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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/092146 A2

(51) International Patent Classification[7]: C07D 277/00

(21) International Application Number: PCT/US2004/011650

(22) International Filing Date: 14 April 2004 (14.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/463, 102 14 April 2003 (14.04.2003) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VAN ZANDT, Michael, C.** [US/US]; 91 Golden Hill Drive, Guilford, CT 06437 (US). **FANG, Haiquan** [US/US]; 304 County Road, Madison, CT 06443 (US). **HU, Shaojing** [US/US]; 900 Mix Avenue, Unit 121, Hamden, CT 06514 (US). **WHITEHOUSE, Darren** [US/US]; 40 Fishing Brook Road, Westbrook, CT 06498 (US).

(74) Agent: **CRAWFORD, Bradley, W.**; Mcdonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).

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

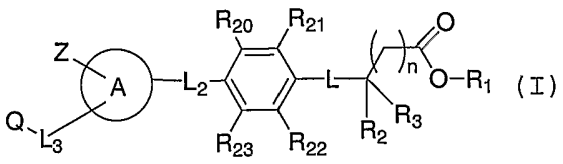
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/092146 A2

(54) Title: SUBSTITUTED PHENYLALKANOIC ACIDS



(57) Abstract: The present invention relates to compounds and pharmaceutically acceptable salts of formula (I), which are useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia. These compounds include inhibitors of protein tyrosine phosphatase (PTP-1B) that are useful in the treatment of diabetes and other PTP-1B mediated diseases, such as cancer, neurodegenerative diseases and the like. The compounds of the invention are also useful in pharmaceutical compositions and methods of treating the aforementioned conditions.

Substituted Phenylalkanoic acids

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to substituted phenylalkanoic acids that are useful in the treatment of diabetes. More specifically, it relates to such compounds that are capable of inhibiting Protein tyrosine phosphatase-1B (PTP-1B), which is a negative regulator of the insulin signaling pathway, and improves insulin-sensitivity.

Description of the Related Art

Protein tyrosine phosphatases are a large family of transmembrane or intracellular enzymes that dephosphorylate substrates involved in a variety of regulatory processes (Fischer et al., 1991, Science 253:401-406). Protein tyrosine phosphatase-1B (PTP-1B) 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-1B 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-1B and the insulin receptor in vitro. Seely constructed a glutathione S-transferase (GST) fusion protein of PTP-1B that had a point mutation in the PTP-1B 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-1B neutralizing antibodies into rat KRC-7 hepatoma cells. The presence of the antibody in the cells resulted in an increase of 42% and 38%, respectively, in insulin stimulated DNA synthesis and phosphatidyinositol 3' kinase activity. Insulin receptor autophosphorylation and insulin receptor substrate-1 tyrosine phosphorylation were increased 2.2 and 2.0-fold, respectively, in the antibody-loaded cells. The antibody-loaded cells also showed a 57% increase in insulin stimulated insulin receptor kinase activity toward exogenous peptide substrates.

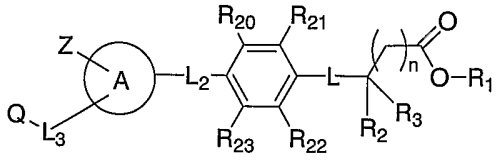
Kennedy et al., 1999, Science 283: 1544-1548 showed that protein tyrosine phosphatase PTP-1B is a negative regulator of the insulin signaling pathway, indicating that inhibitors of this enzyme are beneficial in the treatment of Type 2 diabetes, which appears to involve a defect in an early process in insulin signal transduction rather than a structural defect in the insulin receptor itself. (J. M. Olefsky, W. T. Garvey, R. R. Henry, D. Brillon, S. Matthai and G. R. Freidenberg, G. R. (1988).) Cellular mechanisms of insulin resistance in non-insulin-dependent (Type II) diabetes. (Am. J. Med. 85: Suppl. 5A, 86-105.) A drug that improved insulin sensitivity would have several advantages over traditional therapy of NIDDM using sulfonylureas, which do not alleviate insulin resistance but instead compensate by increasing insulin secretion.

