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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
20 March 2008 (20.03.2008)

(10) International Publication Number
WO 2008/033934 A1

(51) **International Patent Classification:**
C07D 417/10 **(2006.01)** ***A61K 31/435*** **(2006.01)**
C07D 417/14 **(2006.01)** ***A61P 35/00*** **(2006.01)**
A61K 31/41 (2006.01)

(21) **International Application Number:**
PCT/US2007/078285

(22) International Filing Date:
12 September 2007 (12.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/825,539 13 September 2006 (13.09.2006) US

(71) **Applicant** *(for all designated States except US):* **THE INSTITUTES FOR PHARMACEUTICAL DISCOV¬ ERY, LLC** [US/US]; 23 Business Park Drive, Branford, CT 06405 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only):* **VAN ZANDT, Michael, C.** [US/US]; 56 Barker Hill Drive, Guildford, CT 06437 (US).

(74) Agent: SARUSSI, Steven, J.; Mcdonnell Boehnen HuIbert & Berghoff LIp, 300 South Wacker Drive, Suite 3200, Chicago, IL 60606 (US).

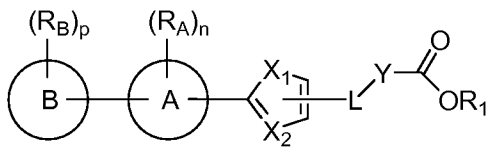
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, **AT, AU, AZ, BA,** BB, **BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR,** CU, **CZ,** DE, **DK, DM, DO, DZ,** EC, EE, **EG,** ES, **FI, GB, GD, GE, GH, GM, GT, HN, HR, HU,** ID, **IL, 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, 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, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, 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*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

WO 2008/033934 A1

(54) Title: SUBSTITUTED HETEROARYL CARBOXYLIC ACID DERIVATIVES AS PTB-IB INHIBITORS



(I)

(57) Abstract: Disclosed are compounds and pharmaceutically acceptable salts of formula (I) : which are useful in the treatment of metabolic disorders related to insulin resistance, leptin resistance, or hyperglycemia. Compounds of the invention include inhibitors of Protein tyrosine phosphatases, in particular Protein tyrosine phosphatase-lB (PTP-IB), that are useful in the treatment of diabetes and other PTP mediated diseases, such as cancer, neurodegenerative diseases and the like. Also disclosed are pharmaceutical compositions comprising compounds of the invention and methods of treating the aforementioned conditions using such compounds.

SUBSTITUTED HETEROARYL CARBOXYLIC ACID DERIVATIVES AS PTB-IB INHIBITORS

BACKGROUND OF THE INVENTION

This application claims the benefit of Provisional Application No. 60/825539, filed September 13, 2006, the dislosure of which in incorporated herein in its entirety.

Field of the Invention

The invention relates to substituted heteroaryl carboxylic acid derivatives and more specifically to such compounds that are useful in the treatment of syndrome X (consisting of such abnormalities as obesity, dyslipidemia, hypercoagulation, hypertension, insulin resistance and leading to heart disease and diabetes), obesity, diabetes, immunological disease, bleeding disorders, and/or cancer. More specifically, it relates to such compounds that are capable of inhibiting Protein tyrosine phosphatases (PTPs), in particular Protein tyrosine phosphatase-lB (PTP-IB) which is a negative regulator of the insulin and leptin signaling pathway and improves insulin-sensitivity.

Description of Related Art

Protein tyrosine phosphatases are a large family of transmembrane or intracellular enzymes that dephosphorylate substrates involved in a variety of regulatory processes (Fischer et al., 1991, Science 253:401-406). Protein tyrosine phosphatase-lB (PTP-IB) is an approximately 50 kd intracellular protein, which is present in abundant amounts in various human tissues (Charbonneau et al., 1989, Proc. Natl. Acad. Sci. USA 86:5252-5256; Goldstein, 1993, Receptor 3:1-15).

Determining which proteins are substrates of PTP-IB has been of considerable interest. One substrate which has aroused

especial interest is the insulin receptor. The binding of insulin to its receptor results in autophosphorylation of the domain. This causes activation of the insulin receptor tyrosine kinase, which phosphorylates the various insulin receptor substrate (IRS) proteins that propagate the insulin signaling event further downstream to mediate insulin's various biological effects.

Seely et al., 1996, Diabetes 45:1379-1385 ("Seely") studied the relationship of PTP-IB and the insulin receptor in vitro. Seely constructed a glutathione S-transferase (GST) fusion protein of PTP-IB that had a point mutation in the PTP-IB catalytic domain. Although catalytically inactive, this fusion protein was able to bind to the insulin receptor, as demonstrated by its ability to precipitate the insulin receptor from purified receptor preparations and from whole cell lysates derived from cells expressing the insulin receptor .

Ahmad et al., 1995, J. Biol. Chem. 270:20503-20508 used osmotic loading to introduce PTP-IB neutralizing antibodies into rat KRC-7 hepatoma cells. The presence of the antibody in the cells resulted in an increase of 42% and 38%, respectively, in insulin stimulated DNA synthesis and phosphatidyinositol 3' kinase activity. Insulin receptor autophosphorylation and insulin receptor substrate-1 tyrosine phosphorylation were increased 2.2 and 2.0-fold, respectively, in the antibody-loaded cells. The antibody-loaded cells also showed a 57% increase in insulin stimulated insulin receptor kinase activity toward exogenous peptide substrates.

Kennedy et al., 1999, Science 283: 1544-1548 showed that protein tyrosine phosphatase PTP-IB is a negative regulator of the insulin signaling pathway, indicating that inhibitors of this enzyme are beneficial in the treatment of Type 2 diabetes, which appears to involve a defect in an early

process in insulin signal transduction rather than a structural defect in the insulin receptor itself. (J. M. Olefsky, W. T. Garvey, R. R. Henry, D. Brillon, S. Matthai and G. R. Freidenberg, G. R. (1988).) Cellular mechanisms of insulin resistance in non-insulin-dependent (Type II) diabetes. (Am. J. Med. 85: Suppl. 5A, 86-105.) A drug that improved insulin sensitivity would have several advantages over traditional therapy of NIDDM using sulfonylureas, which do not alleviate insulin resistance but instead compensate by increasing insulin secretion.

Ragab et al (2003, J. Biol. Chem 278(42), 40923-32) showed that PTP-IB is involved in regulating platelet aggregation. Hence, inhibition of PTP-IB can be predicted to have an effect on bleeding disorder, and cardiovascular disease .

Romsicki et al., (2003, Arch Biochem. Biophys 414(1), 40-50) showed that TC PTP is structurally and functionally very similar. A PTP-IB inhibitor is very likely to also inhibit TC PTP. A knockout of the TC PTP gene produces a phenotype with impaired immune function. (You-Ten et al., 1997, J. Exp. Med. 186(5), 683-93). Hence, inhibitors of PTP IB can be predict to inhibit TC PTP and modulate immune response.

It has also been demonstrated that PTP-IB is a negative regulator of leptin signaling (Kaszua et al. MoI. Cell. Endocrinology, 195:109-118, 2002). PTP-IB deficient mice show enhanced potency for exogenous leptin to suppress food intake (Cheng, et al. Developmental Cell 2:497-503, 2002). Thus, inhibitors of PTP-IB augment the beneficial effects of leptin on food intake, body weight regulation and metabolism, in normal individuals and leptin resistant individuals.

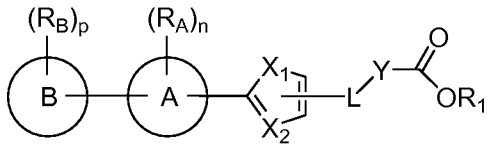
Therefore, inhibitors of PTPs, and inhibitors of PTP-IB in particular, are useful in controlling or treating obesity, syndrome X, Type 2 diabetes, in improving glucose tolerance,

and in improving insulin sensitivity in patients in need thereof. Such compounds are also useful in treating or controlling other PTP mediated diseases, such as the treatment of neurodegenerative diseases, cancer, immunological disorders, bleeding and cardiovascular disorders, and the like.

SUMMARY OF THE INVENTION

In a broad aspect, the invention encompasses the compounds of formula (I) shown below, pharmaceutical compositions containing the compounds and methods employing such compounds or compositions in the treatment of diabetes and/or cancer.

In one aspect, the invention encompasses compounds of formula (I):



(I)

and the pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, or $N(R_{N1})$,

wherein R_{N1} is -H or -$(C_1$-$C_6)$alkyl;

X_2 is CH or N;

R_1 is -H, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkyl-phenyl, or -$(C_3$-$C_6)$alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(C_1$-$C_6)$alkoxy, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-$C_6)$alkoxy, -C(O)$(C_1$-$C_6)$alkyl, -C(O)OH, -CN, -$(C_1$-$C_6)$haloalkoxy, -$(C_1$-$C_6)$haloalkyl, -halogen, -OH, -$(C_1$-$C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(C_1$-$C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C(O)N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-$C_6)$alkoxy, -C(O)$(C_1$-$C_6)$alkyl, or -C(O)H;

L is -0-, -S-, $-S(O)_2-$, $-N(R_{N4})-$, $-N(R_{114})C(O)-$, $-C(O)N(R_{114})-$,

-S(O)$_2$N(RN$_4$)-, -N(RN$_4$)S(O)$_2$-, -(C$_1$-C$_6$)alkyl-0-,
-O-(Ci-C$_6$)alkyl-, -(Ci-C$_6$)alkyl-0-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S-, -S-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S-(Ci-C$_6$)alkyl-, -(Ci-C$_6$)alkyl-S(O)$_2$-,
-S(O)$_2$-(Ci-C$_6$)alkyl-, -(Ci-C$_6$)alkyl-S(O)$_2$-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{114}$)-, -N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-, -N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-C(O)N(Ru$_4$)-, -C(0)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-C(0)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-, -S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-, -N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,
-N(RN$_4$)S(0)$_2$N(RN$_5$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-(Ci-C$_6$)alkyl-,
-N(RN$_4$)C(0)N(RN$_5$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)N(R$_{N5}$)-,
-(Ci-C$_6$)alkyl-N(RN$_4$)C(O)N(RN$_5$)-(C$_I$-C$_6$)alkyl-,
-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-,
-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,
-OC(O)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-OC(O)N(RN$_4$)-, or
-(Ci-C$_6$)alkyl-OC(O)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(O)(Ci-C$_6$)alkyl, -C(O)OH, -(Ci-C$_6$)alkyl-C(0)OH,

-(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -N(RN6RN7), -(Ci-C6)alkyl-N(RN6RN7), or -C(O)N(RN6RN7),

wherein RN4 and RN5 are independently -H or -(C1-C6)alkyl,

wherein RN6 and RN7 are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(0)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, or -C(O)H;

A is -aryl- or -heteroaryl-;

each RA is independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(0)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -OH, -NO2, -N(RN8RN9), -(Ci-C6)alkyl-N(RN8RN9), or -C(0)N(RN8RN9),

wherein RN8 and RN9 are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(0)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, or -C(O)H;

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

B is aryl- or heteroaryl-;

each RB is independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(0)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -OH, -NO2, -N(RNiiRNii), -(Ci-C6)alkyl-N(RNIIORNII), or -C(0)N(RNIIORNII),

wherein RNii and RNii are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(0)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, or -C(O)H;

and

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

The invention also includes synthetic intermediates that are useful in making the compounds of the invention.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods .

The invention also provides pharmaceutical compositions comprising a compound or salt of formula (I) and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent .

The compounds of formula (I) bind to PTPs, and in particular to PTP-IB. The interaction with the enzyme, specifically PTP-IB, preferably results in inhibition of the enzyme .

In another aspect, the invention provides a method for inhibiting protein tyrosine phosphatases, preferably PTP-IB, comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutical composition comprising a compound or salt of formula (I) .

The invention further provides methods of treating diseases such as Type I and Type II diabetes, syndrome X, obesity, cancer, neurodegenerative disease, immunological disease, bleeding disorders, and cardiovascular disease in a patient in need of such treatment, comprising administering to the patient a compound or pharmaceutically acceptable salt of formula (I), or a pharmaceutical composition comprising a compound or salt of formula (I) .

In another aspect, the invention provides a method for treating metabolic disorders related to insulin resistance or hyperglycemia, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutical composition comprising a compound or salt of formula (I) .

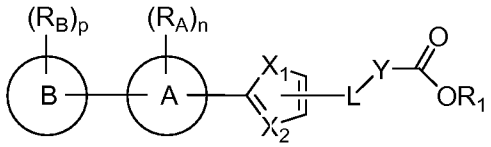
The invention provides formulations and pharmaceutical compositions, as well as methods for combination therapy for treating Type I diabetes, Type II diabetes, and Syndrome X

with the compounds of formula (I) plus therapeutically-effective amounts additional compounds and medicaments. Treatment methods of the invention for Type I diabetes, Type II diabetes, and Syndrome X comprise administration of the inventive compounds of formula (I) as disclosed herein concomitantly, simultaneously or together with a therapeutically-ef fective amount of said additional compounds and medicaments.

The invention also provides the use of a compound or salt according to formula (I) for the manufacture of a medicament for use in treating diabetes or cancer or other diseases related to PTPs.

DETAILED DESCRIPTION OF THE INVENTION

In another embodiment, the invention comprises compounds of formula (I),



(D

or a pharmaceutically acceptable salt thereof, wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl,

and B, L, R_A, R_B, Ri, Xi, X2, Y, n, and p are as defined in formula (I).

