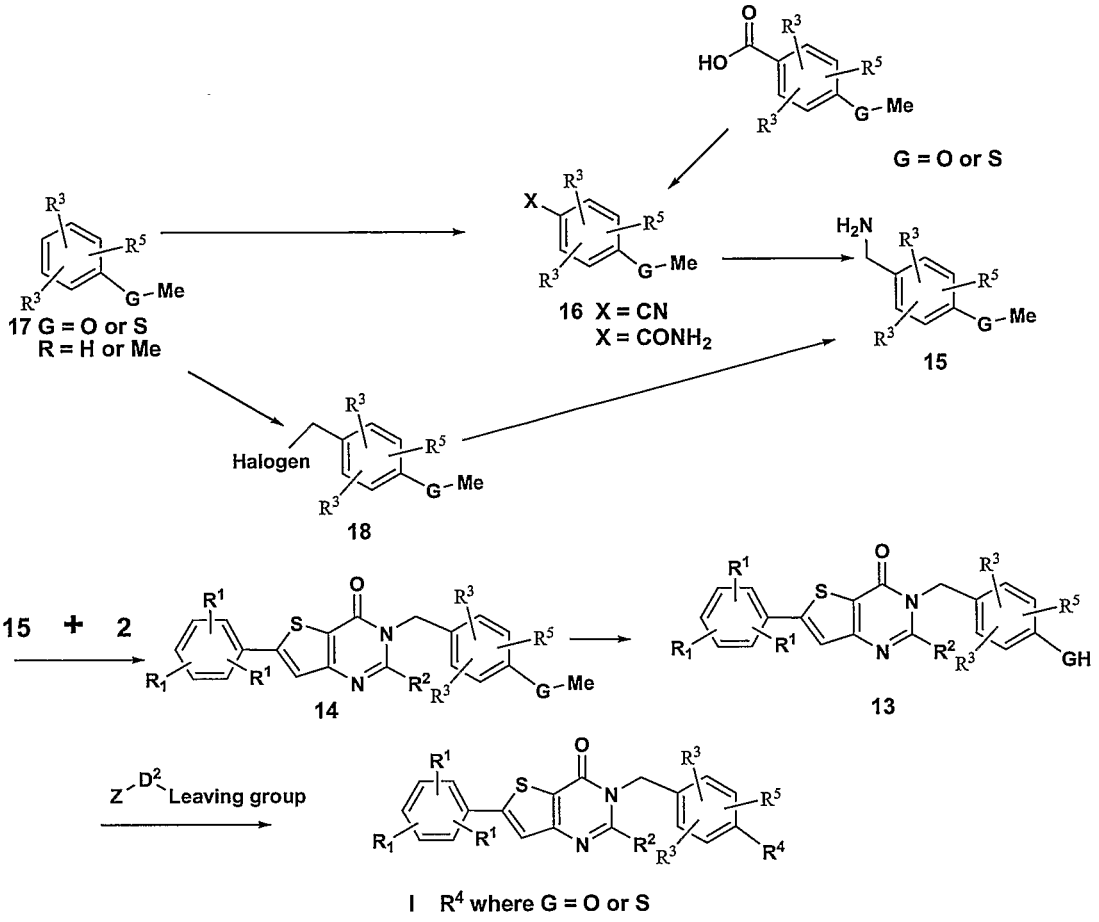
of commercially available aryl acetic and hydrocinnamic acids of formula 12 followed by conversion to the corresponding amide if appropriate.

SCHEME 3



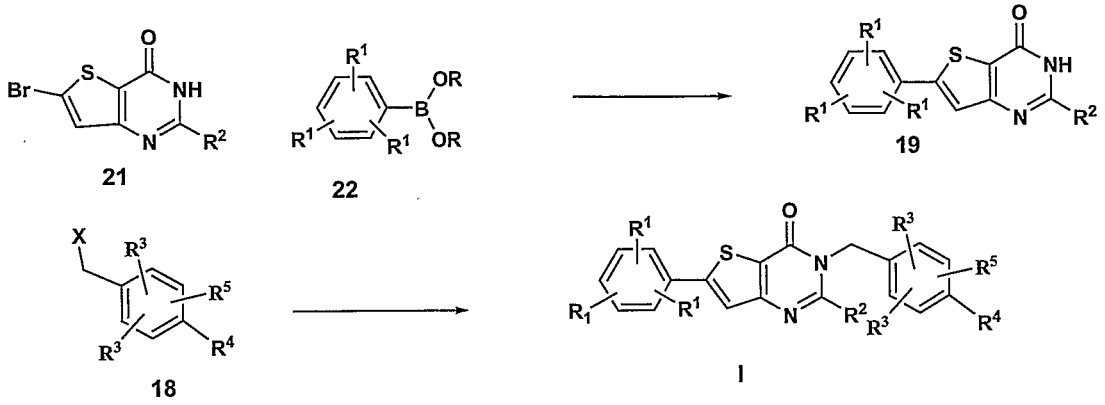
[0023] Compounds of formula I for which D^1 is a methylene and G is O or S (Scheme 4) may be prepared by alkylation of compounds of formula 13 in a solvent such as DMF in the presence of a base such as NaH or Cs_2CO_3 with an agent that will incorporate the fragment Z-D^2 required to transform the substituent GH of 13 into R^4. Compounds of formula 13 can be prepared by demethylation of compounds of formula 14 with a reagent such as BBr_3 in a solvent such as CH_2Cl_2. Compounds of formula 14 can be prepared by condensation of compounds of formula 15 with compounds of formula 2. Compounds of formula 15 which are not commercially available can be obtained reduction of aryl nitriles or primary carboxamides of formula 16 with a reducing agent such $LiAlH_4$ or BH_3 in a solvent such as THF. Compounds of formula 16 can be prepared from commercially available benzoic acids by procedures known to those skilled in the arts. Compounds of formula 15 may also be prepared by chloromethylation of compounds of formula 17 (R = H) or bromination of compounds of formula 17 (R = Me followed by sequential treatment of the resulting benzylic halide 18 with NaN_3 in a solvent such as DMF followed by reduction with either Ph_3P in a solvent such as EtOH or catalytic hydrogenation over Pd in EtOH.

SCHEME 4



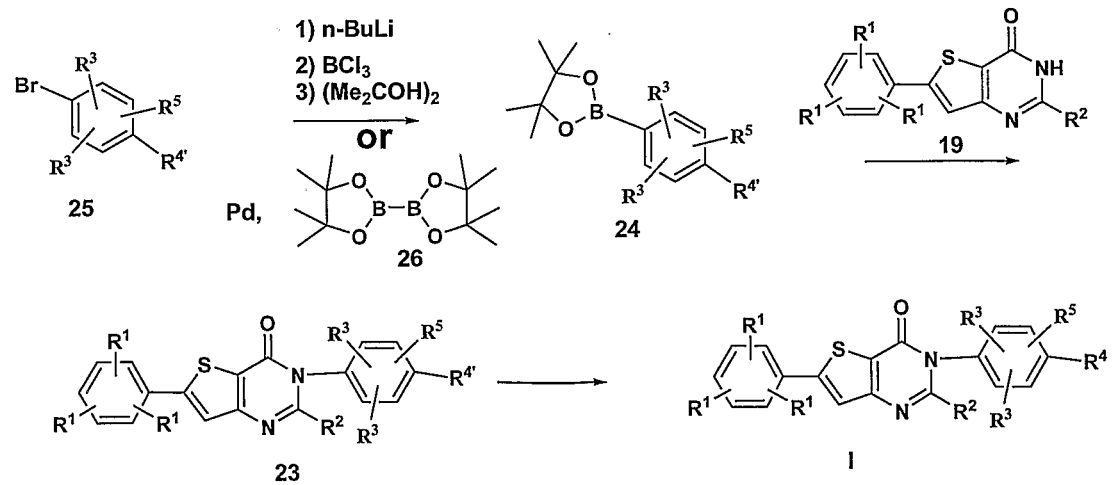
[0024] An alternative route (Scheme 5) for preparation compounds of formula I where D^1 is a methylene entails alkylation of compounds of formula 19 in a solvent such as DMF containing a base such as Cs_2CO_3 with a benzyl halide of formula 20 bearing a fully assembled substituent R^4 described by G-D^2-Z or with benzyl halides of formula 18. Conversion of the alkylation product with 18 to compounds of formula I may be achieved using procedures described in Scheme for the transformation of 14 to I. Compounds of formula 19 may be prepared as described in WO 03/033476 or by coupling compounds of formula 21 with commercial aryl borates of formula 22 in the presence of catalyst such as $(Ph_3P)_4Pd$ in a solvent such dioxane/ aq Na_2CO_3. Compounds of formula 21 may be prepared as described in WO 98/49899.

SCHEME 5



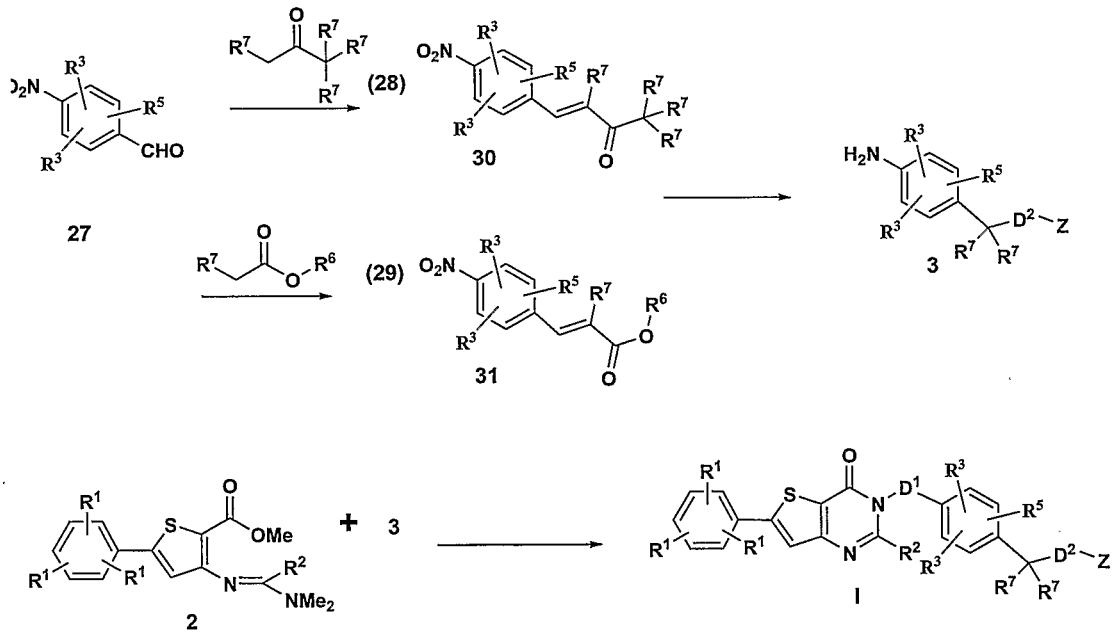
[0025] In Scheme 6 compounds of formula I, where D is a bond, may be prepared by transformation, if necessary, of the substituent $R^{4'}$ of 23 into R^4 by sequential deprotection, alkylation and/or acylation using procedures familiar to those skilled in the arts. Compounds of formula 23 can be prepared by arylation of compounds of formula 19 with a aryl borate of formula 22 in the presence of $Cu(OAc)_2$ in a solvent such as CH_2Cl_2 containing molecular sieves. Aryl borates of formula 24 are commercially available or can be formed by treating commercially compounds of formula 25 either with n-BuLi in a solvent such as THF followed by sequential addition BCl_3 followed by MeOH or alternatively stirring 25 with borate 26 in the presence of a Pd catalyst.

SCHEME 6



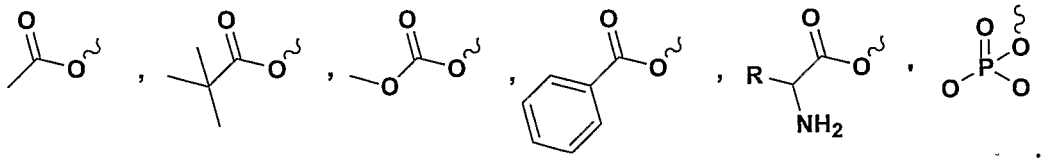
[0026] In Scheme 7 compounds of formula 1 where G = CH_2 and D is a bond can be prepared by condensation of the corresponding benzaldehyde of formula 27 with an appropriate ketone of formula 28 or ester of formula 29 in the presence of a base such as NaOH or $NaOR^6$ in a solvent such as DMF or EtOH by employing procedures readily known to those skilled in the art. Preparation of compounds of formula 3 where G = CH_2 and D is a bond can be completed by reduction of the ketone carbonyl of compounds of formula 30 with a reducing agent such as $NaBH_4$ in a solvent such as EtOH followed by catalyltic hydrogenation using H_2 and Pd/C in EtOH or mixtures of EtOH/EtOAc. Alternatively compounds of formula 31 can be transformed to compounds of formula 3 by catalyltic hydrogenation using H_2 and Pd/C in EtOH or mixtures of EtOH/EtOAc.

SCHEME 7

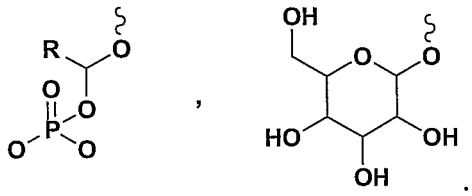


[0027] The term "prodrug" encompasses both the term "prodrug esters" and the term "prodrug ethers". The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates and the like.

[0028] Examples of such prodrug esters include



[0029] The term "prodrug ethers" include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include



[0030] The compounds of formula **I** can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of formula **I** have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms, for example acetic acid, which are unsubstituted or substituted, for example, by halogen as chloroacetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula **I** having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine,

pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tert-butyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula **I** or their pharmaceutically acceptable salts, are also included.

[0031] Preferred salts of the compounds of formula **I** which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate, nitrate or acetate.

[0032] Preferred salts of the compounds of formula **I** which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

[0033] All stereoisomers of the compound of the instant application are contemplated, either in admixture or in pure or substantially pure form. The compound of the present application can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compound of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

EXAMPLES

[0034] The following Examples serve to better illustrate, but not limit, some of the preferred embodiments of the application.

[0035] Where possible a modular convergent approach was utilized to prepare the following examples entailing synthesis of the appropriate aniline, condensation with a formamidine to generate the bicyclic thienopyrimidone core followed by subsequent elaboration if required of a side chain. Two conditions were employed to construct the thienopyrimidone bicycle: The aniline and formamidine were heated at reflux in EtOH for 18 hr. Upon cooling the product precipitated and was isolated by filtration. Yields typically were 20-40% and rarely exceeded 40%. Alternatively aniline and

formamidine in phenol were heated to 130 °C for 10 - 30 minutes; following dilution with MeOH, the product was isolated by filtration in yields approaching 80%. Note however, if the product did not precipitate, isolation became tedious and the yields could plummet.

[0036] The vast majority of the para alkoxy anilines were either commercially available or synthesized by one of three routes: A, B or C.

[0037] Route A (nucleophilic aromatic substitution) required preforming the sodium alkoxide with NaH in DMF followed by addition of 2-chloro-5-nitroanisole. Typically the reaction was heated for 1 hr at 90 °C. After purification by silica gel chromatography, the nitrated aryl ether was reduced to the desired aniline by 10% Pd/C catalyzed hydrogenation (50 psi H_2) in EtOH.

[0038] Route B (base promoted phenol alkylation) entailed heating a mixture of the potassium or sodium salt of the nitrophenol with a alkyl halide in DMF for 2-4 hr at 90 °C. After isolation and purification by silica gel chromatography, the product was reduced to the desired aniline as previously described.

[0039] Route C (base promoted phenol alkylation) was employed when routes A or B were not feasible. A concentrated suspension of the potassium or sodium salt of the phenol, NaH_2PO_4 and the appropriate epoxide in 9:1 MeCN/H_2O was heated to 120 -180 °C for 30 – 90 minutes with a microwave or 1-8 hr in steel bomb. (Buffering with NaH_2PO_4 is essential to prevent reversion of the product to starting phenol as the pH increases during the reaction. Note even for small scale reactions, temperatures greater than 180 °C should be avoided to minimize the probability of explosive decomposition since the potassium salt of 2-chloro-4-nitrophenol rapidly decomposes at ~210 °C producing gaseous products.) Following isolation and purification by silica gel chromatography, the product was reduced to the desired aniline as previously described.

[0040] Several analytical HPLC methods were utilized; all monitored UV absorption at 220 nM:

Method 1. Phenomenex Luna C18 S5 column 4.6 x 50 mm, 4 min gradient at 4 mL/min, 10% MeOH/90% H_2O/0.2% H_3PO_4 to 90% MeOH/10% H_2O/0.2% H_3PO_4 with 1 min hold at the end of the gradient.

Method 2. YMC S5 C18 4.6X50 mm column, 4 min gradient at 4 mL/min, 10% MeOH/90% H_2O/0.2% H_3PO_4 to 90% MeOH/10% H_2O/0.2% H_3PO_4 with 1 min hold at the end of the gradient.

Method 3. Phenomenex S5 C18 4.6X30 mm column, 2 min gradient at 4 mL/min, 10% MeOH/90% H_2O/0.1% TFA to 90% MeOH/10% H_2O/0.1% TFA with 1 min hold at the end of the gradient.

Method 4. Phenomenex S5 C18 4.6X30 mm column, 2 min gradient at 4 mL/min, 10% MeCN/90% H_2O/0.1% TFA to 90% MeCN/10% H_2O/0.1% TFA with 1 min hold at the end of the gradient.

Method 5. Phenomenex Luna C18 S5 column 4.6 x 50 mm, 4 min gradient at 4 mL/min, 10% MeCN/90% H_2O/0.1% TFA and 90% MeCN/10% H_2O/0.1% TFA with 1 min hold at the end of the gradient.

Method 6. Zorbax SB C18 S5 column 4.6 x 75 mm, 8 min gradient from 50% solvent B to 100% solvent B at 2.5 mL/min; Solvent A = 10% MeOH/90% H_2O/0.2% H_3PO_4; Solvent B = 90% MeOH/10% H_2O/0.2% H_3PO_4 with 2 min hold at 100% solvent B.

Method 7. YMC A300-ODS S-5, 4.6 mm x 50 mm; 4 min gradient at 4 mL/min.; A = 90:10 water:methanol + 0.2% phosphoric acid, B = 10:90 water:methanol + 0.2% phosphoric acid; 0% B to100% B over 4 min with 1 min hold at the end of the gradient.

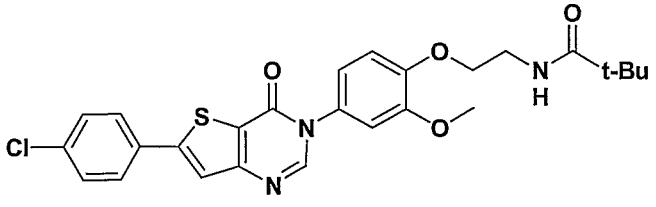
[0041] Preparative HPLC conditions employed YMC C18 columns using employing gradient elutions with appropriate mixtures of 10% MeOH/90% H_2O/0.1% TFA to 90% MeOH/10% H_2O/0.1% TFA. On occasion, mixtures of 10% MeCN/90% H_2O/0.1% TFA and 90% MeCN/10% H_2O/0.1% TFA were employed. If the molecule contained an acid sensitive component, the TFA was omitted.

[0042] Mass spectral data were obtained using a Waters ZMD single quadrapole mass spectrometer.

[0043] Typical conditions were Phenomenex reverse phase C18 column 4.6 x 50 mm, 4 min gradient, 10% MeOH/90% H_2O/0.1% TFA to 90% MeOH/10% H_2O/0.1% TFA, 1 min hold; 4 mL/min, UV detection at 220 nm.

EXAMPLE 1

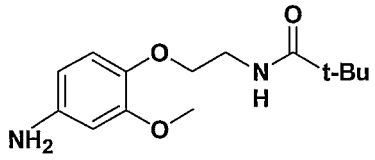
N-(2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)ethyl)pivalamide



Part A. N-(2-hydroxyethyl)pivalamide

[0044] To a stirred 4° aqueous solution containing ethanolamine (610 mg, 10 mmol), KOH (840 mg, 15 mmol) and H_2O (15 mL) was added pivaloyl chloride (1.44 g, 12 mmol) whereupon the reaction was allowed to slowly warm to 20°. After stirring for 18hr, the solution was extracted 4x with EtOAc,. The combined organic layers were washed with brine, dried over Na_2SO_4 prior to concentration using a rotary evaporator to yield 737 mg of a clear oil.

Part B. N-(2-(4-amino-2-methoxyphenoxy)ethyl)pivalamide

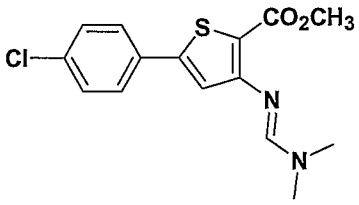


[0045] To a stirred solution of DMF (2 mL) containing N-(2-hydroxyethyl)-pivalamide (360 mg, 2.5 mmol) under N_2 was added 60% NaH/ paraffin (100 mg, 2.5 mmol) . Once gas evolution ceased, 2-chloro-5-nitroaniline (285 mg, 1.55 mmol) was added and the reaction stirred for 18 hr at 20°. The reaction was diluted with H_2O and extracted with EtOAc 3x. The organic layers were washed twice with aq. Na_2CO_3, brine and dried over Na_2SO_4 prior to concentration. Chromatography on silica gel using 25% EtOAc/ CH2Cl2 eluted 360 mg of N-(2-(4-nitro-2-methoxyphenoxy)ethyl)pivalamide as a yellow solid.

[0046] After dissolution of N-(2-(4-amino-2-methoxyphenoxy)ethyl)pivalamide (360 mg, 1.2 mmol) was achieved in EtOH (30 mL) containing 30 mg of 10% Pd/C, the mixture was stirred under 50 psi of H_2 for one hour. The reaction was filtered

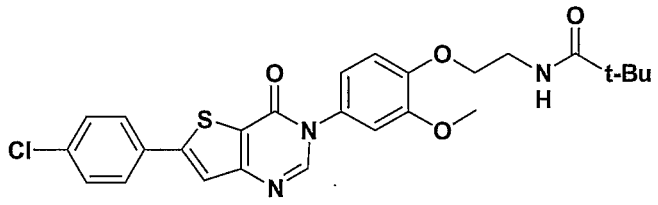
through celite and concentrated prior to chromatographing the residue on silica gel using EtOAc to elute N-(2-(4-amino-2-methoxyphenoxy)ethyl)pivalamide (310 mg).

Part C. Methyl 5-(4-chlorophenyl)-3-((dimethylamino)-methyleneamino)thiophene-2-carboxylate



[0047] The title compound was prepared following the procedure described in WO2003033476. Condensation of 2.00 g of methyl 3-amino-5-(4-chlorophenyl)-thiophene-2-carboxylate with dimethylformamide dimethyl acetal for 3 hr in refluxing EtOH yielded 2.52 g (100%) after removal of the volatiles under vacuum. ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 3.08 (s, 3H), 3.81 (s, 3H), 6.98 (s, 1H), 7.35 (d, J = 8.79 Hz, 2H), 7.53 (d, J= 8.24 Hz, 2H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.31, 40.26, 51.44, 112.43, 122.28, 126.95, 129.09, 132.18, 134.45, 145.79, 156.09, 159.16, 163.22; HPLC (Method #1): 2.45 min retention time; MS (ES): m/z 323 $[M+H]^+$.

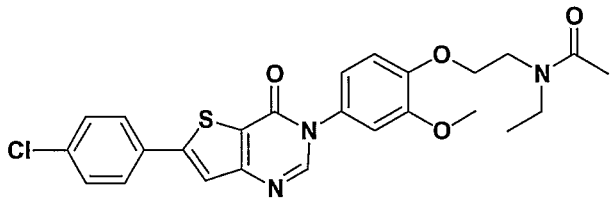
Part D.



[0048] Following the procedure described in WO2003033476, N-(2-(4-amino-2-methoxyphenoxy)ethyl)pivalamide (316 mg, 1.2 mmol) was condensed with methyl 5-(4-chlorophenyl)-3-((dimethylamino)methyleneamino)thiophene-2-carboxylate (355 mg, 1.1 mmol) by heating an EtOH solution (3 mL) of the two components to reflux for 15 hr. Upon cooling and filtration, the title compound was isolated as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 3.71 (m, 2H), 3.90 (s, 3H), 4.176 (t, 2H, J = 5Hz), 6.35 (m, 1H), 6.94 (dd, 1H, J= 8.2 Hz, J = 2.1 Hz), 6.99 (d, 1H, J = 2.1 Hz), 7.05 (d, 1H, J = 8.2 Hz), 7.45 (d, 2H, J_{AB} = 8.9 Hz), 7.54 (s, 1H), 7.67 (d, 2H, J_{AB} = 8.9 Hz), 8.41 (s, 1H); HPLC (Method #1): 3.8 min; LCMS m/z: 512 [M+H].

EXAMPLE 2

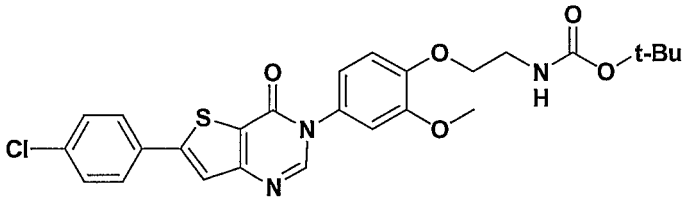
N-(2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)ethyl)-N-ethylacetamide



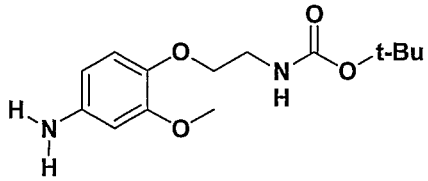
[0049] The same procedure as described in Example 1, was employed to convert N-ethylethanolamine to the title compound. ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 0.75H, J = 7 Hz), 1.24 (t, 2.25H, J = 7 Hz), 2.13 (s, 2.25H), 2.24(s, 0.75H), 2.25 (s, 0.75H), 3.49 (q, 2 H, J = 7 Hz), 3.76 (t, 2H, J = 5.7 Hz), 3.87 (s, 0.75H), 3.885 (s, 2.25H), 4.16 (t, 0.5 5H, J = 5.7 Hz), 4.26 (t, 1.5H, J = 5.7 Hz), 6.95 (m, 2H), 7.06 (d, 1H, 9 Hz), 7.44 (d, 2H, J_{AB} = 8.7 Hz), 7.53 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H). (Rotamers will coalesce upon heating); HPLC (Method #1): 3.67 min; LCMS m/z: 498 [M+H].

EXAMPLE 3

tert-Butyl 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)ethylcarbamate



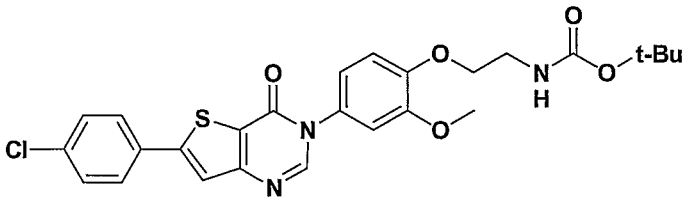
Part A. tert-Butyl 2-(4-amino-2-methoxyphenoxy)ethylcarbamate



[0050] A suspension of K_2CO_3 (280 mg, 2 mmol), NaI (700 mg, 5 mmol), the potassium salt of 2-methoxy-4-nitrophenol (1.37g, 6.6 mmol), and t-butyl 2-chloroethylcarbamate (1.4g, 8 mmol) in DMF (8 mL) was heated at 90° for 6 hr. After

dilution with H_2O, the mixture was extracted 4x with CH_2Cl_2. The combined organic layers were washed 2x with aq. K_2CO_3, then with brine prior to drying over Na_2SO_4. After removal of the solvent under vacuum, the residue was chromatographed on silica gel using 5% EtOAc/CH_2Cl_2 to elute 870 mg of nitrophenyl ether. Pd catalyzed reduction in ethanol as described in Example 1 yielded tert-butyl 2-(4-amino-2-methoxyphenoxy)ethylcarbamate (700 mg) as an off white solid which was carried forward without further purification.

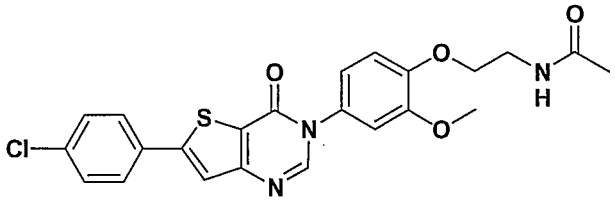
Part B.



[0051] The title compound (560 mg) was obtained by filtering the solid that formed upon standing at 20°C after heating a mixture of tert-butyl 2-(4-amino-2-methoxyphenoxy)ethylcarbamate (700 mg) and methyl 5-(4-chlorophenyl)-3-((dimethylamino)methyleneamino)thiophene-2-carboxylate (800 mg, 2.5 mmol) in EtOH (3 mL) at reflux for 15 hr. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.59 (m, 2H), 3.90 (s, 3H), 4.14 (t, 2H, J = 4.8Hz), 5.14 (m, 1H), 6.94 (dd, 1H, J= 8.4 Hz, J = 2.2 Hz), 6.97 (d, 1H, J = 2.2 Hz), 7.02 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J_{AB} = 8.9 Hz), 7.53 (s, 1H), 7.65 (d, 2H, J_{AB} = 8.9 Hz), 8.13 (s, 1H); HPLC (Method #1) 3.92 min; LCMS m/z: 528 [M+H].

EXAMPLE 4

N-(2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)ethyl)acetamide

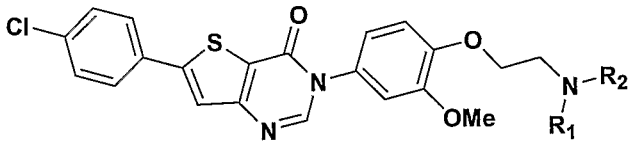


[0052] A 10% TFA/CH_2Cl_2 solution (0.5mL) containing tert-butyl 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-

ethylcarbamate (15 mg, 0.03 mmol) (Example 3) was stirred for 2.5 hr whereupon the volatiles were removed under vacuum. To the residue containing 3-(4-(2-aminoethoxy)-3-methoxyphenyl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one was sequentially added CH_2Cl_2 (0.25 mL), Ac_2O (20 mg, 0.2 mmol) and Et_3N (74 mg, 0.7 mmol). After standing overnight, the reaction was diluted with aq Na_2CO_3 and extracted 4 x with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent the residue was chromatographed on silica gel using 5 – 10% MeOH/EtOAc to elute the desired acetamide (12 mg). ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.72 (m, 2H), 3.91 (s, 3H), 4.16 (t, 2H, J = 4.8Hz), 6.13 (m, 1H), 6.94 (dd, 1H, J= 8.4 Hz, J = 2.2 Hz), 6.98 (d, 1H, J = 2.2 Hz), 7.02 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H); HPLC (Method #1): 3.67 min; LCMS m/z: 498 [M+H].

EXAMPLES 5 TO 11

[0053] These derivatives were prepared in an analogous manner by acylation or sulfonalation of the primary amine described in Example 4 or a close analog thereof.

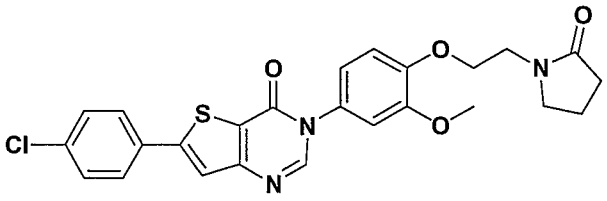


Example #	R1	R2	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
5	$MeSO_2$	H	506	3.35 Method #1	^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 3.60 (m, 2H), 3.89 (s, 3H), 4.20 (t, 2H, J = 4.8Hz), 4.99 (m, 1H), 6.95 (dd, 1H, J= 8.8 Hz, J = 2.2 Hz), 6.98 (d, 1H, J = 2.2 Hz), 7.03 (d, 1H, J = 8.8 Hz), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H)	Prepared by the reaction of MsCl with the amine described in Ex 4
6	Et_2NCO	H	527	3.71 Method #1	^{1}H NMR ($CDCl_3$) δ 1.15 (t, 6H, J = 7.4 Hz), 3.28 (q, 4H, J = 7.4 Hz), 3.7 (m, 2H), 3.89 (s, 3H), 4.18 (t, 2H, J = 4.8Hz), 4.97 (m, 1H), 6.93 (dd, 1H, J= 8.4 Hz, J = 2.2 Hz), 6.97 (d, 1H, J = 2.2 Hz), 7.05 (d, 1H, J = 8.4 Hz), 7.44 (d, 2H, J_{AB} = 8.3 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.3 Hz), 8.14 (s, 1H)	Prepared by the reaction of Et_2NCOCl with the amine described in Ex 4

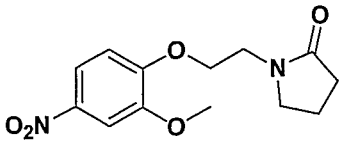
Example #	R1	R2	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
7	BnCO	H	546	3.70 Method #1	^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H), 3.68 (m, 2H), 3.83 (s, 3H), 4.11 (t, 2H, J = 4.8Hz), 6.03 (m, 1H), 6.90 – 6.97 (m, 3H), 7.28 – 7.38 (m, 5H), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.13 (s, 1H)	Prepared by the reaction of BnCOCl with the amine described in Ex 4
8	$BnSO_2$	H	582	3.72 Method #1	^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.90 (m, 2H), 4.06 (t, 2H, J = 4.8Hz), 4.35 (s, 2H), 6.93 – 7.1 (m, 3H), 7.26 (m, 5H), 7.40 M, 1H), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.13 (s, 1H)	Prepared by the reaction of $BnSO_2Cl$ with the amine described in Ex 4
9	CF_3CO	H	524	3.69 Method #1	^{1}H NMR ($CDCl_3$) δ 3.81 (m, 2H), 3.91 (s, 3H), 4.21 (t, 2H, J = 4.8Hz), 6.13 (m, 1H), 6.96 (dd, 1H, J= 8.4 Hz, J = 2.6 Hz), 7.01 (d, 1H, J = 2.6 Hz), 7.08 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H)	Prepared by the reaction of TFAA with the amine described in Ex 4
10	MeOC(O)	H	486	3.5 Method #1	^{1}H NMR ($CDCl_3$) δ 3.65 (m, 2H), 3.70 (s, 3H), 3.89 (s, 3H), 4.14 (t, 2H, J = 4.8Hz), 4.97 (m, 1H), 6.93 (dd, 1H, J= 8.4 Hz, J = 2.2 Hz), 6.97 (d, 1H, J = 2.2 Hz), 7.02 (d, 1H, J = 8.4 Hz), 7.44 (d, 2H, J_{AB} = 8.3 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.3 Hz), 8.14 (s, 1H)	Prepared by the reaction of MeOCOCl with the amine described in Ex 4
11	MeOC(O)	Me	500	3.74 Method #1	^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.71 (br s, 5H), 3.88 (s, 3H), 4.17-4.27 (m, 2H), 6.92-7.04 (m, 3H), 7.44 (d, J = 8.25 Hz, 2H), 7.55 (s, 1H), 7.66 (d, J = 7.70 Hz, 2H), 8.19 (s, 1H)	Prepared by sequential treatment of Ex 129 with $MeNH_2$ then MeOCOCl

EXAMPLE 12

6-(4-Chlorophenyl)-3-(3-methoxy-4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one

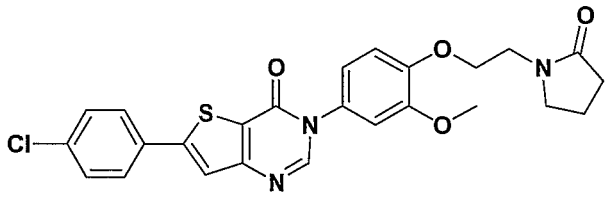


Part A. 1-(2-(2-Methoxy-4-nitrophenoxy)ethyl)pyrrolidin-2-one



[0054] Following the procedure described in Example 1, 2-chloro-5-nitroanisole (200 mg) and 2-hydroxy-1-(pyrrolidin-2-one (0.18 mL) were condensed to obtain 191 mg of the title compound (64%). ^{1}H NMR ($CDCl_3$) δ 2.00-2.06 (m, 2H), 2.36-2.39 (m, 2H), 3.60-3.63 (m, 2H), 3.72-3.74 (m, 2H), 3.92 (s, 3H), 4.22-4.24 (m, 2H), 6.88 (d, J = 8.80 Hz, 1H), 7.73 (d, J = 2.20 Hz, 1H), 7.87 (dd, J = 8.80 Hz, 2.20 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.22, 30.69, 42.08, 49.03, 56.27, 67.84, 106.75, 111.09, 117.66, 141.73, 149.11, 153.46, 175.42; HPLC (Method #1): 2.34 min retention time, (100%); LCMS m/z: 281 [M+H].

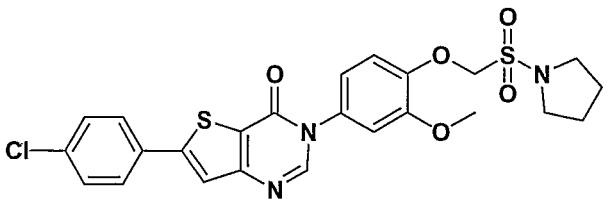
Part B.



[0055] The nitroaryl ether of Part A was converted to Example 12 following the procedure described in Example 1 and isolated as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.02-2.08 (m, 2H), 2.39-2.42 (m, 2H), 3.65-3.68 (m, 2H), 3.74-3.76 (m, 2H), 3.89 (s, 3H), 4.21-4.23 (m, 2H), 6.93 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.97 (d, J = 2.20 Hz, 1H), 6.99 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.25 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.20, 30.77, 42.22, 48.99, 56.11, 67.92, 111.03, 113.22, 119.18, 120.84, 123.17, 127.63, 129.43, 130.28, 131.50, 135.66, 148.12, 148.72, 149.90, 151.66, 156.79, 157.38, 175.36; HPLC (Method #1): 3.56 min retention time; MS (ES): m/z 496 $[M+H]^+$.