Therefore, inhibitors of PTP-1B are useful in controlling or treating Type 2 diabetes, in improving glucose tolerance, and in improving insulin sensitivity in patients in need thereof. The compounds are also useful in treating or controlling other PTP-1B mediated diseases, such as the treatment of cancer, neurodegenerative diseases 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.

In one aspect, the invention encompasses compounds formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein,

n is 0, 1, 2, or 3;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-$C(O)NH_2$, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-heterocycloalkyl, -(C_1-C_4) alkyl-heteroaryl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H or -CO_2R_1,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, arylalkoxy, arylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-aryl, -N(C_1-C_4 alkyl)C(O)aryl, -NHC(O)aryl, NHarylalkyl, NHC(O)-(C_1-C_4) alkyl-aryl, N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-aryl, N(C_1-

C_4)alkyl-aryl, -$NHSO_2$-aryl, -N(C_1-C_4alkyl)SO_2aryl, or -N(C_1-C_4alkyl)arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is -SO_2NH-, -SO_2N(C_1-C_4) alkyl-, -$NHSO_2$-, -O-, -C(O)NH-, -C(O)N(C_1-C_4)alkyl-, -SO_2-, -C(O)-(C_1-C_4) alkyl-, -(C_1-C_4) alkyl-C(O)-, -NH-, -N(C_1-C_4) alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-N(R_9)C(O) -(C_1-C_4)alkyl-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_6)alkyl-, -(C_1-C_6)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, -SO_2aryl, arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, CN, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, aryl, -aryl-carbonyl-aryl, -aryl-alkyl-aryl, -aryl-heteroaryl, -aryl-heterocycloalkyl, -heteroaryl, -heteroaryl-alkyl-aryl, -heterocycloalkyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, aryl(C_1-C_6)alkyl, alkanoyl, arylalkanoyl, alkoxycarbonyl, arylalkoxycarbonyl, heteroarylcarbonyl, heteroaryl, heterocycloalkylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-aryl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl or haloalkoxy, and

Z is absent, H, -NHC(O)aryl, -N(C_1-C_4 alkyl)C(O)aryl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

provided that when L_2 is a bond, the A ring is not phenyl.

Compounds of formula I bind to PTP-1B. Preferably that interaction results in inhibition of the enzyme.

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

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 invention further provides methods of treating disease in a patient in need of such treatment, comprising administering

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 inhibiting protein tyrosine phosphatase comprising administering a therapeutically effective amount of a compound of formula I.

In another aspect, the invention provides a method for treating metabolic disorders related to insulin resistance or hyperglycemia, comprising administering a therapeutically effective amount of a compound of formula I.

The invention also provides the use of a compound or salt according to formula I for the manufacture of a medicament.

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

The invention also provides methods and compositions for combination therapy of Type I and Type II diabetes. In these embodiments, the invention provides formulations and pharmaceutical compositions, as well as methods for treating Type I and Type II diabetes with the PTPase inhibitors of formula I plus additional compounds and medicaments as disclosed in more detail below. In these embodiments, the methods of the invention can comprise treatment methods for Type I and Type II diabetes where the PTPase inhibitors of formula I are formulated with a therapeutically-effective amount of said additional compounds and medicaments. In alternative embodiments, treatment methods of the invention for Type I and Type II diabetes comprise administration of the inventive PTPase inhibitors of formula I as disclosed herein concomitantly, simultaneously or together with a therapeutically-effective amount of said additional compounds and medicaments.

DETAILED DESCRIPTION OF THE INVENTION

A preferred class of compounds of formula I are compounds of formula I-1, wherein,

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-$C(O)NH_2$, -(C_1-C_4) alkyl-$C(O)NH(C_1$-$C_4)$alkyl, -(C_1-C_4) alkyl-$C(O)N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; wherein b is 0, 1, or 2;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, benzofuranyl, benzothienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, dibenzofuranyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl,

C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Particularly preferred compounds of formula I are those where R_1 is H. Compounds of formula I having R_1 groups that are C_1-C_6 alkyl, benzyl and allyl are preferred as intermediates.