In another embodiment, the present invention comprises compounds of formula (I), wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

and L, R_A, R_B, Ri, Xi, X2, Y, n, and p are as defined in formula (D.

In another embodiment, the present invention comprises compounds of formula (I), wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzof uranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci\text{-}C_6)$alkoxy, -$(Ci\text{-}C_6)$alkyl, -$(C_2\text{-}C_6)$alkenyl, -$(C_2\text{-}C_6)$alkynyl, -C(O) $(Ci\text{-}C_6)$alkoxy, -C(O) $(Ci\text{-}C_6)$alkyl, -C(O)OH, -CN, -$(Ci\text{-}C_6)$haloalkoxy, -$(Ci\text{-}C_6)$haloalkyl, -halogen, -OH, -$(Ci\text{-}C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(Ci\text{-}C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C(0)N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci\text{-}C_6)$alkyl, -$(C_2\text{-}C_6)$alkenyl, -$(C_2\text{-}C_6)$alkynyl, -C(O) $(Ci\text{-}C_6)$alkoxy, -$C(0)$ $(Ci\text{-}C_6)$alkyl, or -C(O)H;

and L, R_A, R_B, Ri, Xi, X_2, n, and p are as defined in formula (D .

In another embodiment, the invention comprises compounds of formula (I), wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl,

pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzof uranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci-C_6)$alkoxy, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, -C(O)OH, -CN, -$(Ci-C_6)$haloalkoxy, -$(Ci-C_6)$haloalkyl, -halogen, -OH, -$(Ci-C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(Ci-C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C_{(0)}N_{(R_{N2}R_{N3})}$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, or -C(O)H;

L is -0-, -S-, $-N(R_{N4})-$, $-N(RN_4)C(O)-$, $-C_{(0)}N_{(R_{N4})}-$, -$(Ci-C_6)$alkyl-O-, -0-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-O-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-, -S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl $-N(RN_4)-$, $-N_{(R_{N4})}-(CI-C_6)$alkyl-, or

-(Ci-C$_6$)alkyl-N(R_{N4})-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C$_6$)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, or -C(O)H;

and R_A, R_B, Ri, Xi, X_2, n, and p are as defined in formula (I).

In another embodiment, the invention comprises compounds of formula (I), wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzof uranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl,

wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(C_1-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(R_{N4})C(0)-, -C(0)N(R_{N4})-, -(Ci-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})-, -N(R_{N4})-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

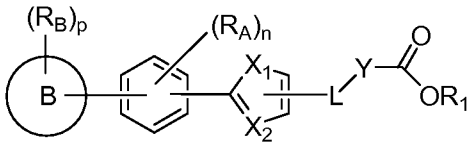
wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, or -C(O)H;

R_i is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, X_1, X_2, n, and p are as defined in formula (I).

In another embodiment, the invention comprises compounds of formula (II),



(ii:)

or a pharmaceutically acceptable salt thereof, wherein

X_i is O, S, or N(R_{N1}),

wherein R_{N1} is -H or -(Ci-C_6)alkyl;

X_2 is CH or N;

R_i is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(O)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(R_{N4})-, -N(R_{N4})C(0)-, -C(0)N(R_{N4})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(CI-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-,

-(Ci-C6)alkyl-S- (Ci-C6)alkyl-, -(Ci-C6)alkyl-S(O)2-, -S(O)2-(Ci-C6)alkyl-, -(Ci-C6)alkyl-S(O)2-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)-, -N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)C(0)-, -N(RN4)C(0)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)C(0)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-C(O)N(RN4)-, -C(0)N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-C(O)N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-S(0)2N(RN4)-, -S(0)2N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-S(0)2N(RN4)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)S(0)2-, -N(RN4)S(0)2-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)S(0)2-(Ci-C6)alkyl-, -N(RN4)S(0)2N(RN5)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)S(0)2N(RN5)-, -(Ci-C6)alkyl-N(RN4)S(0)2N(RN5)-(Ci-C6)alkyl-, -N(RN4)C(0)N(RN5)-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)C(0)N(RN5)-, -(Ci-C6)alkyl-N(RN4)C(O)N(RN5)-(CI-C6)alkyl-, -N(RN4)C(0)0-(Ci-C6)alkyl-, -(Ci-C6)alkyl-N(RN4)C(0)0-, -(Ci-C6)alkyl-N(RN4)C(0)0-(Ci-C6)alkyl-, -OC(O)N(RN4)-(CI-C6)alkyl-, -(Ci-C6)alkyl-OC(O)N(RN4)-, or -(Ci-C6)alkyl-OC(O)N(RN4)-(CI-C6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, -C(O)OH, -(Ci-C6)alkyl-C(0)OH, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -N(RN6RN7), -(Ci-C6)alkyl-N(RN6RN7), or -C(O)N(RN6RN7),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_N7 are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C(0)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

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

B is aryl- or heteroaryl-;

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_Ni_0R_N^{ii}$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(0)N(RNIORNII),

wherein R_Ni_0 and R_Nn are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (II), wherein

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl,

benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

and L, R_A, R_B, Ri, Xi, X2, Y, n, and p are as defined in formula (H).

In another embodiment, the invention comprises compounds of formula (II), wherein

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and L, R_A, RB, RI, Xi, X2, n, and p are as defined in formula (H).

In another embodiment, the invention comprises compounds of formula (II), wherein

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci-C_6)$alkoxy, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, -C(O)OH, -CN, -$(Ci-C_6)$haloalkoxy, -$(Ci-C_6)$haloalkyl, -halogen, -OH, -$(Ci-C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(Ci-C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C_{(0)}N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, $-C_{(0)}$ $(Ci-C_6)$alkyl, or -C(O)H;

L is -0-, -S-, $-N(R_{N4})$-, $-N(RN_4)C(O)$-, $-C_{(0)}N(R_{N4})$-, -$(Ci-C_6)$alkyl-O-, -0- $(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-O- $(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-, -S- $(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S- $(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl $-N(R_{N4})$-, $-N(R_{N4})$- $(CI-C_6)$alkyl-, or -$(Ci-C_6)$alkyl $-N(R_{N4})$- $(Ci-C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

and R_A, R_B, Ri, Xi, X_2, n, and p are as defined in formula (II).

In another embodiment, the invention comprises compounds of formula (II), wherein

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl;

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN,

-(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(O)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(RN_4)-, -N(R_{N4})C(0)-, -C(O)N(R_{114})-, -(Ci-C_6)alkyl-0-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{114})-, -N(R_{114})-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

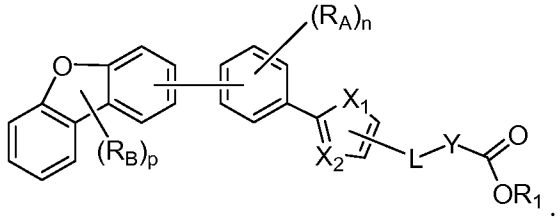
wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, RB, XI, X2, n, and p are as defined in formula (II).

In another embodiment, the invention comprises compounds of formula (III),



(iii)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, or N(R_{N1}),

wherein R_{N1} is -H or -(Ci-C_6)alkyl;

X_2 is CH or N;

R_1 is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(RN_4)-, -N(R_{114})C(0)-, -C(O)N(R_{114})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(C_I-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-, -S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{114})-, -N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})-(Ci-C_6)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(0)-, -N(R_{N4})C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(RN_4)-, -C(0)N(R_{N4})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(R_{N4})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R_{N4})-, -S(0)$_2$N(R_{N4})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R_{N4})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})S(0)$_2$-, -N(R_{N4})S(0)$_2$-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})S(0)$_2$-(Ci-C$_6$)alkyl-,

-N(R_{N4})S(0)$_2$N(R_{N5})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})S(0)$_2$N(R_{N5})-,

-(Ci-C$_6$)alkyl-N(R_{N4})S(0)$_2$N(R_{N5})-(Ci-C$_6$)alkyl-,

-N(R_{N4})C(0)N(R_{N5})-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(0)N(R_{N5})-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(O)N(R_{N5})-(C_I-C$_6$)alkyl-,

-N(R_{N4})C(0)0-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(0)0-,

-(Ci-C$_6$)alkyl-N(R_{N4})C(0)0-(Ci-C$_6$)alkyl-,

-OC(O)N(R_{N4})-(C_I-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-OC(O)N(RN_4)-, or

-(Ci-C$_6$)alkyl-OC(O)N(RN_4)-(C_I-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C_2-C$_6$)alkenyl, -(C_2-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -C(O)OH, -(Ci-C$_6$)alkyl-C(0)OH, -(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen, -N(RN_6RN_7), -(Ci-C$_6$)alkyl-N(RN_6RN_7), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_Ns are independently -H or -(Ci-C$_6$)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C$_6$)alkyl, -(C_2-C$_6$)alkenyl, -(C_2-C$_6$)alkynyl,

-C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -OH, -NO2, -N($R_{N8}R_{N9}$), -(Ci-C6)alkyl-N($R_{N8}R_{N9}$), or -C(O)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -OH, -NO2, -N($R_{NI0}R_{NII}$), -(Ci-C6)alkyl-N($R_{NI0}R_{NII}$), or -C(0)N($R_{N}i_{0}R_{N}$ii),

wherein $R_{N}i_{0}$ and R_{N}n are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (III), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen,

-OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N(R$_{N2}$R$_{N3}$),

-(C$_1$-C$_6$)alkyl-N (R$_{N2}$R$_{N3}$), or -C(0) N(R$_{N2}$R$_{N3}$),

wherein R$_{N2}$ and R$_N$3 are each independently

-H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,

-C(O) (Ci-C$_6$)alkyl, or -C(O)H;

and L, R$_A$, R$_B$, Ri, Xi, X$_2$, n, and p are as defined in formula (III).

In another embodiment, the invention comprises compounds of formula (III), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,

-C(0) (Ci-C$_6$)alkyl, -C(O)OH, -CN,

-(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen,

-OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N(R$_{N2}$R$_{N3}$),

-(Ci-C$_6$)alkyl-N(R$_{N2}$R$_{N3}$), or -C(0) N(R$_{N2}$R$_{N3}$),

wherein R$_{N2}$ and R$_{N3}$ are each independently

-H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,

-C(O) (Ci-C$_6$)alkyl, or -C(O)H;

L is -0-, -S-, -N(R$_{N4}$)-, -N(RN$_4$)C(O)-, -C(0) N(R$_{N4}$)-,

-(Ci-C$_6$)alkyl-O-, -0-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-O-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S-, -S-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl -N(R$_{N4}$)-, -N(R$_{N4}$)-(CI-C$_6$)alkyl-, or

-(Ci-C$_6$)alkyl-N(R_{N4})-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(O)(Ci-C$_6$)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C$_6$)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(O)(Ci-C$_6$)alkyl, or -C(O)H;

and R_A, R_B, Ri, Xi, X_2, n, and p are as defined in formula (III).

In another embodiment, the invention comprises compounds of formula (III), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(O)(Ci-C$_6$)alkyl, -C(O)OH, -CN, -(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen, -OH, -(Ci-C$_6$)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C$_6$)alkyl-N($R_{N2}R_{N3}$), or -C(O)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(O) $(Ci$-$C_6)$alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(R_{N4})C(O)-, -C(0)N(R_{N4})-,

-$(Ci$-$C_6)$alkyl-0-, -0-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-0-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-S-, -S-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-S-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-N(R_{N4})-, -N(R_{N4})-$(CI$-$C_6)$alkyl-, or

-$(Ci$-$C_6)$alkyl-N(R_{N4})-$(Ci$-$C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci$-$C_6)$alkoxy, -$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(O) $(Ci$-$C_6)$alkyl, -C(O)OH, -halogen,

-N(RN_6RN_7), or -C(0)N(RN_6RN_7),

wherein R_{N4} and R_Ns are independently -H or -$(Ci$-$C_6)$alkyl,

wherein R_{N6} and R_{N7} are each independently -H,

-$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl,

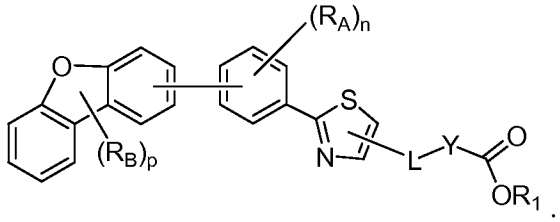
-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(0) $(Ci$-$C_6)$alkyl, or -C(O)H;

Ri is -H, -$(Ci$-$C_6)$alkyl, benzyl, or allyl;

and R_A, RB, XI, X2, n, and p are as defined in formula (III).

