Disclosure 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-IB (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.
Biarylthiazole Carboxylic Acids

BACKGROUND OF THE INVENTION

This application claims the benefit of Provisional Application No. 60/825530, filed September 13, 2006, the disclosure of which is incorporated herein in its entirety.

Field of the Invention

The invention relates to biarylthiazole carboxylic acids 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-1B (PTP-IB) which is a negative regulator of the insulin and leptin signaling pathway and improves insulin-sensitivity.

Description of Related Art

This invention relates to a class of biarylthiazole carboxylic acids that are inhibitors of various PTPs, in particular PTP-IB.

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-1B (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 phosphatidylinositol 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,

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):

![Chemical Structure](image)

and the pharmaceutically acceptable salts thereof, wherein

- \( X_i \) is \( O, S, \) or \( N (R_{N1}) \),
- \( X_2 \) is \( CH \) or \( N \);
- \( R_1 \) is \( -H, - (Ci-C_6)alkyl, - (Ci-C_6)alkyl-phenyl, \) or \( - (C_3-C_6)alkenyl; \)
- \( L_i \) is \( -O- (Ci-C_6)alkyl-, - (CH_2)_{i-6}-O- (Ci-C_6)alkyl-, \)
  \( -S- (Ci-C_6)alkyl-, - (CH_2)_{i-6}-S- (Ci-C_6)alkyl-, \)
  \( -S (O)_{2-} (Ci-C_6)alkyl-, - (CH_2)_{i-6}-S (O)_{2-} (Ci-C_6)alkyl-, \)
  \( -N (R_{N2})- (Ci-C_6)alkyl-, - (CH_2)_{i-6}-N (R_{N2})- (Ci-C_6)alkyl-, \)
  \( -N (R_{N2})C (0)- (Ci-C_6)alkyl-, \)
  \( - (CH_2)_{i-6}N (R_{N2})C (0)- (Ci-C_6)alkyl-, \)
  \( -C (0)N (R_{N2})- (Ci-C_6)alkyl-, \)
  \( - (CH_2)_{i-6}C (0)N (R_{N2})- (C_1-C_6)alkyl-, \)
  \( -S (O)_{2N} (R_{N2})- (Ci-C_6)alkyl-, \)
  \( - (CH_2)_{i-6}-S (O)_{2N} (R_{N2})- (Ci-C_6)alkyl-, \)
  \( -N (R_{N2})S (O)_{2-} (Ci-C_6)alkyl-, \)
  \( - (CH_2)_{i-6}-N (R_{N2})S (O)_{2-} (Ci-C_6)alkyl-, \)
  \( -N (R_{N2})C (0)_{0-} (Ci-C_6)alkyl-, \)
  \( - (CH_2)_{i-6}-N (R_{N2})C (0)_{0-} (Ci-C_6)alkyl-, \)
  \( -N (R_{N2})S (0)_{2N} (R_{N1})- (Ci-C_6)alkyl-, \)
(CH₂)₁₋₆-N(R₈₂)S(O)₂N(R₈₃)-(C₁₋₆alkyl-,
-N(R₈₂)C(O)N(R₈₃)-(C₁₋₆alkyl-), or
-(CH₂)₁₋₆N(R₈₂)C(O)N(R₈₃)-(C₁₋₆alkyl-,
wherein the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that
are independently -(C₁₋₆alkyl), -(C₁₋₆alkoxy,
-(C₂₋₆alkenyl), -(C₂₋₆alkynyl), -C(O) (C₁₋₆alkyl), -C(O)H,
-(C₁₋₆haloalkoxy), -(C₁₋₆haloalkyl), -halogen,
-N(R₈₄R₈₅), -(C₁₋₆alkyl)-N (R₈₄R₈₅), or -C (O) N (R₈₄R₈₅),
wherein R₈₂ and R₈₃ are independently -H or
-(C₁₋₆alkyl),
wherein R₈₄ and R₈₅ are each independently -H,
-(C₁₋₆alkyl), -(C₂₋₆alkenyl), -(C₂₋₆alkynyl,
-C(O) (C₁₋₆alkoxy), -C (O) (C₁₋₆alkyl), or -C(O)H;
A is -aryl- or -heteroaryl-;
each Rₐ is independently -(C₁₋₆alkoxy), -(C₁₋₆alkyl,
-(C₂₋₆alkenyl), -(C₂₋₆alkynyl), -C (O) (C₁₋₆alkoxy,
-C (O) (C₁₋₆alkyl), -C(O)H, -CN, -(C₁₋₆)haloalkoxy,
-(C₁₋₆)haloalkyl, -halogen, -OH, -NO₂, -N(R₈₆R₈₇),
-(C₁₋₆)alkyl-N (R₈₄R₈₅), or -C(O)N (R₈₄R₈₅),
wherein R₈₆ and R₈₇ are each independently -H,
-(C₁₋₆alkyl), -(C₂₋₆alkenyl), -(C₂₋₆alkynyl,
-C(O) (C₁₋₆alkoxy), -C (O) (C₁₋₆alkyl), or -C(O)H;
n is 0, 1, 2, 3, or 4;
L₂ is -N (R₈₈)-, -O-, -S-, -(C₁₋₆alkyl)-N (R₈₈)-,
-N (R₈₈)- (C₁₋₆alkyl)-, -(C₁₋₆alkyl)-N (R₈₈)-(C₁₋₆alkyl-,
-(C₁₋₆alkyl)-O-, -O- (C₁₋₆alkyl)-,
-(C₁₋₆alkyl)-O- (C₁₋₆alkyl)-, -(C₁₋₆alkyl)-S-,
-S- (C₁₋₆alkyl)-, or -(C₁₋₆alkyl)-S- (C₁₋₆alkyl-,
wherein R₈₈ is -H, -(C₁₋₆alkyl,
-(C₂₋₆alkenyl), -(C₂₋₆alkynyl,
-C(O) (C₁₋₆alkoxy), -C(O) (C₁₋₆alkyl),
-C(O) (C₁-C₆)B₁kYl-(C₃-C₈)CyClOaIkYl, or -C(O)H;
B is aryl- or heteroaryl-;
each Rₖ is independently - (Ci-Cₑ) alkoxy, - (Ci-C₆) alkyl,
- (C₂-C₆) alkenyl, - (C₂-C₆) alkynyl, - (C₁-C₆) haloalkoxy,
- (Ci-C₆) alkyl, -C(O)OH, -CN, - (Ci-C₆) haloalkoxy,
- (Ci-C₆) haloalkyl, -halogen, -OH, -NO₂, -N(R₉R₁₀),
- (Ci-C₆) alkyl -N (R₉R₁₀), or -C (0) N (R₉R₁₀),
wherein R₉ and R₁₀ are each independently -H,
- (Ci-C₆) alkyl, - (C₂-C₆) alkenyl, - (C₂-C₆) alkynyl,
- (C₁-C₆) alkyl, -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-effective 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 provides compounds of the formula (I),

\[
\begin{align*}
&\text{A} \quad \text{B}
\end{align*}
\]

and the pharmaceutically acceptable salts thereof, wherein,

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

and \( L_1, L_2, R_A, R_B, R_I, X_1, X_2, n, \) and \( p \) are as defined in formula (I).

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

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

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

and \( L_1, L_2, R_A, R_B, R_I, X_1, X_2, n, \) and \( p \) are as defined in formula (I).

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

A is phenyl, naphthyl, furanyl, thienyl, pyridyl,
pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoaxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
B is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoaxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
L₂ is -N(R₈₈)-, -O-, -S-, -(C₁-C₆)alkyl-N(R₈₈)-, -N(R₈₈)- (C₁-C₆)alkyl-, -(C₁-C₆)alkyl-O-, -O- (C₁-C₆)alkyl-, -(C₁-C₆)alkyl-S-, or -S- (C₁-C₆)alkyl-,
wherein R₈₈ is -H, -(C₁-C₆)alkyl, -allyl, -propargyl, -C(Ø) (C₁-C₆)alkoxy, -C(Ø) (C₁-C₆)alkyl, or -C(Ø) (C₁-C₆)alkyl- (C₃-C₈)cycloalkyl;
and L₁, Rₐ, Rₐ, Rᵢ, X₁, X₂, n, and p are as defined in formula (D).

In another embodiment, the invention provides compounds of formula (I), wherein,
A is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoaxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
B is phenyl, naphthyl, furanyl, thienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoaxozolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
L₂ is -N(R₈₈)-, -O-, -S-, -(C₁-C₆)alkyl-N(R₈₈)-, -N(R₈₈)- (C₁-C₆)alkyl-, -(C₁-C₆)alkyl-O-, -O- (C₁-C₆)alkyl-, -(C₁-C₆)alkyl-S-, or -S- (C₁-C₆)alkyl-,
wherein R₈₈ is -H, -(C₁-C₆)alkyl,
-allyl, -propargyl, -C(O) (Ci-C₆)alkoxy,
-C (O) (Ci-C₆)alkyl, or
-C (O) (Ci-C₆)alkyl- (C₃-C₈)cycloalkyl;

L is -O-(Ci-C₆)alkyl-, -(CH₂)i-6-O-(Ci-C₆)alkyl-, 
-S- (Ci-C₆)alkyl-, -(CH₂)i-6-S-(Ci-C₆)alkyl-, 
-N(R₂)2- (Ci-C₆)alkyl-, 
-CH₂)1-6-N (R₂)- (Ci-C₆)alkyl-, 
wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C₆)alkyl, -(Ci-C₆)alkoxy,
-(C₂-C₆)alkenyl,
-(C₂-C₆)alkynyl, -C(O) (Ci-C₆)alkoxy,
-C (O) (Ci-C₆)alkyl, -C(O)OH, -(Ci-C₆)alkyl-C (O) OH,
-(Ci-C₆)haloalkoxy, -(Ci-C₆)haloalkyl, -halogen,
-N(R₄R₅), -(Ci-C₆)alkyl-N (R₄R₅), or 
-C(O)N(R₄R₅), 
wherein R₂ is -H or -(Ci-C₆)alkyl, 
wherein R₄ and R₅ 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 R, R', R₂, X, X₁, X₂, n, and p are as defined in formula (I). 