Preferred compounds of formula I-1 include compounds of formula I-2, wherein

L is -SO_2NH-, -SO_2N(C_1-C_4) alkyl-, -NHSO_2-, -O-, -C(O)NH-, -C(O)N(C_1-C_4)alkyl-, -SO_2-, -C(O)-(C_1-C_4) alkyl-, -(C_1-C_4) alkyl-C(O)-, -NH-, or -N(C_1-C_4) alkyl-, wherein the alkyl

group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)alkyl-C(O)NR_9-$, $-(C_1-C_4)alkyl-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)alkyl-$, $-N(R_9)C(O)$ $-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-N(R_9)C(O)$ $-(C_1-C_4)alkyl-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R9)-$, $-N(R_9)-(C_1-C_4)alkyl-$, $-O-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-O-$, or $-(C_1-C_4)alkyl-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, anthracenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, $-(C_1-C_4)alkyl-O-$, $-O-(C_1-C_4)alkyl$, $-(C_1-C_4)$ alkyl-, -C(O)-; and

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, NH-phenyl, $-NHC(O)-(C_1-C_4)$ alkyl-phenyl, $-N(C_1-C_4$ alkyl)$C(O)-(C_1-C_4)$ alkyl-phenyl, $N(C_1-C_4)alkyl$-phenyl, $-NHSO_2$-phenyl, $-N(C_1-C_4alkyl)SO_2$phenyl, NHbenzyl, or $-N(C_1-C_6)$alkylbenzyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

Preferred compounds of formula I-2 include compounds of formula I-3, wherein

L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, -C(O)NH-, $-C(O)N(C_1-C_4)alkyl-$, -NH-, or $-N(C_1-C_4)$ alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally

substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)alkyl-C(O)NR_9-$, $-(C_1-C_4)alkyl-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)alkyl-$, $-N(R_9)C(O)-(C_1-C_4)alkyl-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R9)-$, $-N(R_9)-(C_1-C_4)alkyl-$, $-O-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-O-$, or $-(C_1-C_4)alkyl-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, $-(C_1-C_4)alkyl-O-$, $-O-(C_1-C_4)alkyl$, $-(C_1-C_4)$ alkyl-, $-C(O)-$;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-$C(O)NH_2$, $-(C_1-C_4)$ alkyl-$C(O)NH(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl-$C(O)N(C_1-C_4)alkyl(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl-$S(O)_b-(C_1-C_4)$ alkyl, (C_1-C_4) hydroxyalkyl, $-(C_1-C_4)$ alkyl-piperidinyl, $-(C_1-C_4)$ alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; wherein b is 0, 1, or 2;

R_3 is H;

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)alkyl(C_1-C_6)$alkyl, NH-phenyl, $N(C_1-C_4)$alkyl-phenyl, NHbenzyl, or $-N(C_1-C_6)$alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -$(C_1$-$C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-$(C_1$-$C_4)$alkyl-phenyl, imidazolidinyl, dibenzofuranyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

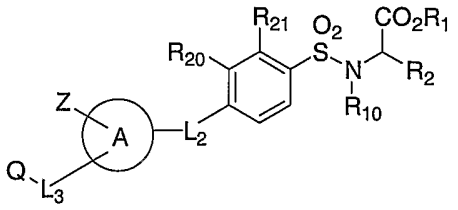
R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_6)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_6)$alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Preferred compounds or salts of formula I-3 include those compounds of formula II:



II

wherein,

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

R_{10} is H, C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, benzyloxy, benzyl, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, N(C_1-C_4)alkyl-phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6

alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

Preferred compounds of formula II include compounds of formula II-1, i.e., compounds wherein

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, naphthyl-CH_2-, anthracenyl-CH_2-, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl-pyridyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, dibenzofuranyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, C_1-C_6

alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Other compounds of formula II-1 include compounds of formula II-2, i.e., compounds wherein

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl,

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2,

3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3;

L_3 is a bond, $-(C_1$-$C_4)$alkyl-O-, -O-$(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$ alkyl-, or -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_2 haloalkoxy, C_1-C_2 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl-$(C_3$-$C_7)$cycloalkyl, or $-N(C_1$-$C_4)$alkylC(O)-$(C_1$-$C_4)$alkyl-$(C_3$-$C_7)$cycloalkyl.