In another embodiment, the invention comprises compounds of formula (IV),



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R_i is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) (Ci-C_6)alkoxy, -C(0) (Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) (Ci-C_6)alkoxy, -C(0) (Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(RN_4)-, -N(R_{114})C(0)-, -C(O)N(R_{114})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(C_I-C_6)alkyl-O-, -0- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S (O)$_2$-, -S(O)$_2$- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S (O)$_2$- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{114})-, -N(R_{114})- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})C(0)-, -N(R_{114})C(0) - (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})C(0) - (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-C (O)N(R_{114})-, -C(O)N(R_{N4})- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-C (O)N(RN_4)- (C_I-C_6)alkyl-, -(Ci-C_6)alkyl-S (0)$_2$N(R_{114})-, -S(0)$_2$N(R_{114})- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S (0)$_2$N(R_{N4})- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{114})S(0)$_2$-, -N(R_{114})S(0)$_2$- (Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})S(0)$_2$- (Ci-C_6)alkyl-, -N(RN_4)S(0)$_2$N(RN_5)- (Ci-C_6)alkyl-,

-(Ci-C_6)alkyl-N (R_{N4})S(0)$_2$N(R_{N5})-,

-(C_1-C_6)alkyl-N (R_{N4})S(0)$_2$N(R_{N5})-(C_1-C_6)alkyl-,

-N(R_{N4})C(0)N(R_{N5})-(C_1-C_6)alkyl-,

-(C_1-C_6)alkyl-N (R_{N4})C(0)N(R_{N5})-,

-(C_1-C_6)alkyl-N (R_{N4})C(O)N(R_{N5})-(C_1-C_6)alkyl-,

-N(R_{N4})C(0)0-(C_1-C_6)alkyl-,

-(C_1-C_6)alkyl-N (R_{N4})C(0)0-,

-(C_1-C_6)alkyl-N (R_{N4})C(0)0-(C_1-C_6)alkyl-,

-OC(O)N(R_{N4})-(C_1-C_6)alkyl-,

-(C_1-C_6)alkyl-OC(O)N(R_{N4})-, or

-(C_1-C_6)alkyl-OC(0)N(R_{N4})-(C_1-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(C_1-C_6JaIkOXy, -C(O)(C_1-C_6)alkyl, -C(O)OH, -(C_1-C_6)alkyl-C(0)OH, -(C_1-C_6)haloalkoxy, -(C_1-C_6)haloalkyl, -halogen, -N(RN_6RN_7), -(C_1-C_6)alkyl-N(RN_6RN_7), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_Ns are independently -H or -(C_1-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(C_1-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, or -C(O)H;

each R_A is independently -(C_1-C_6)alkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(C_1-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, -C(O)OH, -CN, -(C_1-C_6)haloalkoxy, -(C_1-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_N9$), -(C_1-C_6)alkyl-N($R_{N8}R_N9$), or -C(0)N($R_{N8}R_N9$),

wherein R_{N8} and R_N9 are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(C_1-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N}i_0R_{N}ii$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(O)N($R_{N}i_0R_{N}ii$),

wherein $R_{N}i_0$ and $R_{N}n$ are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (IV), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and L, R_A, RB, RI, n, and p are as defined in formula (IV).

In another embodiment, the invention comprises compounds of formula (IV), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(C_1-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(RN_4)C(O)-, -C(0)N(R_{N4})-, -(Ci-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})-, -N(R_{N4})-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N(RN_6RN_7), or -C(0)N(RN_6RN_7),

wherein R_{N4} and R_Ns are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

and R_A, RB, RI, n, and p are as defined in formula (IV).

In another embodiment, the invention comprises compounds of formula (IV), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(RN_4)-, -N(R_{N4})C(0)-, -C(O)N(R_{114})-, -(Ci-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(RN_4)-, -N(R_{N4})-(CI-C_6)alkyl-, or -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4

substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,

-C(O)(Ci-C_6)alkyl, -C(O)OH, -halogen,

-N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or

-(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H,

-(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

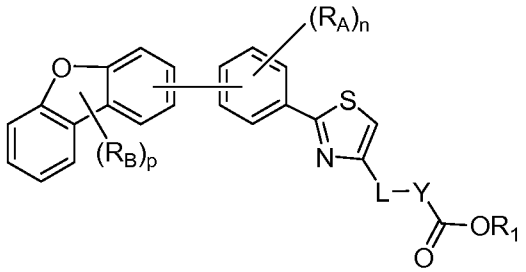
-(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,

-C(O)(Ci-C_6)alkyl, or -C(O)H;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (IV).

In another embodiment, the invention comprises compounds of formula (V),



(V)

or a pharmaceutically acceptable salt thereof, wherein

Ri is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or

-(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,

-C(O)(Ci-C_6)alkyl, -C(O)OH, -CN,

-(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen,

-OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$),

$-(C_1-C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C(0)N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-C(O)(C_1-C_6)$alkoxy, $-C(0)(C_1-C_6)$alkyl, or $-C(O)H$;

L is -0-, -S-, $-S(O)_2-$, $-N(RN_4)-$, $-N(R_{114})C(0)-$, $-C(0)N(R_{N4})-$, $-S(O)_2N(R_{N4})-$, $-N(R_{N4})S(O)_2-$, $-(CI-C_6)$alkyl-0-, -0-(C_1-C_6)alkyl-, $-(C_1-C_6)$alkyl-0-(C_1-C_6)alkyl-, $-(C_1-C_6)$alkyl-S-, -S-(C_1-C_6)alkyl-, $-(C_1-C_6)$alkyl-S-(C_1-C_6)alkyl-, $-(C_1-C_6)$alkyl-S$(O)_2-$, $-S(O)_2-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-S$(O)_2-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{114})-$, $-N(R_{114})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{114})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{N4})C(0)-$, $-N(R_{114})C(0)-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{114})C(0)-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-C$(O)N(R_{N4})-$, $-C(0)N(R_{N4})-(CI-C_6)$alkyl-, $-(C_1-C_6)$alkyl-C$(O)N(R_{N4})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-S$(0)_2N(R_{N4})-$, $-S(0)_2N(R_{N4})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-S$(0)_2N(R_{N4})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{N4})S(0)_2-$, $-N(R_{N4})S(0)_2-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{N4})S(0)_2-(C_1-C_6)$alkyl-, $-N(R_{N4})S(0)_2N(R_{N5})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{N4})S(0)_2N(R_{N5})-$, $-(C_1-C_6)$alkyl$-N(R_{N4})S(0)_2N(R_{N5})-(C_1-C_6)$alkyl-, $-N(R_{N4})C(0)N(R_{N5})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl$-N(R_{N4})C(0)N(R_{N5})-$, $-(C_1-C_6)$alkyl-N$(R_{N4})C(O)N(R_{N5})-(CI-C_6)$alkyl-, $-N(R_{N4})C(0)O-(CI-C_6)$alkyl-, $-(C_1-C_6)$alkyl-N$(R_{N4})C(O)0-$, $-(C_1-C_6)$alkyl-N$(R_{N4})C(O)O-(C_1-C_6)$alkyl-, $-OC(O)N(R_{N4})-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-OC$(O)N(RN_4)-$, or $-(C_1-C_6)$alkyl-OC$(O)N(R_{N4})-(C_1-C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -(Ci-C_6)alkyl-C(0)OH, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -N($R_{N6}R_{N7}$), -(Ci-C_6)alkyl-N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C(0)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{Ni_0}R_{Nii}$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(0)N(RNIORNII),

wherein R_{Ni_0} and R_{N}n are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (V), wherein,

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(C_1$-$C_6)$alkoxy, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-$C_6)$alkoxy, -C(0)$(C_1$-$C_6)$alkyl, -C(O)OH, -CN, -$(C_1$-$C_6)$haloalkoxy, -$(C_1$-$C_6)$haloalkyl, -halogen, -OH, -$(C_1$-$C_6)$alkyl-OH, -NO_2, -$N(R_{N2}R_{N3})$, -$(C_1$-$C_6)$alkyl-$N(R_{N2}R_{N3})$, or -C(0)$N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-C_6JaIkOXy, -C(O)$(C_1$-$C_6)$alkyl, or -C(O)H;

and L, R_A, R_B, R_1, n, and p are as defined in formula (V).

In another embodiment, the invention comprises compounds of formula (V), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-$C_6)$alkoxy, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-C_6JaIkOXy, -C(0)$(C_1$-$C_6)$alkyl, -C(O)OH, -CN, -$(C_1$-$C_6)$haloalkoxy, -$(C_1$-$C_6)$haloalkyl, -halogen,

-OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N(R$_{N2}$R$_{N3}$),

-(C$_1$-C$_6$)alkyl-N(R$_{N2}$R$_{N3}$), or -C(0)N(R$_{N2}$R$_{N3}$),

wherein R$_{N2}$ and R$_{N3}$ are each independently

-H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,

-C(O)(Ci-C$_6$)alkyl, or -C(O)H;

L is -0-, -S-, -N(R$_{N4}$)-, -N(RN$_4$)C(O)-, -C(0)N(R$_{N4}$)-,

-(Ci-C$_6$)alkyl-0-, -0-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-O-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S-, -S-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(Ru$_4$)-, -N(R$_{N4}$)-(C$_I$-C$_6$)alkyl-, or

-(Ci-C$_6$)alkyl-N(R$_{114}$)-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,

-C(O)(Ci-C$_6$)alkyl, -C(O)OH, -halogen,

-N(RN$_6$RN$_7$), or -C(0)N(RN$_6$RN$_7$),

wherein R$_{N4}$ and R$_N$s are independently -H or -(Ci-C$_6$)alkyl,

wherein R$_{N6}$ and R$_{N7}$ are each independently -H,

-(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,

-C(0)(Ci-C$_6$)alkyl, or -C(O)H;

and R$_A$, RB, RI, n, and p are as defined in formula (V).

In another embodiment, the invention comprises compounds of formula (V), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl,

wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(C_1-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(R_{N4})C(0)-, -C(0)N(R_{N4})-, -(Ci-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})-, -N(R_{N4})-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

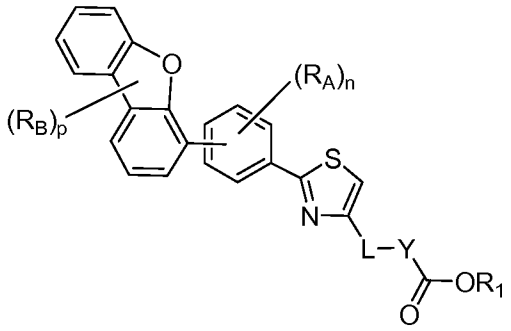
wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, or -C(O)H;

R_i is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (V).

In another embodiment, the invention comprises compounds of formula (VI),



(VI)

or a pharmaceutically acceptable salt thereof, wherein

R_i is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(O)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(R_{N4})-, -N(R_{N4})C(0)-, -C(0)N(R_{N4})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(CI-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-, -S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-(Ci-C_6)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)-, -N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-, -N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(R$_{N4}$)-, -C(0)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-, -S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-, -N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,

-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-N(R$_{N4}$)C(0)N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)N(R$_{N5}$)-,

-(Ci-C$_6$)alkyl-N(RN$_4$)C(O)N(RN$_5$)-(C$_I$-C$_6$)alkyl-,

-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,

-OC(O)N(R$_{N4}$)-(C$_I$-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-OC(O)N(RN$_4$)-, or

-(Ci-C$_6$)alkyl-OC(O)N(RN$_4$)-(C$_I$-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -C(O)OH, -(Ci-C$_6$)alkyl-C(0)OH, -(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen, -N(RN$_6$RN$_7$), -(Ci-C$_6$)alkyl-N(RN$_6$RN$_7$), or -C(O)N(R$_{N6}$R$_{N7}$),

wherein R$_{N4}$ and R$_{N5}$ are independently -H or -(Ci-C$_6$)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C(0)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N}i_0R_{N}ii$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(0)N(RNIORNII),

wherein $R_{N}i_0$ and $R_{N}n$ are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (VI), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,

-C(O)(Ci-C$_6$)alkyl, -C(O)OH, -CN,
-(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen,
-OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N($R_{N2}R_{N3}$),
-(Ci-C$_6$)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),
wherein R_{N2} and R_{N3} are each independently
-H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,
-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,
-C(0)(Ci-C$_6$)alkyl, or -C(O)H;

and L, R_A, R_B, Ri, n, and p are as defined in formula (VI).

In another embodiment, the invention comprises compounds of formula (VI), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently
-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,
-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,
-C(O)(Ci-C$_6$)alkyl, -C(O)OH, -CN,
-(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen,
-OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N($R_{N2}R_{N3}$),
-(Ci-C$_6$)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),
wherein R_{N2} and R_{N3} are each independently
-H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,
-(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,
-C(0)(Ci-C$_6$)alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(RN$_4$)C(O)-, -C(0)N(R_{N4})-,
-(Ci-C$_6$)alkyl-O-, -0-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-O-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S-, -S-(Ci-C$_6$)alkyl-,
-(Ci-C$_6$)alkyl-S-(Ci-C$_6$)alkyl-,

-(Ci-C6)alkyl-N(RN4)-, -N(RN4)-(CI-C6)alkyl-, or -(Ci-C6)alkyl-N(RN4)-(Ci-C6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, -C(O)OH, -halogen, -N(RN6RN7), or -C(O)N(RN6RN7),

wherein RN4 and RN5 are independently -H or -(Ci-C6)alkyl,

wherein RN6 and RN7 are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, or -C(O)H;

and RA, RB, RI, n, and p are as defined in formula (VI).