EXAMPLE 13

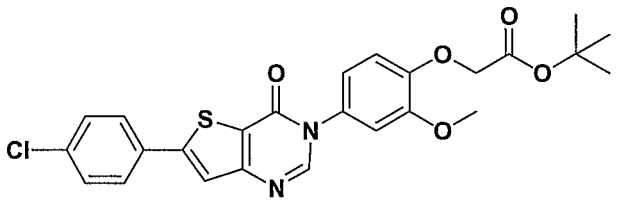
6-(4-Chlorophenyl)-3-(3-methoxy-4-((pyrrolidin-1-ylsulfonyl)methoxy)-phenyl)thieno[3,2-d]pyrimidin-4(3H)-one



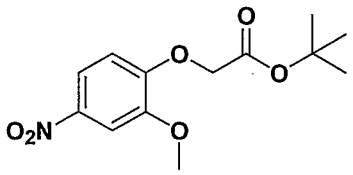
[0056] To a 0°C solution of pyrrolidine (1.23 mL, 14.8 mmol) in CH_2Cl_2 mL) was added a solution of chloromethylsulfonyl chloride (1.0g, 65.71 mmol) over 30 min. The bath was removed and the reaction stirred for 3 hr at 20°C whereupon it was washed with 1N HCl (20 mL). After drying over $MgSO_4$, concentration yielded a yellow solid (899 mg) that was not further purified before being used to alkylate the potassium salt of 2-methoxy-4-nitrophenol to ultimately generate the title compound following the procedure described Example 3. ^{1}H NMR ($CDCl_3$) δ 1.96-1.99 (m, 4H), 3.52 (t, 4H), 3.89 (s, 3H), 5.14 (s, 2H), 6.95 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 7.03 (d, J = 2.75 Hz, 1H), 7.27 (d, J = 8.24 Hz, 1H), 7.45 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H); HPLC (Method #1): 4.23 min retention time; MS (ES): m/z 532 [M+H].

EXAMPLE 14

tert-Butyl 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)acetate



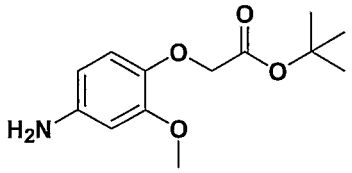
Part A. tert-Butyl 2-(2-methoxy-4-nitrophenoxy)acetate



[0057] A solution of 4-nitroguaiacol potassium salt (613 mg; 2.96 mmol) and t-butyl bromoacetate (0.65 mL; 4.43 mmol) in DMF (7 mL) was stirred at rt for 0.5 h prior to dilution with H_2O and extraction with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Hexanes/EtOAc, 100:0 to 1:1 gradient) to afford the title compound (738 mg; 88%) as a beige solid. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.96 (s, 3H), 4.67 (s, 2H), 6.77 (d, J =

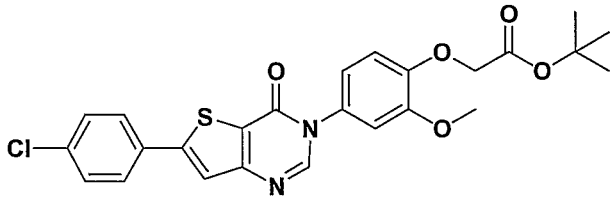
8.79 Hz, 1H), 7.76 (d, J = 2.74 Hz, 1H), 7.85 (dd, J= 8.80 Hz, 2.75 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.98, 56.37, 66.18, 83.09, 107.07, 111.52, 117.28, 142.17, 149.19, 152.69, 166.66; HPLC (Method #1): 3.13 min retention time, (97%); MS (ES): m/z 306 $[M+Na]^+$.

Part B. tert-Butyl 2-(4-amino-2-methoxyphenoxy)acetate



[0058] Reduction of 718 mg of tert-Butyl 2-(2-methoxy-4-nitrophenoxy)acetate of Part A as described in Example 1 yielded 601 mg (94%). ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.48 (br s, 2H), 3.80 (s, 3H), 4.46 (s, 2H), 6.16 (dd, J = 8.80 Hz, 2.75 Hz, 1H), 6.28 (d, J = 2.19 Hz, 1H), 6.70 (d, J= 8.80 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.02, 55.71, 67.98, 81.77, 100.78, 106.36, 116.92, 140.41, 141.97, 150.69, 168.60; HPLC (Method #1): 1.43 min retention time, (100%); MS (ES): m/z 276 $[M+Na]^+$.

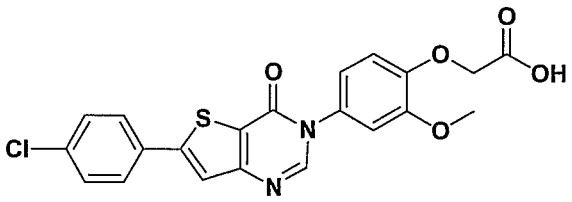
Part C. tert-Butyl 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)acetate



[0059] Condensation of methyl 5-(4-chlorophenyl)-3-((dimethylamino)methylene-amino)-thiophene-2-carboxylate (740 mg) and tert-butyl 2-(4-amino-2-methoxy-phenoxy)acetate Part C (581 mg) as described in Example 1 yielded the title compound 388 mg (34%). ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H), 3.92 (s, 3H), 4.65 (s, 2H), 6.91 (br s, 2H), 6.99 (br s, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.04, 56.21, 66.57, 82.58, 111.28, 113.76, 118.98, 120.86, 123.21, 127.65, 129.45, 130.85, 131.52, 135.68, 148.12, 150.00, 151.66, 156.73, 157.36, 167.51; HPLC (Method #1): 3.89 min retention time; MS (ES): m/z 499 $[M+H]^+$.

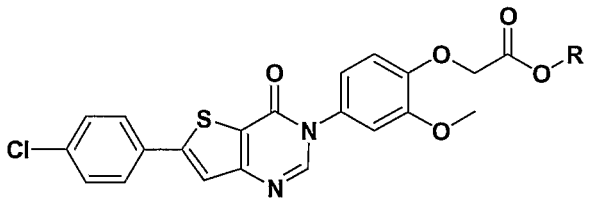
EXAMPLE 15

2-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxy-phenoxy)acetic acid



[0060] A solution of tert-butyl 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)acetate Example 14 (370 mg; 0.741 mmol) in 1:1 TFA/CH_2Cl_2 (6 mL) was stirred at rt for 1 h. After concentration under reduced pressure and azeotroping with toluene, the residue was triturated with MeOH to afford the title compound (290 mg; 88%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H), 4.75 (s, 2H), 6.99-7.04 (m, 2H), 7.22 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.91 (d, J = 8.25 Hz, 2H), 7.97 (s, 1H), 8.40 (s, 1H), 13.06 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.76, 64.86, 111.95, 112.70, 119.41, 121.70, 121.98, 127.83, 129.26, 130.21, 131.18, 134.26, 147.36, 148.80, 149.44, 149.79, 156.06, 157.39, 169.9; HPLC (Method #1): 3.44 min retention time; MS (ES): m/z 443 $[M+H]^+$.

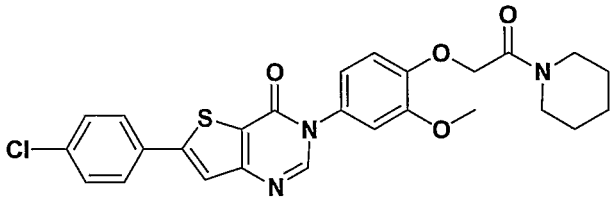
EXAMPLES 16 AND 17



Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic comments
16	O-Et	471	3.70 Method #1	^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 3.92 (s, 3H), 4.29 (q, 2H), 4.75 (s, 2H), 6.91-6.96 (m, 2H), 7.00 (d, J = 2.20 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H)	Procedure analogous to that of Ex 14
17	O-Me	457	3.54 Method #1	^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H), 3.79 (s, 3H), 4.87 (s, 2H), 7.02 (br s, 2H), 7.23 (br s, 1H), 7.57 (d, J = 8.35 Hz, 2H), 7.92 (d, J = 8.35 Hz, 2H), 7.97 (s, 1H), 8.40 (s, 1H)	Procedure analogous to that of Ex 14

EXAMPLE 18

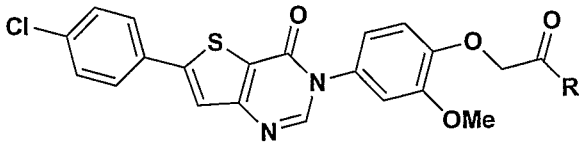
6-(4-Chlorophenyl)-3-(3-methoxy-4-(2-oxo-2-(piperidin-1-yl)ethoxy)phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one



[0061] A solution of 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)acetic acid Example 15 (20 mg; 0.045 mmol), piperidine (7 uL; 0.068 mmol), EDC hydrochloride (10 mg; 0.054 mmol) and hydroxybenzotriazole hydrate (8 mg; 0.054 mmol) in 70 uL of DMF and 415 uL of CH_2Cl_2 was cooled to 0°C. After addition of N-methylmorpholine (6 uL; 0.054 mmol), the solution allowed to warm to rt and stir for 23 h. Following concentration under reduced pressure and dilution with water, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was triturated in MeOH to afford the title compound (20 mg; 87%) as a white solid. ^1H NMR ($CDCl_3$) δ 1.57-1.67 (m, 6H), 3.52-3.59 (m, 4H), 3.90 (s, 3H), 4.81 (s, 2H), 6.91 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.98 (d, J = 2.75 Hz, 1H), 7.09 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.42, 25.54, 26.47, 43.27, 46.39, 56.15, 68.65, 111.13, 113.98, 119.14, 120.86, 123.21, 127.65, 129.45, 130.75, 131.54, 135.68, 148.14, 148.28, 149.88, 151.66, 156.75, 157.40, 165.65; HPLC (Method #1): 3.65 min retention time; MS (ES): m/z 510 $[M+H]^+$.

EXAMPLES 19 TO 29

[0062] The following amides were synthesized from Example 15 and commercially available amines in a similar manner to that described in Example 18.



Example #	R	Mass spec M+H	HPLC retention (min)	H NMR
19	Pyrrolidine	496	3.54 Method #1	^{1}H NMR ($CDCl_3$) δ 1.84-1.91 (m, 2H), 1.96-2.03 (m, 2H), 3.52-3.59 (m, 4H), 3.91 (s, 3H), 4.76 (s, 2H), 6.91 (dd, J = 8.35 Hz, 2.63 Hz, 1H), 6.98 (d, J = 2.20 Hz, 1H), 7.08 (d, J = 8.79 Hz, 1H), 7.45 (d, J = 8.35 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)
20	Morpholine	512	3.40 Method #1	^{1}H NMR ($CDCl_3$) δ 3.36-3.57 (m, 8H), 3.90 (s, 3H), 4.82 (s, 2H), 6.92 (dd, J = 8.80 Hz, 2.20 Hz, 1H), 6.99 (d, J = 2.75 Hz, 1H), 7.10 (d, J = 8.25 Hz, 1H), 7.45 (d, J = 8.25 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H)
21	NEt_2	498	3.63 Method #1	^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H), 1.22 (t, 3H), 3.38-3.43 (m, 4H), 3.89 (s, 3H), 4.80 (s, 2H), 6.89 (dd, J = 8.80 Hz, 2.20 Hz, 1H), 6.97 (d, J = 2.20 Hz, 1H), 7.05 (d, J = 8.25 Hz, 1H), 7.43 (d, J = 8.24 Hz, 2H), 7.51 (s, 1H), 7.64 (d, J = 8.25 Hz, 2H), 8.12 (s, 1H)
22	N(Et) CH_2CH_2OH	514	3.38 Method #1	^{1}H NMR ($CDCl_3$) δ 1.15-1.26 (m, 3H), 3.43-3.56 (m, 4H), 3.77-3.81 (m, 2H), 3.88 (s, 3H), 4.84, 4.88 (s, 2H), 6.88-6.91 (m, 1H), 6.96-6.98 (m, 1H), 7.02-7.04 (m, 1H), 7.41-7.43 (m, 2H), 7.50, 7.51 (s, 1H), 7.62-7.64 (m, 2H), 8.11, 8.12 (s, 1H)
23	$N(CH_2CH_2OH)_2$	530	3.24 Method #1	^{1}H NMR (CD_3OD-$CDCl_3$) δ 3.41 (m, 4H), 3.63 (m, 4H), 3.76 (s, 3H), 3.95 (s, 2H), 4.83 (s, 2H), 6.77 (dd, J = 8.79 Hz, 2.20 Hz, 1H), 6.84 (d, J = 2.75 Hz, 1H), 6.92 (d, J = 8.80 Hz, 1H), 7.31 (d, J = 8.80 Hz, 2H), 7.41 (s, 1H), 7.54 (d, J = 8.80 Hz, 2H), 8.04 (s, 1H)
24	NH_2	442	3.37 Method #1	^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H), 4.51 (s, 2H), 7.01-7.06 (m, 2H), 7.24 (s, 1H), 7.40 (br s, 1H), 7.44 (br s, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.92 (d, J = 8.25 Hz, 2H), 7.97 (s, 1H), 8.40 (s, 1H)
25	$NH(CH_2)_2NMe_2$	513	2.72 Method #1	^{1}H NMR ($CDCl_3$) δ 2.25 (s, 6H), 2.46 (t, 2H), 3.42-3.45 (m, 2H), 3.92 (s, 3H), 4.60 (s, 2H), 6.95 (dd, J = 8.79 Hz, 2.20 Hz, 1H), 7.01-7.03 (m, 2H), 7.30 (br s, 1H), 7.44 (d, J = 8.25 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H)
26	NHBu	498	3.87 Method #1	^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.35-1.42 (m, 2H), 1.53-1.59 (m, 2H), 3.35-3.39 (q, 2H), 3.92 (s, 3H), 4.59 (s, 2H), 6.90 (br s, 1H), 6.95-7.03 (m, 3H), 7.45 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H)
27	$NH(CH_2)_2$-Ph-*p*-OH	562	3.66 Method #1	^{1}H NMR (DMSO-d_6) δ 2.63 (t, 2H), 3.28-3.33 (m, 2H), 3.79 (s, 3H), 4.52 (s, 2H), 6.67 (d, J = 8.35 Hz, 2H), 6.96-7.00 (m, 3H), 7.03 (dd, J = 8.78 Hz, 2.20 Hz, 1H), 7.23 (d, J = 2.19 Hz, 1H), 7.58 (d, J = 8.79 Hz, 2H), 7.92-7.97 (m, 3H), 7.99 (s, 1H), 8.40 (s, 1H), 9.18 (s, 1H)

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR
28	$NH(CH_2)_2$-Ph-*p*-SO_2NH_2	625	3.42 Method #1	^{1}H NMR (DMSO-d_6) δ 2.83 (t, 2H), 3.38-3.43 (m, 2H), 3.79 (s, 3H), 4.53 (s, 2H), 6.96 (d, J = 8.79 Hz, 1H), 7.04 (dd, J = 8.79 Hz, 2.20 Hz, 1H), 7.24 (d, J = 2.20 Hz, 1H), 7.29 (br s, 2H), 7.40 (d, J = 8.34 Hz, 2H), 7.58 (d, J = 8.79 Hz, 2H), 7.74 (d, J = 8.34 Hz, 2H), 7.93 (d, J = 8.79 Hz, 2H), 7.99 (s, 1H), 8.08 (t, 1H), 8.39 (s, 1H)
29	$NH(CH_2)_2$-4-piperdine-NBn	643	2.98 Method #1	^{1}H NMR ($CDCl_3$) δ 1.32 (br s, 3H), 1.50-1.53 (m, 2H), 1.67-1.71 (m, 2H), 1.95 (t, 2H), 2.87-2.91 (m, 2H), 3.37-3.41 (q, 2H), 3.51 (s, 2H), 3.90 (s, 3H), 4.57 (s, 2H), 6.83 (t, 1H), 6.94-7.01 (m, 3H), 7.24-7.31 (m, 5H), 7.45 (d, J = 8.24 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H)

EXAMPLES 30 TO 75

[0063] These amides were prepared as a library using the following procedure.

[0064] The following solutions were sequentially added to a reaction well: 2-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)acetic acid (preparation described in Example 15) (13.29 mg, 30 μmol) in 300 μL of DMF, HOBt (5.07 mg, 38 μmol) in 150 μL of DMF and 150 μL of DMF containing EDC (7.19 mg, 38 μmol) and $NEt(iPr)_2$ (26.1 mg, 150 μmol). After the combined solutions were agitated for 10 min, 150 μL of DMF containing the amine (38 μmol) to be acylated was added. The resulting mixture was agitated overnight at 65°C; whereupon, the reactions were cooled to room temperature and transferred to plastic microtubes, using DMF as a rinse solvent. For purification, the crude reaction mixtures were injected directly from the plastic microtubes onto a preparative LCMS which CMS triggered on the desired mass ion to collect the appropriate fractions. The details of the purification entailed gradient elution using 20-100% solvent B from a Waters Sunfire 19x100 5 micron silica column over 10 min with 5 min hold.

Solvent A: 10/90 Acetonitrile/Water containing 0.1% TFA

Solvent B: 90/10 Acetonitrile/Water containing 0.1% TFA

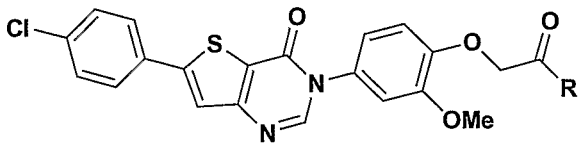
UV @ 220nM; MS @ ESI+

[0065] The fractions were dried overnight, reconstituted in 1 mL of DMF, and transferred to fresh, tared plastic microtubes. A small aliquot was removed for

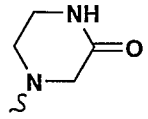
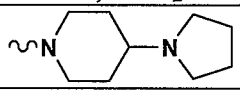
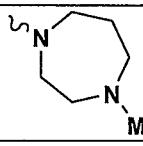
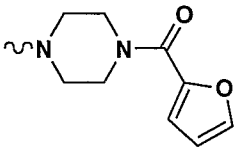
analysis by analytical LCMS, diluted with DMF for solubility. The microtubes were dried overnight and then weighed. The details of the analytical chromatograms comprised Purity was assessed by gradient elution from a Waters Sunfire 4.6 x 50, 5 micron silica column using 0-100% B over 4 min, 1 min hold, total run time 5 min monitoring UV @ 220nM and MS @ ESI+

Solvent A: 10/90 Methanol/Water containing 0.1% TFA

Solvent B: 90/10 Methanol/Water containing 0.1% TFA

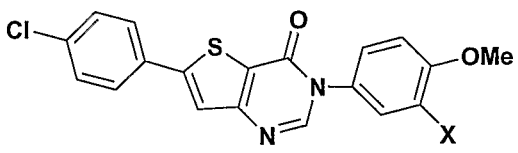


Example #	R	Mass spec M+	HPLC retention (min)
30	NH-*i*-Pentyl	512	4.03
31	$NH(CH_2)_2OH$	486	3.43
32	NH-cyclopentyl	510	3.95
33	N(Me)Et	484	3.61
34	$NH(CH_2)_2CO_2Me$	528	3.63
35	NH-cyclopropyl	482	3.66
36	Piperdine-4-OH	526	3.46
37	Piperdine-4-NMe_2	553	3.01
38	Piperdine-4-Ph	586	4.12
39	Piperazine-4-Me	525	2.99
40	Piperazine-4-Ph	587	3.86
41	Piperazine-4-Ph-p-MeO	617	3.53
42	Piperazine-4-CH_2Ph	601	3.22
43	$NH(CH_2)_2$Pyrrolidine	539	3.05
44	$NHCH_2$-2-THF	576	3.72
45	$NH(CH_2)_2$Morpholine	555	3.04
46	NH CH_2Ph	532	3.96
47	$NH(CH_2)_2Ph$	546	4.04
48	$NH(CH_2)_3Ph$	560	4.11
49	NH-CH_2Ph-*p*-Cl	566	4.1
50	$NH(CH_2)_2OPh$	562	4.01
51	N(Me) CH_2Ph	546	3.94
52	$NHCH_2$-2-thiophene	538	3.87
53	$NH(CH_2)_2$Ph-*p*-OMe	576	4.01
54	$NH(CH_2)_2OEt$	514	3.72
55	NH-*sec*-Bu	498	3.89
56	$NH(CH_2)_2O$-*i*-Pr	528	3.86
57	$NH(CH_2)_3NMe_2$	527	3.01

Example #	R	Mass spec M+	HPLC retention (min)
58		525	3.35
59	$NH(CH_2)CONH_2$	498	3.36
60	$NHCH_2$cyclopropyl	496	3.81
61	NH-cyclobutyl	496	3.84
62	$NH(CH_2)_3$-N-pyrrolidone	567	3.56
63	Piperdine-4-Me	524	3.93
64	Morpholine-3,5-Me_2	540	3.90
65		579	3.03
66		539	3.00
67	$NH(CH_2)_3$-N-morpholine	569	3.02
68	$NHCH_2$Ph-*m*-CF_3	600	4.09
69	NH CH_2Ph-*p*-SO_2NH_2	611	3.48
70	$NMe(CH_2)_2Ph$	560	3.99
71		605	3. 57
72	NHPh-*p*-NMe_2	561	3.17
72	*cis*-NHcyclopropyl-2-Ph	558	4.04
74	$NH(CH_2)_2$-2 –pyrolidine-NMe	553	3.06
75	Piperazine-4-$CH(Ph)_2$	677	3.50

EXAMPLES 76 TO 81

[0066] Following the procedure described in Example 1, Examples 76 to 81 were prepared from the appropriately substituted 4-nitroanisole.

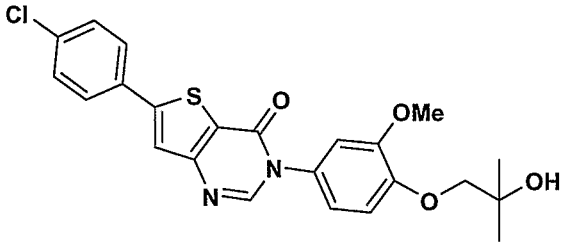


Example #	X	Mass spec M+H	HPLC retention (min)	H NMR
76	OMe	399	3.63 Method #1	^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.93 (s, 3H), 6.9 – 7.0 (m, 3H), 7.43 (d, 2H, J_{AB} = 8.7Hz), 7.51 (s, 1H), 7.63 (d, 2H, J_{AB} = 8.7Hz), 8.12 (s, 1H)

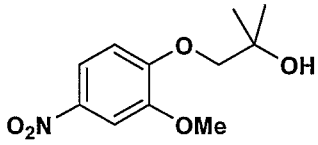
Example #	X	Mass spec M+H	HPLC retention (min)	H NMR
77	H	369	3.78 Method #1	^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.05 (d, 2H, J_{AB} = 8.8Hz), 7.35 (d, 2H, J_{AB} = 8.8Hz), 7.44 (d, 2H, J_{AB} = 8.8Hz), 7.53 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.8Hz), 8.13 (s, 1H)
78	OH	385	3.52 Method #1	^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.85 – 6.95 (m, 3H), 7.38 (d, 2H, J_{AB} = 8.8Hz), 7.46 (s, 1H), 7.51 (d, 2H, J_{AB} = 8.8Hz), 8.06 (s, 1H)
79	Cl	403	3.96 Method #1	^{1}H NMR (DMSO-d_6) δ 3.93 (s, 3H), 7.32 (br s, 1H), 751-7.58 (m, 3H), 7.73 (s, 1H), 7.93-7.98 (m, 3H), 8.41 (s, 1H)
80	CN	394	3.61 Method #1	^{1}H NMR (DMSO-d_6) δ 3.99 (s, 3H), 7.43 (d, J = 8.78 Hz, 1H), 7.58 (d, J = 8.35 Hz, 2H), 7.88-7.94 (m, 3H), 8.00 (s, 1H), 8.04 (d, J = 2.64 Hz, 1H), 8.44 (s, 1H)
81	Me	383	3.96 Method #1	^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.90 (s, 3H), 6.95 (d, J = 7.91 Hz, 1H), 7.20-7.22 (m, 2H), 7.45 (d, J = 8.35 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.79 Hz, 2H), 8.12 (s, 1H)

EXAMPLE 82

6-(4-Chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)-thieno[3,2-d]pyrimidin-4(3H)-one



Part A. 1-(2-Methoxy-4-nitrophenoxy)-2-methylpropan-2-ol



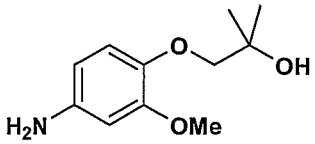
[0067] A steel bomb, fitted with an internal thermocouple, pressure gauge and safety release valve rated at 3000 psi, with ~ 55 mL capacity was charged with the potassium salt of 2-methoxy-4-nitrophenol (6g, 29 mmol), NaH_2PO_4 (3.3g, 27.7mmol), isobutylene oxide (2.8 g, 35 mmol) and 30 mL of 15% H_2O/MeCN. The sealed bomb was heated at 170 °C for three hr. Following cooling, HPLC revealed all starting phenol had been converted to product. The biphasic solution was concentrated using a rotary evaporator before being partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted 3x with CH_2Cl_2; the combined CH_2Cl_2

fractions were washed 3x with aq $KHCO_3/K_2CO_3$ and once with H_2O. After drying over Na_2SO_4, concentration under vacuum yielded 6.9g of desired product as a tan solid.

[0068] (Buffering with NaH_2PO_4 is essential to prevent reversion of the product to starting phenol as the pH increases during the reaction. Note even for small scale reactions, temperatures greater than 180 °C should be avoided to minimize the probability of explosive decomposition since the potassium salt of 2-chloro-4-nitrophenol rapidly decomposes at ~210 °C producing gaseous products.)

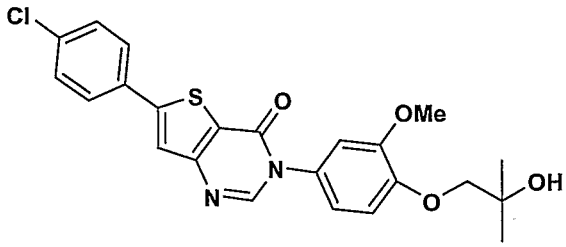
[0069] ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6H), 2.5 (s, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 6.90 (d, J = 9 Hz, 1H), 7.74 (d, J = 2 Hz, 1H), 7.87 (dd, J= 2 Hz and 9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.02, 56.18, 70.00, 77.42, 106.77, 111.74, 117.56, 141.73, 149.37, 153.95; HPLC (Method #1): 3.26 min retention time (99% API); LCMS (ES): m/z 242.1 $[M+H]^+$.

Part B. 1-(4-Amino-2-methoxyphenoxy)-2-methylpropan-2-ol



[0070] A stirred EtOH suspension (320 mL) containing 1-(2-methoxy-4-nitrophenoxy)-2-methylpropan-2-ol Part A (13.6g, 56.4 mmol) and 10% Pd/C (0.25 g) was hydrogenated under 60 psi H_2 for 6hr. HPLC analysis revealed no starting nitro catechol ether remained. The resultant black suspension was filtered through a fiberglass filter paper under a blanket of N_2 gas. The resultant clear wine colored solution was immediately concentrated using a rotary evaporator under vacuum to yield 12.4 of desired product as a dark orange oil which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6H), 3.40, (br s, 2H), 3.74 (s, 2H), 3.78 (s, 3H), 6.20 (dd, J = 8.35 Hz, 2.64 Hz, 1H), 6.28 (d, J = 2.64 Hz, 1H), 6.76 (d, J = 8.35 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.90, 55.67, 70.02, 80.30, 100.76, 106.81, 118.27, 141.55, 141.93, 150.99; HPLC (Method #1): 0.88 min retention time; LCMS (ES): m/z 212.1 [M+H].

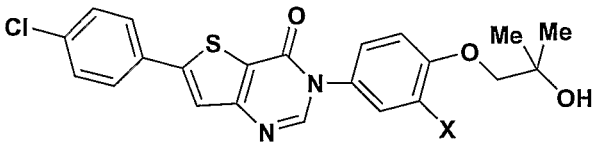
Part C.



[0071] Conversion of 1-(2-methoxy-4-aminophenoxy)-2-methylpropan-2-ol to the title compound was achieved by the procedures described in Example 1. ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H), 2.74, (s, 1H), 3.87 (s, 3H), 3.89 (s, 2H), 6.93 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.96 (d, J = 2.20 Hz, 1H), 7.01 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.80 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.02, 56.11, 70.08, 78.05, 111.19, 114.49, 119.20, 120.82, 123.19, 127.61, 129.43, 130.46, 131.50, 135.66, 148.16, 149.35, 150.30, 151.64, 155.77, 157.34; HPLC (Method #1): 4.29 min retention time, (99% API); LCMS (ES): m/z 457 [M+H].

EXAMPLES 83 TO 88

[0072] These compounds were prepared analogously to Example 82.

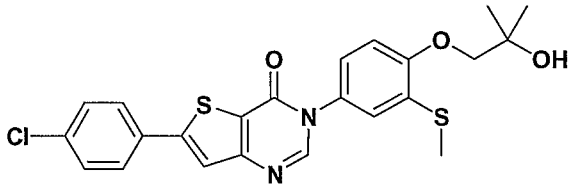


Example #	X	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comment
83	F	4.45	6.37 Method #6	^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6H), 3.92 (s, 2H), 6.93 (ABq, J = 8.3 Hz, 1H), 7.20 (ABq, J = 8.3 Hz, 1H), 7.24 (m, 1H), 7.44 (ABq, J = 8 Hz, 2H), 7.53 (s, 1H), 7.66 (ABq, J = 8 Hz, 2H), 8.11 (s, 1H)	$ArNH_2$ via route C
84	Me	441	7.03 Method #6	^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 2.32 (s, 3H), 3.86 (s, 2H), 7.15 (m, 2H), 7.22 (m, 1H), 7.44 (ABq, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.65 (ABq, J = 8.4 Hz, 2H), 8.12 (s, 1H)	$ArNH_2$ via route C
85	Cl	461	7.04 Method #6	^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6H), 2.05 (s, 1H), 3.91 (s, 2H), 7.05 (d, J = 8.8 Hz, 1H), 7.30 (dd, J = 2.5 Hz, 8.8 Hz, 1H), 7.45 (ABq, J = 8.4 Hz, 2H), 7.49 (dd, J = 2.5 Hz, 1H), 7.53 (s, 1H), 7.65 (ABq, J = 8.4 Hz, 2H), 8.10 (s, 1H)	$ArNH_2$ via route C

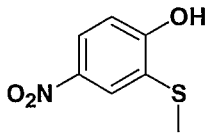
Example #	X	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comment
86	H	427	6.22 Method #6	^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H), 2.24 (s, 1H), 3.86 (s, 2H), 7.07 (ABq, J = 8.7 Hz, 2H), 7.36 (ABq, J = 8.7 Hz, 2H), 7.44 (ABq, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.66 (ABq, J = 8.3 Hz, 2H), 8.13 (s, 1H)	$ArNH_2$ via route C
87	Et	455	7.59 Method #6	^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 1.40 (s, 6H), 2.2 (s, 1H), 2.74 (q, J = 7Hz, 2H), 3.87 (s, 2H), 6.95 (ABq, J = 8.7 Hz, 1H), 7.22 (s, 2H), 7.44 (ABq, J = 7.9 Hz, 2H), 7.53 (s, 1H), 7.65 (ABq, J = 7.9 Hz, 2H), 8.13 (s, 1H)	$ArNH_2$ via route C
88	CN	452	5.64 Method #6	^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6H), 3.89 (s, 1H), 4.02 (s, 2H), 7.48 (d, J = 9.2 Hz, 1H), 7.61 (ABq, J = 8.2 Hz, 2H), 7.89 (dd, J = 2.2 Hz, 9.0 Hz, 1H), 7. (ABq, J = 8.2 Hz, 2H), 8.01 (s, 1H), 8.06 (d, J = 2.6 Hz, 1H), 8.48 (s, 1H)	$ArNH_2$ via route B using 1-chloro-2-methyl-2-propanol

EXAMPLE 89

6-(4-Chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-(methylthio)phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one

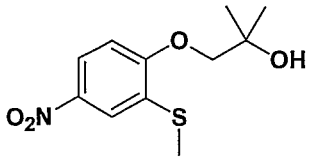


Part A. 2-(Methylthio)-4-nitrophenol



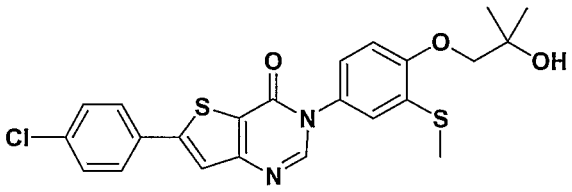
[0073] To a stirred 4 °C solution of NaSMe (710 mg, 10.1mmol) in H_2O (20 ml) was sequentially added Cu powder (30 mg, mmol) followed by aq solution of 2-hydroxy-4-nitrobenzene diazonium BF_4 salt (298 mg, 1.8 mmol) which had been prepared as described by Can J Chem, **1972**, *50*, 2025 – 2030). After stirring for 30 min, the reaction was warmed to 20°C and stirred an additional 2 hr before filtering. The filtrate was adjusted to pH 5 with 1N HCl prior to extracting 3x with EtOAc. After drying over Na_2SO_4 and concentration, the black solid was purified by chromatography on silica gel using 20-30% EtOAc/hexanes to elute (190 mg) as a black solid.

Part B. 2-Methyl-1-(2-(methylthio)-4-nitrophenoxy)propan-2-ol



[0074] A solution of 4-nitro-2-methylthio-1-phenol (60 mg, 0.32 mmol), isobutylene oxide (0.44 mL, 4.9 mmol) and K_2CO_3 (134 mg, 0.97 mmol) in 10% H_2O/MeCN (3 mL) was heated by microwave to 125 °C for 1 hr. After cooling and dilution with H_2O, the mixture was extracted 3x with EtOAc. After drying the combined organic fraction over Na_2SO_4 and concentration, the residue was chromatographed on silica gel using 30-50% EtOAc/hexanes to elute the nitro aryl ether product (70 mg).

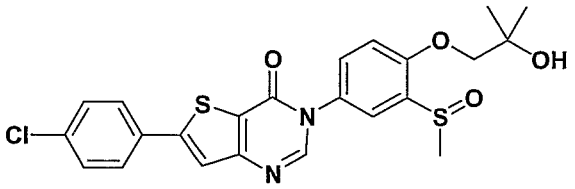
Part C.



[0075] The above product of Part B in MeOH (10 mL) containing 10% Pd/C (20 mg) was stirred under 60 psi H_2 for hr. Once confirmation of complete reduction was provided by LCMS analysis, the reaction was filtered. After concentration, the residue along with the formamidine of Example 1 Part C (119 mg, 0.36 mmol) and phenol (0.5g) was heated to 130 °C for 30 min. Upon cooling and dilution with MeOH, the resultant solid was collected by filtration. Partial oxidation to the corresponding sulfoxide occurred during concentration at 50 °C of the fractions collected in the course of final purification by prep HPLC using an aq MeOH gradient containing 0.1% TFA. Upon repeating the chromatographic separation, pure sulfide and sulfoxide were obtained if the fractions were concentrated at < 20 °C. ^{1}H NMR ($CDCl_3$) δ 141 (s, 6H), 2.45 (s, 3H), 3.93 (s, 2H), 6.45 (d, 1H), 7.13 (s, 2H), 7.45 (ABq, J = 8.3 Hz, 2H), 7.55 (s, 1H), 7.67 (ABq, J = 8.3 Hz, 2H), 8.16 (s, 1H); HPLC (Method #6): 6.83 min; LCMS m/z: 473 (M+H).

EXAMPLE 90

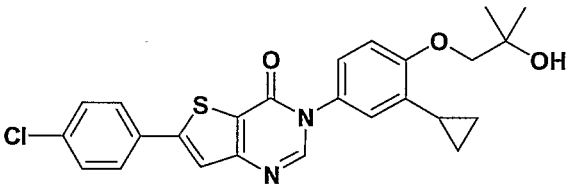
6-(4-Chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-(methylsulfinyl)-phenyl)thieno[3,2-d]pyrimidin-4(3H)-one



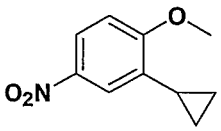
[0076] Preparation and isolation described in Example 89. ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.86 (d, *J* = 2.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.60 (dd, *J*= 8.8, 2.6 Hz, 1H), 7.55 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 1H), 4.02 (d, *J*= 9.0, 1H), 3.96 (d, *J*= 9.0, 1H), 2.91 (s, 3H), 1.42 (s, 6H); HPLC (Method #6): 4.9 min; LCMS m/z: 489 (M+H).

EXAMPLE 91

6-(4-Chlorophenyl)-3-(3-cyclopropyl-4-(2-hydroxy-2-methylpropoxy)phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one



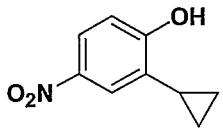
Part A. 2-Cyclopropyl-1-methoxy-4-nitrobenzene



[0077] To a 0.5*M* 9-BBN/THF solution (26.0 mL, 13.0 mmol) was added propargyl bromide (0.71 mL, 6.37 mmol, 80% in toluene) and the mixture was heated at 65 °C for 5h. After cooling to 20 °C, a previously degassed solution of NaOH (749 mg, 18.7 mmol) in water (6.3 mL) was added and stirring was continued for 1,5 h. The mixture was transferred to a second flask containing 2-bromo-4-nitroanisole (1.29 g, 5.45 mmol) and tetrakis(triphenylphosphine)palladium (0) (187 mg, 0.16 mmol) in THF (8.0 mL). After heating at 60 °C for 14h, the reaction mixture was quenched with water (15 mL) and extracted with ether (3 x 40 mL). The combined

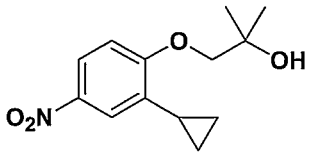
organic extracts wee washed with 2*M* NaOH (3 x20 mL) and water (3 x 20 mL), dried (Na_2SO_4) and concentrated. Purification by two consecutive column chromatographies (SiO_2, 1st eluting with 9/1 hexanes/EtOAc, 2nd eluting with 7/3 hexanes/ CH_2Cl_2) allowed to isolate the title compound (113 mg, 11% yield) as a yellowish oil: LCMS (ES) m/z 194 (M+H).