Preferred compounds of formula II-2 include compounds of formula II-3, i.e., compounds wherein

R_1 is H, or C_1-C_4 alkyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or -SO_2-(C_1-C_4) alkyl;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3; and

at least one of R_{20} and R_{21}, is H, while the other is H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl,

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, or -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, or piperazinyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1,

2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is H, absent, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl (in one aspect, CF_3), C_1-C_2 haloalkoxy (in one aspect, OCF_3), or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl, or $-N(C_1$-$C_4)$alkyl$-C(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl.

Preferred compounds of formula II-3 include compounds of formula II-4, i.e., compounds wherein

L_2 is a bond or $-NR_9-$; wherein

R_9 is H, C_1-C_6 alkyl, or benzyl;

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or $-SO_2-(C_1$-$C_4)$ alkyl;

Q is phenyl, or pyridyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is H, absent, or phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2.

Preferred compounds of formula II-4 include compounds of formula II-5, i.e., compounds wherein the A ring is pyrazolyl, dihydropyrazolyl, thiazolyl, or pyrimidyl each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In a preferred embodiment, the A ring is unsubstituted or substituted with at least one halogen.

Preferred compounds of formula II-5 include compounds of formula II-6, i.e., compounds wherein R_{10} is H or C_1-C_4 alkyl; and L_3 is a bond or -(C_1-C_4) alkyl-. More preferably, R_{10} is H or methyl.

In another aspect, the invention provides compounds of formula II-6-a, i.e., compounds of formula II-5 or II-6 wherein the A ring is pyrazolyl, dihydropyrazolyl, thiazolyl, or pyrimidyl each of which is unsubstituted.

In yet another aspect, the invention provides compounds of formula II-6-b, i.e., compounds of formula II-5, II-6, or II-6-a wherein R_1 is H.

In still another aspect, the invention provides compounds of formula II-6-c, i.e., compounds of formula II-5, II-6, II-6-a, or II-6-b wherein L_3 is a bond, and L_2 is a bond.

In yet another aspect, the invention provides compounds of formula II-6-d, i.e., compounds of formula II-6-c or II-6-b wherein the A ring is pyrazolyl or thiazolyl.

In still yet another aspect, the invention provides compounds of formula II-6-e, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, wherein Z is absent.

In another aspect, the invention provides compounds of formula II-6-f, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, wherein Z is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, C_1-C_2 haloalkyl (in one aspect, CF_3), C_1-C_2 haloalkoxy (in one aspect, OCF_3), or NO_2. In another aspect, the phenyl is optionally substituted with no more than three substituents. In yet another aspect, the phenyl is monosubstituted. In still another aspect, the phenyl ring is unsubstituted.

In yet another aspect, the invention provides compounds of formula II-6-g, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, or II-6-f, wherein Q is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-h i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-g, wherein Q is phenyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-i i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-g wherein Q is phenyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, OCF_3 or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), phenyl(C_1-C_2)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_2)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In yet another aspect, the invention provides compounds of formula II-6-j, i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, or II-6-f, wherein Q is pyridyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_4)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-k i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-j, wherein Q is pyridyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another

aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-6-1 i.e., compounds of formula II-4, II-5, II-6, II-6-a, II-6-b, II-6-c or II-6-d, II-6-e, II-6-f, or II-6-j wherein Q is pyridyl, which is optionally substituted with 1, 2, or 3, groups that are independently C_1-C_6 alkoxycarbonyl (in another aspect, C_1-C_4 alkoxycarbonyl), C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, CF_3, OCF_3 or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), phenyl(C_1-C_2)alkyl, C_2-C_6 alkanoyl, or phenyl(C_1-C_2)alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

Other preferred compounds of formula II-4 include compounds of formula II-7, i.e., compounds wherein

n is 0, 1, 2, or 3;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; wherein b is 0, 1, or 2;

R_3 is H or -CO_2R_1,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, phenylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, NH-phenyl, $-N(C_1-C_4$ alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, $NHC(O)-(C_1-C_4)$ alkyl-phenyl, $N(C_1-C_4$ alkyl)$C(O)-(C_1-C_4)$ alkyl-phenyl, $N(C_1-C_4)$alkyl-phenyl, $-NHSO_2$-phenyl, $-N(C_1-C_4$alkyl)SO_2phenyl, or $-N(C_1-C_4$alkyl)phenylalkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy; and

L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, $-NHSO_2-$, -O-, -C(O)NH-, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, $-N(C_1-C_4)$ alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy.