In another embodiment, the invention comprises compounds of formula (VI), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(0)(Ci-C6)alkyl, -C(O)OH, -CN, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -OH, -(Ci-C6)alkyl-OH, -NO2, -N(RN2RN3), -(Ci-C6)alkyl-N(RN2RN3), or -C(0)N(RN2RN3),

wherein RN2 and RN3 are each independently -H, -(Ci-C6)alkyl, -(C2-C6)alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(O) $(Ci$-$C_6)$alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(R_{N4})C(O)-, -C(0)N(R_{N4})-,

-$(Ci$-$C_6)$alkyl-0-, -0-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-0-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-S-, -S-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-S-$(Ci$-$C_6)$alkyl-,

-$(Ci$-$C_6)$alkyl-N(R_{N4})-, -N(R_{N4})-$(CI$-$C_6)$alkyl-, or

-$(Ci$-$C_6)$alkyl-N(R_{N4})-$(Ci$-$C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci$-$C_6)$alkoxy, -$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(O) $(Ci$-$C_6)$alkyl, -C(O)OH, -halogen,

-N(RN_6RN_7), or -C(0)N(RN_6RN_7),

wherein R_{N4} and R_Ns are independently -H or -$(Ci$-$C_6)$alkyl,

wherein R_{N6} and R_{N7} are each independently -H,

-$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,

-C(0) $(Ci$-$C_6)$alkyl, or -C(O)H;

Ri is -H, -$(Ci$-$C_6)$alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VI).

In another embodiment, the invention comprises compounds of formula (VI), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_N3$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_N3 are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

L is -(Ci-C_6)alkyl-O-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$),

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, or -C(O)(Ci-C_6)alkyl;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VI).

In another embodiment, the invention comprises compounds of formula (VI), wherein

Y is a bond, phenyl, or pyridyl;

L is -(Ci-C_6)alkyl-O-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy,

-C(O) (Ci-C$_6$)alkyl , -C(O) OH, -halogen,

-N($R_{N6}R_{N7}$),

wherein R_{N6} and R_{N7} are each independently -H,

-(Ci-C$_6$)alkyl, -(C_2-C$_6$)alkenyl,

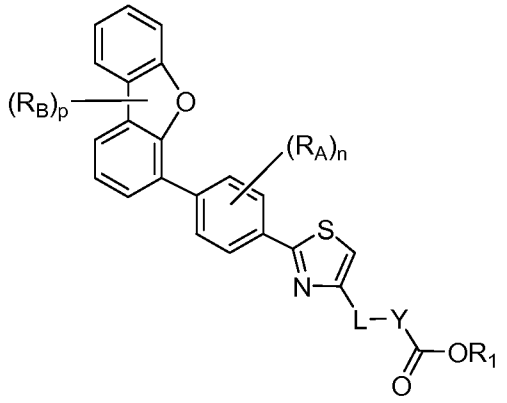
-(C_2-C$_6$)alkynyl,

-C(O) (Ci-C$_6$)alkoxy, or -C(0) (Ci-C$_6$)alkyl;

Ri is -H, -(Ci-C$_6$)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VI).

In another embodiment, the invention comprises compounds of formula (VII),



(VII)

or a pharmaceutically acceptable salt thereof, wherein

Ri is -H, -(Ci-C$_6$)alkyl, -(Ci-C$_6$)alkyl-phenyl, or

-(C_3-C$_6$)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C_2-C$_6$)alkenyl,

-(C_2-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,

-C(0) (Ci-C$_6$)alkyl, -C(O)OH, -CN,

-(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen,

-OH, -(Ci-C$_6$)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$),

-(Ci-C$_6$)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently

-H, -(Ci-C$_6$)alkyl, -(C_2-C$_6$)alkenyl,

-(C_2-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,

-C(O) (Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(RN$_4$)-, -N(R_{114})C(0)-, -C(O)N(R_{114})-, -S(O)$_2$N(RN$_4$)-, -N(RN$_4$)S(O)$_2$-, -(C_1-C_6)alkyl-0-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-, -S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{114})-, -N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})C(0)-, -N(R_{114})C(0)-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{114})C(0)-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-C(O)N(R_{114})-, -C(0)N(R_{N4})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-C(0)N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(0)$_2$N(R_{114})-, -S(0)$_2$N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(0)$_2$N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})S(0)$_2$-, -N(R_{N4})S(0)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})S(0)$_2$-(Ci-C_6)alkyl-, -N(RN$_4$)S(0)$_2$N(RN$_5$)-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{114})S(0)$_2$N(R_{115})-, -(Ci-C_6)alkyl-N(R_{N4})S(0)$_2$N(R_{N5})-(Ci-C_6)alkyl-, -N(RN$_4$)C(0)N(RN$_5$)-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{N4})C(0)N(R_{N5})-, -(Ci-C_6)alkyl-N(RN$_4$)C(O)N(RN$_5$)-(C_I-C_6)alkyl-, -N(R_{N4})C(0)0-(C_I-C_6)alkyl-, -(Ci-C_6)alkyl-N(R_{114})C(0)0-, -(Ci-C_6)alkyl-N(R_{N4})C(0)0-(Ci-C_6)alkyl-, -OC(O)N(R_{N4})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-OC(O)N(RN$_4$)-, or -(Ci-C_6)alkyl-OC(O)N(R_{114})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl, -C(O) (Ci-C_6)alkoxy, -C(O) (Ci-C_6)alkyl, -C(O)OH, -(Ci-C_6)alkyl-C (0) OH, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -N($R_{N6}R_{N7}$), -(Ci-C_6)alkyl-N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) (Ci-C_6)alkoxy, -C (0) (Ci-C_6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C (0) (Ci-C_6)alkoxy, -C(O) (Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C (0) N ($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C (0) (Ci-C_6)alkoxy, -C (0) (Ci-C_6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C (0) (Ci-C_6)alkoxy, -C (0) (Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N (R_Ni$_0$$R_N$^{ii}) , -(Ci-$C_6$)alkyl -N (RNIORNII), or -C (0) N (RNIORNII) ,

wherein R_Ni$_0$ and R_Nn are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C (0) (Ci-C_6)alkoxy, -C (0) (Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl,

pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and L, R_A, R_B, Ri, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently

-H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,
-(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,
-C(0)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(RN_4)-, -N(R_{N4})C(0)-, -C(O)N(R_{114})-,
-(Ci-C_6)alkyl-0-, -0-(Ci-C_6)alkyl-,
-(Ci-C_6)alkyl-0-(Ci-C_6)alkyl-,
-(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-,
-(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-,
-(Ci-C_6)alkyl-N(RN_4)-, -N(R_{N4})-(CI-C_6)alkyl-, or
-(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,
wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently
-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,
-(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy,
-C(0)(Ci-C_6)alkyl, -C(O)OH, -halogen,
-N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),
wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,
wherein R_{N6} and R_{N7} are each independently -H,
-(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,
-(C_2-C_6)alkynyl,
-C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and R_A, RB, RI, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci-C_6)$alkoxy, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, -C(O)OH, -CN, -$(Ci-C_6)$haloalkoxy, -$(Ci-C_6)$haloalkyl, -halogen, -OH, -$(Ci-C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(Ci-C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C(0)N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) (C_1-C_6)alkyl, or -C(O)H;

L is -0-, -S-, $-N(R_{N4})-$, $-N(R_{N4})C(0)-$, $-C(0)N(R_{N4})-$, -$(Ci-C_6)$alkyl-O-, -0-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-O-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-, -S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl $-N(RN_4)-$, $-N(R_{N4})-(CI-C_6)$alkyl-, or -$(Ci-C_6)$alkyl $-N(R_{N4})-(Ci-C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -$(Ci-C_6)$alkoxy, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, $-C(0)(Ci-C_6)$alkyl, -C(O)OH, -halogen, $-N(R_{N6}R_{N7})$, or $-C(O)N(R_{N6}R_{N7})$,

wherein R_{N4} and R_{N5} are independently -H or -$(Ci-C_6)$alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, $-C(0)(Ci-C_6)$alkoxy, $-C(0)(Ci-C_6)$alkyl, or -C(O)H;

Ri is -H, -$(Ci-C_6)$alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(C_1$-$C_6)$alkoxy, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-$C_6)$alkoxy, -C(0)$(C_1$-$C_6)$alkyl, -C(O)OH, -CN, -$(C_1$-$C_6)$haloalkoxy, -$(C_1$-$C_6)$haloalkyl, -halogen, -OH, -$(C_1$-$C_6)$alkyl-OH, -NO_2, -$N(R_{N2}R_{N3})$, -$(C_1$-$C_6)$alkyl-$N(R_{N2}R_{N3})$, or -C(0)$N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-C_6JaIkOXy, -C(O)$(C_1$-$C_6)$alkyl, or -C(O)H;

L is -$(C_1$-$C_6)$alkyl-O-, -$(C_1$-$C_6)$alkyl-O-$(C_1$-$C_6)$alkyl-, -$(C_1$-$C_6)$alkyl-S-, -$(C_1$-$C_6)$alkyl-S-$(C_1$-$C_6)$alkyl-, wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(C_1$-$C_6)$alkyl, -(Ci-$C_6)$alkoxy, -C(0)$(C_1$-$C_6)$alkoxy, -C(0)$(C_1$-$C_6)$alkyl, -C(O)OH, -halogen, $-N(R_{N6}R_{N7})t$

wherein R_{N6} and R_{N7} are each independently -H, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O)$(C_1$-$C_6)$alkoxy, or -C(0)$(C_1$-$C_6)$alkyl;

R_1 is -H, -$(C_1$-$C_6)$alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, phenyl, or pyridyl;

L is -(Ci-C_6)alkyl-O-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, or -C(O)(Ci-C_6)alkyl;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, and

L is -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -halogen, -N($R_{N6}R_{N7}$), wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, allyl, propargyl, acetyl, or -C(O)(Ci-C_6)alkoxy;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is pyridyl, and

L is -(Ci-C_6)alkyl-O- or -(Ci-C_6)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

Y is a bond, and

L is -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-, or

-(C_1-C_6)alkyl-S-(C_1-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(C_1-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(C_1-C_6)alkoxy, -C(0)(C_1-C_6)alkyl, -halogen,

$-N(R_{N6}R_{N7})_t$

wherein R_{N6} and R_{N7} are each independently -H, -(C_1-C_6)alkyl, allyl, propargyl, acetyl, or -C(0)(C_1-C_6)alkoxy;

R_1 is H;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VII), wherein

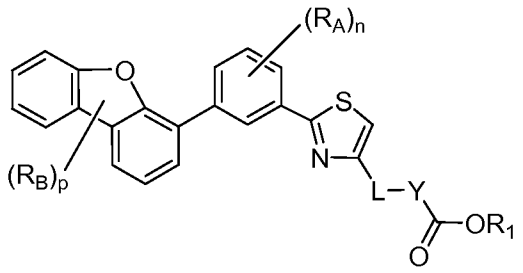
Y is pyridyl, and

L is -(C_1-C_6)alkyl-O- or -(C_1-C_6)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y;

R_1 is H;

and R_A, R_B, n, and p are as defined in formula (VII).

In another embodiment, the invention comprises compounds of formula (VIII),



(VIII)

or a pharmaceutically acceptable salt thereof, wherein

Ri is -H, -(Ci-C_6)alkyl, -(Ci-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(R_{114})-, -N(R_{N4})C(O)-, -C(O)N(R_{114})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(CI-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-, -S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S(O)$_2$-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{114})-, -N(R_{114})-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl -N(R_{N4})-(Ci-C_6)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-, -N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(RN$_4$)-, -C(0)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-C(O)N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-, -S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-S(0)$_2$N(R$_{N4}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-, -N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$-(Ci-C$_6$)alkyl-,

-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)S(0)$_2$N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-N(R$_{N4}$)C(0)N(R$_{N5}$)-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)N(R$_{N5}$)-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(O)N(R$_{N5}$)-(C$_I$-C$_6$)alkyl-,

-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-,

-(Ci-C$_6$)alkyl-N(R$_{N4}$)C(0)0-(Ci-C$_6$)alkyl-,

-OC(O)N(R$_{N4}$)-(C$_I$-C$_6$)alkyl-,

-(Ci-C$_6$)alkyl-OC(O)N(RN$_4$)-, or

-(Ci-C$_6$)alkyl-OC(O)N(RN$_4$)-(C$_I$-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -C(O)OH, -(Ci-C$_6$)alkyl-C(0)OH, -(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen, -N(RN$_6$RN$_7$), -(Ci-C$_6$)alkyl-N(RN$_6$RN$_7$), or -C(O)N(R$_{N6}$R$_{N7}$),

wherein R$_{N4}$ and R$_N$s are independently -H or -(Ci-C$_6$)alkyl,

wherein R$_{N6}$ and R$_{N7}$ are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl,

-$(C_2$-$C_6)$alkynyl ,

-C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C(0)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

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

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{NI0}R_{NII}$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(0)N(RNIORNII),

wherein R_Ni_0 and R_Nn are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN,

-(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(O)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

and L, R_A, R_B, Ri, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -(Ci-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(Ci-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(R_{N4})-, -N(RN_4)C(O)-, -C(0)N(R_{N4})-, -(Ci-C_6)alkyl-O-, -0-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-N(RN_4)-, -N(R_{N4})-(CI-C_6)alkyl-, or

-(Ci-C$_6$)alkyl-N(R_{N4})-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -C(O)OH, -halogen, -N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C$_6$)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(0)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, or -C(O)H;

and R_A, R_B, Ri, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C$_6$)alkoxy, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy, -C(O)(Ci-C$_6$)alkyl, -C(O)OH, -CN, -(Ci-C$_6$)haloalkoxy, -(Ci-C$_6$)haloalkyl, -halogen, -OH, -(Ci-C$_6$)alkyl-OH, -NO$_2$, -N($R_{N2}R_{N3}$), -(Ci-C$_6$)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(Ci-C$_6$)alkyl, -(C$_2$-C$_6$)alkenyl, -(C$_2$-C$_6$)alkynyl, -C(O)(Ci-C$_6$)alkoxy,

