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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 July 2009 (09.07.2009)

PCT

(10) International Publication Number
WO 2009/085256 A1

(51) International Patent Classification:
C07D 417/12 (2006.01) *A61K 31/427* (2006.01)
C07D 417/14 (2006.01) *A61P 31/18* (2006.01)
C07D 495/04 (2006.01)

(21) International Application Number:
PCT/US2008/013999

(22) International Filing Date:
23 December 2008 (23.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/017,042 27 December 2007 (27.12.2007) US

(71) Applicant *(for all designated States except US)*: **PANACOS PHARMACEUTICALS, INC.** [US/US]; 209 Perry Parkway, Suite 7, Gaithersburg, MD 20877 (US).

(71) Applicants and
(72) Inventors: **NITZ, Theodore, J.** [US/US]; 473 Kulp Road, Pottstown, PA 19465 (US). **SALZWEDEL, Karl** [US/US]; 18203 Fox Chase Circle, Olney, MD 20832 (US). **FINNEGAN, Catherine** [US/US]; 1108 E. 36th Street, Baltimore, MD 21218 (US). **BRUNTON, Shirley** [GB/GB]; 39 Bolton Road, Windsor, Berks SL4 3JX (GB). **FLANAGAN, Stuart** [GB/GB]; 21 Saint Georges Road, Wallingford, Oxon OX10 8HW (GB). **MONTALBETTI, Christian** [CH/GB]; 23 Reading Road, Wallingford, Oxon OX10 9DS (GB). **COULTER, Thomas, Stephen** [GB/GB]; Orchard Lodge, Grove Bridge, Oxfordshire, Wantage OX12 7PA (GB).

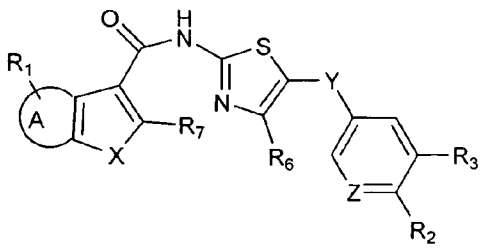
(74) Agents: **COVERT, John, M.** et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

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

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

Published:
— *with international search report*

(54) Title: ANTI-HIV COMPOUNDS



(I)

(57) Abstract: Thiazole derivatives represented by Formula (I) are disclosed, where R_1, R_2, R_3, A, X, Y, Z, R_6 and R_7 are disclosed herein. These thiazole derivatives and pharmaceutical compositions comprising these derivatives are useful in the treatment of HIV mediated diseases and conditions.

WO 2009/085256 A1

ANTI-HIV COMPOUNDS

Background of the Invention

Field of the Invention

[0001] The present invention concerns novel pharmaceutically active thiazole derivatives, pharmaceutical compositions containing the same, their use as medicaments, and the use of thiazole derivatives for the manufacture of specific medicaments. The present invention also concerns a method of treatment involving administration of thiazole derivatives.

[0002] The novel thiazole derivatives are useful as antiretroviral agents. In particular, the novel thiazole derivatives are useful for the treatment of Human Immunodeficiency Virus type 1 (HIV-1).

Related References

[0003] Talukdar et al., in "Electrophilic Substitution in Mesoionic Thiazolo-[3,2-a]-4-pyrimidone Systems," mention thiazoles structurally distinct from the molecules disclosed by the present invention (*Indian Journal of Chemistry*; **1982**, *21B*, 517-521).

Background of the Invention

[0004] Human Immunodeficiency Virus (HIV) is a retrovirus that infects and invades cells of the immune system; it breaks down the body's immune system and renders the patient susceptible to opportunistic infections and neoplasms. The immune defect appears to be progressive and irreversible, with a high mortality rate that approaches 100% over several years when left untreated.

[0005] The inherent tendency of HIV to mutate and become resistant to antiretroviral drugs remains a challenge to successful treatment. Patients with drug-resistant strains have an increasing risk of treatment failure with each subsequent treatment regimen. The concurrent use of multiple antiretroviral drugs has been reported to provide an improved virologic response and reduced probability for viral mutations.

[0006] Drug-resistant strains of HIV often appear over extended periods of time, even when the patient is on combination therapy. In some cases where an HIV strain is resistant to one drug in a therapeutic class, the strain will sometimes be cross-resistant to similar drugs in the same therapeutic class. Cross-resistance is a particular problem if a

patient develops cross-resistance to a whole group of drugs. For example, if a patient has a cross-resistant strain exhibiting resistance to one non-nucleoside reverse transcriptase inhibitor ("NNRTI"), there is a risk that the patient's strain will be resistant to the entire NNRTI class.

[0007] Drugs acting by novel mechanisms of action are needed to treat patients harboring viruses that have mutated to develop resistance to currently approved drugs. Early stage events including viral attachment, fusion and entry have emerged as viable targets of potentially significant therapeutic utility.

[0008] The HIV-1 envelope is a 160 kDa glycoprotein that is cleaved to form a transmembrane subunit and a surface subunit. The transmembrane subunit is termed "gp41." The surface subunit is termed "gp120." Crystallographic analyses of portions of both gp120 and gp41 have contributed to the knowledge base surrounding the biochemistry of HIV-1 envelope (Kwong, P. D., et al., *Nature* (*London*) **1998**, *393*, 648-659 ; Chan, D. C., et al., *Cell* **1997**, *89*, 263-273; Weissenhorn, W., et al., *Nature* **1997**, *387*, 426-430). It is believed that gp120 and gp41 are held together by van der Waals forces and hydrogen bonding. The gp120/gp41 complex is present as a trimer on the virion surface where it mediates viral attachment, fusion and entry.

[0009] HIV-1 infection is initiated by the attachment of gp120 to the CD4 receptor on the cell surface (Salzwedel, K., et al., *J. Virol.* **2000**, *74*, 326-333). Studies indicate that upon binding to CD4, a conformational change occurs in gp120, resulting in the repositioning of the V1 and V2 loops of gp120, and exposure of the gp120 bridging sheet domain. The bridging sheet, along with the V3 loop of gp120, is then available for binding to a co-receptor on the cell surface, predominantly either CXCR4 or CCR5, (Kwong et al., 1998, Rizzuto et al., 1998, Zhang et al., 1999). In laboratory-adapted HIV-1 isolates utilizing the CXCR4 co-receptor, CD4 binding also appears to induce conformational changes in gp41 that result in the formation of an extended intermediate structure (Furuta, R. A., et al., *Nat. Struct. Biol.* **1998**, *5* 276-279; de Rosny, E., et al., *J. Virol.* **2001**, 75, 8859-8863; Kilgore, N. R., et al., *J. Virol.* **2003**, *77*, 7669-7672). In this extended intermediate conformation, the N-terminal fusion peptide is believed to project outwards toward the cellular membrane. This conformation appears to be stabilized by the formation of a trimeric coiled-coil structure by the N-terminal heptad repeat regions of the three gp41 subunits within the ENV trimer (Chen, D. C. and Kim, P. S., *Cell* **1998**, *93*, 681-684).

Whether these gp41 conformational changes occur before or after co-receptor binding in primary, CCR5-using HIV-1 isolates is unclear. However, in both cases, binding of the CD4-bound gp120 subunit to co-receptor allows the N-terminal fusion peptide of gp41 to insert into and disrupt the cellular membrane (Salzwedel et al., 2000; Finnegan, C. M., et al., *J. Virol.* **2002**, *76*, 12123-12134). The gp120 subunit then undergoes further conformational changes, perhaps induced by interaction with co-receptor, which may result in the dissociation of gp120 from gp41. These gp120 conformational changes, in turn, induce a final conformational change in gp41 in which the protein refolds into a hairpin configuration. This hairpin conformation is stabilized by the binding of the C-terminal heptad repeat regions of gp41 into the outer grooves on the trimeric N-terminal heptad repeat coiled-coil intermediate structure. These conformational changes culminate in the formation of a six-helix bundle structure, which promotes fusion of the viral and cellular membranes by bringing them into closer proximity. Formation of the six-helix bundle is required in order for Env-mediated fusion to occur (Eckert, D. M. and Kim, P. S., *Annu. Rev. Biochem.* **2001**, *70*, 777-810; Weiss, C. D., *AIDS Rev.* **2003**, *5*, 214-221). After a fusion pore is formed, the viral core is released into the cellular cytoplasm, thus initiating infection.

[0010] HIV-1 entry inhibitors can generally be divided into three classifications: 1) attachment inhibitors, which inhibit virion attachment to the cell; 2) co-receptor antagonists, which interact with co-receptor to block its binding to gp120, and 3) fusion inhibitors, which interact with Env and disrupt conformational changes that are required for fusion of the viral and cell membranes.

[0011] Fusion inhibitors are a relatively new class of antiretrovirals. FUZEON (enfuvirtide) is the first FDA approved drug that acts at a target other than reverse transcriptase or protease. Enfuvirtide inhibits Env-mediated fusion by preventing formation of the gp41 six-helix bundle structure (Matthews, T., et al., *Nat. Rev. Drug Discov.* **2004**, *3*, 215-225; Kilgore et al., 2003). While the introduction of a new class of antiretrovirals represents an advance in the medicinal arts, enfuvirtide must be injected twice daily with a specialized device. Also, some clinicians have reported non-compliance with treatment regimens due to injection site reactions associated with enfuvirtide treatment. Despite its drawbacks, enfuvirtide has provided proof-of-concept for the validity of viral fusion/entry as a therapeutic target.

[0012] As used herein, "fusion inhibitor" refers to inhibition of at least one of the following steps:

1. Gp120 binding to the CD4 receptor of the target cell;
2. Changes in the conformation of gp120 that are induced by binding to the CD4 receptor;
3. Exposure of the co-receptor binding site on gp120;
4. Changes in the conformation of gp41 that are induced by binding of gp120 to the CD4 receptor;
5. Exposure of the N-terminal fusion peptide in gp41;
6. Formation of the N-heptad repeat coiled-coil structure and extended intermediate conformation of gp41;
7. Gp120 binding to a target cell co-receptor protein, for example, the chemokine receptors CCR5 and CXCR4.
8. Changes in the conformation of gp120 that are induced by binding to co-receptor;
9. Insertion of the gp41 amino terminus into the target cell membrane;
10. Release of gp120 from the gp41-gp120 complex;
11. Changes in the conformation of gp41 that are induced by binding of gp120 to co-receptor;
12. Formation of the six-helix bundle ("6HB") structure in gp41;
13. Fusion of the membranes of the virion particle and target cell;
14. Entry of viral cores into the cellular cytoplasm; and,
15. Non-specific attachment to the target cell via cell surface sugars such as syndecans, C-type lectin receptors ("DC-SIGN" or "CD209"), and heparin sulfate proteoglycans ("HSPG").

[0013] Despite recent progress in the development of HIV therapeutic options, there remains a need for drugs having different or enhanced anti-HIV properties relative to currently marketed pharmaceuticals.

[0014] One technical problem underlying the invention relates to the specific need for a small chemical entity fusion inhibitor.

[0015] Another technical problem underlying the invention relates to the specific need for an orally bioavailable fusion inhibitor.

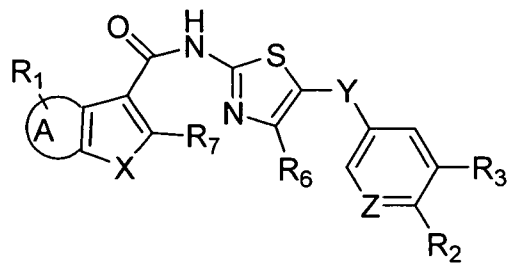
[0016] Another technical problem underlying the invention relates to the specific need for a compound that inhibits viral entry by mediating the interaction of HIV ENV with a cell surface receptor, for example CD-4.

[0017] Another technical problem underlying the invention relates to the specific need for a compound that inhibits viral entry by mediating the interaction of HIV ENV with a co-receptor, for example either or both of the CXCR4 and CCR5 co-receptors.

Brief Summary of the Invention

[0018] It has been discovered that compounds of Formula I are unique compositions exhibiting superior antiretroviral properties.

[0019] Some compounds of the present invention include compounds of Formula I:



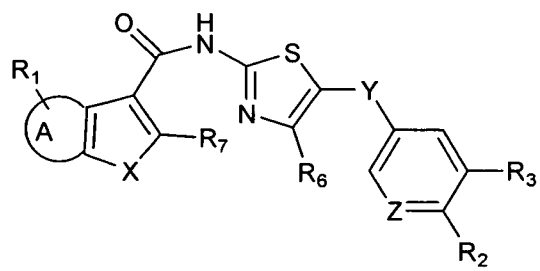
I

where variables are as described below.

Detailed Description of the Invention

[0020] Without wishing to be bound by theory, it is believed that the compounds of the present invention function by inhibiting fusion of the virion and cell membranes or entry of the viral core into the cellular cytoplasm, but not by inhibiting attachment of the virion to the cell.

[0021] Some compounds of the present invention include compounds of Formula I:

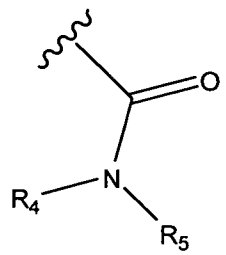


or pharmaceutically acceptable salts or solvates thereof;

wherein A is a 6-7 membered ring system optionally comprising one oxygen which ring system is optionally substituted with one or more R_1 moieties at each carbon;

each R_1 is independently selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, haloalkyl, haloalkoxy, hydroxy, hydrido, alkoxy, cyano, amido, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxyalkoxyalkyl, alkoxycarbonyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoiminoalkyl, hydroxyiminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, heterocyclylamido, alkylheterocyclylamido, sulfonamido, alkylthio, alkylthioalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, cycloalkyl, nitro, alkoxy, alkylcarbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylamino, dialkylaminoalkylcarbonylamino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_2, R_3 and, when present, R_3', are independently selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylthio, alkylthioalkyl, alkylsulfonyl, alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, nitro, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylaminocarbonyl, heterocyclylcarbonyl, arylalkylaminocarbonyl, alkylcarbonylamino, hydroxyimino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur, and



;

or R_2 and R_3 can be taken together to form a fused ring system optionally interrupted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_4 and R_5, when present, are independently selected from the group consisting of hydrido, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, aryl, arylalkyl, or R_4 and R_5 may taken together with the nitrogen to which they are bound to form a heterocyclyl;

R_6 is independently selected from the group consisting of hydrido, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cyanoalkyl, or haloalkyl;

R_7 is independently selected from the group consisting of hydrido and halo;

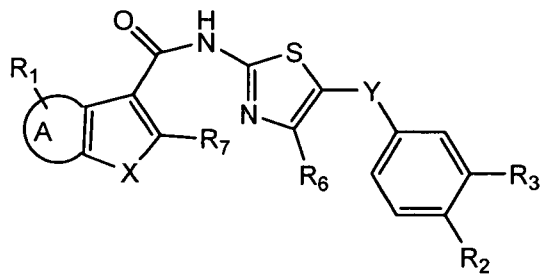
X is sulfur, oxygen, NH or N-alkyl;

Y is oxygen or alkylene; and

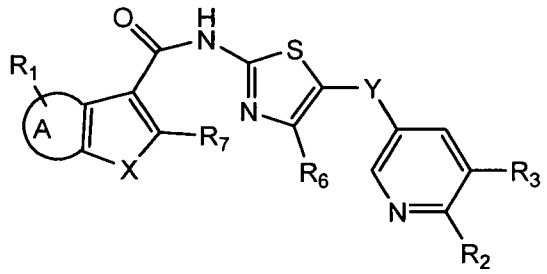
Z is N or CR_3', where R_3' is defined above;

with the proviso that when X is sulfur, A comprises 1 oxygen.

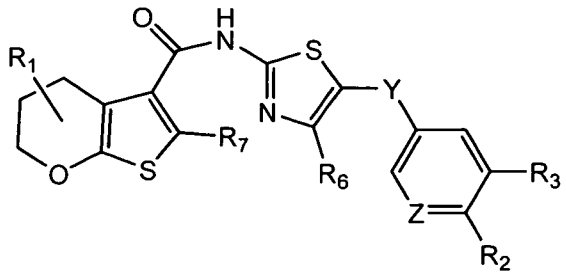
[0022] In some embodiments, Formula I is:



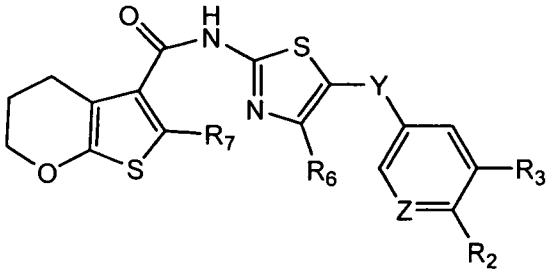
[0023] In some embodiments, Formula I is:



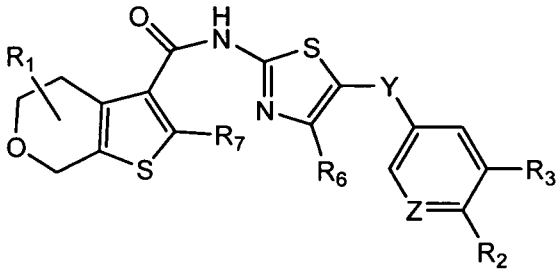
[0024] In some embodiments, Formula I is:



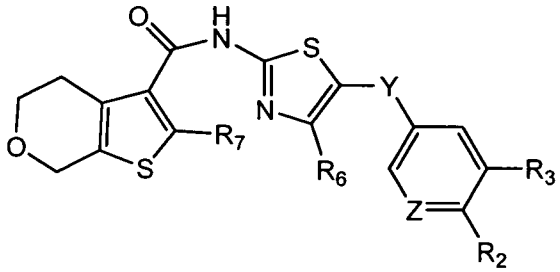
[0025] In some embodiments, Formula I is:



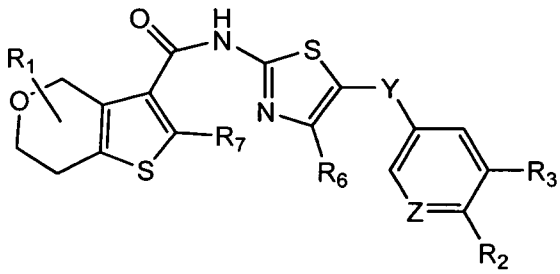
[0026] In some embodiments, Formula I is:



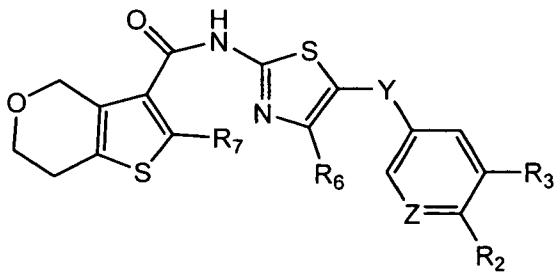
[0027] In some embodiments, Formula I is:



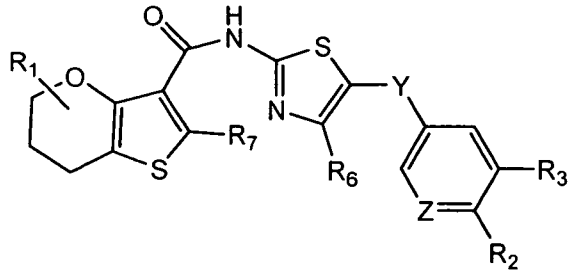
[0028] In some embodiments, Formula I is:



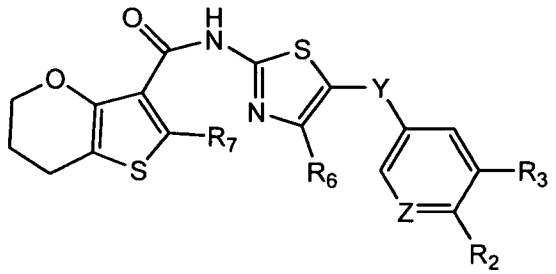
[0029] In some embodiments, Formula I is:



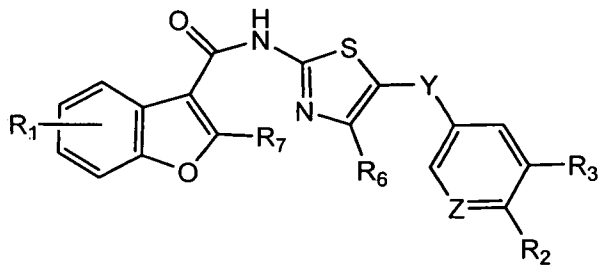
[0030] In some embodiments, Formula I is:



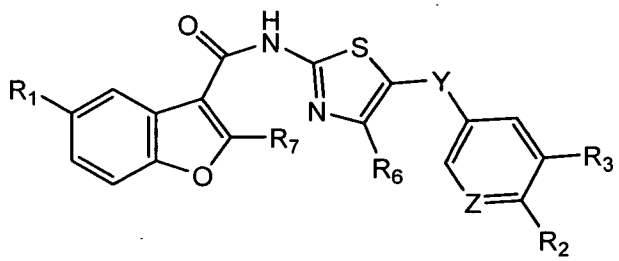
[0031] In some embodiments, Formula I is:



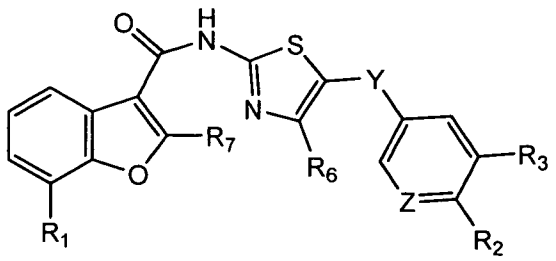
[0032] In some embodiments, Formula I is:



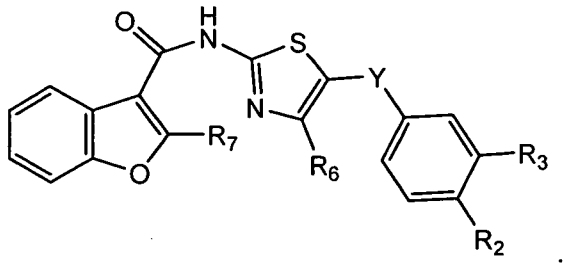
[0033] In some embodiments, Formula I is:



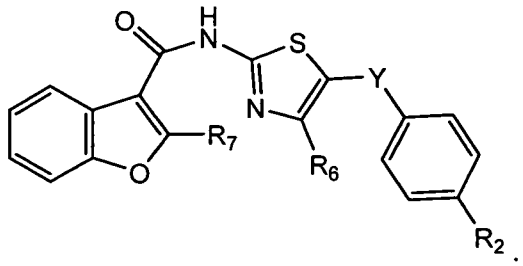
[0034] In some embodiments, Formula I is:



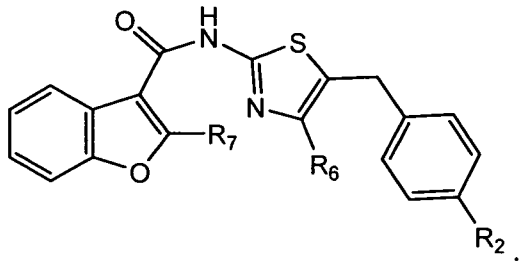
[0035] In some embodiments, Formula I is:



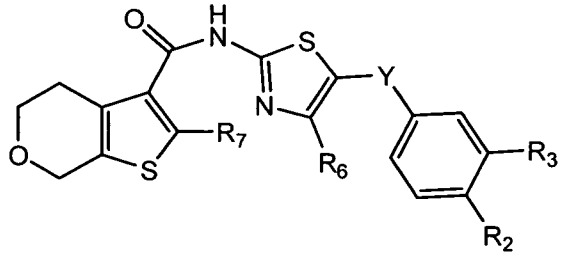
[0036] In some embodiments, Formula I is:



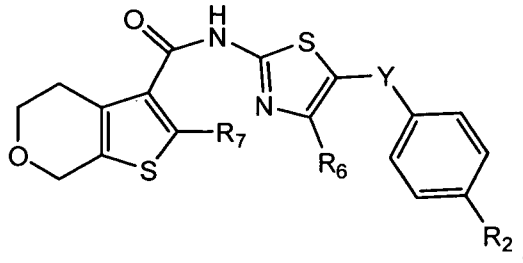
[0037] In some embodiments, Formula I is:



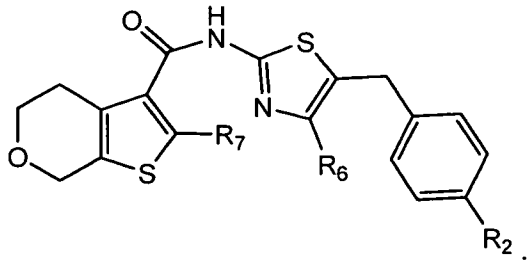
[0038] In some embodiments, Formula I is:



[0039] In some embodiments, Formula I is:



[0040] In some embodiments, Formula I is:



[0041] In some embodiments, R_3' is not present when Z is nitrogen.

[0042] In some embodiments, X is sulfur. In some embodiments, X is oxygen. In some embodiments, X is NH or N-alkyl.

[0043] In some embodiments, Y is oxygen.

[0044] In some embodiments, Y is alkylene. In some embodiments, Y is methylene. In some embodiments, Y is ethylene.

[0045] In some embodiments, Z is nitrogen. In some embodiments, Z is R_3'.

[0046] In some embodiments, A is a 6 membered heterocycle comprising an oxygen atom at the 6 position wherein A is fully saturated.

[0047] In some embodiments, A is a 6 membered carbocycle wherein A is aromatic.

[0048] In some embodiments, A is a 7 membered carbocycle wherein A is fully saturated.

[0049] In some embodiments, A is a 6 membered carbocycle wherein A is fully saturated wherein each of the 5 and 7 positions of the bicyclic ring system that comprises A are substituted with one or two R_1 moieties independently selected from the group consisting of hydrido, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, nitro, alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, cycloalkyl, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

[0050] In some embodiments, A comprises one R_1 moiety selected from the group consisting of hydrido, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, nitro, alkoxycarbonylalkyl, hydroxyalkoxyalkyl,

aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, cycloalkyl, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

[0051] In some embodiments, A is a six membered ring substituted with one R_1 at the 5 position. In some embodiments, R_1 is alkyl. In some embodiments, R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is alkoxy. In some embodiments, R_1 is methoxy. In some embodiments, R_1 is alkoxyalkyl. In some embodiments, R_1 is methoxymethyl. In some embodiments, R_1 is halo. In some embodiments, R_1 is fluoro. In some embodiments, R_1 is chloro. In some embodiments, R_1 is amino. In some embodiments, R_1 is amido. In some embodiments, R_1 is alkylamido. In some embodiments, R_1 is methylamido. In some embodiments, R_1 is ethylamido. In some embodiments, R_1 is dimethylamido. In some embodiments, R_1 is sulfonamido. In some embodiments, R_1 is heterocyclylamido. In some embodiments, R_1 is imidazolylamido. In some embodiments, R_1 is alkylheterocyclylamido. In some embodiments, R_1 is methylimidazolylamido. In some embodiments, R_1 is nitro. In some embodiments, R_1 is alkoxycarbonyl.

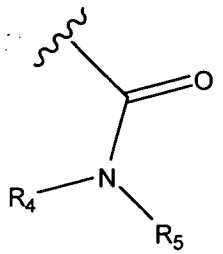
[0052] In some embodiments, A is a six membered ring substituted with one R_1 at the 7 position. In some embodiments, R_1 is alkyl. In some embodiments, R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is halo. In some embodiments, R_1 is fluoro. In some embodiments, R_1 is chloro.

[0053] In some embodiments, each R_1 is independently selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, haloalkyl, haloalkoxy, hydroxy, hydrido, cyano, amido, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoiminoalkyl, hydroxyiminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, cycloalkyl, nitro,

alkoxy, alkylcarbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylamino, dialkylaminoalkylcarbonylamino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

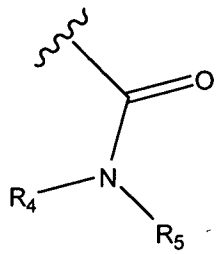
[0054] In some embodiments, A comprises one R_1 moiety selected from the group consisting of alkoxy, halo, amido, alkylamido, sulfonamido, heterocyclylamido, and alkylheterocyclylamido.

[0055] In some embodiments, R_2 and R_3 are independently selected from the group consisting of hydrido, halo, haloalkyl, hydroxyalkyl, cyano, nitro, cyanoalkyl, alkoxy, hydrosulfonyl, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl, alkoxyalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur; and



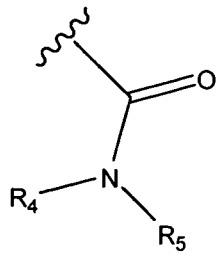
.

[0056] In some embodiments, R_3 is hydrogen and R_2 is selected from the group consisting of hydrido, halo, haloalkyl, hydroxyalkyl, cyano, cyanoalkyl, alkoxy, hydrosulfonyl, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl, alkoxyalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur; and



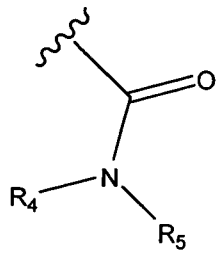
.

[0057] In some embodiments, R_2 is



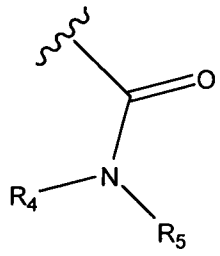
and R_4 and R_5 are independently selected from the group consisting of hydrido, aminoalkyl, alkyl, alkoxyalkyl, cyanoalkyl, cycloalkyl, aryl, and arylalkyl.

[0058] In some embodiments, R_2 is



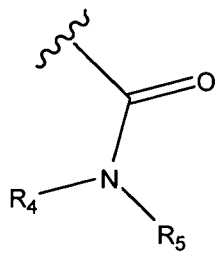
and R_4 and R_5 can be taken together with the nitrogen to which they are bound to form a heterocyclyl.

[0059] In some embodiments, R_2 is



and R_4 and R_5 are independently selected from the group consisting of hydrido, methyl, ethyl, isopropyl, methoxyethyl, ethoxyethyl, ethoxymethyl, cyanoethyl, cyclopropyl, benzyl, and phenyl.

[0060] In some embodiments, R_2 is



and R_4 and R_5 are taken together with the nitrogen to which they are bound to form a heterocyclyl selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, and morpholinyl.

[0061] In some embodiments, R_2 and R_3 are taken together to form a fused ring system optionally interrupted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

[0062] In some embodiments, R_2, R_3 and, when present, R_3', are independently selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl, alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, nitro, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

[0063] In some embodiments, R_2 and R_3 are independently selected from the group consisting of arylaminocarbonyl, heterocyclylcarbonyl, and arylalkylaminocarbonyl, alkylcarbonylamino.

[0064] In some embodiments, R_2 and R_3 are taken together to form a fused heterocycle.

[0065] In some embodiments, R_2 and R_3 are taken together to form a fused thiadiazole.

[0066] In some embodiments, R_2 and R_3 are taken together to form a fused thiazole.

[0067] In some embodiments, R_2 and R_3 are taken together to form a fused furan.

[0068] In some embodiments, R_2 and R_3 are taken together to form a fused carbocycle.

[0069] In some embodiments, R_2 and R_3 are taken together to form a fused benzyl.

[0070] In some embodiments, A is a 6 membered heterocycle comprising an oxygen atom at position 6, wherein A is fully unsaturated, Z is CR_3', R_3' is hydrido, X is sulfur, Y is methylene, and R_1 is hydrido.

[0071] In some embodiments, A is a 6 membered heterocycle comprising an oxygen atom at position 6, wherein A is fully unsaturated, Z is CR_3', X is sulfur, Y is methylene, R_1 selected from the group consisting of hydrido, halo, and alkoxyalkyl, and one or more of R_2, R_3, and R_3' is halo.

[0072] In some embodiments, A is a 6 membered heterocycle comprising an oxygen atom at position 6, wherein A is fully unsaturated, Z is CR_3', R_3' is hydrido, X is sulfur, Y is methylene, R_1 is selected from the group consisting of hydrido, halo, and alkoxyalkyl, and R_2 and R_3 are taken together to form a heteroaryl- or heterocyclyl-containing fused ring system.

[0073] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, R_2 is halo, and R_1 is selected from the group consisting of hydrido, halo, nitro, and alkoxyalkyl.

[0074] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, and R_1 is selected from the group consisting of hydrido, halo, nitro and alkoxyalkyl at the 5 position.

[0075] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, R_2 is halo, and R_1 is selected from the group consisting of hydrido, halo, nitro, and alkoxyalkyl at the 7 position.

[0076] In some embodiments, A is a 6 membered aryl ring, Z is N, X is oxygen, Y is methylene, and R_1 is selected from the group consisting of hydrido, halo, nitro, and alkoxyalkyl.

[0077] In some embodiments, A is a 6 membered aryl ring, Z is N, X is oxygen, Y is methylene, R_1 is hydrido, and R_2 is haloalkyl, alkyl, dialkylaminocarbonyl, aminocarbonyl or cyano.

[0078] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, R_1 is hydrido, and R_2 is carboxy, alkoxycarbonyl, dialkylaminocarbonyl, hydroxyalkyl, heterocyclyl, alkylaminocarbonyl, aminoiminoalkyl, aminocarbonylamido and halo.

[0079] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is ethylene, R_2 is hydrido or halo, and R_1 is selected from the group consisting of hydrido, halo, alkoxy and alkoxyalkyl.

[0080] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, R_2 is halo, and R_1 is selected from the group consisting of hydrido, aryl, sulfonamido, alkylcarbonylamino, dialkylaminocarbonylamino, and alkoxyalkylcarbonylamino.

[0081] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', R_3' is hydrido, X is oxygen, Y is methylene, R_1 is selected from the group consisting of hydrido, halo, alkoxy and alkoxyalkyl, and R_2 and R_3 are taken together to form a heteroaryl-, carbocyclyl-, aryl-, or heteroaryl-containing fused ring system.

[0082] In some embodiments, A is a 6 membered aryl ring, Z is CR_3', X is oxygen, Y is methylene, R_1 is hydrido, R_2 is halo or cyano, and at least one of R_3 or R_3' is halo, alkoxy, or alkyl.

[0083] Throughout this application certain compounds encompassed by generic descriptions have more than one R_1 group. When more than one R_1 group is present, each R_1 group may be independently selected from the group of disclosed R_1 substituents.

[0084] In some embodiments, the present invention comprises a compound as defined in any embodiment described herein for use as a medicament.

[0085] In some embodiments the present invention comprises the use of a compound as defined in any embodiment described herein, for the manufacture of a medicament to treat a disease for which an HIV inhibitor is desired.

[0086] In some embodiments the present invention comprises a method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound as defined in any embodiment described herein, optionally in combination with a therapeutically effective amount of at least one HIV inhibitor selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase inhibitors, nucleotide HIV reverse transcriptase inhibitors; HIV maturation inhibitors, and HIV fusion inhibitors.

[0087] In some embodiments the present invention comprises a pharmaceutical composition which comprises the product prepared by combining an effective amount of (a) a compound as defined in any embodiment described herein, and (b) a pharmaceutically acceptable carrier.

[0088] The compounds of the present invention have utility in antiretroviral applications. Exemplary uses include anti-lentiviral applications, and anti-HIV applications. The treatment of HIV is a preferred use. All forms of HIV-1 are potentially treatable with compounds of the present invention. Compounds of the present invention have utility in treating protease inhibitor resistant HIV, reverse transcriptase inhibitor resistant HIV, and entry/fusion inhibitor resistant HIV. Compounds of the present invention have utility in treating HIV groups M, N, and O. Compounds of the present invention have utility in treating HIV-1, including subtypes A1, A2, B, C, D, F1, F2, G, H, J; and circulating recombinant HIV forms. Compounds of the present invention have utility in treating CCR5 tropic HIV strains as well as CXCR4 tropic HIV strains.

[0089] The compounds of the present invention differ from the referenced background compounds in structure, pharmacological activity, or pharmacological potency. Some

compounds of the invention not only act favorably in terms of their capability to inhibit the replication of HIV-1, but also by their improved ability to inhibit the replication of mutant strains, in particular strains which have become resistant to commercially available drugs.

[0090] The term "9-BBN" means 9-borabicyclo[3.3.1]nonane.

[0091] The term "Ac" means acetyl.