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

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

B is phenyl, naphthyl, furanyl, thiieny, pyridyl, 
pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, 
isoaxazolyl, oxadiazolyl, isothiazolyl, triazolyl, 
pyrrolyl, or pyrazolyl;
**L**₂ is -N(R₈₉)-, -O-, -S-, -(C₁-C₆)alkyl -N(R₈₉)-,
- N(R₈₉)- (Cl-C₆)alkyl-,
- (C₁-C₆)alkyl-O-, -O- (C₁-C₆)alkyl- , - (C₁-C₆)alkyl-S-, or
- S- (C₁-C₆)alkyl-,

wherein R₈₉ is -H, -(Ci-C₆)alkyl,
-allyl, -propargyl, -(C(O) (Ci-C₆)alkoxy,
-C (0) (Ci-C₆)alkyl, or
-C (0) (Ci-C₆)alkyl- (C₃-C₈)cycloalkyl;

**L**₁ is -O- (Ci-C₆)alkyl-, -(CH₂)₁-6-O- (Ci-C₆)alkyl-,
-S- (Ci-C₆)alkyl-, -(CH₂)₁-6-S- (Ci-C₆)alkyl-,
-N(R₂₉)- (C₁-C₆)alkyl-,,
-(CH₂)₁-6-N (RN₂)₉- (Ci-C₆)alkyl-,

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C₆)alkyl, -(Ci-C₆)alkoxy,
-(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(R₄₉RN₈), -(Ci-C₆)alkyl-N (RN₈)₉, or
-C(O) N(R₄₉RN₈),

wherein R₂₉ is -H or -(Ci-C₆)alkyl,

wherein R₄₉ and RN₈ 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;

**R**₁ is -H, -(Ci-C₆)alkyl, benzyl, or allyl;

and R₉, RB, XI, X₂, n, and p are as defined in formula (I).

In another embodiment, the invention provides compounds of the formula (II),
and the pharmaceutically acceptable salts thereof, wherein,

\[ X_i \] is 0, 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;

\[ L_i \] is -O- (Ci-C_6) alkyl-, - (CH_2)_i-6-O- (Ci-C_6) alkyl-,

- S- (Ci-C_6) alkyl-, - (CH_2)_i-6-S- (Ci-C_6) alkyl-,

- S (O) _2- (Ci-C_6) alkyl-, - (CH_2)_i-6-S (O) _2- (Ci-C_6) alkyl-,

- N (R_{N2})- (Ci-C_6) alkyl-, - (CH_2)_i-6-N (R_{N2})- (Ci-C_6) alkyl-,

- C (0) N (R_{N2})- (Ci-C_6) alkyl-,

- (CH_2)_i-6-C (0) N (R_{N2})- (Ci-C_6) alkyl-,

- S (O) _2N (R_{N2})- (Ci-C_6) alkyl-,

- (CH_2)_i-6-S (O) _2N (R_{N2})- (Ci-C_6) alkyl-,

- N (R_{N2}) S (O) _2- (Ci-C_6) alkyl-,

- (CH_2)_i-6-N (R_{N2}) S (O) _2- (Ci-C_6) alkyl-,

- N (R_{N2}) C (O) N (R_{N3})- (Ci-C_6) alkyl-,

- (CH_2)_i-6-N (R_{N2}) C (O) N (R_{N3})- (Ci-C_6) alkyl-,

wherein the alkyl portion of each of the above is

substituted with 1, 2, 3, or 4 substituents that

are independently - (Ci-C_6) alkyl, - (Ci-C_6) alkoxy,

- (C_2-C_6) alkenyl, - (C_2-C_6) alkynyl, - C (0) (Ci-C_6) alkoxy,
-C (0) (C\textsubscript{1}-C\textsubscript{6}) alkyl, -C(O)OH, -(Ci-C\textsubscript{6}) alkyl-C (0) OH,
- (Ci-C\textsubscript{6}) haloalkoxy, - (Ci-C\textsubscript{6}) haloalkyl, -halogen,
-N(R\textsubscript{N}R\textsubscript{N}), - (Ci-C\textsubscript{6}) alkyl -N (RN\textsubscript{4}RN\textsubscript{4}), or -C (0) N (RN\textsubscript{4}RN\textsubscript{4}),
wherein R\textsubscript{N}2 and R\textsubscript{N}3 are independently -H or -(Ci-C\textsubscript{6}) alkyl,
wherein R\textsubscript{N}4 and R\textsubscript{N}5 are each independently -H,
- (Ci-C\textsubscript{6}) alkyl, - (C\textsubscript{2}-C\textsubscript{6}) alkenyl, - (C\textsubscript{2}-C\textsubscript{6}) alkynyl,
- C (0) (Ci-C\textsubscript{6}) alkoxy, - C (0) (Ci-C\textsubscript{6}) alkyl, or -C(O)H;
A is -aryl- or -heteroaryl-;
each R\textsubscript{A} is independently - (Ci-C\textsubscript{6}) alkoxy, - (Ci-C\textsubscript{6}) alkyl,
- (C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkynyl, - C (0) (Ci-C\textsubscript{6}) alkoxy,
- C (0) (Ci-C\textsubscript{6}) alkyl, -C(O)OH, -CN, - (Ci-C\textsubscript{6}) haloalkoxy,
- (Ci-C\textsubscript{6}) haloalkyl, -halogen, -OH, -NO\textsubscript{2}, -N(R\textsubscript{N}R\textsubscript{N})
, or -C (0) N (RN\textsubscript{N}RN\textsubscript{N}),
wherein R\textsubscript{N}6 and R\textsubscript{N}7 are each independently -H,
- (Ci-C\textsubscript{6}) alkyl, - (C\textsubscript{2}-C\textsubscript{6}) alkenyl, - (C\textsubscript{2}-C\textsubscript{6}) alkynyl,
- C(0) (Ci-C\textsubscript{6}) alkoxy, - C (0) (Ci-C\textsubscript{6}) alkyl, or -C(O)H;

n is 0, 1, 2, 3, or 4;
R\textsubscript{3} is -H, - (Ci-C\textsubscript{6}) alkyl, -allyl, -propargyl, -C(O) (Ci-C\textsubscript{6}) alkoxy,
- C(0) (Ci-C\textsubscript{6}) alkyl, or -C (0) (Ci-C\textsubscript{6}) alkyl- (C\textsubscript{3}-C\textsubscript{8}) cycloalkyl;
B is aryl- or heteroaryl-;
each R\textsubscript{B} is independently - (Ci-C\textsubscript{6}) alkoxy, - (Ci-C\textsubscript{6}) alkyl,
- (C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkynyl, - C (0) (Ci-C\textsubscript{6}) alkoxy,
- C (0) (Ci-C\textsubscript{6}) alkyl, -C(O)OH, -CN, - (Ci-C\textsubscript{6}) haloalkoxy,
- (Ci-C\textsubscript{6}) haloalkyl, -halogen, -OH, -NO\textsubscript{2}, -N(R\textsubscript{N}R\textsubscript{N})
, or -C (0) N (RN\textsubscript{N}RN\textsubscript{N}),
wherein R\textsubscript{N}9 and R\textsubscript{N}10 are each independently -H,
- (Ci-C\textsubscript{6}) alkyl, - (C\textsubscript{2}-C\textsubscript{6}) alkenyl, - (C\textsubscript{2}-C\textsubscript{6}) alkynyl,
- C(0) (Ci-C\textsubscript{6}) alkoxy, - C (0) (Ci-C\textsubscript{6}) alkyl, or -C(O)H; and

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

In another embodiment, the invention provides compounds of
formula (II), wherein,
A is phenyl, naphthyl, furanyl, thieryl, pyridyl,
pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl,
and B, Li, R_A, R_B, R_i, R_3, X_i, X_2, n, and p are as defined in formula (II).

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

A is phenyl, naphthyl, furanyl, thiényl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
B is phenyl, naphthyl, furanyl, thiényl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
and Li, R_A, R_B, R_i, R_3, X_i, X_2, n, and p are as defined in formula (II).

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

A is phenyl, naphthyl, furanyl, thiényl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
B is phenyl, naphthyl, furanyl, thiényl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;
Li is -O-(Ci-C_6)alkyl-, -O-(CH_2)_1-6-O-(Ci-C_6)alkyl-, -S-(Ci-C_6)alkyl-, -O-(CH_2)_1-6-S-(Ci-C_6)alkyl-, -N(R_N_2)-(Ci-C_6)alkyl-, -N(R_N_2)_2-(Ci-C_6)alkyl-, wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that
are independently -(C\textsubscript{2}-C\textsubscript{6}) alkyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl,
-(C\textsubscript{2}-C\textsubscript{6}) alkynyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-(C\textsubscript{2}-C\textsubscript{6}) alkenyl, -(C\textsubscript{2}-C\textsubscript{6}) alkoxy,
-(C\textsubscript{6}) alkyl, -(C\textsubscript{6}) alkoxy,
-C(O) (Ci-C₆)alkyl, -C(O)OH, - (Ci-C₆)alkyl-C (0) OH,
- (Ci-C₆)haloalkoxy, - (Ci-C₆)haloalkyl, -halogen,
-N(R₉₄R₉₅), - (Ci-C₆)alkyl-N (RN₄RN₅), or
-C(O)N(R₉₄R₉₅),

wherein R₉₂ is -H or - (Ci-C₆)alkyl,
wherein R₉₄ and R₉₅ 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;
Rᵢ is -H, - (Ci-C₆)alkyl, benzyl, or allyl;
and Rₐ, Rₐ, R₃, X₁, X₂, n, and p are as defined in formula (II).

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

and the pharmaceutically acceptable salts thereof, wherein,
X₁ is O, S, or N(R₉₁),

wherein R₉₁ is -H or - (Ci-C₆)alkyl;
X₂ is CH or N;
Rᵢ is -H, - (Ci-C₆)alkyl, - (Ci-C₆)alkyl-phenyl, or
- (C₃-C₆)alkenyl;
Lᵢ is -0- (Ci-C₆)alkyl-, - (CH₂)ᵢ₋₆-0- (Ci-C₆)alkyl-,
-S- (Ci-C₆)alkyl-, - (CH₂)ᵢ₋₆-S- (Ci-C₆)alkyl-,
-S (0) _₂- (Ci-C₆)alkyl-, - (CH₂)ᵢ₋₆-S (0) _₂- (Ci-C₆)alkyl-,
-N (R₉₂)- (Ci-C₆)alkyl-, - (CH₂)ᵢ₋₆-N (R₉₂)- (Ci-C₆)alkyl-,
-N (R₉₂)C (0) - (Ci-C₆)alkyl-,
- (CH₂)ᵢ₋₆-N (R₉₂)C (0) - (Ci-C₆)alkyl-,
-C(O)N(R₉₂) - (Ci-C₆)alkyl-,
- (CH₂)ᵢ₋₆-C (O)N (R₉₂) - (Ci-C₆)alkyl-,