-C(O) (Ci-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -N(RN_4)-, -N(R_{N4})C(0)-, -C(O)N(R_{114})-,

-(Ci-C_6)alkyl-0-, -0-(Ci-C_6)alkyl-,

-(Ci-C_6)alkyl-0-(Ci-C_6)alkyl-,

-(Ci-C_6)alkyl-S-, -S-(Ci-C_6)alkyl-,

-(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-,

-(Ci-C_6)alkyl-N(RN_4)-, -N(R_{N4})-(CI-C_6)alkyl-, or

-(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl, -C(O) (Ci-C_6)alkoxy,

-C(0) (Ci-C_6)alkyl, -C(O)OH, -halogen,

-N($R_{N6}R_{N7}$), or -C(O)N($R_{N6}R_{N7}$),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C_6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-(C_2-C_6)alkynyl,

-C(O) (Ci-C_6)alkoxy, -C(0) (Ci-C_6)alkyl, or -C(O)H;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, RB, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl,

-$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy,
-C(O) $(Ci$-$C_6)$alkyl, -C(O)OH, -CN,
-$(Ci$-$C_6)$haloalkoxy, -$(Ci$-$C_6)$haloalkyl, -halogen,
-OH, -$(Ci$-$C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$,
-$(Ci$-$C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C(0)N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy, $-C(0)$ $(Ci$-$C_6)$alkyl, or -C(O)H;

L is -$(Ci$-$C_6)$alkyl-O-, -$(Ci$-$C_6)$alkyl-O- $(Ci$-$C_6)$alkyl-, -$(Ci$-$C_6)$alkyl-S-, -$(Ci$-$C_6)$alkyl-S- $(Ci$-$C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -$(Ci$-$C_6)$alkyl, -$(Ci$-$C_6)$alkoxy, $-C(0)$ $(Ci$-$C_6)$alkoxy, $-C(0)$ $(Ci$-$C_6)$alkyl, -C(O)OH, -halogen, $-N(R_{N6}R_{N7})t$

wherein R_{N6} and R_{N7} are each independently -H, -$(Ci$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -C(O) $(Ci$-$C_6)$alkoxy, or $-C(0)$ $(Ci$-$C_6)$alkyl;

Ri is -H, -$(Ci$-$C_6)$alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, phenyl, or pyridyl;

L is -$(Ci$-$C_6)$alkyl-O-, -$(Ci$-$C_6)$alkyl-O- $(Ci$-$C_6)$alkyl-, -$(Ci$-$C_6)$alkyl-S-, -$(Ci$-$C_6)$alkyl-S- $(Ci$-$C_6)$alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -$(Ci$-$C_6)$alkyl, -$(Ci$-$C_6)$alkoxy, $-C(0)$ $(Ci$-$C_6)$alkoxy, -C(O) $(Ci$-$C_6)$alkyl, -C(O)OH, -halogen,

-N($R_{N6}R_{N7}$),

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, or -C(0)(Ci-C_6)alkyl;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is a bond, and

L is -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -halogen, -N($R_{N6}R_{N7}$), wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, allyl, propargyl, acetyl, or -C(0)(Ci-C_6)alkoxy;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is pyridyl, and

L is -(Ci-C_6)alkyl-O- or -(Ci-C_6)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y;

Ri is -H, -(Ci-C_6)alkyl, benzyl, or allyl;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another embodiment, the present invention comprises compounds of formula (VIII), wherein

Y is a bond, and

L is -(Ci-C_6)alkyl-0- (Ci-C_6)alkyl- , or

-(Ci-C_6)alkyl-S- (Ci-C_6)alkyl- ,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -halogen, -N($R_{N6}R_{N7}$),

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, allyl, propargyl, acetyl, or -C(0)(Ci-C_6)alkoxy;

Ri is H;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another embodiment, the invention comprises compounds of formula (VIII), wherein

Y is pyridyl, and

L is -(Ci-C_6)alkyl-O- or -(Ci-C_6)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y;

Ri is H;

and R_A, R_B, n, and p are as defined in formula (VIII).

In another aspect, the invention includes synthetic intermediates that are useful in making the compounds of the invention.

In another aspect, the invention provides methods of preparing the compounds of the invention and the intermediates used in those methods.

In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least

one pharmaceutically acceptable solvent, carrier, adjuvant, or excipient .

In another aspect, the invention provides a methods of treating Type I diabetes, Type II diabetes, and Syndrome X (consisting of such abnormalities as obesity, dyslipidemia, hypercoagulation, hypertension, insulin resistance and leading to heart disease and diabetes) , comprising administering either a pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

The compounds of the invention inhibit PTP-IB, and therefore, are useful in the treating or controlling other PTP-IB mediated diseases, including controlling or treating Type 2 diabetes, improving glucose tolerance, and in improving insulin sensitivity in patients in need thereof.

In another aspect, the invention encompasses a method of inhibiting PTP-IB comprising administering to a patient in need thereof, either a pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention encompasses a method of treating cancer comprising administering to a patient in need thereof, either a pharmaceutically acceptable amount of a compound or salt of formula (I), or a pharmaceutical composition comprising a compound or salt of formula (I) .

In another aspect, the invention encompasses a method of treating neurodegenerative diseases comprising administering to a patient in need thereof, either a pharmaceutically acceptable amount of a compound or salt of formula (I), or a

pharmaceutical composition comprising a compound or salt of formula (I).

In another aspect, the invention provides a method of treating immunological disease comprising administering either a pharmaceutically acceptable amount of a compound of formula (I), or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

In another aspect, the invention provides a method of treating bleeding disorders comprising administering either a pharmaceutically acceptable amount of a compound of formula (I), or a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

The invention also provides methods of using PTP-IB inhibitors of formula (I) for improving the cardiovascular or cerebrovascular risk profile in patients experiencing or subject to type II diabetes (non-insulin-dependent diabetes mellitus) or Syndrome X, preferably in patients experiencing or subject to human type II diabetes. These methods may also be characterized as the reduction of risk factors for heart disease, stroke, or heart attack in patients experiencing or subject to type II diabetes or Syndrome X.

The invention also provides methods and compositions for combination therapy of Type I diabetes, Type II diabetes, and Syndrome X. In the following table, Table 1, methods for using a pharmacological combination of one or more PTP-IB inhibitor and one or more combination agent are described for the treatment of Type II diabetes or Syndrome X in a patient in need of such treatment. In the following embodiments, such treatments comprise administration of the inventive compounds of formula (I) as disclosed herein either concomitantly, simultaneously, or together with a therapeutically-ef fective

amount of said additional compounds and medicaments. In the case of combination therapy methods involving insulins as the associated agent, the methods are for the treatment of Type I or Type II diabetes in a patient in need of such treatment.

Table 1

Agent	Method to	Example Agents
Angiotensin Converting Enzyme (ACE) inhibitors	1. Improve cardiovascular risk profile 2. Reduce risk factors for heart disease, stroke, or heart attack 3. Reduce hyperlipidemia 4. Decrease low density lipoprotein (LDL) blood levels 5. Increase high density lipoprotein (HDL) blood levels 6. Inhibit, prevent or reduce atherosclerosis and reduce the risk factors thereof 7. Decrease free fatty acid blood levels and triglyceride levels	quinapril, ramipril, verapamil, captopril, diltiazem, clonidine, hydrochlorthiazide, benazepril, prazosin, fosinopril, lisinopril, atenolol, enalapril, perindropril, perindropril tert-butylamine, trandolapril, moexipril
Biguanide agents and, (optional) Sulfonlylurea agents	1. Treat type II diabetes or Syndrome X 2. Treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia 3. Modulate blood glucose levels	glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, tolazamide
α-Glucosidase inhibitors	1. Improve cardiovascular risk profile 2. Reduce of risk factors for heart disease, stroke or heart attack 3. Reduce of hyperlipidemia 4. Decrease low density lipoprotein (LDL) blood levels 5. Increase high density	Miglitol, acarbose

	lipoprotein (HDL) blood levels 6. Inhibit, prevent, or reduce atherosclerosis or the risk factors 7. Decrease free fatty acid blood levels and triglyceride levels	
Sulfonylurea agent	1. Improve cardiovascular risk profile 2. Reduce risk factors in such patients for heart disease, stroke or heart attack 3. Reduce hyperlipidemia 4. Decrease low density lipoprotein (LDL) blood levels, high density lipoprotein (HDL) blood levels, and overall blood lipoprotein levels 5. Inhibit, prevent or reduce atherosclerosis or the risk factors thereof 6. Decrease free fatty acid blood levels and triglyceride levels	glipizide, glyburide (glibenclamide), chlorpropamide, tolbutamide, tolazamide, glimepriride
Thiazolidinedione agents	1. Treat, inhibit, or maintenance of Syndrome X or type II diabetes 2. Treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia 3. Modulate blood glucose levels	Pioglitizone, rosiglitazone
Antilipemic agents	1. Improve cardiovascular risk profile 2. Reduce risk factors for heart disease, stroke or heart attack 3. Reduce hyperlipidemia 4. Decrease low density lipoprotein (LDL) blood levels	Bile acid sequestrants (colestipol and colesevelam), fibric acid derivatives (clifofibrate, gemfibrozil and fenofibrate), HMG-

	5. Increase high density lipoprotein (HDL) blood levels 6. Inhibit, prevent or reduce atherosclerosis or the risk factors 7. Decrease free fatty acid blood levels and triglyceride levels	CoA reductase inhibitors (cerivastatin, fluvastatin, atorvastatin, lovastatin, pravastatin and simvastatin),nicotinic acid compounds (Niacin), lipase inhibiting agents (orlistat)
Aldose Reductase Inhibitors (ARI)	1. Treat, inhibit, or prevent type II diabetes, or its related and associated symptoms, disorders and maladies 2. Treat, prevent, or inhibit diabetic neuropathy, diabetic nephropathy, retinopathy, keratopathy, diabetic uveitis, cataracts 3. Inhibit or reduce risk factors for heart disease, stroke or heart attack 4. Reduce hyperlipidemia and/or low density lipoprotein (LDL) blood levels 5. Inhibit, prevent, or reduce atherosclerosis or the risk factors 6. Decrease free fatty acid blood levels and triglyceride levels.	ARIs are disclosed in U.S. Patent Nos. 6,420,426 and 6,214,991
Insulin(s)	1. Management of type I or type II diabetes 2. Improve the cardiovascular and cerebrovascular risk profiles 3. Inhibit or reduce risk factors for heart disease, stroke or heart attack	Naturally occurring and synthetic insulins; *vide infra*

Insulins useful with the methods and combinations of this invention include rapid acting insulins, intermediate acting insulins, long acting insulins and combinations of intermediate and rapid acting insulins.

Rapid acting commercially available insulin products include HUMALOG® Brand Lispro Injection (rDNA origin); HUMULIN® Regular Human Injection, USP [rDNA origin]; HUMULIN® Regular U-500 Concentrated Human Injection, USP [rDNA origin] ; REGULAR ILETIN® II (insulin injection, USP, purified pork) available from Eli Lilly and Co.; and the NOVALIN® Human Insulin Injection and VENOSULIN® BR Buffered Regular Human Injection, each available from Novo Nordisk Pharmaceuticals.

Commercially available intermediate acting insulins useful with this invention include, but are not limited to, the HUMULIN® L brand LENTE® human insulin [rDNA origin] zinc suspension, HUMULIN® N NPH human insulin [rDNA origin] isophane suspension, LENTE® ILETIN. RTM. II insulin zinc suspension, USP, purified pork, and NPH ILETIN® II isophane insulin suspension, USP, purified pork, available from Eli Lilly and Company, LANTUS® insulin glargine [rDNA origin] injection, available from Aventis Pharmaceuticals, and the NOVOLIN L Lente® human insulin zinc suspension (recombinant DNA origin) , and NOVOLIN® N NPH human insulin isophane suspension (recombinant DNA origin) products available from Novo Nordisk Pharmaceuticals, Inc, Princeton N.J.

Also useful with the methods and formulations of this invention are intermediate and rapid acting insulin combinations, such as the HUMALOG® Mix 75/25 (75% Insulin Lispro Protamine Suspension and 25% Insulin Lispro Injection), HUMULIN® 50/50 (50% Human Insulin Isophane Suspension and 50% Human Insulin Injection) and HUMULIN® 70/30 (70% Human Insulin

Isophane Suspension and 30% Human Insulin Injection), each available from Eli Lilly and Company. Also useful are the NOVALIN® 70/30 (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection) line of combination products available from Novo Nordisk Pharmaceuticals.

A commercially available long acting insulin for use with this invention is the HUMULIN® U Ultralente® human insulin [rDNA origin] extended zinc suspension, available from Eli Lilly and Company.

Also useful in the methods of this invention are inhaled insulin products, such as the EXUBERA® inhaled insulin product developed by Pfizer Inc. and Aventis SA.

Each of these insulin products can be administered as directed by a medical professional using administrations, dosages and regimens known in the art, such as those published for each product in the Physicians' Desk Reference, 55 Edition, 2001, published by Medical Economics Company, Inc. at Montvale, N.J., the relevant sections of which are incorporated herein by reference.