[0092] The term "alkyl", as used alone or within other terms such as "haloalkyl" and "alkylsulfonyl", means an acyclic alkyl radical, linear or branched, preferably containing from 1 to about 10 carbon atoms and more preferably containing from 1 to about 6 carbon atoms. "Alkyl" also encompasses the sub-genera of alkenes and alkynes, such as ethenyl, ethynyl, propenyl, propynyl, isopropenyl, and other linear, branched or cyclic structures having 2-10 carbon atoms. "Alkyl" also encompasses the sub-genus of cyclic alkyl radicals containing from 3 to about 7 carbon atoms, preferably from 3 to 5 carbon atoms. Such an alkyl group may optionally be substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and C_1-C_6 alkylamino. Examples of alkyl radicals include methyl, ethyl, chloroethyl, hydroxyethyl, *n*-propyl, isopropyl, *n*-butyl, cyanobutyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, aminopentyl, isoamyl, hexyl, octyl, cyclopropyl, cyclohexyl, cyclohexenyl, and propynyl.

[0093] The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of 1 to about 6 carbon atoms, preferably 1 to about 3 carbon atoms, such as a methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy.

[0094] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of 1 to about 6 carbon atoms, attached to a divalent sulfur atom. An example of lower alkylthio, i.e., C_1-C_6 thio, is methylthio (CH_3S).

[0095] The term "alkylthioalkyl" embraces alkylthio radicals, attached to an alkyl group. An example of alkylthioalkyl is methylthiomethyl.

[0096] The terms "amido" when used independently or in conjunction with other terms such as "amidoalkyl", "*N*-monoalkylamido", "*N*-monoarylamido", "*N*,*N*-dialkylamido", "*N*-alkyl-*N*-arylamido", "*N*-alkyl-*N*-hydroxyamido" and "*N*-alkyl-*N*-hydroxyamidoalkyl", embraces carbonylamino radicals including radicals where the nitrogen is covalently bonded to 2 hydrogen atoms, to 1 hydrogen and 1 atom other than hydrogen, and to 2 atoms other than hydrogen.

[0097] The term "amu" means atomic mass unit.

[0098] The term "app" in reference to spectral data means apparent.

[0099] The term "approx" means approximately.

[00100] The term "aryl" means a fully unsaturated mono- or multi-ring carbocycle. Examples of such radicals include substituted or unsubstituted phenyls, naphthyls, and anthracenyls. The term "aryl", as used alone or within other terms, means a mono- or multi-ring aromatic ring structure containing between one and four rings wherein such rings may be attached together in a pendent manner or may be fused. Such an "aryl" group may be optionally substituted with one or more substituents such as C_1-C_6 alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and C_1-C_6 alkylamino. The term "aryl" refers to both cyclic structures consisting only of carbon (carboaryls), and cyclic structures comprising carbon and one or more heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen (heteroaryls).

[00101] The term "BOC" or "Boc" means *tert*-butoxycarbonyl.

[0100] The term "br" in reference to spectral data means broad.

[0101] The term "*n*-Bu" refers to normal (primary) butyl.

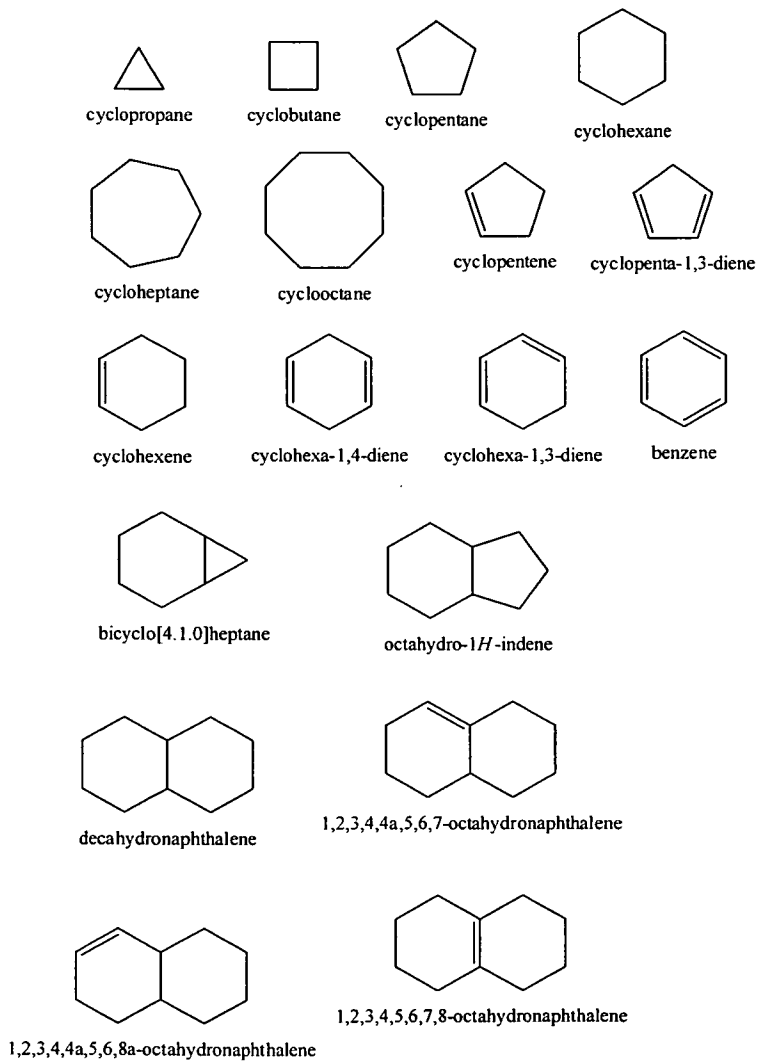
[0102] The term "°C" means degrees Celsius.

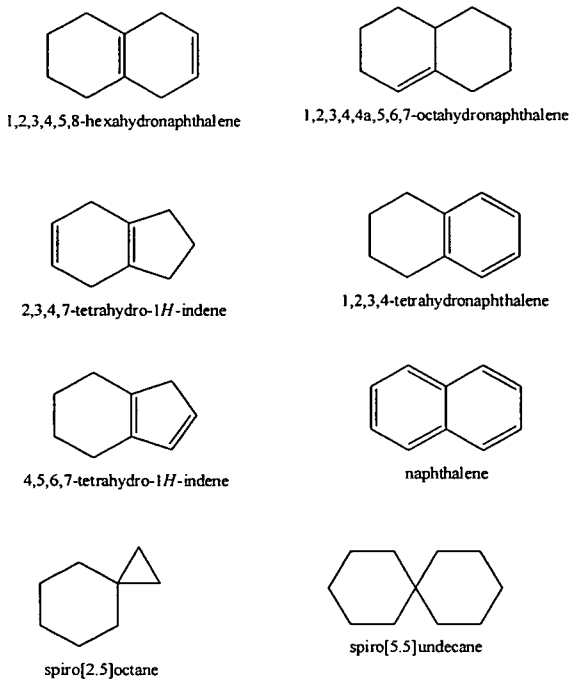
[0103] The term "cat" means catalytic.

[0104] The term "conc' or "concd" means concentrated.

[0105] The term "carbocycle" as used alone or within other terms, means a mono- or multi-ring ring structure consisting only of carbon containing between one and four rings wherein such rings may be attached together in a pendent manner or may be fused. The term "carbocycle" refers to fully saturated and unsaturated ring systems as well as partially unsaturated ring systems. The term "carbocycle" additionally encompasses spiro

systems wherein one cycloalkyl ring has a carbon ring atom in common with another cycloalkyl ring. The term "carbocycle" additionally encompasses bridged systems. Illustrative examples of monocyclic, bicyclic or tricyclic saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4.2.0]octanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, cyclononanyl, cyclodecanyl, decahydronapthalenyl, and tetradecahydroanthracenyl. Illustrative examples of monocyclic, bicyclic or tricyclic partially saturated carbocycles include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octenyl, bicyclo[4.2.0]octenyl, cyclononenyl, cyclodecenyl, octahydronaphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, and 1,2,3,4,4a,9,9a,10-octahydroanthracenyl. Illustrative examples of monocyclic, bicyclic or tricyclic aromatic carbocycles include phenyl, naphthalenyl, and anthracenyl. Thus, the term "carbocycle" includes the following exemplary structures:





[0106] The terms "carboxy" and "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

[0107] The term "combination therapy" refers to the administration of a compound of the present invention and a secondary anti-infective or pharmaceutical agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. For example, one combination of the present invention comprises a

reverse transcriptase inhibitor and a fusion inhibitor of the present invention administered as separate agents at the same or different times or they can be formulated as a single, co-formulated pharmaceutical composition comprising the two compounds. As another example, a combination of the present invention comprises a reverse transcriptase inhibitor and a fusion inhibitor of the present invention formulated as separate pharmaceutical compositions that can be administered at the same or different time. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, one component of a particular combination may be administered by intravenous injection while the other component(s) of the combination may be administered orally. The components may be administered in any therapeutically effective sequence.

[0108] The term "δ" means chemical shift in parts per million downfield from tetramethylsilane.

[0109] The term "d" in reference to time means days; the term "d" in reference to spectral data means doublet.

[0110] The term "*d*" means density.

[0111] The term "Δ" means reflux.

[0112] The term "DCE" means 1,2-dichloroethane.

[0113] The term "DCM" means dichloromethane.

[0114] The term "DIPEA" means *N,N*-diisopropylethylamine.

[0115] The term "DMA" means *N,N*-dimethylacetamide.

[0116] The term "DME" means 1,2-dimethoxyethane.

[0117] The term "DMF" means *N,N*-dimethylformamide.

[0118] The term "DMP" means Dess-Martin periodinane.

[0119] The term "DMSO" means dimethyl sulfoxide.

[0120] The term "DPPA" means diphenylphosphoryl azide.

[0121] The term "EC_{50}" means the drug concentration that results in a 50% reduction in virus replication.

[0122] The term "equiv" or "eq" means equivalents.

[0123] The term "ES" or "ES+" means electrospray ionization.

[0124] The term "Et" means ethyl.

[0125] The term "g" means grams.

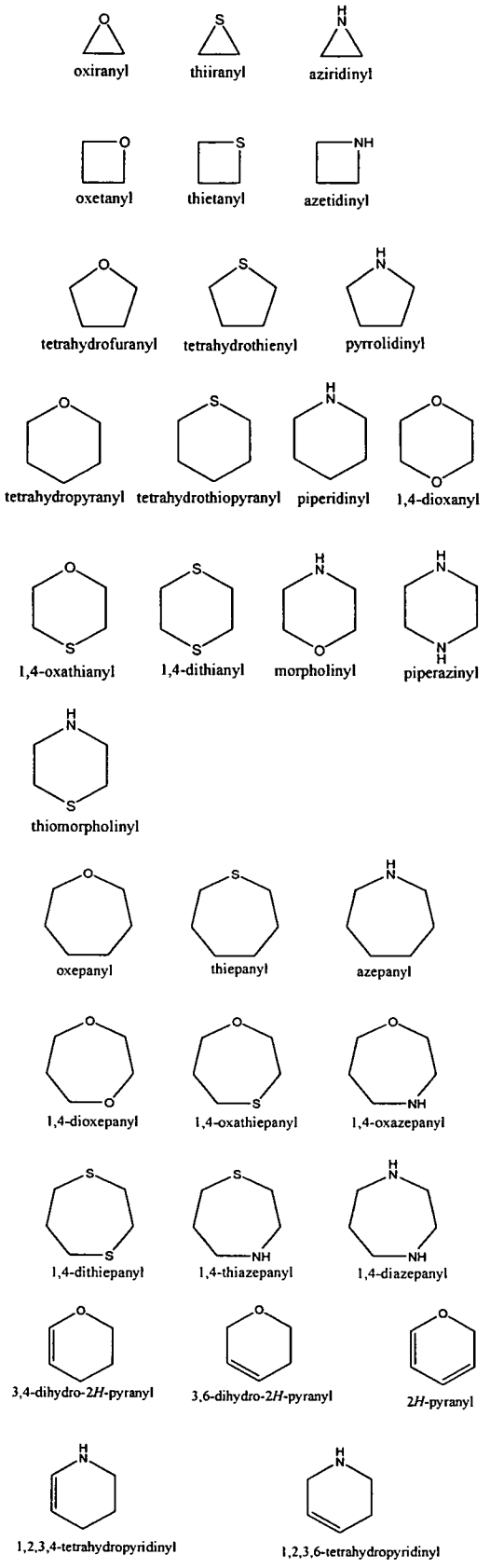
[0126] The term "h" or "hr" means hours.

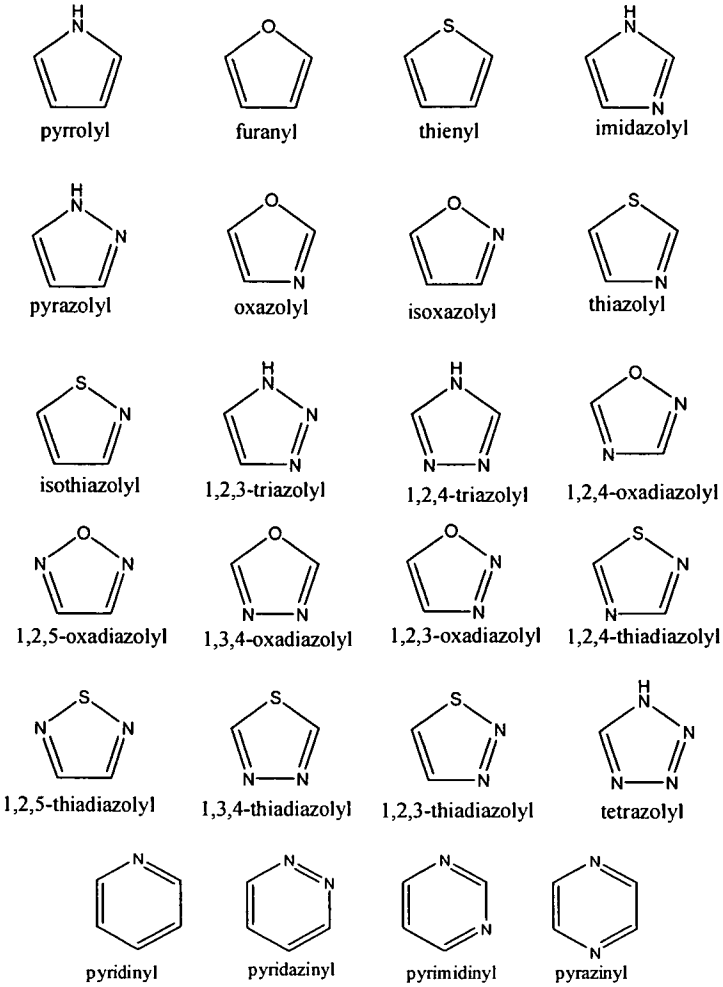
[0127] The term "halo" means a halogen radical derived from fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, polyhaloalkyl, and perhalo radicals. A monohaloalkyl radical, for one example, may have one atom selected from the group consisting of iodo, bromo, chloro and fluoro atoms within the radical. Polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means an alkyl radical having all hydrido radicals replaced with fluorine atoms. Examples include trifluoromethyl and pentafluoroethyl.

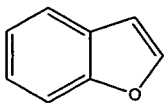
[0128] The term "HATU" means *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate.

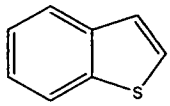
[0129] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. The term "heterocycle" refers to fully saturated and unsaturated ring systems as well as partially unsaturated ring systems. The term "heterocycle" is intended to include all the possible isomeric forms of the heterocycle, for example, pyrrolyl comprises 1*H*-pyrrolyl and 2*H*-pyrrolyl. Illustrative examples of monocyclic, bicyclic or tricyclic saturated heterocycles include tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl, tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl, triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyrazinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, decahydroquinolinyl, and octahydroindolyl. Illustrative examples of monocyclic, bicyclic or tricyclic partially saturated heterocycles include azetyl, pyrrolinyl, imidazolinyl, pyrazolinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolanyl, 2,3-dihydro-1,4-benzodioxinyl, indolinyl and the like. Illustrative examples of monocyclic,

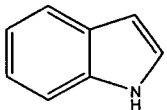
bicyclic or tricyclic aromatic heterocycles include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolizinyl, indolyl, isoindolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinolizinyl, phthalazinyl, quinoxalinyl, quinazolinyl, naphthyridinyl, pteridinyl, benzopyranyl, pyrrolopyridinyl, thienopyridinyl, furanopyridinyl, isothiazolopyridinyl, thiazolopyridinyl, isoxazolopyridinyl, oxazolopyridinyl, pyrazolopyridinyl, imidazopyridinyl, pyrrolopyrazinyl, thienopyrazinyl, furanopyrazinyl, isothiazolopyrazinyl, thiazolopyrazinyl, isoxazolopyrazinyl, oxazolopyrazinyl, pyrazolopyrazinyl, imidazopyrazinyl, pyrrolopyrimidinyl, thienopyrimidinyl, furanopyrimidinyl, isothiazolopyrimidinyl, thiazolopyrimidinyl, isoxazolopyrimidinyl, oxazolopyrimidinyl, pyrazolopyrimidinyl, imidazopyrimidinyl, pyrrolopyridazinyl, thienopyridazinyl, furanopyridazinyl, isothiazolopyridazinyl, thiazolopyridazinyl, isoxazolopyridazinyl, oxazolopyridazinyl, pyrazolopyridazinyl, imidazopyridazinyl, oxadiazolopyridinyl, thiadiazolopyridinyl, triazolopyridinyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, triazolopyrimidinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, imidazooxazolyl, imidazothiazolyl, imidazoimidazolyl, isoxazolotriazinyl, isothiazolotriazinyl, pyrazolotriazinyl, oxazolotriazinyl, thiazolotriazinyl, imidazotriazinyl, oxadiazolotriazinyl, thiadiazolotriazinyl, triazolotriazinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl. Thus, the term "heterocycle" includes the following exemplary structures which are not depicted as radicals as each may form be attached through a covalent bond to any atom so long as appropriate valences are maintained:

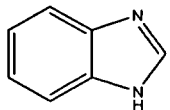

oxiranyl
thiiranyl
aziridinyl
oxetanyl
thietanyl
azetidinyl
tetrahydrofuranyl
tetrahydrothienyl
pyrrolidinyl
tetrahydropyranyl
tetrahydrothiopyranyl
piperidinyl
1,4-dioxanyl
1,4-oxathianyl
1,4-dithianyl
morpholinyl
piperazinyl
thiomorpholinyl
oxepanyl
thiepanyl
azepanyl
1,4-dioxepanyl
1,4-oxathiepanyl
1,4-oxazepanyl
1,4-dithiepanyl
1,4-thiazepanyl
1,4-diazepanyl
3,4-dihydro-2H-pyranyl
3,6-dihydro-2H-pyranyl
2H-pyranyl
1,2,3,4-tetrahydropyridinyl
1,2,3,6-tetrahydropyridinyl

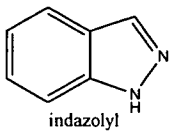

pyrrolyl
furanyl
thienyl
imidazolyl
pyrazolyl
oxazolyl
isoxazolyl
thiazolyl
isothiazolyl
1,2,3-triazolyl
1,2,4-triazolyl
1,2,4-oxadiazolyl
1,2,5-oxadiazolyl
1,3,4-oxadiazolyl
1,2,3-oxadiazolyl
1,2,4-thiadiazolyl
1,2,5-thiadiazolyl
1,3,4-thiadiazolyl
1,2,3-thiadiazolyl
tetrazolyl
pyridinyl
pyridazinyl
pyrimidinyl
pyrazinyl

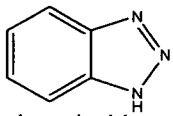

benzofuranyl

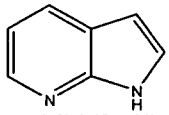

benzothienyl

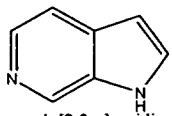

indolyl

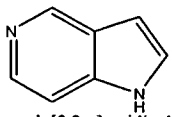

benzimidazolyl

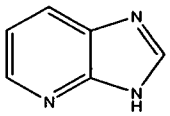

indazolyl

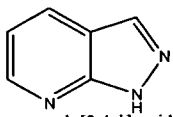

benzotriazolyl

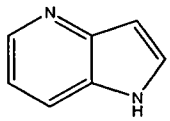

pyrrolo[2,3-*b*]pyridinyl

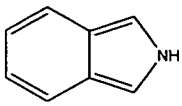

pyrrolo[2,3-*c*]pyridinyl

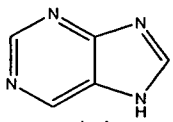

pyrrolo[3,2-*c*]pyridinyl

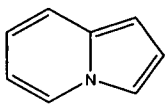

imidazo[4,5-*b*]pyridinyl

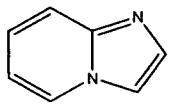

pyrazolo[3,4-*b*]pyridinyl

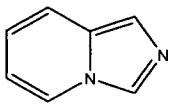

pyrrolo[3,2-*b*]pyridinyl

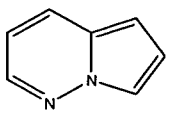

isoindolyl

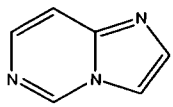

purinyl

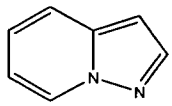

indolizinyl

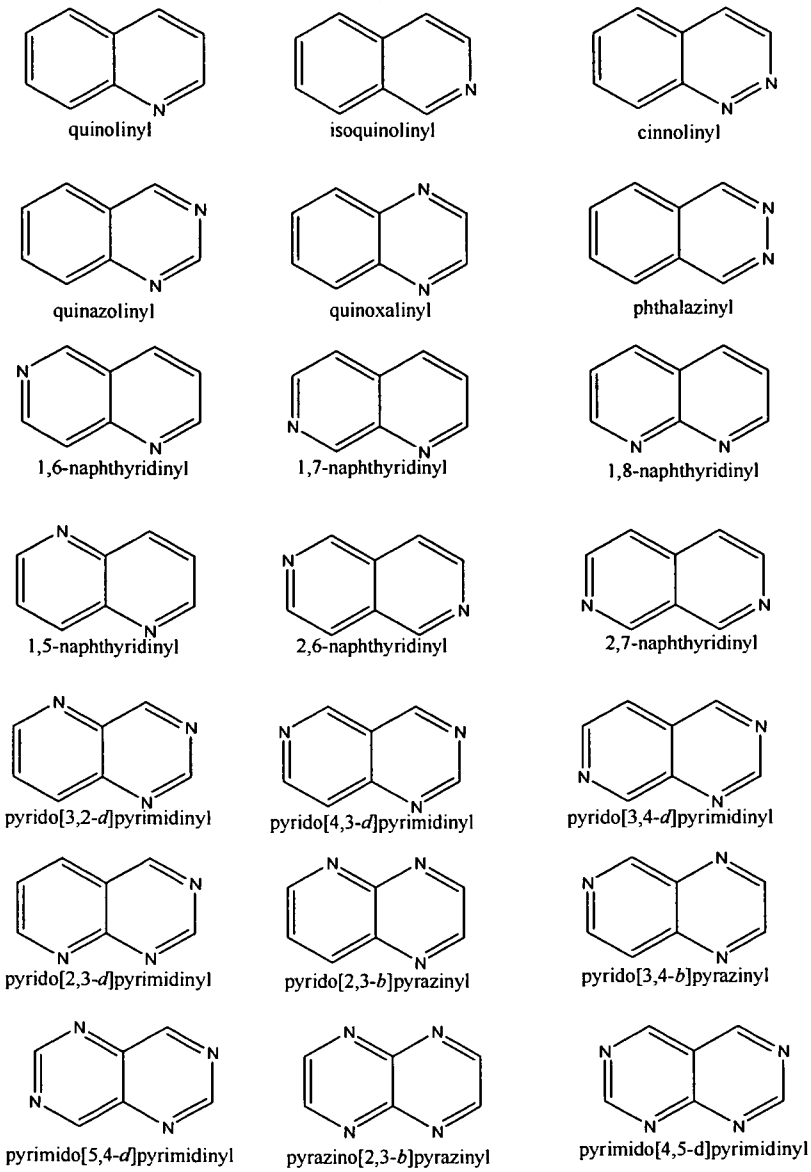

imidazo[1,2-*a*]pyridinyl


imidazo[1,5-*a*]pyridinyl


pyrrolo[1,2-*b*]pyridazinyl


imidazo[1,2-*c*]pyrimidinyl


pyrazolo[1,5-*a*]pyridinyl



[0130] The term "heteroaryl" means a fully unsaturated heterocycle.

[0131] With regard to any of "carbocycle," "aryl," "heterocycle," or "heteroaryl", the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring. For terms such as aralkyl, and heteroarylalkyl, the moiety may be linked through any ring atom or through any atom of the alkyl portion so long as the resultant molecule is chemically stable. The presence of charge, for example when a pyridinyl radical is attached via the ring nitrogen to yield a quaternary nitrogen, does not in and of itself mean that the resultant molecule is not chemically stable. The use of "carbocycle," "aryl," "heterocycle," and "heteroaryl" moieties includes divalent attachment at appropriate substitutable sites.

[0132] The term "HPLC" means high performance liquid chromatography.

[0133] The term "hydrido" means a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical (-OH) or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical.

[0134] The term "Hz" means hertz; "MHz" means megahertz

[0135] The term "IBX" means *o*-iodoxybenzoic acid.

[0136] Depending on context, the term "IC_{50}" means either the drug concentration that results in inhibition of 50% of virus replication when referring to virus replication assays, or the drug concentration that results in inhibition of 50% of 6HB formation when referring to the 6HB assay.

[0137] The term "L" means liters.

[0138] The term "LAH" means lithium aluminum hydride.

[0139] The term "LC" means liquid chromatography.

[0140] The term "μ" means 10^{-6}.

[0141] The term "m" in reference to an amount means 10^{-3}; the term "m" in reference to a spectral data means multiplet.

[0142] The term "M" means molar.

[0143] The term "Me" means methyl.

[0144] The term "min" means minutes.

[0145] The term "mol" means moles.

[0146] The term "Ms" refers to mesyl, methanesulfonyl.

[0147] The term "MS" means mass spectrometry.

[0148] The term "MT-2 cells" refers to human T-cell leukemia cells isolated from cord blood lymphocytes and co-cultured with cells from patients with adult T-cell leukemia. The MT-2 cell line was acquired from the AIDS Research and Reference Reagent Program.

[0149] The term "MTBE" means methyl *tert*-butyl ether.

[0150] The term "*m/z*" means mass-to-charge ratio.

[0151] The term "NMO" means *N*-methylmorpholine *N*-oxide.

[0152] The term "NMP" means *N*-methylpyrrolidinone.

[0153] The term "NMR" means nuclear magnetic resonance.

[0154] The term "obs" in reference to spectral data means obscured.

[0155] The term "*o*-Tol" means *o*-tolyl.

[0156] The term "oxo" means a doubly bonded oxygen.

[0157] The term "PCC" means pyridinium chlorochromate.

[0158] The term "Ph" means phenyl.

[0159] The term "ppm" means parts per million.

[0160] The term "prodrug" means a chemical derivative of an active parent drug that releases the active parent drug upon spontaneous or enzymatic biotransformation. The term "prodrug" includes variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions including solvolysis or enzymatic degradation. In some embodiments of the present invention the prodrug is either pharmacologically inactive or exhibits reduced activity relevant to its active parent drug.

[0161] The term "q" in reference to spectral data means quartet.

[0162] The term "rt" means room temperature.

[0163] The term "s" in reference to spectral data means singlet.

[0164] The term "satd" means saturated.

[0165] The term "selective" as referring to a particular event means that the particular event occurs with greater frequency than other potential event(s).

[0166] The term "solvate" means a molecular complex comprising a compound of the present invention and a proportional number of solvent molecules. The term "hydrate" means a solvate where the solvent is water. In some embodiments of the present invention the solvate comprises a fractional amount of a solvent molecule per molecule of the present invention, for example, a hemisolvate. In some embodiments of the present invention the solvate comprises one solvent molecule per molecule of the present invention, for example, a monosolvate. In some embodiments of the present invention the solvate comprises two solvent molecules per molecule of the present invention, for example, a disolvate.

[0167] The term "t" in reference to spectral data means triplet.

[0168] The term "*t*-Bu" means tertiary butyl.

[0169] The term "TEA" means triethylamine.

[0170] The term "TEOF" means triethylorthoformate.

[0171] The term "TFA" means trifluoroacetic acid.

[0172] "Therapeutic effect" as used herein means some extent of relief of one or more of the symptoms of an HIV-related disorder. In reference to the treatment of HIV, a therapeutic effect refers to one or more of the following: 1) reduction in the number of infected cells; 2) reduction in the number of virions present in serum; 3) inhibition (i.e., slowing to some extent, preferably completely) the rate of HIV replication; 4) relieving or reducing to some extent one or more of the symptoms associated with HIV; and 5) relieving or reducing the side effects associated with the administration of other antiretroviral agents.

[0173] "Therapeutically effective amount" as used herein means the amount required to achieve a therapeutic effect.

[0174] The term "THF" means tetrahydrofuran.

[0175] The term "TLC" means thin layer chromatography.

[0176] The term "TPAP" means tetra-*n*-propylammonium perruthenate.

[0177] The term "t_R" in reference to chromatographic analysis means retention time.

[0178] "Weight percent" as used herein means the weight percent of a specified ingredient based upon the total weight of all ingredients of the composition.

[0179] Compounds of the present invention include all regioisomers (e.g., *cis* and *trans* isomers) and stereoisomers (e.g. *R* and *S* enantiomers) of the compound of Formula I as well as racemic and diastereomeric forms of such isomers. The present invention includes an enantiomeric excess of any particular stereoisomer that is described herein. Enantiomeric excesses include excesses of whereby a particular enantiomer is provided in a relative percentage of 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% and 95% compared to its other enantiomer. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active base and then separation of the mixture of diastereoisomers by crystallization, followed by liberation of the optically active bases from such salts. Alternatively, diastereoisomeric salts may be treated with an optically active acid and then separation of the mixture of diastereoisomers by crystallization, followed by liberation of the optically active acids from such salts. Examples of appropriate bases are brucine, dehydroabietylamine, quinine, cinchonidine, ephedrine, α-methylbenzylamine, deoxyphedrine, 2-amino-1-butanol, and 1-(1-naphthyl)ethylamine. Examples of appropriate acids are tartaric, diacetyltartaric,

dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules. In some methods, the synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the present invention can likewise be obtained by utilizing an optically active starting material or reagent. These isomers may be in the form of a free acid, a free base, an ester, a salt, an amide or a prodrug.

[0180] When any variable (e.g. R_3, heteroatom, X) occurs more than one time in any moiety, the choice of a variable is independently selected in each occurrence.

[0181] When present, any or all of alkyl, alkoxy, carboxamido, aryl, carbocycle, heterocyclyl, and heteroaryl radicals may be substituted at any position with a C_1-C_6 alkyl, hydroxyl, halo, amino, alkylamino, dialkylamino, carboxy, or cyano group so long as appropriate valences are maintained.

[0182] Some compounds of Formula I and their respective prodrugs can exist in several tautomeric forms, including the keto-enol form and enamine-imine form and geometric isomers and mixtures thereof. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

Unit Dosages

[0183] Dosages described in this application refer to mass of the free acid equivalent of the relevant compound.

[0184] Illustrative dosage unit forms of the pharmaceutical compositions can typically contain about, 100, 200, 250, 300, 350, 400, 450, or 500 mg of a compound of the present invention. In some embodiments, the dosage unit form contains about 200, 300, 400, or 500 mg of a compound of the present invention. The dosage unit form can be selected to accommodate the desired frequency of administration used to achieve the specified daily dosage. The amount of the unit dosage form of the pharmaceutical composition that is administered and the dosage regimen for treating the condition or disorder depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the

severity of the condition or disorder, the route and frequency of administration, and thus can vary widely, as is well known.

[0185] Where it is desired to formulate dosage units in which each unit consists of less than a therapeutically effective amount of a compound of the present invention, multiple dosage units, each containing smaller amounts of a compound of the present invention, can be administered to constitute the daily dose.

[0186] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0187] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

Prodrugs

[0188] The present invention further provides pharmaceutical compositions and methods of treatment comprising prodrugs of a compound of Formula I. Prodrugs of this invention may be called single, double, or triple, depending on the number of biotransformation steps required to release the active parent drug, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism. Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, an ester prepared by reaction of a parent acid with a suitable alcohol, or an amide prepared by reaction of the parent acid compound with an amine, or a basic group reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability. For example, a compound of Formula I having one or more free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds comprising an amino acid residue, or a polypeptide chain of two or more amino acid residues which are covalently joined through peptide bonds to a free amino, hydroxy or carboxylic acid groups of compounds of the invention. Amino acid

residues useful in accordance with the present invention include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, 2-aminovaleric acid, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of a compound of the invention through the carbonyl carbon prodrug sidechain. Prodrugs also include compounds wherein the administered compound undergoes oxidative metabolism to produce the active species.

Salts

[0189] The present invention further provides a pharmaceutically acceptable salt of a compound of the present invention composition.

[0190] Pharmaceutically acceptable salts of the compounds of the invention can be prepared by contacting the base forms of these compounds with a stoichiometric amount of the appropriate base or acid in an aqueous solvent, such as water, or in an organic solvent, or in a mixture of aqueous and organic solvents. In some embodiments of the present invention, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

[0191] The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of Formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid. Such salts are also known as acid addition salts. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 1955; 66:219, which are known to the skilled artisan.

[0192] Examples of acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, and phosphoric acid, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, benzenesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, and acetic acid. Example of such pharmaceutically

acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogen phosphate, dihydrogen phosphate, bromide, iodide, acetate, propionate, decanoate, formate, hydrochloride, heptanoate, propiolate, glucuronate, glutamate, salicylate, oxalate, malonate, succinate, maleate, hydroxymaleate, mandelate, mesylate, nitrate, stearate, phthalate, terephthalate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, hemi-tartrate, benzenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, mandelate, and tartarate. In one embodiment, the pharmaceutically acceptable salt is a hydrochloride salt of a compound of the present invention. In one embodiment, the pharmaceutically acceptable salt is a hydrobromide salt of a compound of the present invention. In one embodiment, the pharmaceutically acceptable salt is a methanesulfonate salt of a compound of the present invention.

[0193] Examples of suitable base salts, hydrates, esters, or solvates of a compound of the present invention include hydroxides, carbonates, bicarbonates, alkali metal salts, and alkaline earth metal salts. Bases commonly employed to form salts of the present invention include inorganic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc and organic salts made from lysine, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine.

[0194] It should be recognized that any salt may exist as a hydrate or solvate and that such hydrates and solvates are contemplated by the present invention.

[0195] Multiple salts forms are included within the scope of the present invention where a chemical of the present invention contains more than one group capable of forming such a salt. In some embodiments, disalts are preferred. Examples of typical mono-salt forms include, but are not limited to hydrochloride and methanesulfonate. Examples of suitable multiple salt forms include, but are not limited to dihydrochloride and dimethanesulfonate.

[0196] The present invention also provides all pharmaceutically-acceptable isotopically labeled compounds of the present invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature.

[0197] Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, for example ^{2}H or ^{3}H, carbon, for example ^{11}C, ^{13}C, or ^{14}C, chlorine, for example ^{36}Cl, fluorine, for example ^{18}F, iodine, for example ^{123}I or ^{125}I, nitrogen, for example ^{13}N or ^{15}N, oxygen, for example ^{15}O, ^{17}O, or ^{18}O, phosphorus, for example ^{32}P, and sulfur, for example ^{35}S.

[0198] Certain isotopically labeled compounds of the present invention are useful in drug or substrate tissue studies. The radioactive isotopes tritium (^{3}H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0199] Substitution with heavier isotopes, for example deuterium (^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half life or reduced dosage requirements.

[0200] Substitution with positron emitting isotopes, for example ^{11}C, ^{18}F, ^{15}O, or ^{13}N, may be useful in positron emission topography (PET) studies for examining substrate-receptor occupancy.

[0201] Isotopically labeled compounds of the present invention can be prepared by conventional techniques known to those skilled in the art or by synthetic processes analogous to those described in the present application using appropriate isotopically labeled reagents in place of the non-labeled reagent mentioned therein.