Other preferred compounds of formula II-7 include compounds of formula II-8, i.e., compounds wherein

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)alkyl-C(O)NR_9-$, $-(C_1-C_4)alkyl-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)alkyl-$, $-N(R_9)C(O)-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-$, $-(C_1-C_4)alkyl-N(R_9)C(O)-(C_1-C_4)alkyl-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)alkyl-$, $-O-(C_1-C_6)alkyl-$, $-(C_1-C_6)alkyl-O-$, or $-(C_1-C_4)alkyl-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)alkyl-O-$, $-O-(C_1-C_4)alkyl$, $-(C_1-C_4)$ alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, furanyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -$(C_1$-$C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-$(C_1$-$C_4)$alkyl-phenyl, -pyrimidyl-$(C_1$-$C_4)$alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_6)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_6)$alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2,

OH, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, -NHC(O)phenyl, $-N(C_1-C_4$ alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

Other preferred compounds of formula II-8 include compounds of formula II-9, i.e., compounds wherein

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, $N(C_1-C_4)$alkyl-phenyl, $-NHSO_2-$phenyl, $-N(C_1-C_4$alkyl$)SO_2$phenyl, or $-N(C_1-C_4$alkyl)phenyl(C_1-C_6)alkyl, wherein each of the preceding phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3;

L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, $-NHSO_2-$, -O-, -C(O)NH-, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, $-N(C_1-C_4)$ alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy; or

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-N(R_9)C(O)-(C_1-C_4)$alkyl-, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-O-, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4

alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl-O-, -O-(C_1-C_4)alkyl, $-(C_1-C_4)$ alkyl-, -alkenyl-, C(O);

R_1 is H, C_1-C_6 alkyl;

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-pyridinyl, (C_1-C_4) hydroxyalkyl, wherein the phenyl ring is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl $-(C_1-C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6

alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

In another aspect, the invention provides compounds of formula II-10, i.e., compounds of formula II-9 wherein

R_{22} and R_{23} are both H; and

R_{20}, and R_{21}, are independently H, phenyl(C_1-C_4)alkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, and NO_2, wherein each of the preceding phenyl groups is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3;

In another aspect, the invention provides compounds of formula II-11, i.e., compounds of formula II-9 wherein

R_{22} and R_{23} are both H; and

R_{20}, and R_{21}, are independently H, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein each of the preceding phenyl groups is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula II-12, i.e., compounds of formula II-10 or II-11 wherein R_1 is H or methyl (preferably H.)

In another aspect, the invention provides compounds of formula II-13, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, -O-, $-C(O)NH-$, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, or $-N(C_1-C_4)$ alkyl-, wherein each of the preceding alkyl groups is optionally substituted with phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in another aspect, C_1-C_4 alkyl), C_1-C_6 alkoxy (in another aspect, C_1-C_4 alkoxy), halogen, OH, NO_2, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-14, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, $-NHSO_2-$, -O-, $-C(O)NH-$, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, or $-N(C_1-C_4)$ alkyl-.

In yet another aspect, the invention provides compounds of formula II-15, i.e., compounds of formula II-10, II-11, or 11-12 wherein L is $-SO_2NH-$, $-SO_2N(C_1-C_3)$ alkyl-, -O-, or $-C(O)-(C_1-C_4)$ alkyl -.

In still yet another aspect, the invention provides compounds of formula II-16, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl-$C(O)NR_9-$, $-(C_1-C_4)$alkyl-$N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, or $-N(R_9)C(O)-(C_1-C_4)$alkyl-, wherein

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl(C_1-C_4)alkyl, or naphthylalkyl, wherein each of the preceding aryl groups is optionally substituted with 1, 2, or 3

groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula II-17, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-N(R_9)SO_2-$, or $-SO_2N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In yet another aspect, the invention provides compounds of formula II-18, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-N(R_9)-$, $-N(R_9)-(C_1$-$C_4)$alkyl-, or $-(C_1$-$C_4)$alkyl-$N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In still another aspect, the invention provides compounds of formula II-19, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is $-O-(C_1$-$C_6)$alkyl-, or $-(C_1$-$C_6)$alkyl-O-.