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- S(O)₂N(R₁) - (C₁-C₆)alkyl-,  
- (CH₂)ₙ₋₆S(O)₂N(Rn₂) - (C₁-C₆)alkyl-,  
- N(Rn₂)S(0)₂ - (C₁-C₆)alkyl-,  
- (CH₂)ₙ₋₆N(Rn₂)S(0)₂ - (C₁-C₆)alkyl-,  
- N(Rn₂)C(0)₀ - (C₁-C₆)alkyl-,  
- (CH₂)ₙ₋₆N(Rn₂)C(0)₀ - (C₁-C₆)alkyl-,  
- N(Rn₂)S(0)₂N(Rn₃) - (C₁-C₆)alkyl-,  
- N(Rn₂)C(0)₀N(Rn₃) - (C₁-C₆)alkyl-, or  
- (CH₂)ₙ₋₆N(Rn₂)C(0)₀N(Rn₃) - (C₁-C₆)alkyl-,  

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (C₁-C₆)alkyl, -(C₁-C₆)alkoxy,  
- (C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -C(0)ₙ(C₁-C₆)alkoxy,  
- C(0)(C₁-C₆)alkyl, -C(O)OH, -(C₁-C₆)alkyl-C(0)OH,  
- (C₁-C₆)haloalkoxy, -(C₁-C₆)haloalkyl, -halogen,  
- N(R₄R₅), -(C₁-C₆)alkyl-N(R₄R₅), or -C(0)ₙN(R₄R₅),  

wherein Rn₂ and Rn₃ are independently -H or  
-(C₁-C₆)alkyl,  

wherein R₄ and R₅ are each independently -H,  
- (C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,  
- C(0)(C₁-C₆)alkoxy, -(C₁-C₆)alkyl, or -(C₁-C₆)alkoxy,  

A is -aryl- or -heteroaryl-;  
each Rₐ is independently - (C₁-C₆)alkoxy, -(C₁-C₆)alkyl,  
- (C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₆)alkoxy,  
- C(0)(C₁-C₆)alkyl, -C(O)OH, -CN, -(C₁-C₆)haloalkoxy,  
- (C₁-C₆)haloalkyl, -halogen, -OH, -NO₂, -N(R₆R₇),  
- (C₁-C₆)alkyl-N(R₄R₅), or -C(O)ₙN(R₄R₅),  

wherein R₆ and R₇ are each independently -H,  
- (C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,  
- C(0)(C₁-C₆)alkoxy, -(C₁-C₆)alkyl, or -(C₁-C₆)alkoxy,  
n is 0, 1, 2, 3, or 4;
R$_3$ is -H, -(Ci-C$_6$)alkyl, -allyl, -propargyl, -C (O) (C$_1$-C$_6$)alkoxy, -C(O) (Ci-C$_6$)alkyl, or -C(O) (C$_1$-C$_6$)BikYl-(C$_3$-C$_8$)CylClOaIkYl; and R$_B$ is -(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$_N$S)R$_{N^0}$, 
- (Ci-C$_6$)alkyl -N (R$_N$S)R$_{N^0}$, or - C (O) N (R$_N$S)R$_{N^0}$, 
wherein R$_N$S and R$_N$S 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.

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

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

and Li, R$_A$, R$_B$, R$_i$, R$_3$, X$_1$, X$_2$, and n are as defined in formula (III).

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

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

Li is -O-(Ci-C$_6$)alkyl-, -(CH$_2$)$_{1-6}$-O-(Ci-C$_6$)alkyl-, 
-S-(Ci-C$_6$)alkyl-, -(CH$_2$)$_{1-6}$-S-(Ci-C$_6$)alkyl-, 
-N(R$_H$)$_2$-(Ci-C$_6$)alkyl-, 
-(CH$_2$)$_{1-6}$-N (R$_H$)$_2$-(Ci-C$_6$)alkyl-,

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently -(Ci-C$_6$)alkyl, -(Ci-C$_6$)alkoxy, 
- (C$_2$-C$_6$)alkenyl, 
- (C$_2$-C$_6$)alkynyl, -C(O) (Ci-C$_6$)alkoxy,
-C(O) (Ci-C₆)alkyl, -C(O)OH, -(Ci-C₆)alkyl-C (0) OH, 
-(Ci-C₆)haloalkoxy, -(Ci-C₆)haloalkyl, -halogen, 
-N(R₄R₅), -(Ci-C₆)alkyl-N (RN₄RN₅), or
-C(O)N(R₄R₅),

wherein R₂ is -H or -(Ci-C₆)alkyl,

wherein R₄ and RN₅ are each independently -H, 
-(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, 
-(C₂-C₆)alkynyl, 
-C(O) (Ci-C₆)alkoxy, -C(O) (Ci-C₆)alkyl, or
-C(O)H;

and R₆, R₇, R₈, X₁, X₂, and n are as defined in formula (III).

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

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

L is -O- (Ci-C₆)alkyl-, -(CH₂)ᵢ₋₁₋₆₋O- (Ci-C₆)alkyl-, 
-S- (Ci-C₆)alkyl-, -(CH₂)ᵢ₋₁₋₆₋S- (Ci-C₆)alkyl-, 
-N(R₄) - (C₁-C₆)alkyl-, 
-(CH₂)₁₋₆₋N (RN₅) - (Ci-C₆)alkyl-,

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C₆)alkyl, -(Ci-C₆)alkoxy, 
-(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(R₄RN₅), -(Ci-C₆)alkyl-N (RN₄RN₅), or
-C(O)N(R₄RN₅),

wherein R₅ is -H or -(Ci-C₆)alkyl,

wherein R₄ and R₅ are each independently -H,
In another embodiment, the invention provides compounds of formula (III), wherein, 

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

Ri is -H, -(Ci-C₆)alkyl, benzyl, or allyl; 

and Rₐ, Rᵢ, R₃, X₁, X₂, and n are as defined in formula (III).

In another embodiment, the invention provides compounds of the formula (IV),
and the pharmaceutically acceptable salts thereof, wherein,

R1 is -H, -(C1-C6)alkyl, -(C1-C6)alkyl-phenyl, or
- (C3-C6)alkenyl;

L1 is -0- (C1-C6)alkyl-, -(CH2)1-6-0- (C1-C6)alkyl-, -S- (C1-C6)alkyl-, -(CH2)1-6-S- (C1-C6)alkyl-, -S (O)2- (C1-C6)alkyl-, -(CH2)1-6-S (O)2- (C1-C6)alkyl-, -N (R1R2) - (C1-C6)alkyl-, -(CH2)1-6-N (R1R2) - (C1-C6)alkyl-, -N (R1R2) C (O) - (C1-C6)alkyl-, -(CH2)1-6-N (R1R2) C (O) - (C1-C6)alkyl-, -C(O)N (R1R2) - (C1-C6)alkyl-, -(CH2)1-6-C (O) N (R1R2) - (C1-C6)alkyl-, -S (O)2 N (R1R2) - (C1-C6)alkyl-, -(CH2)1-6-S (O)2N (R1R2) - (C1-C6)alkyl-, -N (R1R2) S (O)2- (C1-C6)alkyl-, -(CH2)1-6-N (R1R2) S (O)2- (C1-C6)alkyl-, -N (R1R2) C (O) O- (C1-C6)alkyl-, -(CH2)1-6-N (R1R2) C (O) O- (C1-C6)alkyl-, -N (R1R2) S (O)2N (R1R2) - (C1-C6)alkyl-, -(CH2)1-6-N (R1R2) S (O)2N (R1R2) - (C1-C6)alkyl-, -N (R1R2) C (O) N (R1R2) - (C1-C6)alkyl-, or
- (CH2)1-6-N (R1R2) C (O)N (R1R2) - (C1-C6)alkyl-, wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (C1-C6)alkyl, - (C1-C6)alkoxy,
- (C2-C6)alkenyl, - (C2-C6)alkynyl, -C (O) (C1-C6)alkoxy,
- C (O) (C1-C6)alkyl, -C(O)OH, - (C1-C6)alkyl-C (O) OH,
- (C1-C6)haloalkoxy, - (C1-C6)haloalkyl, -halogen,
- N (R4R5), - (C1-C6)alkyl-N (R4R5), or -C (O) N (R4R5), wherein R1R2 and R1R3 are independently -H or
- (C$_1$-C$_6$) alkyl,
wherein $R_{N4}$ and $R_{N5}$ are each independently $-H$,
- (C$_1$-C$_6$) alkenyl, - (C$_2$-C$_6$) alkynyl,
- C (0) (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 (0) (Ci-C$_6$) alkyl, - C(O)OH, - CN, - (Ci-C$_6$) haloalkoxy,
- (Ci-C$_6$) haloalkyl, - halogen, - OH, - NO$_2$, - N(R$_{N6}$R$_{N7}$),
- (Ci-C$_6$) alkyl-N(R$_{N6}$), or - C (0) 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, - C (0) (Ci-C$_6$) alkyl, or - C(O)H;
n is 0, 1, 2, 3, or 4;
$R_3$ is - H, - (Ci-C$_6$) alkyl, - allyl, - propargyl, - C (0) (Ci-C$_6$) alkoxy,
- C (0) (Ci-C$_6$) alkyl, or - C (0) (Ci-C$_6$) alkyl- (C$_3$-C$_8$) cycloalkyl; and
$R_8$ is - (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$_{N9}$R$_{N10}$),
- (Ci-C$_6$) alkyl-N(R$_{N9}$), or - C (0) N (R$_{N9}$R$_{N10}$),
wherein $R_{N9}$ and $R_{N10}$ 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.
In another embodiment, the invention provides compounds of
formula (IV), wherein,
A is phenyl, naphthyl, furanyl, thieryl, pyridyl,
pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl,
isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl,
pyrrolyl, or pyrazolyl,
and Li, $R_A$, $R_8$, RI, R3, and n are as defined in formula (IV).
In another embodiment, the invention provides compounds of
formula (IV), wherein,
A is phenyl, naphthyl, furanyl, thieryl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl;

Li is -0- (Ci-C₆)alkyl-, - (CH₂)ⁿ⁻₀- (Ci-C₆)alkyl-, -S- (Ci-C₆)alkyl-, - (CH₂)ⁿ⁻S- (Ci-C₆)alkyl-, -N (R₄₂) - (Ci-C₆)alkyl-, - (CH₂)ⁿ⁻N (R₄₂) - (Ci-C₆)alkyl-,

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C₆)alkyl, - (Ci-C₆)alkoxy, - (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 (R₄₄R₅₅), - (Ci-C₆)alkyl -N (RN₄RN₅), or -C(O)N (RN₄RN₅),

wherein R₄₂ is -H or - (Ci-C₆)alkyl,

wherein R₄₄ and R₅₅ 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, R₉®, R₁, R₃, and n are as defined in formula (IV).