Activity Assays

Generation of chronically infected H9 cells:

[0202] $3x10^{6}$ H9 cells were incubated with 1 mL of HIV-1 (strain RF) supplemented with 40 μg/mL of DEAE-dextran. Virus and cells were incubated together at 37 °C for 2-4 hours with sporadic shaking to resuspend cells. 10 mL of media (RPMI 1640 containing 10% fetal bovine serum and supplemented with 50 μg/mL gentamicin) was then added and the virus-cell coculture was incubated at 37 °C in a humidified 5% CO_2 incubator. 3 days post-infection and every 2-3 days thereafter, the infected H9/HIV-1_{RF} cells were centrifuged, the supernatant was removed, and the cells were resuspended at a density of 0.3 x 10^{6} cells/mL in media (RPMI 1640 containing 10% fetal bovine serum and supplemented with 50 μg/mL gentamicin). Chronically infected H9/HIV-1_{RF} cells were used in experiments starting 12-15 days after infection and up to 40 days post-infection.

Indicator cells for virus infection:

[0203] HeLa-CD4/LTR-β-gal (MAGI) cells were propagated in Dulbecco's Modified Eagle's Medium containing 10% fetal bovine serum and supplemented with 200 μg/mL G418 and 100 μg/mL hygromycin B.

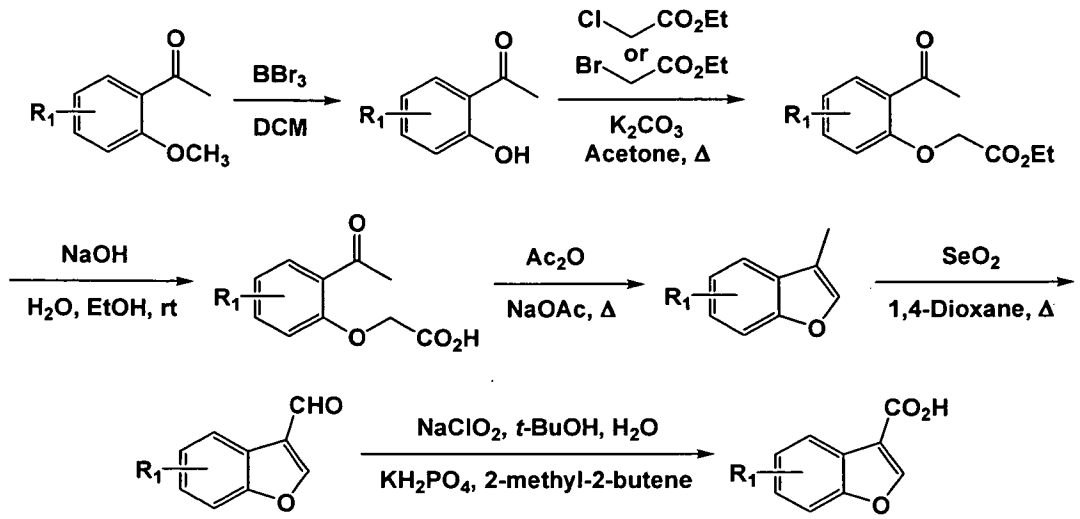
Six-helix bundle (6HB) assay:

[0204] This assay determines the effect of compounds on conformational changes in HIV envelope glycoprotein (Env) that are required in order for Env to mediate the fusion of the viral and cellular membranes during virus entry and infection. Specifically, this assay measures the effect of compounds on the formation of the HIV Env six-helix bundle (6HB) structure.

[0205] H9 cells chronically infected with HIV-1 (H9/HIV-1_{RF}) were resuspended in Stain/Wash Buffer (1% bovine serum albumin, 0.1% sodium azide in phosphate-buffered saline) and aliquoted at 2.5 x 10^5 cells per well into 96-well V-bottom plates containing various concentrations of test compounds. Cells and compounds were incubated for 30 minutes at 37 °C. Recombinant soluble CD4 (sCD4) was then added to a final concentration of 1 μg/mL. Negative control wells contained no sCD4 and no test compound. Positive control wells contained sCD4 but no test compound. The plate was incubated for 1 hour at 37 °C to allow the sCD4 to bind to HIV Env and induce conformational changes in the Env protein. Antibody that is specific for the HIV Env six-helix bundle conformation was then added (1 μL polyclonal rabbit serum per well), and the plate was incubated for an additional 1 hour at 37 °C to permit antibody binding. The cells were then washed once with Stain/Wash Buffer to remove compound and excess antibody. The cells were resuspended in Stain/Wash Buffer containing PE-labeled anti-rabbit secondary antibody (KPL) at 0.25 μg per well. The cells were incubated for 45 min at 4 °C to permit secondary antibody binding. Fluorescence was detected using a BD FACSArray™ bioanalyzer. Compounds that inhibited Env conformational changes were identified as those that decreased primary antibody binding to the six-helix bundle epitope resulting in a decrease in fluorescence signal.

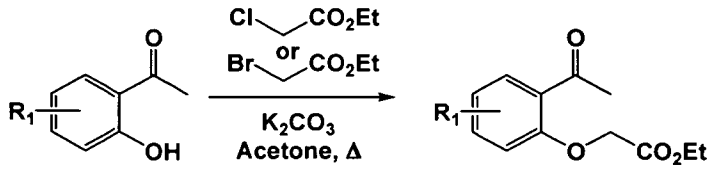
Examples: Synthetic Processes

General Route A: Synthesis of 3-Benzofurancarboxylic Acids



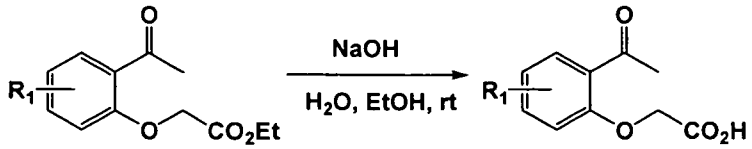
Methods:

Method A



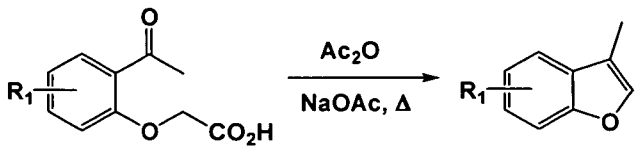
[0206] In accordance with the procedure of Nielek and Lesiak (*Chem. Ber.*, **1982**, *115*, 1247-1251), a suspension of the phenol (1 equiv) and K_2CO_3 (2-4 equiv) in acetone (5 vol) stirring at rt is treated with the α-haloacetate (1.2-1.4 equiv) then heated at reflux for 2-16 h. Reaction progress is monitored by LC/MS. On completion, the reaction mixture is allowed to cool to rt then filtered. The filter cake is washed with EtOAc (10 vol) and the filtrate is concd *in vacuo* to afford the desired product.

Method B



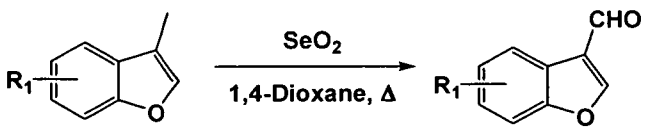
[0207] A solution of the ethyl ester (1 equiv) in EtOH (3 vol) stirring at rt is treated with 3 M NaOH (1.5 vol) and stirring continued at this temperature for 0.5-2 h. Reaction progress is monitored by LC/MS. On completion the EtOH is removed *in vacuo* and the residual aqueous cooled to 0 °C and treated with concd HCl until pH 1-2. The resultant precipitate is collected by filtration and washed with water (1.5 vol) to afford on drying (vacuum oven) the desired product.

Method C



[0208] In accordance with the procedure of Nielek and Lesiak (*Chem. Ber.*, **1982**, *115*, 1247-1251), a suspension of the carboxylic acid (1 equiv) and NaOAc (6 equiv) in Ac_2O (6 vol) is warmed to reflux and stirred 2-16 h. Reaction progress is monitored by LC/MS. On completion the reaction mixture is allowed to cool to rt then poured onto ice (6 vol). The resultant aqueous suspension is extracted with EtOAc (3 x 3 vol) and the combined organic phases washed with water (2 x 3 vol), dried (Na_2SO_4), filtered and the filtrate concd *in vacuo* to afford the desired product.

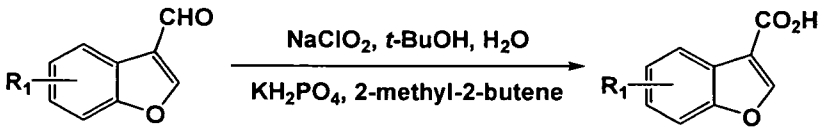
Method D



[00102] In accordance with the procedure of Zaidlewicz *et al.* (*Heterocycles*, **2001**, *55*, 569-577), a suspension of the 3-methylbenzofuran (1 equiv) and SeO_2 (1.2 equiv) in 1,4-dioxane (6 vol) is warmed to reflux and stirred 24 h. At this juncture, reaction progress is

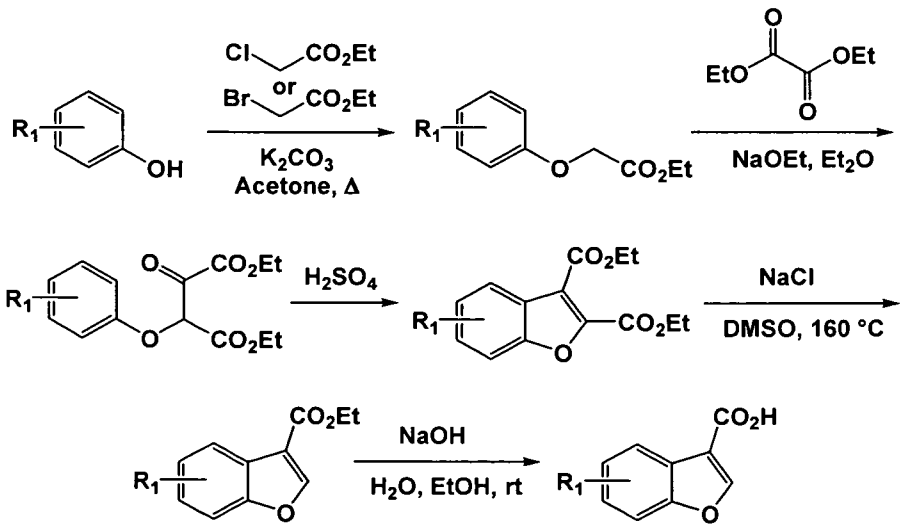
assessed by TLC or LC/MS. If the reaction is incomplete, a further portion of SeO_2 (1.2 equiv) is added and stirring continued at reflux for a further 24 h. On completion the reaction mixture is allowed to cool to rt and filtered through Celite® 521. The filter cake is washed with EtOAc (12 vol), the filtrate concd *in vacuo*, and the residue purified by column chromatography (silica gel, 5-40% EtOAc in heptanes) affording the desired product.

Method E

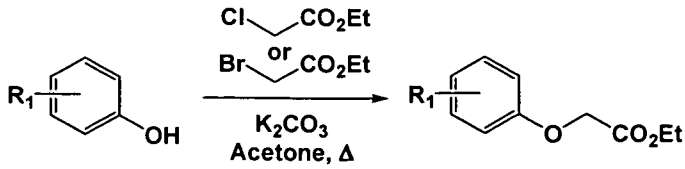


[0209] To an rt solution of the benzofuran-3-carboxaldehyde (1 equiv) in a 4:1 mixture of *t*-BuOH and water (25 vol) is added 2-methyl-2-butene (7 equiv) and KH_2PO_4 (1 equiv) and stirred at this temperature for 30 min. $NaClO_2$ (3.3 equiv) is added and the reaction stirred at rt a further 16 h. Reaction progress is monitored by LC/MS. On completion the reaction mixture is diluted with satd NH_4Cl (25 vol) and extracted with EtOAc (3 x 10 vol). The combined organic phases are washed with brine (10 vol), dried (Na_2SO_4) and filtered and the filtrate concd *in vacuo* to afford the desired product.

General Route B: Synthesis of 3-Benzofurancarboxylic Acids

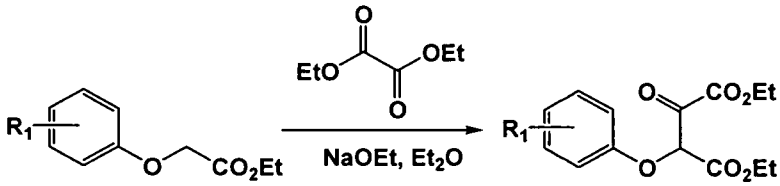


Methods:



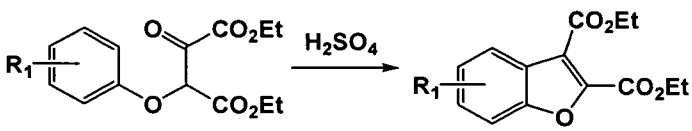
Ether formation is achieved employing **Method A**.

Method F



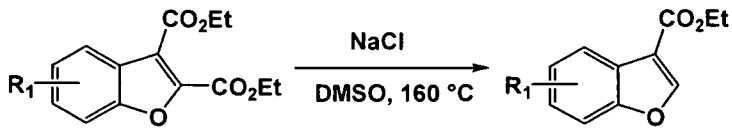
[0210] A stirred suspension of NaH (1.05 equiv) in Et_2O (10 vol) at rt is treated with EtOH (1 equiv) dropwise over 5 min, followed by diethyl oxalate (1.16 equiv). On warming to reflux, a solution of the ethyl ester (1 equiv) in Et_2O (2 vol) is added dropwise over 10 min, then stirring at reflux continued for a further 2 h. Reaction progress is monitored by TLC or LC/MS. On completion, the reaction mixture is allowed to cool to rt, poured onto a mixture of ice (7 vol) and 2 M HCl (7 vol), and extracted with Et_2O (3 x 20 vol). The combined organic phases are dried (Na_2SO_4), filtered and the filtrate concd *in vacuo* to give the desired product.

Method G



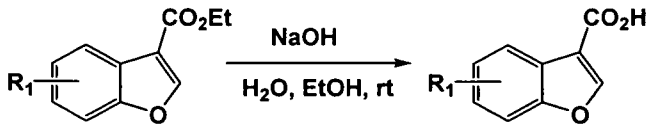
[0211] The diester (1 equiv) is added dropwise with stirring to cold (-15 °C) conc H_2SO_4. The reaction mixture is then allowed to warm to rt over the course of 4-5 h. Reaction progress is monitored by TLC or LC/MS. On completion, the reaction mixture is poured onto ice (40 vol) and the resultant aqueous suspension extracted with EtOAc (3 x 10 vol). The combined organic phases are washed with water (2 x 10 vol), brine (10 vol), dried (Na_2SO_4), filtered and the filtrate concd *in vacuo*. Purification by column chromatography (silica gel, 20% EtOAc in heptanes) provides the desired product.

Method H



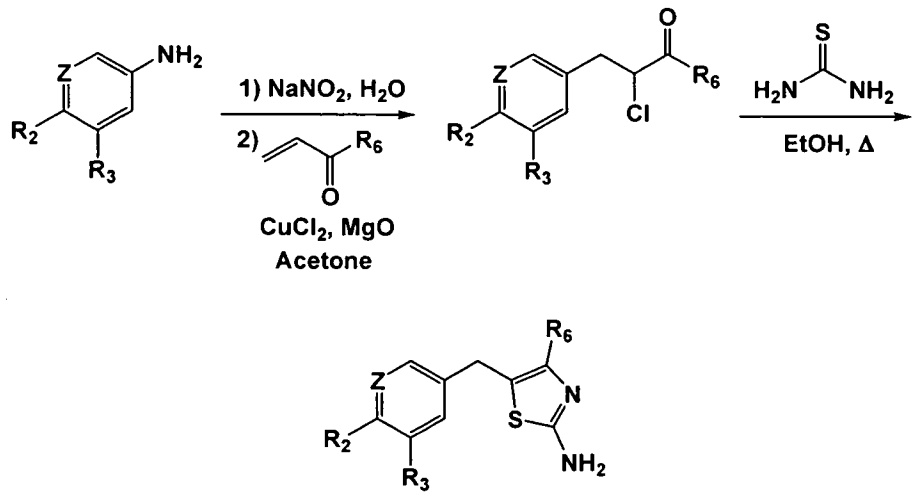
[0212] A stirred solution of the diester (1 equiv) in DMSO (7 vol) is treated with NaCl (2 equiv) followed by water (2 equiv) then warmed to 160 °C for 5-16 h. Reaction progress is monitored by TLC or LC/MS. On completion, the DMSO is removed *in vacuo* and the residue purified by column chromatography (silica gel, 5% EtOAc in heptanes) to give the desired product.

Method I

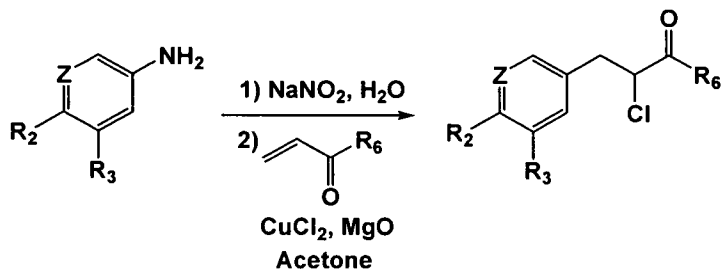


[0213] A stirred solution of the ester (1 equiv) in EtOH (8 vol) and THF (1.6 vol) is treated with a solution of NaOH (4 equiv) in water (3.2 vol) at rt. The reaction mixture is stirred at rt until judged complete by TLC or LC/MS analysis. On completion, the volatiles are removed *in vacuo* and the aqueous residue acidified to pH 1-2 by the addition of 2 M HCl. The resultant precipitate is extracted into EtOAc (3 x 40 vol), the combined EtOAc phases washed with brine (40 vol), dried (Na_2SO_4), filtered, and the filtrate concd *in vacuo* providing the desired product.

General Route C: Synthesis of 4-(Arylmethyl)- or 4-(Heteroarylmethyl)-2-Thiazolamines

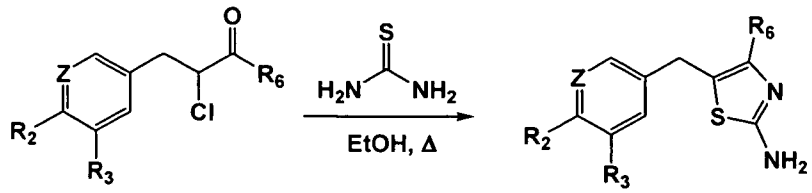


Method J



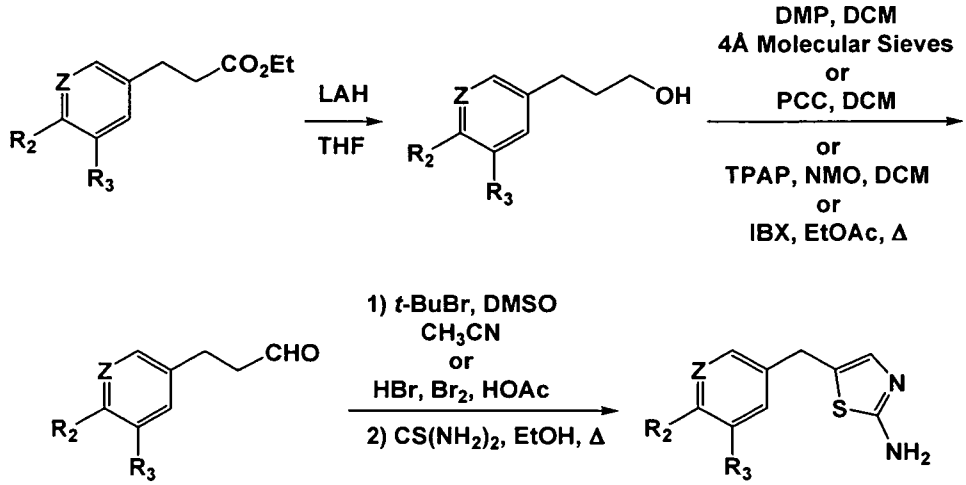
[0214] Following the procedure of Boushak *et al.* (*Russ. J. Org. Chem.*, **2004**, *40*, 412-417), to a chilled (0 °C) suspension of the aniline or amino heterocycle (1 equiv) in water (10 vol) and conc HCl (2.8 vol) is added a solution of $NaNO_2$ (1.1 equiv) in water (4 vol) over 5-10 min. The reaction is then allowed to warm to 10 °C over 30 min before carefully neutralizing the solution to pH 6 by the addition of solid $NaHCO_3$. This cooled (0 °C) solution is added dropwise over 15 min to a rapidly stirred suspension of $CuCl_2 \cdot H_2O$ (0.3 equiv), MgO (2.5 molar %) and acrolein or a vinyl ketone (1 equiv) in acetone (2.2 vol) at rt. On stirring a further 16 h at this temperature, the reaction mixture is diluted with water (10 vol) and extracted with EtOAc (3 x 10 vol). The combined organic phases are dried (Na_2SO_4), filtered and the filtrate concd *in vacuo* to afford the desired product.

Method K

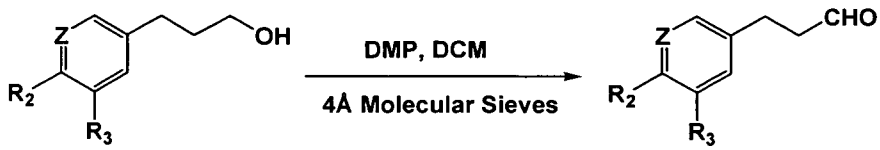


[0215] A stirred solution of the α-chloroaldehyde or α-chloroketone (1 equiv) and thiourea (0.85-2.10 equiv) in EtOH (4.5 vol) is refluxed for 2 h. Reaction progress is monitored by LC/MS. On completion, the reaction mixture is worked-up and purified as detailed in the examples given below to give the desired product.

General Route D: Synthesis of 4-(Arylmethyl)- or 4-(Heteroarylmethyl)-2-Thiazolamines



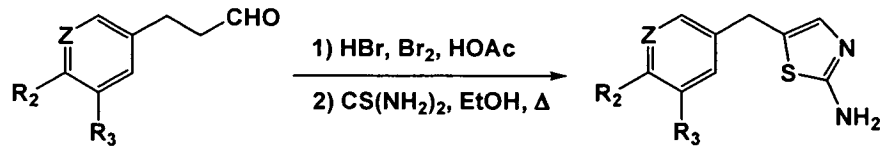
Method L



[0216] Dess-Martin periodinane (1.1 equiv) is added to a rapidly stirred rt suspension of the alcohol (1 equiv) in DCM (60 vol) and molecular sieves (4Å, 8-12 mesh). Reaction progress is monitored by TLC. On completion, the molecular sieves are removed by filtration and the filtrate concd *in vacuo*. Column chromatography (silica gel, EtOAc) provides the desired product. Alternatively, after filtration the reaction mixture is partitioned between Et_2O (60 vol) and 1 M NaOH (60 vol) and the two phases separated.

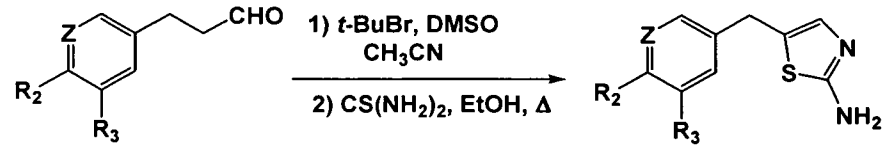
The organic phase is washed with 1 M NaOH (2 x 60 vol) and brine (60 vol), dried ($MgSO_4$), filtered and concd *in vacuo* to give the desired product.

Method M1



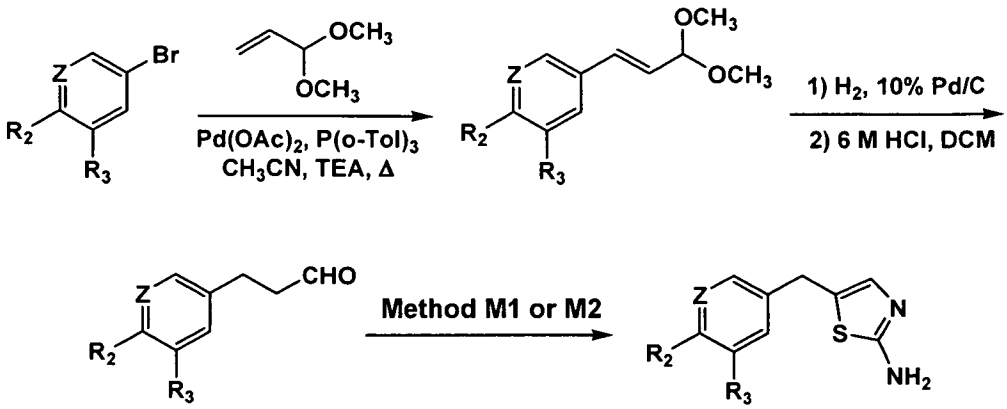
[0217] A solution of the aldehyde (1 equiv) in AcOH (15 vol) is cooled to 5 °C and treated with a solution of 33% HBr in AcOH (1.1 equiv) dropwise over 5-10 min. A solution of bromine (1.1 equiv) in AcOH (15 vol) is then added over 5 min. After warming to rt and stirring for 3 h, the reaction mixture is concd *in vacuo*. The residue is redissolved into DCM (15 vol) and concd *in vacuo* three times. The residue thus obtained is dissolved in EtOH (15 vol), thiourea (1.1 equiv) is added and heated at reflux for 2 h. The progress of the cyclization is monitored by LC/MS. On completion, reaction mixture is allowed to cool to rt and the resultant precipitate isolated by filtration. The solid thus obtained is treated with satd $NaHCO_3$ (45 vol) and extracted into EtOAc (3 x 45 vol). The combined EtOAc phases are dried (Na_2SO_4), filtered and the filtrate concd *in vacuo* affording the desired product.

Method M2-Alternative Bromination Procedure

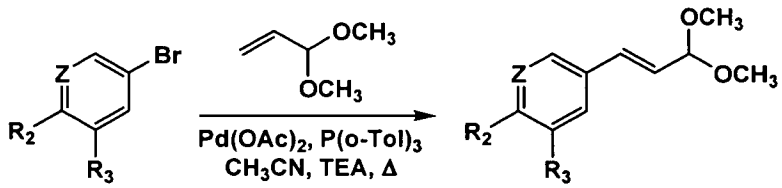


[0218] To a solution of the aldehyde (1 equiv) and *t*-BuBr (4 equiv) in MeCN (20 vol) is added a solution of DMSO (2 equiv) in MeCN (20 vol) and warmed to 65 °C for 3 h. Reaction progress is monitored by LC/MS. On completion of the bromination, the reaction mixture is reduced *in vacuo* and treated with thiourea (1.1 equiv) in accordance with **Method M1** as detailed above.

General Route E: Synthesis of 4-(Arylmethyl)- or 4-(Heteroarylmethyl)-2-Thiazolamines

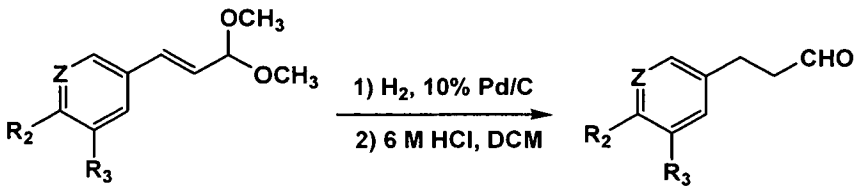


Method N



[0219] A degassed (N_2) solution of the aryl or heteroaryl bromide (1 equiv), acrolein dimethyl acetal (1.25 equiv) and tri-*o*-tolylphosphine (0.20 equiv) in TEA (4-5 vol) and MeCN (4-5 vol) is treated with $Pd(OAc)_2$ (5 molar %) and heated at reflux for 4-16 h. Reaction progress is monitored by LC/MS. On completion the reaction mixture is allowed to cool to rt and the solvents evaporated. Purification of the residue using column chromatography (silica gel, 25% EtOAc in heptanes) gives the desired product.

Method O

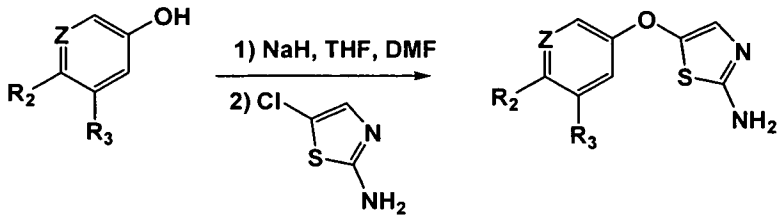


[0220] A rapidly stirred suspension of the alkene (1 equiv) and 10% Pd/C (20% by wt) in EtOH (60 vol) at rt is placed under an atmosphere of H_2 (1 bar) and stirred 2 h, or until the alkene reduction is judged to be complete by LC/MS analysis. On completion, the reaction mixture is filtered through Celite® 521. The filter cake is washed with EtOH (180 vol), the combined filtrates concd *in vacuo*, the residue redissolved in DCM (20 vol), and 6 M HCl (40 vol) is added. The biphasic mixture is stirred 1 h before carefully neutralizing to pH 7-8 by the addition of solid $NaHCO_3$. The mixture is

extracted with EtOAc (3 x 40 vol), the combined organic phases dried (Na_2SO_4), filtered, and the filtrate concd *in vacuo*. Column chromatography (silica gel, 30-40% EtOAc in heptanes) provides the desired product.

General Route F: Synthesis of 4-(Aryloxy)- or 4-(Heteroaryloxy)-2-Thiazolamines

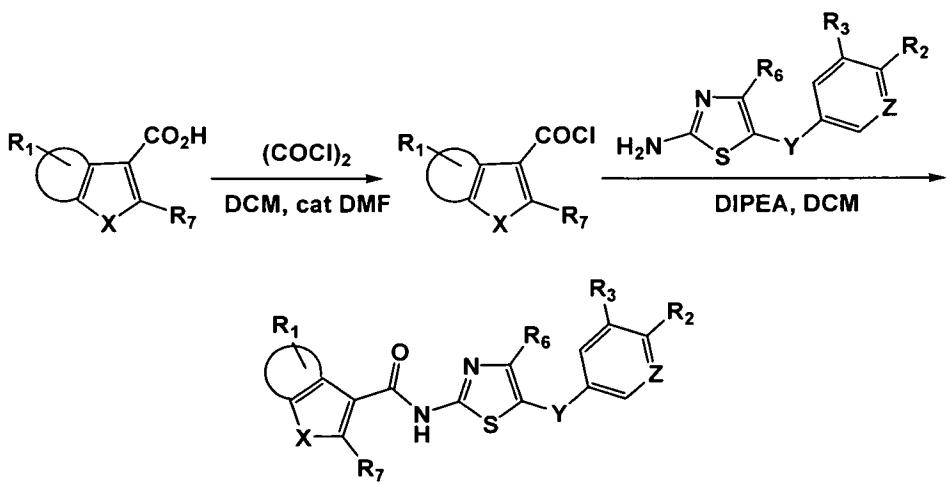
Method P



[0221] In accordance with a literature procedure (WO2005/075435), NaH (2.2 equiv) is carefully added portionwise to a stirring solution of the phenol or hydroxy heterocycle (2 equiv) in 9:1 THF/DMF (20 vol) at over 5 min. A suspension of 2-amino-5-chlorothiazole hydrochloride (1 equiv) in a 9:1 THF/DMF (20 vol) is added dropwise over 10 min and stirring at rt continued for a further 30 min. Reaction progress is monitored by TLC. On completion, the reaction mixture is diluted with water (40 vol) and extracted with MTBE (3 x 40 vol). The combined organic phases are dried (Na_2SO_4), filtered, and concd *in vacuo*. Column chromatography (silica gel, 60-70% MTBE in heptanes) gives the desired product.

General Route G: Synthesis of *N*-Thiazolyl Carboxamides

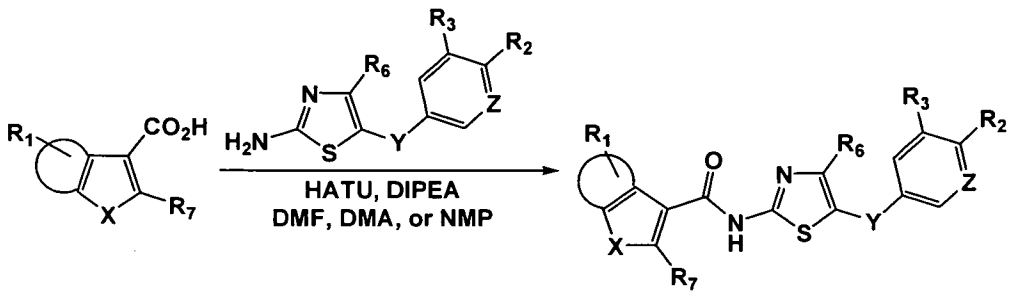
Method Q



[0222] A stirred suspension of the carboxylic acid in DCM (20 vol) at rt is treated with oxalyl chloride (1.3-3.0 equiv) followed by a few drops of DMF and the reaction mixture stirred for 0.5-1 h. The DCM and oxalyl chloride are evaporated and the residue redissolved in DCM (10 vol). A solution of the appropriate aminothiazole (0.85-1.0 equiv) and DIPEA (1.0-1.4 equiv) in DCM (10 vol) is added to the cooled (0 °C) reaction mixture over 5-10 min, after which time it is warmed to rt and stirred a further 2-16 h. Amide formation is monitored by LC/MS. On completion, the reaction mixture is diluted with satd $NaHCO_3$ (50 vol) and extracted into DCM (3 x 50 vol). The combined DCM phases are washed with water (50 vol) and brine (50 vol), dried (Na_2SO_4), filtered and concd to afford the desired product. Further purification by column chromatography (silica gel, EtOAc in heptanes) or recrystallization (DCM) is performed as necessary.

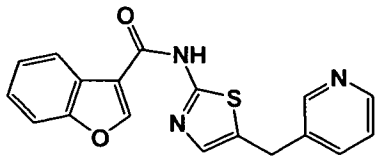
General Route H: Synthesis of *N*-Thiazolyl Carboxamides

Method R



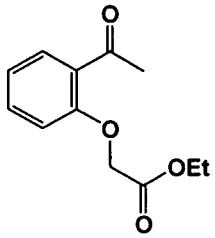
[0223] The carboxylic acid (1 equiv) in DMF (50 vol) is treated with HATU (1.0-1.2 equiv) followed by DIPEA (1.1-1.2 equiv) and stirred 5-10 min at rt. This solution is transferred to a flask containing the amine (0.9-1.2 equiv) and the reaction stirred at rt for 16 h or 80 °C for 1 h. Reaction progress is monitored by LC/MS. On completion the reaction mixture is diluted with water (100 vol) and extracted into EtOAc (3 x 50 vol). The combined organic phases are washed with water (2 x 50 vol), brine (50 vol), dried (Na_2SO_4), filtered and concd *in vacuo*. Column chromatography (silica gel, EtOAc in heptanes) provides the desired product. Further purification by recrystallization (MeCN) is performed as necessary.

Examples of Compounds Prepared Using General Routes A-H



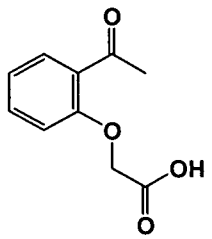
8

Example 1: 2-(2-Acetylphenoxy)acetic Acid Ethyl Ester (1)



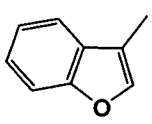
[0224] 2'-Hydroxyacetophenone (10.0 g, 73.5 mmol) is treated with ethyl bromoacetate (11.4 mL, 0.103 mol, *d* 1.506) and K_2CO_3 (40.5 g, 0.294 mol) in accordance with **Method A** to afford the title compound (20.7 g) as a white wax which is used as is without further purification: LC/MS t_R 1.82 min; MS (ES+) *m/z* 223 (M+H), 245 (M+Na); ^{1}H NMR (360 MHz, $CDCl_3$, δ_H) 7.76 (1H, dd), 7.44 (1H, ddd), 7.05 (1H, app td), 6.83 (1H, dd), 4.72 (2H, s), 4.28 (2H, q), 2.72 (3H, s), 1.30 (3H, t).