In another aspect, the invention provides compounds of formula II-20, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15 wherein L_2 is a bond, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, or $-N(R_9)-$, and wherein R_9 is as defined for formula II-16.

In yet another aspect, the invention provides compounds of formula II-21, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is phenyl, phenyl$(C_1$-$C_4)$alkyl (in another aspect, benzyl), wherein the phenyl portion of each of the preceding is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1$-$C_4)$ alkyl, CF_3 or OCF_3.

In yet another aspect, the invention provides compounds of formula II-22, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is phenyl or benzyl.

In yet another aspect, the invention provides compounds of formula II-23, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, or II-20, wherein R_2 is C_1-C_6 alkyl, -(C_1-C_4) alkyl-pyridinyl, or (C_1-C_4) hydroxyalkyl.

In still another aspect, the invention provides compounds of formula II-24, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is phenyl or naphthyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-25, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, pyrimidyl, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-26, i.e., compounds of formula II-9, II-10, II-11,

II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, or II-23 wherein the A ring is benzofuranyl, dibenzofuranyl, quinazolinyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A-ring is unsubstituted.

In still another aspect, the invention provides compounds of formula II-27, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_6)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_6)$alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In still another aspect, the invention provides compounds of formula II-28, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20,

II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or phenyl.

In still another aspect, the invention provides compounds of formula II-29, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is -phenyl-carbonyl-phenyl, -phenyl-(C_1-C_4)alkyl-phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-pyridyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In still another aspect, the invention provides compounds of formula II-30, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is -phenyl-carbonyl-phenyl, -phenyl-(C_1-C_4)alkyl-phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-pyridyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, or 3 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or phenyl.

In still another aspect, the invention provides compounds of formula II-31, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is C_1-C_6 alkyl, halogen, CF_3, OCF_3, or C_1-C_6 alkoxycarbonyl.

In still another aspect, the invention provides compounds of formula II-32, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26, wherein Q is H.

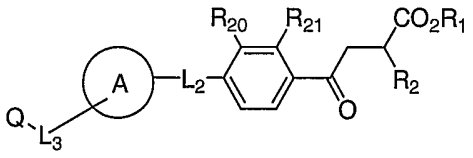
In still another aspect, the invention provides compounds of formula II-33, i.e., compounds of formula II-27 or II-29, wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_4 alkanoyl, phenyl(C_1-C_4)alkanoyl, C_1-C_4 alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, wherein each of the preceding cyclic groups is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-34, i.e., compounds of formula II-27 or II-29, wherein R_6 and R_7 are independently H, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1-C_4)alkyl$, $-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl$, or $-SO_2$-phenyl, wherein each of the preceding cyclic groups is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl(C_1-C_6)alkyl$, CF_3, or OCF_3.

In still another aspect, the invention provides compounds of formula II-35, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, II-26, II-27, II-28, II-29, II-30, II-31, II-32, wherein Z is absent or H.

In still another aspect, the invention provides compounds of formula II-36, i.e., compounds of formula II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, II-26, II-27, II-28, II-29, II-30, II-31, II-32, wherein Z is phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NO_2. In another aspect, the phenyl group is monosubstituted. In yet another aspect, the phenyl group is unsubstituted.

Preferred compounds or salts of formula II-9 include compounds of formula III,



III

wherein

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

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, -CH_2-pyridyl, or (C_1-C_4) hydroxyalkyl, wherein the phenyl and pyridyl portions are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

Preferred compounds of formula III include compounds of formula III-1, i.e., compounds wherein

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dibenzofuranyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6

alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

Preferred compounds of formula III-1 include compounds of formula III-2, i.e., compounds wherein

R_1 is H;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, C(O);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, -CH_2-pyridyl, or C_1-C_6 alkyl wherein the phenyl and the pyridyl portions are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally

substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In another aspect, the invention provides compounds of formula III-2-a, i.e., compounds of formula III-2 wherein L_3 is -(C_1-C_4)alkyl-O-, or -O-(C_1-C_4)alkyl.