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

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

Li is -0- (Ci-C₆)alkyl-, - (CH₂)ⁿ⁻₀- (Ci-C₆)alkyl-, -S- (Ci-C₆)alkyl-, - (CH₂)ⁿ⁻S- (Ci-C₆)alkyl-, -N (R₄₂) - (Ci-C₆)alkyl-, -
wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (C2-C6) alkyl, - (C2-C6) alkoxy, - (C2-C6) alkenyl, - (C2-C6) alkynyl, - C(O) (C2-C6) alkoxy, - C(O) (C2-C6) alkyl, - C(O) (C2-C6) alkyl-C(O)OH, - (C2-C6) halogen, -N(R4R5), - (C2-C6) alkyl -N(R4R5), or -C(O)N(R4R5), wherein R2 is -H or - (C2-C6) alkyl, wherein R4 and R5 are each independently -H, - (C2-C6) alkyl, - (C2-C6) alkenyl, - (C2-C6) alkynyl, - C(O) (C2-C6) alkoxy, - C(O) (C2-C6) alkyl, or -C(O)H; 

R1 is -H, - (C2-C6) alkyl, benzyl, or allyl; and R4, RB, R3, and n are as defined in formula (IV).

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

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

R1 is -H, - (C2-C6) alkyl, benzyl, or allyl;

L1 is - (CH2)1-6-0- (C2-C6) alkyl- or - (CH2)1-6-S- (C2-C6) alkyl-, wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (C2-C6) alkyl, - (C2-C6) alkoxy, - (C2-C6) alkenyl, - (C2-C6) alkynyl, - C(O) (C2-C6) alkoxy, - C(O) (C2-C6) alkyl, - C(O) (C2-C6) alkyl-C(O)OH, - (C2-C6) alkyl-C(O)OH,
- (Ci-C₆)haloalkoxy,  - (Ci-C₆)haloalkyl,  -halogen,
-N(R₄R₅),  - (Ci-C₆)alkyl-N (R₄R₅), or
-C(O)N(R₄R₅),
wherein  R₄  and  R₅  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  R₆,  R₇,  R₈,  and  n  are as defined in formula  (IV).

In another embodiment, the invention provides compounds of
formula  (IV), wherein,  A  is phenyl, and  L₁,  R₆,  R₇,  R₈,  R₉,  R₁₀, and
n  are as defined in formula  (IV).

In another embodiment, the invention provides compounds of
formula  (IV), wherein,
A  is phenyl;
L₁ is  -0- (Ci-C₆)alkyl-,  - (CH₂)₁₋₆₋₀- (Ci-C₆)alkyl-,  
- (Ci-C₆)alkyl-,  - (CH₂)₁₋₆₋₀- (Ci-C₆)alkyl-,  
-N (R₆₂) - (Ci-C₆)alkyl-,  
-CH₂)₁₋₆₋₀- (R₆₂) - (Ci-C₆)alkyl-
wherein the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that
are independently  - (Ci-C₆)alkyl,  - (Ci-C₆)alkoxy,
- (C₂-C₆)alkenyl,
- (C₂-C₆)alkynyl,  -C(O) (Ci-C₆)alkoxy,
-C(O) (Ci-C₆)alkyl,  -C(O)OH,  - (Ci-C₆)alkyl-C (O) OH,
- (Ci-C₆)haloalkoxy,  - (Ci-C₆)haloalkyl,  -halogen,
-N(R₄₅R₅),  - (Ci-C₆)alkyl-N (R₄₅R₅), or
-C(O)N(R₄₅R₅),
wherein  R₆₂  is  -H  or  - (Ci-C₆)alkyl,
wherein  R₄  and  R₅  are each independently  -H,
- (Ci-C₆)alkyl,  - (C₂-C₆)alkenyl,
- (C₂-C₆)alkynyl,
-C(O) (Ci-C₆)alkoxy,  -C(O) (Ci-C₆)alkyl, or
and $R_A$, $R_B$, $R_1$, $R_3$, and $n$ are as defined in formula (IV).

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

A is phenyl;

$L_1$ is $-O-(C_1-C_6)alkyl-$, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl-$, $-S-(C_1-C_6)alkyl-$, $-(CH_2)_{1-6}-S-(C_1-C_6)alkyl-$, $-N(R_{N2})-(C_1-C_6)alkyl-$, $-(CH_2)_{1-6}-N(R_{N2})-(C_1-C_6)alkyl-$, where the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkoxy$, $-(C_1-C_6)alkyl$, $-(C_1-C_6)haloalkoxy$, $-(C_1-C_6)alkyl$, or $-(C_1-C_6)haloalkyl$, $-halogen$, $-N(R_{N4}R_{N5})$, or $-(C_1-C_6)alkyl-N(R_{N4}R_{N5})$, or $-C(O)N(R_{N4}R_{N5})$, wherein $R_{N2}$ is $-H$ or $-(C_1-C_6)alkyl$, wherein $R_{N4}$ and $R_{N5}$ are each independently $-H$, $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_1-C_6)alkoxy$, or $-C(O)H$;

$L_1$ is $-H$, $-(C_1-C_6)alkyl$, benzyl, or allyl;

and $R_A$, $R_B$, $R_3$, and $n$ are as defined in formula (IV).

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

A is phenyl;

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

$L_1$ is $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl-$ or $-(CH_2)_{1-6}-S-(C_1-C_6)alkyl-$, where the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that are independently - (C₁-C₆)alkyl, - (C₁-C₆)alkoxy,
- (C₂-C₆)alkenyl,
- (C₂-C₆)alkynyl, -C(O) (C₁-C₆)alkoxy,
-C(O) (C₁-C₆)alkyl, -C(O)OH, - (C₁-C₆)alkyl-C(O)OH,
- (C₁-C₆)haloalkoxy, - (C₁-C₆)haloalkyl, -halogen,
-N(R₄N₅), - (C₁-C₆)alkyl-N(R₄N₅), or
-C(O)N(R₄N₅),

wherein R₄ and R₅ are each independently -H, 
- (C₁-C₆)alkyl, - (C₂-C₆)alkenyl,
- (C₂-C₆)alkynyl,
-C(O) (C₁-C₆)alkoxy, -C(O)H, 
and R₆, R₇, and n are as defined in formula (IV).

In another embodiment, the invention provides compounds of the formula (V) or (VI),

and the pharmaceutically acceptable salts thereof, wherein, 
Rᵢ is -H, - (C₁-C₆)alkyl, - (C₁-C₆)alkyl-phenyl, or
- (C₃-C₆)alkenyl;
Lᵢ is -O- (C₁-C₆)alkyl-, - (CH₂)₁₋₆-O- (C₁-C₆)alkyl-, 
-S- (C₁-C₆)alkyl-, - (CH₂)₁₋₆-S- (C₁-C₆)alkyl-, 
-S (O)₂ (C₁-C₆)alkyl-, - (CH₂)₁₋₆-S (O)₂ (C₁-C₆)alkyl-, 
-N (R₃N₄) - (C₁-C₆)alkyl-, - (CH₂)₁₋₆-N (R₃N₄) - (C₁-C₆)alkyl-, 
-N (R₃N₄) C (O) - (C₁-C₆)alkyl-, 
- (CH₂)₁₋₆-N (R₃N₄) C (O) - (C₁-C₆)alkyl-, 
-C (O)N (R₃N₄) - (C₁-C₆)alkyl-, 
- (CH₂)₁₋₆-C (O)N (R₃N₄) - (C₁-C₆)alkyl-, 

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- S(O)$_2$N(R$_{n2}$) - (C$_1$-C$_6$)alkyl-
- (CH$_2$)$_{6}$- S(O)$_2$N(R$_{n2}$) - (C$_1$-C$_6$)alkyl-
- N(R$_{n2}$) S(0)$_2$- (C$_1$-C$_6$)alkyl-
- (CH$_2$)$_{6}$- N(R$_{n2}$) S(0)$_2$- (C$_1$-C$_6$)alkyl-
- N(R$_{n2}$) C(0) 0- (C$_1$-C$_6$)alkyl-
- (CH$_2$)$_{6}$- N(R$_{n2}$) C(0) 0- (C$_1$-C$_6$)alkyl-
- N(R$_{n2}$) S(0)$_2$N(R$_{n3}$) - (C$_1$-C$_6$)alkyl-
- (CH$_2$)$_{6}$- N(R$_{n2}$) S(0)$_2$N(R$_{n3}$) - (C$_1$-C$_6$)alkyl-
- N(R$_{n2}$) C(0) N(R$_{n3}$) - (C$_1$-C$_6$)alkyl-
- (CH$_2$)$_{6}$- N(R$_{n2}$) C(0) N(R$_{n3}$) - (C$_1$-C$_6$)alkyl-

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently -(C$_1$-C$_6$)alkyl, -(C$_1$-C$_6$)alkeny,l -(C$_1$-C$_6$)alkynyl, -(C$_1$-C$_6$)alkoxy,
-(C$_1$-C$_6$)alkyl, -(C$_1$-C$_6$)alkyl-C(0)OH, -(C$_1$-C$_6$)alkyl-C(0)OH,
-(C$_1$-C$_6$)haloalkoxy, -(C$_1$-C$_6$)haloalkyl, -halogen,
-N(R$_{n4}$R$_{n5}$), -(C$_1$-C$_6$)alkyl-N (R$_{n4}$R$_{n5}$), or -(C$_0$) N (R$_{n4}$R$_{n5}$),
wherein R$_{n2}$ and R$_{n3}$ are independently -H or
-(C$_1$-C$_6$)alkyl,
wherein R$_{n4}$ and R$_{n5}$ are each independently -H,
-(C$_1$-C$_6$)alkyl, -(C$_2$-C$_6$)alkeny,l, -(C$_2$-C$_6$)alkynyl,
-(C$_0$) (C$_1$-C$_6$)alkoxy, -(C$_0$) (C$_1$-C$_6$)alkyl, or -(C$_0$)OH;
each R$_A$ is independently -(C$_1$-C$_6$)alkoxy, -(C$_1$-C$_6$)alkyl,
-(C$_2$-C$_6$)alkeny,l, -(C$_2$-C$_6$)alkynyl, -(C$_0$) (C$_1$-C$_6$)alkoxy,
-(C$_0$) (C$_1$-C$_6$)alkyl, -(C$_0$)OH, -CN, -(C$_1$-C$_6$)haloalkoxy,
-(C$_1$-C$_6$)haloalkyl, -halogen, -OH, -NO$_2$, -N(R$_{n6}$R$_{n7}$),
-(C$_1$-C$_6$)alkyl-N (R$_{n6}$R$_{n7}$), or -(C$_0$)N (R$_{n6}$R$_{n7}$),
wherein R$_{n6}$ and R$_{n7}$ are each independently -H,
-(C$_1$-C$_6$)alkyl, -(C$_2$-C$_6$)alkeny,l, -(C$_2$-C$_6$)alkynyl,
-(C$_0$) (C$_1$-C$_6$)alkoxy, -(C$_0$) (C$_1$-C$_6$)alkyl, or -(C$_0$)OH;
n is 0, 1, 2, 3, or 4;
R$_3$ is -H, -(C$_1$-C$_6$)alkyl, -allyl, -propargyl, -(C$_0$) (C$_1$-C$_6$)alkoxy,
-(C$_0$) (C$_1$-C$_6$)alkyl, or -(C$_0$) (C$_1$-C$_6$)alkyl- (C$_3$-C$_8$)cycloalkyl; and
Rb is \(-\text{(Ci-C}_6\text{)}\)alkoxy, \(-\text{(Ci-C}_6\text{)}\)alkyl, \(-\text{(C}_2\text{C}_6\text{)}\)alkenyl, \(-\text{(C}_2\text{C}_6\text{)}\)alkynyl, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkoxy, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkyl, \(-\text{C}(\text{O})\) \text{OH}, \(-\text{CN}\), \(-\text{(Ci-C}_6\text{)}\)haloalkoxy, \(-\text{(Ci-C}_6\text{)}\)haloalkyl, \(-\text{halogen}\), \(-\text{OH}\), \(-\text{NO}_2\), \(-\text{N}(\text{R}_9\text{R}_\text{i}0)\), \(-\text{(Ci-C}_6\text{)}\)alkyl-N \(\text{(R}_3\text{R}_4\text{R}_5\text{)}\), or \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkyl, or \(-\text{C}(\text{O})\) \text{H}.