Example 2: 2-(2-Acetylphenoxy)acetic Acid (2)



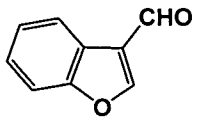
[0225] Ethyl ester **1** (20.7 g) is saponified in accordance with **Method B** to afford the title compound (17.3 g) as an off-white powder which is used as is without further purification: ^{1}H NMR (360 MHz, CD_3OD, δ_H) 7.68 (1H, dd), 7.50 (1H, app td), 6.99-7.07 (2H, m), 4.82 (2H, s), 2.69 (3H, s).

Example 3: 3-Methylbenzofuran (3)



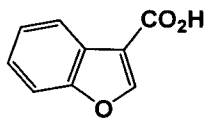
[0226] Carboxylic acid **2** (17.3 g) is reacted in accordance with **Method C** affording the title compound (5.08 g) as a light brown oil: LC/MS t_R 2.13 min; ^{1}H NMR (360 MHz, $CDCl_3$, δH) 7.55 (1H, dd), 7.47 (1H, dd), 7.42 (1H, q), 7.31 (1H, app td), 7.26 (1H, app td), 2.27 (3H, d).

Example 4: 3-Benzofurancarboxaldehyde (4)



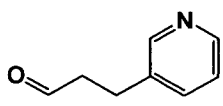
[0227] 3-Methylbenzofuran **3** (5.08 g, 38.5 mmol) is treated with SeO_2 (5.10 g, 46.2 mmol) in accordance with **Method D** affording the title compound (3.08 g) after column chromatography (silica gel, 5% EtOAc in heptanes) as a light yellow wax: ^{1}H NMR (360 MHz, $CDCl_3$, δH) 10.19 (1H, s), 8.28 (1H, s), 8.20 (1H, dd), 7.57 (1H, dd), 7.43 (1H, app td), 7.40 (1H, app td).

Example 5: 3-Benzofurancarboxylic Acid (5)



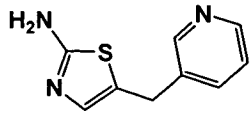
[0228] 3-Benzofurancarboxaldehyde **4** (3.08 g, 21.1 mmol) is treated with KH_2PO_4 (2.86 g, 21.1 mmol), 2-methyl-2-butene (15.6 mL, 0.148 mol, *d* 0.662), and $NaClO_2$ (6.30 g, 69.6 mmol) in accordance with **Method E** providing the title compound (3.48 g) as a white powder: ^{1}H NMR (360 MHz, CD_3OD, δ_H) 8.32 (1H, s), 8.06 (1H, dd), 7.53 (1H, dd), 7.35 (1H, app td), 7.32 (1H, app td).

Example 6: 3-Pyridinepropanal (6)



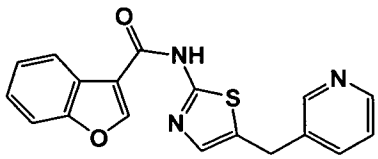
[0229] 3-Pyridinepropanol (0.50 g, 3.6 mmol) is treated with DMP (1.70 g, 4.01 mmol) in accordance with **Method L** affording the title compound (0.34 g) after column chromatography (silica gel, EtOAc) as a light yellow crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 9.81 (1H, t), 8.41-8.49 (2H, m), 7.53 (1H, ddd), 7.22 (1H, ddd), 2.95 (2H, t), 2.81 (2H, app tt).

Example 7: 5-(3-Pyridinylmethyl)-2-thiazolamine (7)

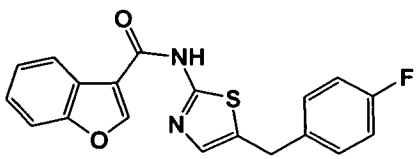


[0230] Aldehyde **6** (150 mg, 1.11 mmol) is treated with Br_2 (60 μL, 1.2 mmol, *d* 3.02) and HBr in AcOH in accordance with **Method M1**. The α-bromoaldehyde thus obtained is treated directly with thiourea (93 mg, 1.2 mmol) as detailed **Method M1** affording the title compound (106 mg) as an off-white powder: LC/MS t_R 0.22 min; MS (ES+) *m/z* 192 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 9.31 (2H, br s), 8.93 (1H, s), 8.85 (1H, d), 8.48 (1H, d), 8.01 (1H, dd), 7.29 (1H, s), 4.26 (2H, s).

Example 8: *N*-[5-(3-Pyridinylmethyl)-2-thiazolyl]-3-benzofurancarboxamide (8)

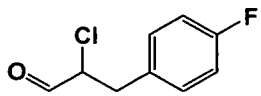


[0231] Acid **5** (42 mg, 0.26 mmol) is treated with HATU (104 mg, 0.290 mmol), DIPEA (50 μL, 0.29 mmol, *d* 0.742) and aminothiazole **7** (50 mg, 0.26 mmol) in accordance with **Method R** providing the title compound (17 mg) after column chromatography (silica gel, 50-75% EtOAc in heptanes) as a cream powder: LC/MS t_R 1.45 min; MS (ES+) *m/z* 336 (M+H), 377; ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.55 (1H, d), 8.52 (1H, dd), 8.28 (1H, s), 8.14 (1H, dd), 7.60 (1H, dd), 7.55 (1H, app dt), 7.44 (1H, app td), 7.39 (1H, app td), 7.25 (1H, dd), 6.96 (1H, s), 4.10 (2H, s).



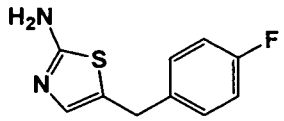
11

Example 9: 2-Chloro-3-(4-fluorophenyl)propanal (9)



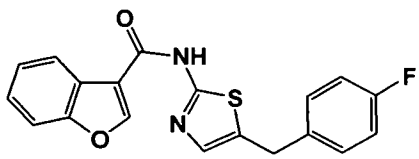
[0232] The diazonium salt of 4-fluoroaniline (4.32 mL, 45.0 mmol, *d* 1.157) is formed using $NaNO_2$ (3.4 g, 50 mmol) in aqueous HCl in accordance with **Method J**. The salt thus formed is reacted directly with acrolein (3.0 mL, 45 mmol, *d* 0.839), $CuCl_2 \cdot H_2O$ (2.30 g, 13.5 mmol) and MgO (44 mg, 1.1 mmol) as detailed in **Method J** affording the title compound (6.50 g) as a brown oil: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 9.55 (1H, d), 7.21 (2H, dd), 7.02 (2H, t), 4.36 (1H, ddd), 3.36 (1H, dd), 3.06 (1H, dd).

Example 10: 5-[(4-Fluorophenyl)methyl]-2-thiazolamine (10)

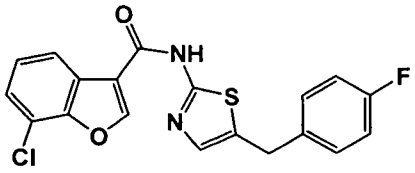


[0233] α-Chloroaldehyde **9** (6.50 g, 35.0 mmol) is reacted with thiourea (3.60 g, 47.0 mmol) in accordance with **Method K**. On completion, the reaction mixture is allowed to cool to rt and the solvent evaporated. Recrystallization of the residue (EtOAc) afforded the title compound (1.37 g) as a light brown crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 7.19 (2H, dd), 7.00 (2H, t), 6.79 (1H, s), 4.97 (2H, br s), 3.94 (2H, s). The mother liquor is reduced *in vacuo* and the residue purified by column chromatography (silica gel, 80% EtOAc in heptanes) providing a second batch of the title compound (1.63 g), also as a light brown crystalline solid.

Example 11: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (11)

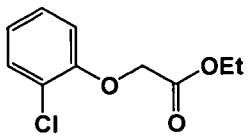


[0234] In accordance with **Method Q**, acid **5** (0.50 g, 3.1 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (0.80 mL, 9.3 mmol, *d* 1.455) and catalytic DMF (10 μL) then treated with DIPEA (0.53 mL, 3.1 mmol, *d* 0.742) and aminothiazole **10** (0.64 g, 3.1 mmol). Recrystallization (DCM) affords the title compound (0.35 g) as an off-white solid: LC/MS t_R 2.44 min; MS (ES+) *m/z* 353 (M+H); ^{1}H NMR (250 MHz, acetone-d_6, δ_H) 8.85 (1H, s), 8.23 (1H, dd), 7.64 (1H, dd), 7.32-7.50 (4H, m), 7.25 (1H, s), 7.10 (2H, t), 4.16 (2H, s).



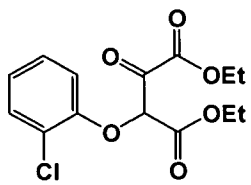
17

Example 12: 2-(2-Chlorophenoxy)acetic Acid Ethyl Ester (12)



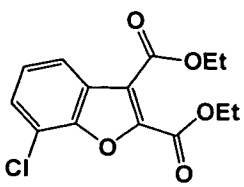
[0235] 2-Chlorophenol (1.61 mL, 15.6 mmol, *d* 1.241) is treated with ethyl chloroacetate (2.0 mL, 19 mmol, *d* 1.145) and K_2CO_3 (4.3 g, 31 mmol) in accordance with **Method A** providing the title compound (5.5 g) as a dark brown oil which is used as is without further purification: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 7.38 (1H, dd), 7.19 (1H, app td), 6.94 (1H, app td), 6.84 (1H, dd), 4.68 (2H, s), 4.25 (2H, q), 1.28 (3H, t).

Example 13: 2-(2-Chlorophenoxy)-3-oxobutanedioic Acid Diethyl Ester (13)



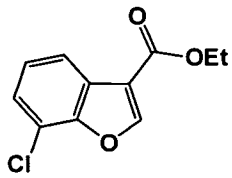
[0236] Ethyl ester **12** (5.5 g) is treated with diethyl oxalate (2.3 mL, 17.0 mmol, *d* 1.076) and NaOEt, generated *in situ* using EtOH (0.90 mL, 15 mmol, *d* 0.789) and NaH (0.68 g, 17 mmol, 60% dispersion in mineral oil) in accordance with **Method F** affording the title compound (6.6 g) as a caramel oil which is used as is without further purification: LC/MS t_R 2.10 min; MS (ES+) *m/z* 315, 317 (M+H).

Example 14: 7-Chloro-2,3-benzofurandicarboxylic Acid Diethyl Ester (14)



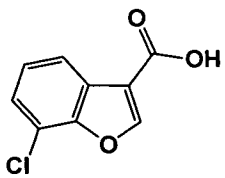
[0237] Diethyl ester **13** (6.6 g) is treated with concd H_2SO_4 in accordance with **Method G** providing the title compound (0.27 g) after column chromatography (silica gel, 20% EtOAc in heptanes) as a pale yellow oil: LC/MS t_R 2.38 min; MS (ES+) *m/z* 297, 299 (M+H); ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 7.85 (1H, dd), 7.49 (1H, dd), 7.33 (1H, t), 4.50 (2H, q), 4.47 (2H, q), 1.45 (3H, t), 1.44 (3H, t).

Example 15: 7-Chloro-3-benzofurancarboxylic Acid Ethyl Ester (15)



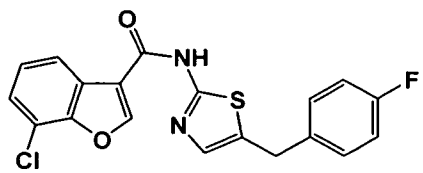
[0238] Diethyl ester **14** (265 mg, 0.900 mmol) is heated with NaCl (104 mg, 1.80 mmol) in DMSO and water (33 μL, 1.8 mmol) in accordance with **Method H**. Column chromatography (silica gel, 5% EtOAc in heptanes) affords the title compound (79 mg) as a yellow oil: LC/MS t_R 2.35 min; ^{1}H NMR (360 MHz, $CDCl_3$, δH) 8.29 (1H, s), 7.96 (1H, dd), 7.36 (1H, dd), 7.28 (1H, t), 4.42 (2H, q), 1.43 (3H, t).

Example 16: 7-Chloro-3-benzofurancarboxylic Acid (16)

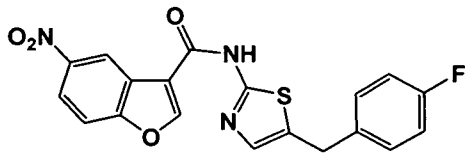


[0239] Ethyl ester **15** (79 mg, 0.35 mmol) is hydrolyzed in accordance with **Method I** affording the title compound (67 mg) as an off-white powder; LC/MS t_R 1.82 min; ^{1}H NMR (360 MHz, CD_3OD, δ_H) 8.51 (1H, s), 7.99 (1H, dd), 7.42 (1H, dd), 7.34 (1H, t).

Example 17: 7-Chloro-*N*-[5-(4-fluorophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (17)

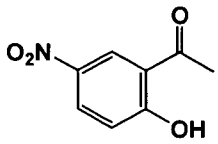


[0240] In accordance with **Method Q**, acid **16** (67 mg, 0.34 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (42 μL, 0.48 mmol, *d* 1.455) and catalytic DMF (5 μL) then treated with DIPEA (82 μL, 0.48 mmol, *d* 0.742) and aminothiazole **10** (71 mg, 0.34 mmol). Column chromatography (silica gel, 20% EtOAc in heptanes) affords the title compound (11 mg) as a cream colored solid: LC/MS t_R 2.50 min; MS (ES+) *m/z* 387, 389 (M+H); ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.63 (1H, br s), 9.05 (1H, br s), 8.09 (1H, d), 7.56 (1H, dd), 7.42 (1H, t), 7.34 (2H, dd), 7.33 (1H, s), 7.16 (2H, t), 4.12 (2H, s).

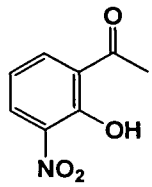


26

Example 18: 1-(2-Hydroxy-5-nitrophenyl)ethanone (18) and 1-(2-Hydroxy-3-nitrophenyl)ethanone (19)



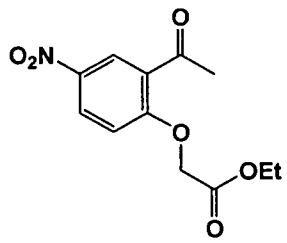
(18)



(19)

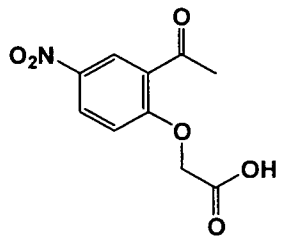
[0241] In accordance with the procedure of Mackman *et al.* (*J. Med. Chem.*, **2001**, *44*, 2753-2771), fuming HNO_3 (6.30 mL, 0.150 mol, *d* 1.50) is added dropwise to a chilled (0 °C) solution of 2'-hydroxyacetophenone (13.6 g, 0.100 mol) in AcOH (100 mL) over 30 min. The reaction mixture is stirred 16 h at rt before removing the solvents *in vacuo*. The residue thus obtained is treated with water (100 mL) and the resultant precipitate isolated by filtration. The solid obtained is redissolved in MTBE (100 mL), washed with water (4 x 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concd *in vacuo*. Purification by column chromatography (silica gel, 20-40% EtOAc in heptanes) separated the title compounds. For **18**: yellow crystalline solid (6.50 g); ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.72 (1H, d), 8.37 (1H, dd), 7.10 (1H, d), 2.76 (3H, s). For **19**: pale yellow needles (4.80 g); ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.21 (1H, dd), 8.06 (1H, dd), 7.05 (1H, t), 2.74 (3H, s).

Example 19: 2-(2-Acetyl-4-nitrophenoxy)acetic Acid Ethyl Ester (20)



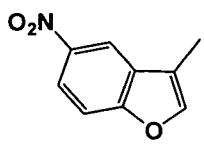
[0242] Nitrophenol **18** (6.50 g, 33.0 mmol) is treated with ethyl bromoacetate (5.10 mL, 46.2 mmol, *d* 1.506) and K_2CO_3 (18.2 g, 0.132 mol) in accordance with **Method A** providing the title compound (12.0 g) as a white wax which is used as is without further purification: LC/MS t_R 1.79 min; MS (ES+) *m/z* 268 (M+H), 290 (M+Na), 331; ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.65 (1H, d), 8.33 (1H, dd), 6.94 (1H, d), 4.85 (2H, s), 4.32 (2H, q), 2.74 (3H, s), 1.33 (3H, t).

Example 20: (2-Acetyl-4-nitrophenoxy)acetic Acid (21)



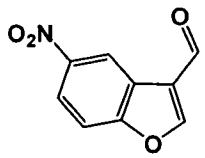
[0243] Ethyl ester **20** (12.0 g) is hydrolyzed in accordance with **Method B** providing the title compound (6.70 g) as a dark red oil: LC/MS t_R 1.44 min; ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.44 (1H, br s), 8.34-8.39 (2H, m), 7.35 (1H, dd), 5.05 (2H, s), 2.66 (3H, s).

Example 21: 3-Methyl-5-nitrobenzofuran (22)

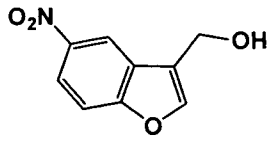


[0244] Acid **21** (1.30 g, 5.43 mmol) is reacted in accordance with **Method C** providing the title compound (0.52 g) as a brown solid: LC/MS t_R 2.06 min; ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.47 (1H, d), 8.23 (1H, dd), 7.57 (1H, q), 7.53 (1H, d), 2.31 (3H, d).

Example 22: 5-Nitro-3-benzofurancarboxaldehyde (23) and (5-Nitro-3-benzofuranmethanol (24)



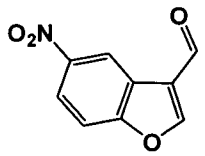
(23)



(24)

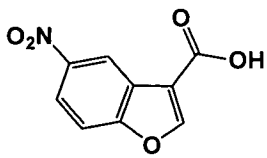
[0245] 3-Methyl-5-nitrobenzofuran **21** (505 mg, 2.85 mmol) is treated with SeO_2 (348 mg, 3.14 mmol) in accordance with **Method D**. Column chromatography (silica gel, 5-40% EtOAc in heptanes) separated the title compounds from the unreacted starting material (195 mg). For **23**: white crystalline solid (113 mg); LC/MS t_R 1.72 min; ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 10.23 (1H, s), 9.13 (1H, d), 8.44 (1H, s), 8.37 (1H, dd), 7.70 (1H, d). For **24**: white crystalline solid (104); LC/MS t_R 1.53 min; ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 8.64 (1H, d), 8.27 (1H, dd), 7.78 (1H, br s), 7.59 (1H, d), 4.93 (2H, dd), 1.78 (1H, t).

Example 23: 5-Nitro-3-benzofurancarboxaldehyde (23)



[0246] 5-Nitro-3-benzofuranmethanol **24** (330 mg, 1.70 mmol) is treated with DMP (1.08 g, 2.56 mmol) employing the procedure of **Method L**. On completion of the reaction, the mixture is partitioned between Et_2O (20 mL) and 1 M NaOH (20 mL) and the two phases separated. The organic phase is washed with 1 M NaOH (2 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concd *in vacuo* providing the title compound (0.34 g) as a white crystalline solid with spectral characteristics consistent with that of **23** as prepared in Example **22**.

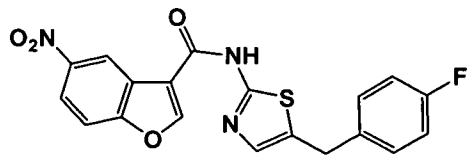
Example 24: 5-Nitrobenzofuran-3-carboxylic acid (25)



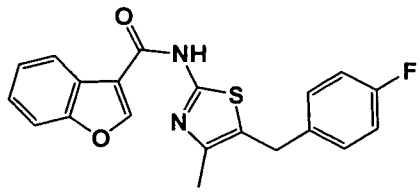
[0247] Aldehyde **23** (0.450 g, 2.35 mmol) is treated with KH_2PO_4 (0.96 g, 7.05 mmol), 2-methyl-2-butene (1.74 mL, 16.5 mmol, *d* 0.662) and $NaClO_2$ (0.70 g, 7.76 mmol) in accordance with **Method E**. Purification by column chromatography (silica gel, 5%

MeOH in DCM) affords the title compound (0.24 g) as an off-white powder: LC/MS t_R 1.62 min; MS (ES+) *m/z* 208 (M+H); ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 13.49 (1H, br s), 8.95 (1H, s), 8.78 (1H, d), 8.32 (1H, dd), 7.99 (1H, d).

Example 25: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-5-nitro-3-benzofurancarboxamide (26)

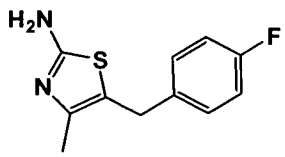


[0248] Benzofuran-3-carboxylic acid **25** (0.45 g, 2.18 mmol) is treated with HATU (0.99 g, 2.6 mmol), DIPEA (0.45 mL, 2.6 mmol, *d* 0.742) and aminothiazole **10** (0.54 g, 2.6 mmol) in accordance with **Method R** providing the title compound (0.55 g) after column chromatography (silica gel, 30-50% EtOAc in heptanes) and recrystallization (MeCN) as a white crystalline solid: LC/MS t_R 2.30 min; MS (ES+) *m/z* 398 (M+H), 439; ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.76 (1H, br s), 9.13 (1H, br s), 8.94 (1H, d), 8.33 (1H, dd), 7.99 (1H, d), 7.30-7.39 (3H, m), 7.16 (2H, t), 4.13 (2H, s).



28

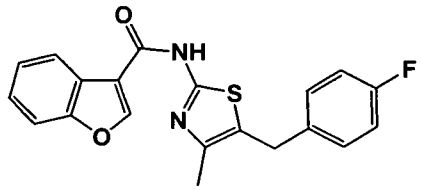
Example 26: 5-[(4-Fluorophenyl)methyl-4-methyl]-2-thiazolamine (27)



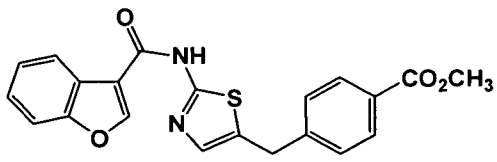
[0249] The diazonium salt of 4-fluoroaniline (0.95 mL, 10 mmol, *d* 1.157) is formed using $NaNO_2$ (0.76 g, 11 mmol) in aqueous HCl in accordance with **Method J**. The salt thus formed is treated directly with methyl vinyl ketone (0.81 mL, 10 mmol, *d* 0.864), $CuCl_2.H_2O$ (0.51 g, 3.0 mmol) and MgO (10 mg, 0.25 mmol) as detailed in **Method J** affording the crude α-chloroketone (1.6 g) as a brown oil. Due to its inherent instability, the α-chloroketone (845 mg, approx 4.21 mmol) is immediately treated with thiourea (250 mg, 3.28 mmol) as described in **Method K.** On completion, the reaction

mixture is allowed to cool to rt and the solvent evaporated. The residue thus obtained is dissolved in 1 M HCl (20 mL) and this solution washed with EtOAc (3 x 20 mL). The aqueous phase is carefully basified by the addition of solid Na_2CO_3 to pH 12 and extracted once more with EtOAc (3 x 20 mL). The combined EtOAc phases are washed with brine (20 mL), dried ($MgSO_4$), filtered and the filtrate concd *in vacuo* to afford the title compound (78 mg) as a light brown crystalline solid: LC/MS t_R 1.29 min; MS (ES+) *m/z* 223 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.14 (2H, dd), 6.98 (2H, t), 4.70 (2H, br s), 3.88 (2H, s), 2.19 (3H, s).

Example 27: *N*-[5-(4-Fluorophenyl)methyl-4-methyl-2-thiazolyl]-3-benzofurancarboxamide (28)

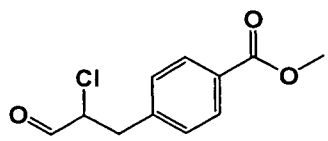


[0250] Benzofuran-3-carboxylic acid **5** (35 mg, 0.22 mmol) is treated with HATU (82 mg, 0.22 mmol), DIPEA (38.3 μL, 0.22 mmol, *d* 0.742) and aminothiazole **27** (49 mg, 0.22 mmol) in accordance with **Method R** to afford the title compound (12 mg) after column chromatography (silica gel, 20-30% EtOAc in heptanes) followed by reverse phase preparative HPLC (5-95% MeCN in water) as a cream powder: LC/MS t_R 2.40 min; MS (ES+) *m/z* 367 (M+H); ^{1}H NMR (400 MHz, CD_3OD, δ_H) 8.59 (1H, s), 8.07 (1H, d), 7.44 (1H, d), 7.28 (2H, obs m), 7.07 (2H, dd), 6.89 (2H, t), 3.92 (2H, obs s), 2.26 (3H, s).



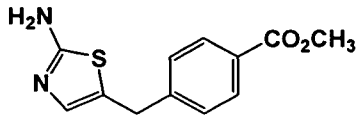
31

Example 28: 4-(2-Chloro-3-oxopropyl)benzoic Acid Methyl Ester (29)



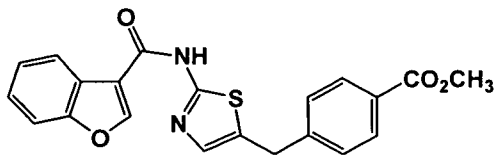
[0251] The diazonium salt of methyl 4-aminobenzoate (10 g, 66.2 mmol) is formed using $NaNO_2$ (5.10 g, 72.8 mmol) in aqueous HCl in accordance with **Method J**. The salt thus formed is reacted directly with acrolein (4.40 mL, 66.2 mmol, *d* 0.839), $CuCl_2.H_2O$ (3.40 g, 19.8 mmol) and MgO (66 mg, 1.70 mmol) as detailed in **Method J** affording the title compound (13.3 g) as a dark brown oil which is used as is without further purification: ^1H NMR (360 MHz, $CDCl_3$, δ_H) 9.56 (1H, d), 8.00 (2H, d), 7.31 (2H, d), 4.41 (1H, ddd), 3.91 (3H, s), 3.44 (1H, dd), 3.11 (1H, dd).

Example 29: 4-[(2-Amino-5-thiazolyl)methyl]benzoic Acid Methyl Ester (30)

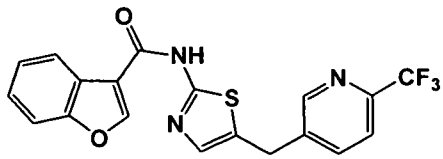


[0252] α-Chloroaldehyde **29** (13.3 g) is reacted with thiourea (6.10 g, 79.8 mmol) in accordance with **Method K** providing the title compound (2.70 g) on filtration of the cooled (rt) reaction mixture as a light brown solid: LC/MS t_R 1.15 min; MS (ES+) *m/z* 249 (M+H), 290. Reduction of the filtrate *in vacuo* followed by trituration of the residue with DCM (15 mL) afforded a second batch of the title compound (1.80 g) as a light brown solid.

Example 30: 4-[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]benzoic Acid Methyl Ester (31)

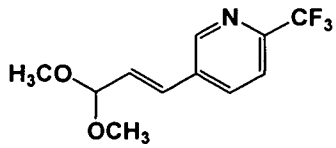


[0253] In accordance with **Method Q**, the acid chloride of acid **5**, prepared from **5** (1.0 g, 6.20 mmol), oxalyl chloride (1.60 mL, 18.5 mmol, *d* 1.455), and catalytic DMF (15 μL), is treated with DIPEA (1.0 mL, 6.2 mmol, *d* 0.742) and aminothiazole **30** (1.50 g, 6.20 mmol). On completion of the reaction, the mixture is diluted with satd $NaHCO_3$ (10 mL), affording a cream colored precipitate in the organic layer. The DCM phase is filtered providing on drying (vacuum oven) the title product (1.20 g) as a cream colored solid: LC/MS t_R 2.27 min; MS (ES+) *m/z* 393 (M+H); ^1H NMR (250 MHz, DMSO-d_6, δ_H) 8.95 (1H, s), 8.12 (1H, dd), 7.93 (2H, d), 7.70 (1H, dd), 7.34-7.49 (5H, m), 4.22 (2H, s), 3.84 (3H, s).



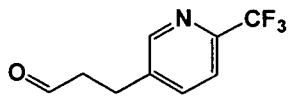
35

Example 31: 5-[(1*E*)-3,3-Dimethoxy-1-propen-1-yl]-2-(trifluoromethyl)pyridine (32)



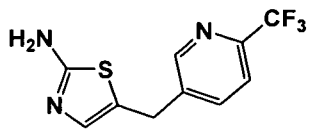
[0254] 5-Bromo-2-(trifluoromethyl)pyridine (1.0 g, 4.43 mmol) is treated with acrolein dimethyl acetal (0.65 mL, 5.5 mmol, *d* 0.862), $Pd(OAc)_2$ (49 mg, 0.22 mmol) and tri-*o*-tolylphosphine (0.27 g, 0.88 mmol) in accordance with **Method N**. Purification by column chromatography (silica gel, 25% EtOAc in heptane) affords the title compound (0.24 g) as a colorless oil: LC/MS t_R 1.88 min; MS (ES+) *m/z* 248 (M+H).

Example 32: 6-Trifluoromethyl-3-pyridinepropanal (33)



[0255] Alkene **32** (0.24 g, 0.97 mmol) is hydrogenated and the acetal hydrolyzed in accordance with **Method O** affording the title compound (0.11 g) after column chromatography (silica gel, 30-40% EtOAc in heptanes) as a colorless oil: LC/MS t_R 1.55 min; MS (ES+) *m/z* 204 (M+H), 222; ^1H NMR (250 MHz, $CDCl_3$, δ_H) 9.84 (1H, s), 8.60 (1H, app br s), 7.74 (1H, dd), 7.62 (1H, d), 3.05 (2H, t), 2.88 (2H, t).

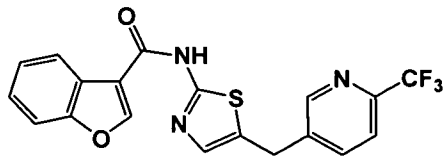
Example 33: 5-[[(6-Trifluoromethyl)-3-pyridinyl]methyl]-2-thiazolamine (34)



[0256] Aldehyde **33** (0.11 g, 0.53 mmol) is treated with *t*-BuBr (0.24 mL, 2.1 mmol, *d* 1.22) and DMSO (75.5 μL, 1.06 mmol, *d* 1.10) providing the α-bromoaldehyde which is treated directly with thiourea (44 mg, 0.58 mmol) in accordance with **Method M2** affording the title compound (65 mg) as light brown crystalline solid: LC/MS t_R 1.10 min;

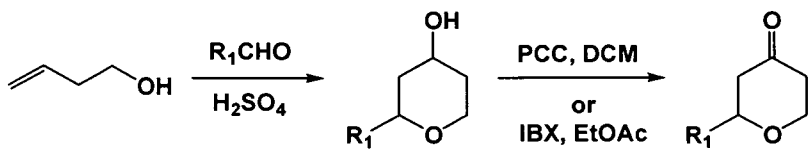
MS (ES+) *m/z* 260 (M+H); ^{1}H NMR (250 MHz, CD_3OD, δ_H) 8.61 (1H, app br s), 7.91 (1H, dd), 7.76 (1H, d), 6.79 (1H, s), 4.11 (2H, s).

Example 34: *N*-[5-[[(6-Trifluoromethyl)-3-pyridinyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (35)

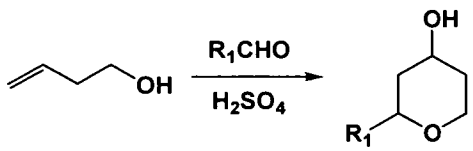


[0257] Acid **5** (45 mg, 0.28 mmol) is treated with HATU (106 mg, 0.280 mmol), DIPEA (53 μL, 0.30 mmol, *d* 0.742) and aminothiazole **34** (65 mg, 0.25 mmol) in accordance with **Method R** providing the title compound (23 mg) after column chromatography (silica gel, 40-50% EtOAc in heptanes) as a cream colored solid: LC/MS t_R 2.20 min; MS (ES+) *m/z* 404 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.96 (1H, s), 8.77 (1H, app br s), 8.12 (1H, dd), 8.01 (1H, dd), 7.88 (1H, d), 7.71 (1H, dd), 7.34-7.50 (3H, m), 4.31 (2H, s).

General Route I: Synthesis of Tetrahydro-4*H*-pyran-4-ones

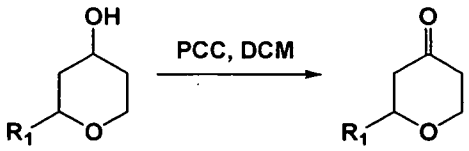


Method S



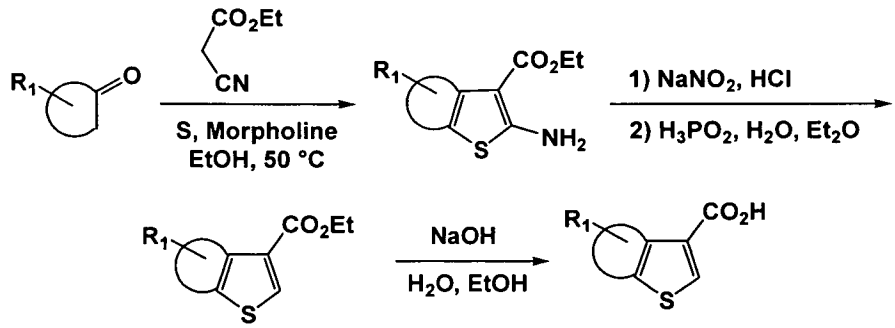
[0258] In accordance with the procedure of Ernst Hanschke (*Chem. Ber.*, **1955**, *88*, 1053-1059), the aldehyde (1 equiv) and 3-buten-1-ol (1 equiv) are combined with 20% H_2SO_4 (10 vol) in a pressure tube. The tube is sealed and the reaction mixture warmed to 80 °C for 3 h. Reaction progress is monitored by TLC. On completion, the reaction mixture is allowed to cool to rt, carefully neutralized (pH 8-9) by the addition of concd ammonia, and extracted with EtOAc (3 x 5 vol). The combined organic phases are dried (Na_2SO_4), filtered, and the filtrate concd *in vacuo* providing the desired product.

Method T

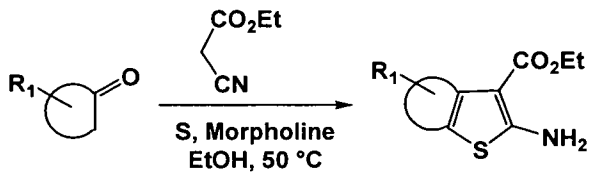


[0259] To a rapidly stirred rt suspension of the tetrahydro-4*H*-pyran-4-ol (1 equiv) and molecular sieves (4Å, 8-12 mesh) in DCM (48 vol) is added PCC (1.2 equiv) portionwise over 2 min. Reaction progress is monitored by TLC. After 16 h at rt, the DCM is evaporated and the residue suspended and stirred in Et_2O (100 vol). After 1 h at rt, the reaction mixture is filtered through Celite® 521, washing the filter cake with Et_2O (100 vol). The combined filtrates are concd *in vacuo* and the oil obtained purified by column chromatography (silica gel, 20% EtOAc in heptanes) providing the desired product.

General Route J: Synthesis of Thiophenecarboxylic Acids

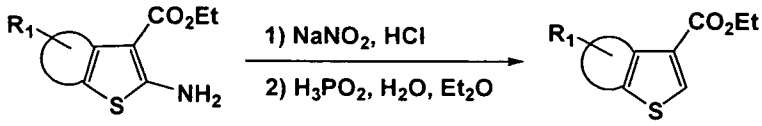


Method U



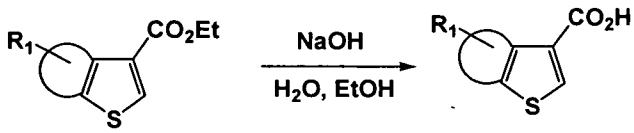
[0260] Following the procedure of Anderson and Møller *et al.* (*J. Med Chem.*, **2002**, *45*, 4443-4459), morpholine (1.5 equiv) is added to a solution of the ketone (1 equiv), sulfur (1.1 equiv), and ethyl cyanoacetate (1.1 equiv) in EtOH (30 vol). The mixture is stirred at 50 °C for 16 h. Reaction progress is monitored by LC/MS. On completion the reaction mixture is filtered, the filter cake washed with EtOAc (30 vol), and the filtrate concd *in vacuo*. The residue obtained is purified by column chromatography (silica gel, 10-20% EtOAc in heptanes) affording the desired product.