In yet another aspect, the invention provides compounds of formula III-2-b, i.e., compounds of formula III-2 wherein L_3 is -(C_1-C_4) alkyl-, or C(O). In one aspect, L_3 is C(O). In another aspect, L_3 is -(C_1-C_3) alkyl-.

In yet another aspect, the invention provides compounds of formula III-2-c, i.e., compounds of formula III-2, III-2-a or III-2-b wherein R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl. In another aspect, at least one of R_{20} and R_{21} are H.

In yet another aspect, the invention provides compounds of formula III-2-d, i.e., compounds of formula III-2, III-2-a or III-2-b wherein R_{20} and R_{21}, are independently selected from H, NH-phenyl, NHbenzyl, N(C_1-C_4)alkyl-phenyl, -NHSO_2-phenyl, -N(C_1-C_4 alkyl)SO_2phenyl, or -N(C_1-C_4 alkyl)phenyl(C_1-C_6)alkyl, wherein each of the preceding phenyl groups are optionally substituted with 1, 2, 3, or 4 groups (in another aspect, 1, 2, or 3 groups) that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3. In another aspect, at least one of R_{20} and R_{21} are H.

In yet another aspect, the invention provides compounds of formula III-2-e, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, or III-2-d wherein R_2 is phenyl, or phenyl(C_1-C_4)alkyl, wherein the phenyl portion is optionally substituted

with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3.

In yet another aspect, the invention provides compounds of formula III-2-f, i.e., compounds of formula III-2-e wherein R_2 is phenyl, which is optionally substituted with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In another aspect, the phenyl is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-g, i.e., compounds of formula III-2-e wherein R_2 is phenyl(C_1-C_4)alkyl, which is optionally substituted with a total of 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In a more preferred aspect, R_2 is benzyl, which is optionally substituted as above. In still another aspect, the benzyl is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-h, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, or III-2-d wherein R_2 is -CH_2-pyridyl, or C_1-C_6 alkyl wherein the pyridyl group is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3. In another aspect, R_2 is unsubstituted -CH_2-pyridyl. In still another aspect, R_2 is C_1-C_6 alkyl. In yet still another aspect, R_2 is C_1-C_4 alkyl.

In still yet another aspect, the invention provides compounds of formula III-2-i, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, or III-2-h, wherein Q is H, phenyl, naphthyl, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the

aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

In yet another aspect, the invention provides compounds of formula III-2-j, i.e., compounds of formula III-2-i, wherein Q is phenyl, naphthyl, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, benzyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl.

In still yet another aspect, the invention provides compounds of formula III-2-k, i.e., compounds of formula III-2-i or III-2-j, wherein Q is phenyl or naphthyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl. In another aspect, Q is phenyl, which is optionally substituted as described above.

In still yet another aspect, the invention provides compounds of formula III-2-l, i.e., compounds of formula III-2-i or III-2-j, wherein Q is pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently

H, C_1-C_6 alkyl, benzyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl. In another aspect, Q is pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, each of which is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-m, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, or III-2-h, wherein Q is -phenyl-pyridyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_4)alkyl, N(C_1-C_4)alkyl(C_1-C_4)alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-n, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is phenyl, or naphthyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl. In another aspect, the A ring is phenyl, which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl. In another aspect, the A ring is substituted with at least one group. In still another aspect, the A ring is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-o, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h,

III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, or pyrimidyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

In another aspect, the invention provides compounds of formula III-2-p, i.e., compounds of formula III-2-o wherein the A ring is thiazolyl, which is optionally substituted with one group that is halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the thiazolyl ring is unsubstituted.

In another aspect, the invention provides compounds of formula III-2-q, i.e., compounds of formula III-2-o wherein the A ring is pyrazolyl, which is optionally substituted with one group that is halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the pyrazolyl ring is unsubstituted.

In still another aspect, the invention provides compounds of formula III-2-r, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is dibenzofuranyl, benzofuranyl, quinazolinyl, or benzo[b]thienyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

In still another aspect, the invention provides compounds of formula III-2-s, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, or III-2-m wherein the A ring is dibenzofuranyl or benzofuranyl, each of which is

optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl. In another aspect, the A ring is dibenzofuranyl, which is optionally monosubstituted with a group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_4)$alkyl, or $N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl. In yet another aspect, the dibenzofuranyl group is unsubstituted.