Pharmaceutical Formulations

The compounds of general Formula (I) may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula (I) and a pharmaceutically acceptable carrier. One or more compounds of

general Formula (I) may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula (I) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate,

calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Formulations for oral use may also be presented as lozenges .

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions

may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring, and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among

the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides . In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the present invention may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene

glycol, butane-1, 3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulf oxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier (s) with or without stabilizer (s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of

the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate,

polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). 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. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

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, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to the feed or drinking water. Preferred non-human animals include domesticated animals.

Definitions

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge. Examples of alkoxy groups include, for example, methoxy, ethoxy, propoxy and isopropoxy.

The term "alkyl" as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl .

The term "alkenyl" as used herein, means a straight or branched chain hydrocarbon containing the designated number of carbon atoms and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon group containing the designated number of carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring. The aromatic ring may optionally be fused or otherwise attached to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene and biphenyl. Preferred examples of aryl groups include phenyl, naphthyl, and anthracenyl. More preferred aryl groups are phenyl and naphthyl. Most preferred is phenyl.

The term "cycloalkyl" refers to a cyclic hydrocarbon. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, and iodine.

The term "haloalkoxy" as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

The term "haloalkyl" as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

The term "heterocycloalkyl" refers to a ring or ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl ring is optionally fused to or otherwise attached to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. Preferred heterocycloalkyl groups have from 3 to 7 members. Examples of heterocycloalkyl groups include, for example, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, morpholinyl, piperidinyl, tetrahydrofuranyl, pyrrolidinyl, pyridinonyl, and pyrazolidinyl . Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, pyridinonyl, dihydropyrrolidinyl, and pyrrolidinonyl .

The term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heteroaryl ring may be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridine, furan, thienyl, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl .

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic or diastereomers . In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can

be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included. The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art.

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

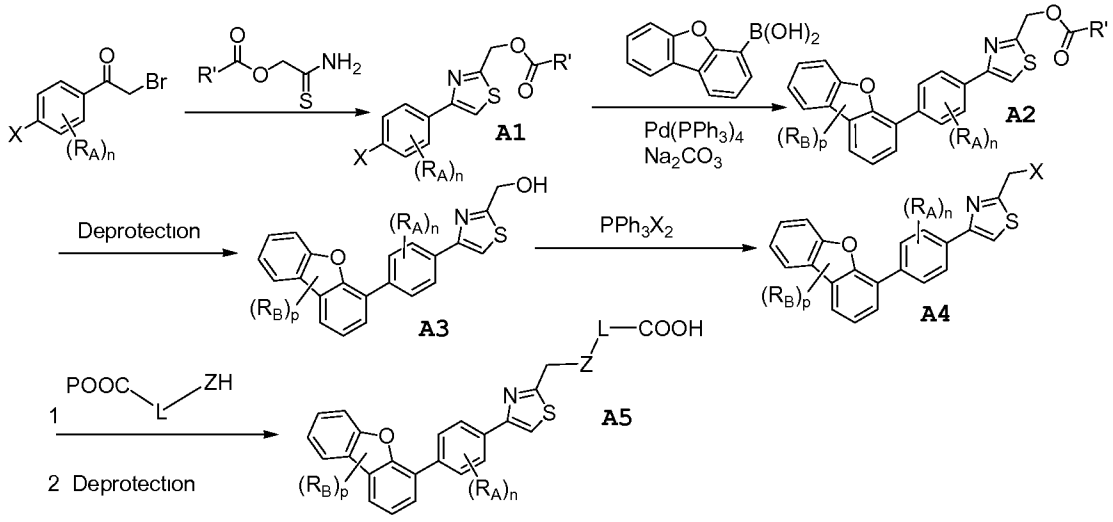
It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for

protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (Protective Groups In Organic Synthesis, Wiley and Sons, 1999) .

Compounds herein are named using ACD/ChemSketch version 8.17 (commercially available from Advanced Chemistry Development, Inc., Toronto, ON, Canada).

Methods of Preparation

Compounds of the invention can be generally prepared according to the methods outlined in Scheme A . R_A, R_B, n and p are as defined in formula (I) . Variable L represents a linker, and Z represents 0, S, or NR, where R is H or any functionality which does not interefer with the required reactivity outlined below; protecting groups are designated by P . X represents a halogen or leaving group such as tosylate, triflate and the like, which are familiar to those skilled in the art. The following scheme is a representation of a specific example to illustrate the general synthetic methods. Those skilled in the art will recognize that the regiochemistry of the products in the following scheme can be readily adjusted without modification of the particular synthetic steps by substitution of the appropriate starting materials. For example, substitution of 3-bromo-α-bromoacetophenone for 4-bromo-α-bromoacetophenone in the initial synthetic step would impart a *meta*- regiochemistry between the halogen and thiazole in Al, and ultimately a *meta*-regiochemistry between the thaizole and dibenzofuran in the final product, A5 .



Scheme A

To begin the synthesis, a dehydrative cyclization reaction between 4-halo- α-bromoacetophenone and for example, 2,2-dimethylpropionic acid thiocarbamoylmethyl ester yields a thiazole of structure Al, where R' is t-butyl. R' may be any group which will not interfere with the subsequently required reactivity, such as phenyl, n-alkyl, s-alkyl, t-alkyl, and the like. Further, Al and 4-dibenzofuranylboronic acid are coupled according to standard Suzuki palladium catalyzed conditions, involving $Pd(PPh_3)_4$ and a base, such as Na_2CO_3 to yield A2. This conversion of may also be performed via palladium catalysis utilizing organozinc (Negishi), organomagnesium (Kumada), or organotin (Stille) reactants with aryl halides with suitably protected starting materials if chemical incompatibilities would exist otherwise. The haloarene may be an iodo-, bromo-, or chloroarene. The palladium source may be, for example, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(dppf)$, $PdCl_2(dppp)$, $PdCl_2(dppe)$, $PdCl_2(COD)$, $Pd(PCy_3)_2$, or $Pd(tBu_3P)_2$, all of which are available commercially from either Aldrich Chemical (Milwaukee, WI) or Strem Chemical (Newburyport, MA). In particular, those skilled in the art will recognize that alternative palladium

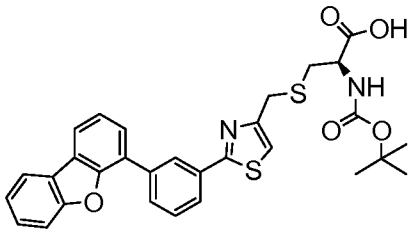
catalysts may be prepared from $Pd_2(dba)_3$ in situ by the addition of a ligand source, such as dppf, dppe, dppp, PCy3, $P(o\text{-}tol)_3$, $P(2\text{-}furyl)_3$, BINAP, $P(tBu_3)2(biphenyl)$, and N-heterocyclic carbenes, such as Arduengo's carbene, N, N'-bis (2, 6-diisopropylphenyl) imidazol-2-ylidene, or N, N'-bis (2,4,6-trimethylphenyl) imidazolidin-2-ylidene, and the like.

Following deprotection of A2 by hydrolysis under basic conditions, to yield A3, A4 is prepared by treatment of A3 with a nucleophilic activation and reaction agent such as PPh_3Br_2, PBr_3, $POBr_3$, or PPh_3 and CBr_4. The benzyl chloride may be prepared anagously with PPh_3Cl_2, $POCl_3$, PCl_5, or PPh_3 and CCl_4. Likewise, the benzyl iodide may be prepared using PPh_3I_2.

A5 can be prepared by two final steps; first, alkylation of a thiol, alcohol, or amine in the presence of a base with A4, then deprotection of the carboxylic acid. For example, an ester protecting group may be hydrolyzed under basic conditions to yield the carboxylic acid. In scheme A, L represents a linker, and Z represents 0, S, or NR, where R is H or any functionality which does not interefer with the required reactivity. The thiol, alcohol, or amine necessarily includes an appropriately protected carboxylic acid. Such bases include, but are not limited to, Na_2CO_3, K_2CO_3, Cs_2CO_3, triethylamine, diethylisopropylamine, NaOH, and KOH. Catalysts may be added to facilitate the reaction, including KI, $n\text{-}Bu_4NI$, and the like. Appropriate thiols, alcohols, and amines for preparation of compounds of the present invention include, but are not limited to, BOC-protected amino acid esters, such as, alkyl N-BOC-Cys, alkyl N-BOC-Ser, alkyl N-BOC-Thr, alkyl N-BOC-His, alkyl N-BOC-Lys, alkyl N-BOC-Tyr, alkyl N-BOC homoserine, alkyl N-BOC homocysteine; straight and branched alkyl thiols, alcohols, and amines such as alkyl

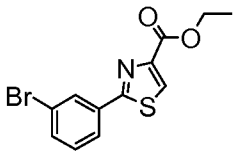
mercaptoacetates, alkyl 2-mercaptopropanoates, alkyl 3-mercaptopropanoates, alkyl hydroxyacetates, alkyl 2-hydroxypropanoates, alkyl 3-hydroxypropanoates, alkyl glycinates, alkyl β-alaninates, alkyl alinates, alkyl ω-aminoalkanoates, alkyl ω-mercaptoalkanoates, alkyl ω-hydroxyalkanoates, and the like.

Example 1



2-tert-butoxycarbonylamino-3- [2- (3-dibenzofuran-4-yl-phenyl) -thiazol-4-ylmethylsulfanyl] -propionic acid

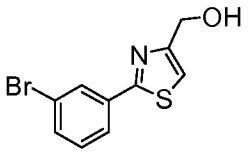
Example 1a



Preparation of 2- (3-bromo-phenyl) -thiazole-4-carboxylic acid ethyl ester

A solution of 3-bromo-thiobenzamide (6.4 g, 29.6 mmol) and 3-bromo-2-oxo-propionic acid ethyl ester (6.4 g, 33.1 mmol) in ethanol (50 mL, 0.6 M) is refluxed for 16 hours. After evaporation of the solvent, the residue is purified by flash chromatography (15% ethyl acetate in heptane) to give 2-(3-bromo-phenyl) -thiazole-4-carboxylic acid ethyl ester (7.3 g, 79%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18-8.16 (m, 2 H), 7.89 (dd, J_1 = 1.8 Hz, J_2 = 1.0 Hz, 1 H), 7.56 (dd, J_1 = 1.8 Hz, J_2 = 1.0 Hz, 1 H), 7.31 (t, J = 7.9 Hz, 1 H), 4.44 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H).

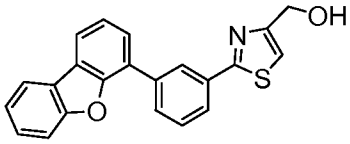
Example Ib



Preparation of [2-(bromo-phenyl)-thiazol-4-yl]-methanol

A solution of 2-(3-bromo-phenyl)-thiazole-4-carboxylic acid ethyl ester (6.0 g, 19.2 mmol) in THF (40 mL, 0.3 M) is cooled to 0 ^{0}C. Lithium aluminum hydride ($LiAlH_4$) (1 M in THF; 17.2 mL, 17.2 mmol) is added dropwise over 5 minutes. After stirring for 30 minutes, the solution is diluted with ethyl acetate (40 mL), saturated aq. NaCl (15 mL) and methanol (40 mL). $MgSO_4$ is added and the solution is filtered and concentrated. Purification by flash chromatography (15-25% ethyl acetate in heptane) gives [2-(bromo-phenyl)-thiazol-4-yl]-methanol (4.1 g, 79%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (t, J = 1.9 Hz, 1 H), 7.82 (dd, J_1 = 1.9 Hz, J_2 = 1.0 Hz, 1 H), 7.53 (dd, J_1 = 1.9 Hz, J_2 = 1.0 Hz, 1 H), 7.29 (t, J = 7.9 Hz, 1 H), 7.20 (s, 1 H), 4.82 (d, J = 5.9 Hz, 2 H)

Example 1c

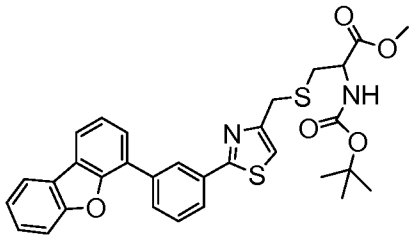


Preparation of [2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-yl]-methanol

A solution of [2-(bromo-phenyl)-thiazol-4-yl]-methanol (2.0 g, 7.4 mmol), 4-dibromobenzene boronic acid (1.9 g, 9.0 mmol), and tetrakistriphenylphosphine palladium ($Pd(Ph_3)_4$) (0.2 g, 0.2 mmol) in DME (18 mL, 0.4M) is treated with 2M Na_2CO_3 (4.5 mL, 9.0 mmol). The reaction mixture is heated to

90 ^{0}C for 8 hours, cooled to room temperature, and the solution is diluted with H_2O (20 mL). The organics are extracted with ethyl acetate (2 x 50 mL). Purification by flash chromatography (40% ethyl acetate in heptane) affords [2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-yl]-methanol (2.5 g, 96%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (t, *J* = 1.8 Hz, 1 H), 8.00-7.94 (m, 4 H), 7.65 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.61-7.56 (m, 2 H), 7.48-7.41 (m, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.19 (s, 1 H), 4.84 (d, J = 5.8 Hz, 2 H)