Part B. 2-Cyclopropyl-4-nitrophenol



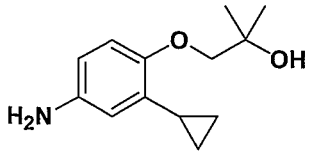
[0078] To a solution of the Part A compound (113 mg, 0.59 mmol) in CH_2Cl_2 (1.0 mL) was added boron trifluoride-dimethyl sulfide complex (0.37 mL, 3.52 mmol) and the mixture was stirred at 20 °C for 7.5 h. After addition of MeOH (6.0 mL), the mixture was stirred for 20 min and evaporated *in vacuo*. Chromatography (SiO_2 230-400 mesh, 4/1 hexanes/EtOAc) of the residue gave the title compound (44.3 mg, 42% yield) as a reddish solid: LCMS (ES) m/z 180 (M+H).

Part C. 1-(2-Cyclopropyl-4-nitrophenoxy)-2-methylpropan-2-ol



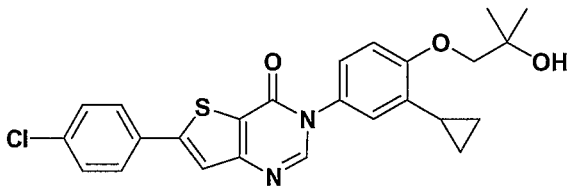
[0079] A mixture of Part B compound (84.0 mg, 0.47 mmol), potassium carbonate (195 mg, 1.41 mmol), CH_3CN (4.0 mL), water (0.4 mL) and isobutylene oxide (0.26 mL, 2.84 mmol) was heated at 130 °C for 3 h in a microwave reactor. The final mixture was evaporated and, the residue was partitioned between EtOAc (50 mL) and water (8.0 mL). The organic layer was washed with brine (8.0 mL), dried (Na_2SO_4) and concentrated. Chromatography (SiO_2 230-400 mesh, 7/3 to 3/2 hexanes/EtOAc) of the crude furnished the title compound (73.0 mg, 62% yield) as a white solid: LCMS (ES) m/z 252 (M+H).

Part D. 1-(4-Amino-2-cyclopropylphenoxy)-2-methylpropan-2-ol



[0080] To a solution of the Part C (43.5 mg, 0.17 mmol) compound in EtOAc (2.5 mL) was added 5% Pd-C (9.0 mg) and the suspension was hydrogenated (1 atm.) for 40 min.. The suspension was filtered through celite and the filter cake was rinsed with MeOH (20 mL). The combined filtrates were evaporated to yield the title compound (38.0 mg, quant. but contains 6% of its n-propyl derivative) as a colorless oil: LCMS (ES) m/z 222 (M+H).

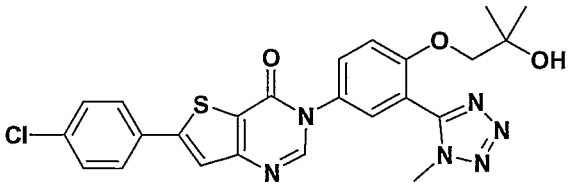
Part E.



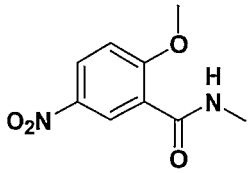
[0081] The product of Part D (62.2 mg, 0.27 mmol) and the formamidine described in Part C of Example 1 (185 mg, 0.57 mmol) were mixed with phenol (430 mg) and heated at 130 °C for 35 min. After cooling to 20 °C, the mixture was dissolved in ether (8.0 mL) and allowed to stand for 1h. The ethereal solution was decanted and the solid formed was crystallized from CH_2Cl_2/ether to afford the desired compound (65.0 mg, 50% yield, contains 5% of its *n*-propyl derivative) as an off-white solid: ^{1}H NMR ∂ (CD_2Cl_2, ppm) 8.09 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.56 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.18 (dd, J= 8.5, 2.4 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 3.90 (s, 2H), 2.21 (m, 1H), 1.38 (s, 6H), 0.98 (m, 2H), 0.67 (m, 2H); HPLC (Method #6): 8.18 min; LCMS (ES): m/z 467 (M+H).

EXAMPLE 92

6-(4-Chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-(1-methyl-1H-tetrazol-5-yl)phenyl)thieno[3,2-d]pyrimidin-4(3H)-one

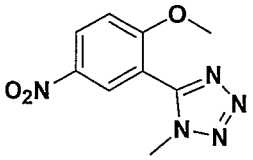


Part A. 2-Methoxy-N-methyl-5-nitrobenzamide



[0082] To a solution of methyl 2-methoxy-5-nitrobenzoate (389 mg, 1.84 mmol) in THF (3.0 mL) was added 33% $MeNH_2$ /EtOH solution (2.0 mL, 16.0 mmol) and the mixture was stirred at 20 °C overnight. The solution was evaporated and the residue was chromatographed (SiO_2 230-400 mesh) eluting with 7:3 hexanes/EtOAc to remove 2-(methylamino)-5-nitrobenzoate derivatives. Further elution with EtOAc provided the title compound (268.5 mg, 70% yield) as a yellowish solid: LCMS (ES) m/z 211 (M+H).

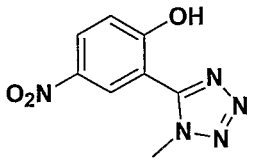
Part B. 5-(2-Methoxy-5-nitrophenyl)-1-methyl-1H-tetrazole



[0083] To a solution of Part A compound (268.5 mg, 1.28 mmol), Ph_3P (370 mg, 1.41 mmol) and azidotrimethylsilane (0.19 mL, 1.44) in THF (12.6 mL) was added diethylazodicarboxylate (0.23 mL, 1.42 mmol) and the mixture was stirred at 20 °C for 15.5 h. Additional amounts of PPh_3 (370 mg), $TMSN_3$ (0.19 mL) and DEAD (0.23 mL) were added and the mixture was heated at 50 °C for 14h. A third portion of each PPh_3 (370 mg), $TMSN_3$ (0.19 mL) and DEAD (0.23 mL) was added and heating at 50 °C was continued for 15h. The majority of solvent was removed by blowing nitrogen

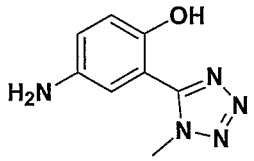
onto the reaction mixture. The residue was chromatographed (SiO_2 230-400 mesh, 1/1 to 7/3 hexanes/EtOAc) to give the desire tetrazole contaminated with Ph_3PO. Purification by chromatography (SiO_2 230-400 mesh, 9/1 to 4/1 CH_2Cl_2/ether) furnished the title compound (150.8 mg, 50% yield) as a yellowish solid: LCMS (ES) m/z 236 (M+H).

Part C. 2-(1-Methyl-1H-tetrazol-5-yl)-4-nitrophenol



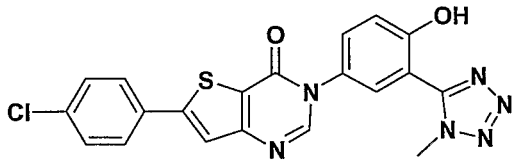
[0084] To a solution of the Part A compound (150.8 mg, 0.64 mmol) in CH_2Cl_2 (1.0 mL) was added boron trifluoride-dimethyl sulfide complex (0.41 mL, 3.90 mmol) and the mixture was stirred at 20 °C for 28 h. After addition of MeOH (6.0 mL), the mixture was stirred for 1h and evaporated *in vacuo*. Chromatography (SiO_2 230-400 mesh, 4:1 CH_2Cl_2/ether) of the residue provided the title compound (135 mg, 96% yield) as a reddish solid: LCMS (ES) m/z 222 (M+H).

Part D. 4-Amino-2-(1-methyl-1H-tetrazol-5-yl)phenol



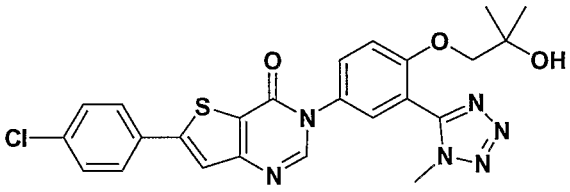
[0085] To a solution of the Part C (64.0 mg, 0.29 mmol) compound in EtOAc (5.0 mL) and MeOH (0.3 mL) was added 5% Pd-C (15.0 mg) and the suspension was hydrogenated (1 atm.) for 4.5 h. The suspension was filtered through celite and the filter cake was rinsed with MeOH (20 mL). The combined filtrates were evaporated to furnish the title compound (52.2 mg, 93% yield) as a reddish oil: MS (electrospray, + ions) m/z 192 (M+H).

Part E. 6-(4-Chlorophenyl)-3-(4-hydroxy-3-(1-methyl-1H-tetrazol-5-yl)phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one



[0086] The product of Part D (52.2 mg, 0.27 mmol) and the formamidine described in Part C of Example 1 (175 mg, 0.54 mmol) were mixed with phenol (295 mg) and heated at 125 °C for 46 min. After cooling to 20 °C, the mixture was dissolved in ether (8.0 mL) and allowed to stand for 1h. The ethereal solution was decanted and the solid formed was crystallized from CH_2Cl_2/ether to afford the title compound (64.5 mg, 55% yield) as an off-white solid: MS (electrospray, + ions) m/z 437 (M+H).

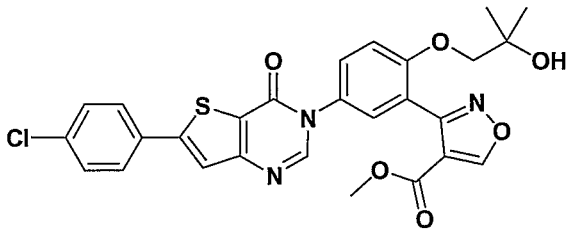
Part F.



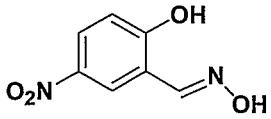
[0087] A mixture of the product of Part E (30.3 mg, 0.07 mmol), K_2CO_3 (11.0 mg, 0.08 mmol), CH_3CN (2.0 mL), water (0.2 mL) and isobutylene oxide (45 µL, 0.51 mmol) was heated at 125 °C for 2.5 h in a microwave reactor. The final mixture was diluted with CH_2Cl_2 (40 mL) and washed with water (5.0 mL). The aqueous wash was back extracted with CH_2Cl_2 (2 x5 mL) and, the combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography (SiO_2 230-400 mesh, 1/4 to 1/9 CH_2Cl_2/EtOAc) of the crude furnished the title compound (17.0 mg, 48 % yield) as a yellowish solid: ^{1}H NMR ∂ (CD_2Cl_2 + CD_3OD drops, 35 °C, ppm) 8.23 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.66 (dd, J= 8.8, 2.6 Hz, 1H), 7.58 (s, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 1H), 4.09 (s, 3H), 3.95 (s, 2H), 1.15 (s, 6H); HPLC (Method #6): 6.85 min; LCMS (ES): m/z 509 (M+H).

EXAMPLE 93

Methyl 3-(5-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-(2-hydroxy-2-methylpropoxy)phenyl)isoxazole-4-carboxylate

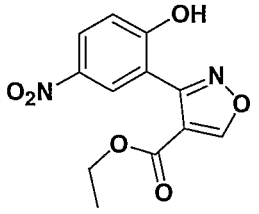


Part A. 2-Hydroxy-5-nitrobenzaldehyde oxime



[0088] To a solution of 2-hydroxy-5-nitrobenzaldehyde (2.10 g, 12.6 mmol) in pyridine (31.0 mL) and EtOH (5.0 mL) was added hydroxylamine hydrochloride (1.75 g, 25.2 mmol) . After stirring at 20 °C for 10h, the mixture was diluted with CH_2Cl_2 (125 mL) and washed with water (4 x 70 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was triturated with EtOH and filtered. The resulting solid was rinsed with ether and dried under vacuum to obtain the title compound (1.86 g, 81% yield) as a yellowish solid: MS (electrospray, + ions) m/z 183 (M+H).

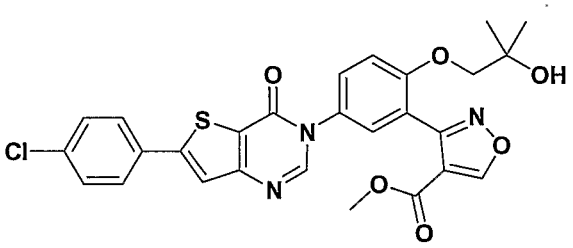
Part B. Ethyl 3-(2-hydroxy-5-nitrophenyl)isoxazole-4-carboxylate



[0089] To a solution of Part A compound (365 mg, 1.96mmol) and pyridine (35 µL, 0.43 mmol) in 1,2-DCE (6.0 mL) was added *N*-chlorosuccinimide (296 mg, 2.17 mmol) in portions over 15 min. After the addition was complete, the mixture was stirred at 20 °C for 25 min and at 50 °C for 20 min. An additional amount of NCS (150 mg, 1.10 mmol) was added and heating at 50 °C was continued for 20 min. At this time, ethyl (dimethylamino)acrylate (0.56 mL, 3.91 mmol) was added followed

by addition of a solution Et_3N (0.30 mL, 2.15 mmol) in 1,2-DCE (3.0 mL) over a 40 min period. Stirring was then continued at 50 °C for 1.5 h and at 20 °C overnight. The mixture was diluted with EtOAc (100 mL) and, washed with 0.5 M KH_2PO (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by two consecutive chromatographies (SiO_2 230-400 mesh, 1st eluent: 7:3 hexanes/EtOAc, 2nd eluent: 95/5 CH_2Cl_2/ether) to afford the title compound (134.6 mg, 25% yield) as a yellowish solid: : MS (electrospray, + ions) m/z 279 (M+H).

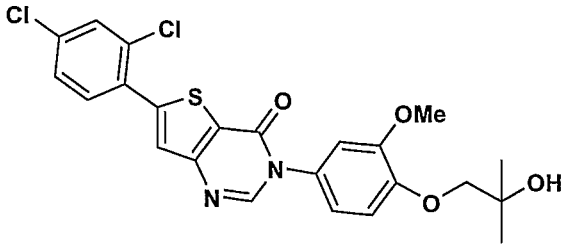
Part C.



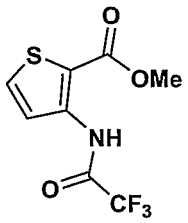
[0090] Similar procedures as described in Parts D, E and F of Example 92 were employed to convert the product of Part B to the corresponding carboxylic acid of the title compound. Treatment of this acid with 3*M* HCl/ CH_2Cl_2, MeOH, MeOAc (prepared by addition of AcCl to a 3:2 CH_2Cl_2/MeOH solution at 0 °C and then stirring at 20 °C for 30 min) yielded the desired methyl ester compound. ^1H NMR ∂ (CD_2Cl_2 + CD_3OD drops, ppm) 8.36 (s, 1H), 8.21 (s, 1H), 8.05 (d, J = 2.6 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.61 (s, 1H), 7.57 (dd, J= 8.8, 2.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H); HPLC (Method #6): 7.63 min; LCMS (ES): 552 (M+H).

EXAMPLE 94

1-(4-(6-(2,4-dichlorophenyl)-4-oxo-thieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol

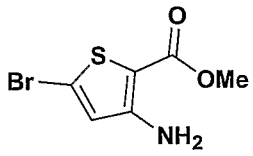


Part A. Methyl 3-(2,2,2-trifluoroacetamido)thiophene-2-carboxylate



[0091] To a 0 °C solution of methyl 3-amino-2-thiophenecarboxylate (10 g, 64 mmol) and pyridine (6.2 mL, 76 mmol) in MeCN (130 mL) was added, dropwise at such a rate so as to maintain the internal temperature below 7 °C, TFAA (12 mL, 83 mmol). After stirring for 5 min, the reaction was allowed to warm to room temperature. After 30 min at that temperature, the reaction was poured into ice-cold water (1.5 L). The mixture was stirred for 40 min. The solid was collected by filtration, rinsed with water (2 x 50 mL), and partially dried on the filter. The residue was coevaporated three times with EtOH (200-mL portions) to provide methyl 3-(trifluoroacetylamino)-2-thiophenecarboxylate as a yellow solid (15 g, 96%).

Part B. Methyl 3-amino-5-bromothiophene-2-carboxylate

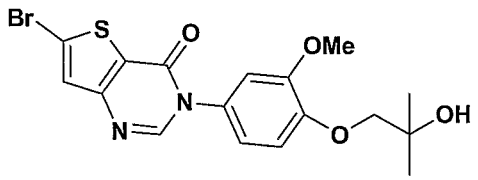


[0092] To a stirred solution of *i*-Pr_2NH (6.2 mL, 3.2 mmol) in THF (100 mL) in a dry ice-*i*-PrOH bath was added, dropwise, n-butyllithium (2.5 N in hexanes, 17 mL, 43 mmol). After 5 min, the mixture was placed in an ice-water bath. After an additional 5 min, the mixture was cooled in a dry ice- *i*-PrOH bath. To this stirred solution was added, dropwise over 2 min, a solution of the methyl 3-(trifluoroacetylamino)-2-thiophenecarboxylate (3.5 g, 14 mmol) in THF (15 mL). After 5 min, 1,2-dibromoethane (4 mL) was added in one portion. After 5 min, MeOH (3.5 mL) and saturated $NaHCO_3$ (150 mL) containing sodium thiosulfate (5 g) were sequentially added. The mixture was removed from the cold bath and allowed to warm to room temperature whereupon EtOAc (250 mL) was added. After partition, the aqueous layer was extracted with EtOAc (2 x 100 mL). The three combined

organic layers were washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was absorbed onto Celite® 545 and chromatographed (12 g silica gel, 10% EtOAc-hexanes to 25% EtOAc /hexanes, 50 mL/min). The product-containing fractions were combined and rechromatographed (12 g silica gel, 10% EtOAc -hexanes, 50 mL/min) to provide methyl 5-bromo-3-(trifluoroacetylamino)-2-thiophenecarboxylate as a pale yellow solid 0.98 g (21%).

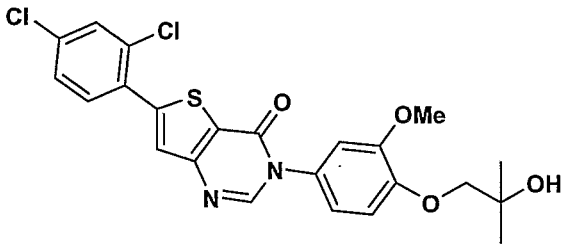
[0093] Methyl 5-bromo-3-(trifluoroacetylamino)-2-thiophenecarboxylate (2.0 g, 6.2 mmol) was stirred in 120 mL of 0.25 N K_2CO_3 in 7:3 MeOH/water. After 2.5 h, the bulk of the MeOH was removed in vacuo. The residue was partitioned between brine (75 mL) and CH_2Cl_2 (100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide methyl 5-bromo-3-amino-2-thiophenecarboxylate as a yellow solid (1.4 g, 100%).

Part C.



[0094] A solution of ethyl 5-bromo-3-amino-2-thiophenecarboxylate (1.0 g, 4.2 mmol) and dimethylformamide dimethylacetal (1.1 mL, 8.5 mmol) in EtOH (30 mL). was heated to reflux for 50 min. After cooling, the solvent was removed in vacuo. The residue was coevaporated with toluene (2 x 20 mL) to yield methyl 5-bromo-3-(((dimethylamino)methylene)amino)-2-thiophenecarboxylate . The residue and 1-((4-amino-2-methoxy)phenoxy)-2-methyl-2-propanol (0.90 mg, 4.2 mmol) (described in Part B of Example 82) were mixed with phenol (4 g) prior to heating at 130 °C for 40 min. After cooling, the mixture was chromatographed (120 g silica, CH_2Cl_2 to 50% EtOAc- CH_2Cl_2) to provide 1-(4-(6-bromo-4-oxo-thieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol as a tan solid (1.2 g, 67%).

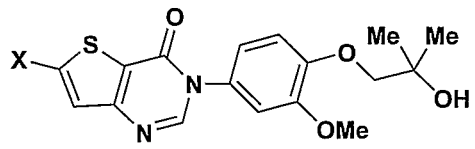
Part D.



[0095] A mixture of 1-(4-(6-bromo-4-oxo-thieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol (50 mg, 0.12 mmol), 2,4-dichlorobenzeneboronic acid (21 mg, 0.18 mmol), Na_2CO_3 (31 mg, 0.29 mmol), tetrakis(triphenylphosphine)palladium (10 mg, 0.0088 mmol), N_2-degassed dioxane (1 mL) and N_2-degassed water (0.5 mL) was heated in a 110 °C bath for 30 min. The mixture, upon cooling, was poured into half-saturated $NaHCO_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (4 g silica, CH_2Cl_2 to 50% EtOAc- CH_2Cl_2) to provide 1-(4-(6-(2,4-dichlorophenyl)-4-oxo-thieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol as an off-white solid (41 mg, 71%). ^{1}H-NMR ($CDCl_3$) δ 8.09 (s, 1 H), 7.54 (s, 1 H), 7.49 (m, 2 H), 7.29 (dd, J = 8, 2 Hz, 1 H), 6.84-6.96 (m, 3 H), 3.81 (s, 5 H), 1.30 (s, 6H); HPLC (Method #7) 4.2 min; LCMS (ES) m/z 491 (M+H).

EXAMPLES 95 TO 103

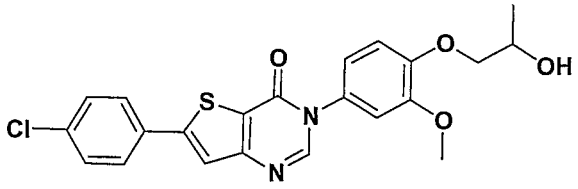
[0096] The following compounds were prepared from 1-(4-(6-bromo-4-oxo-thieno[3,2-d]-pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol using procedures similar to that described in Example 94 Part E. Reaction times varied from 20 min to 17h and temperatures varied from room temperature to 100 °C. In some cases, a larger excess (up to 3 equivalents) of the appropriate boronic acid was used. Trituration of the chromatographed products with methanol was used to remove traces of 1-(4-oxo-thieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methyl-2-propanol. For chromatography, mixtures of MeOH/CH_2Cl_2, EtOAc/CH_2Cl_2 or EtOAc/hexanes were used as the solvents.



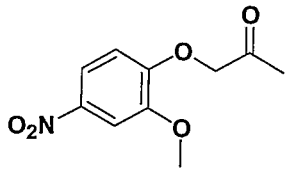
Example #	X	Mass spec M+H	HPLC retention (min)	H NMR
95	4-Cl-2-Me-Ph	471	4.1 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.16 (s, 1 H), 7.40 (m, 1 H), 7.28-7.34 (m, 3 H), 7.01-7.04 (m, 1 H), 6.92-6.97 (m, 2 H), 3.89 (s, 5 H), 2.46 (s, 3 H), 1.38 (s, 6 H)
96	3,4-Me_2-Ph	451	4.2 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.06 (s, 1 H), 7.39-7.44 (m, 3 H), 7.15-7.17 (m, 1 H), 6.84-6.96 (m, 3 H), 3.82 (s, 5 H), 2.28 (s, 3 H), 2.25 (s, 3 H), 1.30 (s, 6 H)
97	4-MeO-Ph	453	3.8 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.04 (s, 1 H), 7.58-7.60 (m, 2 H), 7.37 (s, 1 H), 6.83-6.95 (m, 5 H), 3.80 (s, 5 H), 3.79 (s, 3 H), 2.50 (br s, 1 H), 1.29 (s, 6 H)
98	4-Et-Ph	451	4.2 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.06 (s, 1 H), 7.46 (s, 1 H), 7.22-7.60 (Ar A_2B_2, 4 H), 6.84-6.96 (m, 3 H), 3.82 (s, 5 H), 2.64 (q, J = 8 Hz, 2 H), 1.30 (s, 6 H), 1.21 (t, J = 8 Hz)
99	4-CF_3-Ph	491	4.0 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.09 (s, 1 H), 7.66-7.79 (Ar A_2B_2, 4 H), 7.57 (s, 1 H), 6.95-6.97 (m, 1 H), 6.85-6.90 (m, 2 H), 3.82 (s, 5 H), 1.31 (s, 6 H)
100	4-CN-Ph	448	3.5 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.19 (s 1 H), 7.78-7.87 (Ar A_2B_2, 4 H), 7.68 (s, 1 H), 7.05 (d, J = 8 Hz, 1 H), 6.94-6.98 (m, 2 H), 3.91 (s, 5 H), 1.40 (s, 6 H)
101	3-CN-Ph	448	3.5 Method #7	^{1}H NMR ($CDCl_3$) δ: 8.09 (s, 1 H), 7.93 (t, J = 1 Hz, 1 H), 7.87-7.89 (m, 1 H), 7.64-7.66 (m, 1 H), 7.52-7.54 (m, 2H), 6.96 (d, J = 8 Hz, 1 H), 6.85-6.90 (m, 2 H), 3.82 (s, 5 H), 2.51 (br s, 1 H), 1.31 (s, 6H)
102	4-NH_2-Ph	438	2.9 Method #7	^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1 H), 7.56 (d, *J* = 9 Hz, 2 H), 7.39 (s, 1 H), 6.91-7.0 (m, 3 H), 6.74 (d, *J* = 8 Hz, 2 H), 3.88 (s, 5 H), 1.37 (s, 6 H)
103	4-NMe_2-Ph	466	3.8 Method #7	^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1 H), 7.56 (d, *J* = 9 Hz, 2 H), 7.32 (s, 1 H), 6.84-6.96 (m, 3 H), 6.70 (m, 2 H), 3.81 (s, 5 H), 2.98 (s, 6 H), 1.30 (s, 6 H)

EXAMPLE 104

6-(4-Chlorophenyl)-3-(4-(2-hydroxypropoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one

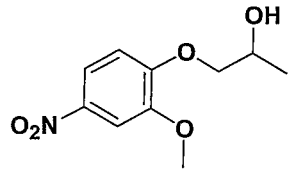


Part A. 1-(2-Methoxy-4-nitrophenoxy)propan-2-one



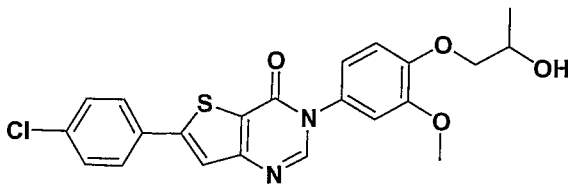
[0097] A mixture of the potassium salt of 4-nitroguaiacol (2.00 g, 9.65 mmol) and chloroacetone (1.15 mL, 14.5 mmol) in 20 mL of DMF was heated at 80°C for 3 h. The suspension was cooled to rt and diluted with water. A precipitate formed which was filtered, washed with water and dried under vacuum to afford the title compound (1.63 g) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.96 (s, 3H), 4.71 (s, 2H), 6.74 (d, J = 8.80 Hz, 1H), 7.76 (d, J = 2.20 Hz, 1H), 7.84 (dd, J = 8.79 Hz, 2.20 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.37, 56.33, 73.62, 107.11, 111.88, 117.36, 142.33, 149.23, 152.49, 203.40; HPLC (Method #1): 1.98 min, (100%); LCMS (ES): m/z 226 $[M+H]^+$.

Part B. 1-(2-Methoxy-4-nitrophenoxy)propan-2-ol



[0098] To a mixture of 1-(2-methoxy-4-nitrophenoxy)propan-2-one (300 mg, 1.33 mmol) in 1.3 mL of MeOH and 1.3 mL of H_2O at rt was added a solution of $NaBH_4$ (53 mg, 1.40 mmol) in 0.5 mL of H_2O dropwise over 5 min. The suspension was stirred at rt for 1 h and diluted with 0.2 mL of HOAc followed by 2 mL of H_2O. The precipitate was filtered, washed with H_2O and dried under vacuum to afford the title compound (270 mg) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.05 Hz, 3H), 2.68, (s, 1H), 3.87-3.92 (m, 4H), 4.03-4.05 (m, 1H), 4.23-4.29 (m, 1H), 6.89 (d, J = 9.35 Hz, 1H), 7.72 (d, J = 2.20 Hz, 1H), 7.86 (dd, J = 8.80 Hz, 2.75 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.66, 56.19, 65.90, 74.84, 106.73, 111.66, 117.60, 141.79, 149.21, 153.62; HPLC (Method # 1) 2.29 min retention time, (100%); LCMS (ES): m/z 228 $[M+H]^+$.

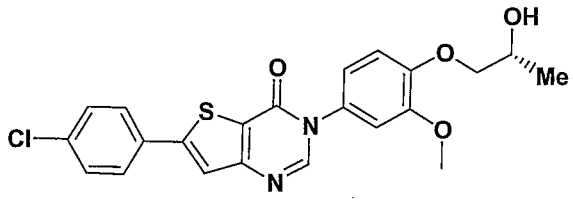
Part C. 6-(4-Chlorophenyl)-3-(4-(2-hydroxypropoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one



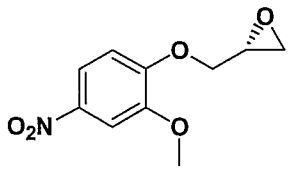
[0099] 1-(2-methoxy-4-nitrophenoxy)propan-2-ol was converted to the title compound in a similar manner as previously described in Example 1. ^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.05 Hz, 3H), 3.77-3.82, (m, 4H), 3.88-3.91 (m, 1H), 3.94-4.02 (m, 1H), 4.89 (d, J = 4.39 Hz, 1H), 7.03 (dd, J = 8.79 Hz, 1.64 Hz, 1H), 7.10 (d, J = 8.25 Hz, 1H), 7.18 (d, J = 1.65 Hz, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.92 (d, J = 8.25 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.03, 55.58, 64.21, 73.88, 111.63, 112.68, 119.43, 121.56, 121.84, 127.66, 129.10, 129.57, 131.02, 134.09, 148.27, 148.80, 149.32, 149.60, 155.91, 157.23; HPLC (Method # 1) 3.64 min retention time, (100%); LCMS (ES): m/z 443 $[M+H]^+$.

EXAMPLE 105

(R)-6-(4-chlorophenyl)-3-(4-(2-hydroxypropoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one



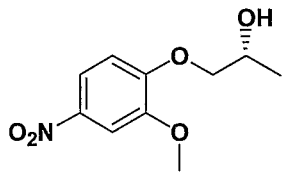
Part A. (R)-2-((2-methoxy-4-nitrophenoxy)methyl)oxirane



[00100] To a solution of Ph_3P (23.3 g; 88.7 mmol) in 450 mL of THF cooled to 0°C was added a solution of di-t-butylazodicarboxylate (20.4 g; 88.7 mmol) in 50 ml of THF over 15 min. After stirring at 0°C for 10 min 4-nitroguaiacol (10.0 g; 59.1 mmol) was added followed by (S)-glycidol (6.3 mL; 94.6 mmol) over 10 min and the

mixture allowed to warm to rt and stir for 2 h. The solution was concentrated and the residue dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 1:3 gradient). Impure fractions were concentrated under reduced pressure and the residue further purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 0:100 gradient). Pure fractions from both purifications were combined and concentrated under reduced pressure to afford 9.58 g (72%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.78-2.80 (m, 1H), 2.94-2.96 (m, 1H), 3.40-3.43 (m, 1H), 3.96 (s, 3H), 4.06-4.11 (m, 1H), 4.41-4.44 (m, 1H), 6.98 (d, J = 8.79 Hz, 1H), 7.75 (d, J = 2.20 Hz, 1H), 7.89 (dd, J = 8.79 Hz, 2.19 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.20, 44.57, 49.75, 56.28, 70.17, 106.80, 111.71, 117.50, 141.92, 149.20, 153.38; HPLC (Method #1) 2.09 min retention time; LCMS (ES): m/z 226 $[M+H]^+$.

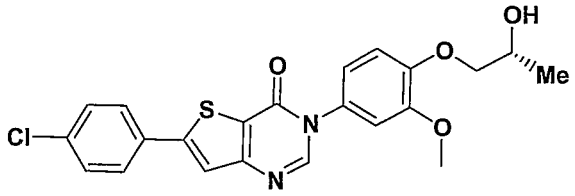
Part B. (R)-1-(2-methoxy-4-nitrophenoxy)propan-2-ol



[00101] To 160 mL of Et_2O cooled to 0°C was added $LiClO_4$ (80 g; 752 mmol) in portions over 20 min. The mixture was allowed to warm to rt and (R)-2-((2-methoxy-4-nitrophenoxy)methyl)oxirane (9.55 g; 42.5 mmol) was added. The suspension was stirred for 10 min, borane dimethylamine (3.40 g; 46.6 mmol) was added and the suspension was stirred at rt for 2.5 h. The suspension was diluted with CH_2Cl_2 and stirred in a beaker with H_2O until gas evolution ceased. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was triturated in CH_2Cl_2, filtered and the filtrate purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 100:0 gradient) to afford 6.83 g (70%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.59 Hz, 3H), 2.77 (br s, 1H), 3.90-3.94 (m, 4H), 4.05-4.08 (m, 1H), 4.24-4.32 (m, 1H), 6.92 (d, J = 9.35 Hz, 1H), 7.74 (d, J = 2.75 Hz, 1H), 7.88 (dd, J = 8.79 Hz, 2.74 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.64, 56.18, 65.87, 74.85, 106.73,

111.66, 117.60, 141.76, 149.20, 153.63; HPLC (Method #1) 2.17 min retention time; LCMS (ES): m/z 228 $[M+H]^+$.

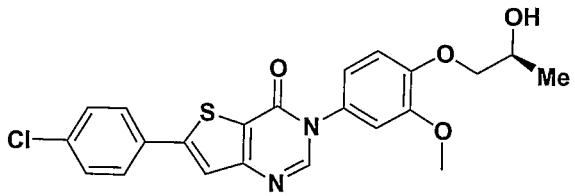
Part C.



[00102] Conversion of (R)-1-(2-methoxy-4-aminophenoxy)-propan-2-ol to the title compound was achieved in a phenol melt as described in Example 89. ^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.05 Hz, 3H), 3.77-3.82, (m, 4H), 3.88-3.91 (m, 1H), 3.94-4.02 (m, 1H), 4.89 (d, J = 4.39 Hz, 1H), 7.03 (dd, J = 8.79 Hz, 1.64 Hz, 1H), 7.10 (d, J = 8.25 Hz, 1H), 7.18 (d, J = 1.65 Hz, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.92 (d, J = 8.25 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.03, 55.58, 64.21, 73.88, 111.63, 112.68, 119.43, 121.56, 121.84, 127.66, 129.10, 129.57, 131.02, 134.09, 148.27, 148.80, 149.32, 149.60, 155.91, 157.23; $[a]_{589}$ = -10.1° at 23 °C for 12.3 mg in 1 mL CH_2Cl_2; HPLC (Method # 1) 3.64 min retention time, (100%); LCMS (ES): m/z 443 $[M+H]^+$.

EXAMPLE 106

(S)-6-(4-chlorophenyl)-3-(4-(2-hydroxypropoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one

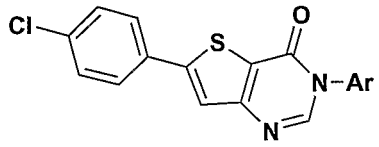


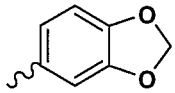
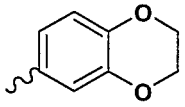
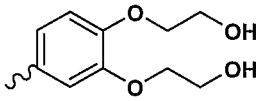
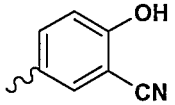
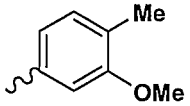
[00103] The title compound was prepared as described for Example 105 except for the substitution of (R)-glycidol for (S)-glycidol. ^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.05 Hz, 3H), 3.77-3.82, (m, 4H), 3.88-3.91 (m, 1H), 3.94-4.02 (m, 1H), 4.89 (d, J = 4.39 Hz, 1H), 7.03 (dd, J = 8.79 Hz, 1.64 Hz, 1H), 7.10 (d, J = 8.25 Hz, 1H), 7.18 (d, J = 1.65 Hz, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.92 (d, J = 8.25 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.03, 55.58, 64.21, 73.88, 111.63, 112.68,

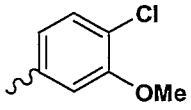
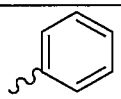
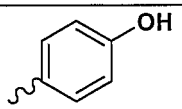
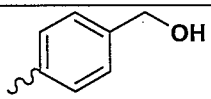
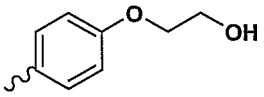
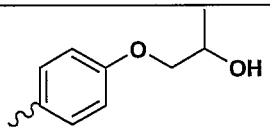
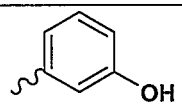
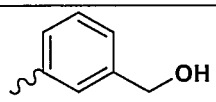
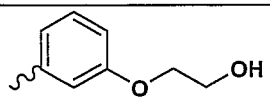
119.43, 121.56, 121.84, 127.66, 129.10, 129.57, 131.02, 134.09, 148.27, 148.80, 149.32, 149.60, 155.91, 157.23; $[a]_{589}$ = +9.5° at 23 °C for 10.08 mg in 1 mL CH_2Cl_2; HPLC (Method # 1) 3.64 min retention time, (100%); LCMS (ES): m/z 443 $[M+H]^+$.

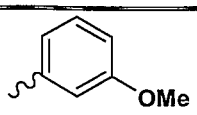
EXAMPLES 107 TO 121

[00104] These examples were prepared following the method described in Example 1. Except as indicated, the aniline component was commercially available.