In another embodiment, the invention provides compounds of formula (V) or (VI), wherein,

Li is \(\text{0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{(CH}_2\text{)}\text{i}_\text{o-0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{S-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{(CH}_2\text{)}\text{i-6-0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{-N(\text{R}_2\text{)}}\) \text{(C}_1\text{-C}_6\text{)}\)alkyl-, \(\text{-N(\text{R}_2\text{)}}\) \text{1-6-N(\text{R}_2\text{)}}\) \text{(Ci-C}_6\text{)}\)alkyl-, wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently \(-\text{(Ci-C}_6\text{)}\)alkyl, \(-\text{(Ci-C}_6\text{)}\)alkoxy, \(-\text{C}(\text{C}_2\text{C}_6\text{)}\)alkenyl, \(-\text{(C}_2\text{C}_6\text{)}\)alkynyl, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkoxy, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkyl, \(-\text{C}(\text{O})\) \text{OH}, \(-\text{(Ci-C}_6\text{)}\)alkyl-C \text{(0) OH}, \(-\text{(Ci-C}_6\text{)}\)haloalkoxy, \(-\text{(Ci-C}_6\text{)}\)haloalkyl, \(-\text{halogen}, \text{-N(\text{R}_4\text{R}_5\text{)}}\), \(-\text{(Ci-C}_6\text{)}\)alkyl-N \(\text{(R}_4\text{R}_5\text{)}\), or \(-\text{C}(\text{O})\) \text{N(\text{R}_4\text{R}_5\text{)}}\), wherein \(\text{R}_2\) is \(-\text{H}\) or \(-\text{(Ci-C}_6\text{)}\)alkyl, wherein \(\text{R}_4\) and \(\text{R}_5\) are each independently \(-\text{H}\), \(-\text{(Ci-C}_5\text{)}\)alkyl, \(-\text{(C}_2\text{C}_6\text{)}\)alkenyl, \(-\text{(C}_2\text{C}_6\text{)}\)alkynyl, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkoxy, \(-\text{C}(\text{O})\) \text{(Ci-C}_6\text{)}\)alkyl, or \(-\text{C}(\text{O})\) \text{H}; and \(\text{R}_\text{A}, R\text{b}, R\text{i}, R\text{3}, \text{and n are as defined in formula (VI).}

In another embodiment, the invention provides compounds of formula (V) or (VI), wherein,

Li is \(\text{0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{(CH}_2\text{)}\text{i-6-0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{S-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{(CH}_2\text{)}\text{i-6-0-}\) \text{(Ci-C}_6\text{)}\)alkyl-, \(\text{-N(\text{R}_2\text{)}}\) \text{(Ci-C}_6\text{)}\)alkyl-,
- (CH$_2$)$_1$-6-N(R$_{N2}$)- (C$_i$-C$_6$) alkyl-

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C$_6$) alkyl, - (Ci-C$_6$) alkoxy, - (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 (O) OH, - (Ci-C$_6$) haloalkoxy, - (Ci-C$_6$) haloalkyl, - halogen, -N(R$_{N4}$R$_{N5}$), - (Ci-C$_6$) alkyl -N (RN$_{N4}$RN$_{N5}$), or - C(O)N (R$_{N4}$R$_{N5}$),

wherein R$_{N2}$ is -H or - (Ci-C$_6$) alkyl, wherein R$_{N4}$ and R$_{N5}$ 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;

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

and R$_A$, RB, R3, and n are as defined in formula (VI).

In another embodiment, the invention provides compounds of formula (V) or (VI), wherein,

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

L$_i$ is - (CH$_2$)$_i$-6-O- (Ci-C$_6$) alkyl- or - (CH$_2$)$_1$-6-S- (Ci-C$_6$) alkyl-,

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (Ci-C$_6$) alkyl, - (Ci-C$_6$) alkoxy, - (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 (O) OH, - (Ci-C$_6$) haloalkoxy, - (Ci-C$_6$) haloalkyl, - halogen, -N(R$_{N4}$R$_{N5}$), - (Ci-C$_6$) alkyl -N (RN$_{N4}$RN$_{N5}$), or - C(O)N (R$_{N4}$R$_{N5}$),

wherein R$_{N4}$ and R$_{N5}$ 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, Rₜ, R₃, and n are as defined in formula (VI).

In another embodiment, the invention provides compounds of
formula (V) or (VI), wherein,

Rᵢ is -H, - (Ci-C₆) alkyl, benzyl, or allyl;
Lᵢ is - (CH₂)₁⁻⁶-S- (Ci-C₆) alkyl-,
wherein the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that
are independently - (Ci-C₆) alkyl, - (Ci-C₆) alkoxy,
allyl, propargyl, -C(O) (Ci-C₆) alkoxy,
acetyl, -halogen, or -N(R₄R₅),
wherein R₄ and R₅ are each independently -H,
- (Ci-C₆) alkyl, allyl, propargyl
-C(O) (Ci-C₆) alkoxy, or acetyl;

and Rₐ, Rₜ, R₃, and n are as defined in formula (VI).

In another embodiment, the invention provides compounds of
formula (V) or (VI), wherein,

Rᵢ is -H, - (Ci-C₆) alkyl, benzyl, or allyl;
Lᵢ is - (CH₂)₁⁻⁶-S- (Ci-C₆) alkyl-,
wherein the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that
are independently - (Ci-C₆) alkyl, - (Ci-C₆) alkoxy,
allyl, propargyl, -C(O) (Ci-C₆) alkoxy,
acetyl, -halogen, or -N(R₄R₅),
wherein R₄ and R₅ are each independently -H,
- (Ci-C₆) alkyl, allyl, propargyl
-C(O) (Ci-C₆) alkoxy, or acetyl;

R₃ is -H or - (Ci-C₆) alkyl;

and Rₐ, Rₜ, and n are as defined in formula (VI).
In another embodiment, the invention provides compounds of formula (V) or (VI), wherein,

- $R_i$ is $-H$, $-(\text{Ci-C}_6)\text{alkyl}$, benzyl, or allyl;
- $L_i$ is $-(\text{CH}_2)\text{1-6-S-}(\text{Ci-C}_6)\text{alkyl-}$,
  wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently $-(\text{Ci-C}_6)\text{alkyl}$, $-(\text{Ci-C}_6)\text{alkoxy}$, allyl, propargyl, $-\text{C(O)}(\text{Ci-C}_6)\text{alkoxy}$, acetyl, $-\text{halogen}$, or $-\text{N}(\text{R}_{N4}\text{R}_{N5})$,
  wherein $\text{R}_{N4}$ and $\text{R}_{N5}$ are each independently $-H$, $-(\text{Ci-C}_6)\text{alkyl}$, allyl, propargyl $-\text{C(O)}(\text{C}_1-\text{C}_6)\text{alkoxy}$, or acetyl;
- $R_3$ is $-H$ or $-(\text{Ci-C}_6)\text{alkyl}$;
- $R_B$ is $-(\text{Ci-C}_6)\text{alkyl}$;

and $R_A$ and $n$ are as defined in formula (VI).

In another embodiment, the invention provides compounds of formula (V) or (VI), wherein,

- $L_i$ is $-(\text{CH}_2)\text{1-6-S-}(\text{Ci-C}_6)\text{alkyl-}$,
  wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently $-(\text{Ci-C}_6)\text{alkyl}$, $-(\text{Ci-C}_6)\text{alkoxy}$, allyl, propargyl, $-\text{C(O)}(\text{Ci-C}_6)\text{alkoxy}$, acetyl, $-\text{halogen}$, or $-\text{N}(\text{R}_{N4}\text{R}_{N5})$,
  wherein $\text{R}_{N4}$ and $\text{R}_{N5}$ are each independently $-H$, $-(\text{Ci-C}_6)\text{alkyl}$, allyl, propargyl $-\text{C(O)}(\text{Ci-C}_6)\text{alkoxy}$, or acetyl;
- $R_3$ is $-H$ or $-(\text{Ci-C}_6)\text{alkyl}$;
- $R_B$ is $-(\text{Ci-C}_6)\text{alkyl}$;
- $R_i$ is $H$;

and $R_A$ and $n$ are as defined in formula (VI).