Example Id

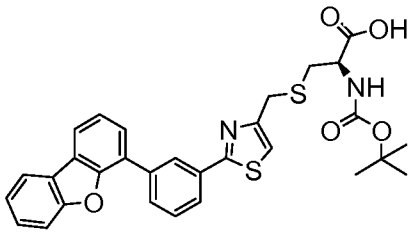


Preparation of 2-tert-butoxycarbonylamino-3-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethylsulfanyl]-propionic acid methyl ester

A solution of [2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-yl]-methanol (0.20 g, 0.56 mmol), 2-tert-butoxycarbonylamino-3-mercapto-propionic acid methyl ester (0.26 g, 1.1 mmol), 1,1'-(azodicarbonyl) dipiperidine (0.25 g, 1.2 mmol), and imidazole (0.07 g, 1.2 mmol) in dichloromethane (7 mL, 0.1 M) is treated with trimethylphosphine (1 M in THF; 1.1 mL, 1.1 mmol). After stirring for 2 hours at room temperature, the solution is diluted with heptane (10 mL) and the precipitate is removed by filtration. The filtrate is concentrated and purified by flash chromatography (25% ethyl acetate in heptane) to afford 2-tert-butoxycarbonylamino-3-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethylsulfanyl]-propionic acid methyl ester (0.27 g, 84%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.43 (t, J = 1.8 Hz, 1 H), 8.04--

7.94 (m, 4 H), 7.67 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.61-7.57 (m, 2 H), 7.49-7.43 (m, 2 H), 7.37 (t, J = 7.5 Hz, 1 H), 7.16 (s, 1 H), 5.86 (d, *J* = 7.9 Hz, 1 H), 4.66-4.61 (m, 1 H), 3.94 (d, J = 3.8 Hz, 2 H), 3.71 (s, 3 H), 3.06-2.98 (m, 2 H), 1.41 (s, 9 H)

Example Ie

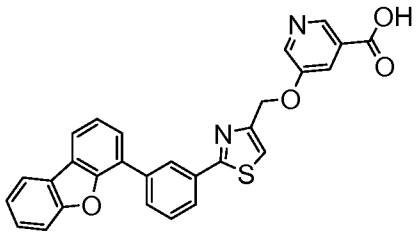


Preparation of 2-tert-butoxycarbonylamino-3- [2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethylsulfanyl]-propionic acid

A solution of 2-tert-butoxycarbonylamino-3- [2-(3-dibenzofuran-4-yl-phenyl) -thiazol-4-ylmethylsulf anyl] -propionic acid methyl ester (0.26 g, 0.45 mmol) in THF (5 mL) and methanol (1 mL) (0.1 M) is treated with 2 M NaOH (1.3 mL, 2.3 mmol) at 0 ^{0}C. The solution is stirred for 2 hours and then acidified with 2N HCl to a pH of 3. The organics are extracted with ethyl acetate (2 x 20 mL) and dried over $MgSO_4$. Purification by flash chromatography (5% methanol in dichloromethane) affords 2-tert-butoxycarbonylamino-3- [2-(3-dibenzof uran-4-yl-phenyl) -thiazol-4-ylmethylsulf anyl] -propionic acid (0.18 g, 71%) as a white foam. mp 115-116 ^{0}C; Rf 0.36 (15% methanol in dichloromethane) ^{1}H NMR (DMSO, 300 MHz) δ 8.37 (m, 1 H), 8.21-8.17 (m, 2 H), 8.01-7.97 (m, 2 H), 7.77-7.71 (m, 2 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.59-7.49 (m, 3 H), 7.42 (t, J = 7.6 Hz, 1 H), 4.00-3.94 (m, 1 H), 3.89 (s, 2 H), 2.97 (dd, J_1 = 13.4 Hz, J_2 = 4.5 Hz, 1 H), 2.82 (dd, J_1 =

13.4 Hz, J_2 = 7.0 Hz, 1 H), 1.35 (s, 9 H) ESI-LCMS *m/z* calcd for $C_{30}H_{28}N_2O_5S_2$: 560.7; found 561.3 $(M+1)^+$.

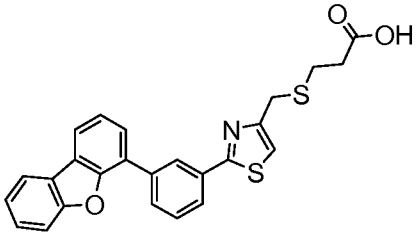
Example 2



Preparation of 5-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethoxy]-nicotinic acid (Compound 2)

The title compound (alternatively named 5-{[2-(3-dibenzo*[b, d]*furan-4-ylphenyl)-1,3-thiazol-4-yl]methoxy jnicotinic acid) is prepared in a manner analogous to that set forth above in Example 1, except 5-hydroxy-nicotinic acid methyl ester is used instead of *2-tert*-butoxycarbonylamino-3-mercapto-propionic acid methyl ester in step 4 to give, after saponification using the conditions outlined in step 5, 5-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethoxy]-nicotinic acid . mp 268-270 ^{0}C; R_f 0.20 (15% methanol in dichloromethane) ^{1}H NMR (DMSO, 300 MHz) δ 8.67 (s, 1 H), 8.61 (s, 1 H), 8.40 (s, 1 H), 8.20 (d, J = 7.6 Hz, 2 H), 8.03-7.90 (m, 4 H), 7.77-7.67 (m, 3 H), 7.53 (t, J = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 5.41 (s, 2 H) ESI-LCMS *m/z* calcd for $C_{28}H_{18}N_2O_4S$: 478.5; found 479.3 $(M+1)^+$.

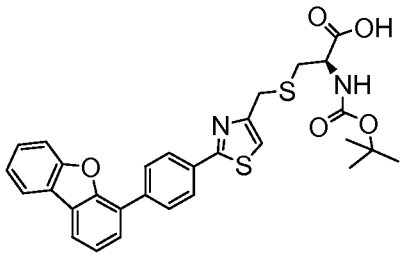
Example 3



Preparation of 3-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethylsulfanyl]-propionic acid (Compound 3)

The title compound (alternatively named 3-({[2-(3-dibenzo[b,d]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}thio)propanoic acid) is prepared in a manner analogous to that set forth above in Example 1, except 3-mercapto-propionic acid methyl ester was used instead of 2-tert-butoxycarbonylamino-3-mercapto-propionic acid methyl ester in step 4 to give, after saponification using the conditions outlined in step 5, 3-[2-(3-dibenzofuran-4-yl-phenyl)-thiazol-4-ylmethylsulfanyl]-propionic acid. mp 70-80 °C; Rf 0.31 (5% methanol in dichloromethane) ^{1}H NMR (DMSO, 300 MHz) δ 8.38 (m, 1 H), 8.21-8.17 (m, 2 H), 8.02-7.97 (m, 2 H), 7.77-7.71 (m, 2 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.58 (s, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 3.92 (s, 2 H), 2.73 (t, *J* = 6.8 Hz, 2 H), 2.56 (t, *J* = 6.8 Hz, 2 H). ESI-LCMS *m/z* calcd for $C_{25}H_{19}NO_3S_2$: 445.5; found 446.3 $(M+l)^+$.

Example 4

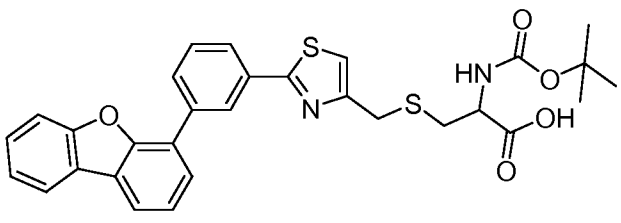


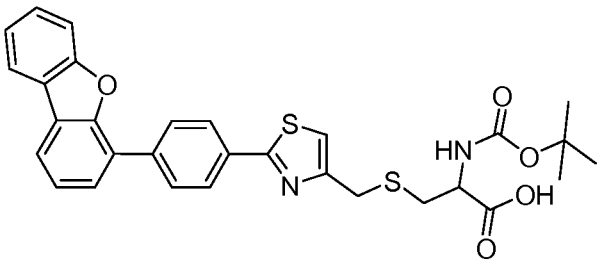
Preparation of 2-tert-butoxycarbonylamino-3- [2- (4-dibenzofuran -4-yl -phenyl)-thiazol-4 -ylmethylsulfanyl]- propionic acid

The title compound is prepared in a manner analogous to that set forth above in Example 1, except 4-bromo-thiobenzamide was used instead of 3-bromo-thiobenzamide in step 1 to give 2- (4-bromo-phenyl) -thiazole-4-carboxylic acid ethyl ester. This compound is then submitted to the conditions described in steps 2-5 to afford *2-tert-*butoxycarbonylamino-3- [2- (4-dibenzofuran-4-yl-phenyl) -thiazol-4-ylmethylsulf anyl] -propionic acid, mp 125-135 ^{0}C; R_f 0.21 (10% methanol in dichloromethane) ^{1}H NMR (DMSO, 300 MHz) δ 8.20-8.15 (m, 2 H), 8.09 (d, J = 8.7 Hz, 2 H), 8.03 (d, J = 8.7 Hz, 2 H), 7.76-7.72 (m, 2 H), 7.56 (s, 1 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 4.08-4.04 (m, 1 H), 3.91 (s, 2 H), 3.00 (dd, J_1 = 13.4 Hz, J_2 = 4.4 Hz, 1 H), 2.83 (dd, J_1 = 13.4 Hz, J_2 = 7.9 Hz, 1 H), 1.38 (s, 9 H). ESI-LCMS *m/z* calcd for $C_{30}H_{28}N_2O_5S_2$: 560.7; found 561.3 $(M+l)^+$.

Example 5

The following compounds may be prepared essentially according to the procedures outlined in Scheme A and described in the above examples.

Compound 1	*N*-(*tert*-butoxycarbonyl)-*S*-{[2-(3-dibenzo[*b*,*d*]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}cysteine	

Compound 4	*N*-(*tert*-butoxycarbonyl)-*S*-{[2-(4-dibenzo[*b*,*d*]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}cysteine	

BIOLOGY EXAMPLES

Example 6

Method for measuring PTP-IB activity

The test compounds are evaluated for their *in vitro* inhibitory activity against recombinant human PTP-IB with phosphotyrosyl dodecapeptide TRDI(P)YETD(P)Y(P)YRK. This corresponds to the 1142-1153 insulin receptor kinase regulatory domain, phosphorylated on the 1146, 1150 and 1151 tyrosine residues; IR-triphosphopeptide as a source of substrate. Enzyme reaction progression is monitored via the release of inorganic phosphate as detected by the malachite green - ammonium molybdate method for the phosphopeptide .

Preferred compounds of the invention exhibit IC_{50} values of less than 10 μM; more preferred compounds of the invention exhibit IC_{50} values of less than 1 μM. Particularly preferred compounds exhibit IC_5O values of less than 300 nM.

It is understood that the foregoing detailed description and accompanying Examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined by the appended claims. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

Example 7

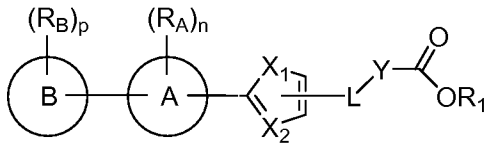
Results of PTP-IB activity testing

COMPOUND NO.	IC_{50} (nM)
1	1,080
2	4,040
3	5,980
4	920

It is understood that the foregoing detailed description and accompanying Examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined by the appended claims. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

What we claim is:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, or N(R_{N1}),

wherein R_{N1} is -H or -(Ci-C_6)alkyl;

X_2 is CH or N;

R_1 is -H, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-phenyl, or -(C_3-C_6)alkenyl;

Y is a bond, -aryl-, or -heteroaryl-, wherein the aryl or the heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-(Ci-C_6)alkoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(C_1-C_6JaIkOXy, -C(O)(C_1-C_6)alkyl, -C(O)OH, -CN, -(C_1-C_6)haloalkoxy, -(C_1-C_6)haloalkyl, -halogen, -OH, -(C_1-C_6)alkyl-OH, -NO_2, -N($R_{N2}R_{N3}$), -(C_1-C_6)alkyl-N($R_{N2}R_{N3}$), or -C(0)N($R_{N2}R_{N3}$),

wherein R_{N2} and R_{N3} are each independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(C_1-C_6JaIkOXy, -C(0)(C_1-C_6)alkyl, or -C(O)H;

L is -0-, -S-, -S(O)$_2$-, -N(RN_4)-, -N(R_{114})C(0)-, -C(O)N(R_{114})-, -S(O)$_2$N(RN_4)-, -N(RN_4)S(O)$_2$-, -(C_1-C_6)alkyl-O-, -0-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-S-, -S-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)$_2$-, -S(O)$_2$-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-S(O)$_2$-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl -N(R_{114})-, -N(R_{114})-(C_1-C_6)alkyl-,

-(Ci-C6)alkyl-N(RN4)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)C(0)-, -N(RN4)C(0)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)C(0)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-C(O)N(RN4)-, -C(0)N(RN4)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-C(O)N(RN4)-(CI-C6)alkyl-,

-(Ci-C6)alkyl-S(0)2N(RN4)-, -S(0)2N(RN4)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-S(0)2N(RN4)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)S(0)2-, -N(RN4)S(0)2-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)S(0)2-(Ci-C6)alkyl-,

-N(RN4)S(0)2N(RN5)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)S(0)2N(RN5)-,