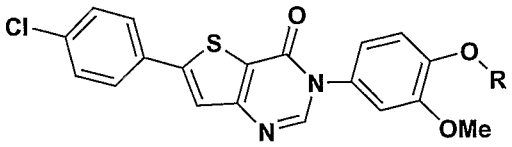


Example #	Ar	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comment
107		383	3.72 Method #1	^{1}H NMR (DMSO-d_6) δ 6.13 (s, 2H), 7.00 (dd, J = 8.35 Hz, 2.20 Hz, 1H), 7.07 (d, J = 8.35 Hz, 1H), 7.18 (d, J = 1.76 Hz, 1H), 7.57 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H), 7.97 (s, 1H), 8.37 (s, 1H)	
108		397	3.79 Method #1	^{1}H NMR (DMSO-d_6) δ 4.30 (s, 4H), 6.99-7.02 (m, 2H), 7.11 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.35 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H), 7.96 (s, 1H), 8.36 (s, 1H)	
109		459	3.39 Method #1	^{1}H NMR (DMSO-d_6) δ 3.69-3.76 (m, 4H), 3.99-4.07 (m, 4H), 4.84-4.90 (m, 2H), 7.03 (dd, J = 8.79 Hz, 2.63 Hz, 1H), 7.12 (d, J = 8.35 Hz, 1H), 7.20 (d, J = 2.64 Hz, 1H), 7.58 (d, J = 8.35 Hz, 2H), 7.93 (d, J = 8.35 Hz, 2H), 7.98 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ by route B
110		380	3.55 Method #1	^{1}H NMR (DMSO-d_6) δ 7.03 (d, J = 8.79 Hz, 1H), 7.56-7.58 (m, 3H), 7.76 (br s, 1H), 7.91 (d, J = 8.35 Hz, 2H), 7.96 (s, 1H), 8.39 (s, 1H)	
111		383	3.99 Method #1	^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.86 (s, 3H), 6.88-6.89 (m, 2H), 7.26-7.29 (m, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.15 (s, 1H)	

Example #	Ar	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comment
112		403	3.93 Method #1	^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 7.16 (dd, J = 8.35 Hz, 2.19 Hz, 1H), 7.43 (d, J = 2.20 Hz, 1H), 7.58 (d, J = 8.79 Hz, 2H), 7.61 (d, J = 8.35 Hz, 1H), 7.93 (d, J = 8.35 Hz, 2H), 8.00 (s, 1H) 8.45 (s, 1H)	
113		339	3.73 Method #1	^{1}H NMR ($CDCl_3$) δ 7.44-7.46 (m, 4H), 7.52-7.59 (m, 4H), 7.65-7.69 (m, 2H), 8.15 (s, 1H)	
114		355	3.59 Method #1	^{1}H NMR (DMSO-d_6) δ 6.89 (d, J = 8.79 Hz, 2H), 7.31 (d, J = 8.79 Hz, 2H), 7.57 (d, J = 8.35 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H), 7.96 (s, 1H), 8.36 (s, 1H) 9.89 (br s, 1H)	
115		369	3.53 Method #1	^{1}H NMR (DMSO-d_6) δ 4.57 (d, J = 5.71 Hz, 2H), 5.35 (t, 1H), 7.48 (s, 4H), 7.59 (d, J = 8.79 Hz, 2H), 7.93 (d, J = 8.79 Hz, 2H), 7.98 (s, 1H), 8.41 (s, 1H)	
116		399	3.51 Method #1	^{1}H NMR (DMSO-d_6) δ 3.72-3.76 (m, 2H), 4.05 (t, 2H), 4.92 (t, 1H), 7.09 (d, J = 9.23 Hz, 2H), 7.44 (d, J = 9.23 Hz, 2H), 7.57 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.35 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ by route B
117		413	3.68 Method #1	^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.16 Hz, 3H), 3.33 (s, 3H), 3.83-4.00 (m, 3H), 4.92 (d, J = 4.84 Hz, 1H), 7.08 (d, J = 9.23 Hz, 2H), 7.44 (d, J = 9.23 Hz, 2H), 7.58 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.35 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ by route B
118		355	3.61 Method #1	^{1}H NMR (DMSO-d_6) δ 6.90-6.94 (m, 3H), 7.32-7.36 (m, 1H), 7.58 (d, J = 8.35 Hz, 2H), 7.92 (d, J = 8.34 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H) 9.93 (br s, 1H)	
119		369	3.51 Method #1	^{1}H NMR (DMSO-d_6) δ 4.57 (d, J = 5.71 Hz, 2H), 5.37 (t, 1H), 7.39-7.54 (m, 4H), 7.58 (d, J = 8.79 Hz, 2H), 7.93 (d, J = 8.35 Hz, 2H), 7.98 (s, 1H), 8.41 (s, 1H)	
120		399	3.55 Method #1	^{1}H NMR ($CDCl_3$) δ 2.05 (br s, 1H), 3.99 (br m, 2H), 4.14 (t, 2H), 7.01-7.08 (m, 3H), 7.44-749 (m, 3H), 7.54 (s, 1H), 7.65-7.68 (m, 2H), 8.14 (s, 1H)	$ArNH_2$ by route B

Example #	Ar	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comment
121		369		^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 7.02-7.1 (m, 3H), 7.48 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 8.27 (s, 1H)	

EXAMPLES 122 TO 153



Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
122	H	385	3.62 Method #1	^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3H), 6.88-6.93 (m, 2H), 7.12 (d, J = 1.65 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.92 (d, J = 8.24 Hz, 2H), 7.96 (s, 1H), 8.37 (s, 1H), 9.42 (s, 1H)	
123	Ac	427	4.48 Method #1	^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 3.80 (s, 3H), 7.15 (dd, J = 8.79 Hz, 2.20 Hz, 1H), 7.27 (d, J = 8.24 Hz, 1H), 7.40 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.92 (d, J = 8.24 Hz, 2H), 7.97 (s, 1H), 8.46 (s, 1H)	Acylation of Ex 122
124	CH_2CN	424	3.56 Method #1	^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H), 5.22 (s, 2H), 7.14 (dd, J = 8.35 Hz, 2.20 Hz, 1H), 7.27 (d, J = 8.35 Hz, 1H), 7.32 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.79 Hz, 2H), 7.93 (d, J = 8.35 Hz, 2H), 7.98 (s, 1H) 8.43 (s, 1H)	$ArNH_2$ by route B

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
125	$(CH_2)_4Me$	455	4.19 Method #1	^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.7 Hz, 3H), 1.38- 1.52 (m, 4H), 2.43 (quintet, J = 7 Hz, 2H), 3.89 (s, 3H), 4.07 (t, 2H, J = 7.0 Hz), 6.91 – 6.95 (m, 2H), 6.98 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.53 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H)	$ArNH_2$ by route B
126	$(CH_2)_4CO_2Me$	499	3.78 Method #1	^{1}H NMR ($CDCl_3$) δ 1.81- 1.96 (m, 4H), 2.43 (t, 2H, J = 4.4 Hz), 3.69 (s, 3H), 3.89 (s, 3H), 4.09 (t, 2H, J = 6.1 Hz), 6.91 – 6.95 (m, 2H), 6.98 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J_{AB} = 8.7 Hz), 7.54 (s, 1H), 7.66 (d, 2H, J_{AB} = 8.7 Hz), 8.14 (s, 1H)	$ArNH_2$ by route B
127	$(CH_2)_4CONH_2$	484	3.39 Method #1	^{1}H NMR ($CDCl_3$) δ 1.81- 1.96 (m, 4H), 2.43 (t, 2H,), 3.89 (s, 3H), 4.13 (t, 2H), 6.91 – 7.04 (m, 3H), 7.45 (d, 2H), 7.54 (s, 1H), 7.66 (d, 2H), 8.14 (s, 1H)	Heating Ex 126 with NH_3/MeOH
128	CH_2CH_2OH	429	3.49 Method #1	^{1}H NMR (DMSO-d_6) δ 3.72-3.75 (m, 2H), 3.77 (s, 3H), 4.03 (t, 2H), 4.91 (t, 1H), 7.03 (dd, J = 8.80 Hz, 2.20 Hz, 1H), 7.10 (d, J = 8.80 Hz, 1H), 7.18 (d, J = 2.75 Hz, 1H), 7.56 (d, J = 8.79 Hz, 2H), 7.91 (d, J = 8.80 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ by route B

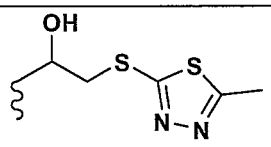
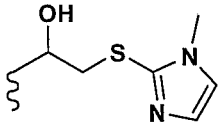
Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
129	$CH_2CH_2OSO_2Me$	507	3.53 Method #1	^{1}H NMR ($CDCl_3$) δ 3.17 (s, 3H), 3.88 (s, 3H), 4.33-4.35 (m, 2H), 4.64-4.66 (m, 2H), 6.95 (dd, J = 8.79 Hz, 2.20 Hz, 1H), 6.99 (d, J = 2.20 Hz, 1H), 7.02 (d, J = 8.24 Hz, 1H), 7.44 (d, J = 8.80 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H)	Treatment of Ex 128 with MsCL
130	$CH_2CH_2OCONHMe$	486	3.54 Method #1	^{1}H NMR (DMSO-d_6) δ 2.82 (d, J = 4.95 Hz, 3H), 3.90 (s, 3H), 4.29 (t, 2H), 4.48 (t, 2H), 6.92 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.96 (d, J = 2.75 Hz, 1H), 7.03 (d, J = 8.24 Hz, 1H), 7.26 (s, 1H), 7.45 (d, J = 8.80 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.14 (s, 1H)	Acylation of Ex 128 with MeNCO
131	CH_2CH_2OMe	443	3.64 Method #1	^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H), 3.80-3.83 (m, 2H), 3.88 (s, 3H), 4.23 (t, 2H), 6.91 (dd, J = 8.80 Hz, 2.20 Hz, 1H), 6.94 (d, J = 2.20 Hz, 1H), 7.03 (d, J = 8.24 Hz, 1H), 7.43 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.64 (d, J = 8.80 Hz, 2H), 8.14 (s, 1H)	Methylation of Ex 128 with MeI
132	CH_2COMe	441	3.64 Method #1	^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.92 (s, 3H), 4.66 (s, 2H), 6.87-6.94 (m, 2H), 7.01 (d, J = 2.20 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.24 Hz, 2H), 8.13 (s, 1H)	$ArNH_2$ by route B

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
133	$CH_2CH(OH)CO_2H$	473	3.5 Method #1	^{1}H NMR ($DMSO-d_6$) δ 3.77 (s, 3H), 3.92-3.97 (m, 2H), 4.24-4.29 (m, 1H), 6.73-6.76 (m, 1H), 7.01 (dd, J = 8.79 Hz, 2.64 Hz, 1H), 7.08-7.16 (m, 3H), 7.57 (d, J = 8.79 Hz, 2H), 7.92 (d, J = 8.79 Hz, 2H), 7.97 (s, 1H), 8.40 (s, 1H)	$ArNH_2$ by route C
134	$CH_2CH(Bu)OH$	485.6	7.34 Method #6	^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 1.37-1.40 (m, 4H), 1.46-1.58 (m, 2H), 3.89 (s, 3H), 3.89-3.91 (m, 1H), 4.12 (d, J=7 Hz, 2H), 6.93 (dd, J = 2.6 Hz, 8.4 HZ, 1H), 6.95 (d, JAB= 8.6, 1H), 7.03 (d, JAB= 8.6, 1H), 7.44 (d, J = 8.8, 2H), 7.54 (s, 2H), 7.66 (d, J = 8.8 Hz, 2H), 8.14 (s, 1H)	$ArNH_2$ by route C
135	$CH_2CH(Pr)OH$	4.71	6.76 Method #6	^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 1.41-1.55 (m, 4H), 3.89 (s, 3H), 3.90-3.92 (m, 1H), 4.09 (d, J = 7.5 Hz), 6.92 – 6.98 (m, 2H), 7.03 (d, J= 7.5 Hz, 1H), 7.45 (d, J = 8.8, 2H), 7.54 (s, 2H), 7.66 (d, J = 8.8 Hz, 2H), 8.17 (s, 1H)	$ArNH_2$ by route C
136	$CH_2CH(Et)OH$	457	6.12 Method #6	^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H), 1.61 (m, 2H), 4.0 (m, 1H), 4.12 (d, J = 8 Hz, 2H), 6.94 (dd, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 8.14 (s, 1H)	$ArNH_2$ by route C

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
137	$CH_2C(Me)(Et)OH$	471	6.64 Method #6	^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3H), 1.31 (s, 3H), 1.71 (m, 2H), 3.89 (s, 3H), 3.91(m, 2H), 6.92-6.96 (m, 2H), 7.03 (d, J=8.3 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.58 (s, 2H), 7.66 (d, J= 8.8 Hz), 2H), 8.15 (s, 1H)	$ArNH_2$ by route C
138	$CH_2CH_2C(Me)_2OH$	471	6.14 Method #6	^1H NMR ($CDCl_3$) δ 1.44 (s, 6H), 2.02 (t, J = 5.6 Hz, 2H), 3.87 (s, 3H), 3.94(ABq, 2H), 6.91 (dd, J = 2.6, 8.3 Hz, 1H), 6.99 (d, J = 2.6 Hz, 1H), 7.19 (d, J=8.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.54 (s, 2H), 7.67 (d, J= 8.8 Hz), 2H), 8.27 (s, 1H)	$ArNH_2$ by route B
139	$CH_2CHOHCH_2OH$	459	3.40 Method #1	^1H NMR (DMSO-d_6) δ 3.43-3.50 (m, 2H), 3.77 (s, 3H), 3.77-3.85 (m, 1H), 3.90-3.94 (m, 1H), 4.02-4.05 (m, 1H), 4.68 (t, 1H), 4.98 (d, J = 4.83 Hz, 1H), 7.03 (dd, J = 8.35 Hz, 2.20 Hz, 1H), 7.10 (d, J = 8.79 Hz, 1H), 7.18 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.35 Hz, 2H), 7.92 (d, J = 8.35 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ by route B
140	$CH_2COH(Me)CH_2OH$	473	3.43 Method #1	^1H NMR (DMSO-d_6) δ 1.15 (s, 3H), 3.32-3.43 (m, 2H), 3.78-3.90 (m, 5H), 4.53 (s, 1H), 4.65 (t, 1H), 7.02 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 7.10 (d, J = 8.24 Hz, 1H), 7.17 (d, J = 2.75 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.91 (d, J = 8.25 Hz, 2H), 7.96 (s, 1H), 8.38 (s, 1H)	$ArNH_2$ by route B employing 1) alkylation with methallyl Br 2) OsO_4

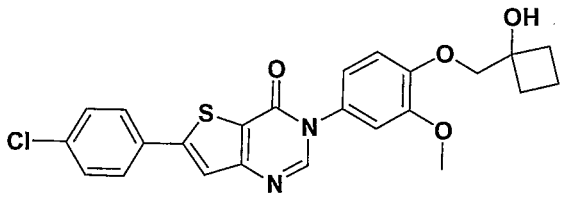
Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
141	$CH_2CHOHCH_2Cl$	477	3.70 Method #1	^1H NMR ($CDCl_3$) δ 3.09 (d, J = 4.95 Hz, 1H), 3.75-3.83 (m, 2H), 3.88 (s, 3H), 4.19 (d, J = 5.50 Hz, 2H), 4.26-4.29 (m, 1H), 6.94 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.98 (d, J = 2.20 Hz, 1H), 7.06 (d, J = 8.80 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.14 (s, 1H)	$ArNH_2$ by route B using epichlorohydrin; 2) $HCl/CHCL_3$ 3) Fe, NH_4Cl
142	$CH_2CHOHCH_2SEt$	503	3.88 Method #1	^1H NMR ($CDCl_3$) δ 1.29 (t, 3H), 2.60-2.90 (m, 4H), 3.21 (br s, 1H), 3.86 (s, 3H), 4.10-4.19 (m, 3H), 6.93 (d, J = 8.25 Hz, 1H), 6.97 (s, 1H), 7.05 (d, J = 8.25 Hz, 1H), 7.43 (d, J = 8.80 Hz, 2H), 7.52 (s, 1H), 7.64 (d, J = 8.25 Hz, 2H), 8.14 (s, 1H)	route B using epichlorohydrin; 2) EtSH
143	$CH_2CHOHCH_2S(O)Et$	519	3.39 Method #1	^1H NMR ($CDCl_3$) δ 1.39 (t, 3H), 2.84-3.11 (m, 4H), 3.87-3.91 (m, 4H), 4.09-4.28 (m, 2H), 4.69-4.77 (m, 1H), 6.95 (dd, J = 8.35 Hz, 2.20 Hz, 1H), 6.97 (d, J = 2.63 Hz, 1H), 7.07 (d, J = 8.35 Hz, 1H), 7.45 (d, J = 7.91 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.14 (s, 1H)	mCBA oxidation of Ex 142
144	$CH_2CHOHCH_2SO_2Et$	535	3.44 Method #1	^1H NMR ($CDCl_3$) δ 1.46 (t, 3H), 3.16-3.38 (m, 5H), 3.89 (s, 3H), 4.14-4.15 (m, 2H), 4.63-4.69 (m, 1H), 6.95 (dd, J = 8.35 Hz, 2.63 Hz, 1H), 6.99 (d, J = 2.20 Hz, 1H), 7.06 (d, J = 8.35 Hz, 1H), 7.45 (d, J = 8.35 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.35 Hz, 2H), 8.14 (s, 1H)	mCBA oxidation of Ex 142

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
145	$CH_2C(Me)_2OCH_2SMe$	517	4.42 Method #1	^1H NMR ($CDCl_3$) δ 1.42 (s, 6H), 2.20 (s, 3H), 3.87 (s, 3H), 3.97 (s, 2H), 4.73 (s, 2H), 6.91 (dd, J = 8.25 Hz, 2.75 Hz, 1H), 6.95 (d, J = 2.20 Hz, 1H), 7.00 (d, J = 8.80 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)	Treatment of Ex 82 with Ac_2O and DMSO in AcOH
146	CH_2CH_2SMe	459	3.90 Method #1	^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.97 (t, 2H), 3.90 (s, 3H), 4.26 (t, 2H), 6.93 (dd, J = 8.24 Hz, 2.19 Hz, 1H), 6.97 (d, J = 2.20 Hz, 1H), 7.01 (d, J = 8.25 Hz, 1H), 7.45 (d, J = 8.25 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.14 (s, 1H)	Treatment of Ex 131 with NaSMe
147	$CH_2COH(CH_3)CO_2H$	487	3.58 Method #1	^1H NMR (CD_3OD) δ 1.52 (s, 3H), 3.90 (s, 3H), 4.09 (d, J = 9.67 Hz, 1H), 4.34 (d, J = 9.66 Hz, 1H), 7.00 (dd, J = 8.35 Hz, 2.19 Hz, 1H), 7.09 (d, J = 2.63 Hz, 1H), 7.13 (d, J = 8.35 Hz, 1H), 7.48 (d, J = 8.79 Hz, 2H), 7.63 (s, 1H), 7.75 (d, J = 8.35 Hz, 2H), 8.29 (s, 1H)	$ArNH_2$ via Path C
148	$CH_2CHOHCF_3$	497	4.00 Method #1	^1H NMR (DMSO-d_6) δ 3.78 (s, 3H), 4.10-4.13 (m, 1H), 4.22-4.25 (m, 1H), 4.40-4.45 (m, 1H), 6.71 (d, J = 6.59 Hz, 1H), 7.06 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 7.18 (d, J = 8.80 Hz, 1H), 7.23 (d, J = 2.20 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.91 (d, J = 8.80 Hz, 2H), 7.97 (s, 1H), 8.39 (s, 1H)	$ArNH_2$ via Path C

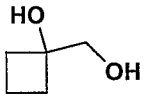
Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
149	$CH_2CH(Me)OPO(OMe)_2$	551	3.71 Method #1	^{1}H NMR ($CDCl_3$) δ 1.50 (d, J = 6.05 Hz, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.07-4.18 (m, 2H), 4.89-4.92 (m, 1H), 6.93 (dd, J = 7.70 Hz, 1.10 Hz, 1H), 6.97 (s, 1H), 7.03 (d, J = 8.79 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.54 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.17 (s, 1H)	Sequential treatment of Ex 102 in pyridine with $POCl_3$ followed by MeOH
150		573	3.69 Method #1	^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3H), 3.54-3.58 (m, 1H), 3.71-3.75 (m, 1H), 3.86 (s, 3H), 4.16-4.22 (m, 2H), 4.49 (br s, 2H), 6.93 (dd, J = 8.25 Hz, 1.65 Hz, 1H), 6.97 (d, J = 2.20 Hz, 1H), 7.05 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.64 (d, J = 8.80 Hz, 2H), 8.14 (s, 1H)	Treatment of Ex 141 with Na salt of 2-mercaptothiadiazole
151		555	2.76 Method #1	^{1}H NMR ($CDCl_3$) δ 3.32-3.36 (m, 1H), 3.48-3.51 (m, 1H), 3.61 (s, 3H), 3.87 (s, 3H), 4.10-4.14 (m, 1H), 4.23-4.25 (m, 1H), 4.45-4.48 (m, 1H), 6.89-6.96 (m, 4H), 7.07 (d, J = 8.80 Hz, 1H), 7.43 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.64 (d, J = 8.25 Hz, 2H), 8.14 (s, 1H)	Treatment of Ex 141 with Na salt of 2-mercaptoimidazole
152	$CH_2CH(OH)CH_2CF_3$	511	3.56 Method #1	^{1}H NMR (DMSO-d_6) δ 2.28-2.56 (m, 2H), 3.68 (s, 3H), 3.82-3.93 (m, 2H), 4.04-4.05 (m, 1H), 5.37 (d, J = 6.05 Hz, 1H), 6.95 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 7.02 (d, J = 8.79 Hz, 1H), 7.11 (d, J = 2.20 Hz, 1H), 7.46 (d, J = 8.79 Hz, 2H), 7.81 (d, J = 8.79 Hz, 2H), 7.86 (s, 1H), 8.29 (s, 1H)	$ArNH_2$ via Path C

Example #	R	Mass spec M+H	HPLC retention (min)	H NMR	Synthetic Comments
153	$CH_2CHOHCH_2F$	461	3.66 Method #1	^{1}H NMR ($CDCl_3$) δ 3.14 (br s, 1H), 3.86 (s, 3H), 4.14-4.34 (m, 3H), 4.53-4.70 (m, 2H), 6.94 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.98 (d, J = 2.19 Hz, 1H), 7.05 (d, J = 8.80 Hz, 1H), 7.43 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.64 (d, J = 8.79 Hz, 2H), 8.14 (s, 1H)	$ArNH_2$ via Path C

EXAMPLE 154



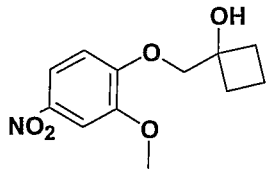
Part A. 1-(Hydroxymethyl)cyclobutanol



[00105] Mg turnings (1.38g, 57 mmol) were added to a well dried N_2 flushed round bottom flask equipped with a condenser, magnetic stirbar and addition funnel which was charged with THF (70 mL) and chloromethyldimethylisopropoxysilane (9.5g, 57 mmol). After adding ~10 mL of the THF solution and 1,2-dibromoethane (30 μL), the solution above the Mg became cloudy and warm. The remaining solution was added over 30 min at a rate that maintained a gentle reflux. Upon completion, the reaction was heated to reflux for 45 min before cooling to 0°C whereupon a solution of cyclobutanone (3g, 42.7 mmol) in THF (17 mL) was added dropwise over 40 min. The reaction was stirred for an additional 45 min prior to quenching by slow addition of 10% aq NH_4Cl over 40 min. After transferal of the reaction to a separatory funnel, the phases were separated and the aq phase was extracted 3x with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated .

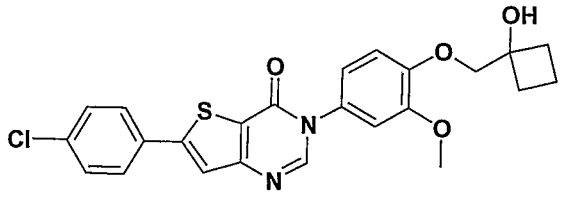
[00106] To the resulting residue was added THF (43 mL), MeOH (43 mL), $KHCO_3$ (4.27g, 42.7 mmol) and KF (4.96g, 84.4 mmol). To this stirred mixture was added in one portion 30% H_2O_2 (116 mL, 140 mmol). As the reaction stirred for 2.5 hr, the temperature rose to ~ 46°C before falling. The residual H2O2 was destroyed by addition of 32g of powdered $Na_2S_2O_3 \cdot H_2O$ and stirring for 15 min. Following dilution with Et_2O (200 mL), the mixture was filtered through celite and concentrated to ~50g without heating. A second portion of Et_2O (200 mL) was added and the solution dried over Na_2SO_4. The residue after concentration was chromatographed on silica gel employing Et2O as the eluant. Upon concentration, 2.64 g of product diol was obtained

Part B. 1-((2-Methoxy-4-nitrophenoxy)methyl)cyclobutanol



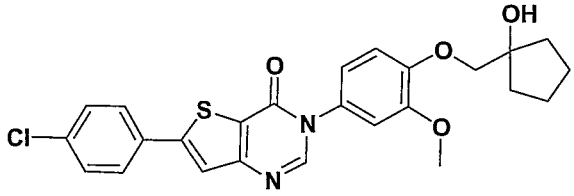
[00107] The 1-(hydroxymethyl)cyclobutanol (1.27g, 12.5 mmol) was added to a suspension of 60% NaH/mineral oil dispersion (0.50g, 12.5 mmol) in DMSO (14.6 mL). Subsequently, 30 min after cessation of gas evolution, 2-bromo-4-nitroanisole (1.95g, 8.4 mmol) in 5.9 mL of DMSO was added to the stirred solution. The reaction was stirred for 2.5 hr before being poured into 0.1N HCl (300 mL). The mixture was extracted 2x with Et2O; the combined organic layers were washed with brine, dried over MgSO4 and concentrated under vacuum. The residue was chromatographed on silica gel; gradient elution CH_2Cl_2 to 1:1 CH_2Cl_2/EtOAc yielded 0.65 g of desired product. ($CDCl_3$) 7.89 (dd, J = 2.6, 8.8 Hz, 1H), 7.74 (d, J = 2.6 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 4.10 (s, 2H), 3.93 (s, 3H), 3.05 (br s, 1H), 2.22 (m, 4H), 1.87 (m, 1H), 1.62 (m, 1H)

Part C.



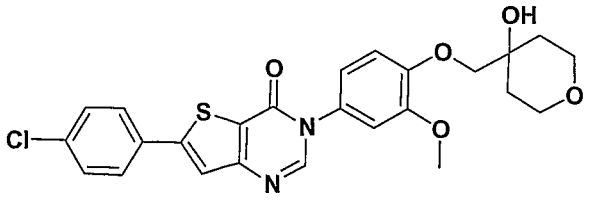
[00108] Using the procedure described in Part C of Example 89, the product of Part B was converted to the title compound upon sequential reduction and condensation with the formamidine of Example 1 part C. ^{1}H NMR ($CDCl_3$) 8.07 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.85 (dd, J = 2.2, 7.6 Hz, 1 H), 4.01 (s, 2H), 3.80 (s, 3H), 3.09 (br s, 1H), 2.15 (m, 4H), 1.80 (m, 1H), 1.53 (m, 1H); HPLC (method #5) 4.32 min; LCMS m/z: 469 [M+H].

EXAMPLE 155

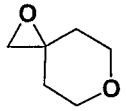


[00109] 1-(Hydroxymethyl)cyclopentanol, prepared in an analogous manner as that described for 1-(hydroxymethyl)cyclobutanol in Example 154, was converted to Example 155 using the procedure employed to synthesize Example 154. ^{1}H NMR ($CDCl_3$) 8.14 (s, 1H), 7.67 (d, J = 9.4 Hz, 2H), 7.52 (s, 1H), 7.46 (d, J = 9.4 Hz, 2H), 7.03 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 2.2, 8.2 Hz, 1 H), 4.01 (s, 2H), 3.87 (s, 3H), 2.37 (s, 1H), 1.90-1.60 (m, 8H); HPLC (Method #5) 4.46 min; LCMS m/z: 483 [M+H].

EXAMPLE 156

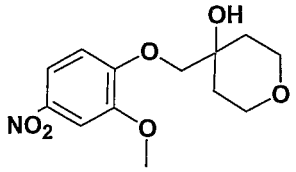


Part A. 1,6-Dioxaspiro[2.5]octane



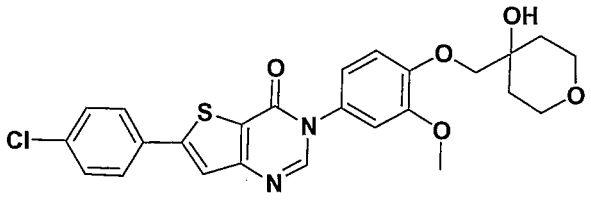
[00110] To a suspension of NaH (287 mg, 11.98 mmol) in dry THF (30 ml) was added trimethylsulfoxonium iodide (2.64 g, 11.98 mmol). The reaction mixture was stirred at reflux for 2 h and then cooled to room temperature. A solution of tetrahydro-4H-pyran-4-one (1.54 g, 15.41 mmol) in THF (1 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 1.5 hours. The mixture diluted with Et_2O, washed with a solution of saturated $NaHCO_3$ (2 x 50 ml), dried over Na_2SO_4 and concentrated giving the epoxide(2.27 g) as a brown solid.

Part B. 4-((2-Methoxy-4-nitrophenoxy)methyl)tetrahydro-2H-pyran-4-ol



[00111] To a solution of epoxide of Part A (1.03 g, 9.03 mmol) was added NaH_2PO_4 (1.12 g, 8.13 mmol) and 4-nitro-guaiacol potassium salt hydrate (1.87 g, 9.03 mmol) in 15% H_2O/acetonitrile. The reaction mixture was stirred at 180 °C in a steel bomb for 5 hours, cooled to room temperature, diluted with EtOAc (50 mL) and washed with a solution of saturated $NaHCO_3$ (2 x 50 mL). The EtOAc layer was dried over Na_2SO_4 and concentrated to give the desired nitro aryl ether (2.27 g) as brown solid.

Part C.

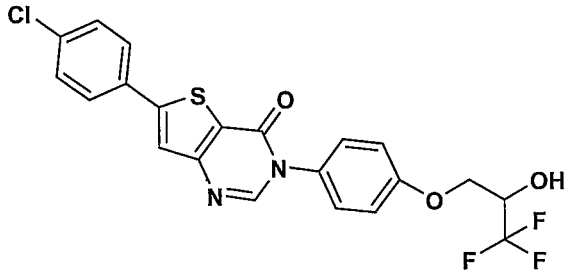


[00112] Using the procedure described in Part C of Example 89, the product of Part B (2.27g) was converted to the title compound upon sequential reduction and condensation in phenol with the formamidine of Example 1 part C. ^1H NMR ($CDCl_3$)

δ ppm 1.70 - 1.87 (m, 4 H), 3.78 - 3.96 (m, 9 H), 6.91 - 6.96 (m, 1 H), 6.97 (d, 1 H), 7.03 (d, 1 H), 7.45 (d, 2 H), 7.51 - 7.57 (m, 1 H), 7.66 (d, 2 H); HPLC (Method #4): 3.13 min; LCMS (ES) m/z: 499 (M+H).

EXAMPLE 157

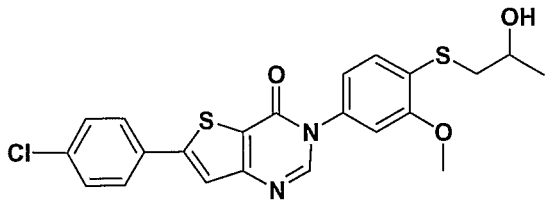
6-(4-Chlorophenyl)-3-(4-(3,3,3-trifluoro-2-hydroxypropoxy)phenyl)thieno-[3,2-d]-pyrimidin-4(3H)-one



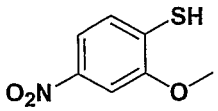
[00113] Following the procedure described in Example 82, p-nitrophenol was alkylated with 3,3,3-trifluoropropylene oxide to generate 1-(4-amino-2-methoxyphenoxy)-3,3,3-trifluoropropan-2-ol. Using the procedure described in Part C of Example 89, this alcohol was converted to the title compound upon sequential reduction and condensation in phenol with the formamidine of Example 1 part C. ^{1}H NMR (DMSO-d_6) δ 4.13-4.17 (m, 1H), 4.24-4.28 (m, 1H), 4.40-4.46 (m, 1H), 6.72 (d, J = 6.59 Hz, 1H), 7.14 (d, J = 9.4 Hz, 2H), 7.47 (d, J = 8,79 Hz, 2H), 7.56 (d, J = 8.79 Hz, 2H), 7.90 (d, J = 8.80 Hz, 2H), 7.95 (s, 1H), 8.38 (s, 1H); HPLC (Method #4): 4.05 min; LCMS (ES) m/z: 467 (M+H).

EXAMPLE 158

6-(4-Chlorophenyl)-3-(4-(2-hydroxypropylthio)-3-methoxyphenyl)thieno-[3,2-d]pyrimidin-4(3H)-one

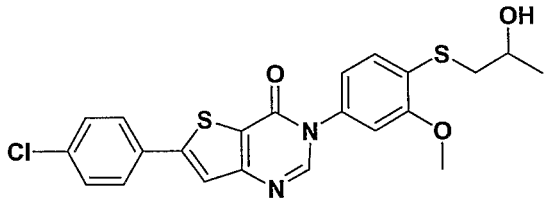


Part A. 2-Methoxy-4-nitrobenzenethiol



[00114] To a suspension of 2-chloro-5-nitroanisole (1.00 g; 5.33 mmol) in 10 mL of ethanol at rt was added a solution of sodium sulfide nonahydrate (1.30 g; 5.41 mmol) in 1.4 mL of water and 0.8 mL of ethanol in three portions over 3 minutes. The resulting suspension was heated at 100°C for 10 min. The suspension was cooled and concentrated under reduced pressure to a dark solid which was used immediately in the next step. HPLC 2.23 min retention time; LCMS (ES): m/z 186 $[M+H]^+$.

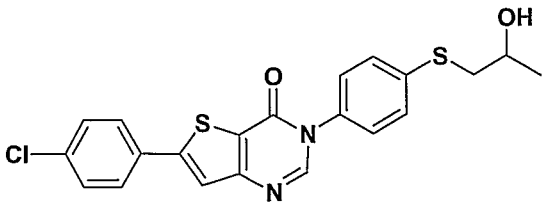
Part B.



[00115] 2-Methoxy-4-nitrobenzenethiol was converted to the title compound following the procedures described in Example 104. ^{1}H NMR (DMSO-d_6) δ 1.18 (d, J = 6.05 Hz, 3H), 2.87-3.03 (m, 2H), 3.78-3.83 (m, 4H), 4.98 (d, J = 4.94 Hz, 1H), 7.11 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 7.20 (d, J = 2.20 Hz, 1H), 7.38 (d, J = 8.79 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.92 (d, J = 8.24 Hz, 2H), 7.98 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.58, 56.05, 64.87, 110.26, 119.92, 121.75, 121.95, 126.20, 126.68, 127.84, 129.28, 131.16, 134.29, 134.62, 149.27, 149.88, 155.80, 155.92, 157.39; HPLC (Method #1) 3.91 min retention time, (98%); LCMS (ES): m/z 459 $[M+H]^+$.

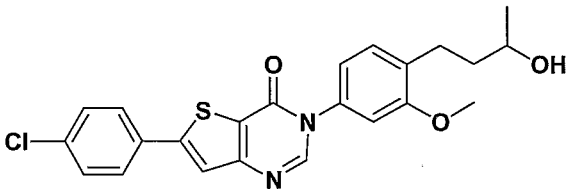
EXAMPLE 159

6-(4-Chlorophenyl)-3-(4-(2-hydroxypropylthio)-phenyl)thieno-[3,2-d]-pyrimidin-4(3H)-one

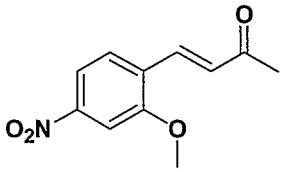


[00116] Commercial 4-nitrothiophenol was converted to the title compound following the procedures described in Example 104. ^{1}H NMR (DMSO-d_6) δ 1.19 (d, J = 6.04 Hz, 3H), 2.97-3.11 (m, 2H), 3.80-3.85 (m, 1H), 4.99 (d, J = 4.95 Hz, 1H), 7.47 (s, 4H), 7.56 (d, J = 8.80 Hz, 2H), 7.91 (d, J = 8.79 Hz, 2H), 7.96 (s, 1H), 8.40 (s, 1H); HPLC (Method #1) 4.00 min; LCMS (ES) m/z 429 (M+H).

EXAMPLE 160

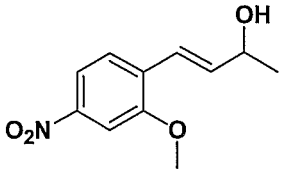


Part A. 4-(2-Methoxy-4-nitrophenyl)but-3-en-2-one



[00117] To a mixture of 2-methoxy-4-nitrobenzaldehyde (10.0 g; 55.2 mmol) in 11 mL of water and 11 mL of acetone at 65°C was added a 1% solution of NaOH (13.8 mL) over 30 minutes. The mixture was heated at 65°C for 2 h, cooled in an ice bath and neutralized with 10% HCl. A solid precipitated which was filtered, washed with water and dried under vacuum to afford 12.2 g (100%) of the title compound as a reddish-brown solid. HPLC (Method #1) 2.48 min retention time, (80%); MS (ES): m/z 222 $[M+H]^+$.

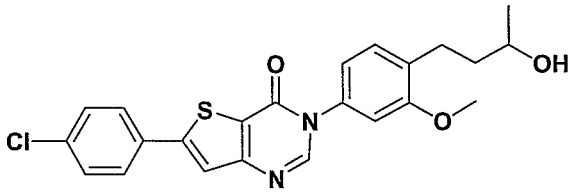
Part B. 4-(2-Methoxy-4-nitrophenyl)but-3-en-2-ol



[00118] To a suspension of 4-(2-methoxy-4-nitrophenyl)but-3-en-2-one (12.2 g; 55.2 mmol) in 150 mL of ethanol at rt was added $NaBH_4$ (2.30 g; 60.7 mmol) over 5

minutes. The suspension was stirred at rt for 1 h, diluted with 1M $NaHPO_4$ (~60 mL) followed by water (100 mL) and concentrated under reduced pressure to remove ethanol. After extracting the aqueous residue with CH_2Cl_2, the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered. Concentration of the filtrate under reduced pressure afforded 12.3 g (100%) of the title compound as a dark, red gum. HPLC (Method #1) 3.68 min retention time, (50%); MS (ES): m/z 206 $[M\text{-}OH]^+$.

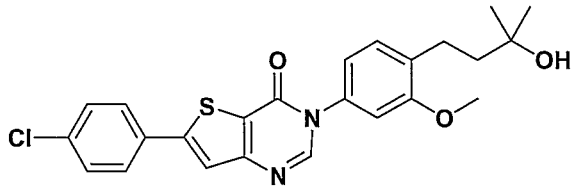
Part C.



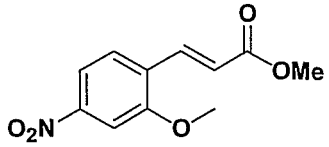
[00119] The above nitro allylic alcohol, after being reduced to the corresponding aniline bearing a saturated hydroxyalkyl ether with H_2/Pd/C in EtOH was heated in molten phenol at 130 with the formamidine of Example 1 to generate the title compound.