Method V



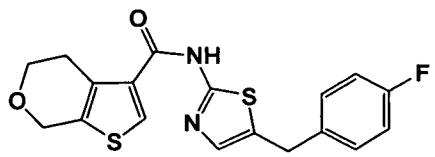
[0261] In accordance with the procedure of Tsuri *et al.* (*J. Med. Chem.*, **2003**, *46*, 2446-2455), to a chilled (0 °C) solution of the aminothiophene (1 equiv) in 1,4-dioxane (17 vol) is added concd HCl (11 vol) and a solution of $NaNO_2$ (1.1 equiv) in water (17 vol). After 30 min, aqueous H_3PO_2 (17 vol; 50%) and Et_2O (34 vol) are added and the resultant biphasic mixture stirred rapidly for 30 min. The reaction is poured into iced water (34 vol) and extracted with EtOAc (3 x 100 vol). The combined organic phases are dried (Na_2SO_4), filtered, and the filtrate concd *in vacuo*. Column chromatography (silica gel, 5-10% EtOAc in heptanes) gives the desired product.

Method W



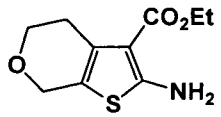
[0262] To a stirred solution of the ester (1 equiv) in EtOH (16 vol) is added 1 M NaOH (16 vol) and warmed to reflux for 15 min or until the reaction is judged complete by TLC or LC/MS analysis. On completion, the reaction mixture is cooled to rt and the EtOH removed *in vacuo*. The aqueous residue is acidified to pH 1-2 with 1.2 M HCl and the resultant precipitate isolated by filtration and dried *in vacuo* affording the desired product.

Examples of Compounds Prepared Using General Routes I-J.



39

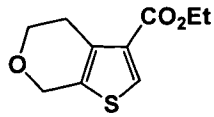
Example 35: 2-Amino-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylic Acid Ethyl Ester (36)



[0263] Tetrahydro-4*H*-pyran-4-one (10.0 g, 0.100 mol) is reacted with ethyl cyanoacetate (11.7 mL, 0.110 mol, *d* 1.063) in the presence of sulfur (4.38 g, 0.11 mol) and morpholine (13.1 mL, 0.15 mol, *d* 0.996) in accordance with **Method U** providing the title compound

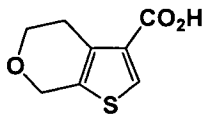
(20.9 g) after column chromatography (silica gel, 20% EtOAc in heptanes) as a yellow powder: LC/MS t_R 1.83 min; MS (ES+) *m/z* 228 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 6.00 (2H, br s), 4.57 (1H, d), 4.56 (1H, d), 4.28 (2H, q), 3.92 (2H, t), 2.83 (2H, app tt), 1.34 (3H, t).

Example 36: 4,7-Dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylic Acid Ethyl Ester (37)



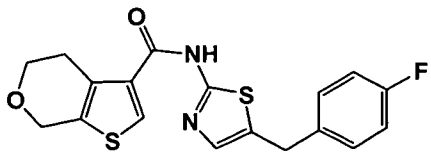
[0264] The diazonium salt of amine **36** (1.5 g, 6.60 mmol) is formed using $NaNO_2$ (0.50 g, 7.30 mmol) in 1,4-dioxane and aqueous HCl, then treated directly with 50% aqueous H_3PO_2 in accordance with **Method V**. Column chromatography (silica gel, 10% EtOAc in heptanes) affords the title compound (0.45 g) as a colorless oil: LC/MS t_R 2.02 min; MS (ES+) *m/z* 213 (M+H), 254; ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.98 (1H, s), 4.79 (2H, s), 4.31 (2H, q), 3.95 (2H, t), 3.01 (2H, app tt), 1.36 (3H, t).

Example 37: 4,7-Dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxylic acid (38)



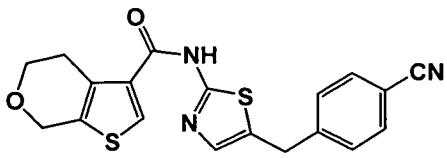
[0265] Ethyl ester **37** (0.52 g, 2.45 mmol) is hydrolyzed in accordance with **Method W** providing the title compound (0.40 g) as a white powder: LC/MS t_R 1.48 min; MS (ES+) *m/z* 185 (M+H), 226; ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 8.14 (1H, s), 4.82 (2H, s), 3.98 (2H, t), 3.04 (2H, app tt).

Example 38: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxamide (39)



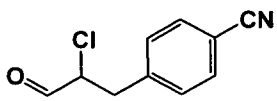
[0266] In accordance with **Method Q**, acid **38** (0.40 g, 2.2 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (0.56 mL, 6.5 mmol, *d* 1.455) and catalytic DMF (10 μL), then treated with DIPEA (0.38 mL, 2.2 mmol, *d* 0.742) and aminothiazole **10** (0.46 g, 2.2 mmol) to afford the title compound (0.65 g) as an off-white solid: LC/MS

t_R 2.18 min; MS (ES+) *m/z* 375 (M+H); ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 7.82 (1H, s), 7.20 (2H, dd), 7.00 (2H, t), 6.83 (1H, s), 4.84 (2H, s), 4.03 (2H, s), 3.97 (2H, t), 3.07 (2H, t).



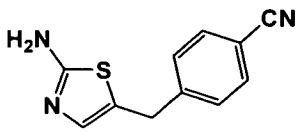
42

Example 39: 4-(2-Chloro-3-oxopropyl)benzonitrile (40)



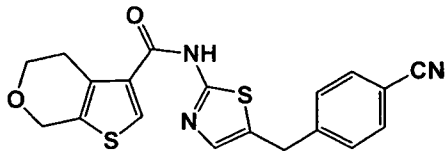
[0267] The diazonium salt of 4-aminobenzonitrile (0.78 g, 6.80 mmol) is formed using $NaNO_2$ (0.52 g, 7.48 mmol) in aqueous HCl in accordance with **Method J**. The salt thus formed is reacted directly with acrolein (0.45 mL, 6.80 mmol, *d* 0.839), $CuCl_2 \cdot H_2O$ (0.35 g, 2.04 mmol) and MgO (12 mg, 0.30 mmol) as detailed in **Method J** providing the title compound (1.31 g) as a dark brown oil which is used as is without further purification: ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 9.58 (1H, d), 7.64 (2H, d), 7.37 (2H, d), 4.41 (1H, app dd), 3.46 (1H, dd), 3.12 (1H, dd).

Example 40: 4-[(2-Amino-5-thiazolyl)methyl]benzonitrile (41)

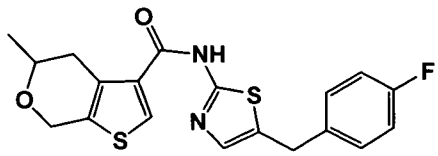


[0268] α-Chloroaldehyde **40** (1.31 g, 6.77 mmol) is reacted with thiourea (0.43 g, 5.7 mmol) in accordance with **Method K**. On completion, the reaction mixture is allowed to cool to rt and the solvent evaporated. The residue obtained is purified by column chromatography (silica gel, 10% DCM in EtOAc) to afford the title compound (0.50 g) as a light brown crystalline solid.

Example 41: *N*-[5-(4-Cyanophenyl)methyl-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxamide (42)

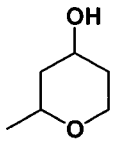


[0269] In accordance with **Method Q**, acid **38** (122 mg, 0.660 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (0.17 mL, 2.0 mmol, *d* 1.455) and catalytic DMF (5 μL), and then treated with DIPEA (0.14 mL, 0.78 mmol, *d* 0.742) and aminothiazole **41** (120 mg, 0.56 mmol) providing the title compound (0.10 g) after column chromatography (silica gel, 60-70% EtOAc in heptanes) as an off-white solid: LC/MS t_R 2.16 min; MS (ES+) *m/z* 382 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.41 (1H, s), 7.80 (2H, d), 7.50 (2H, d), 7.35 (1H, s), 4.74 (2H, s), 4.22 (2H, s), 3.83 (2H, t), 2.87 (2H, t).



48

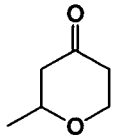
Example 42: Tetrahydro-2-methyl-4*H*-pyran-4-ol (43)



[0270] A mixture of acetaldehyde (1.56 mL, 28.2 mmol, *d* 0.785) and 3-buten-1-ol (2.40 mL,

28.2 mmol, *d* 0.838) is treated with 20% aqueous H_2SO_4 in accordance with **Method S** providing the title compound (2.80 g, 86%) as an orange oil: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 4.00 (1H, ddd), 3.77 (1H, app tt), 3.34-3.47 (2H, m), 1.82-1.99 (2H, m), 1.80 (1H, br s), 1.49 (1H, ddd), 1.21 (3H, d), 1.16-1.29 (1H, obs m).

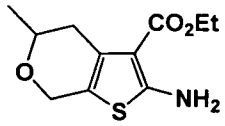
Example 43: Tetrahydro-2-methyl-4*H*-pyran-4-one (44)



[0271] Alcohol **43** (3.98 g, 34.3 mmol) is treated with PCC (8.86 g, 41.1 mmol) in accordance with **Method T** to afford the title compound (1.30 g) after column

chromatography (silica gel, 20% EtOAc in heptanes) as a dark orange oil: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 4.29 (1H, ddd), 3.61-3.82 (2H, m), 2.59 (1H, ddd), 2.20-2.47 (3H, m), 1.33 (3H, d).

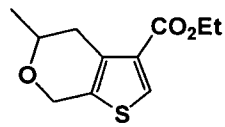
Example 44: 2-Amino-4,7-dihydro-5-methyl-5*H*-thieno[2,3-*c*]pyran-3-carboxylic Acid Ethyl Ester (45)



[0272] Tetrahydro-4*H*-pyran-4-one **44** (1.30 g, 11.4 mol) is reacted with ethyl cyanoacetate

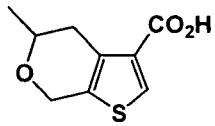
(1.33 mL, 12.5 mol, *d* 1.063) in the presence of sulfur (0.400 g, 12.5 mol) and morpholine (1.48 mL, 17.0 mol, *d* 0.996) in accordance with **Method U** affording the title compound (2.10 g) after column chromatography (silica gel, 10% EtOAc in heptanes) as a yellow powder: LC/MS t_R 2.01 min; MS (ES+) *m/z* 196, 242 (M+H); ^{1}H NMR (250 MHz, CD_3OD, δ_H) 4.47-4.63 (2H, m), 4.23 (2H, q), 3.62-3.81 (1H, m), 2.84 (1H, app dt), 2.40 (1H, app ddt), 1.32 (3H, t), 1.29 (3H, d).

Example 45: 4,7-Dihydro-5-methyl-5*H*-thieno[2,3-*c*]pyran-3-carboxylic Acid Ethyl Ester (46)



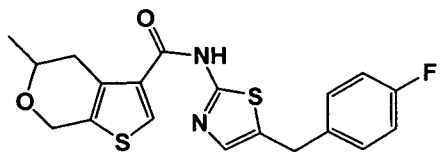
[0273] The diazonium salt of amine **45** (1.10 g, 4.60 mmol) is formed using $NaNO_2$ (0.35 g, 5.1 mmol) in 1,4-dioxane and aqueous HCl, then treated directly with 50% aqueous H_3PO_2 in accordance with **Method V**. Column chromatography (silica gel, 5% EtOAc in heptanes) provides the title compound (0.27 g) as a colorless oil: ^{1}H NMR (250 MHz, CD_3OD, δ_H) 8.07 (1H, s), 4.85 (1H, d), 4.77 (1H, app dt), 4.29 (2H, q), 3.67-3.83 (1H, m), 3.06 (1H, ddd), 2.56 (1H, app ddt), 1.36 (3H, t), 1.34 (3H, d).

Example 46: 4,7-Dihydro-5-methyl-5*H*-thieno[2,3-*c*]pyran-3-carboxylic Acid (47)



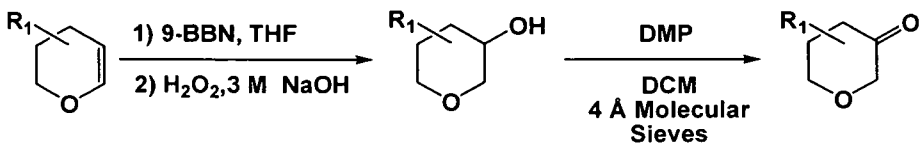
[0274] Ethyl ester **46** (0.25 g, 1.11 mmol) is hydrolyzed in accordance with **Method W** providing the title compound (0.13 g) as a white powder: ^{1}H NMR (250 MHz, CD_3OD, δ_H) 8.08 (1H, s), 4.73-4.90 (2H, obs m), 3.69-3.85 (1H, m), 3.08 (1H, ddd), 2.56 (1H, app ddt), 1.35 (3H, d).

Example 47: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-4,7-dihydro-5-methyl-5*H*-thieno[2,3-*c*]pyran-3-carboxamide (48)

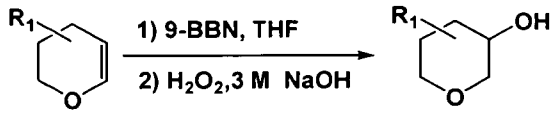


[0275] In accordance with **Method Q**, acid **47** (134 mg, 0.680 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (0.18 mL, 2.0 mmol, *d* 1.455) and catalytic DMF (5 μL) then treated with DIPEA (0.12 mL, 0.68 mmol, *d* 0.742) and aminothiazole **10** (141 mg, 0.680 mmol) to afford the title compound (82 mg) after recrystallization (DCM) as an off-white solid: LC/MS t_R 2.22 min; MS (ES+) *m/z* 389 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.39 (1H, s), 7.32 (2H, dd), 7.30 (1H, s), 7.15 (2H, t), 4.84 (1H, d), 4.70 (1H, d), 4.09 (2H, s), 3.60-3.77 (1H, m), 2.98 (1H, app d), 2.51 (1H, obs m), 1.26 (3H, d).

General Route K: Synthesis of Dihydro-2*H*-pyran-3(4*H*)-ones

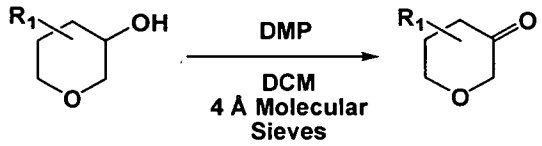


Method X



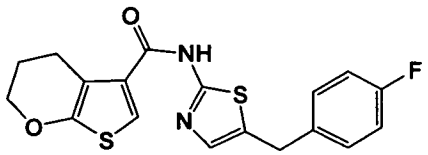
[0276] A solution of the dihydropyran (1 equiv) in THF (2.5 mL/mmol) is added dropwise to a chilled (0 °) solution of 0.5 M 9-BBN in THF (1 equiv). The ice bath is removed, the solution stirred at rt for 2 h, then recooled to 0 °C, after which 3 M NaOH (3 equiv) is added, followed by the dropwise addition of 30% H_2O_2 (2.5 mL/mmol) to the rapidly stirred mixture. The mixture is stirred overnight at rt and at 55 °C for 3 h. The mixture is chilled to 0 °C, satd Na_2SO_3 is added until a negative peroxide test is obtained, and MTBE is added (2 vol). The organic phase is separated and the aqueous phase extracted with MTBE (4 x 1 vol). The combined organic phases are washed with brine, dried (Na_2SO_4), filtered, and concd *in vacuo* at 100 mm Hg. Column chromatography (silica gel, 1:2 EtOAc in heptanes) provides the 3-pyranols.

Method Y



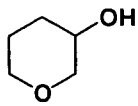
[0277] To a suspension of the 3-pyranol (1 equiv) and 4 Å molecular sieves (2 g/g 3-pyranol) in DCM (5 mL/mmol) is added DMP (1 equiv) portionwise over 20 min. Reaction progress is monitored by TLC. Additional DMP (0.2 equiv) is added as required. After 1 h, the reaction mixture is partitioned between DCM and 2 M K_2CO_3. The organic phase is separated and the aqueous extracted with DCM (3 x). The combined organic phases are washed with brine, dried ($MgSO_4$), filtered, and concd in vacuo. Column chromatography (silica gel, 1:2 EtOAc in heptanes) provides the 3-pyranones.

Examples of Compounds Prepared Using General Routes J and K.



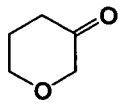
48

Example 48: Tetrahydro-2*H*-pyran-3-ol (49)



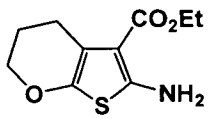
[0278] Hydroboration of 3,4-dihydropyran (6.3 g, 75 mmol) and oxidation of the resulting organoborane in accordance with the procedure described in **Method X** provides the title compound (2.8 g): ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 3.79-3.57 (m, 4H), 3.41 (app q, 1H), 2.12 (br s, 1H), 1.92-1.76 (m, 2H), 1.64-1.49 (m, 2H).

Example 49: Dihydro-2*H*-pyran-3(4*H*)-one (50)

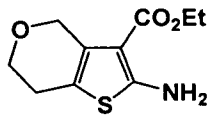


[0279] Oxidation of alcohol **49** (2.12 g, 20.8 mmol) with DMP (9.91 g, 23.3 mmol) in accordance with **Method Y** provides the pyranone **50** (1.78 g): ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 4.03 (s, 2H), 3.86 (app t, 2H), 2.54 (app t, 2H), 2.12 (m, 2H).

Example 50: 2-Amino-3,4-dihydro-2*H*-thieno[2,3-*b*]pyran-3-carboxylic Acid Ethyl Ester (51) and 2-Amino-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-3-carboxylic Acid Ethyl Ester (52)



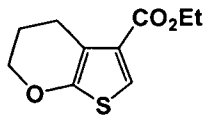
51



52

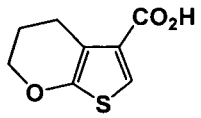
[0280] Dihydro-2*H*-pyran-3(4*H*)-one **50** (1.00 g, 10.0 mol) is reacted with ethyl cyanoacetate (1.38 mL, 13.0 mol, *d* 1.063) in the presence of sulfur (0.42 g, 13 mol) and morpholine (1.14 mL, 13.0 mol, *d* 0.996) in accordance with **Method U** affording **51** (550 mg) and **52** (50 mg) following column chromatography (silica gel, 10% EtOAc in heptanes); for **51**: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 5.72 (br s, 2H), 4.25 (app q, 2H), 4.15 (app t, 2H), 2.69 (app t, 2H), 1.98 (m, 2H), 1.33 (t, 3H).

Example 51: 3,4-Dihydro-2*H*-thieno[2,3-*b*]pyran-3-carboxylic Acid Ethyl Ester (53)



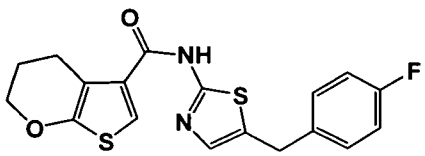
[0281] The diazonium salt of amine **51** (50 mg, 0.22 mmol) is formed using $NaNO_2$ (18 mg, 0.26 mmol) in EtOH (3 mL) and H_2SO_4 (80 mg) at -8 °C for 1 h, then slowly warmed to 50 °C. After nitrogen evolution has ceased, the mixture is cooled to rt, poured into satd $NaHCO_3$, and extracted with EtOAc. The organic phase is dried (Na_2SO_4), filtered, and concd in vacuo. Column chromatography (silica gel, 1:6 EtOAc in heptanes) provides the title compound (22 mg) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$, δ_H) 7.33 (1H, s), 4.29 (q, 2H), 4.24 (app t, 2H), 2.88 (app t, 2H), 2.02 (m, 2H), 1.36 (t, 3H).

Example 52: 3,4-Dihydro-2*H*-thieno[2,3-*b*]pyran-3-carboxylic Acid (54)

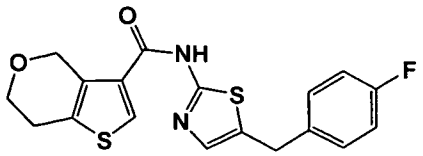


[0282] Ethyl ester **53** (22 mg) is hydrolyzed in accordance with **Method W** providing the title compound (20 mg) as a white powder.

Example 53: *N*-[5-[(4-Fluorophenyl)methyl]-2-thiazolyl]-3,4-dihydro-2*H*-thieno[2,3-*b*]pyran-5-carboxamide (48)

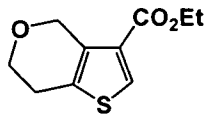


[0283] In accordance with **Method Q**, acid **54** (20 mg, 0.11 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (20 mg, 0.15 mmol, *d* 1.455) then treated with DIPEA (20 mg, 0.15 mmol) and aminothiazole **10** (22 mg, 0.11 mmol) to afford the title compound (21 mg) after silica gel chromatography (2:1 EtOAc in heptane): LC/MS t_R 2.34 min; MS (ES+) *m/z* 375 (M+H); ^1H NMR (250 MHz, $CDCl_3$, δ_H) 7.25, (s, 1H), 7.21 (m, 3H), 7.02 (m, 2H), 6.93 (br s, 1H), 4.30 (app t, 2H), 4.06 (s, 2H), 2.92 (app t, 2H), 2.04 (m, 2H).



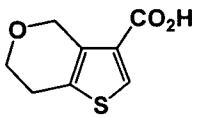
57

Example 54: 6,7-Dihydro-4*H*-thieno[3,2-*c*]pyran-3-carboxylic Acid Ethyl Ester (58)



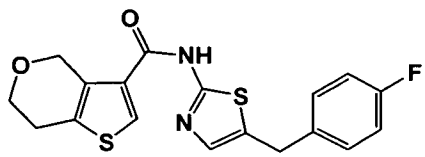
[0284] The diazonium salt of amine **52** (42 mg, 0.18 mmol) is formed using $NaNO_2$ (15 mg, 0.22 mmol) in 1,4-dioxane (2 mL) and 6 N HCl (1 mL) at -12 °C for 1 h, then treated directly with 50% aqueous H_3PO_2 in accordance with **Method V** providing the title compound (22 mg) as a colorless oil.

Example 55: 6,7-Dihydro-4*H*-thieno[3,2-*c*]pyran-3-carboxylic Acid (59)



[0285] Ethyl ester **58** is hydrolyzed in accordance with **Method W** providing the title compound (30 mg) as a white powder.

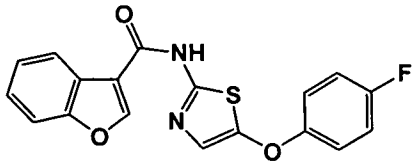
Example 56: *N*-[5-[(4-Fluorophenyl)methyl]-2-thiazolyl]-3,4-dihydro-2*H*-thieno[2,3-*b*]pyran-5-carboxamide (57)



[0286] In accordance with **Method Q**, acid **59** (30 mg, 0.16 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (30 mg, 0.14 mmol, *d* 1.455) then treated with DIPEA (30 mg, 0.24 mmol) and aminothiazole **10** (30 mg, 0.14 mmol) to afford the title compound after silica gel chromatography (3:1 EtOAc in heptane followed by 10:1 DCM/MeOH): LC/MS t_R 4.57 min; MS (ES+) *m/z* 375 (M+H); ^{1}H NMR (250 MHz,

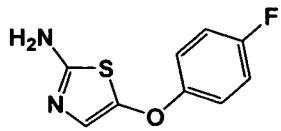
acetone-d_6, δ_H) 8.26 (s, 1H), 7.25 (m, 2H), 7.10 (s, 1H), 6.96 (m, 2H), 4.76 (s, 2H), 4.01 (s, 2H), 3.78 (app t, 2H), 2.05 (m, 2H, obs by acetone-d_6).

Examples of Compounds Prepared Using General Route F.



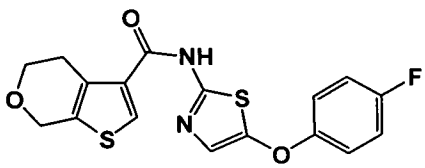
60

Example 57: 5-(4-Fluorophenoxy)-2-thiazolamine (61)



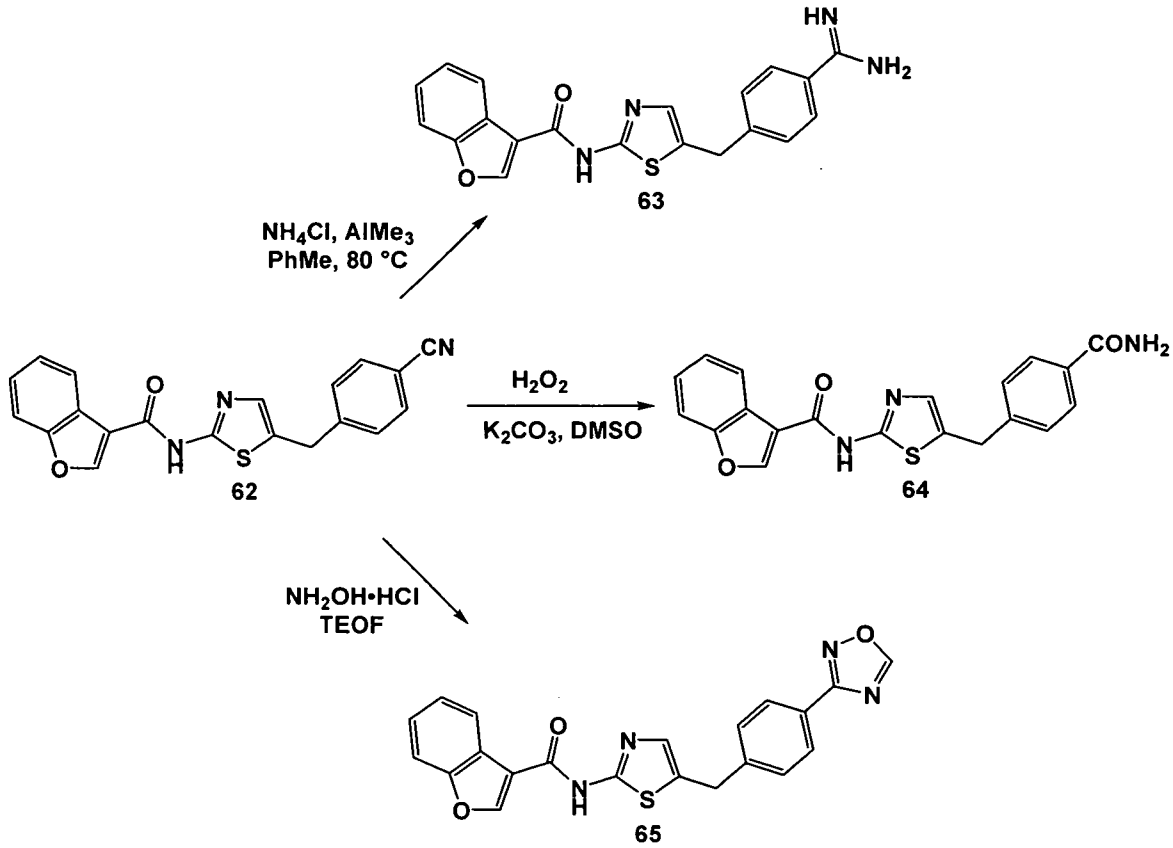
[0287] 2-Amino-5-chlorothiazole hydrochloride (0.50 g, 3.60 mmol) is reacted with 4-fluorophenol (0.81 g, 7.20 mmol) and NaH (0.32 g, 8.00 mmol, 60% dispersion in mineral oil) in accordance with **Method P** to afford the title compound (95 mg) after column chromatography (silica gel, 60-70% MTBE in heptanes) as a yellow crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 6.96-7.09 (m, 4H), 6.76 (s, 1H), 4.73 (2H, br s).

Example 58: *N*-[5-(4-Fluorophenoxy)-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-3-carboxamide (60)

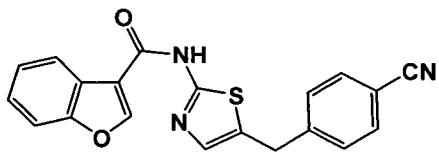


[0288] In accordance with **Method Q**, acid **38** (40 mg, 0.22 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (25 μL, 0.28 mmol, *d* 1.455) and catalytic DMF (5 μL), and then treated with DIPEA (46 μL, 0.27 mmol, *d* 0.742) and aminothiazole **61** (40 mg, 0.19 mmol) affording the title compound (40 mg) after column chromatography (silica gel, 40% EtOAc in heptanes) as a light yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 7.82 (s, 1H), 6.98-7.13 (m, 4H), 6.77 (s, 1H), 4.83 (s, 2H), 3.97 (t, 2H), 3.06 (t, 2H).

Scheme 1. Examples of Compounds Synthesized from *N*-[5-(4-Cyanophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (62)

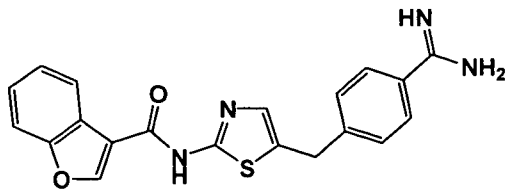


Example 59: *N*-[5-(4-Cyanophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (62)



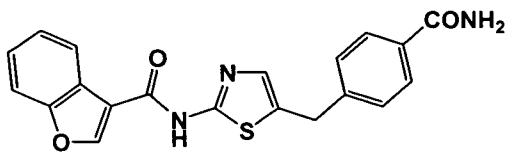
[0289] In accordance with **Method Q**, benzofuran-3-carboxylic acid **5** (500 mg, 3.09 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (0.80 mL, 9.3 mmol, *d* 1.455) and catalytic DMF (5 μL), and then treated with DIPEA (0.50 mL, 3.1 mmol, *d* 0.742) and aminothiazole **41** (663 mg, 3.08 mmol) affording the title compound (455 mg) as a light brown powder: LC/MS t_R 2.32 min; MS (ES+) *m/z* 360 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6, δ_H) 8.96 (1H, s), 8.13 (app dd, 1H), 7.83 (d, 2H), 7.71 (m, 1H), 7.53 (d, 2H), 7.43 (m, 2H), 7.39 (s, 1H), 4.25 (s, 2H).

Example 60. *N*-[5-[[4-(Aminoiminomethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (63)



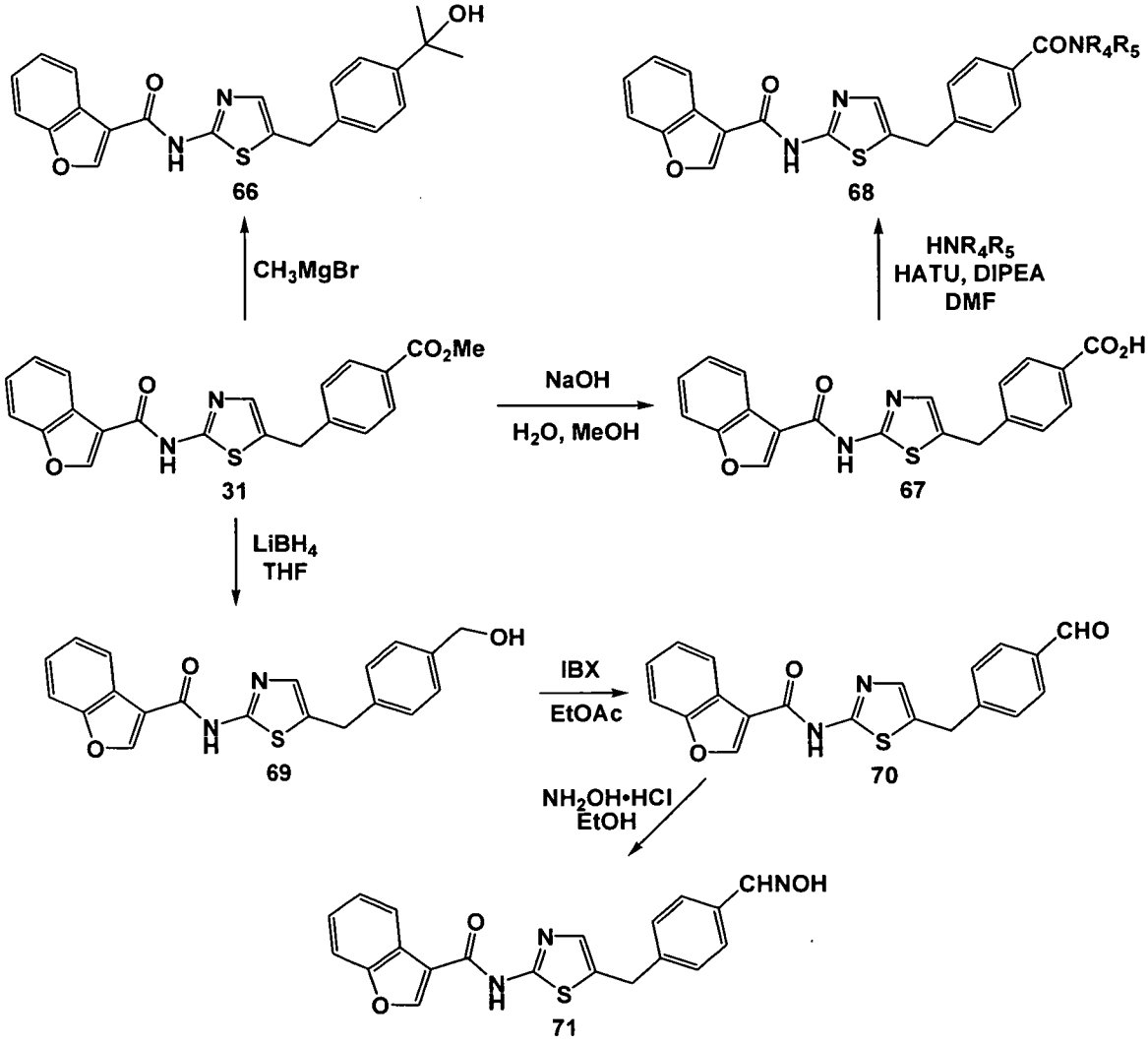
[0290] To a suspension of NH_4Cl (26 mg, 0.50 mmol) in toluene (3 mL) at 0 °C is added dropwise 2 M Me_3Al in toluene (0.24 mL, 0.47 mmol). The ice bath is removed and the mixture stirred at rt until gas evolution ceases. The nitrile **62** (100 mg, 0.28 mmol) is added followed by additional 2 M Me_3Al (1.4 mL) and the mixture heated at 80 °C for 20 h. Additional 2 M Me_3Al (1.4 mL) is added and heating is continued for 24 h, after which the mixture is cooled to rt and treated with satd $NaHCO_3$, providing a yellow precipitate The solids are filtered and the filtrate extracted with EtOAc. The combined solids and filtrate are recrystallized from EtOAc providing amidine **63** as a yellow powder: LC/MS t_R 3.25 min; MS (ES+) *m/z* 377 (M+H); ^1H NMR (250 MHz, CD_3OD, δ_H) 8.60 (s, 1H), 8.22 (d, 1H), 7.81 (d, 2H), 7.61 (m, 3H), 7.40 (m, 2H), 7.32 (s, 1H), 4.32 (s, 2H).

Example 61. *N*-[5-[[4-(Aminocarbonyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (64)

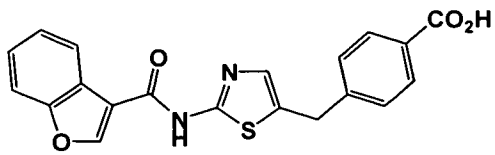


[0291] To a suspension of nitrile **62** (80 mg, 0.22 mmol) and K_2CO_3 (250 mg, 1.8 mmol) in DMSO (2 mL) is added a few drops of 30% H_2O_2. The flask is immersed into a 0 °C ice bath. The dropwise addition of 30% H_2O_2 (0.48 mL in total) is resumed. The mixture is stirred at rt for 4 h and then treated with satd Na_2SO_3 resulting in the formation of a white precipitate that is filtered, washed with water, and dried *in vacuo* providing amide **64** as a white powder: LC/MS t_R 3.62 min; MS (ES+) *m/z* 378 (M+H); ^1H NMR (250 MHz, DMSO-d_6, δ_H) 8.90 (s, 1H), 8.13 (m, 1H), 7.97 (br s, 1H), 7.80-7.66 (m, 2H), 7.43-7.32 (m, 6H), 4.15 (s, 2H).