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 method 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-effective 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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Method to</th>
<th>Example Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin Converting Enzyme (ACE)</td>
<td>1. Improve cardiovascular risk profile</td>
<td>quinapril, ramipril, verapamil, captopril, diltiazem, clonidine,</td>
</tr>
<tr>
<td>inhibitors</td>
<td>2. Reduce risk factors for heart disease, stroke, or heart attack</td>
<td>hydrochlorothiazide, benazepril, prazosin, fosinopril, lisinopril,</td>
</tr>
<tr>
<td></td>
<td>3. Reduce hyperlipidemia</td>
<td>atenolol, enalapril, perindopril, perindopril tert-butyamine,</td>
</tr>
<tr>
<td></td>
<td>4. Decrease low density lipoprotein (LDL) blood levels</td>
<td>trandolapril, moexipril</td>
</tr>
<tr>
<td></td>
<td>5. Increase high density lipoprotein (HDL) blood levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Inhibit, prevent or reduce atherosclerosis and reduce the risk factors thereof</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Decrease free fatty acid blood levels and triglyceride levels</td>
<td></td>
</tr>
<tr>
<td>Biguanide agents and, (optional) Sulfonlurea agents</td>
<td>1. Treat type II diabetes or Syndrome X</td>
<td>glyburide, glyburide, glipizide, glimepiride, chlorpropamide,</td>
</tr>
<tr>
<td></td>
<td>2. Treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia</td>
<td>tolbutamide, tolazamide</td>
</tr>
<tr>
<td></td>
<td>3. Modulate blood glucose levels</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>1. Improve cardiovascular risk profile</td>
<td>Miglitol, acarbose</td>
</tr>
<tr>
<td><strong>Sulfonylurea agent</strong></td>
<td><strong>Thiazolidinedione agents</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>1. Improve cardiovascular risk profile</td>
<td>1. Treat, inhibit, or maintenance of Syndrome X or type II diabetes</td>
<td></td>
</tr>
<tr>
<td>2. Reduce risk factors in such patients for heart disease, stroke or heart attack</td>
<td>2. Treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>3. Reduce hyperlipidemia</td>
<td>3. Modulate blood glucose levels</td>
<td></td>
</tr>
<tr>
<td>4. Decrease low density lipoprotein (LDL) blood levels, high density lipoprotein (HDL) blood levels, and overall blood lipoprotein levels</td>
<td>glipizide, glyburide (glibenclamide), chlorpropamide, tolbutamide, tolazamide, glimepiride</td>
<td></td>
</tr>
<tr>
<td>5. Inhibit, prevent or reduce atherosclerosis or the risk factors thereof</td>
<td>Pioglitizone, rosiglitazone</td>
<td></td>
</tr>
<tr>
<td>6. Decrease free fatty acid blood levels and triglyceride levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 lipoprotein (HDL) blood levels
6. Inhibit, prevent, or reduce atherosclerosis or the risk factors
7. Decrease free fatty acid blood levels and triglyceride levels
| 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  
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 | Bile acid sequestrants (colestipol and colesvelam), fibric acid derivatives (clifofibrate, gemfibrozil and fenofibrate), HMG-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 | Naturally occurring and synthetic |
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 insulin products 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-butandiol. 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 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 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 dimethylsulfoxide 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-butylnyl, 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, containing no heteroatoms. 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 pentfluoroethoxy.

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, pentfluoroethyl, 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, pyrrolidinonyl, and pyrazolidinyl. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, pyrrolidinonyl, 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, thiophen, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thiophenyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzothiazolyl, 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.

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

**Methods of Preparation**

The compounds and processes of the 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 of the invention can be generally prepared
according to the methods outlined in Scheme A below. In the
following scheme, variable $R_B$ is as defined in formula (I) and
$R_3$ is as defined in formula (II). $X$ represents halogens or
leaving groups such as tosylate, triflate, mesylate, and the
like, which are familiar to those skilled in the art.

Protecting groups are designated by $P$, and linkers are noted by
$L$. $Z$ may consist of $S$, $O$, or $NR$, where $R$ is $H$ or any
substitution with does not interfere with an alkylation
reaction.
In this method, starting with a benzene substituted with a para-directing group, as known to those skilled in the art, as in compound A1, generally alkyl, alkoxy, aryloxy, amino, alkylamino, or dialkylamino, and the like, can be brominated to give the bromobenzene compound as in structure A2. Appropriate brominating agents include elemental bromine, N-bromosuccinimide, DBU complex with hydrogen tribromide, or 2,4,4,6-tetrabromo-2,5-cyclohexadienone.

Amination of A2 with a primary amine to yield the secondary amine, A3, may be performed under palladium-catalyzed conditions according to Buchwald-Hartwig methodology, with Pd2(dba)₃, a ligand, and a base. Representative primary amines include, but are not limited to, alkyl and cyclic amines such as, methylamine, ethylamine, propylamine, isopropylamine, butylamine, isoamylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, and aniline, any of which are readily commercially available or prepared by those skilled in the art. The primary amine may be functionalized with any group which does not interfere with the catalytic amination.
reaction. The palladium source may be, for example, Pd(PPh₃)₄, Pd₂(dba)₃, Pd(OAc)₂, PdCl₂(PPh₃)₂, PdCl₂(MeCN)₂, PdCl₂(PhCN)₂, PdCl₂(dppe), PdCl₂(dppf), PdCl₂(dppp), PdCl₂(dppe), PdCl₂(COD), Pd(PCy₃)₂, or Pd(tBu₃P)₂, all of which are available commercially from either Aldrich Chemical (Milwaukee, WI) or Strem Chemical (Newburyport, MA). Appropriate ligands include t-Bu₃P, BINAP, P(tBu₃)₂(biphenyl), P(2-furyl)₃, dppe, dppp, dpf, 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. Bases that may be utilized include NaOtBu, K₃PO₄, Cs₂CO₃, Na₂CO₃, K₂CO₃, NaOAc, CsOAc, NaOMe, KOME, KOH, NaOH, and the like.

Alternately, amination of a haloarene, such as A2, with a primary amine may be achieved through copper catalysis, utilizing a copper (I) source, such as CuI or CuOAc, in the presence of K₃PO₄ and a ligand. Appropriate ligands include, for example, N,N-diethyalsalicylamide or ethylene glycol.

A3 may be alkylated, in the presence of a base, with compounds of structure A4 or A4', where R' is any group which will not interfere with the subsequently required reactivity, such as phenyl, n-alkyl, s-alkyl, t-alkyl, and the like, to yield tertiary amines of structure A5. Such bases include, but are not limited to, Na₂CO₃, K₂CO₃, Cs₂CO₃, triethylamine, diethylisopropylamine, NaOH, and KOH. Catalysts may be added to facilitate the reaction, including KI, n-Bu₄NI, and the like. The preparation of A4 will be discussed below with respect to Scheme B. Ester hydrolysis to the 2-hydroxymethyl thiazole derivative and subsequent conversion to the 2-halomethyl thiazole derivative yields compounds of structure A6. Use of a nucleophilic activation and reaction agent such as PPh₃Br₂, PBr₃, POBr₃, or PPh₃ and CBr₄ yields the 2-bromomethyl thiazole derivative of structure A6; the 2-chloromethyl thiazole derivative of structure A6 may be prepared analogously.
with PPh₃Cl₂, POCl₅, PCl₅, or PPh₃ and CCl₄. Likewise, the 2-iodomethyl thiazole derivative of structure A6 may be prepared using PPh₃I₂.

Finally, the 2-halomethyl thiazole derivative, A6, may alkylate a thiol, alcohol, or amine under Williamson ether synthesis conditions, involving an appropriate base. For the purposes of the present invention, the thiol, alcohol, or amine necessarily includes an appropriately protected carboxylic acid. Such bases include, but are not limited to, Na₂CO₃, K₂CO₃, Cs₂CO₃, triethylamine, diethylisopropylamine, NaOH, and KOH. Ultimately, deprotection of the carboxylic acid reveals compounds of structure A7, wherein Z may consist of S, O, or NR, where R is H or any substitution with does not interfere with the preceding alkylation reaction. For example, an ester protecting group may be hydrolyzed under basic conditions to yield the carboxylic acid. Appropriate thiols, alcohols, and amines for preparation of compounds of the present invention include, but are not limited to, N-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, and the like.

![Scheme B](image)

Compounds of structure A4 may be prepared according to the conditions outlined in Scheme B. For example, condensation of 4-(bromoacetyl) benzoic acid with 2,2-dimethylpropionic acid thiocarbamoylemethyl ester yields a thiazole of structure B1, where R' is t-butyl. The carboxylic acid may be reduced to the alcohol, by activation with benzotriazol-1-ylxyloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP).
in the presence of diisopropylamine (DIPA) followed by treatment with sodium borohydride. Alternative, methods for the reduction of the carboxylic acid in the presence of an ester include addition of 1,1'-carbonyldiimidazole or a dicarbonate, such as di-t-butyl dicarbonate, diallyl dicarbonate, di-t-amyl dicarbonate, diethyl dicarbonate, dibenzyl dicarbonate, or dimethyl dicarbonate, followed by treatment with sodium borohydride; preparation of the N-succinimidyl ester, with N-hydroxysuccinimide and a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC), diethylazodicarboxylate (DEAD) and triphenylphosphine, or the like, followed by reduction with sodium borohydride; and reduction with borane. Finally, under conditions previously described for conversion of the resulting benzyl alcohol derivative to the benzyl halide derivative, A4, can be prepared.

Example 1

\[
\text{N- (tert-butoxycarbonyl) -S- } \{4-[4-([4-(1-ethylpropyl) phenyl] (isopropyl) amino) methyl)phenyl]-1,3-thiazol-2-yl} \text{ methyl) cysteine (Compound 1)}
\]

Example 1a
Preparation of 4-[2-(2,2-dimethyl-propionyloxymethyl)-thiazol-4-yl]-benzoic acid

4-(2-bromo-acetyl)-benzoic acid (4.5 g, 18.5 mmol) and 2,2-dimethyl-propionic acid thiocarbamoylmethyl ester (3.2 g, 18.5 mmol) are refluxed for 1 hour in methanol (80 inL, 0.2 M). After evaporation of the solvent, the residue is recrystallized in dichloromethane along with a minimal amount of methanol to afford 4-[2-(2,2-dimethyl-propionyloxymethyl)-thiazol-4-yl]-benzoic acid (4.1 g, 70%) as a white crystalline solid. $^1$H NMR (DMSO, 300 MHz) $\delta$ 12.98 (s, 1 H), 8.31 (s, 1 H), 8.05 (d, J = 8.6 Hz, 2 H), 7.98 (d, J = 8.6 Hz, 2 H), 5.44 (s, 2 H), 1.21 (s, 9 H).

Example 1b

Preparation of 2,2-dimethyl-propionic acid 4-(4-hydroxymethyl-phenyl)-thiazol-2-ylmethyl ester

W,W-diisopropylamine (1.3 g, 9.9 mmol) is added to a stirred suspension of 4-[2-(2,2-dimethyl-propionyloxy)methyl]-thiazol-4-yl] -benzoic acid (2.6 g, 8.3 mmol) and benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP reagent) (4.0 g, 9.1 mmol) in THF (40 mL, 0.2 M) at room temperature. The solution is stirred for 5 minutes, then sodium borohydride (NaBH₄) (0.68 g, 16.6 mmol) is added. After stirring for 20 minutes, the solvent is evaporated and the residue is taken up in diethyl ether (50 mL) and washed with 5% HCl (2 x 50 mL), saturated aq NaHCO₃ (2 x 50 mL), saturated aq NaCl (2 x 50 mL), then dried over Na₂SO₄. Purification by flash chromatography (30-40% ethyl acetate in heptane) affords 2,2-dimethyl-propionic acid 4-(4-hydroxymethyl-phenyl)-thiazol-2-ylmethyl ester (2.4 g, 95%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.88 (d, J = 8.2 Hz, 2 H), 7.48 (s, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 5.45 (s, 2 H), 4.74 (s, 2 H), 1.29 (s, 9 H).