EXAMPLE 161

6-(4-Chlorophenyl)-3-(4-(3-hydroxy-3-methylbutyl)-3-methoxyphenyl)thieno-[3,2-d]pyrimidin-4(3H)-one



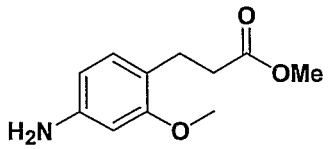
Part A. Methyl 3-(2-methoxy-4-nitrophenyl)acrylate



[00120] A solution of 2-methoxy-4-nitrobenzaldehyde (904 mg, 4.99 mmol) and methyl (triphenylphosphoranylidene) acetate (2.04 g, 5.86 mmol) in CH_2Cl_2 (25.0

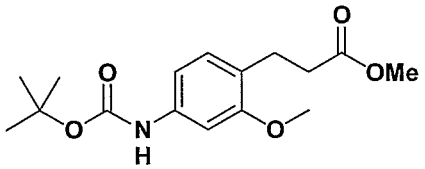
mL) was stirred at 20 °C for 14h. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2 230-400 mesh, 4/1 hexanes/EtOAc) to give the title compound (1.18g, 4/1 E/Z isomeric mixture, quant.) as a white solid. MS (electrospray, + ions) m/z 238 (M+H).

Part B. Methyl 3-(4-amino-2-methoxyphenyl)propanoate



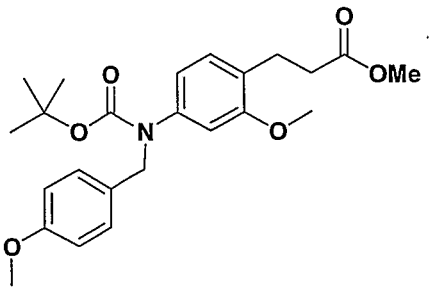
[00121] To a solution of Part A compound (1.15g, 4.85 mmol) in 1/1 THF/MeOH (26.0 mL) was added 5% Pd-C (275 mg, Degussa type) and the suspension was hydrogenated (1 atm.) for 2h.. The suspension was filtered through celite and the filter cake was rinsed with MeOH (70 mL). The combined filtrates were evaporated to furnish the title compound (1.01 g, quant.) as a brownish oil. MS (electrospray, + ions) m/z 210 (M+H).

Part C. Methyl 3-(4-(tert-butoxycarbonylamino)-2-methoxyphenyl)propanoate



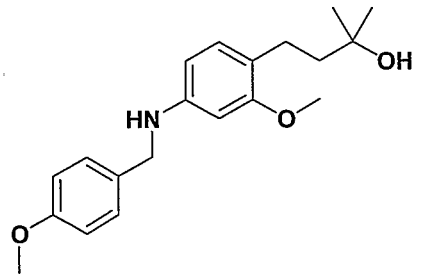
[00122] A solution of Part B compound (1.01 g, 4.83 mmol) and di-*t*-butyl dicarbonate (2.11 g, 9.67 mmol) in dioxane (36.0 mL) was heated at 95 °C under argon for 4.5 h. after cooling to 20 °C, the solvent was removed *in vacuo* and the residue was chromatographed (SiO_2 230-400 mesh, 4/1 to 3/2 hexanes/EtOAc) to provide the title compound (1.41 g, 94% yield) as a white solid. MS (electrospray, + ions) m/z 254 (M+H - isobutylene).

Part D. Methyl 3-(4-(tert-butoxycarbonyl(4-methoxybenzyl)amino)-2-methoxyphenyl)propanoate



[00123] To a solution of Part C compound (1.41 g, 4.56 mmol) in DMF, under argon, were added cesium carbonate (4.45 g, 13.7 mmol) and tetrabutyl ammonium iodide (5.13 g, 13.6 mmol). After stirring for 40 min. at 20 °C, 4-methoxybenzyl chloride (1.27 mL, 9.36 mmol) was added to the suspension and stirring was continued for 7h at 20 °C. Water (25.0 mL) was added and the mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with water (2x30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated. Chromatography (SiO_2 230-400 mesh, 4/1 hexanes/EtOAc) of the crude afforded the title compound (1.90 g, 97% yield) as a colorless oil. MS (electrospray, + ions) m/z 452 (M+Na).

Part E. 4-(2-Methoxy-4-(4-methoxybenzylamino)phenyl)-2-methylbutan-2-ol



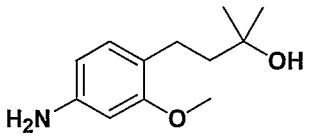
[00124] A 3*M* methylmagnesium iodide/ether solution (6.9 mL, 20.7 mmol) was diluted with ether (7.0 mL) and cooled to 0 °C. To the resulting solution was added dropwise a solution of Part D compound (1.90 g, 4.42 mmol) in ether (5.0 mL). After stirring at 0 °C for 35 min, 1*M* HCl (15 mL) was slowly added and the aqueous mixture pH was adjusted to 6.5 by further addition of 1*M* HCl. The mixture was extracted with CH_2Cl_2 (3x40 mL) and the combined extracts were dried (Na_2SO_4) and evaporated. Chromatography (SiO_2 230-400 mesh, 3/2 to1/1 hexanes/EtOAc)

gave the desired tertiary alcohol as a 3/2 BOC- carbamate/amine mixture (1.75 g, colorless oil).

[00125] A portion of the above mixture (82.1 mg) was treated with ~3*M* HCl/MeOH, MeOAc [prepared by addition of AcCl (1.3 mL) to MeOH (5.0 mL) at 0 °C and stirring at 20 °C for 30 min] for 3h. After evaporation of the solution, the title compound (78.1 mg, quant. yield from Part D compound, yellowish solid) was obtained as its hydrochloride salt: MS (electrospray, + ions) m/z 330 (M+H).

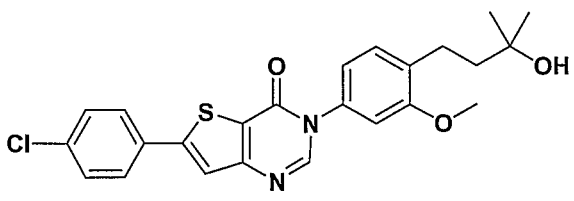
[00126] The above HCl salt (78.1) was dissolved in *i*-PrOH (3.0 mL) and water (10 mL) and the aqueous mixture pH was adjusted to 10 by addition of 1*M* K_2CO_3. The mixture was extracted with CH_2Cl_2 (3x30 mL) and, the combined extracts were dried (Na_2SO_4) and concentrated. Drying under vacuum provided the title compound (68.0 mg, quant. yield) as a colorless oil. MS (electrospray, + ions) m/z 330 (M+H).

Part F. 4-(4-Amino-2-methoxyphenyl)-2-methylbutan-2-ol



[00127] To a solution of Part F compound (68.0 mg, 0.21 mmol) and ammonium formate in MeOH was added 10% Pd-C (8.0 mg) and the suspension was heated at 62 °C, under argon, for 50 min. After cooling to 20 °C, the mixture was filtered through celite and the filter cake was rinsed with MeOH (20 mL). The combined filtrates were evaporated and, the residue was taken up in CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4) and evaporated. Chromatography (SiO_2 230-400 mesh, 95/5 CH_2Cl_2/MeOH) of the crude afforded the title compound (38.0 mg, 87% yield) as a colorless oil. MS (electrospray, + ions) m/z 210 (M+H).

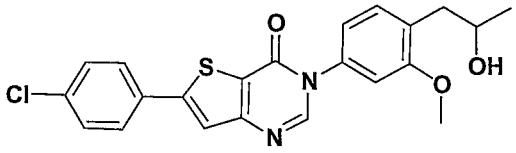
Part G.



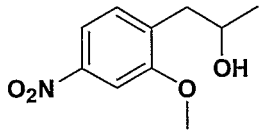
[00128] The Part F compound (57.1 mg, 0.27 mmol), the formamidine of Example 1-Part C (185 mg, 0.57 mmol) and phenol (480 mg) were mixed and heated at 130 °C for 45 min. The mixture was allowed to stand at 20 °C for 20 min and then treated with MeOH (2.0 mL) and filtered. The isolated solid was rinsed with MeOH (4 x 0.5 mL) and CH_2Cl_2 (2 x 0.25 mL), and dried under vacuum to provide the desired compound (49.6 mg, 41% yield) as an off-white solid. ^{1}H NMR ∂ ($CDCl_3$ + CD_3OD drops, ppm) 8.16 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.55 (s, 1H)., 7.45 (d, J = 8.8 Hz, 2H), 7.31 (m, 1H), 6.91 (m + s, 2H), 3.87 (s, 3H), 2.76 (m, 2H), 1.78 (m, 2H), 1.31 (s, 6H); HPLC (Method #6): 7.21 min; LCMS (ES): m/z 455 (M+H).

EXAMPLE 162

6-(4-Chlorophenyl)-3-(4-(2-hydroxypropyl)-3-methoxyphenyl)thieno[3,2-*d*]-pyrimidin-4-(3*H*)-one



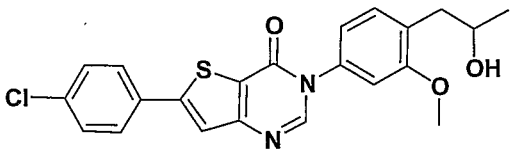
Part A. 1-(2-Methoxy-4-nitrophenyl)propan-2-ol



[00129] To a stirred -78 °C solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 1.43 mL, 1.43 mmol) in anhydrous Et_2O (7 mL) was added MeLi (1.6 M in Et_2O, 0.9 mL, 1.43 mmol) dropwise over a period of 20 min. The reaction mixture was allowed to slowly warm to -30 °C at which point a solution of 2-(2-methoxy-4-nitrophenyl)acetaldehyde (275 mg, 1.43 mmol) (prepared as described in PCT WO 2000/73288 A1) in anhydrous Et_2O (0.750 mL) was added dropwise and allowed slowly warm to -10 °C. The reaction mixture was poured into cold water and extracted with Et_2O (3 x 50 mL). The combined ether extracts were washed with water (1 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford 0.253 g (85%) of the title compound as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 3 H), 1.62 (br. s., 1 H), 2.81 (dd, J = 13.2, 7.7 Hz, 1 H), 2.89 - 2.94 (m, 1 H),

3.93 (s, 3 H), 4.06 - 4.15 (m, 1 H), 7.32 (d, J = 8.2 Hz, 1 H), 7.72 (d, J = 2.2 Hz, 1 H), 7.82 (dd, J = 8.2, 2.2 Hz, 1 H); HPLC (Method #1): 2.68 min retention time, (89%); LCMS (ES): m/z 194 $[M-H_2O+H]^+$.

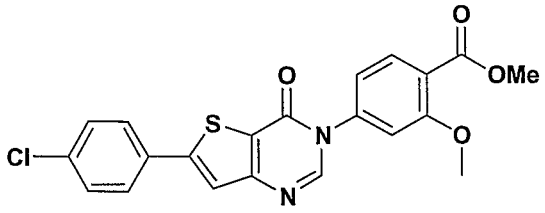
Part B.



[00130] Following the procedure described in Example 89, 253 mg of 1-(2-methoxy-4-nitrophenyl)propan-2-ol was reduced to the corresponding aniline prior to condensation with the formamidine (0.288 g, 0.894 mmol) of Example 1 Part C in 1.0 g of phenol at 130°C for 0.25 h to afford the title compound (0.072 g). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.19 - 1.23 (m, 3 H), 1.72 (br. s., 1 H), 2.72 (dd, J = 13.2, 8.2 Hz, 1 H), 2.86 (dd, J = 13.2, 4.4 Hz, 1 H), 3.82 (s, 3 H), 4.01 - 4.09 (m, 1 H), 6.91 (s, 1 H), 6.93 (s, 1 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.53 (s, 1 H), 7.67 (d, J = 8.8 Hz, 2 H), 8.11 (s, 1 H); HPLC (Method #1): 3.75 min retention time, (100%); LCMS (ES): m/z 427 $[M+H]^+$.

EXAMPLE 163

Methyl 4-(6-(4-chlorophenyl)-4-oxothieno- [3,2-*d*]pyrimidin-3-(4*H*)-yl)-2-methoxybenzoate

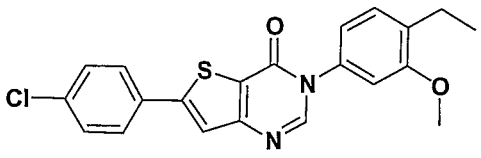


[00131] Following the procedure described in Example 89, commercially available methyl 4-amino-2-methoxybenzoate (0. g, 0.894 mmol) was condensed with the formamidine (0.312 g, 0.967 mmol) of Example 1 Part C in 1.0 g of phenol at 130°C for 0.25 h to afford the title compound (0.039 g) as a colorless solid. ^{1}H NMR (500 MHz, DMSO) δ 3.84 (d, J = 12.6 Hz, 6 H), 7.22 (d, J = 8.2 Hz, 1 H), 7.44 (s, 1 H), 7.58 (d, J = 8.2 Hz, 2 H), 7.79 (d, J = 8.2 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 2 H), 8.01 (s,

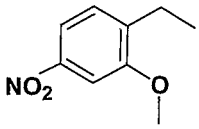
1 H), 8.48 (s, 1 H); HPLC (Method #1):3.66 min retention time, (99%); LCMS (ES): m/z 427 $[M+H]^+$.

EXAMPLE 164

6-(4-Chlorophenyl)-3-(4-(2-ethyl)-3-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-(3*H*)-one

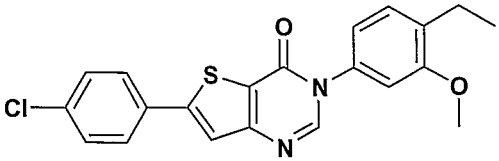


Part A. 1-Ethyl-2-methoxy-4-nitrobenzene



[00132] Following published procedures 2-ethyl aniline was nitrated (Bergman, J.; Sand, P. *Tetrahedron* **1990,** *46*, 1085) and then converted to 2-ethyl-5-nitrophenol (PCT WO 1995/15954). A mixture of 2-ethyl-5-nitrophenol (0.320 g, 1.92 mmol), K_2CO_3 (0.200 g, 1.44 mmol) and MeI (0.300 g, 2.11 mmol) in acetone (4.0 mL) was heated at 70 °C for 15 h. The solution was cooled to rt, diluted with H_2O, concentrated and extracted with CH_2Cl_2 (3x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound (0.347 g) as an orange oil which was used in the next step without further purification. HPLC (Method #1): 3.46 min retention time, (75%); LCMS (ES): m/z 182 $[M+H]^+$.

Part B.

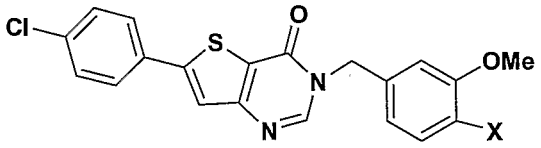


[00133] Following the procedure described in Example 89, 253 mg of 1-ethyl-3-methoxy-4-nitrobenzene was reduced to the corresponding aniline prior to condensation with the formamidine (0.265 g, 0.821 mmol) of Example 1 Part C in

0.75 g of phenol at 130°C for 0.25 h to afford the title compound (149 mg) as a gray solid. ^{1}H NMR (500 MHz, DMSO) δ 1.16 (t, J = 7.7 Hz, 3 H), 2.62 (q, J = 7.5 Hz, 2 H), 3.80 (s, 3 H), 7.04 (d, J = 7.7 Hz, 1 H), 7.17 (s, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 2 H), 7.98 (s, 1 H), 8.42 (s, 1 H); HPLC (Method #1) 4.50 min retention time, (98%); LCMS (ES): m/z 397 $[M+H]^+$.

EXAMPLES 165 AND 166

[00134] The following examples were prepared following the procedure described in Example 1 except for substitution of the appropriate commercially available benzyl amine for the aniline component.

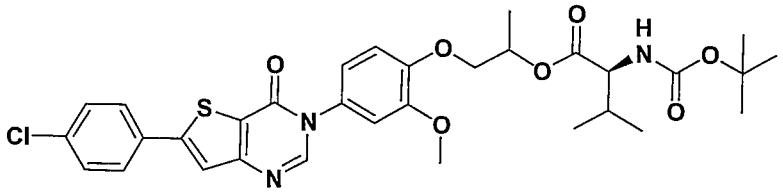


Example #	X	Mass spec M+H	HPLC retention (min)	H NMR
165	OMe	413	3.7 Method #1	^{1}H NMR ($CDCl_3$) δ 3.864 (s, 3H), 3.868 (s, 3H), 5.16 (s, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.92 (s, !H), 7.42 (d, J = 8Hz, 2H),7.46 (s, 1H), 7.63 (d, J = 8 Hz, 2H), 8.11 (s, 1H)
166	OH	399	3.56 Method #1	^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 5.09 (s, 2H), 6.71 (d, J = 7.91 Hz, 1H), 6.78 (dd, J = 7.91 Hz, 1.76 Hz, 1H), 7.04 (d, J = 1.76 Hz, 1H), 7.55 (d, J = 8.78 Hz, 2H), 7.87 (d, J = 8.79 Hz, 2H), 7.88 (s, 1H), 8.63 (s, 1H), 9.05 (br s, 1H)

[00135] Prodrugs were prepared of selected secondary and tertiary alcohols to improve solubility and exposure. Standard conditions, employed to generate amino acid esters of all but the glycine ester of the tertiary alcohols, are exemplified in Example 167. Preparation of the glycine ester of the tertiary alcohols is exemplified in Example 168. The respective half-esters of oxalic, malonic, succinic and glutaric acids are exemplified in Examples 169 to 172. Example 173 exemplifies preparation of an O-glucoside prodrug; Example 174 exemplifies preparation of a mono-phosphate ester.

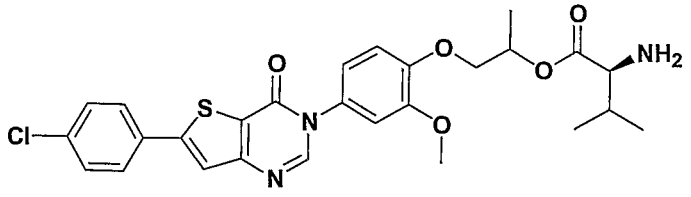
EXAMPLE 167

Part A. (2S)-1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)propan-2-yl 2-(tert-butoxycarbonyl)-3-methylbutanoate



[00136] A mixture of the alcohol described in Example 104 (50 mg, 0.113 mmol), diisopropylcarbodiimide (21 uL, 0.135 mmol), 4-dimethylaminopyridine (1 mg, 0.011 mmol) and N-(t-butoxycarbonyl)-L-valine (29 mg, 0.135 mmol) in 1 mL of CH_2Cl_2 was stirred at rt for 1 h. Additional diisopropylcarbodiimide (5 uL, 0.032 mmol) and N-(t-butoxy-carbonyl)-L-valine (5 mg, 0.023 mmol) were added and the mixture stirred at rt for 3.5 h. The suspension was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH, 100:0 to 98:2 gradient) to afford the title compound (76 mg) as a white solid. ^1H NMR ($CDCl_3$) δ 0.90-0.95 (m, 3H), 0.97-1.02 (m, 3H), 1.40 (d, 3H), 1.45 (s, 9H), 2.15-2.19 (m, 1H), 3.86 (d, 3H), 4.05-4.27 (m, 3H), 5.05-5.08 (m, 1H), 5.35-5.41 (m, 1H), 6.92-6.96 (m, 2H), 7.00-7.05 (m, 1H), 7.45 (d, J = 8.79 Hz, 2H), 7.54 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.15 (d, 1H); HPLC (Method #1) 4.73 min retention time, (99%); LCMS (ES): m/z 642 [M+H].

Part B.

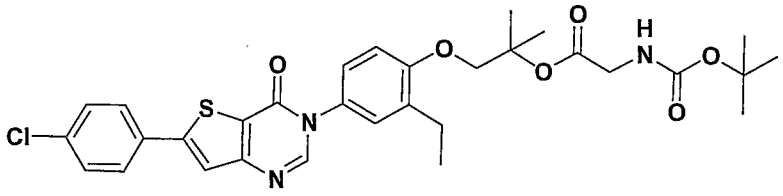


[00137] The product of part A was dissolved in a 1:2 mixture of TFA/CH_2Cl_2 (1 mL). By HPLC analysis after 1 hr at 20 °C the reaction was complete whereupon the volatiles were removed under vacuum. The residue upon dissolution in CH_2Cl_2 was washed 2x with aq $NaHCO_3/Na_2CO_3$ followed by brine prior to drying over Na_2SO_4. Upon concentration, 65 mg (94%) of the title compound was obtained. ^1H NMR

(DMSO-d_6) δ 0.97-1.01 (m, 6H), 1.34-1.36 (m, 3H), 2.11-2.18 (m, 1H), 3.75 (d, 3H), 3.94-3.97 (m, 1H), 4.09-4.21 (m, 2H), 5.29-5.37 (m, 1H), 7.04-7.07 (m, 1H), 7.12-7.16 (m, 1H), 7.20-7.23 (m, 1H), 7.58 (d, J = 8.25 Hz, 2H), 7.92 (d, J = 8.80 Hz, 2H), 7.98 (s, 1H), 8.34 (br s, 3H), 8.39 (s, 1H); HPLC (Method #1) 3.07 min; MS (ES): m/z 542 $[M+H]^+$.

EXAMPLE 168

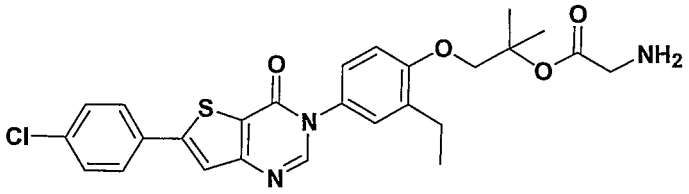
1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-ethylphenoxy)-2-methylpropan-2-yl 2-(tert-butoxycarbonylamino)acetate



[00138] To a solution of 6-(4-chlorophenyl)-3-(3-ethyl-4-(2-hydroxy-2-methylpropoxy)-phenyl)thieno[3,2-d]pyrimidin-4(3H)-one (0.96 g, 2.11 mmol), 4-pyrrolidinopyridine (0.31 g, 2.11 mmol) and N-(tert-butoxycarbonyl)glycine (1.11 g, 6.33 mmol) in 20 mL of CH_2Cl_2 heated at reflux was added diisopropylcarbodiimide (0.98 mL; 6.33 mmol) over 3 h via syringe pump. The suspension was heated at reflux for 1 h and additional N-(tert-butoxycarbonyl)glycine (0.55 g, 3.17 mmol) was added followed by diisopropylcarbodiimide (0.55 mL, 3.17 mmol) over 2 hrs via syringe pump. The suspension heated at reflux for 1 h and cooled to rt. Hydrazine monohydrate (0.34 mL, 7.01 mmol) was added and the suspension stirred at rt for 2 h. The suspension was cooled to 0°C, filtered and the filtrate washed with cold, 1N HCl, cold, dilute $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes, 0:100 to 1:1 gradient) to afford 1.37 g (100%) of the title compound as an off-white solid. ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.45 (s, 9H), 1.64 (s, 6H), 2.68-2.73 (m, 2H), 3.85 (d, J = 4.95 Hz, 2H), 4.18 (s, 2H), 4.98 (br s, 1H), 6.92 (d, J = 9.35 Hz, 1H), 7.20-7.22 (m, 2H), 7.44 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.68, 23.39, 23.67, 28.28, 42.87, 72.72, 79.86, 81.86, 111.48, 120.82, 123.25, 125.42, 127.62, 129.42, 129.67, 131.54, 134.25, 135.59, 148.29, 151.50, 155.58, 156.69,

156.92, 157.37, 169.47; HPLC (Method #1) 4.80 min retention time; LCMS (ES): m/z 612 $[M+H]^+$.

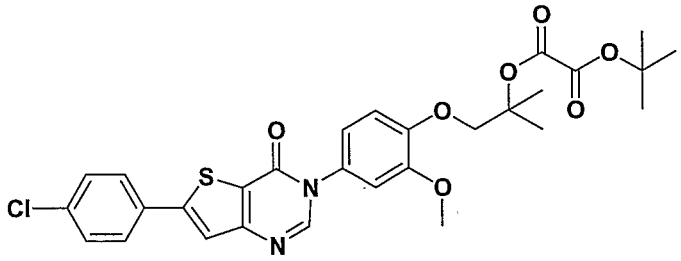
Part B.



[00139] Following the procedure described in Part B of Example 167, the BOC group was cleaved and the title compound isolated as a white solid. ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.48 (br s, 2H), 1.64 (s, 6H), 2.68-2.74 (m, 2H), 3.38 (s, 2H), 4.19 (s, 2H), 6.93 (d, J = 9.34 Hz, 1H), 7.19-7.22 (m, 2H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.68, 23.42, 23.75, 44.54, 72.72, 81.02, 111.43, 120.82, 123.22, 125.45, 127.62, 129.42, 129.62, 131.54, 134.17, 135.59, 148.27, 151.50, 156.77, 156.92, 157.37, 173.56; HPLC (Method #1): 3.27 min retention time, (100%); LCMS (ES): m/z 512 $[M+H]^+$.

EXAMPLE 169

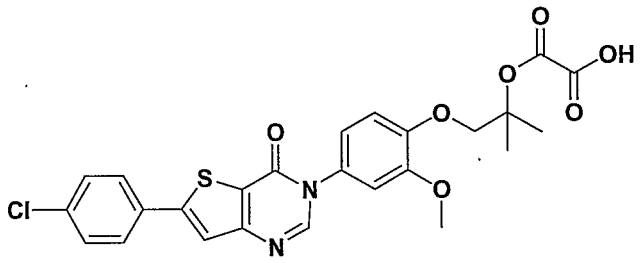
tert-Butyl 1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl oxalate



[00140] To oxalyl chloride (0.50 mL; 5.91 mmol) cooled to 0°C was added t-butanol (0.28 mL; 2.95 mmol) over 30 min. After warming the solution to rt and concentration under reduced pressure, the residue was dissolved in 1 mL of CH_2Cl_2 whereupon 6-(4-chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)thieno[3,2-d]-pyrimidin-4(3H)-one (100 mg; 0.219 mmol) (the product of Example 82) and pyridine (42 uL; 0.522 mmol) were added. After the suspension was stirred at rt for 1.5 h, the solution was diluted with CH_2Cl_2, washed

with 1N HCl and brine, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 1:1 gradient) to afford 120 mg (94%) of the title compound as a white foam. ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 1.70 (s, 6H), 3.87 (s, 3H), 4.24 (s, 2H), 6.92 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.96 (d, J = 2.20 Hz, 1H), 7.04 (d, J = 8.24 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.14, 27.74, 56.36, 74.39, 84.26, 84.51, 111.76, 115.30, 119.27, 120.84, 123.22, 127.65, 129.47, 130.78, 131.54, 135.67, 148.19, 149.25, 150.64, 151.63, 156.77, 157.22, 157.35, 157.60; HPLC (Method #1) 4.40 min retention time, (100%); MS (ES): m/z 585 $[M+H]^+$.

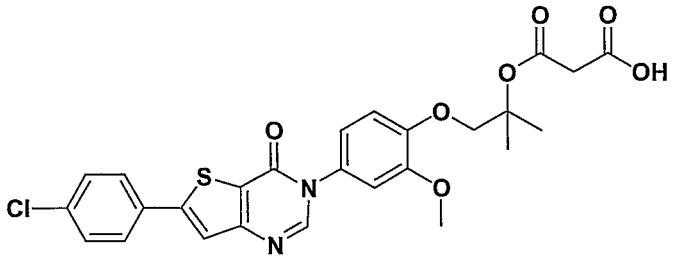
Part B. 2-(1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yloxy)-2-oxoacetic acid



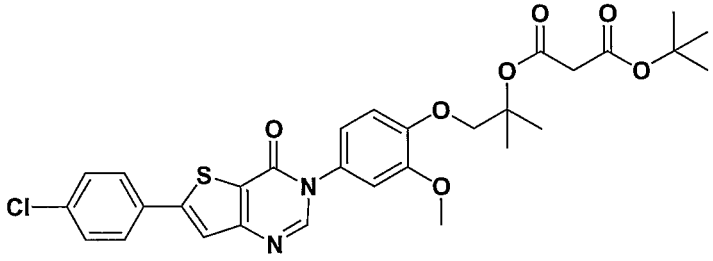
[00141] A solution of tert-butyl 1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl oxalate (124 mg; 0.212 mmol) in 0.5 mL of TFA and 1 mL of CH_2Cl_2 was stirred at rt for 1.5 h. The solution was concentrated under reduced pressure to afford 102 mg (91%) of the title compound as a white foam. ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6H), 3.86 (s, 3H), 4.30 (s, 2H), 6.91-6.94 (m, 2H), 7.09 (d, J = 8.80 Hz, 1H), 7.45 (d, J = 8.79 Hz, 2H), 7.66-7.69 (m, 3H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.76, 56.26, 74.60, 85.93, 111.25, 116.62, 119.30, 122.64, 127.93, 129.47, 129.70, 130.35, 136.86, 148.88, 151.00, 151.55, 155.17, 155.98, 157.04, 158.59, 159.55, 159.95; HPLC (Method #1) 4.13 min retention time, (99%); MS (ES): m/z 529 $[M+H]^+$.

EXAMPLE 170

3-(1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yloxy)-3-oxopropanoic acid



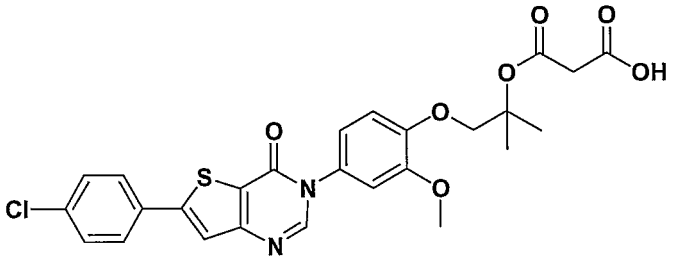
Part A. tert-Butyl 1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl malonate



[00142] A suspension of 6-(4-chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-methoxy-phenyl)-thieno[3,2-d]pyrimidin-4(3H)-one (100 mg; 0.219 mmol) (Example 82), 3-tert-butoxy-3-oxopropanoic acid (83 uL; 0.538 mmol), diisopropylcarbodiimide (83 uL; 0.538 mmol) and 4-N,N-dimethylaminopyridine (27 mg; 0.219 mmol) in 1 mL of CH_2Cl_2 was stirred at rt for 17 h. Additional 3-tert-butoxy-3-oxopropanoic acid (83 uL; 0.538 mmol) and diisopropylcarbodiimide (83 uL; 0.538 mmol) were added and the suspension stirred at rt for 3 h. The suspension was diluted with CH_2Cl_2, filtered and the filtrate washed with 1N HCl, saturated aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 1:1 gradient) to afford 104 mg (79%) of the title compound as a beige foam. ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.64 (s, 6H), 3.23 (s, 2H), 3.87 (s, 3H), 4.20 (s, 2H), 6.91 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.95 (d, J = 2.20 Hz, 1H), 7.02 (d, J = 8.24 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.37, 27.92, 44.04, 56.23, 74.44, 81.83, 82.01, 111.53, 114.75, 119.20, 120.87, 123.22, 127.65, 129.47,

130.51, 131.54, 135.67, 148.19, 149.30, 150.49, 151.63, 156.79, 157.40, 165.85, 166.20; HPLC (Method #1) 4.46 min retention time, (97%); MS (ES): m/z 599 $[M+H]^+$.

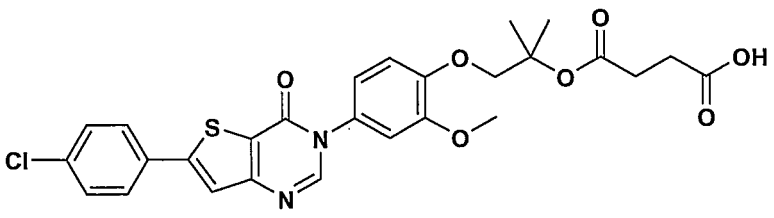
Part B. 3-(1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yloxy)-3-oxopropanoic acid



[00143] Following the procedure described in Example 169 Part B, the product of Part A was converted to the title compound. ^1H NMR ($CDCl_3$) δ 1.65 (s, 6H), 3.23 (s, 2H), 3.89 (s, 3H), 4.32 (s, 2H), 6.91-6.94 (m, 2H), 7.09 (d, J = 8.80 Hz, 1H), 7.45 (d, J = 8.24 Hz, 2H), 7.55 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.89, 42.14, 56.20, 75.00, 83.88, 111.58, 116.26, 119.60, 120.54, 122.82, 127.72, 129.52, 130.00, 131.32, 135.95, 148.09, 149.58, 150.82, 152.62, 157.40, 157.58, 166.43, 167.52; HPLC (Method #1) 4.22 min retention time; MS (ES): m/z 529 $[M+H]^+$.

EXAMPLE 171

4-(1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yloxy)-4-oxobutanoic acid

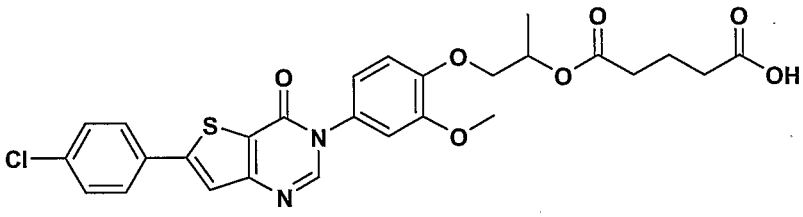


[00144] To a mixture of Example 82 (140 mg, 0.306 mmol) and DMAP (56 mg, 0.459 mmol.) in DMA (0.6 mL) at 140 °C was added succinic anhydride (183 mg, 1.83 mmol) over 5 hours. The reaction mixture was stirred at 140 °C for additional 2 h and was then cooled to room temperature. The mixture was diluted with DCM and was loaded onto a silica gel column. Elution with DCM to DCM:ACN:HOAc

(90:5:5) afforded partially purified product which was recrystallized from EtOH giving the title compound (90 mg, 53% yield) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ ppm 2.48 - 2.57 (m, 4 H), 3.90 (s, 3 H), 4.32 (s, 2 H), 6.89 - 6.96 (m, 2 H), 7.03 (d, *J*=8.14 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.45 (d, *J*=8.65 Hz, 2 H), 7.54 (s, 1 H), 7.66 (d, *J*=8.65 Hz, 2 H), 8.16 (s, 1 H). HPLC (Method #1) 4.71 min retention time; MS (ES): m/z 557 $[M+H]^+$.

EXAMPLE 172

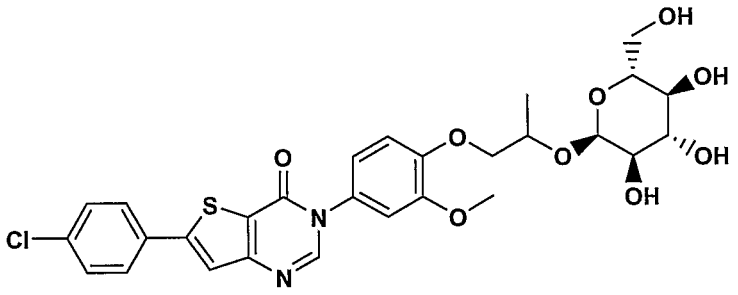
5-(1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)propan-2-yloxy)-5-oxopentanoic acid



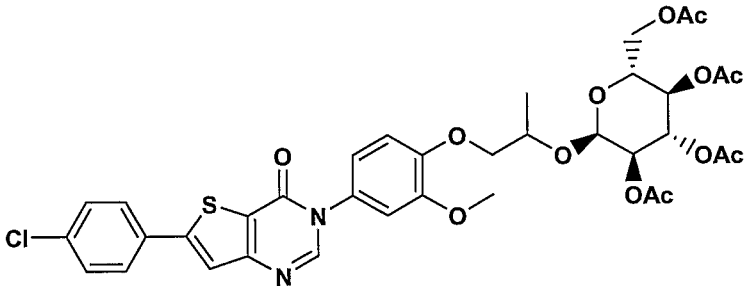
[00145] A solution of Example 104 (100 mg, 0.225 mmol) in DMF (1 mL) was added to a solution of sodium hydride (8.1 mg, 0.338 mmol) in DMF (2 mL). The reaction was stirred at room temperature for 30 minutes. Glutaric anhydride (129 mg, 1.128 mmol) was then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into a solution of 1.0N HCl (40 mL) and extracted with EtOAc (30 mL). The EtOAc layer was dried over sodium sulfate and concentrated. The crude product was purified by Prep-HPLC (ODS, water-MeOH_TFA 90:10:0.1 to 10:90:0.1 gradient) to give the title compound (114 mg, white solid). ^{1}H NMR ($CDCl_3$) δ ppm 1.81 - 1.92 (m, 2 H), 2.31 (q, 4 H), 3.89 (s, 3 H), 4.25 (s, 2 H), 6.88 - 6.96 (m, 2 H), 7.04 (d, *J*=8.65 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.45 (d, *J*=8.65 Hz, 2 H), 7.54 (s, 1 H), 7.66 (d, *J*=8.65 Hz, 2 H), 8.16 (s, 1 H); HPLC (Method #1) 3.50 min retention time; MS (ES): m/z 557 $[M+H]^+$.

EXAMPLE 173

6-(4-Chlorophenyl)-3-(3-methoxy-4-(2-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)propoxy)phenyl)thieno[3,2-d]pyrimidin-4(3H)-one

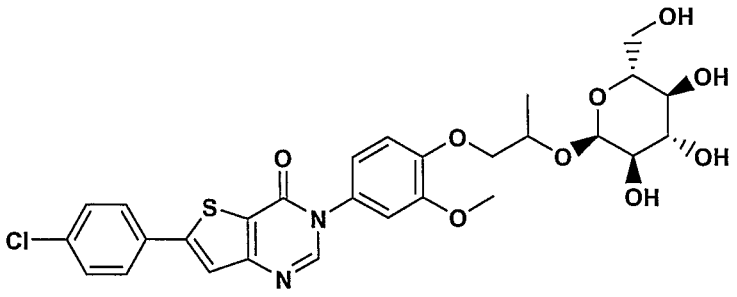


Part A.