Scheme 2. Examples of Compounds Synthesized from 4-[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]benzoic Acid Methyl Ester (31)

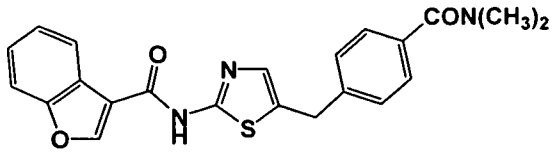


Example 62. 4-[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]benzoic Acid (67)



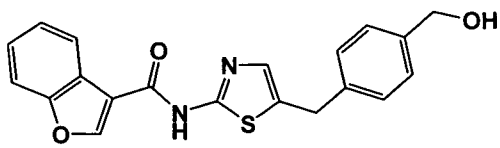
[0292] A mixture of ester **31** (400 mg, 1.02 mmol), EtOH (6 mL), and 1 M NaOH (3 mL) is heated at 70 °C for 10 min. The EtOH is removed and the residue is acidified with 1.2 M HCl providing a white precipitate that if filtered, washed with water, and dried *in vacuo* provides acid **67** (330 mg) as a white powder: LC/MS t_R 4.26 min; MS (ES+) *m/z* 379 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.93 (s, 1H), 8.10 (dd, 1H), 7.90 (d, 2H), 7.68 (m, 1H), 7.43-7.37 (m, 4H), 7.35 (s, 1H), 4.19 (s, 2H).

Example 63. *N*-[5-[[4-(Dimethylaminocarbonyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide ($NR_4R_5 = N(CH_3)_2$, 68a)



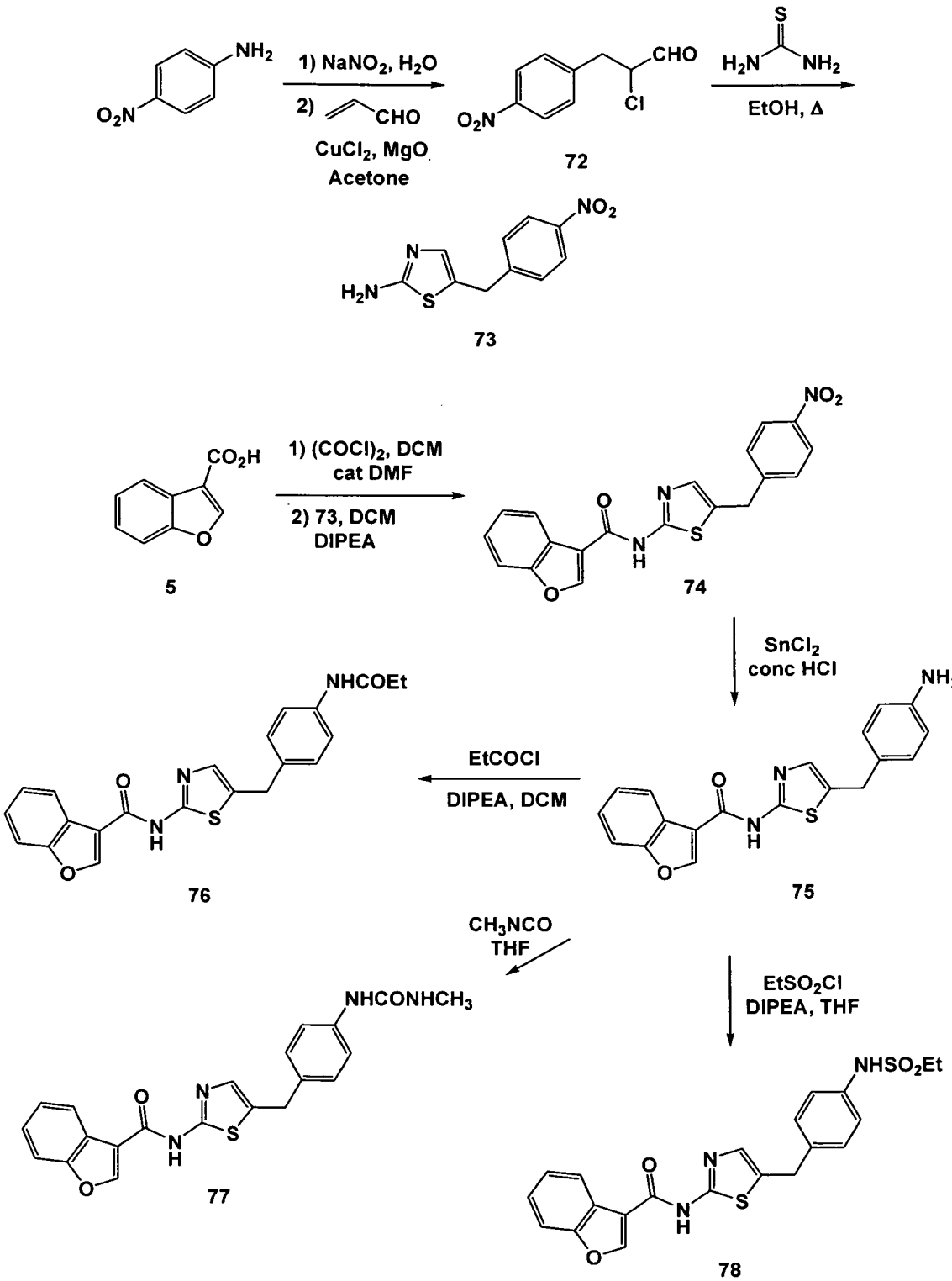
[0293] A solution of acid **67** (100 mg, 0.26 mmol), DIPEA (48 mL, 0.28 mmol), and HATU (110 mg, 0.28 mmol) in DMF is stirred at rt for 30 min, after which dimethylamine HCl (73 mg, 0.28 mmol) is added. After 1 h, an additional equiv of dimethylamine HCl is added and stirred for 1 h. Water is added providing a solid that is purified by column chromatography (silica gel, 3:2 EtOAc/heptane) affording the amide **68a** (51 mg) as a white powder: LC/MS t_R 4.28 min; MS (ES+) *m/z* 406 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.96 (s, 1H), 8.14 (app dd, 1H), 7.72 (app dd, 1H), 7.43 (m, 2H), 7.41 (m, 5H), 4.19 (s, 2H), 2.98 (br s, 3H), 2.93 (br s, 3H).

Example 64. *N*-[5-[[4-(Hydroxymethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (69)

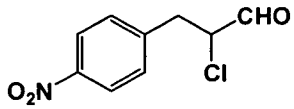


[0294] To a solution of ester **31** (200 mg, 0.51 mmol) in THF (3 mL) is added $LiBH_4$ (14 mg, 0.61 mmol). After 16 h at rt, additional $LiBH_4$ (3 x 1.2 equiv) is added over 6 h. After an additional 2 h after the last addition, water is added and the mixture extracted with EtOAc (3 x 15 mL). The combined organic phases are dried (Na_2SO_4), filtered, and concd *in vacuo*. The residue is slurried with DCM and filtered providing alcohol **69** (50 mg) as a white powder: LC/MS t_R 4.28 min; MS (ES+) *m/z* 365 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.97 (9s, 1H), 8.13 (app dd, 1H), 7.72 (app dd, 1H), 7.45 (m, 2H), 7.39 (s 1H), 7.26 (m, 4H), 6.54 (s, 1H), 5.15 (app t, 1 H), 4.49 (d, 2H), 4.12 (s, 2H).

Scheme 3. Examples of Compounds Synthesized from *N*-[5-[(4-Aminophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide (75)

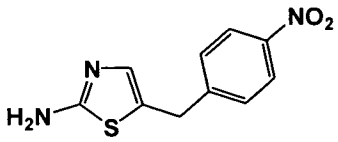


Example 65: 2-Chloro-3-(4-nitrophenyl)propanal (72)



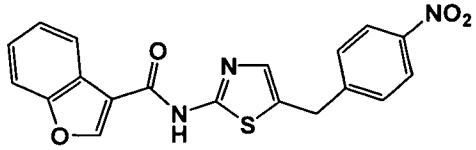
[0295] The diazonium salt of 4-nitroaniline (10.0 g, 72.5 mmol) is formed using $NaNO_2$ (5.5 g, 80 mmol) in conc HCl (28 mL) in accordance with **Method J**. The salt thus formed is reacted directly with acrolein (4.8 mL, 72 mmol, *d* 0.839), $CuCl_2$ (2.9 g, 22 mmol) and MgO (73 mg, 1.8 mmol) in acetone (23 mL) as detailed in **Method J** providing the title compound admixed with 4-nitrophenol (14.8 g) as a red brown oil which is used as is without further purification: ^{1}H NMR (250 MHz, $CDCl_3$, δ_H) 9.59 (1H, d), 8.21 (d, 2H), 7.42 (d, 2H), 4.45 (ddd, 1H), 3.52 (dd, 1H), 3.17 (dd, 1H).

Example 66: 5-[(4-Nitrophenyl)methyl]-2-thiazolamine (73)



[0296] α-Chloroaldehyde **72** (14.8 g) is reacted with thiourea (7.1 g, 94 mmol) in accordance with **Method K**. On completion, the reaction mixture is allowed to cool to rt and basified with NH_4OH and extracted into EtOAc (3 x 100 mL). The combined organic phases are washed with brine, dried (Na_2SO_4), filtered, and concd *in vacuo*. The residue is partitioned between DCM and 1.2 M HCl. The aqueous phase is washed with EtOAc, basified with 4 M NaOH, and extracted into EtOAc (3 x 50 mL). The combined organic phases are washed with brine, dried (Na_2SO_4), filtered, and concd *in vacuo* providing thiazolamine **73** as a brown solid: LC/MS t_R 1.14 min; MS (ES+) *m/z* 236 (M+H); ^{1}H NMR (250 MHz, DMSO-d_6, δ_H) 8.17 (d, 2H), 7.50 (d, 2H), 6.79 (s, 2H), 6.77 (s, 1H), 4.06 (s, 2H).

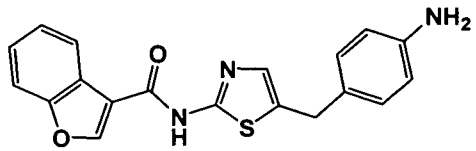
Example 67. *N*-[5-[(4-Nitrophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide (74)



[0297] In accordance with **Method Q**, 3-benzofurancarboxylic acid **5** (2.10 g, 13.0 mmol) is converted to the acid chloride *via* treatment with oxalyl chloride (3.3 mL, 38 mmol, *d* 1.455) and catalytic DMF (20 μL), and then treated with DIPEA (2.2 mL, 13

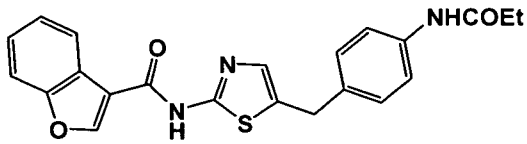
mmol, *d* 0.742) and aminothiazole **73** (3.00 g, 12.8 mmol) affording the title compound (1.00 g) following slurring in acetonitrile: LC/MS t_R 2.26 min; MS (ES+) *m/z* 380 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6, δ_H) 8.95 (s, 1H), 8.19 (d, 2H), 8.10 (d, 1H), 7.69 (d, 1H), 7.58 (d, 2H), 7.40 (m, 3H), 4.29 (s, 2H).

Example 68. *N*-[5-[(4-Aminophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide (75)



[0298] The nitroarene **74** (1.00 g, 2.64 mmol) is dissolved into conc HCl (15 mL) and chilled to 0 °C, after which $SnCl_2$ (2.4 g, 11 mmol) is added. The ice bath is removed and the mixture warmed to rt, then to 80 °C for 30 min. The cooled rt reaction mixture is diluted with water and basified with 2 M NaOH and filtered. The solid obtained is washed with water and slurried in THF and filtered. The filtrate is concd *in vacuo* providing amine **75** (256 mg): LC/MS t_R 3.58 min; MS (ES+) *m/z* 350 (M+H); ^{1}H NMR (400 MHz, CD_3OD, δ_H) 8.58 (s, 1H), 8.15 (m, 1H), 7.58 (m, 1H), 7.41-7.36 (m, 2H), 7.16 (s, 1H), 7.03 (d, 2H), 6.71 (d, 2H), 3.99 (s, 2H).

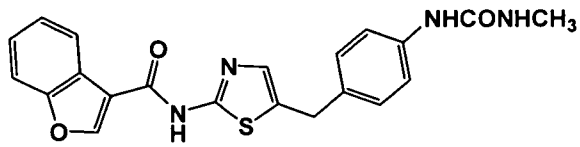
Example 69. *N*-[5-[[4-[(1-Oxopropyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (76)



[0299] A solution of amine **75** (50 mg, 0.14 mmol), DIPEA (24 μL, 0.14), propionyl chloride (12 μL, 0.14 mmol) in THF (2 mL) is stirred at rt for 30 min. A few drops of NH_4OH are added and stirred for 30 min, after which the mixture is diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic phases are washed with water, dried (Na2SO4), filtered, and concd *in vacuo*. Recrystallization from DCM provides the amide **76** as a yellow solid: LC/MS t_R 3.48 min; MS (ES+) *m/z* 406 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6, δ_H) 9.83 (s, 1H), 8.94 (s, 1H), 8.12 (app dd, 1H), 7.70

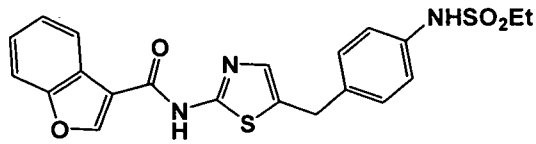
(app dd, 1H), 7.53 (d, 2H), 7.40 (m, 2H), 7.29 (s, 1H), 7.19 (d, 2H), 4.04 (s 2H), 2.28 (q, 2H), 1.05 (t, 3H).

Example 70. *N*-[5-[[4-[[(Methylamino)carbonyl]amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (77)



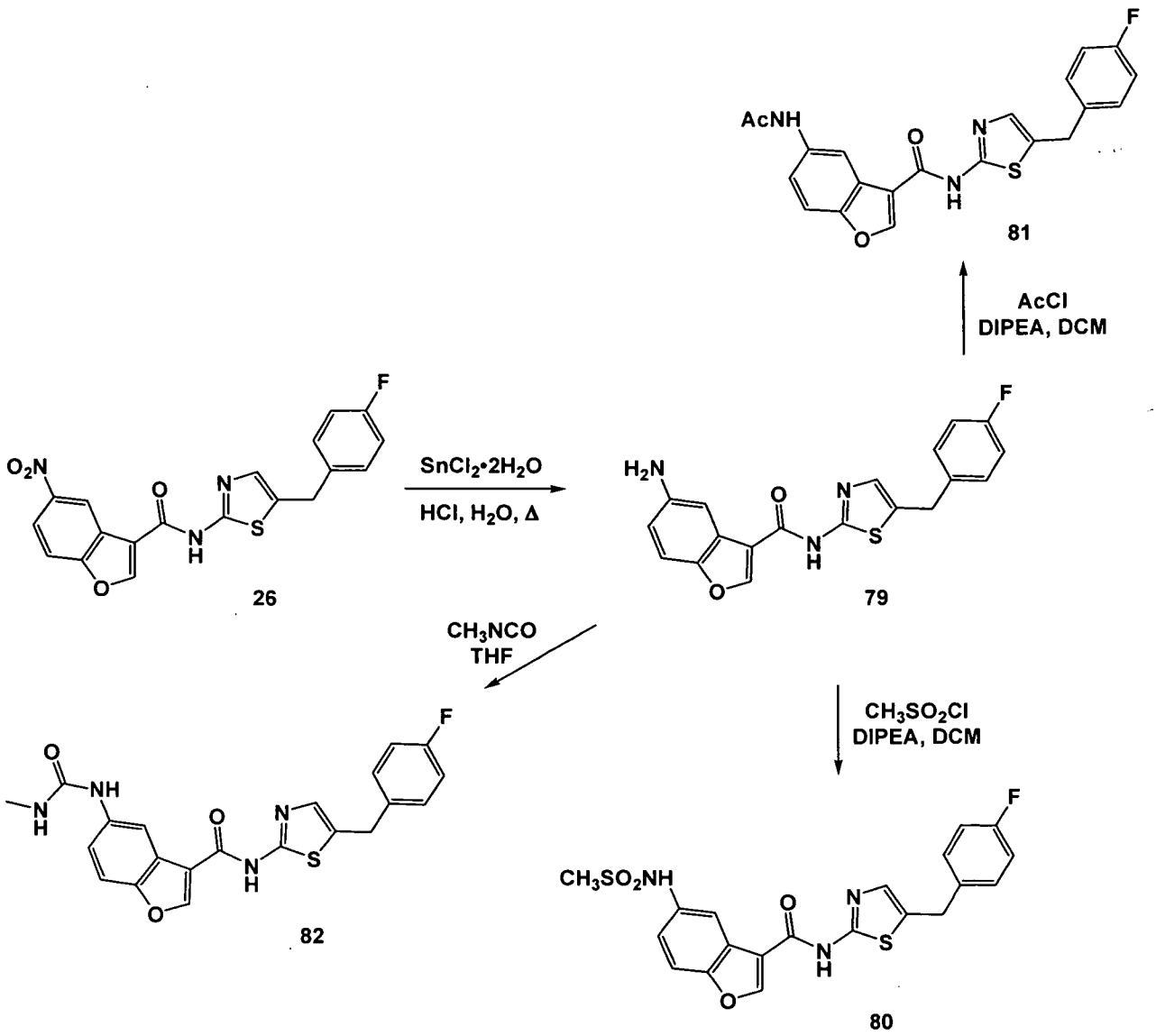
[0300] Methyl isocyanate (20 μL, 0.34 mmol) is added to a solution of amine **75** (100 mg, 0.29 mmol) in THF (2 mL). After 4 h at rt, a few drops of 2 M NaOH and water are added. The mixture is filtered and the filtrate extracted with EtOAc (3 x 10 mL). The combined organic phases are washed with water, dried (Na_2SO_4), filtered, and concd *in vacuo*. Recrystallization from DCM provides the urea **78** as a yellow solid: LC/MS t_R 4.14 min; MS (ES+) *m/z* 407 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6, δ_H) 8.86 (s, 1H), 8.50 (s, 1H), 8.12 (d, 1H), 7.69 (d, 1H), 7.40 (m, 2H), 7.32 (d, 2H), 7.28 (s, 1H), 7.16 (d, 2H), 6.00 (br q, 1H), 4.01 (s, 2H), 2.62 (d, 3H).

Example 71. *N*-[5-[[4-[(Ethylsulfonyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide (78)

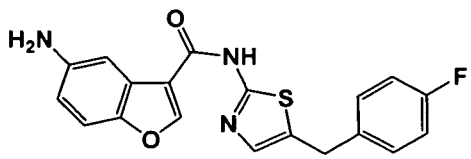


[0301] The sulfonamide **77** is isolated as a white solid by using the procedure described in **Example 69** employing ethylsulfonyl chloride as the derivatizing agent: LC/MS t_R 4.40 min; MS (ES+) *m/z* 442 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6, δ_H) 9.72 (s, 1H), 8.94 (s, 1H), 8.10 (app dd, 1H), 7.68 (m, 1H), 7.40 (m, 2H), 7.30 (s, 1H), 7.24 (d, 2H), 7.15 (d, 2H), 4.05 (s 2H), 3.04 (q, 2H), 1.17 (t, 3H).

Scheme 4. Examples of Compounds Synthesized from 5-Amino-*N*-[5-(4-fluorophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (79)



Example 72: 5-Amino-*N*-[5-(4-fluorophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (79)

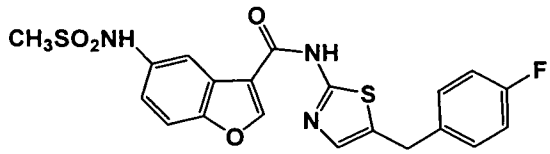


[0302] A stirred suspension of nitrobenzofuran **26** (200 mg, 0.50 mmol) in concd HCl (8 mL) is cooled to 0 °C and treated with $SnCl_2 \cdot H_2O$ (455 mg, 2.02 mmol) portion-wise over

5 min. The reaction mixture is heated to 70 °C and stirred a further 45 min at this temperature. Reaction progress is assessed by LC/MS. On completion the reaction

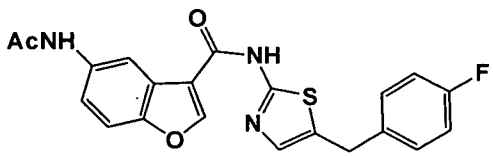
mixture is cooled to 0 °C and treated with 4 M NaOH until pH 14. The resultant precipitate is isolated by filtration to afford, on drying (vacuum oven), the title compound (169 mg) as a pale yellow powder: LC/MS t_R 1.58 min; MS (ES+) *m/z* 368 (M+H), 431; ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.36 (1H, br s), 8.76 (1H, s), 7.25-7.36 (5H, m), 7.16 (2H, t), 6.66 (1H, dd), 5.06 (2H, br s), 4.11 (2H, s).

Example 73: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-5-[(methylsulfonyl)amino]-3-benzofurancarboxamide (80)



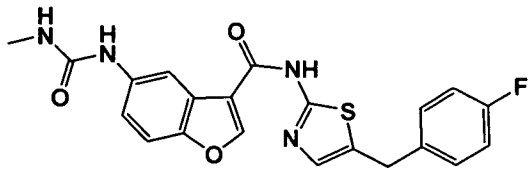
[0303] A solution of 5-aminobenzofuran **79** (40 mg, 0.11 mmol) and DIPEA (19 µL, 0.11 mmol, *d* 0.742) in DCM (2 mL) stirring at rt is treated with MsCl (7 µL, 0.09 mmol, *d* 1.48) and stirred at rt for 2 h, at which juncture reaction progress is assessed by LC/MS. A further equivalent of MsCl is added (7 µL, 0.09 mmol, *d* 1.48) and the reaction stirred an additional 18 h before filtering. The filtrate is diluted with DCM (10 mL) and washed with 1 M NaOH (10 mL). The DCM phase is dried ($MgSO_4$), filtered, and concd *in vacuo*. Column chromatography (silica gel, 1% MeOH in DCM) afforded the title compound (18 mg) as a white crystalline solid: LC/MS t_R 2.00 min; MS (ES+) *m/z* 446 (M+H); ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.53 (1H, br s), 9.75 (1H, br s), 8.95 (1H, s), 8.03 (1H, d), 7.68 (1H, d), 7.26-7.37 (4H, m), 7.16 (2H, t), 4.12 (2H, s), 2.94 (3H, s).

Example 74: 5-(Acetylamino)-*N*-[5-(4-fluorophenyl)methyl-2-thiazolyl]-3-benzofurancarboxamide (81)



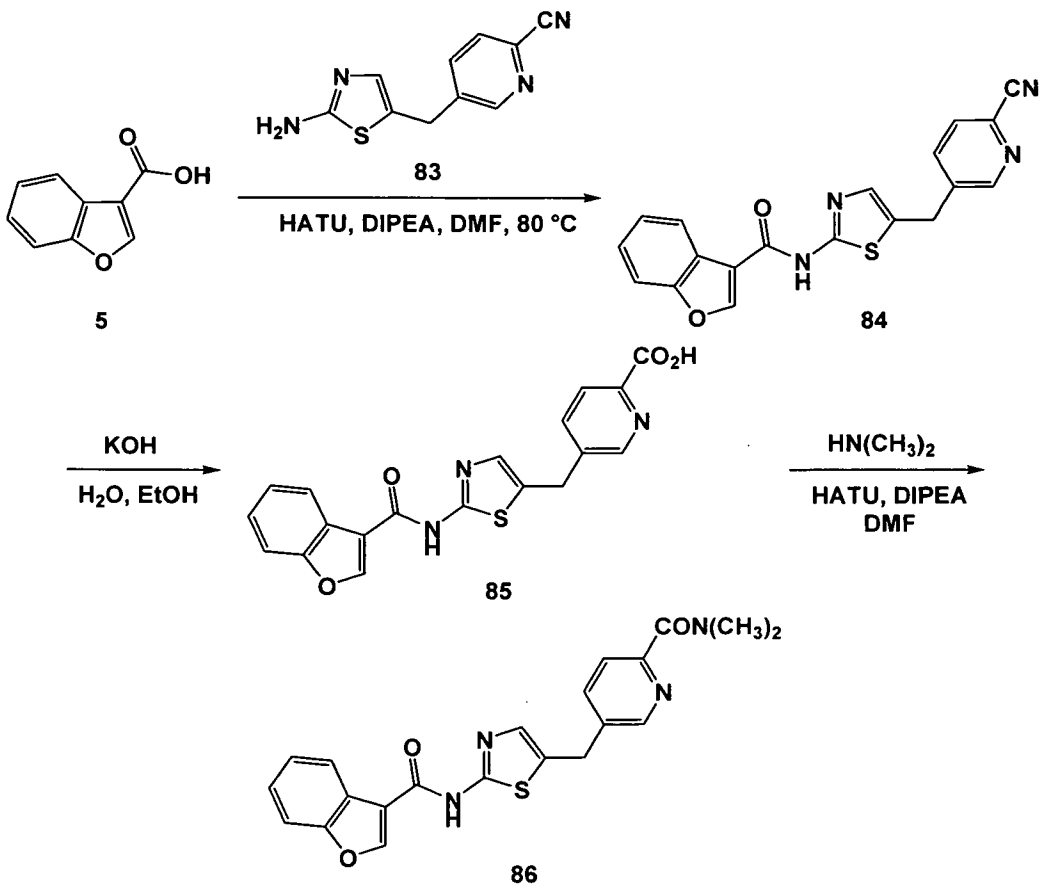
[0304] Acetamide **81** can be prepared using the procedure described in **Example 73** using acetyl chloride as the acylating agent: LC/MS t_R 4.26 min; MS (ES+) *m/z* 410 (M+H); ^{1}H NMR (360 MHz, CD_3OD, δ_H) 8.62 (s, 1H), 8.34 (s, 1H), 7.67 (d, 1H), 7.57 (d, 1H), 7.35 (m, 2H), 7.26 (br s, 1H), 7.10 (m, 2H), 4.17 (s, 2H), 2.20 (s, 3H).

Example 75: *N*-[5-(4-Fluorophenyl)methyl-2-thiazolyl]-5-[[(methylamino)carbonyl]amino]-3-benzofurancarboxamide (82)

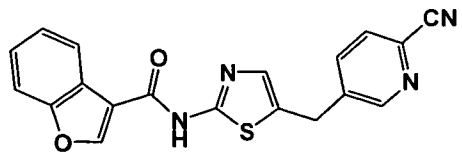


[0305] Urea **82** can be prepared using the procedure described in **Example 70**: LC/MS t_R 4.16 min; MS (ES+) *m/z* 425 (M+H); ^{1}H NMR (360 MHz, DMSO-d_6, δ_H) 12.47 (br s, 1H), 8.88 (s, 1H), 8.64 (s, 1H), 8.22 (d, 1H), 7.55 (d, 1H), 7.43-7.34 (m, 3H), 7.32 (s, 1H), 7.18 (app t, 2H), 5.97 (q, 1H), 4.14 (s, 2H), 2.66 (d, 3H).

Scheme 5. Preparation of 5-[[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]-*N*,*N*-dimethyl-2-pyridinecarboxamide (86)

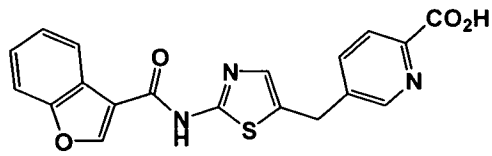


Example 76. *N*-[5-[(6-Cyano-3-pyridinyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide (84)



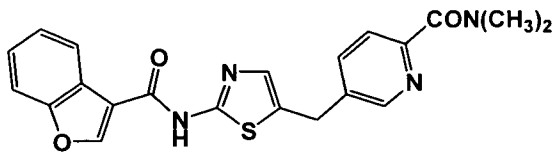
[0306] 5-[(2-Amino-5-thiazolyl)methyl]-2-pyridinecarbonitrile (**83**) can be prepared from 5-bromo-2-pyridinecarbonitrile using the procedures described **Methods N**, **O**, and **M1**. The amide **84** is prepared from 3-benzofurancarboxylic acid **5** and thiazolamine **83** using the procedure described in **Method R**: LC/MS t_R 4.64 min; MS (ES+) *m/z* 361 (M+H); ^{1}H NMR (360 MHz, CD_3OD, δ_H) 8.73 (d, 1H), 8.65 (s, 1H), 8.20 (app ddd, 1H), 7.97 (app dd, 1H), 7.88 (app dd, 1H), 7.64 (app ddd, 1H), 7.50-7.40 (m, 2H), 7.37 (s, 1H), 4.35 (s, 2H).

Example 77. 5-[[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]-2-pyridinecarboxylic Acid (85)



[0307] A mixture of nitrile **84** (120 mg, 0.333 mmol) in EtOH (2 mL) and 2 M KOH (2 mL) is heated at 80 °C for 15 min. The mixture is cooled to 0 °C then conc HCl is added until a pH of 1-2 is achieved. The EtOH is then removed *in vacuo* and the resultant precipitate filtered, washed with water and dried *in vacuo* providing acid **85** (103 mg).

Example 78. 5-[[2-[(3-Benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]-*N*,*N*-dimethyl-2-pyridinecarboxamide (86)



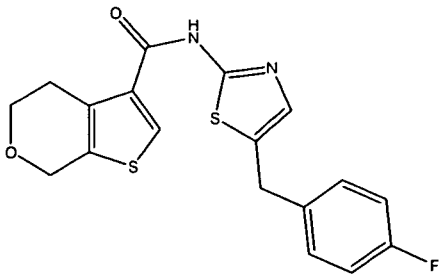
Amide **86** is prepared from acid **85** and dimethylamine hydrochloride using the procedure described in **Method R**: LC/MS t_R 4.00 min; MS (ES+) *m/z* 407 (M+H); ^{1}H NMR (360 MHz,

$CDCl_3$, δ_H) 10.69 (br s, 1H), 8.42 (s, 1H), 8.22 (s, 1H), 8.04 (m, 1H), 7.58-7.51 (m, 3H), 7.35 (m, 2H), 7.00 (s, 1H), 4.07 (s, 2H), 3.07 (s, 3H), 3.03 (s, 3H).

Examples: Structure & In Vitro Activity Data

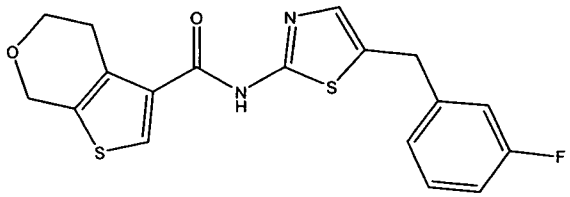
[0308] The following species comprise some representative species of the present invention. For all 6HB (six-helix bundle formation) assays, activity profiles for compounds having or exhibiting an IC_{50} equal or less than 1.0 μM are accorded a "+++" designation; activity profiles for compounds having or exhibiting an IC_{50} between 1.1 μM and 10.0 μM are accorded a "++" designation; and activity profiles for compounds having or exhibiting an IC_{50} greater than 10.1 μM are accorded a "+" designation. The following embodiments are illustrative of the claimed invention and are not intended to limit the scope of the present invention to the embodiments listed below.