Example 1c

Preparation of 2,2-dimethyl-propionic acid 4-(4-bromomethyl-phenyl)-thiazol-2-ylmethyl ester

To a solution of 2,2-dimethyl-propionic acid 4-(4-hydroxymethyl-phenyl)-thiazol-2-ylmethyl ester (2.3 g, 7.6 mmol) in dichloromethane (20 mL, 0.4 M) is added dibromotriphenyl phosphorane (6.4 g, 15.0 mmol). After 30 minutes at room temperature, the reaction is diluted with H₂O (50 mL) and extracted with ethyl acetate (2 x 100 mL). Purification by flash chromatography (20% ethyl acetate in heptane) gives 2,2-dimethyl-propionic acid 4-(4-bromomethyl-
phenyl) -thiazol-2-ylmethyl ester (2.7 g, 98%) as a white solid.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.85 (d, $J = 8.2$ Hz, 2 H), 7.48 (s, 1 H), 7.43 (d, $J = 8.2$ Hz, 2 H), 5.43 (s, 2 H), 4.52 (s, 2 H), 1.28 (s, 9 H).

**Example I**

**Preparation of 2,2-dimethyl-propionic acid 4-[[4-(1-ethyl-propyl)-phenyl]-isopropyl-amino]-methyl)-phenyl]-thiazol-2-ylmethyl ester**

To a stirred solution of [4-(1-ethyl-propyl)-phenyl]-isopropyl-amine (.75 g, 3.7 mmol) in DMF (12 mL, 0.3 M) is added K$_2$CO$_3$ (0.76 g, 5.5 mmol). After 10 minutes, 2,2-dimethyl-propionic acid 4-(4-bromomethyl-phenyl) -thiazol-2-ylmethyl ester (1.4 g, 3.7 mmol) is added and the solution is heated to 80 °C for 5 hours. The solution is diluted with ethyl acetate (50 mL) and washed with saturated LiCl (3 x 50 mL). Purification by flash chromatography (2-5% ethyl acetate in heptane) affords 2,2-dimethyl-propionic acid 4-[[4-(1-ethyl-propyl)-phenyl]-isopropyl-amino]-methyl)-phenyl]-thiazol-2-ylmethyl ester (1.5 g, 83%) as a colorless oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.80 (d, $J = 8.1$ Hz, 2 H), 7.41 (s, 1 H), 7.35 (d, $J = 8.1$ Hz, 2 H), 6.91 (d, $J = 8.4$ Hz, 2 H), 6.63 (d, $J = 8.4$ Hz, 2 H), 5.43 (s, 2 H), 4.40 (s, 2 H), 4.25-4.21 (m, 1 H), 2.23-2.15 (m, 1 H), 1.65-1.57 (m, 2 H), 1.51-1.41 (m, 2 H), 1.28 (s, 9 H), 1.20 (d, $J = 6.3$ Hz, 6 H), 0.76 (t, $J = 7.2$ Hz, 6 H).
Example Ie

Preparation of \(4-\{4-\{4-\{(1-ethyl-propyl)-phenyl\}-isopropyl-amino\}-methyl\}-phenyl\}-thiazol-2-yl\)-methanol

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{S} & \quad \text{N} \\
\text{Br} & \quad 1
\end{align*}
\]

2,2-dimethyl-propionic acid 4-\{4-\{4-\{(1-ethyl-propyl)-phenyl\}-isopropyl-amino\}-methyl\}-phenyl\}-thiazol-2-ylmethyl ester (1.5 g, 3.6 mmol) is dissolved in 10 mL of THF and 10 mL of methanol (0.2 M). The solution is treated with 2N NaOH (7.3 mL, 14.7 mmol). The reaction is stirred at room temperature for 2 hours and then acidified with 2N HCl to a pH of 3. The organics are extracted with ethyl acetate (2 x 50 mL) and dried over MgSO\(_4\). The residue is purified by flash chromatography (20% ethyl acetate in heptane) to afford 4-\{4-\{4-\{(1-ethyl-propyl)-phenyl\}-isopropyl-amino\}-methyl\}-phenyl\}-thiazol-2-yl\)-methanol (1.2 g, 94%) as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.79 (d, \(J = 8.3\) Hz, 2 H), 7.39 (s, 1 H), 7.35 (d, \(J = 8.3\) Hz, 2 H), 6.90 (d, \(J = 8.5\) Hz, 2 H), 6.62 (d, \(J = 8.5\) Hz, 2 H), 4.99 (d, \(J = 5.8\) Hz, 2 H), 4.39 (s, 2 H), 4.27-4.18 (m, 1 H), 2.18-2.13 (m, 1 H), 1.65-1.55 (m, 2 H), 1.50-1.41 (m, 2 H), 1.19 (d, \(J = 6.4\) Hz, 6 H), 0.75 (t, \(J = 7.3\) Hz, 6 H).

Example If

\[
\begin{align*}
\text{Br} & \quad 1
\end{align*}
\]
Preparation of [4- (2-bromomethyl-thiazol-4-yl) -benzyl] -[4- (1-ethyl-propyl) -phenyl] -isopropyl-amine

To a solution of [4- [4- ([4- (1-ethyl-propyl) -phenyl] -isopropyl-amine ]-methyl) -phenyl] -thiazol-2-yl ]-methanol (1.2 g, 2.9 mmol) in dichloromethane (15 mL, 0.2 M) is added dibromotriphenyl phosphorane (2.5 g, 5.8 mmol). After 30 minutes at room temperature, the reaction is diluted with H₂O (50 mL) and extracted with ethyl acetate (2 x 50 mL). Purification by flash chromatography (5% ethyl acetate in heptane) gives [4- (2-bromomethyl-thiazol-4-yl) -benzyl] -[4- (1-ethyl-propyl) -phenyl] -isopropyl-amine (1.2 g, 90%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (d, J = 8.2 Hz, 2 H), 7.45 (s, 1 H), 7.34 (d, J = 8.2 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 6.61 (d, J = 8.5 Hz, 2 H), 4.77 (s, 2 H), 4.39 (s, 2 H), 4.25-4.20 (m, 1 H), 2.21-2.14 (m, 1 H), 1.63-1.54 (m, 2 H), 1.50-1.41 (m, 2 H), 1.19 (d, J = 6.6 Hz, 6 H), 0.75 (t, J = 7.3 Hz, 6 H).

Example Ig

Preparation of 2-tert-butoxycarbonylamino-3-{4-[4-(4-((4-(1-ethyl-propyl)-phenyl)-isopropyl-amine]-methyl)-phenyl]-thiazol-2-ylmethylsulfanyl }-propionic acid

To a stirred solution of 2-tert-butoxycarbonylamino-3-mercapto-propionic acid (0.07 g, 0.32 mmol) in acetone (5 mL, 0.1 M) is added 2M Na₂CO₃ (0.40 mL, 0.84 mmol). After 10 minutes, [4- (2-bromomethyl-thiazol-4-yl) -benzyl] -[4- (1-ethyl-
propyl) -phenyl] -isopropyl-amine (0.10 g, 0.20 \( \text{mol} \)) is added and the solution is stirred at room temperature for 18 hours. The reaction is acidified with 2N HCl to a pH of 3 and the organics are extracted with ethyl acetate (3 x 50 mL). Purification by flash chromatography (5% methanol in dichloromethane) affords 2-tert-butoxycarbonylamino-3- \{4-\{4-([4-(1-ethyl-propyl) -phenyl] -isopropyl-amino )-methyl) -phenyl] -thiazol-2-ylmethylsulfanyl \} -propionic acid (0.12 g, 88%) as a white foam. \( R_f \) 0.24 (10% methanol in dichloromethane) 

\[ \text{lH NMR (DMSO, 300 MHz) } \delta 7.93 (s, 1 H), 7.83 (d, \( J = 8.2 \text{ Hz, 2 H} \)), 7.30 (d, \( J = 8.2 \text{ Hz, 2 H} \)), 6.86 (d, \( J = 8.6 \text{ Hz, 2 H} \)), 6.59 (d, \( J = 8.6 \text{ Hz, 2 H} \)), 4.35 (s, 2 H), 4.24-4.17 (m, 1 H) 4.11 (s, 2 H), 3.94-3.89 (br s, 1 H) 3.00 (dd, \( J_1 = 13.2, J_2 = 4.1 \text{ Hz, 1 H} \)), 2.83 (dd, \( J_1 = 13.2, J_2 = 7.4 \text{ Hz, 1 H} \)) 2.12 -2.08 (m, 1 H), 1.59-1.50 (m, 2 H), 1.43-1.36 (m, 11 H), 1.14 (d, \( J = 6.4 \text{ Hz, 6 H} \)), 0.67 (t, \( J = 7.3 \text{ Hz, 6 H} \)) ESI-LCMS m/z calcd for \( C_{33}H_{45}N_3O_4S_2 \) : 611.9; found 612.3 (M+) 

**Example 2**

The following compound may be prepared essentially according to the procedures outlined in Schemes A and B and described in the above examples.
BIOLOGY EXAMPLES

Example 3

Method for measuring PTP-IB activity

The test compounds are evaluated for their in vitro inhibitory activity against recombinant human PTP-IB with phosphoryl 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_{50} values of less than 300 nM.