[00146] To a mixture of Example 104 (100 mg, 0.225 mmol), silver carbonate (311 mg, 1.12 mmol) and 4 Å molecular sieves (500 mg) in chloroform (7 mL) was slowly added a solution of acetobromo-a-D-glucose (232 mg, 0.564 mmol) in chloroform (3 mL). The reaction mixture was stirred at reflux for 48 hours. The precipitated material was filtered and the filtrate was concentrated and subjected to ISCO flash chromatography (silica gel/hexane-EtOAc 100:0 to 0:100 gradient) to give the title compound (139 mg, 80% yield) as a brown gum.

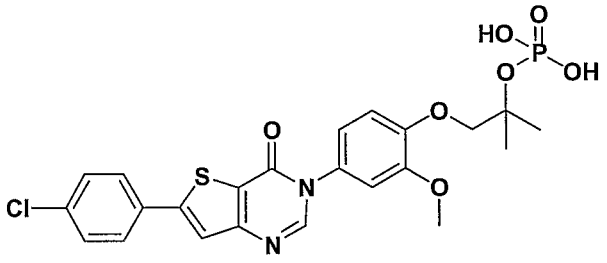
Part B.



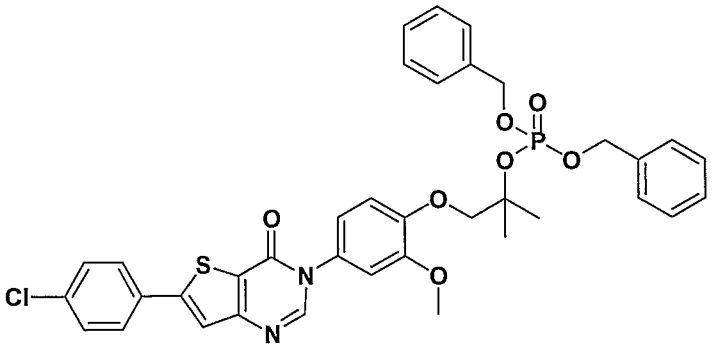
[00147] Sodium (75 mg, 3.12 mmol) was added to MeOH (3 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The NaOMe solution thus prepared was then added to a solution of compound A (60 mg, 0.077 mmol) in MeOH (1 mL). The reaction was stirred at room temperature for 1.5 hour. The mixture was then concentrated and the residue was dissolved in water (10 mL) and loaded onto an ODS column (10 g). The column was initially eluted with water and then with 100% water to 100% MeOH gradient to give the title compound (39 mg, 83% yield) as a white solid. ^{1}H NMR (MeOD) δ ppm 1.20 - 1.32 (m, 3 H), 3.06 - 3.15 (m, 1 H), 3.24 - 3.32 (m, 1 H), 3.52 - 3.63 (m, 1 H), 3.68 - 3.82 (m, 5 H), 3.90 - 4.04 (m, 2 H), 4.11 - 4.30 (m, 2 H), 4.33 - 4.59 (m, 1 H), 6.88 - 6.95 (m, 1 H), 7.02 - 7.10 (m, 2 H), 7.39 - 7.45 (m, 2 H), 7.59 - 7.64 (m, 1 H), 7.69 - 7.76 (m, 2 H), 8.22 - 8.29 (m, 1 H); HPLC (Method #2) 2.65 min retention time; MS (ES): m/z 605 $[M+H]^+$.

EXAMPLE 174

1-(4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl dihydrogen phosphate

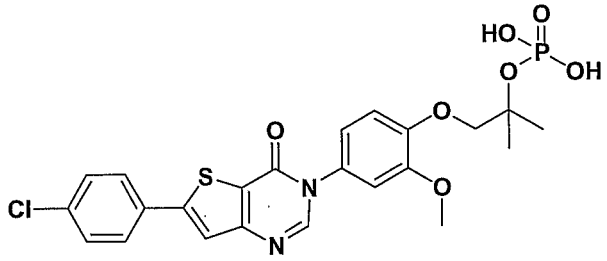


Part A. Dibenzyl 1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl phosphate



[00148] A suspension of 6-(4-chlorophenyl)-3-(4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (Example 82) (3.00 g; 6.56 mmol), 1,2,4-triazole (1.36 g; 19.7 mmol) and dibenzyl N,N-diisopropylphosphoramidite (6.62 mL; 19.7 mmol) in 40 mL of CH_2Cl_2 was heated at reflux for 16 h. The solution was cooled to rt, 30% H_2O_2 in water (4.00 mL; 35.3 mmol) was added and the solution stirred at rt for 2.5 h. The solution was diluted with CH_2Cl_2, washed with 1M sodium metabisulfite, 1N HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Hexanes/EtOAc; 100:0 to 0:100 gradient) to afford 3.79 g (80%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 6H), 3.75 (s, 3H), 4.07 (s, 2H), 5.04-5.06 (m, 4H), 6.87-6.96 (m, 3H), 7.29-7.35 (m, 10H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.25 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.56, 25.04, 56.08, 68.98, 69.03, 75.36, 82.87, 111.30, 113.91, 119.15, 120.87, 127.42, 127.67, 127.88, 128.33, 128.48, 129.47, 130.33, 131.54, 135.69, 136.07, 148.19, 149.10, 150.19, 151.63, 156.79, 157.37; HPLC (Method #1) 4.85 min retention time, (100%); MS (ES): m/z 717 $[M+H]^+$.

Part B.



[00149] A solution of dibenzyl 1-(4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)-2-methylpropan-2-yl phosphate (166 mg; 0.231 mmol) in 2 mL of TFA and 0.11 mL of water was stirred at rt for 2 h. The solution was diluted with methanol and concentrated under reduced pressure. The residue was purified by prep HPLC to afford 59 mg (48%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.52 (s, 6H), 3.79 (s, 3H), 4.03 (s, 2H), 7.04-7.12 (m, 2H), 7.20 (s, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.91 (d, J = 8.80 Hz, 2H), 7.96 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.00, 56.42, 75.75, 79.18, 112.54, 113.80, 120.13, 122.12, 122.40, 128.25, 129.66, 130.47, 131.61, 134.67, 148.84, 149.52,

149.88, 150.18, 156.48, 157.82; HPLC (Method #1) 3.73 min retention time, (98%); MS (ES): m/z 537 $[M+H]^+$.

EXAMPLES 175 TO 207

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
175	104	L-alanine ester	514	2.91 Method # 1	^{1}H NMR (DMSO-d_6) δ 1.34 (d, 3H), 1.37-1.41 (m, 3H), 3.77 (d, 3H), 4.08-4.25 (m, 3H), 5.25-5.32 (m, 1H), 7.06 (d, 1H), 7.15 (d, 1H), 7.22-7.23 (m, 1H), 7.58 (d, J = 8.80 Hz, 2H), 7.92 (d, J = 8.25 Hz, 2H), 7.98 (s, 1H), 8.32 (br s, 3H), 8.39 (s, 1H)
176	104	761232 D-valine	542	Method # 1	^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.59 Hz, 3H), 1.00 (d, J = 7.15 Hz, 3H), 1.40 (d, J = 6.60 Hz, 3H), 1.45 (br s, 2H), 2.01-2.09 (m, 1H), 3.30 (d, J = 4.49 Hz, 1H), 3.87 (s, 3H), 4.08-4.19 (m, 2H), 5.35-5.39 (m, 1H), 6.92 (dd, J = 8.24 Hz, 2.19 Hz, 1H), 6.96 (d, J = 2.75 Hz, 1H), 7.03 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.24 Hz, 2H), 8.13 (s, 1H)
177	104	α-Me -Ala ester	528	2.92 Method # 1	^{1}H NMR (DMSO-d_6) δ 1.34 (d, J = 6.60 Hz, 3H), 1.43 (s, 3H), 1.45 (s, 3H), 3.76 (s, 3H), 4.09-4.14 (m, 1H), 4.23-4.26 (m, 1H), 5.27-5.31 (m, 1H), 7.06 (dd, J = 8.79 Hz, 2.64 Hz, 1H), 7.16 (d, J = 8.79 Hz, 1H), 7.22 (d, J = 2.19 Hz, 1H), 7.58 (d, J = 8.79 Hz, 2H), 7.93 (d, J = 8.35 Hz, 2H), 7.99 (s, 1H), 8.33 (br s, 2H), 8.38 (s, 1H)
178	104	L-lysine ester	571	2.40 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.25-1.84 (m, 13H), 2.63-2.72 (m, 2H), 3.43-3.47 (m, 1H), 3.87 (s, 3H), 4.02-4.18 (m, 2H), 5.33-5.41 (m, 1H), 6.92-7.04 (m, 3H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.25 Hz, 2H), 8.14 (d, 1H)
179	104	L-aspartate ester	558	2.89 Method # 1	^{1}H NMR (DMSO-d_6) δ 1.15-1.25 (m, 3H), 1.79 (br s, 1H), 1.96-2.00 (m, 1H), 2.41-2.75 (m, 3H), 3.70 (s, 3H), 3.78-4.35 (m, 3H), 5.04-5.15 (m, 1H), 6.97 (dd, J = 8.25 Hz, 1.65 Hz, 1H), 7.03-7.08 (m, 1H), 7.14 (s, 1H), 7.50 (d, J = 8.80 Hz, 2H), 7.86 (d, J = 8.25 Hz, 2H), 7.91 (s, 1H), 8.32 (s, 1H)
180	104	L-glutamate ester	558	2.89 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.25-1.46 (m, 4H), 2.23 (br s, 2H), 2.63 (br s, 2H), 3.79 (d, 3H), 4.14-4.24 (m, 3H), 5.41-5.47 (m, 1H), 6.90-7.02 (m, 3H), 7.42 (d, 2H), 7.60 (d, 3H), 8.11 (br s, 2H), 8.56 (s, 1H)

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
181	104	Glycine ester	500	3.00 Method # 1	^{1}H NMR ($CDCl_3$+CD_3OD) δ 1.42 (d, J = 6.60 Hz, 3H), 3.72-3.79 (m, 2H), 3.87 (s, 3H), 4.17 (d, J = 4.95 Hz, 2H), 5.40-5.44 (m, 1H), 6.97 (dd, J = 8.80 Hz, 2.75 Hz, 1H), 7.05 (d, J = 2.20 Hz, 1H), 7.09 (d, J = 8.80 Hz, 1H), 7.45 (d, J = 8.25 Hz, 2H), 7.60 (S, 1H), 7.71 (d, J = 8.80 Hz, 2H), 8.25 (s, 1H)
182	104	Phe ester	590	3.26 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.32-1.40 (m, 3H), 1.48 (br s, 2H), 2.88-3.11 (m, 2H), 3.72-3.78 (m, 1H), 3.85 (d, 3H), 4.00-4.16 (m, 2H), 5.32-5.36 (m, 1H), 6.91-7.02 (m, 3H), 7.21-7.36 (m, 5H), 7.44 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.12 (s, 1H)
183	104	Proline ester	540	2.99 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 6.05 Hz, 3H), 1.71-1.95 (m, 3H), 2.08-2.19 (m, 2H), 2.89-2.95 (m, 1H), 3.06-3.13 (m, 1H), 3.76-3.80 (m, 1H), 3.87 (d, 3H), 4.08-4.18 (m, 2H), 5.33-5.41 (m, 1H), 6.92-7.05 (m, 3H), 7.45 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.13 (d, 1H)
184	104	Leu ester	556	3.23 Method # 1	^{1}H NMR ($CDCl_3$) δ 0.91-0.96 (m, 6H), 1.39-1.47 (m, 6H), 1.54-1.62 (m, 1H), 1.77-1.85 (m, 1H), 3.45-3.50 (m, 1H), 3.87 (d, 3H), 4.07-4.19 (m, 2H), 5.32-5.38 (m, 1H), 6.92-7.05 (m, 3H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)
185	104	'634 Half oxalate ester acid	515	4.49	^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.49 (m, 3H), 3.84 (m, 3H), 4.14-4.24 (m, 2H), 5.41-5.45 (m, 1H), 6.92-7.08 (m, 3H), 7.41-7.44 (m, 2H), 7.53 (m, 1H), 7.65-7.68 (m, 2H), 8.18 (m, 1H)
186	104	'634 Half malonate ester acid	529	4.22	^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.43 (m, 3H), 3.41 (m, 2H), 3.90 (m, 3H), 4.13-4.23 (m, 2H), 5.34-5.41 (m, 1H), 6.96-7.13 (m, 3H), 7.46-7.51 (m, 2H), 7.59 (m, 1H), 7.70-7.74 (m, 2H), 8.23 (m, 1H)
187	104	'634 Half succinate ester	543	3.47***	^{1}H NMR (THF-D8) δ ppm 1.35 (d, 3 H), 2.42 - 2.51 (m, 4 H), 3.81 - 3.88 (m, 3 H), 4.01 - 4.16 (m, 2 H), 4.67 - 4.76 (m, 1 H), 5.19 - 5.29 (m, 1 H), 6.93 - 6.99 (m, 1 H), 7.05 - 7.13 (m, 2 H), 7.47 - 7.53 (m, 2 H), 7.67 - 7.73 (m, 1 H), 7.78 - 7.87 (m, 2 H), 8.16 - 8.23 (m, 1 H)

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
188	105	L-valine ester	542	2.84 Method # 1	^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.59 Hz, 3H), 1.00 (d, J = 7.15 Hz, 3H), 1.40 (d, J = 6.60 Hz, 3H), 1.45 (br s, 2H), 2.01-2.09 (m, 1H), 3.30 (d, J = 4.49 Hz, 1H), 3.87 (s, 3H), 4.08-4.19 (m, 2H), 5.35-5.39 (m, 1H), 6.92 (dd, J = 8.24 Hz, 2.19 Hz, 1H), 6.96 (d, J = 2.75 Hz, 1H), 7.03 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.24 Hz, 2H), 8.13 (s, 1H)
189	105	$OPO(OH)_2$	523	3.70 Method # 1	^{1}H NMR (DMSO-d_6) δ 1.35 (d, J = 6.05 Hz, 3H), 3.79 (s, 3H), 4.01-4.13 (m, 2H), 4.55 (br s, 1H), 7.03 (dd, J = 8.25 Hz, 1.10 Hz, 1H), 7.13 (d, J = 8.24 Hz, 1H), 7.20 (s, 1H), 7.57 (d, J = 8.25 Hz, 2H), 7.91 (d, J = 8.25 Hz, 2H), 7.96 (s, 1H), 8.39 (s, 1H)
190	106	L-valine ester	542	2.78 Method # 1	^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7.15 Hz, 3H), 1.00 (d, J = 6.60 Hz, 3H), 1.40 (d, J = 6.60 Hz, 3H), 1.50 (br s, 2H), 2.01-2.09 (m, 1H), 3.31 (d, J = 4.95 Hz, 1H), 3.86 (s, 3H), 4.06-4.16 (m, 2H), 5.34-5.42 (m, 1H), 6.92 (dd, J = 8.25 Hz, 2.20 Hz, 1H), 6.96 (d, J = 2.20 Hz, 1H), 7.02 (d, J = 8.79 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)
191	82	L-alanine ester	528	3.03 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 7.03 Hz, 3H), 1.53 (br s, 2H), 1.62 (s, 6H), 3.43-3.49 (m, 1H), 3.87 (s, 3H), 4.20-4.25 (m, 2H), 6.92 (dd, J = 8.35 Hz, 2.64 Hz, 1H), 6.95 (d, J = 2.20 Hz, 1H), 7.00 (d, J = 8.35 Hz, 1H), 7.44 (d, J = 8.35 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.35 Hz, 2H), 8.13 (s, 1H)
192	82	L-valine ester	556	3.15 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.05-1.08 (m, 6H), 1.61 (s, 3H), 1.65 (s, 3H), 2.33-2.36 (m, 1H), 3.75 (br d, 1H), 3.84 (s, 3H), 4.21-4.30 (m, 2H), 6.92-6.93 (m, 2H), 7.00 (d, J = 8.25 Hz, 1H), 7.44 (d, J = 8.79 Hz, 2H), 7.58 (s, 1H), 7.64 (d, J = 8.80 Hz, 2H), 7.86 (br s, 2H), 8.37 (s, 1H)
193	82	Glycine ester	514	3.69 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.42 (br s, 2H), 1.62 (s, 6H), 3.34 (s, 2H), 3.87 (s, 3H), 4.23 (s, 2H), 6.91 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.95 (d, J = 2.75 Hz, 1H), 7.01 (d, J = 8.24 Hz, 1H), 7.43 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
194	82	Phe ester	604	3.34 Method # 1	^{1}H NMR ($CDCl_3$) δ 1.59 (s, 6H), 1.70 (s, 2H), 2.84-2.89 (m, 1H), 3.05-3.10 (m, 1H), 3.64-3.67 (m, 1H), 3.83 (s, 3H), 4.14-4.19 (m, 2H), 6.91-6.99 (m, 3H), 7.21-7.30 (m, 5H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.24 Hz, 2H), 8.12 (s, 1H)
195	82	'482 Half glutarate ester acid	571	4.82 Method # 1	^{1}H NMR ($CDCl_3$) δ ppm 1.81 - 1.92 (m, 2 H), 2.31 (q, 4 H), 3.89 (s, 3 H), 4.25 (s, 2 H), 6.88 - 6.96 (m, 2 H), 7.04 (d, *J*=8.65 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.45 (d, *J*=8.65 Hz, 2 H), 7.54 (s, 1 H), 7.66 (d, *J*=8.65 Hz, 2 H), 8.16 (s, 1 H)
196	83	Glycine ester	502	2.91 Method #1	^{1}H NMR ($CDCl_3$) δ 1.54 (br s, 2H), 1.62 (s, 6H), 3.37 (s, 2H), 4.28 (s, 2H), 7.09-7.16 (m, 2H), 7.22-7.25 (m, 1H), 7.45 (d, J = 8.25 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.80 Hz, 2H), 8.10 (s, 1H)
197	84	Glycine ester	498	3.05 Method #1	^{1}H NMR ($CDCl_3$) δ 1.54 (br s, 2H), 1.63 (s, 6H), 2.29 (s, 3H), 3.38 (s, 2H), 4.19 (s, 2H), 6.92 (d, J = 8.35 Hz, 1H), 7.18-7.21 (m, 2H), 7.44 (d, J = 8.35 Hz, 2H), 7.52 (s, 1H), 7.66 (d, J = 8.79 Hz, 2H), 8.11 (s, 1H)
198	85	Glycine ester	518	3.13 Method #1	^{1}H NMR ($CDCl_3$) δ 1.53 (br s, 2H), 1.64 (s, 6H), 3.39 (s, 2H), 4.28 (s, 2H), 7.05 (d, J = 8.80 Hz, 1H), 7.29 (dd, J = 8.80 Hz, 2.20 Hz, 1H), 7.45 (d, J = 8.79 Hz, 2H), 7.48 (d, J = 2.20 Hz, 1H), 7.53 (s, 1H), 7.65 (d, J = 8.80 Hz, 2H), 8.09 (s, 1H)
199	86	Glycine ester	484	2.83 Method #1	^{1}H NMR ($CDCl_3$) δ 1.54 (br s, 2H), 1.61 (s, 6H), 3.37 (s, 2H), 4.19 (s, 2H), 7.06 (d, J = 8.79 Hz, 2H), 7.34 (d, J = 8.79 Hz, 2H), 7.44 (d, J = 8.24 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.24 Hz, 2H), 8.12 (s, 1H)
200	148	L-Valine ester	5.96	3.23 Method #1	^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.59 Hz, 3H), 1.02 (d, J = 7.15 Hz, 3H), 1.58 (br s, 2H), 2.07-2.15 (m, 1H), 3.41 (d, J = 4.39 Hz, 1H), 3.87 (s, 3H), 4.31-4.49 (m, 2H), 5.79-5.87 (m, 1H), 6.94 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.99 (d, J = 2.20 Hz, 1H), 7.06 (d, J = 8.79 Hz, 1H), 7.45 (d, J = 8.79 Hz, 2H), 7.53 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
201	139	bis-L-Valine ester	657	2.13 Method # 1	^{1}H NMR ($CDCl_3$) δ 0.90-1.02 (m, 12H), 1.55 (br s, 4H), 1.98-2.11 (m, 2H), 3.30-3.36 (m, 2H), 3.86 (d, 3H), 4.23-4.26 (m, 2H), 4.35-4.41 (m, 1H), 4.57-4.64 (m, 1H), 5.50-5.51 (m, 1H), 6.93 (dd, J = 8.24 Hz, 2.20 Hz, 1H), 6.97 (d, J = 2.20 Hz, 1H), 7.03-7.05 (m, 1H), 7.45 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.80 Hz, 2H), 8.13 (s, 1H)
202	161	Glycine ester	512	6.96 Method #6	^{1}H NMR NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.54 (s, 1H)., 7.45 (d, *J* = 8.6 Hz, 2H), 7.28 (m, 1H), 6.91 (m + s, 2H), 3.86 (s, 3H), 3.32 (s, 2H), 2.70 (m, 2H), 2.09 (m, 2H), 1.55 (s, 6H)
203	158	L-Valine ester	558	3.13 Method #1	^{1}H NMR ($CDCl_3$) δ 0.89-0.94 (m, 3H), 0.97-1.02 (m, 3H), 1.39-1.41 (m, 3H), 1.55 (br s, 2H), 1.98-2.12 (m, 1H), 2.98-3.05 (m, 1H), 3.20-3.30 (m, 2H), 3.93 (s, 3H), 5.08-5.17 (m, 1H), 6.96-6.99 (m, 2H), 7.44 (d, J = 8.79 Hz, 2H), 7.51-7.53 (m, 2H), 7.65 (d, J = 8.79 Hz, 2H), 8.14 (s, 1H)
204	160	L-Valine ester	540	3.18 Method # 1	^{1}H NMR ($CDCl_3$) δ 0.92-1.04 (m, 6H), 1.29-1.31 (m, 3H), 1.54 (br s, 2H), 1.79-2.15 (m, 3H), 2.62-2.79 (m, 2H), 3.28-3.31 (m, 1H), 3.85 (s, 3H), 4.99-5.06 (m, 1H), 6.90-6.92 (m, 2H), 6.26 (d, J = 8.24 Hz, 1H), 7.43 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.14 (d, 1H)
205	159	L-Valine ester	528	3.50 Method #1	^{1}H NMR ($CDCl_3$) δ 0.89-0.94 (m, 3H), 0.97-1.02 (m, 3H), 1.39-1.41 (m, 3H), 1.56 (br s, 2H), 1.98-2.11 (m, 1H), 3.02-3.09 (m, 1H), 3.20-3.30 (m, 2H), 5.11-5.17 (m, 1H), 7.37 (d, J =8.25 Hz, 2H), 7.44 (d, J = 8.24 Hz, 2H), 7.52-7.55 (m, 3H), 7.65 (d, J = 8.24 Hz, 2H), 8.12 (s, 1H)
206	152	L-Valine ester	610	3.15 Method #1	^{1}H NMR ($CDCl_3$) δ 0.090 (t, 3H), 1.00 (t, 3H), 1.51 (br s, 2H), 2.02-2.14 (m, 1H), 2.68-2.78 (m, 2H), 3.33-3.35 (m, 1H), 3.87 (d, 3H), 4.19 (t, 2H), 5.51-5.60 (m, 1H), 6.92-6.94 (m, 1H), 6.98 (d, J = 2.20 Hz, 1H), 7.02-7.05 (m, 1H), 7.45 (d, J = 8.24 Hz, 2H), 7.53 (s, 1H), 7.66 (d, J = 8.25 Hz, 2H), 8.13 (s, 1H)

Example #	Prodrug of Example #	Prodrug	Mass spec M+H	HPLC retention (min)	H NMR
207	153	L-Valine ester	560	3.27	^{1}H NMR ($CDCl_3$) δ 0.090-1.02 (m, 6H), 1.52 (br s, 2H), 2.03-2.13 (m, 1H), 3.37-3.41 (m, 1H), 3.87 (d, 3H), 4.26-4.29 (m, 2H), 4.65-4.84 (m, 2H), 5.42-5.50 (m, 1H), 6.92-7.07 (m, 3H), 7.44 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.79 Hz, 2H), 8.13 (s, 1H)

BIOLOGICAL EVALUATION

Radioligand Binding Assay for Assessment of MCHR1 Activity

[00150] Membranes from stably transfected HEK-293 cells expressing a mutated (E4Q, A5T) hMCHR1 receptor were prepared by dounce homogenization and differential centrifugation. Binding experiments were carried out with 0.5 -1.0 ug of membrane protein incubated in a total of 0.2 ml in 25 mM HEPES (pH 7.4) with 10 mM $MgCl_2$, 2 mM EGTA, and 0.1% BSA (Binding Buffer) for 90 min. For competition binding assays, reactions were carried out in the presence of with 0.06 - 0.1 nM [Phe^{13}, [^{125}I]Tyr^{19}]-MCH and increasing concentrations of unlabeled test molecules. Reactions were terminated by rapid vacuum filtration over 96 well-GFC Unifilter plates pre-coated with 0.075 ml binding buffer containing 1% BSA, and washed 3 times with 0.4 ml of Phospho-buffered Saline (pH 7.4) containing 0.01% TX-100. Filters were dried, 0.05 ml microscint 20 was added to each well and radioactivity was subsequently quantified by scintillation counting on a TopCount™ microplate scintillation counter (Packard). Inhibitory constants were determined by nonlinear least squares analysis using a four parameter logistic equation.

UTILITIES AND COMBINATIONS

Utilities

[00151] The compounds of the present application can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to metabolic and eating disorders as well as conditions associated with metabolic disorders (e.g., obesity, diabetes, arteriosclerosis, hypertension, polycystic ovary disease, cardiovascular disease, osteoarthritis, dermatological disorders, impaired glucose hemostasis, insulin

resistance, hypercholesterolemia, hypertriglyceridemia, choletithiasis, dislipidemic conditions, bulimia nervosa and compulsive eating disorders); sleep disorders; and psychiatric disorders, such as depression, anxiety, schizophrenia, substance abuse, cognition-enhancement and Parkinson's disease.

[00152] The compounds described in the present application could be used to enhance the effects of cognition-enhancing agents, such as acetylcholinesterase inhibitors (e.g., tacrine), muscarinic receptor-1 agonists (e.g., milameline), nicotinic agonists, glutamic acid receptor (AMPA and NMDA) modulators, and nootropic agents (e.g., piracetam, levetiracetam). Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present application include donepezil, tacrine, revastigraine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

[00153] The compounds described in the present application could be used to enhance the effects of agents used in the treatment of Parkinson's Disease. Examples of agents used to treat Parkinson's Disease include: levadopa with or without a COMT inhibitor, antiglutamatergic drugs (amantadine, riluzole), alpha-2 adrenergic antagonists such as idazoxan, opiate antagonists, such as naltrexone, other dopamine agonists or transportor modulators, such as ropinirole, or pramipexole or neurotrophic factors such as glial derived neurotrophic factor (GDNF).

Combinations

[00154] The present application includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present application can be used alone, in combination with other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-obesity agents; anti-diabetic agents, appetite suppressants; cholesterol/lipid-lowering agents, HDL-raising agents, cognition enhancing agents, agents used to treat neurodegeneration, agents used to treat respiratory conditions, agents used to treat bowel disorders, anti-inflammatory

agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; cardiac glycosides; and anti-tumor agents.

[00155] Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the melanin-concentrating hormone receptor (MCHR) antagonists in accordance with the application.

[00156] Examples of suitable anti-obesity agents for use in combination with the compounds of the present application include melanocortin receptor (MC4R) agonists, cannabinoid receptor modulators, growth hormone secretagogue receptor (GHSR) antagonists, galanin receptor modulators, orexin antagonists, CCK agonists, GLP-1 agonists, and other Pre-proglucagon-derived peptides; NPY1 or NPY5 antagonsist, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H3) modulators, aP2 inhibitors, PPAR gamma modulators, PPAR delta modulators, acetyl-CoA carboxylase (ACC) inhibitors, 11-β-HSD-1 inhibitors, adinopectin receptor modulators; beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a thyroid receptor beta modulator, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and WO 00/039077 (KaroBio), a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), serotonin receptor agonists, (e.g., BVT-933 (Biovitrum)), monoamine reuptake inhibitors or releasing agents, such as fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol, anorectic agents such as topiramate (Johnson & Johnson), CNTF (ciliary neurotrophic factor) /Axokine® (Regeneron), BDNF (brain-derived neurotrophic factor), leptin and leptin receptor modulators, or cannabinoid-1 receptor antagonists, such as SR-141716 (Sanofi) or SLV-319 (Solvay).

[00157] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present application include: insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, aldose reductase inhibitors, PPAR γ agonists such as thiazolidinediones, PPAR α

agonists (such as fibric acid derivatives), PPAR δ antagonists or agonists, PPAR α/γ dual agonists, 11-β-HSD-1 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors including tapagliflozin and seraglifozin, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1), GLP-1 agonist, and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor).

[00158] The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl. Where the antidiabetic agent is a biguanide, the compounds of the present application will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

[00159] The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the beta-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms. The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

[00160] The compounds of the present application may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

[00161] The compounds of the present application may be employed with a PPARα/γ dual agonist such as MK-767/KRP-297 (Merck/Kyorin; as described in , K. Yajima, et. al., *Am. J. Physiol. Endocrinol. Metab.*, 284: E966-E971 (2003)), AZ-242

(tesaglitazar; Astra-Zeneca; as described in B. Ljung, et. al., *J. Lipid Res.*, 43, 1855-1863 (2002)); muraglitazar; or the compounds described in US patent 6,414,002.

[00162] The compounds of the present application may be employed in combination with anti-hyperlipidemia agents, or agents used to treat arteriosclerosis. An example of an hypolipidemic agent would be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pitavastatin (Nissan/Sankyo's nisvastatin (NK-104) or itavastatin), disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca rosuvastatin (visastatin (ZD-4522)) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent Nos. 5,506,219 and 5,691,322. In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

[00163] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller, et al., *J. Med. Chem.*, 31, 1869-1871 (1998) including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., *Current Pharmaceutical Design*, 2, 1-40 (1996).

[00164] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano, et al., *J. Med. Chem.*, 20, 243-249 (1977), the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, *J. Am. Chem. Soc.*, 98, 1291-1293 (1976), phosphinylphosphonates reported by McClard, R.W. et al., *J. Am. Chem. Soc.*, 109, 5544 (1987) and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

[00165] Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (SECHOLEX, POLICEXIDE) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[00166] The other hypolipidemic agent may be an ACAT inhibitor (which also has anti-atherosclerosis activity) such as disclosed in, *Drugs of the Future*, 24, 9-15

(1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al., *Atherosclerosis* (Shannon, Irel), 137 (1), 77-85 (1998); "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, *Cardiovasc. Drug Rev.*, 16 (1), 16-30 (1998); "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al., *Bioorg. Med. Chem. Lett*, 6 (1), 47-50 (1996); "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al., Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., *Inflammation: Mediators Pathways*, 173-98 (1995), Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al., *Curr. Med. Chem.*, 1 (3), 204-25 (1994); "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)-methyl]ureas with enhanced hypocholesterolemic activity", Stout et al., *Chemtracts: Org. Chem.*, 8 (6), 359-62 (1995), or TS-962 (Taisho Pharmaceutical Co. Ltd), as well as F-1394, CS-505, F-12511, HL-004, K-10085 and YIC-C8-434.

[00167] The hypolipidemic agent may be an upregulator of LDL receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly). The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 (ezetimibe) as well as those disclosed in *Atherosclerosis* 115, 45-63 (1995) and *J. Med. Chem.* 41, 973 (1998).

[00168] The other lipid agent or lipid-modulating agent may be a cholesteryl transfer protein inhibitor (CETP) such as Pfizer's CP-529,414 as well as those disclosed in WO/0038722 and in EP 818448 (Bayer) and EP 992496, and Pharmacia's SC-744 and SC-795, as well as CETi-1 and JTT-705.

[00169] The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999). The ATP citrate lyase inhibitor which may be employed in the combination of the application may include, for example, those disclosed in U.S. Patent No. 5,447,954.

[00170] The other lipid agent also includes a phytoestrogen compound such as disclosed in WO 00/30665 including isolated soy bean protein, soy protein concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycitein or equol, or phytosterols, phytostanol or tocotrienol as disclosed in WO 2000/015201; a beta-lactam cholesterol absorption inhibitor such as disclosed in EP 675714; an HDL upregulator such as an LXR agonist, a PPAR α-agonist and/or an FXR agonist; an LDL catabolism promoter such as disclosed in EP 1022272; a sodium-proton exchange inhibitor such as disclosed in DE 19622222; an LDL-receptor inducer or a steroidal glycoside such as disclosed in U.S. Patent No. 5,698,527 and GB 2304106; an anti-oxidant such as beta-carotene, ascorbic acid, α-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E; isoniazid as disclosed in WO 97/35576; a cholesterol absorption inhibitor, an HMG-CoA synthase inhibitor, or a lanosterol demethylase inhibitor as disclosed in WO 97/48701; a PPAR δ agonist for treating dyslipidemia; or a sterol regulating element binding protein-I (SREBP-1) as disclosed in WO 2000/050574, for example, a sphingolipid, such as ceramide, or neutral sphingomyelenase (N-SMase) or fragment thereof. Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, pitavastatin and rosuvastatin, as well as niacin and/or cholestagel.

[00171] The compounds of the present application may be employed in combination with anti-hypertensive agents. Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present application include beta adrenergic blockers, calcium channel blockers (L-type and/or T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and

compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[00172] MCHR1 antagonists could be useful in treating other diseases associated with obesity, including sleep disorders. Therefore, the compounds described in the present application could be used in combination with therapeutics for treating sleep disorders. Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present application include melatonin analogs, melatonin receptor antagonists, ML 1 B agonists, GABA receptor modulators; NMDA receptor modulators, histamine-3 (H3) receptor modulators, dopamine agonists and orexin receptor modulators.

[00173] MCHR1 antagonists may reduce or ameliorate substance abuse or addictive disorders. Therefore, combination of cannabinoid receptor modulators with agents used to treat addictive disorders may reduce the dose requirement or improve the efficacy of current addictive disorder therapeutics. Examples of agents used to treat substance abuse or addictive disorders are: selective serotonin reuptake inhibitors (SSRI), methadone, buprenorphine, nicotine and bupropion.

[00174] MCHR1 antagonists may reduce anxiety or depression; therefore, the compounds described in this application may be used in combination with anti-anxiety agents or antidepressants. Examples of suitable anti-anxiety agents for use in combination with the compounds of the present application include benzodiazepines (e.g., diazepam, lorazepam, oxazepam, alprazolam, chlordiazepoxide, clonazepam, chlorazepate, halazepam and prazepam), 5HT1A receptor agonists (e.g., buspirone, flesinoxan, gepirone and ipsapirone), and corticotropin releasing factor (CRF) antagonists.

[00175] Examples of suitable classes of anti-depressants for use in combination with the compounds of the present application include norepinephrine reuptake inhibitors (tertiary and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine, paroxetine and sertraline), monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, tranylcypromine, selegiline), reversible inhibitors of monoamine oxidase (RIMAs) (moclobemide), serotonin and

norepinephrine reuptake inhibitors (SNRIs) (venlafaxine), corticotropin releasing factor (CRF) receptor antagonists, alpah-adrenoreceptor antagonists, and atypical antidepressants (bupropion, lithium, nefazodone, trazodone and viloxazine).

[00176] The combination of a conventional antipsychotic drug with a MCHR1 antagonist could also enhance symptom reduction in the treatment of psychosis or mania. Further, such a combination could enable rapid symptom reduction, reducing the need for chronic treatment with antipsychotic agents. Such a combination could also reduce the effective antipsychotic dose requirement, resulting in reduced probability of developing the motor dysfunction typical of chronic antipsychotic treatment.

[00177] Examples of suitable antipsychotic agents for use in combination with the compounds of the present application include the phenothiazine (chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine), thioxanthine (chlorprothixene, thiothixene), heterocyclic dibenzazepine (clozapine, olanzepine and aripiprazole), butyrophenone (haloperidol), dipheyylbutylpiperidine (pimozide) and indolone (molindolone) classes of antipsychotic agents. Other antipsychotic agents with potential therapeutic value in combination with the compounds in the present application include loxapine, sulpiride and risperidone.

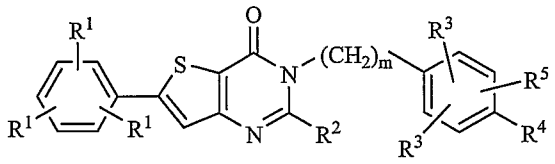
[00178] Combination of the compounds in the present application with conventional antipsychotic drugs could also provide an enhanced therapeutic effect for the treatment of schizophrenic disorders, as described above for manic disorders. As used here, schizophrenic disorders include paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform disorder, shcizoaffective disorder, delusional disorder, brief psychotic disorder and psychotic disorder not specified. Examples of suitable antipsychotic drugs for combination with the compounds in the present application include the antipsychotics mentioned above, as well as dopamine receptor antagonists, muscarinic receptor agonists, 5HT2A receptor antagonists and 5HT2A/dopamine receptor antagonists or partial agonists (e.g., olanzepine, aripiprazole, risperidone, ziprasidone).

[00179] It should be understood that while this application has been described herein in terms of specific embodiments set forth in detail, such embodiments are

presented by way of illustration of the general principles of the application, and the application is not necessarily limited thereto. Certain modifications and variations in any given material, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present application, and all such modifications and variations should be considered within the scope of the claims that follow.

WHAT IS CLAIMED IS:

1. A compound or a pharmaceutically acceptable salt or a stereoisomer or a prodrug or a solvate thereof according to Formula I:



I

wherein,

R^1 is independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, aryl, CF_3, CN, NR^7R^7, OR^6 and SR^6;

R^2 is selected from the group consisting of hydrogen and lower alkyl;

R^3 is independently selected from the group consisting of hydrogen and lower alkyl;

R^4 is selected from the group consisting of hydroxyl or $G\text{-}D^2\text{-}Z_n$, wherein R^4 and R^5 may be taken together to form a ring of 4 to 7 atoms;

R^5 is selected from the group consisting of hydrogen, hydroxyl, halogen, lower alkyl, lower cycloalkyl, CF_3, SR^6, lower alkoxy, lower cycloalkoxy, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^7SO_2R^6$ and COR^6;

m is an integer from 0 to 1;

n is an integer from 1 to 3;

G is selected from the group consisting of a direct bond, O, S and CR^7R^7;

D^2 is selected from the group consisting of a direct bond, lower alkyl, lower cycloalkyl and a 4 to 6-membered non-basic heterocycle;

Z is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkoxy, lower cycloalkyl, lower cycloalkoxy, $OCOR^6$, $OCONR^7R^7$, CN, $CONR^7R^7$, OSO_2R^6, SR^6, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CONR^7R^7$, $NR^7CO_2R^7$, CO_2R^7, heterocycle, $OPO(OR^6)_2$, $NR^7SO_2R^6$ and COR^6;

R^6 is independently selected from the group consisting of lower alkyl, lower cycloalkyl, heterocycle and heteroaryl; and

R^7 is independently selected from the group consisting of hydrogen, lower alkyl, lower cycloalkyl and heterocycle, wherein two R^7 and the atom to which they are attached may optionally form a ring of 4 to 7 atoms.