Structure:



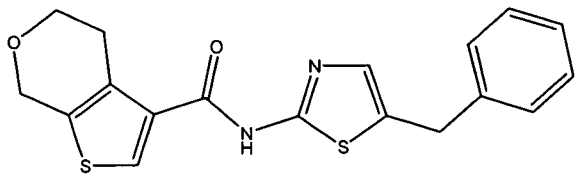
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 374.46
6 HB activity profile: +++

Structure:



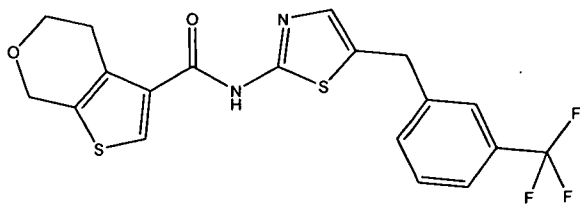
Name: *N*-[5-[(3-fluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 374.46
6 HB activity profile: +

Structure:



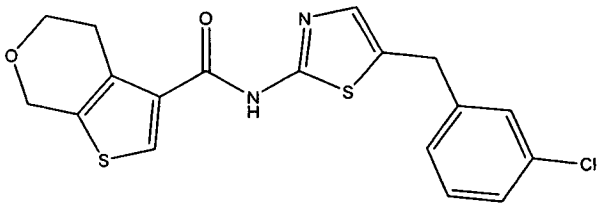
Name: 4,7-dihydro-*N*-[5-(phenylmethyl)-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 356.47
6 HB activity profile: +++

Structure:



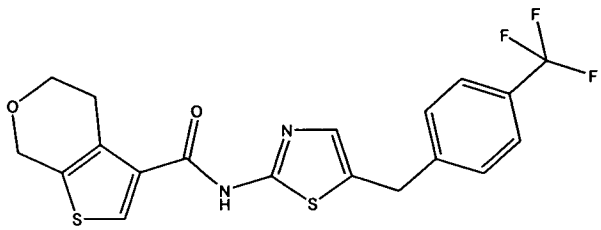
Name: 4,7-dihydro-*N*-[5-[[3-(trifluoromethyl)phenyl]methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 424.47
6 HB activity profile: +++

Structure:



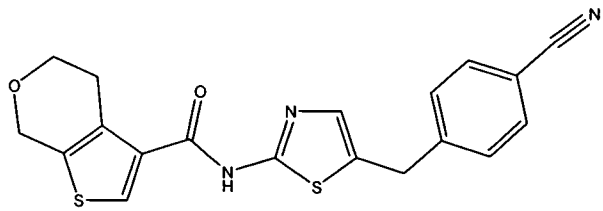
Name: *N*-[5-[(3-chlorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 390.91
6 HB activity profile: +++

Structure:



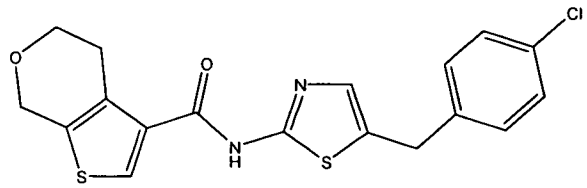
Name: 4,7-dihydro-*N*-[5-[[4-(trifluoromethyl)phenyl]methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 424.47
6 HB activity profile: +++

Structure:



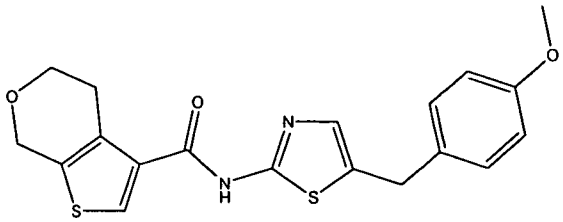
Name: *N*-[5-[(4-cyanophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 381.48
6 HB activity profile: +++

Structure:



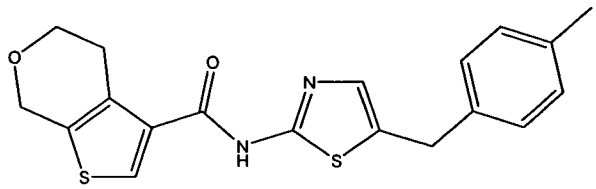
Name: *N*-[5-[(4-chlorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 390.91
6 HB activity profile: +++

Structure:



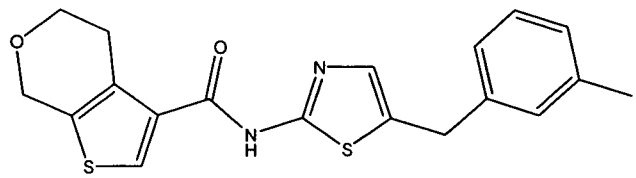
Name: 4,7-dihydro-*N*-[5-[(4-methoxyphenyl)methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 386.49
6 HB activity profile: +

Structure:



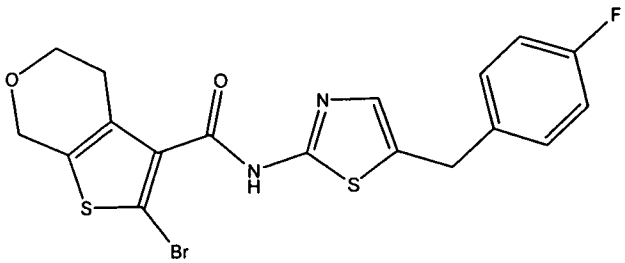
Name: 4,7-dihydro-*N*-[5-[(4-methylphenyl)methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 370.50
6 HB activity profile: ++

Structure:



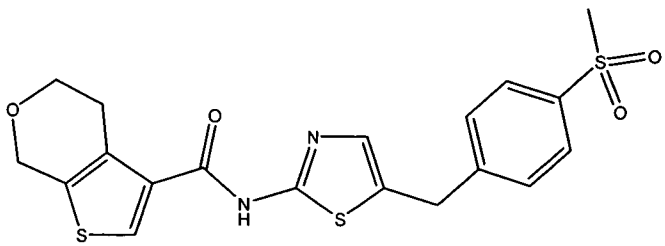
Name: 4,7-dihydro-*N*-[5-[(3-methylphenyl)methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 370.50
6 HB activity profile: ++

Structure:



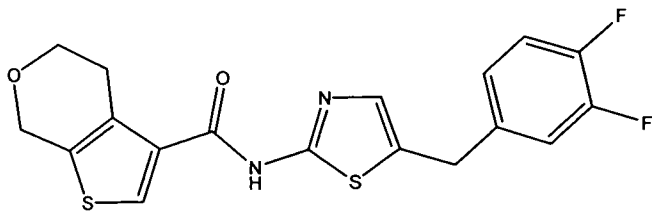
Name: 2-bromo-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 453.35
6 HB activity profile: ++

Structure:



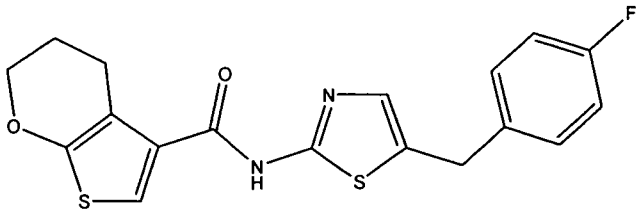
Name: 4,7-dihydro-*N*-[5-[[4-(methylsulfonyl)phenyl]methyl]-2-thiazolyl]-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 434.56
6 HB activity profile: +++

Structure:



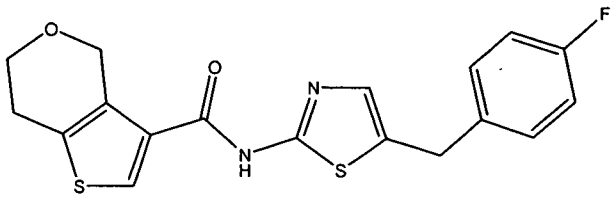
Name: *N*-[5-[(3,4-difluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 392.54
6 HB activity profile: +++

Structure:



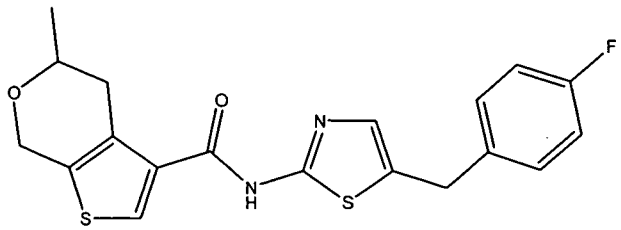
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3,4-dihydro-2*H*-thieno[2,3-b]pyran-5-carboxamide
Molecular Weight: 374.46
6 HB activity profile: +++

Structure:



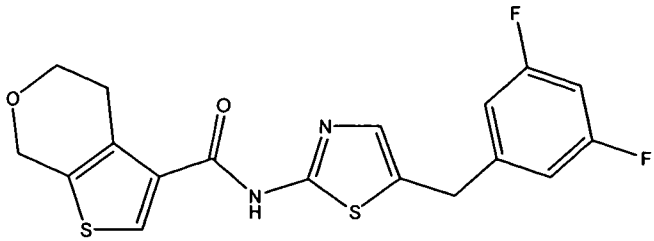
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-6,7-dihydro-4*H*-thieno[3,2-c]pyran-3-carboxamide
Molecular Weight: 374.46
6 HB activity profile: +++

Structure:



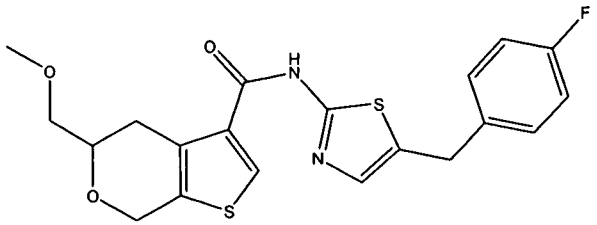
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5-methyl-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 388.49
6 HB activity profile: +++

Structure:



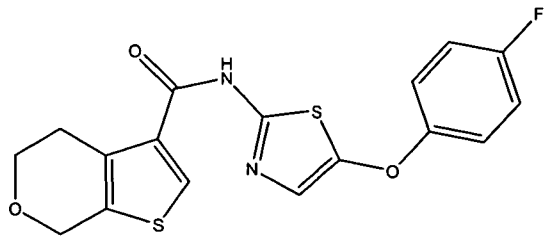
Name: *N*-[5-[(3,5-difluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 392.45
6 HB activity profile: ++

Structure:



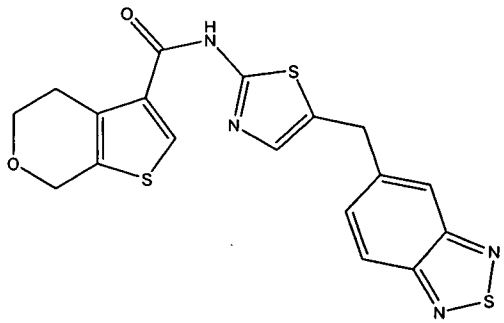
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-4,7-dihydro-5-(methoxymethyl)-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 418.51
6 HB activity profile: ++

Structure:



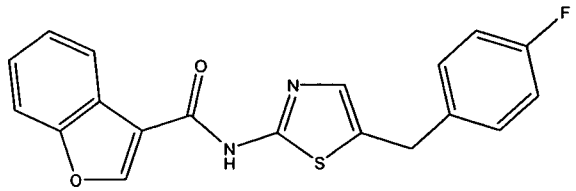
Name: *N*-[5-(4-fluorophenoxy)-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 376.43
6 HB activity profile: ++

Structure:



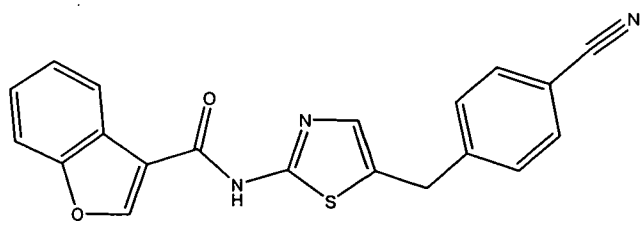
Name: *N*-[[5-(2,1,3-benzothiadiazol-5-yl)methyl]-2-thiazolyl]-4,7-dihydro-5*H*-thieno[2,3-c]pyran-3-carboxamide
Molecular Weight: 414.53
6 HB activity profile: +++

Structure:



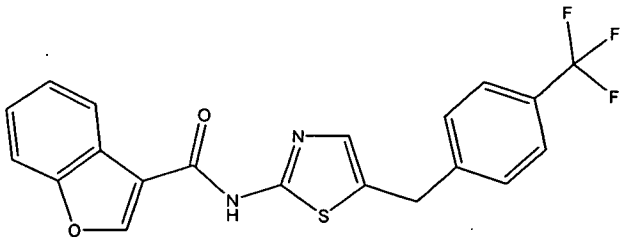
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 352.39
6 HB activity profile: +++

Structure:



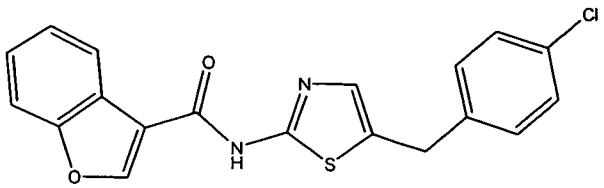
Name: *N*-[5-[(4-cyanophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 359.41
6 HB activity profile: +++

Structure:



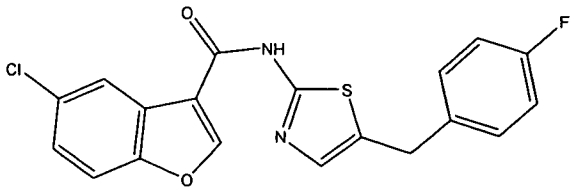
Name: *N*-[5-[[4-(trifluoromethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 402.40
6 HB activity profile: +++

Structure:



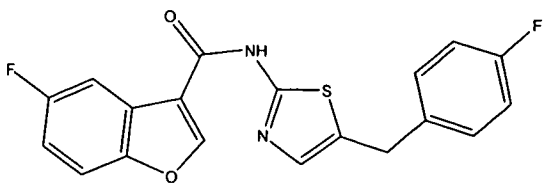
Name: *N*-[5-[(4-chlorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 368.84
6 HB activity profile: +++

Structure:



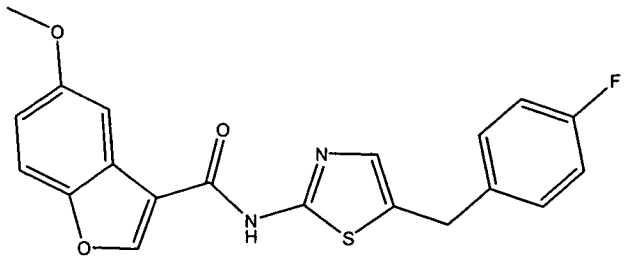
Name: 5-chloro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 386.84
6 HB activity profile: +++

Structure:



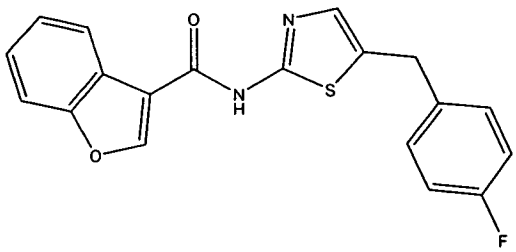
Name: 5-fluoro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 370.38
6 HB activity profile: +

Structure:



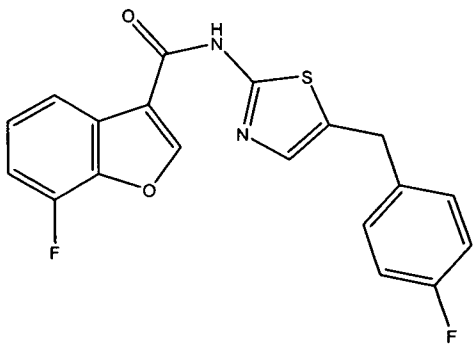
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-5-methoxy-3-benzofurancarboxamide
Molecular Weight: 382.42
6 HB activity profile: ++

Structure:



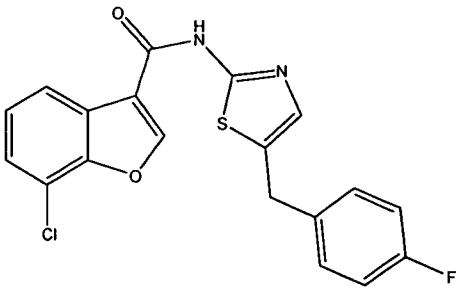
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 388.85
6 HB activity profile: ++

Structure:



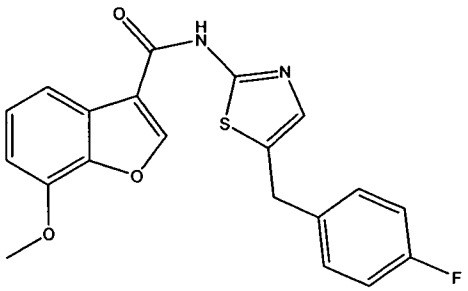
Name: 7-fluoro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 370.38
6 HB activity profile: +++

Structure:



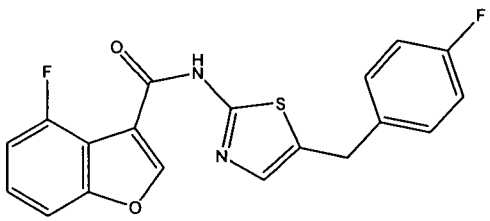
Name: 7-chloro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 386.84
6 HB activity profile: +++

Structure:



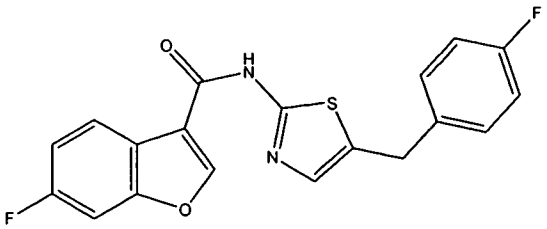
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-7-methoxy-3-benzofurancarboxamide
Molecular Weight: 382.42
6 HB activity profile: +

Structure:



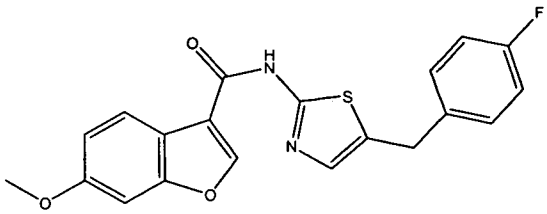
Name: 4-fluoro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 370.38
6 HB activity profile: +

Structure:



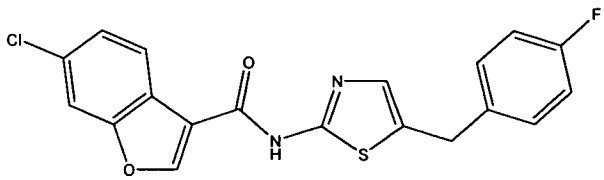
Name: 6-fluoro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 370.38
6 HB activity profile: ++

Structure:



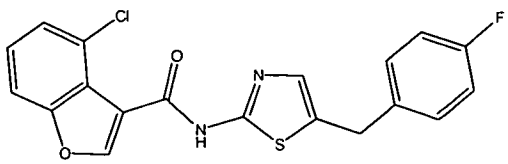
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-6-methoxy-3-benzofurancarboxamide
Molecular Weight: 382.42
6 HB activity profile: ++

Structure:



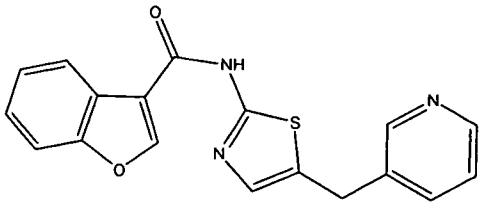
Name: 6-chloro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 500.86
6 HB activity profile: +

Structure:



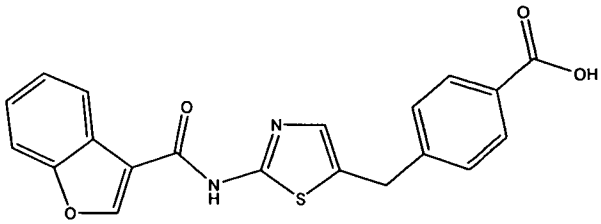
Name: 4-chloro-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 500.86
6 HB activity profile: +

Structure:



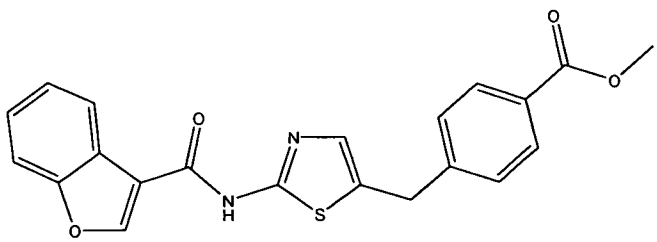
Name: *N*-[5-(3-pyridinylmethyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 335.39
6 HB activity profile: +++

Structure:



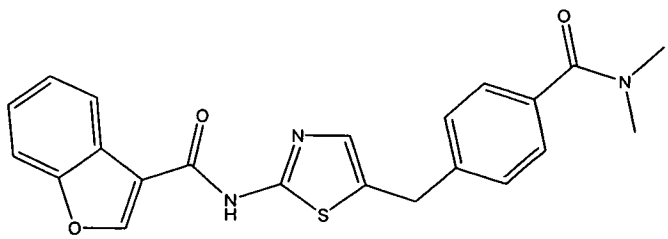
Name: 4-[[2-[(3-benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]benzoic acid
Molecular Weight: 378.41
6 HB activity profile: +

Structure:



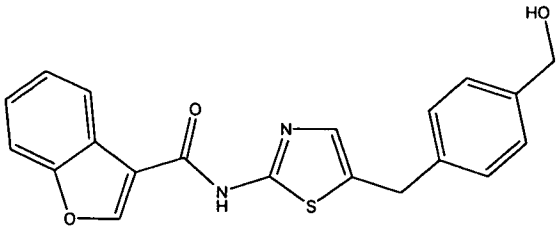
Name: 4-[[2-[(3-benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]benzoic acid, methyl ester
Molecular Weight: 392.44
6 HB activity profile: ++

Structure:

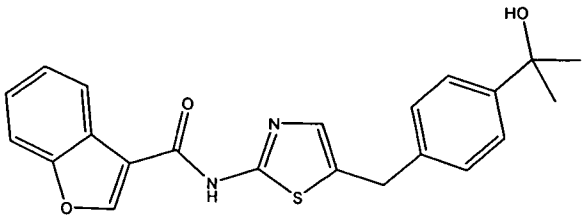


Name: *N*-[5-[[4-[(dimethylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 405.48
6 HB activity profile: +++

Structure:

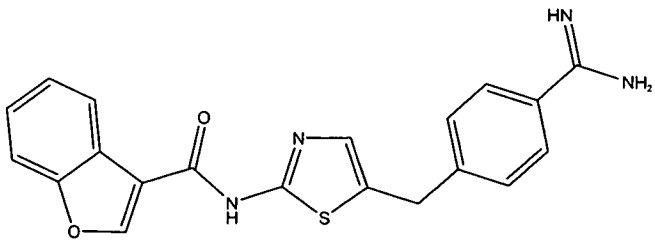


Name: *N*-[5-[[4-(hydroxymethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 364.43
6 HB activity profile: +++
Structure:



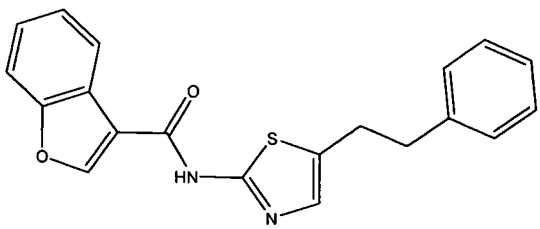
Name: *N*-[5-[[4-(1-hydroxy-1-methylethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 392.48
6 HB activity profile: ++

Structure:



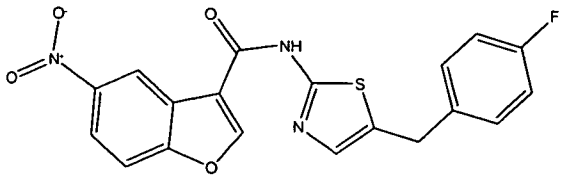
Name: *N*-[5-[[4-(aminoiminomethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 376.44
6 HB activity profile: +++

Structure:



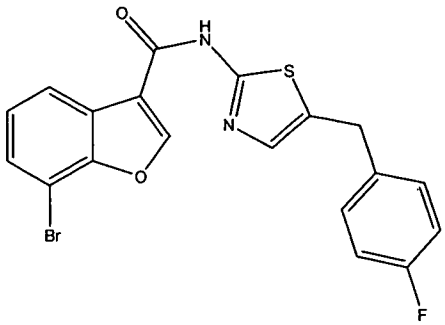
Name: *N*-[5-(2-phenylethyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 348.43
6 HB activity profile: +

Structure:



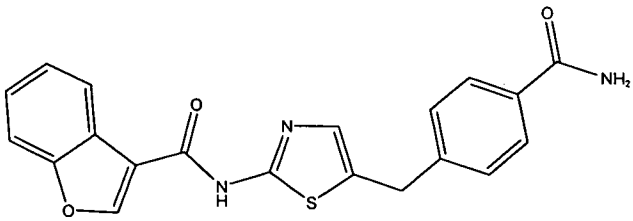
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-5-nitro-3-benzofurancarboxamide
Molecular Weight: 397.39
6 HB activity profile: ++

Structure:



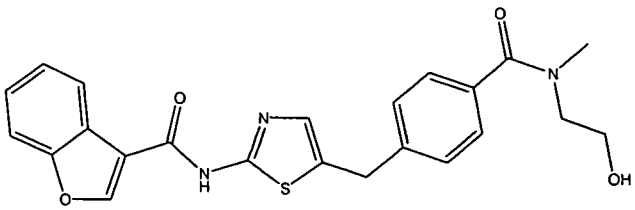
Name: 7-bromo-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 431.29
6 HB activity profile: +++

Structure:



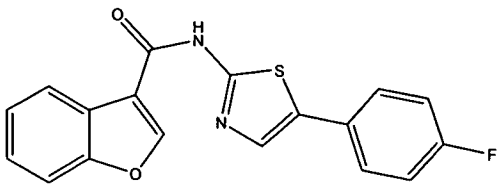
Name: *N*-[5-[[4-(aminocarbonyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 377.42
6 HB activity profile: ++

Structure:

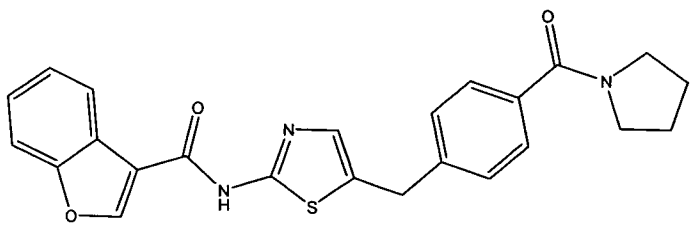


Name: *N*-[5-[[4-[[(2-hydroxyethyl)methylamino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 435.51
6 HB activity profile: +

Structure:

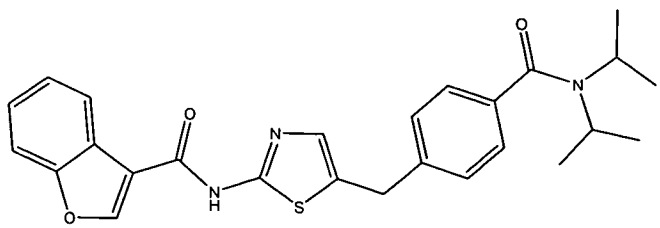


Name: *N*-[5-(4-fluorophenyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 338.36
6 HB activity profile: +
Structure:



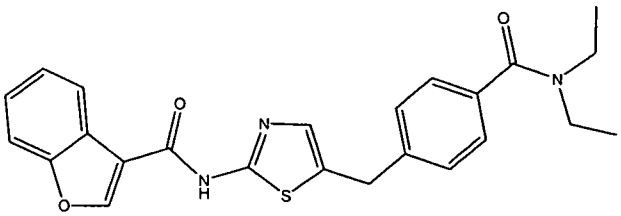
Name: *N*-[5-[[4-(1-pyrrolidinylcarbonyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 431.52
6 HB activity profile: ++

Structure:



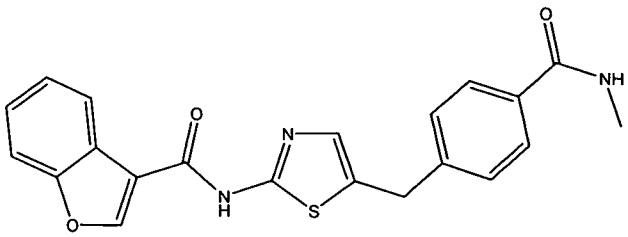
Name: *N*-[5-[[4-[[bis(1-methylethyl)amino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 461.59
6 HB activity profile: +

Structure:



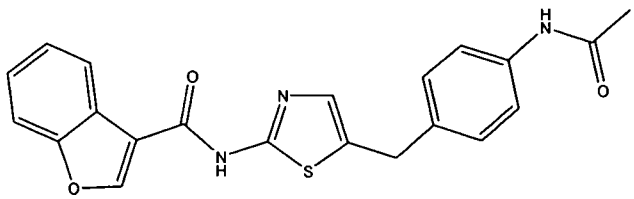
Name: *N*-[5-[[4-[(diethylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 433.53
6 HB activity profile: +

Structure:



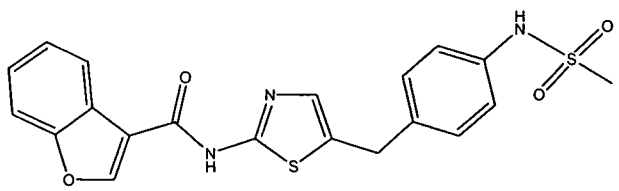
Name: *N*-[5-[[4-[(methylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 391.45
6 HB activity profile: ++

Structure:



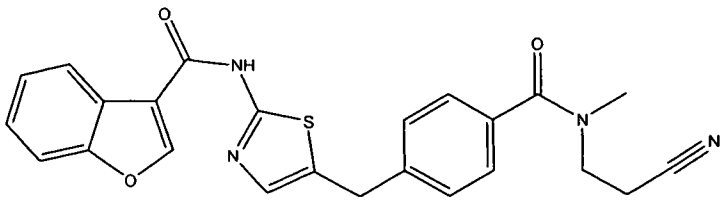
Name: *N*-[5-[[4-(acetylamino)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 391.45
6 HB activity profile: ++

Structure:



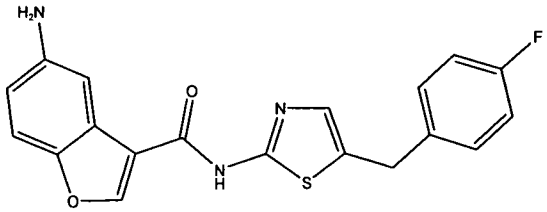
Name: *N*-[5-[[4-[(methylsulfonyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 427.50
6 HB activity profile: ++

Structure:



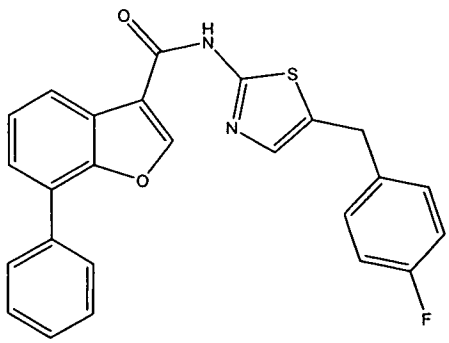
Name: *N*-[5-[[4-[[(2-cyanoethyl)methylamino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 444.52
6 HB activity profile: +

Structure:



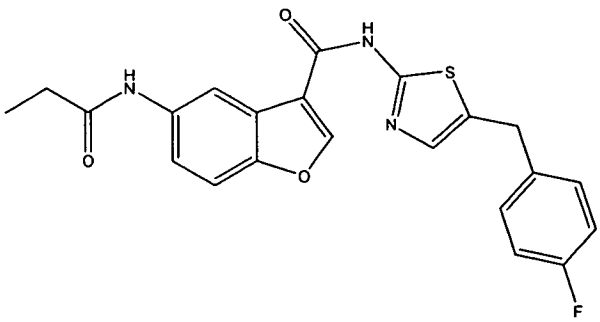
Name: 5-amino-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 367.40
6 HB activity profile: +++

Structure:



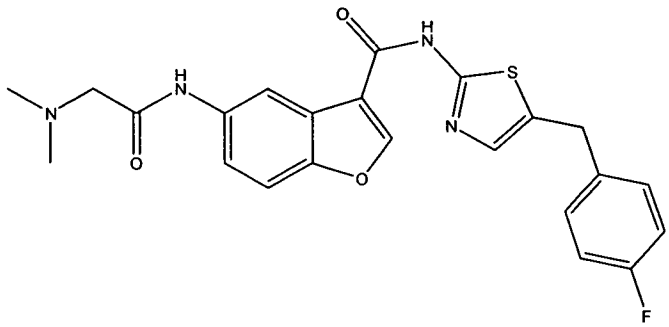
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-7-phenyl-3-benzofurancarboxamide
Molecular Weight: 428.49
6 HB activity profile: ++

Structure:



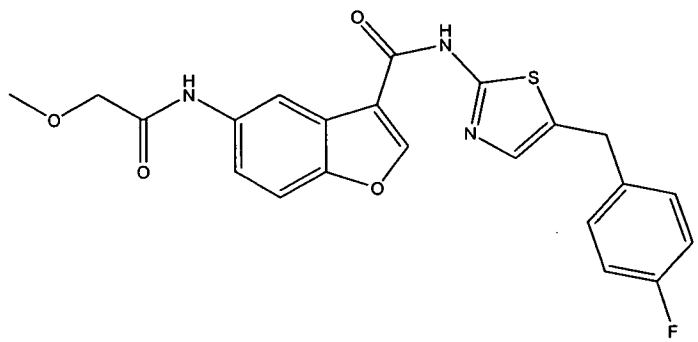
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-5-[(1-oxopropyl)amino]-3-benzofurancarboxamide
Molecular Weight: 423.47
6 HB activity profile: ++

Structure:



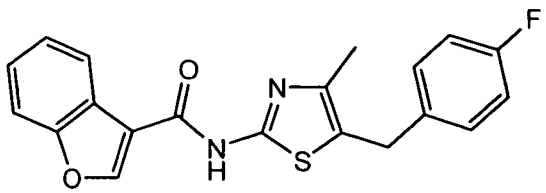
Name: 5-[[2-(dimethylamino)acetyl]amino]-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 452.51
6 HB activity profile: +

Structure:



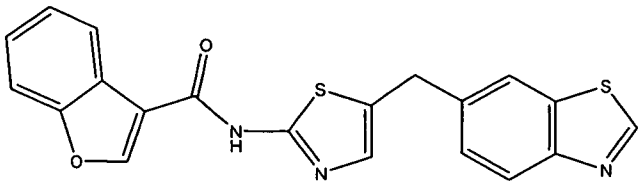
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-5-[(2-methoxyacetyl)amino]-3-benzofurancarboxamide
Molecular Weight: 439.47
6 HB activity profile: +

Structure:



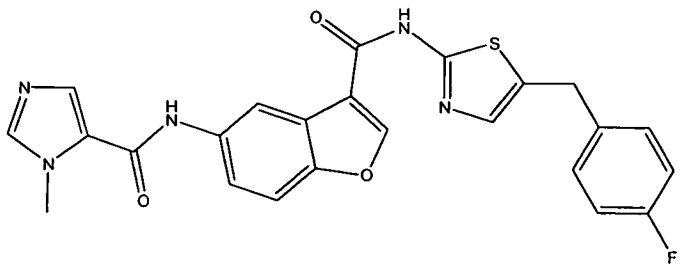
Name: *N*-[5-[(4-fluorophenyl)methyl]-5-methyl-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 366.41
6 HB activity profile: +++

Structure:



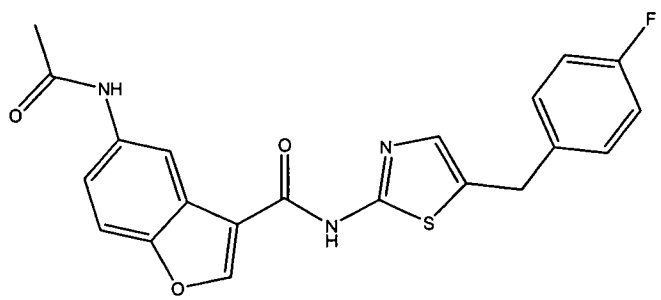
Name: *N*-[5-(6-benzothiazolylmethyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 391.47
6 HB activity profile: +++

Structure:



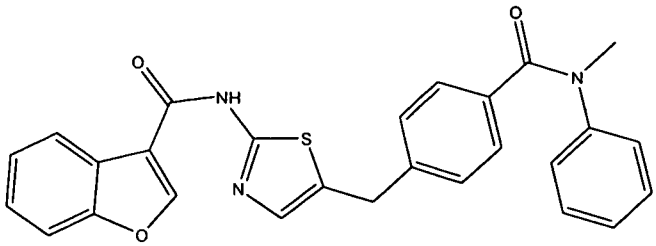
Name: *N*-[3-[[[5-[(4-fluorophenyl)methyl]-2-thiazolyl]amino]carbonyl]-5-benzofuranyl]-1-methyl-1*H*-imidazole-5-carboxamide
Molecular Weight: 475.51
6 HB activity profile: ++

Structure:



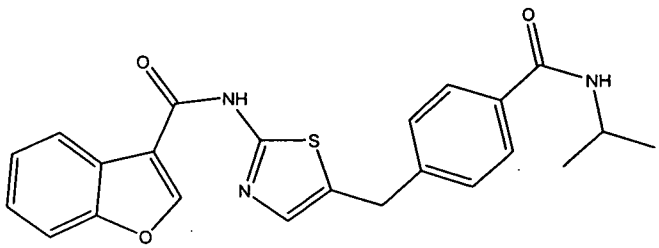
Name: 5-(acetylamino)-*N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 409.44
6 HB activity profile: ++

Structure:



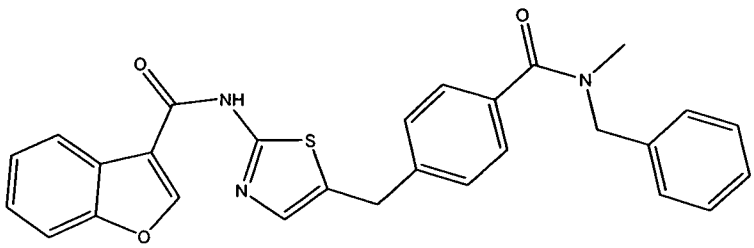
Name: *N*-[5-[[4-[(methylphenylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 467.55
6 HB activity profile: ++

Structure:



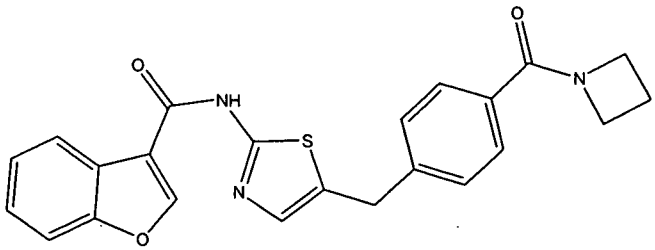
Name: *N*-[5-[[4-[[(1-methylethyl)amino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 419.51
6 HB activity profile: ++

Structure:



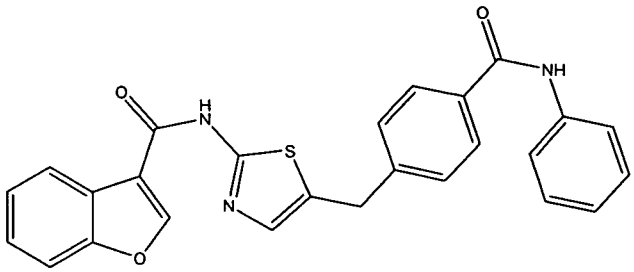
Name: *N*-[5-[[4-[[methyl(phenylmethyl)amino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 481.58
6 HB activity profile: +

Structure:



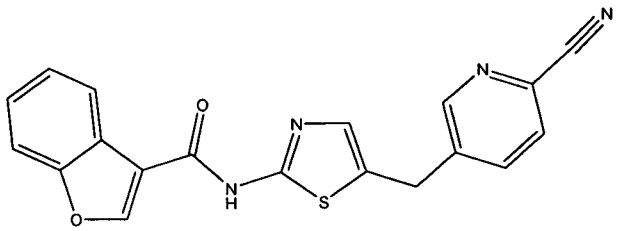
Name: *N*-[5-[[4-(1-azetidinylcarbonyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 417.49
6 HB activity profile: ++

Structure:



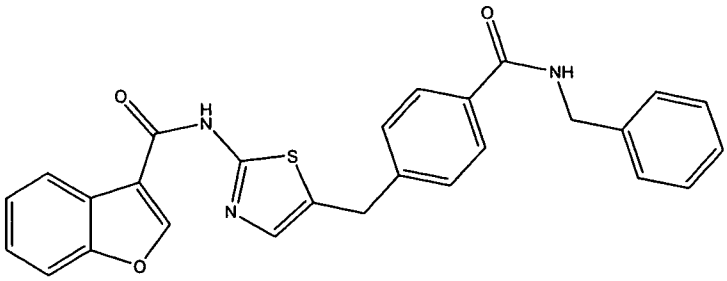
Name: *N*-[5-[[4-[(phenylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 453.52
6 HB activity profile: +