Example 4

Results of PTP-IB activity testing

<table>
<thead>
<tr>
<th>COMPOUND NO.</th>
<th>IC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
</tr>
</tbody>
</table>

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

\[ X_i = 0, \, S, \, \text{or} \, N \left( R_N \right), \]

wherein \( R_N \) is -H or -\((\text{C}_1-\text{C}_6)\)alkyl;

\[ X_2 = \text{CH or N}; \]

\[ R_i = -H, \, -\text{(C}_1-\text{C}_6)\text{alkyl}, \, -\text{(C}_1-\text{C}_6)\text{alkyl-phenyl}, \, \text{or} \]

\[ -\text{(C}_3-\text{C}_6)\text{alkenyl}; \]

\[ L_i = -0- \text{(C}_1-\text{C}_6)\text{alkyl}-, \, -\text{(CH}_2)_i-6-0- \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -S- \text{(C}_1-\text{C}_6)\text{alkyl}-, \, -\text{(CH}_2)_i-6-S- \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -\text{S(O)}_2- \text{(C}_1-\text{C}_6)\text{alkyl}-, \, -\text{(CH}_2)_i-6-\text{S(O)}_2- \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -N \left( R_{N_2} \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \, -\text{(CH}_2)_i-6-N \left( R_{N_2} \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -N \left( R_{N_2} \right) C \left( O \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -\text{(CH}_2)_i-6-\text{N} \left( R_{N_2} \right) C \left( O \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -\text{C(O)}_2- \text{(C}_1-\text{C}_6)\text{alkyl}-, \, -\text{(CH}_2)_i-6-\text{C(O)}_2- \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -\text{N} \left( R_{N_2} \right) C \left( O \right) \left( R_{N_3} \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

\[ -\text{(CH}_2)_i-6-N \left( R_{N_2} \right) C \left( O \right) \left( R_{N_3} \right) - \text{(C}_1-\text{C}_6)\text{alkyl}-, \]

wherein the alkyl portion of each of the above is
substituted with 1, 2, 3, or 4 substituents that
are independently -(Ci-C₆)alkyl, -(Ci-C₆)alkoxy,
- (C₂-C₆) alkenyl,
- (C₂-C₆) alkynyl, -C(O) (Ci-C₆) alkoxy,
- C(O) (Ci-C₆) alkyl, -C(O)OH, - (Ci-C₆) alky1-C (0) OH,
- (Ci-C₆) haloalkoxy, - (Ci-C₆) haloalkyl, -halogen,
- N(R₄₅R₆₅), - (Ci-C₆) alkyl -N (RN₄R₅), or
- C(O) N(R₄₅R₆₅),
wherein R₄₂ and R₅₃ are independently -H or
- (Ci-C₆) alkyl,
wherein R₄₄ and R₅₅ 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;
A is -aryl- or -heteroaryl-;
each Rₐ 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(R₆₆R₇₇),
- (Ci-C₆) alkyl-N (RN₆₇R₇₇), or - C(O) N(R₆₆R₇₇),
wherein R₆₆ and R₇₇ 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;
L₂ is -N(R₈₈)-, -O-, -S-, -(Ci-C₆) alkyl -N(R₈₈)-,
- N(R₈₈)-(Ci-C₆) alkyl-, -(Ci-C₆) alkyl - N(R₈₈)-(Ci-C₆) alkyl-,
- (Ci-C₆) alkyl-O-, -O- (Ci-CJ alkyl-,
- (Ci-C₆) alkyl-O- (Ci-C₆) alkyl-, -(Ci-C₆) alkyl-S-,
- S- (Ci-C₆) alkyl-, or -(Ci-C₆) alkyl-S (Ci-C₆) alkyl-,
wherein R₈₈ is -H, -(Ci-C₆) alkyl,
- (C₂-C₆) alkenyl, - (C₂-C₆) alkynyl,
- C(O) (Ci-C₆) alkoxy, - C(O) (Ci-C₆) alkyl,
- C(O) (Ci-C₆) alkyl- (C₃-C₈) cycloalkyl, or - C(O)H;
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\(_6\)(O) (Ci-C\(_6\)) alkyl, - C\(_6\)(O)OH, - CN, - (Ci-C\(_6\)) haloalkoxy, - (Ci-C\(_6\)) haloalkyl, - halogen, - NO\(_2\), - N(R\(_N\)R\(_N^{10}\)), - (Ci-C\(_6\)) alkyl-N (R\(_N\)R\(_N^{10}\)), or - C\(_6\)(O)H; and

\( p \) is 0, 1, 2, 3, or 4.

2. A compound according to claim 1, wherein
   \( A \) is phenyl, naphthyl, furanyl, thiienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl.

3. A compound according to claim 2, wherein
   \( B \) is phenyl, naphthyl, furanyl, thiienyl, pyridyl, pyrazolyl, pyrimidyl, imidazolyl, furanyl, thiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, triazolyl, pyrrolyl, or pyrazolyl.

4. A compound according to claim 3, wherein
   \( L_2 \) is -N(R\(_N^8\))^-, -O-, -S-, - (Ci-C\(_6\)) alkyl-N (R\(_N^8\))^-, -N(R\(_N^8\))^- (Ci-C\(_6\)) alkyl-, - (Ci-C\(_6\)) alkyl-0-, -0- (Ci-C\(_6\)) alkyl-, - (Ci-C\(_6\)) alkyl-S-, or -S- (Ci-C\(_6\)) alkyl-, wherein R\(_N^8\) is -H, - (Ci-C\(_6\)) alkyl, -allyl, -propargyl, - C\(_6\)(O) (Ci-C\(_6\)) alkoxy, - C\(_6\)(O) (Ci-C\(_6\)) alkyl, or - C\(_6\)(O) (Ci-C\(_6\)) alkyl- (C\(_3\)-C\(_8\)) cycloalkyl;

5. A compound according to claim 4, wherein
L is -O- (C₆₋C₆)alkyl-, -(CH₂)₁₋₆-O- (C₆₋C₆)alkyl-, -S- (C₆₋C₆)alkyl-, -(CH₂)₁₋₆-S- (C₆₋C₆)alkyl-, -N(Rₙ₂) - (C₁₋C₆)alkyl-, -(CH₂)₁₋₆-N(Rₙ₂) - (C₆₋C₆)alkyl-, wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently - (C₁₋C₆)alkyl, - (C₁₋C₆)alkoxy, - (C₂₋C₆)alkenyl, - (C₂₋C₆)alkynyl, -C(O) (C₁₋C₆)alkoxy, -C(O) (C₁₋C₆)alkyl, -C(O)OH, - (C₁₋C₆)alkyl-C(O)OH, - (C₁₋C₆)haloalkoxy, - (C₁₋C₆)haloalkyl, -halogen, -N(Rₙ₄Rₙ₅), - (C₁₋C₆)alkyl -N (RN₄RN₅), or -C(O)N(Rₙ₄Rₙ₅), wherein Rₙ₂ is -H or - (C₁₋C₆)alkyl, wherein Rₙ₄ and Rₙ₅ are each independently -H, - (C₁₋C₆)alkyl, - (C₂₋C₆)alkenyl, - (C₂₋C₆)alkynyl, -C(O) (C₁₋C₆)alkoxy, -C(O) (C₁₋C₆)alkyl, or -C(O)H.

6. A compound according to claim 5, wherein R₁ is -H, - (C₁₋C₆)alkyl, benzyl, or allyl;

7. A compound according to claim 6, having the formula,

or a pharmaceutically acceptable salt thereof, wherein R₃ is -H, - (C₁₋C₆)alkyl, -allyl, -propargyl,
8. A compound according to claim 7, having the formula,

\[
\begin{align*}
-\text{C}(\text{O})(\text{Ci-C}_6)\text{alkoxy}, & \quad -\text{C}(\text{O})(\text{Ci-C}_6)\text{alkyl}, \quad \text{or} \\
-\text{C}(\text{O})(\text{Ci-C}_6)\text{alkyl-}(\text{C}_3-\text{C}_8)\text{cycloalkyl}.
\end{align*}
\]

9. A compound according to claim 8, wherein

\[
\text{Li is} \quad -(\text{CH}_2)_{1-6}-\text{O}- (\text{Ci-C}_6)\text{alkyl-} \quad \text{or} \\
- (\text{CH}_2)_{1-6}\text{S-}(\text{C}_1-\text{C}_6)\text{alkyl-},
\]

wherein the alkyl portion of each of the above is substituted with 1, 2, 3, or 4 substituents that are independently \(-(\text{Ci-C}_6)\text{alkyl}, -(\text{Ci-C}_6)\text{alkoxy}, -(\text{C}_2-\text{C}_6)\text{alkenyl}, -(\text{C}_2-\text{C}_6)\text{alkynyl}, -\text{C}(\text{O})(\text{Ci-C}_6)\text{alkoxy}, -\text{C}(\text{O})(\text{Ci-C}_6)\text{alkyl}, -\text{C}(\text{O})\text{OH}, -(\text{Ci-C}_6)\text{alkyl-}\text{C}(\text{O})\text{OH}, -(\text{Ci-C}_6)\text{haloalkoxy}, -(\text{Ci-C}_6)\text{haloalkyl}, -\text{halogen}, -\text{N}(\text{R}_4\text{R}_5), -(\text{Ci-C}_6)\text{alkyl-}\text{N}(\text{R}_4\text{R}_5), \text{or} \\
-\text{C}(\text{O})\text{N}(\text{R}_4\text{R}_5),
\]

wherein \(\text{R}_4\) and \(\text{R}_5\) are each independently \(-\text{H}, -(\text{Ci-C}_6)\text{alkyl}, -(\text{C}_2-\text{C}_6)\text{alkenyl}, -(\text{C}_2-\text{C}_6)\text{alkynyl}, -\text{C}(\text{O})(\text{Ci-C}_6)\text{alkoxy}, -\text{C}(\text{O})(\text{Ci-C}_6)\text{alkyl}, \text{or} -\text{C}(\text{O})\text{H}.

10. A compound according to claim 9, having the formula,
or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 10, wherein
   A is phenyl.

12. A compound according to claim 11, of formula (V) or (VI),

or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12 wherein
   L₁ is - (CH₂)₁₋₆-S- (C₁-C₆)alkyl-,
   wherein the alkyl portion of each of the above is
   substituted with 1, 2, 3, or 4 substituents that
   are independently - (C₁-Cₑ) alkyl, - (C₁-Cₑ) alkoxy,
   allyl, propargyl, -C(O) (C₁-C₆) alkoxy,
   acetyl, -halogen, or -N(R₄Rₛ),
   wherein R₄ and Rₛ are each independently -H,
   - (C₁-Cₑ) alkyl, allyl, propargyl
   -C(O) (C₁-C₆) alkoxy, or acetyl.

14. The compound according to claim 13, wherein
   R₃ is -H or - (C₁-C₆) alkyl.
15. The compound according to claim 14, wherein
   \( R_B \) is \(-(\text{C}_i\text{-C}_6)\)alkyl.

16. The compound according to claim 15, wherein
   \( R_i \) is \( H \).

18. The compound according to claim 1 that is
   \( N-(\text{tert-butoxycarbonyl}) \quad 5- \quad ((5- [4- [([4- (1- \text{ethylpropyl}) \text{ phenyl}] (\text{isopropyl} \text{ amino} \text{ methyl}) \text{ phenyl}] -1,3- \text{thiazol-}2\text{-yl} \text{ methyl}) \text{ cysteine}; \text{ or} \)
   \( N-(\text{tert-butoxycarbonyl}) \quad 5- \quad ((4- [4- [([4- (1- \text{ethylpropyl}) \text{ phenyl}] (\text{isopropyl} \text{ amino} \text{ methyl}) \text{ phenyl}] -1,3- \text{thiazol-}2\text{-yl} \text{ methyl}) \text{ cysteine}.

19. A pharmaceutical composition comprising a compound of
   claim 1 and at least one pharmaceutically acceptable solvent,
   carrier, adjuvant or excipient.

20. 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.

21. A method of treating syndrome \( X \), obesity, diabetes,
   immunological disease, bleeding disorders, or cancer comprising
   administering a pharmaceutically composition of claim 19 to a
   patient in need of such treatment.

22. 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.
23. A method of treating Type II diabetes comprising administering a pharmaceutically composition of claim 19 to a patient in need of such treatment.