2. The compound according to Claim 1 wherein, R^5 is selected from the group consisting of hydrogen, lower alkyl and lower alkoxy.

3. The compound according to Claim 2 wherein, at least one R^1 is hydrogen.

4. The compound according to Claim 3 wherein, at least one R^1 is selected from the group consisting of halogen and lower alkyl.

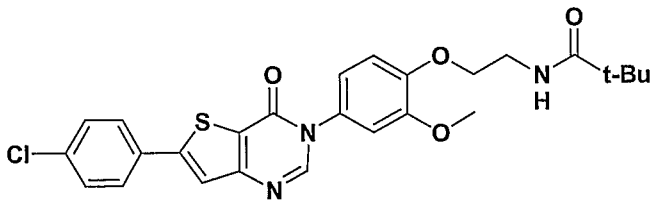
5. The compound according to Claim 4 wherein, the halogen is chloro.

6. The compound according to Claim 5 wherein, R^4 is $G\text{-}D^2\text{-}Z_n$; and n is an integer from 1 to 2.

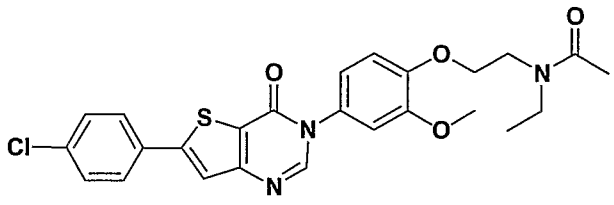
7. The compound according to Claim 6 wherein G is O.

8. The compound according to Claim 7 wherein R^2 is hydrogen and at least one R^3 is hydrogen.

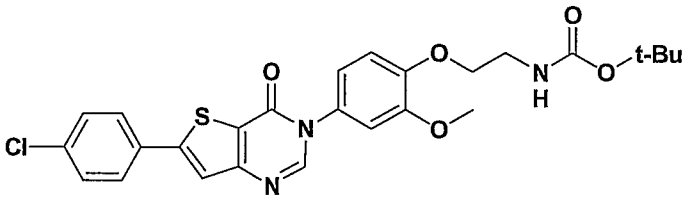
9. The compound according to Claim 1 wherein the compound is selected from the group consisting of:



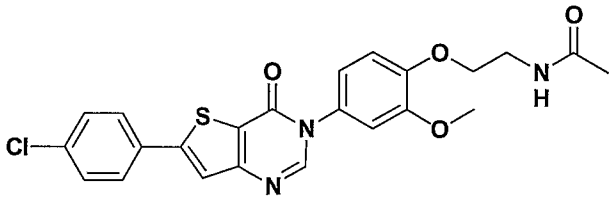
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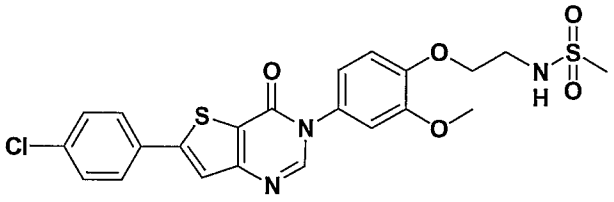
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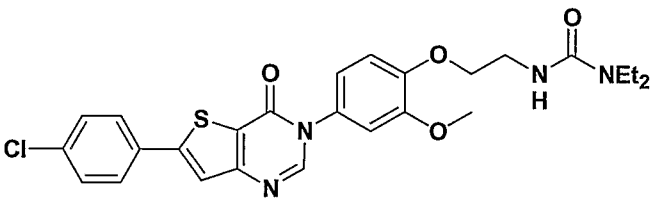
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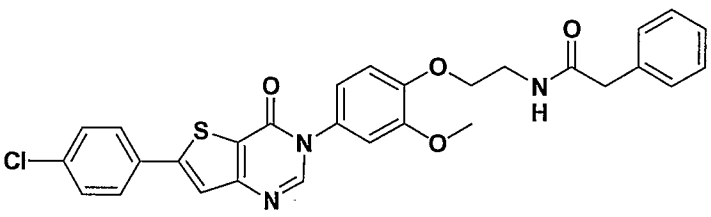
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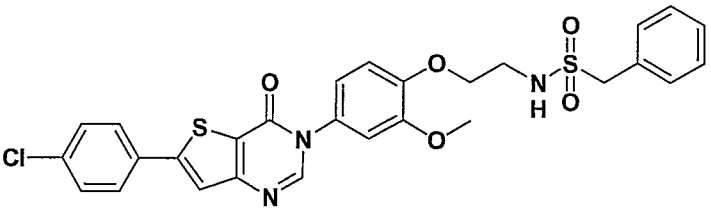
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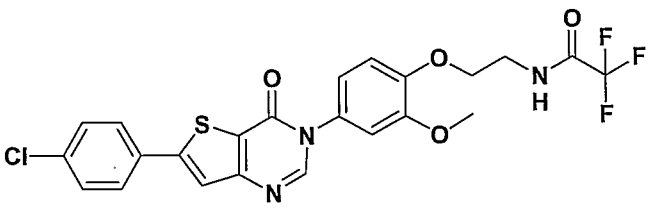
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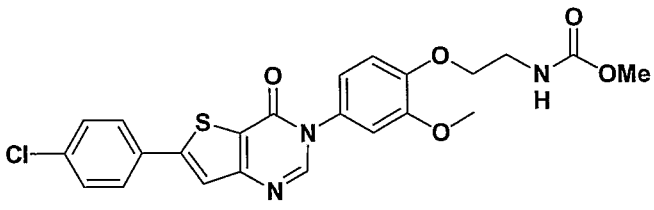


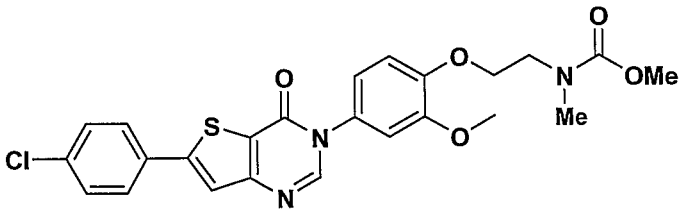
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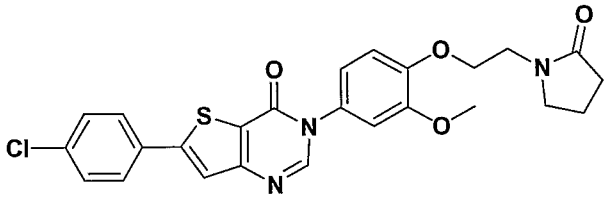


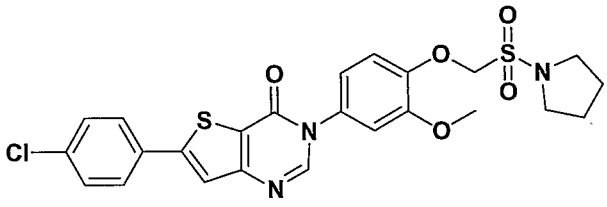
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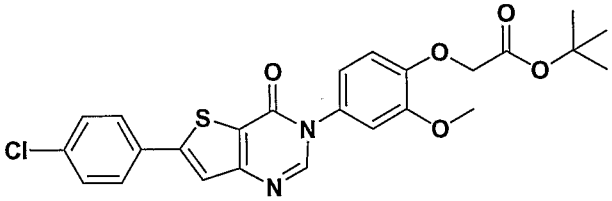

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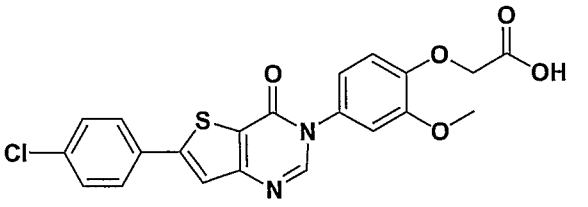

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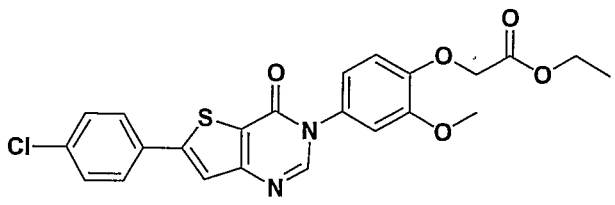

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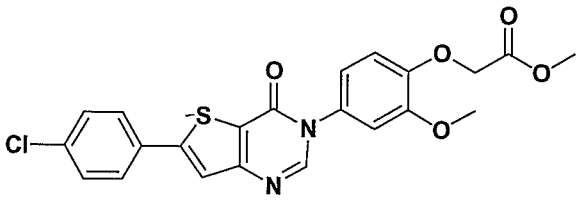

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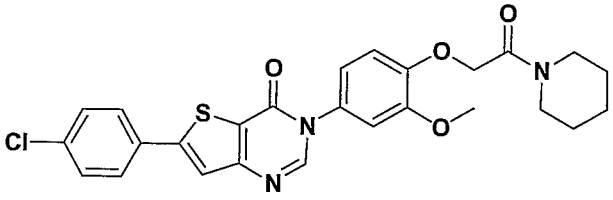

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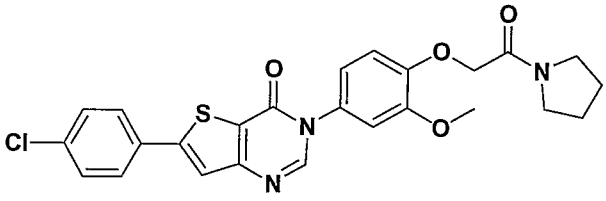
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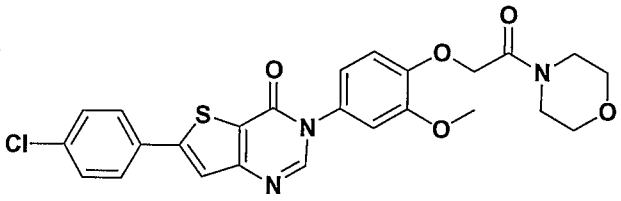
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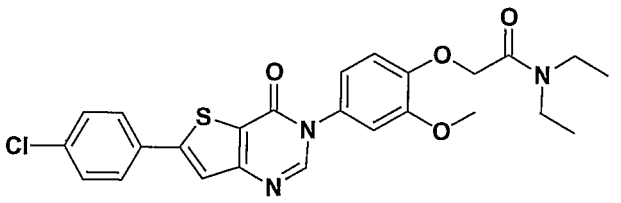
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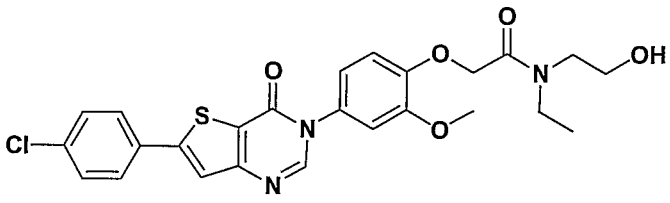
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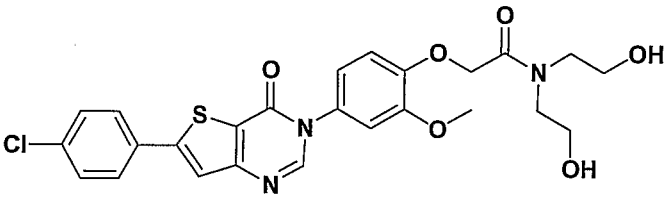
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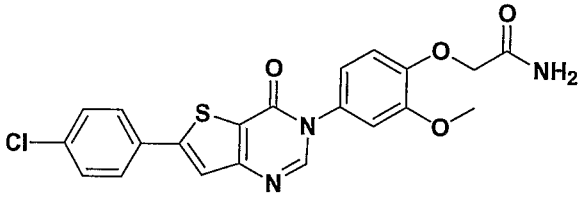
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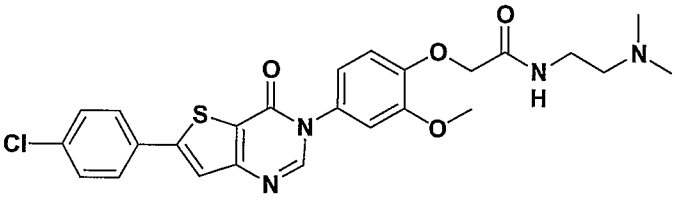
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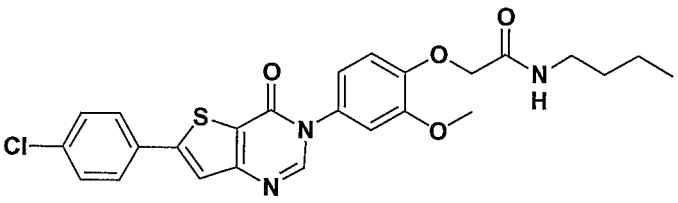
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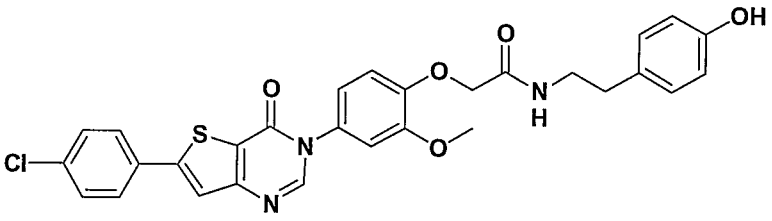
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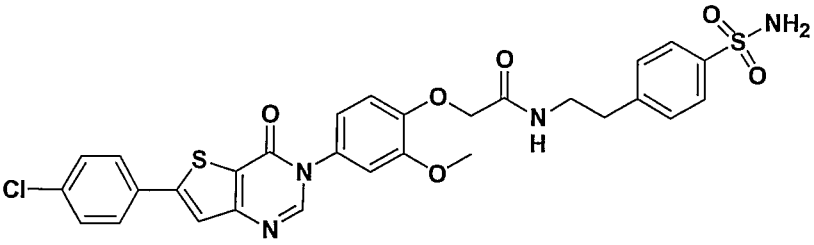
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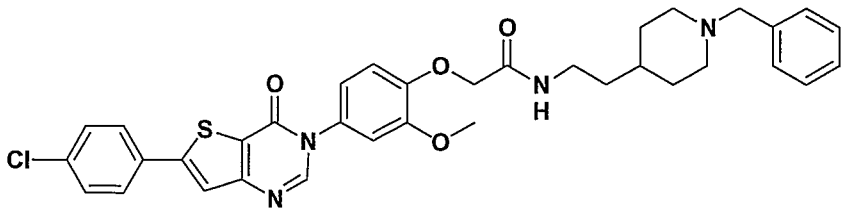


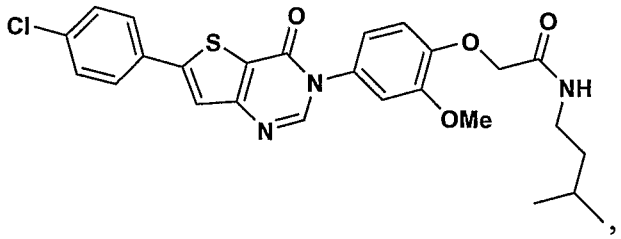
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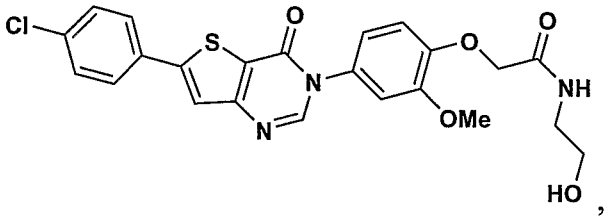


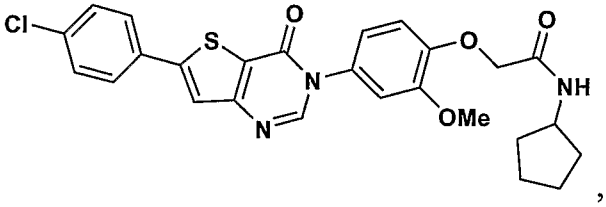
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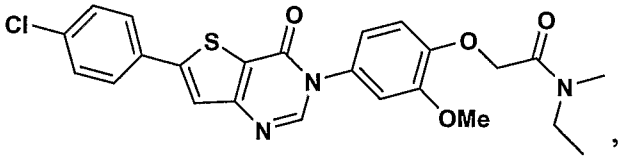
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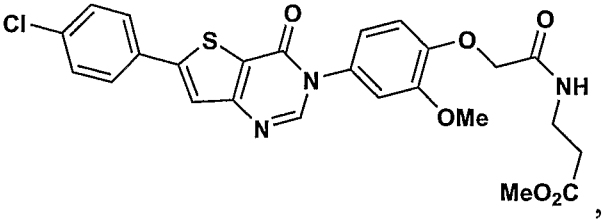

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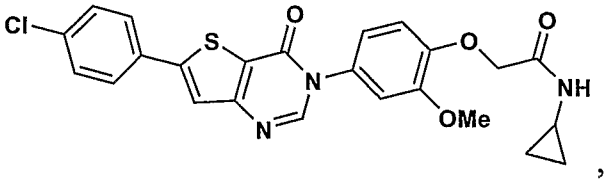

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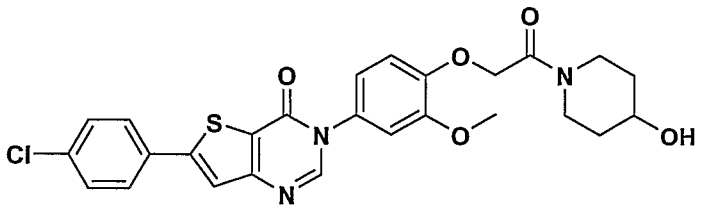

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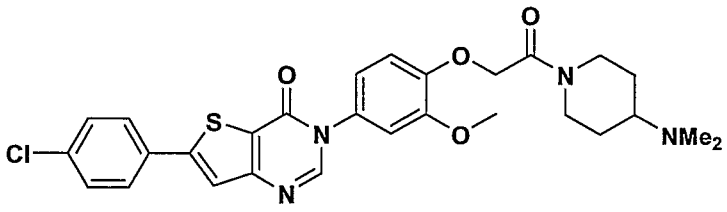

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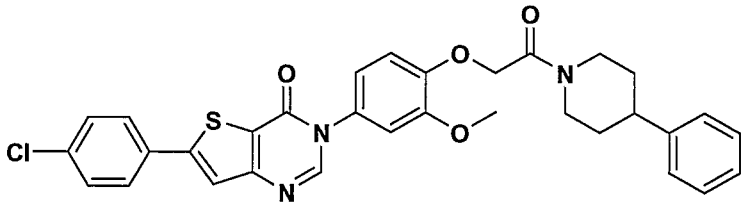

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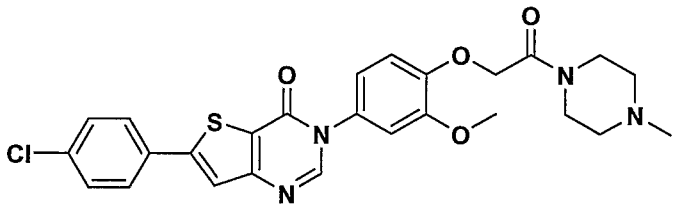

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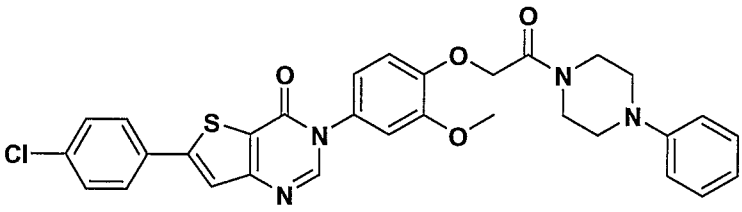

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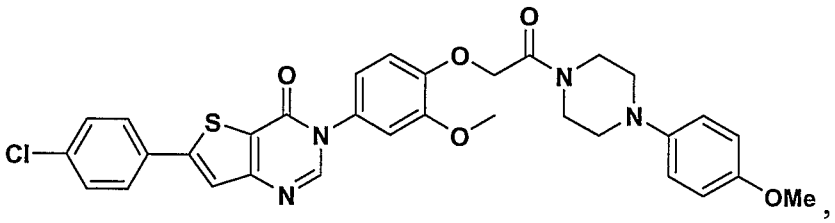

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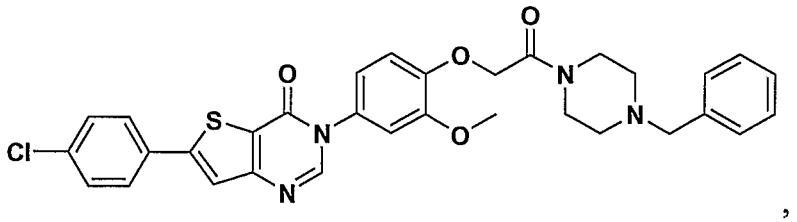

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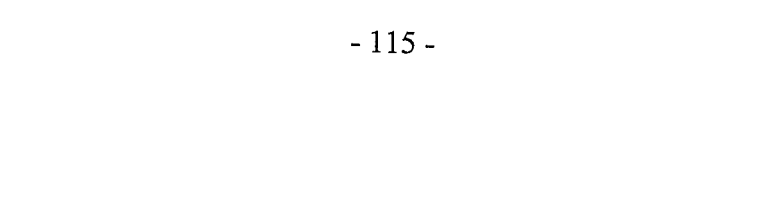

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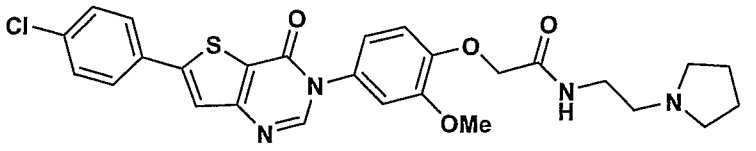

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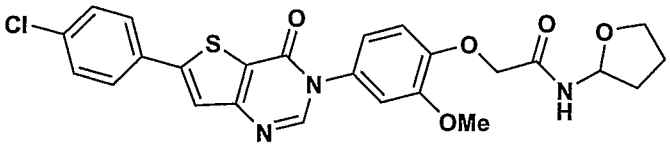
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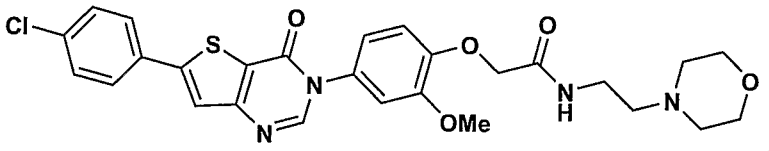

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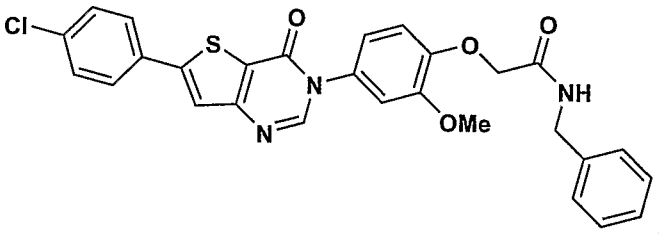

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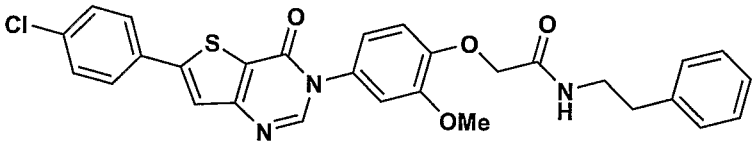

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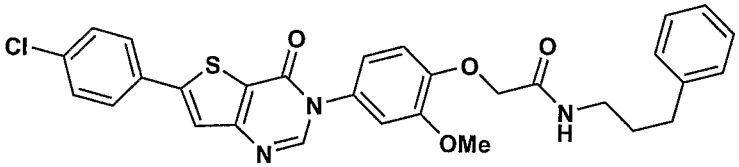

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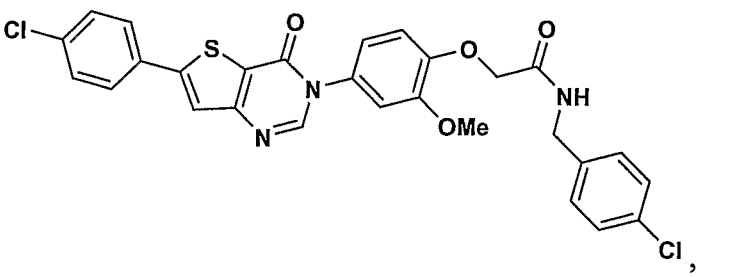

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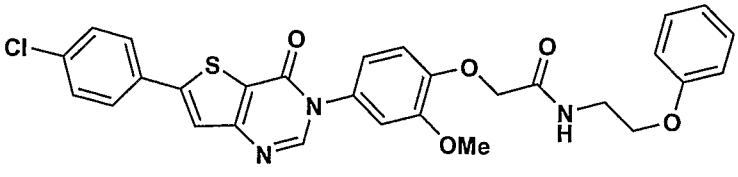

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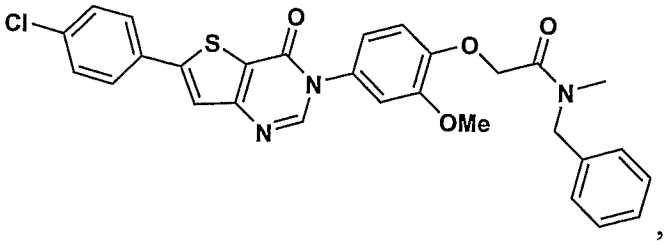

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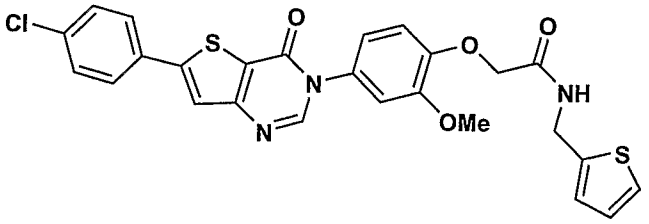

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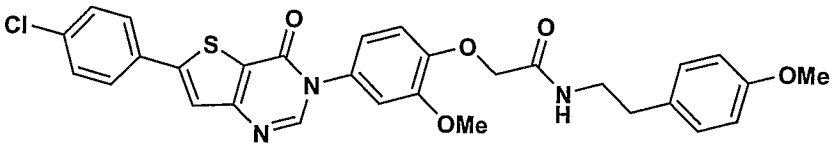

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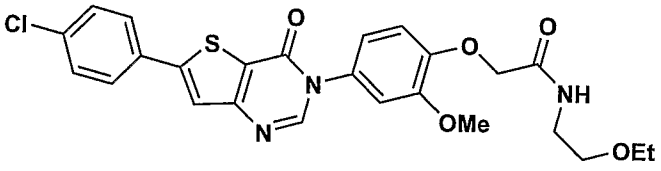
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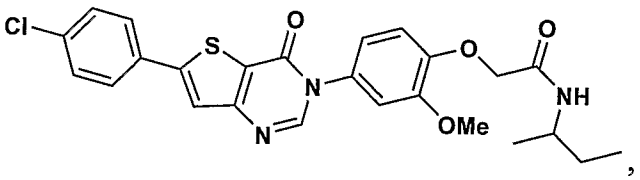
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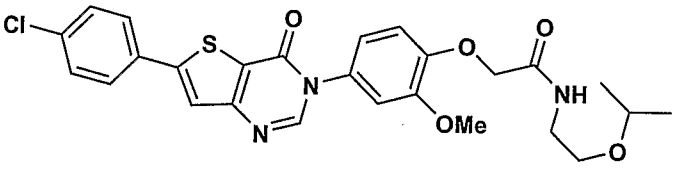
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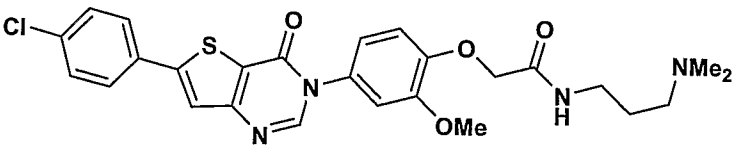
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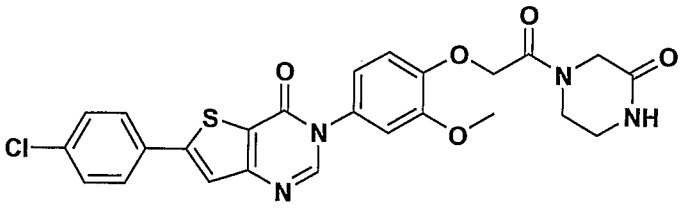
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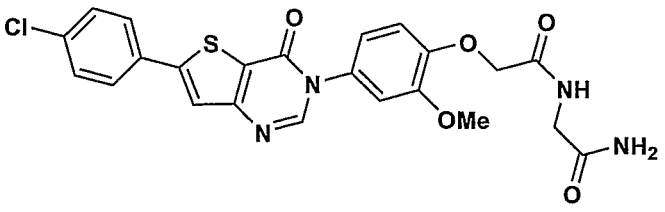
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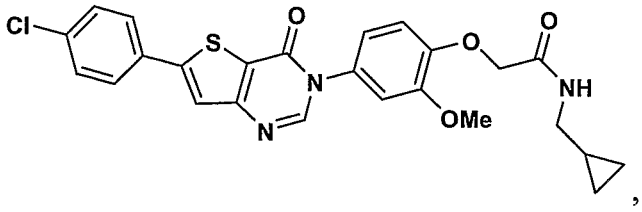


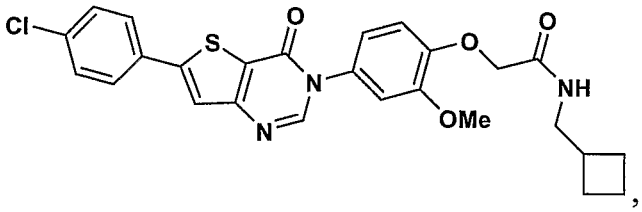
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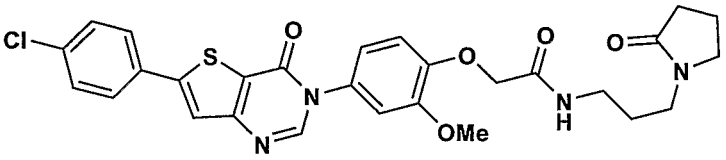


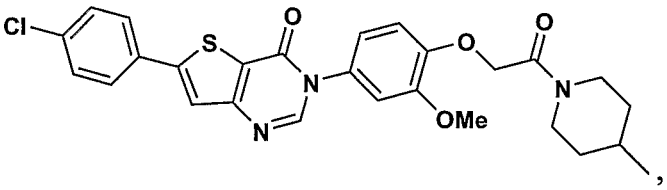
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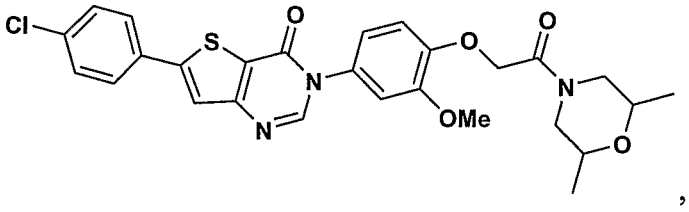