Structure:



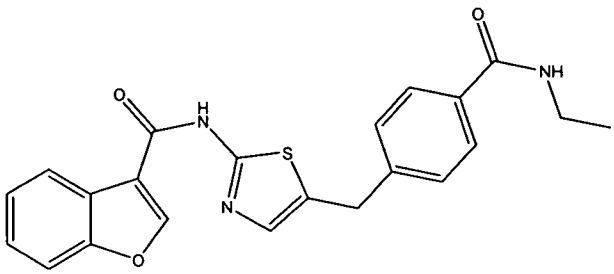
Name: *N*-[5-[(6-cyano-3-pyridinyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 360.40
6 HB activity profile: +++

Structure:



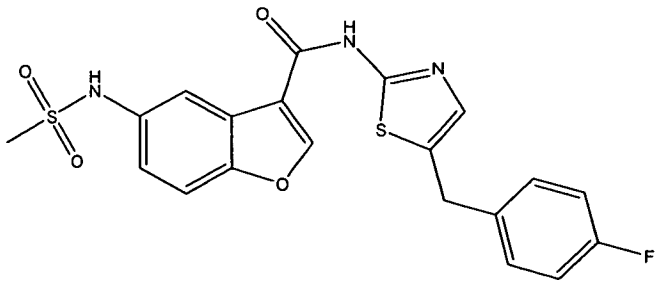
Name: *N*-[5-[[4-[[(phenylmethyl)amino]carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 467.55
6 HB activity profile: +

Structure:



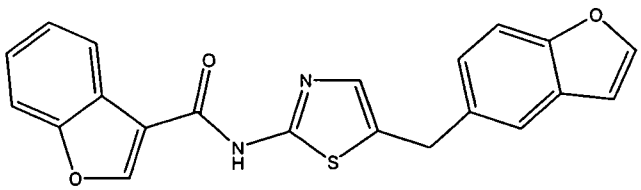
Name: *N*-[5-[[4-[(ethylamino)carbonyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 405.48
6 HB activity profile: ++

Structure:



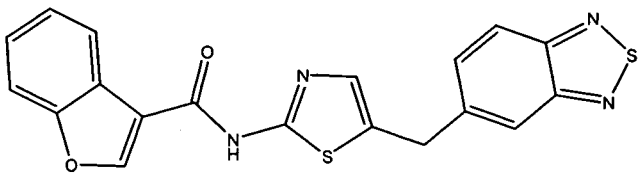
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-5-[(methylsulfonyl)amino]-3-benzofurancarboxamide
Molecular Weight: 445.49
6 HB activity profile: ++

Structure:

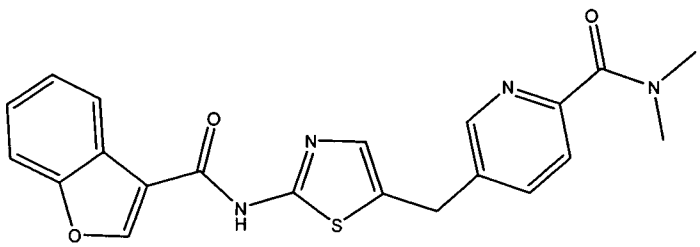


Name: *N*-[5-(5-benzofuranylmethyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 374.42
6 HB activity profile: +++

Structure:

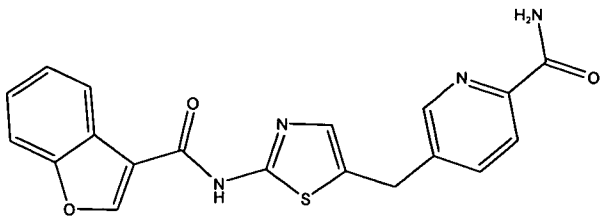


Name: *N*-[[5-(2,1,3-benzothiadiazol-5-yl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 392.46
6 HB activity profile: +++
Structure:



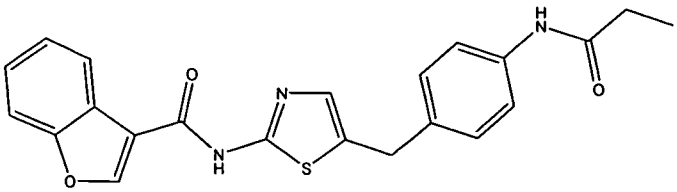
Name: 5-[[2-[(3-benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]-*N*,*N*-dimethyl-2-pyridinecarboxamide
Molecular Weight: 406.47
6 HB activity profile: ++

Structure:



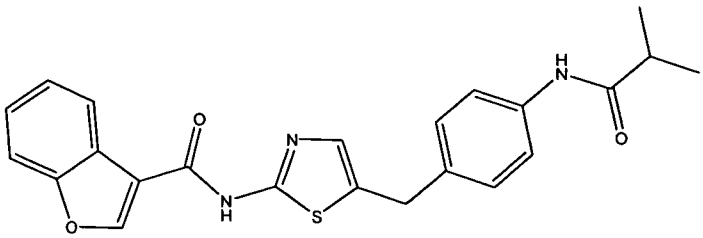
Name: 5-[[2-[(3-benzofuranylcarbonyl)amino]-5-thiazolyl]methyl]-2-pyridinecarboxamide
Molecular Weight: 378.41
6 HB activity profile: ++

Structure:

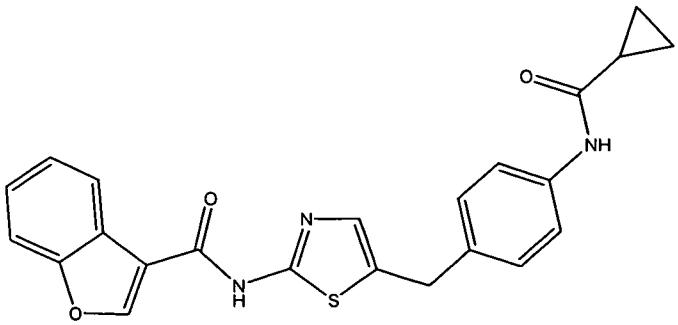


Name: *N*-[5-[[4-[(1-oxopropyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 405.48
6 HB activity profile: ++

Structure:

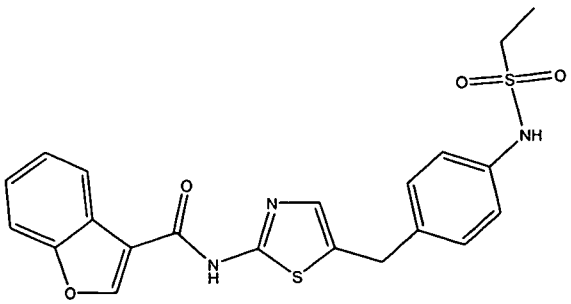


Name: *N*-[5-[[4-[(2-methyl-1-oxopropyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 419.51
6 HB activity profile: ++
Structure:



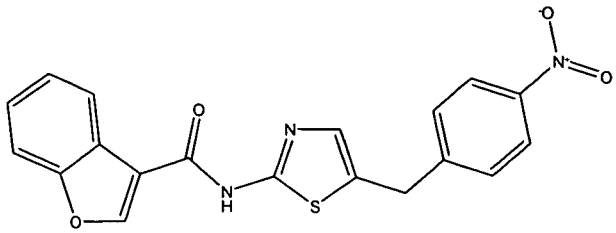
Name: *N*-[5-[[4-[(cyclopropylcarbonyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 417.49
6 HB activity profile: ++

Structure:



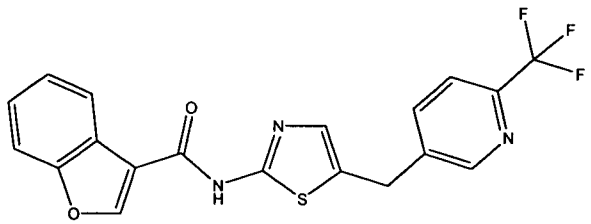
Name: *N*-[5-[[4-[(ethylsulfonyl)amino]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 441.53
6 HB activity profile: ++

Structure:



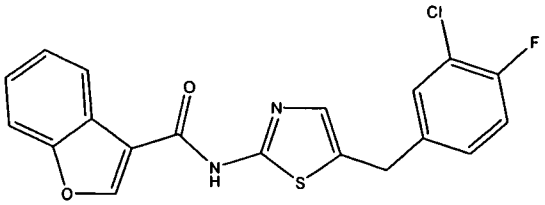
Name: *N*-[5-[(4-nitrophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 493.42
Viral Entry activity profile: n/d
6 HB activity profile: +++

Structure:



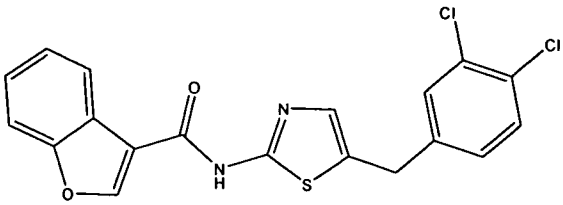
Name: *N*-[5-[[6-(trifluoromethyl)-3-pyridinyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight:
6 HB activity profile: +++

Structure:



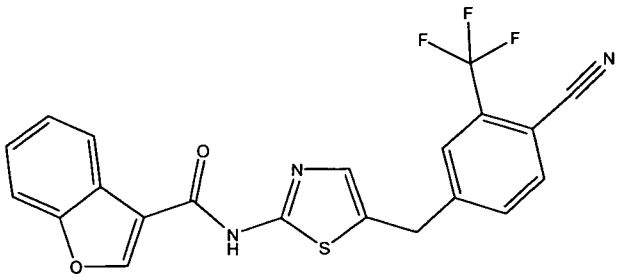
Name: *N*-[5-[(3-chloro-4-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 386.84
6 HB activity profile: +++

Structure:



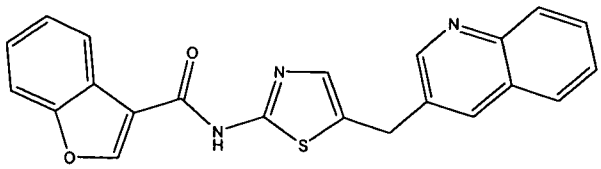
Name: *N*-[5-[(3,4-dichlorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 403.29
6 HB activity profile: +++

Structure:



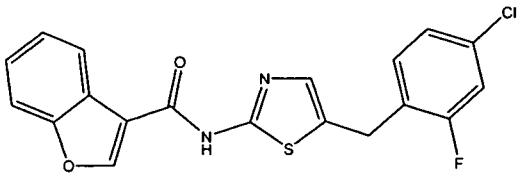
Name: *N*-[5-[[4-cyano-3-(trifluoromethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 427.41
6 HB activity profile: +++

Structure:



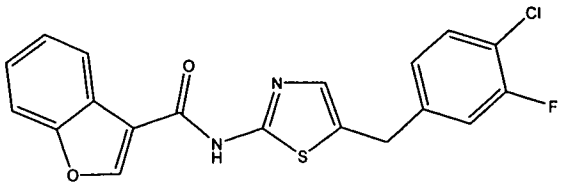
Name: *N*-[5-(3-quinolinylmethyl)-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 385.45
6 HB activity profile: +++

Structure:



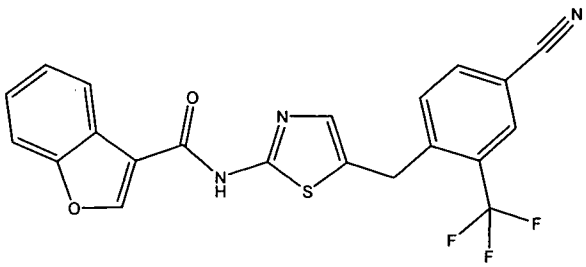
Name: *N*-[5-[(4-chloro-2-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 386.84
6 HB activity profile: +++

Structure:



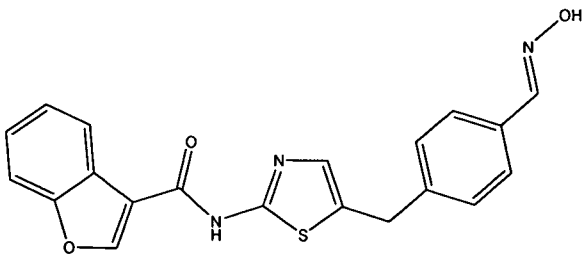
Name: *N*-[5-[(4-chloro-3-fluorophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 386.84
6 HB activity profile: +++

Structure:



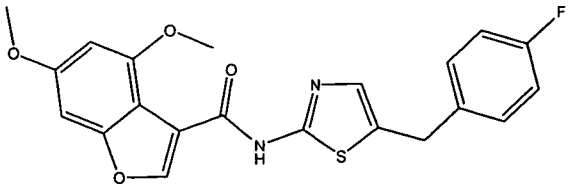
Name: *N*-[5-[[4-cyano-2-(trifluoromethyl)phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 427.41
6 HB activity profile: +++

Structure:



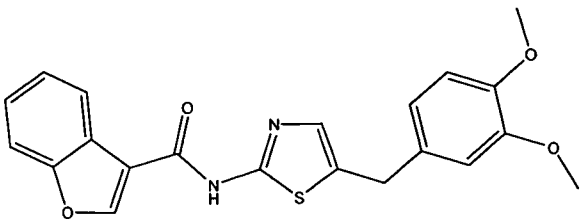
Name: *N*-[5-[[4-[(*E*)-(hydroxyimino)methyl]phenyl]methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 377.42
6 HB activity profile: ++

Structure:



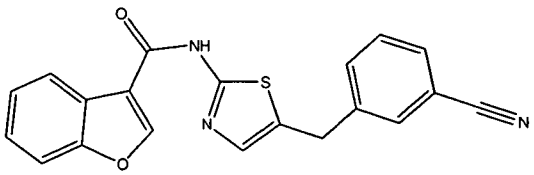
Name: *N*-[5-[(4-fluorophenyl)methyl]-2-thiazolyl]-4,6-dimethoxy-3-benzofurancarboxamide
Molecular Weight: 412.44
6 HB activity profile: +

Structure:



Name: *N*-[5-[(3,4-dimethoxyphenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 394.45
6 HB activity profile: ++

Structure:

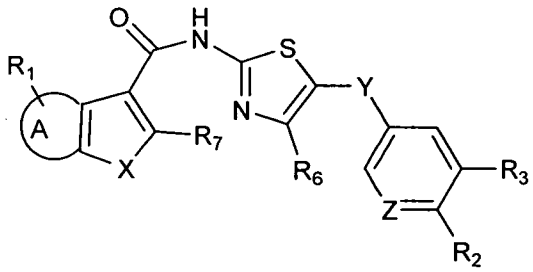


Name: *N*-[5-[(3-cyanophenyl)methyl]-2-thiazolyl]-3-benzofurancarboxamide
Molecular Weight: 359.41
6 HB activity profile: +++

[0309] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein, as well as the entirety of Provisional Patent Appl. No. 61/017,042, filed December 27, 2007 are fully incorporated by reference herein in their entirety.

What Is Claimed:

1. A compound according to Formula I:

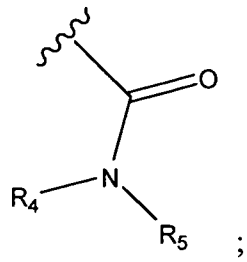


or a pharmaceutically acceptable salt or solvate thereof;

wherein A is a 6-7 membered ring system optionally comprising one oxygen which ring system is optionally substituted with one or more R_1 moieties at each carbon;

each R_1 is independently selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, haloalkyl, haloalkoxy, hydroxy, hydrido, alkoxy, cyano, amido, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxyalkoxyalkyl, alkoxycarbonyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoiminoalkyl, hydroxyiminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, heterocyclylamido, alkylheterocyclylamido, sulfonamido, alkylthio, alkylthioalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, cycloalkyl, nitro, alkoxy, alkylcarbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylamino, dialkylaminoalkylcarbonylamino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_2, R_3 and, when present, R_3', are independently selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylthio, alkylthioalkyl, alkylsulfonyl, alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, nitro, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylaminocarbonyl, heterocyclylcarbonyl, arylalkylaminocarbonyl, alkylcarbonylamino, hydroxyimino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur, and



;

or R_2 and R_3 can be taken together to form a fused ring system optionally interrupted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_4 and R_5, when present, are independently selected from the group consisting of hydrido, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, cycloalkyl, aryl, arylalkyl, or R_4 and R_5 may taken together with the nitrogen to which they are bound to form a heterocyclyl;

R_6 is independently selected from the group consisting of hydrido, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cyanoalkyl, or haloalkyl;

R_7 is independently selected from the group consisting of hydrido and halo;

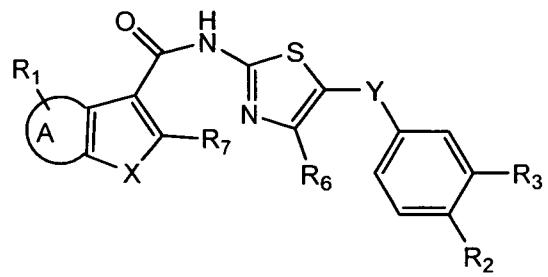
X is sulfur, oxygen, NH or N-alkyl;

Y is oxygen or alkylene; and

Z is nitrogen or CR_3', where R_3' is defined above;

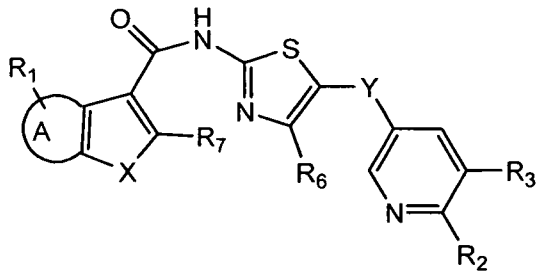
with the proviso that when X is sulfur, A comprises 1 oxygen.

2. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:

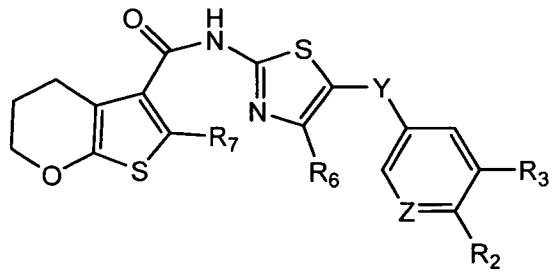


.

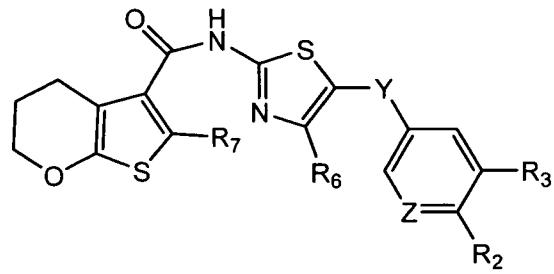
3. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



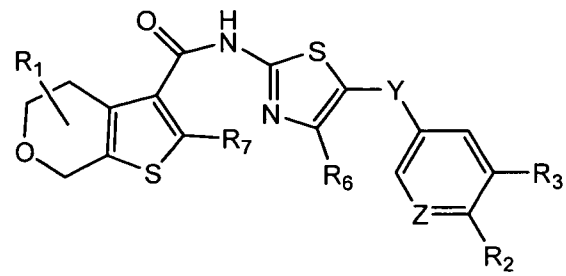
4. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



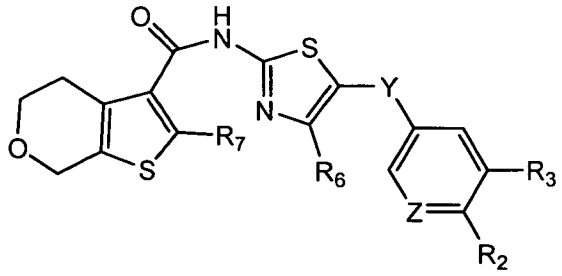
5. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



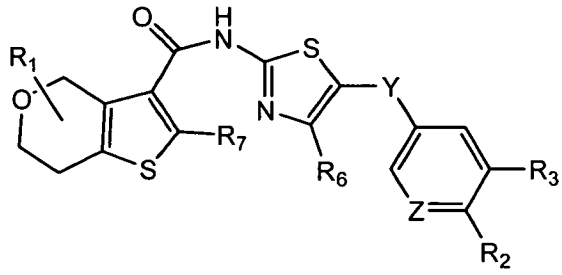
6. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



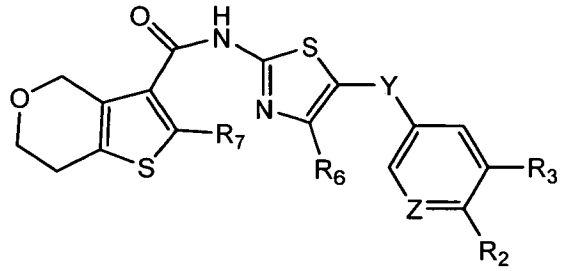
7. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



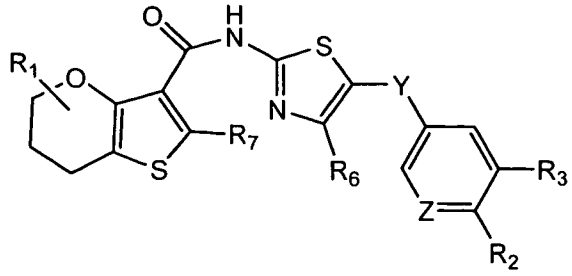
8. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



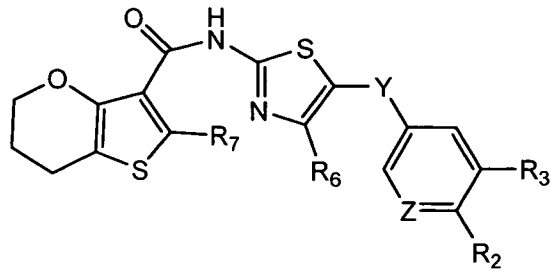
9. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



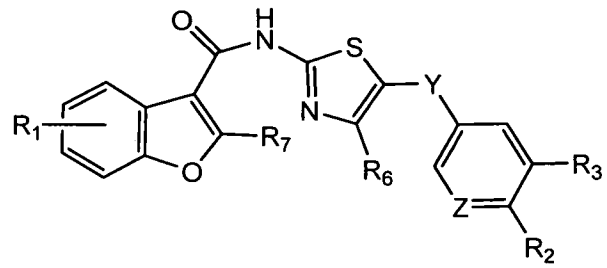
10. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



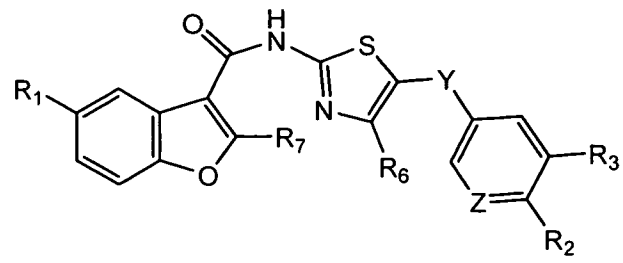
11. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



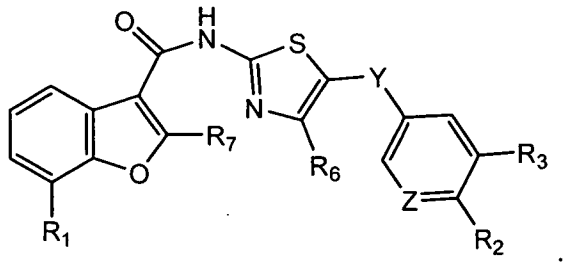
12. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



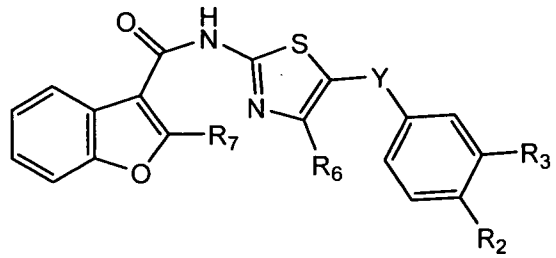
13. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



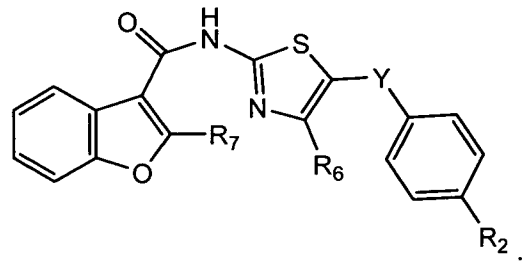
14. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



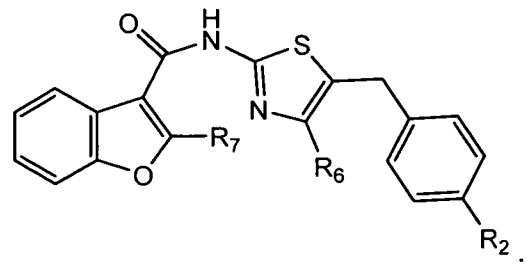
15. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



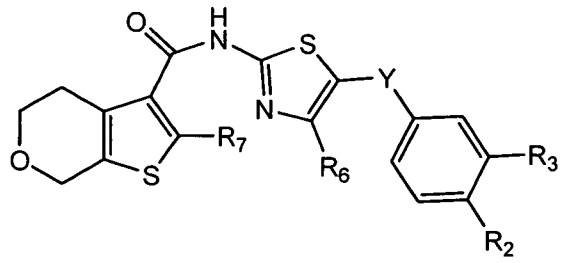
16. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



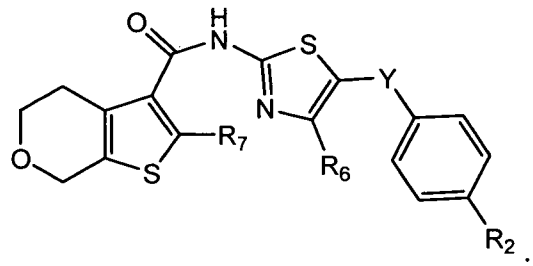
17. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



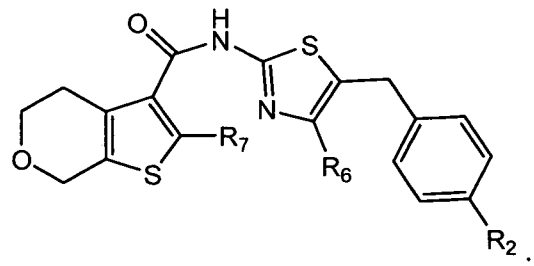
18. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



19. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



20. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Formula I is:



21. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein X is sulfur.

22. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein X is oxygen.

23. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Y is oxygen.

24. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Y is alkyl.

25. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Y is methylene.

26. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Y is ethylene.

27. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Z is nitrogen.

28. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein Z is carbon.

29. A compound according to Claim 1 wherein A is a 6 membered heterocycle comprising an oxygen at the 6 position wherein A is fully saturated.

30. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A is a 6 membered carbocycle wherein A is aromatic.

31. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A is a 7 membered carbocycle wherein A is fully saturated.

32. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A is a 6 membered carbocycle wherein A is fully saturated, and wherein each of the 5 and 7 positions of A are substituted with one or two R_1 moieties independently selected from the group consisting of hydrido, alkyl, amino, amido, alkoxy, alkoxycarbonyl, alkoxycarbonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, nitro, alkylsulfonyl, arylsulfonyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, alkylsulfonylamino, arylsulfonylamino, cycloalkyl, and alkyl

interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

33. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A comprises one R_1 moiety selected from the group consisting of hydrido, alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, nitro, alkoxy, amido, alkylcarbonylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, cycloalkyl, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

34. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A is a six membered ring substituted with R_1 at the 5 position.

35. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkyl.

36. A compound according to Claim 35 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methyl.

37. A compound according to Claim 35 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is ethyl.

38. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkoxy.

39. A compound according to Claim 38 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methoxy.

40. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkoxyalkyl.

41. A compound according to Claim 40 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methoxymethyl.

42. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is halo.

43. A compound according to Claim 42 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is fluoro.

44. A compound according to Claim 42 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is chloro.

45. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is amino.

46. A compound according to Claim 42 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is dimethylamino

47. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is amido.

48. A compound according to Claim 47 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkylamido.

49. A compound according to Claim 48 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methylamido.

50. A compound according to Claim 48 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is ethylamido.

51. A compound according to Claim 48 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is dimethylamido.

52. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkylsulfonylamino or arylsulfonylamino.

53. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is heterocyclylamido.

54. A compound according to Claim 53 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is imidazolylamido.

55. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkylheterocyclylamido.

56. A compound according to Claim 55 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methylimidazolylamido.

57. A compound according to Claim 34 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is nitro.

58. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein A is a six membered ring substituted with R_1 at the 7 position.

59. A compound according to Claim 58 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is alkyl.

60. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is methyl.

61. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is ethyl.

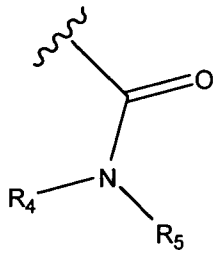
62. A compound according to Claim 58 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is halo.

63. A compound according to Claim 62 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is fluoro.

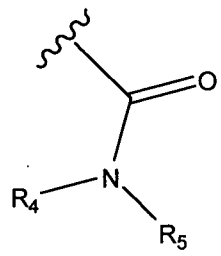
64. A compound according to Claim 62 or a pharmaceutically acceptable salt or solvate thereof wherein R_1 is chloro.

65. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are independently selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl,

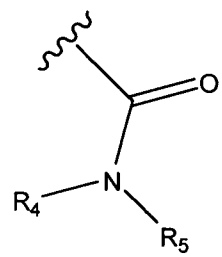
alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur, and



66. A compound according to Claim 65 or a pharmaceutically acceptable salt or solvate thereof wherein R_3 is hydrogen and R_2 is selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl, alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur, and

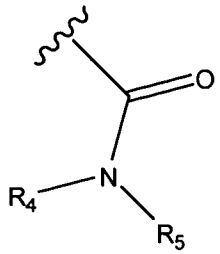


67. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 is



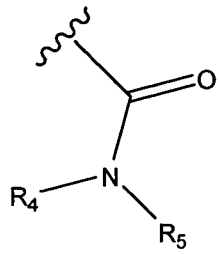
and R_4 and R_5 are independently selected from the group consisting of hydrido, aminoalkyl, alkyl, alkoxyalkyl, cyanoalkyl, aryl, and arylalkyl.

68. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 is



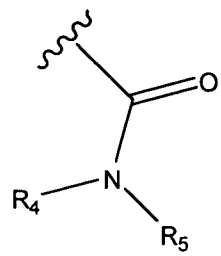
and R_4 and R_5 may be taken together with the nitrogen to which they are bound to form a heterocyclyl.

69. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 is



and R_4 and R_5 are independently selected from the group consisting of hydrido, aminomethyl, methyl, ethyl, dimethyl, diethyl, isopropyl, methoxyethyl, ethoxyethyl, ethoxymethyl, cyanoethyl, benzyl, and phenyl.

70. A compound according to Claim 59 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 is



and R_4 and R_5 are taken together with the nitrogen to which they are bound to form a heterocyclyl selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, and morpholinyl.

71. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused ring system optionally

interrupted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur.

72. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused heterocycle.

73. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused thiadiazole.

74. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused thiazole.

75. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused furan.

76. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused carbocycle.

77. A compound according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof wherein R_2 and R_3 are taken together to form a fused benzyl.

78. A compound or salt as defined in any one of claims 1 to 77 for use as a medicament.

79. The use of a compound or salt as defined in any one of claims 1 to 77, for the manufacture of a medicament to treat a disease for which an HIV inhibitor is desired.

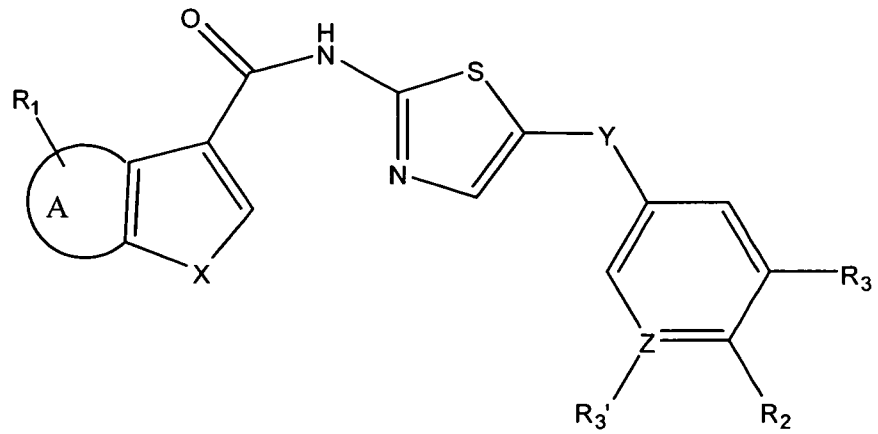
80. A pharmaceutical composition which comprises the product prepared by combining an effective amount of (a) a compound or salt according to any one of claims 1 to 77, and (b) a pharmaceutically acceptable carrier.

81. A method of preventing, treating or delaying the onset of HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound or salt as defined in any one of claims 1-77.

82. The method of 81, wherein the compound is administered in combination with a therapeutically effective amount of at least one HIV inhibitor selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase

inhibitors, nucleoside HIV reverse transcriptase inhibitors, nucleotide HIV reverse transcriptase inhibitors, HIV maturation inhibitors, vaccines, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, CCR5 antibodies, CXCR4 antibodies, immunomodulators, and HIV fusion inhibitors.

83. A compound according to the Formula:

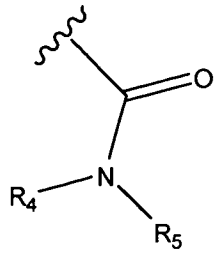


wherein A is a 6-7 membered ring system optionally comprising 1 oxygen which ring system is optionally substituted with one or more R_1 moieties at each carbon;

each R_1 is independently selected from the group consisting of alkyl, amino, amido, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyl, carboxyalkyl, alkanoyloxyalkyl, alkoxyalkyl, hydroxyalkyl, cyanoalkyl, alkoxyalkoxyalkyl, alkoxycarbonylaminoalkoxyalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkyl, hydroxyalkoxyalkyl, aminoiminoalkyl, hydroxyiminoalkyl, aminoalkoxyalkyl, alkylcarbonylaminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroarylalkyl, arylalkyl, arylcarbonylaminoalkyl, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, cycloalkyl, nitro, alkoxy, alkylcarbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylamino, dialkylaminoalkylcarbonylamino, and alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_2, R_3 and, when present, R_3', are independently selected from the group consisting of hydrido, alkyl, alkoxy, arylalkyl, amino, amido, alkylsulfonylalkyl, aminoalkyl, aminoalkoxyalkyl, alkoxycarbonylamino, alkoxycarbonylalkyl, alkylsulfonyl, alkoxyalkyl, alkoxycarbonyl, alkylsulfonylamino, aminoiminomethyl, aryl, cyano, cyanoalkyl, cycloalkyl, carboxy, hydroxyiminoalkyl, halo, haloalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl,

heteroarylalkyl, alkyl interrupted by one or more atoms independently selected from the group consisting of oxygen, nitrogen and sulfur, and



; or R_2 and R_3 can be taken together to form a fused ring system optionally interrupted by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur;

R_4 and R_5, when present, are independently selected from the group consisting of hydrido, aminoalkyl, alkyl, alkoxyalkyl, cyanoalkyl, aryl, arylalkyl, or R_4 and R_5 may taken together with the nitrogen to which they are bound to form a heterocyclyl;

X is sulfur or oxygen;

Y is oxygen or alkylene; and

Z is nitrogen or carbon;

with the proviso that when X is sulfur, A comprises 1 oxygen.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/013999

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 C07D417/14 C07D495/04 A61K31/427 A61P31/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/100232 A1 (SUMMERS MICHAEL F [US] ET AL SUMMERS MICHAEL F [US] ET AL) 11 May 2006 (2006-05-11) See claim 1.	1-83

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2009	25/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Menchaca, Roberto

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/013999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006100232 A1	11-05-2006	NONE	