-(Ci-C6)alkyl-N(RN4)S(0)2N(RN5)-(Ci-C6)alkyl-,

-N(RN4)C(0)N(RN5)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)C(0)N(RN5)-,

-(Ci-C6)alkyl-N(RN4)C(0)N(RN5)-(Ci-C6)alkyl-,

-N(RN4)C(0)0-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-N(RN4)C(0)0-,

-(Ci-C6)alkyl-N(RN4)C(0)0-(Ci-C6)alkyl-,

-OC(O)N(RN4)-(Ci-C6)alkyl-,

-(Ci-C6)alkyl-OC(O)N(RN4)-, or

-(Ci-C6)alkyl-OC(O)N(RN4)-(Ci-C6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C6)alkoxy, -(Ci-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C(O)(Ci-C6)alkoxy, -C(O)(Ci-C6)alkyl, -C(O)OH, -(Ci-C6)alkyl-C(0)OH, -(Ci-C6)haloalkoxy, -(Ci-C6)haloalkyl, -halogen, -N(RN6RN7), -(Ci-C6)alkyl-N(RN6RN7), or -C(O)N(RN6RN7),

wherein R_{N4} and R_{N5} are independently -H or -(Ci-C6)alkyl,

wherein R_{N6} and R_{N7} are each independently -H,

-(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

A is -aryl- or -heteroaryl-;

each R_A is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(O)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_{N8}R_{N9}$), -(Ci-C_6)alkyl-N($R_{N8}R_{N9}$), or -C(0)N($R_{N8}R_{N9}$),

wherein R_{N8} and R_{N9} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

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

B is aryl- or heteroaryl-;

each R_B is independently -(Ci-C_6)alkoxy, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -CN, -(Ci-C_6)haloalkoxy, -(Ci-C_6)haloalkyl, -halogen, -OH, -NO_2, -N($R_Ni_0R_{N^{ii}}$), -(Ci-C_6)alkyl-N(RNIORNII), or -C(0)N(RNIORNII),

wherein R_Ni_0 and R_Nn are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, or -C(O)H;

and

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

2. A compound according to claim 1, wherein

A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl.

3. A compound according to claim 2, wherein

B is phenyl, naphthyl, furanyl, thienyl, benzothienyl,

pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzof uranyl, thiazolyl, benzothiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, lH-indazolyl, or benzopyrazolyl .

4. A compound according to claim 3, wherein

Y is a bond, phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoindoyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl, wherein the aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents that are independently

-$(Ci-C_6)$alkoxy, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, -C(O)OH, -CN, -$(Ci-C_6)$haloalkoxy, -$(Ci-C_6)$haloalkyl, -halogen, -OH, -$(Ci-C_6)$alkyl-OH, $-NO_2$, $-N(R_{N2}R_{N3})$, -$(Ci-C_6)$alkyl-$N(R_{N2}R_{N3})$, or $-C_{(0)}N(R_{N2}R_{N3})$,

wherein R_{N2} and R_{N3} are each independently -H, -$(Ci-C_6)$alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(O) $(Ci-C_6)$alkoxy, -C(O) $(Ci-C_6)$alkyl, or -C(O)H.

5. A compound according to claim 4, wherein

L is -0-, -S-, $-N(R_{N4})-$, $-N(RN_4)C(O)-$, $-C_{(0)}N(R_{N4})-$, -$(Ci-C_6)$alkyl-O-, -0-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-O-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-, -S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl-S-$(Ci-C_6)$alkyl-, -$(Ci-C_6)$alkyl $-N(RN_4)-$, $-N(R_{N4})-(CI-C_6)$alkyl-, or

$-(Ci-C_6)alkyl-N(R_{N4})-(Ci-C_6)alkyl-$,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently

$-(Ci-C_6)alkoxy$, $-(Ci-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-C(O)(Ci-C_6)alkoxy$, $-C(O)(Ci-C_6)alkyl$, -C(O)OH, -halogen, $-N(R_{N6}R_{N7})$, or $-C(O)N(R_{N6}R_{N7})$,

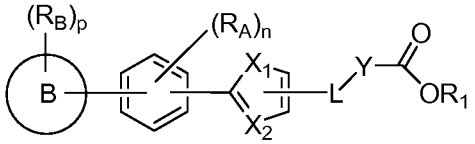
wherein R_{N4} and R_{N5} are independently -H or $-(Ci-C_6)alkyl$,

wherein R_{N6} and R_{N7} are each independently -H, $-(Ci-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-C(O)(Ci-C_6)alkoxy$, $-C(O)(Ci-C_6)alkyl$, or -C(O)H.

6. A compound according to claim 5, wherein

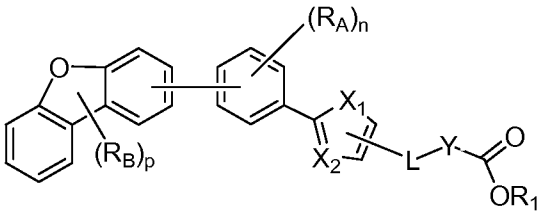
Ri is -H, $-(Ci-C_6)alkyl$, benzyl, or allyl.

7. A compound according to claim 6, having the formula,



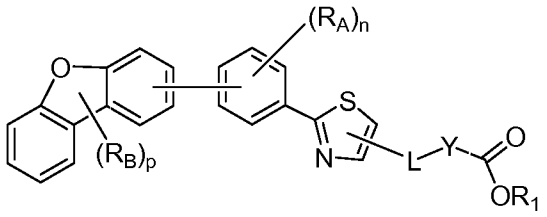
or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 7, having the formula,



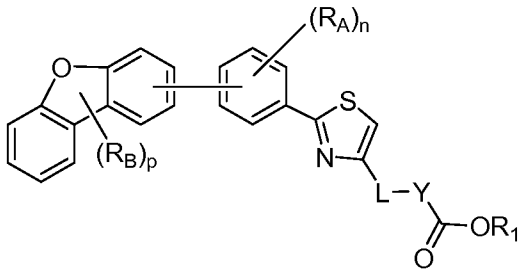
or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8, having the formula,



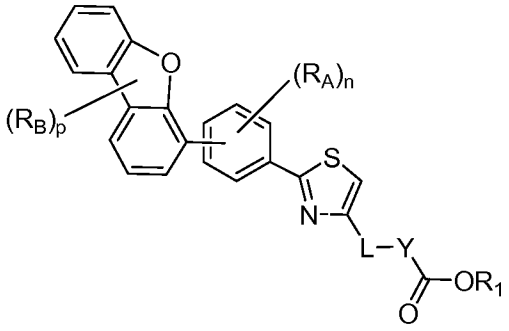
or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 9, having the formula,



or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 10, having the formula,



or a pharmaceutically acceptable salt thereof.

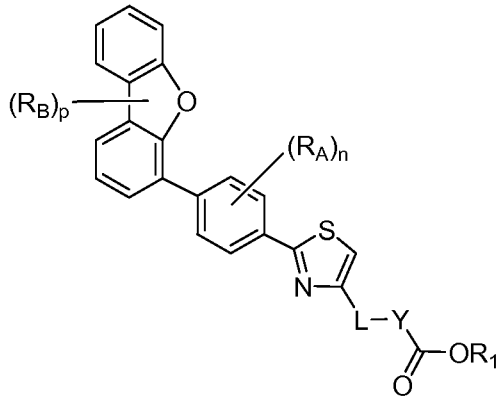
12. A compound according to claim 11, wherein

L is -(Ci-C_6)alkyl-O-, -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, -(Ci-C_6)alkyl-S-, -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-, wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -C(O)OH, -halogen, -$N(R_{N6}R_{N7})$, wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -C(0)(Ci-C_6)alkoxy, or -C(0)(C_1-C_6)alkyl.

13. A compound according to claim 12, wherein

Y is a bond, phenyl, or pyridyl .

14. A compound according to claim 13, having the formula,



or a pharmaceutically acceptable salt thereof..

15. A compound according to claim 14, wherein

Y is a bond, and

L is -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, or -(Ci-C_6)alkyl-S-(Ci-C_6)alkyl-,

wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C_6)alkyl, -(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkoxy, -C(0)(Ci-C_6)alkyl, -halogen, $-N(R_{N6}R_{N7})t$

wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C_6)alkyl, allyl, propargyl, acetyl, or -C(0)(Ci-C_6)alkoxy.

16. A compound according to claim 14, wherein

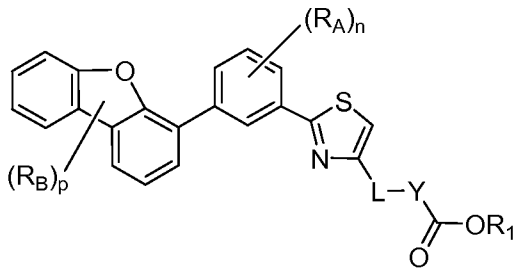
Y is pyridyl, and

L is -(Ci-C_6)alkyl-O- or -(Ci-C_6)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y.

17. A compound according to claim 15, wherein Ri is H.

18. A compound according to claim 16, wherein Ri is H.

19. A compound according to claim 13, having the formula,



or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 19, wherein

Y is a bond, and

L is -(Ci-C_6)alkyl-O-(Ci-C_6)alkyl-, or

-(Ci-C$_6$)alkyl-S- (Ci-C$_6$)alkyl- ,
wherein the alkyl portion of each of the above are optionally substituted with 1, 2, 3, or 4 substituents that are independently
-(Ci-C$_6$)alkyl, -(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkoxy, -C(0)(Ci-C$_6$)alkyl, -halogen, -N($R_{N6}R_{N7}$),
wherein R_{N6} and R_{N7} are each independently -H, -(Ci-C$_6$)alkyl, allyl, propargyl, acetyl, or -C(0)(Ci-C$_6$)alkoxy.

21. A compound according to claim 19, wherein
Y is pyridyl, and
L is -(Ci-C$_6$)alkyl-O- or -(Ci-C$_6$)alkyl-S-, wherein, the alkyl terminus is attached to the thiazole ring and the oxygen or sulfur terminus is attached to Y.

22. A compound according to claim 20, wherein Ri is H.

23. A compound according to claim 21, wherein Ri is H.

24. A compound according to claim 1 which is
N-(tert-butoxycarbonyl)-5-{[2-(3-dibenzo[b,d]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}cysteine;
5-{[2-(3-dibenzo[b,d]furan-4-ylphenyl)-1,3-thiazol-4-yl]methoxy}nicotinic acid;
3-({[2-(3-dibenzo[b,d]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}thio)propanoic acid; or
N-(tert-butoxycarbonyl)-S-{[2-(4-dibenzo[b,d]furan-4-ylphenyl)-1,3-thiazol-4-yl]methyl}cysteine.

25. A pharmaceutical composition comprising a compound of claim 1 and at least one pharmaceutically acceptable solvent, carrier, adjuvant or excipient.

26. A method of treating syndrome X, obesity, diabetes, immunological disease, bleeding disorders, or cancer comprising administering a pharmaceutically acceptable amount of a compound of claim 1 to a patient in need of such treatment .

27. A method of treating syndrome X, obesity, diabetes, immunological disease, bleeding disorders, or cancer comprising administering a pharmaceutical composition claim 25 to a patient in need of such treatment.

28. A method of treating Type II diabetes comprising administering a pharmaceutically acceptable amount of a compound of claim 1 to a patient in need of such treatment.

29. A method of treating Type II diabetes comprising administering a pharmaceutical composition claim 25 to a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078285

A. CLASSIHCATION **OF** SUBJECT **MATTER**
INV. C07D417/10 C07D417/14 A61K31/41 A61K31/435 A61P3/00
A61P35/00

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, 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
X	WO 2006/055708 A (INST FOR PHARM DISCOVERY INC [US]; WHITEHOUSE DARREN [US]; HU SHAOJING) 26 May 2006 (2006-05-26) Examples, cf. esp. ex. 2 ; claim 1	1-29
A	WO 2006/050212 A (INST FOR PHARM DISCOVERY INC [US]; VAN ZANDT MICHAEL C [US]; WHITEHOUS) 11 May 2006 (2006-05-11) the whole document	1-29
A	WO 2004/099170 A (INST OF PHARMACEUTICAL DISCOVE [US]; WHITEHOUSE DARREN [US]; HU SHAOJI) 18 November 2004 (2004-11-18) the whole document	1-29

D Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

"A" document defining the general state of lhe 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 doubls on prionty 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 Io involve an inventive step when the documenl 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 docu¬ments, 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
23 January 2008	29/01/2008

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, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Fritz, **Martin**

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078285

Box No. **II** Observations where certain claims were **found** unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 LxJ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely

Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 [ ] Claims Nos
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3 [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 **of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows-

1 [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims

2. { J As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos :

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos

Remark on Protest

[ ] The additional search fees were accompanied by the applicant ⅓s protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation

[ ] No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/078285

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006055708 A	26-05-2006	AU 2005307718 A1	26-05-2006
		CA 2588766 A1	26-05-2006
		EP 1844043 A2	17-10-2007
WO 2006050212 A	11-05-2006	AU 2005302409 A1	11-05-2006
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		BR PI0409916 A	25-04-2006
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		EP 1620422 A2	01-02-2006
		JP 2006525365 T	09-11-2006
		KR 20060006954 A	20-01-2006
		MX PA05011536 A	23-01-2006