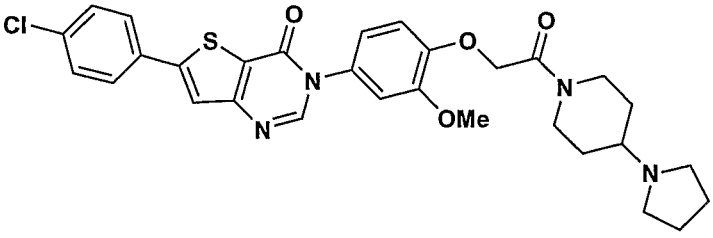


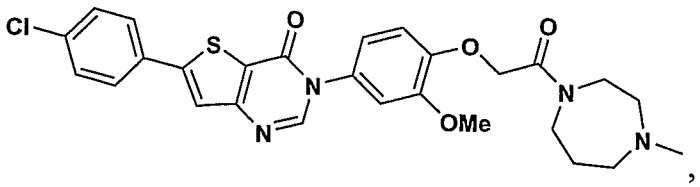


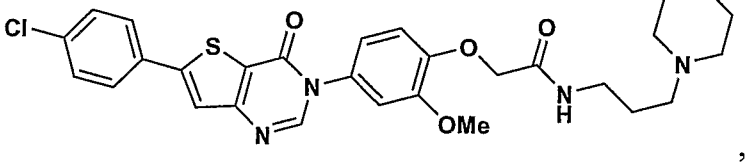


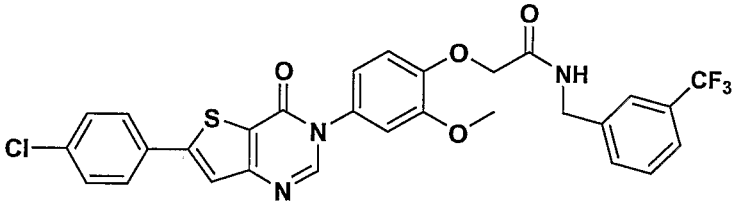


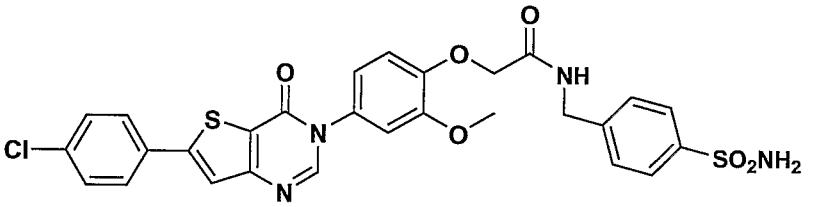


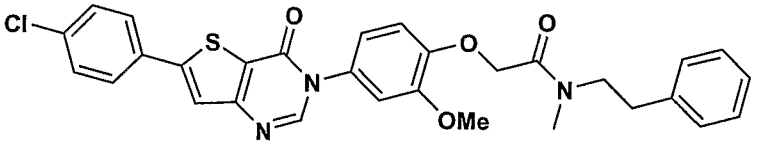


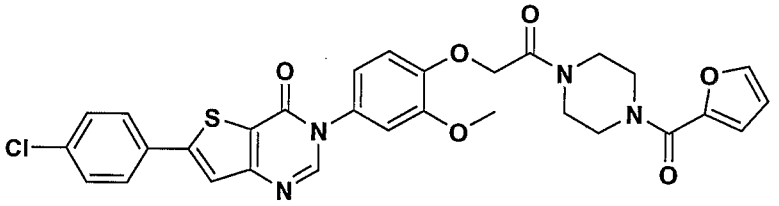


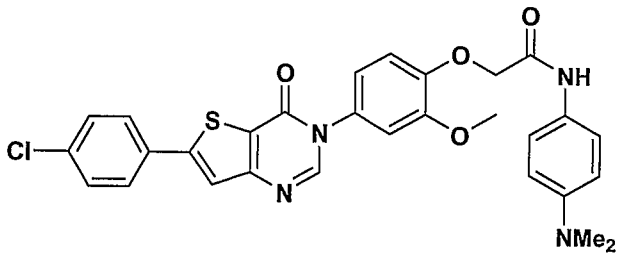




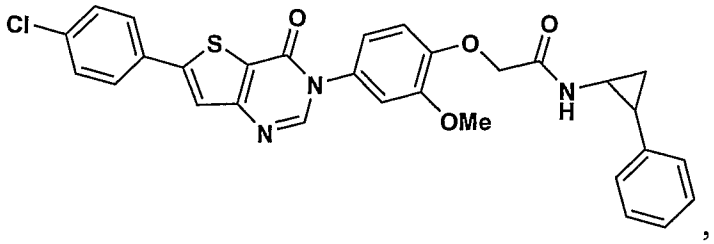




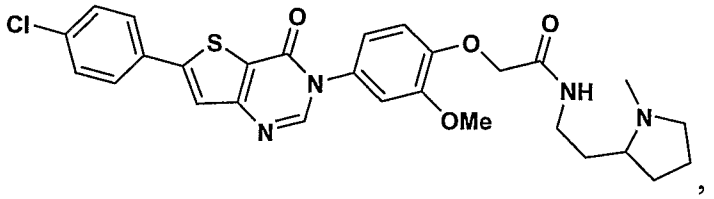




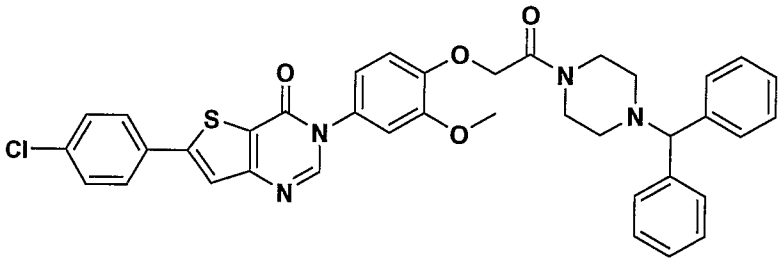
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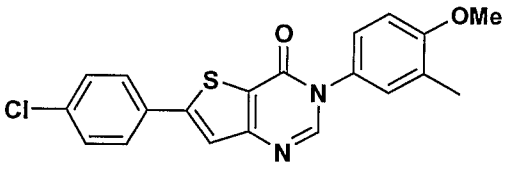
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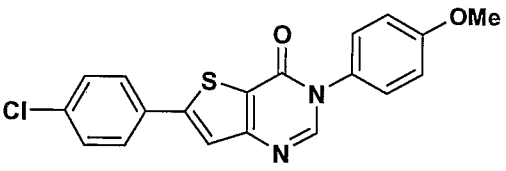
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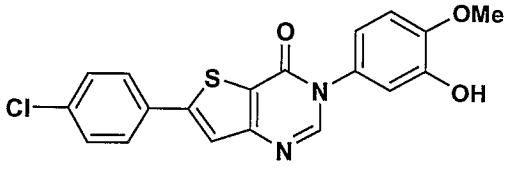
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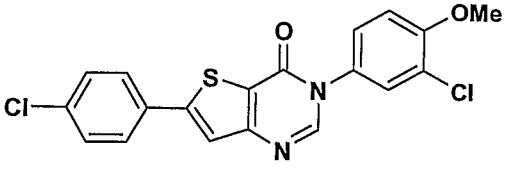
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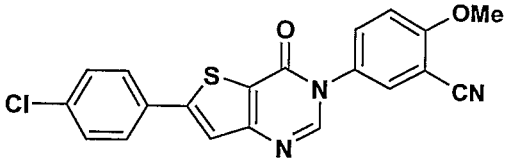
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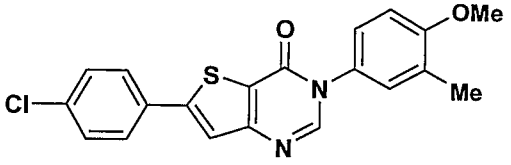
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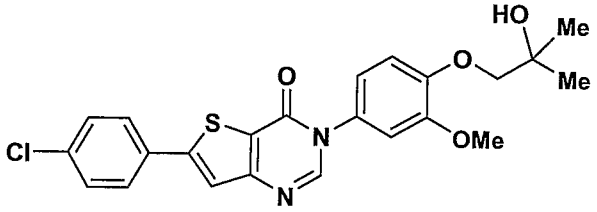
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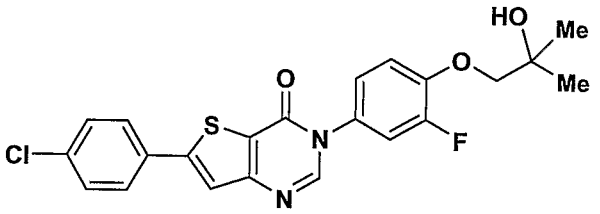
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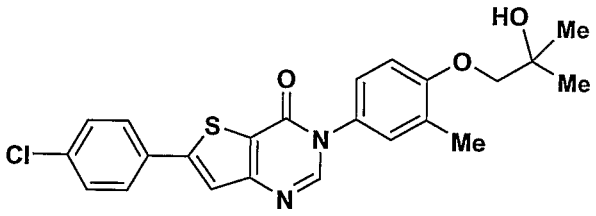
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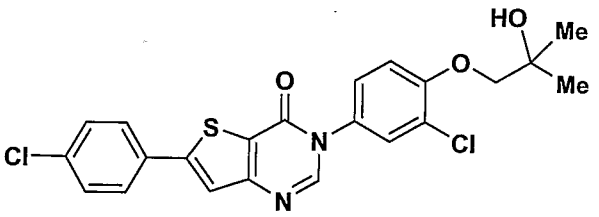
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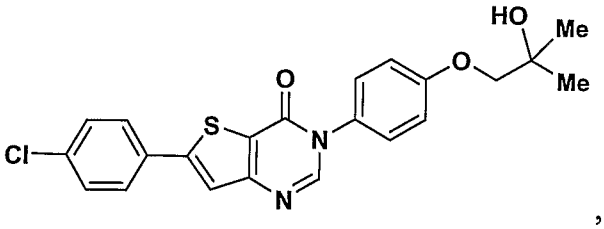
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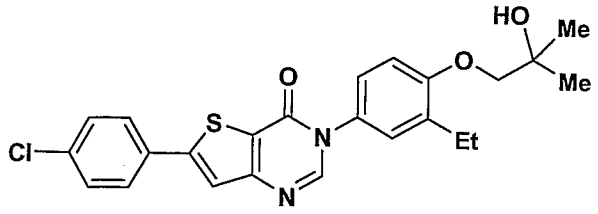
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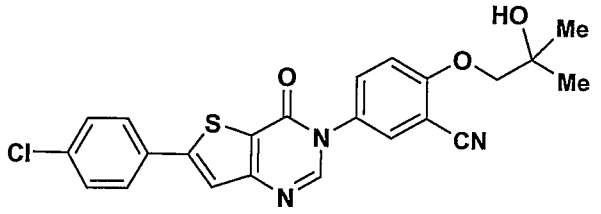
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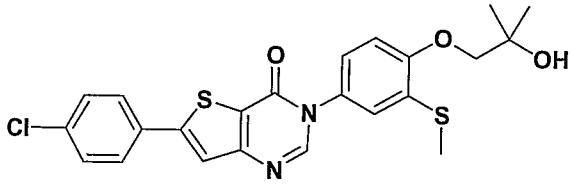
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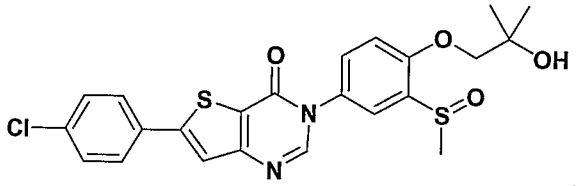
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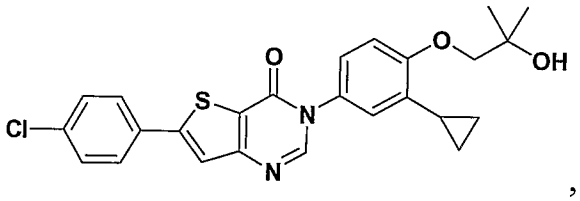
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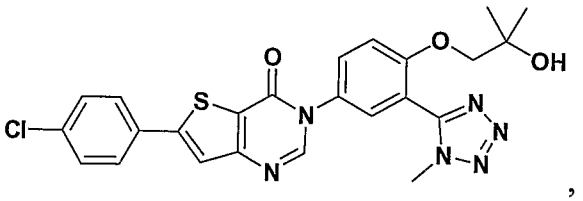
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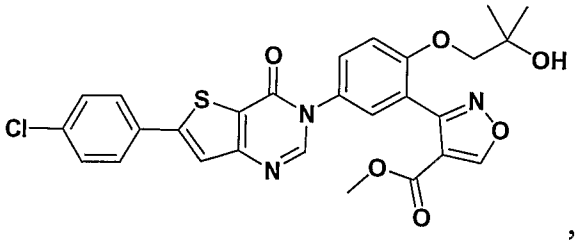
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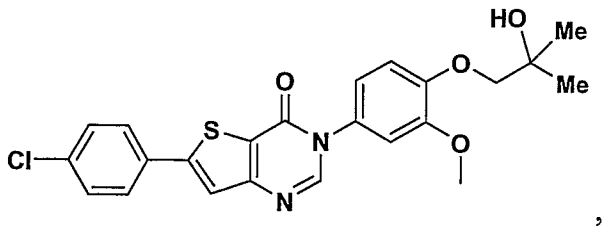
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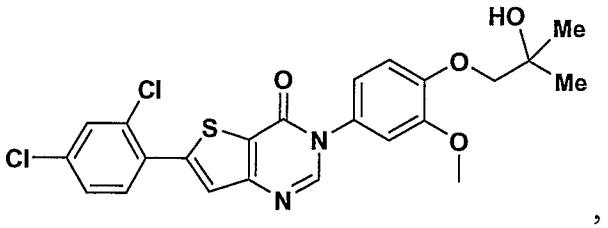

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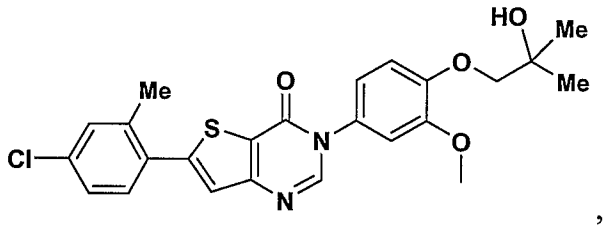
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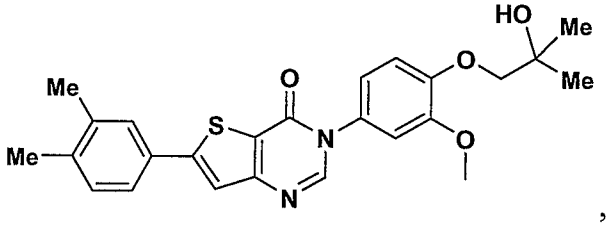

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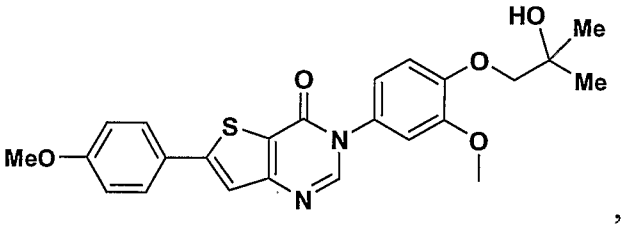
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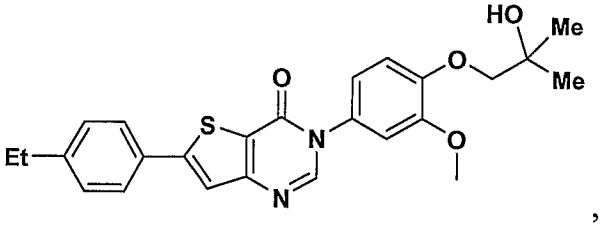

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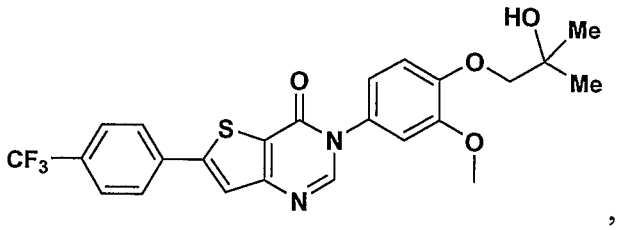

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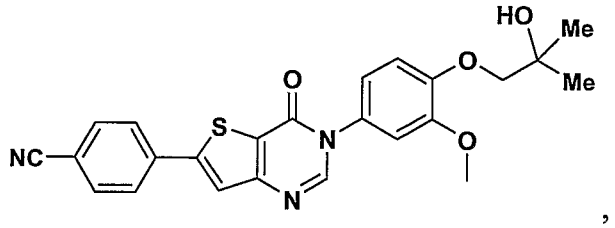

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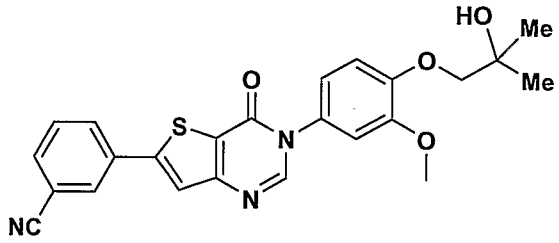

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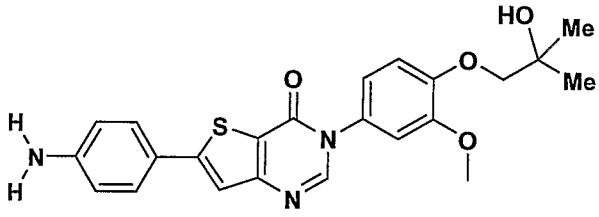
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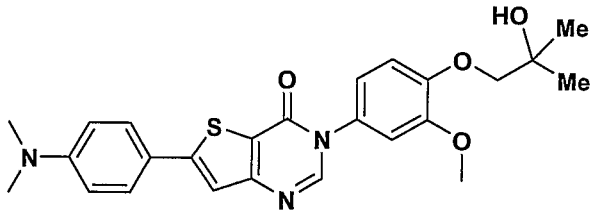
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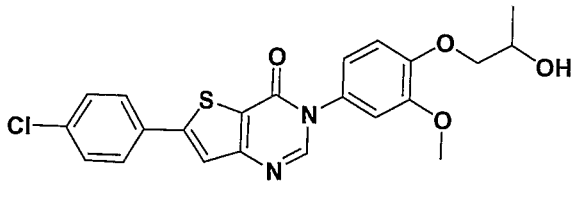
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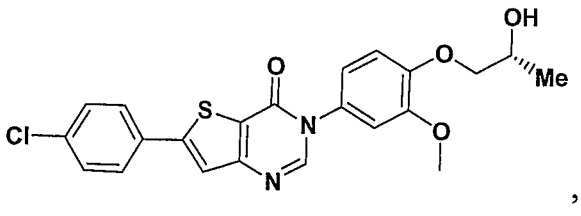
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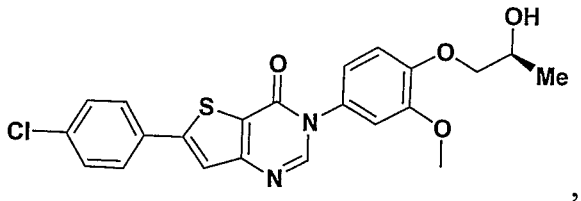


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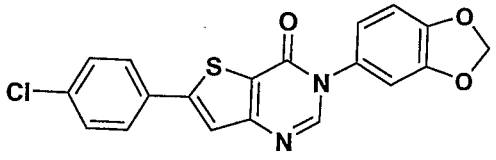


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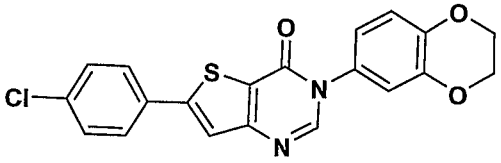
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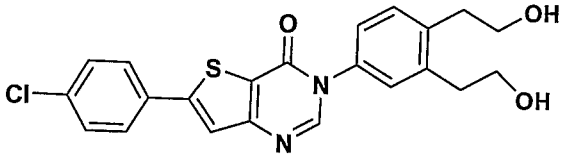
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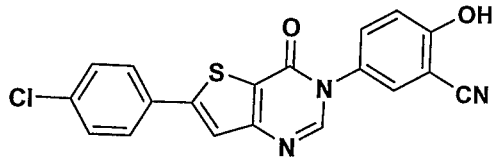
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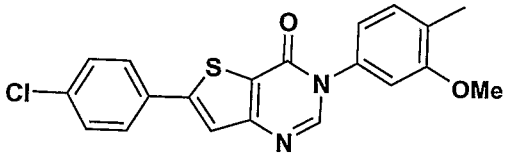
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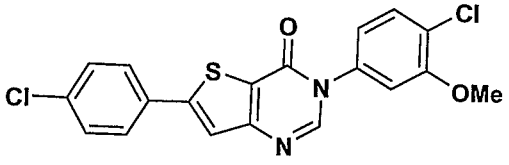
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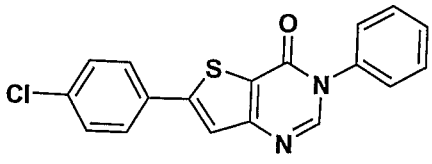
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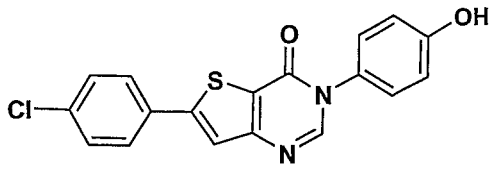


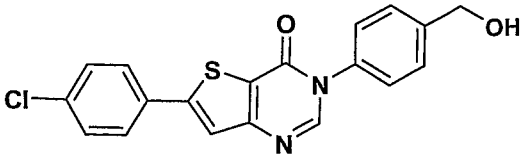
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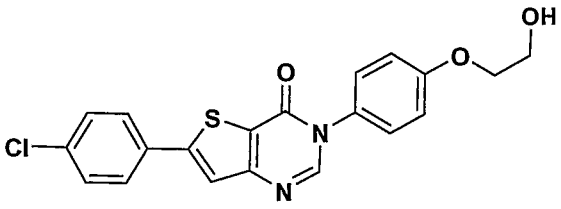


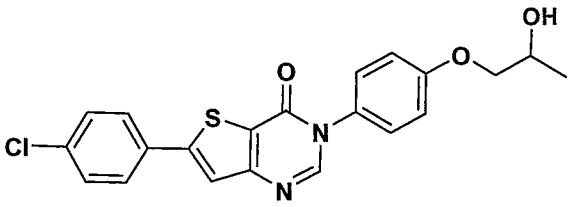
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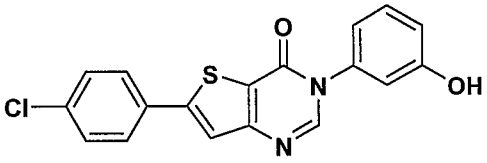
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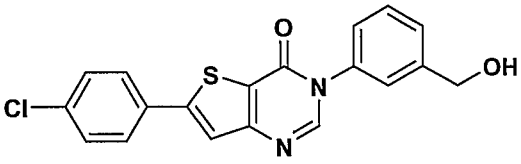

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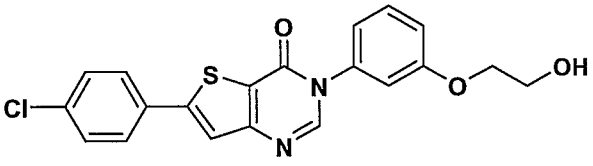

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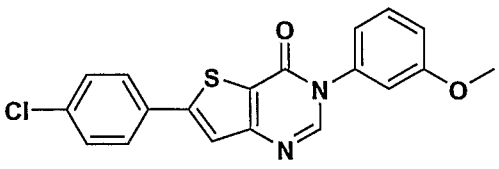

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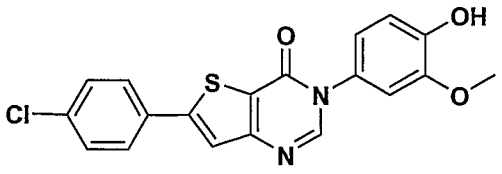

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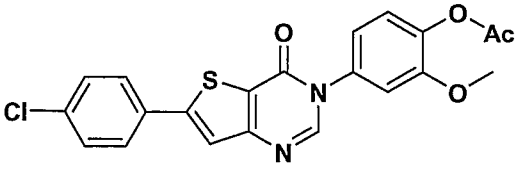

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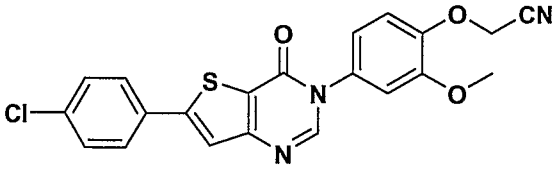

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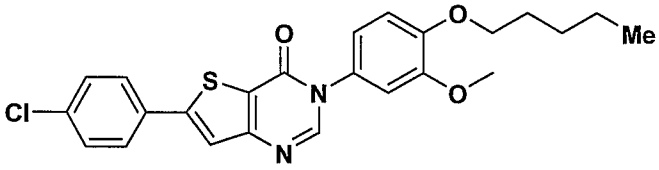
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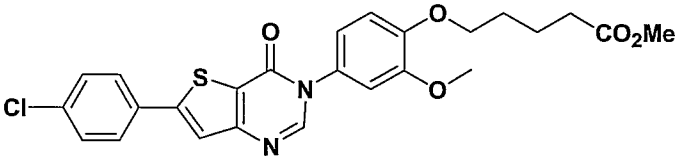
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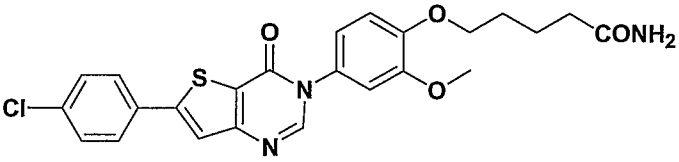
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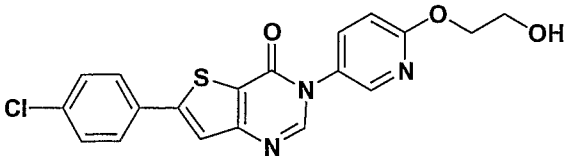
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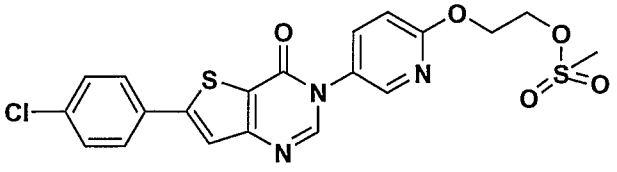
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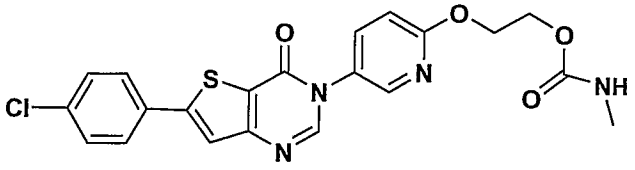


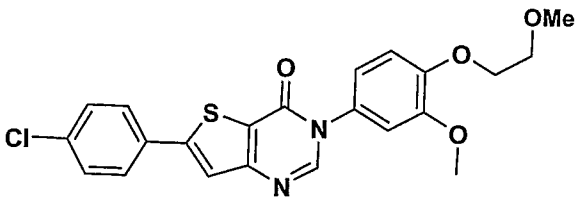
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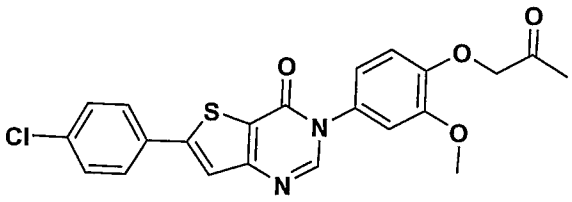


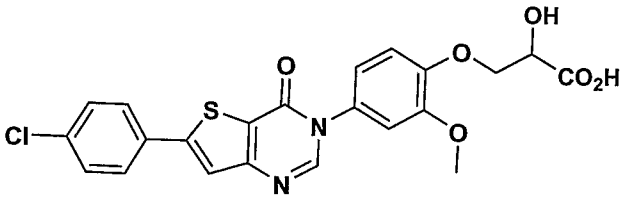
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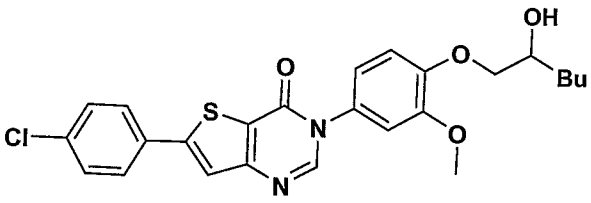
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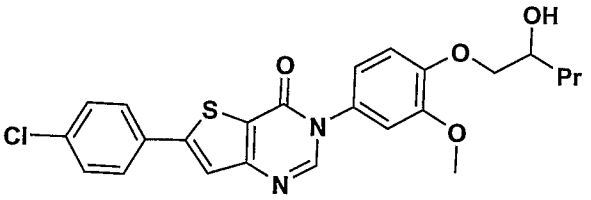

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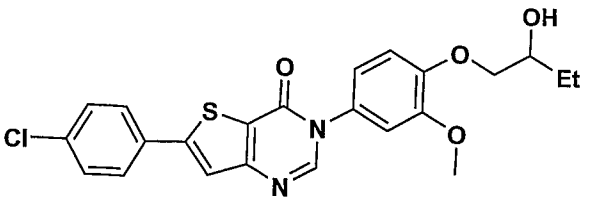

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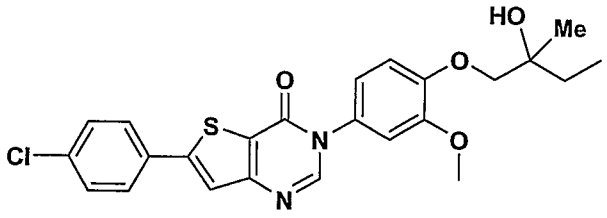

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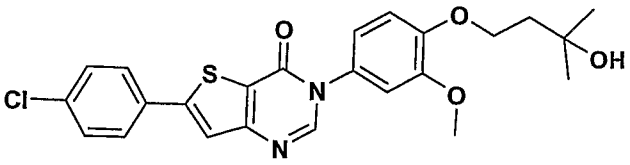

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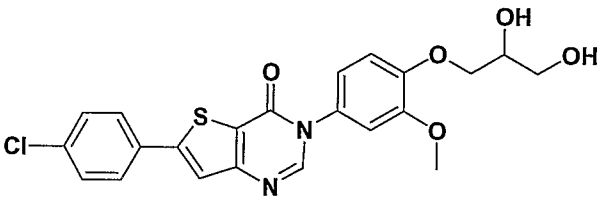

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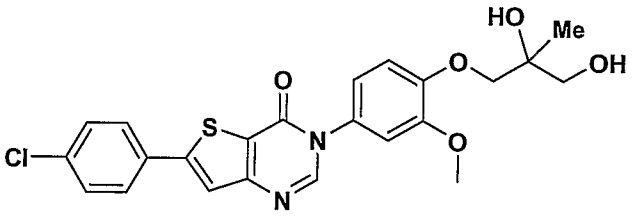
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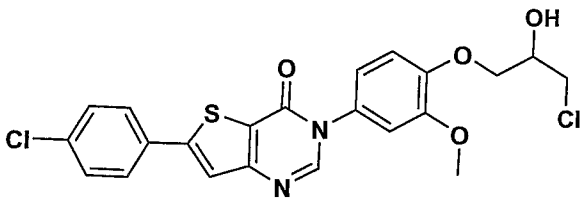
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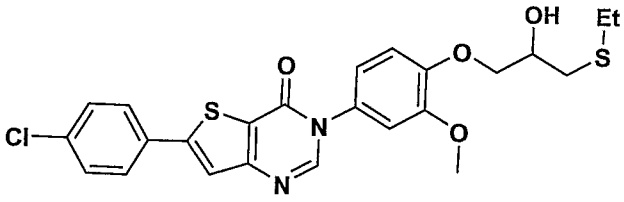

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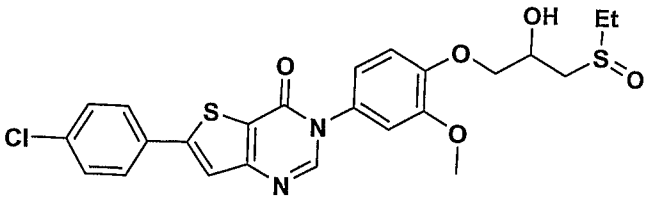

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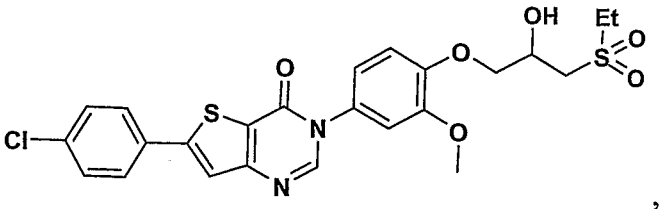

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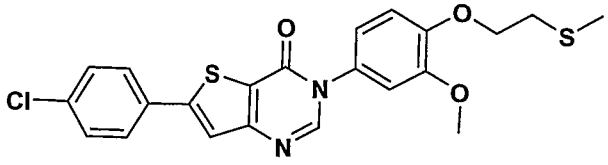

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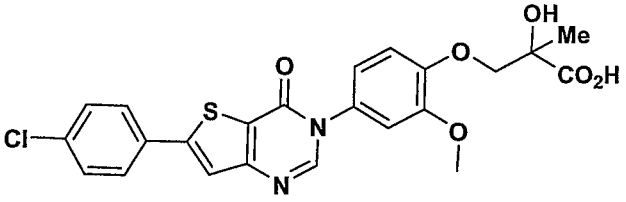

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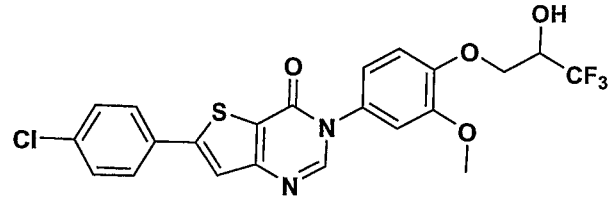

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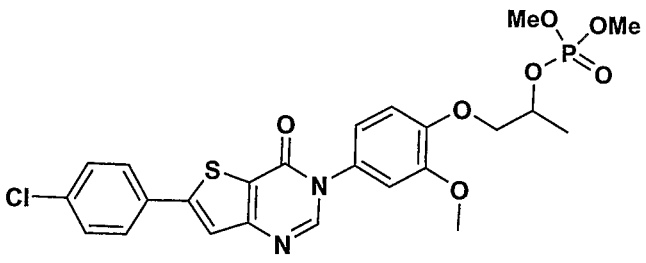

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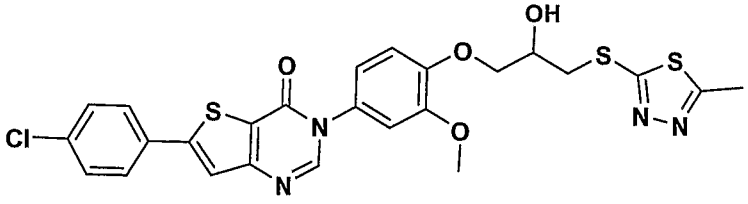

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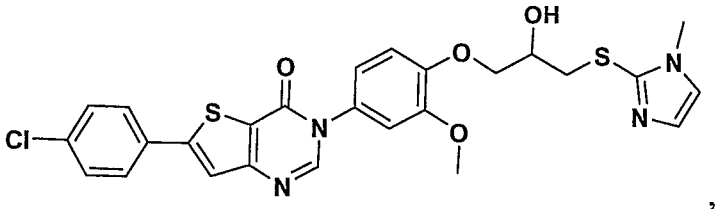

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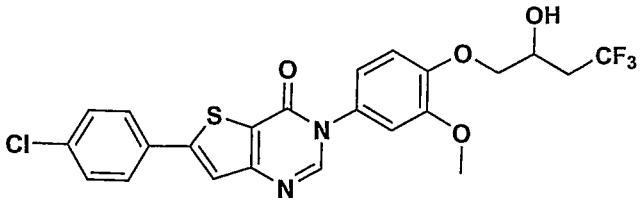
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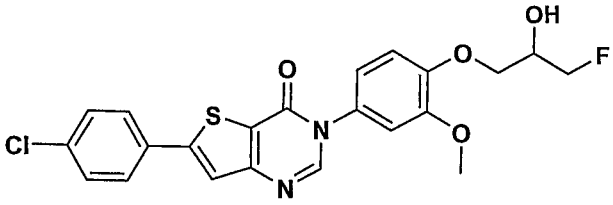

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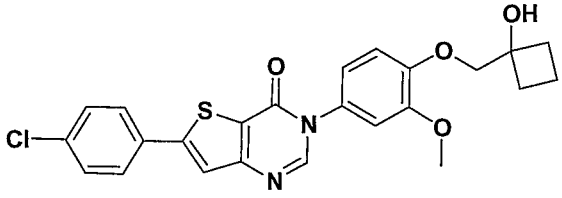

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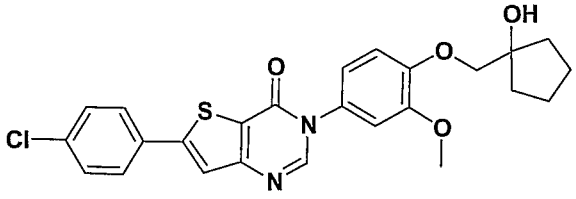
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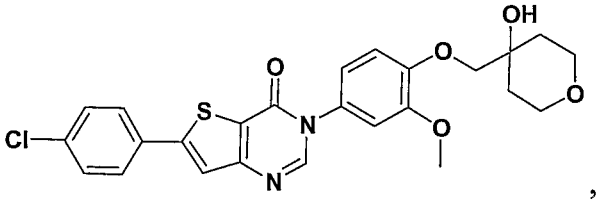
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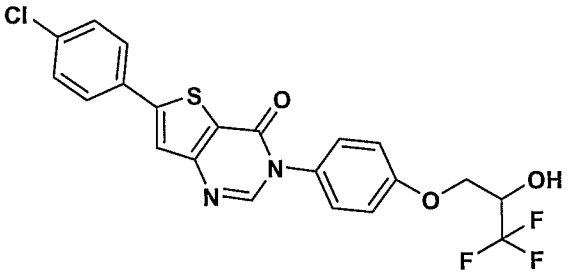
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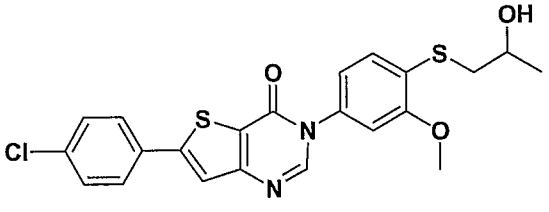
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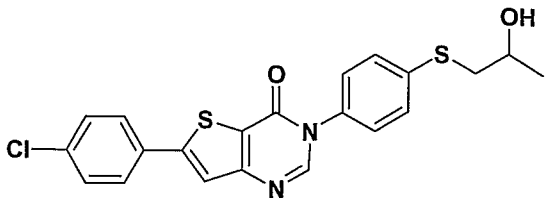


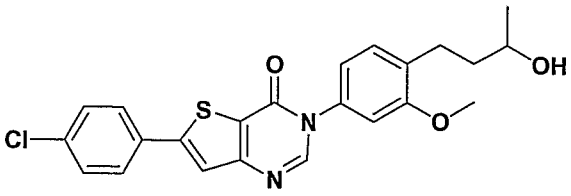
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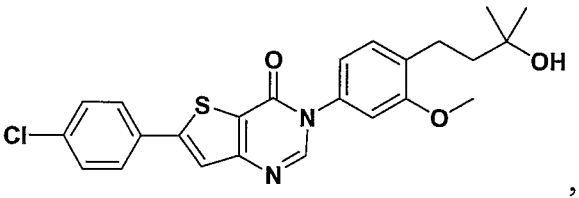


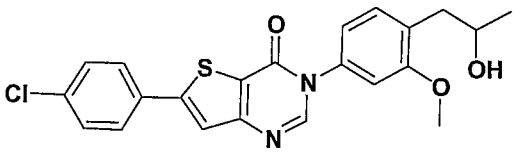
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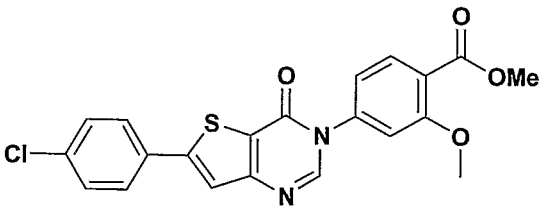
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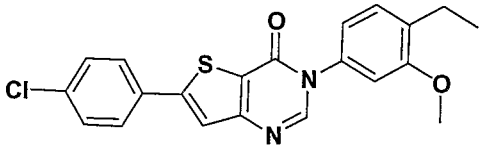

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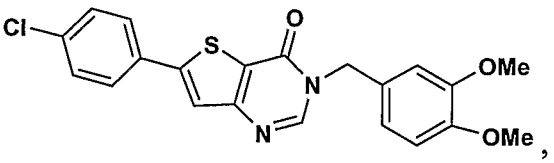

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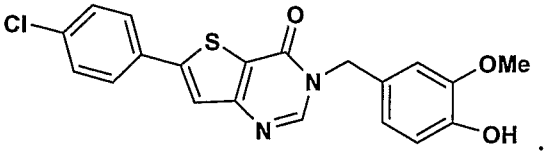

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and


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10. A pharmaceutical composition, comprising:

at least one compound according to Claim 1; and

at least one pharmaceutically acceptable diluent or carrier.

11. The pharmaceutical composition according to Claim 10, further comprising:

at least one additional therapeutic agent.

12. A pharmaceutical combination, comprising:

at least compound according to Claim 1; and

at least one additional therapeutic agent,

wherein the additional therapeutic agent may be administered before the compound according to Claim 1, concurrently with the compound according to Claim 1 or after the compound according to Claim 1.

13. A method for treating obesity, comprising administering a therapeutically effective amount of at least one compound according to Claim 1 alone or in combination with one or more therapeutic agents to a patient in need.

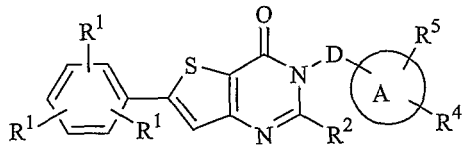
14. A method for treating diabetes, comprising administering a therapeutically effective amount of at least one compound according to Claim 1 alone or in combination with one or more therapeutic agents to a patient in need.

15. The method according to Claim 14 wherein the diabetes is Type II diabetes.

16. A method for treating depression, comprising administering a therapeutically effective amount of at least one compound according to Claim 1 alone or in combination with one or more therapeutic agents to a patient in need.

17. A method for treating anxiety, comprising administering a therapeutically effective amount of at least one compound according to Claim 1 alone or in combination with one or more therapeutic agents to a patient in need.

18. A compound or a pharmaceutically acceptable salt or a stereoisomer or a prodrug or a solvate thereof according to Formula II:



II

wherein,

A is selected from the group consisting of phenyl and a monocyclic heteroaryl;

D is selected from the group consisting of CH_2 and a direct bond;

R^1 is independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, CF_3, OR^6 and SR^6;

R^2 is selected from the group consisting of hydrogen and lower alkyl;

R^4 is selected from the group consisting of hydroxyl or $G\text{-}D^2\text{-}Z_n$;

n is an integer from 1 to 3;

R^5 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower cycloalkyl, CF_3, SR^6, lower alkoxy, lower cycloalkoxy, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^7SO_2R^6$ and COR^6;

G is selected from the group consisting of O, S and CR^7R^7;

D^2 is selected from the group consisting of a direct bond, lower alkyl, lower cycloalkyl and a 4 to 6-membered non-basic heterocycle;

Z is selected from the group consisting of hydrogen, hydroxyl, lower alkoxy, lower cycloalkoxy, $OCONR^7R^7$, CN, $CONR^7R^7$, SOR^6, SO_2R^6, NR^7COR^7, $NR^7CO_2R^7$, CO_2R^6, heteroaryl, $NR^6SO_2R^6$ and COR^6;

R^6 is independently selected from the group consisting of lower alkyl and lower cycloalkyl; and

R^7 is independently selected from the group consisting of hydrogen, lower alkyl and lower cycloalkyl, wherein two R^7 and the atom to which they are attached may optionally form a ring of 4 to 7 atoms.

19. The compound according to Claim 18 wherein, R^5 is lower alkoxy.

20. The compound according to Claim 19 wherein, at least one R^1 is hydrogen.

21. The compound according to Claim 20 wherein, at least one R^1 is halogen.

22. The compound according to Claim 21 wherein, the halogen is chloro.

23. The compound according to Claim 22 wherein, R^4 is $G\text{-}D^2\text{-}Z_n$; and n is an integer from 1 to 2.

24. The compound according to Claim 23 wherein G is O.

25. The compound according to Claim 24 wherein D^2 is lower alkyl.