In yet another aspect, the invention provides compounds of formula III-2-t, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is a bond.

In another aspect, the invention provides compounds of formula III-2-u, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-C(O)NR_9-$, $-N(R_9)C(O)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-v, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-w, i.e., compounds of formula III-2, III-2-a, III-2-b, III-2-c, III-2-d, III-2-e, III-2-f, III-2-g, III-2-h, III-2-i, III-2-j, III-2-k, III-2-l, III-2-m, III-2-n, III-2-o, III-2-p, III-2-q, III-2-r, or III-2-s wherein L_2 is $-N(R_9)-$, $-N(R_9)-(C_1$-$C_4)$alkyl-, or $-(C_1$-$C_4)$alkyl-$N(R_9)-$, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenyl$(C_1$-$C_4)$alkyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3 or OCF_3.

In still another aspect, the invention provides compounds of formula III-2-x, i.e., compounds of formula III-2-u, III-2-v, or III-2-w, wherein R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, benzyl, or naphthyl-CH_2-, wherein the aryl groups are optionally substituted with 1, 2, 3, or 4 groups (in another aspect, the aryl groups are optionally substituted with 1 or 2 groups) that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_4)$alkyl, $N(C_1$-$C_4)$alkyl$(C_1$-$C_4)$alkyl, CF_3 or OCF_3. In another aspect, the phenyl groups are not substituted. In still another aspect, the phenyl groups are monosubstituted.

Preferred compounds of formula III-2 include compounds of formula III-3, i.e., compounds wherein

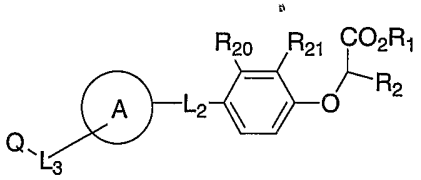
L_3 is a bond;

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1$-$C_4)$ alkyl, CF_3, or OCF_3;

Q is H, or phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; and

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, quinazolinyl, and benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl.

Other preferred compounds or salts of formula II-8 include compounds of formula IV



IV

wherein

R_1 is H or methyl (preferably H);

R_2 is phenyl, phenyl$(C_1$-$C_4)$alkyl, C_1-C_6 alkyl, or $(C_1$-$C_4)$ hydroxyalkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1$-$C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

Preferred compounds of formula IV include compounds of formula IV-1, i.e., compounds wherein,

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, furanyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, CF_3, OCF_3, CN, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, NH-phenyl, $-N(C_1$-C_4 alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, $N(C_1$-$C_4)$alkyl-phenyl, $-NHSO_2$-phenyl, $-N(C_1$-C_4alkyl)SO_2phenyl, or $-N(C_1$-C_4alkyl)phenyl$(C_1$-$C_6)$alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

Preferred compounds of formula IV-1 include compounds of formula IV-2, i.e., compounds wherein,

L_2 is a bond or $-C(O)NR_9$-, $-N(R_9)C(O)$-, $-N(R_9)SO_2$-, $-SO_2N(R_9)$-, $-N(R_9)$-, $-N(R_9)$-$(C_1$-$C_4)$alkyl-, or -$(C_1$-$C_4)$alkyl-$N(R_9)$-,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -$(C_1$-$C_4)$alkyl-O-, -O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$ alkyl-, C(O);

R_2 is phenyl, phenyl$(C_1$-$C_4)$alkyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2$-$(C_1$-$C_4)$ alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_6)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_6)$alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are

independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

Preferred compounds of formula IV-2 include compounds of formula IV-3, i.e., compounds wherein, Q is H or phenyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3.

Preferred compounds of formula IV-3 include compounds of formula IV-4, i.e., compounds wherein

L_3 is a bond;

R_1 is H or C_1-C_4 alkyl; and

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1$-$C_4)$ alkyl, CF_3, or OCF_3.

In another aspect, the invention provides compounds of formula IV-5, i.e., compounds of formula IV, IV-4, IV-3, VI-2, or IV-1, wherein at least one of R_{20} and R_{21} is H.

Other compounds of formula IV-4 include compounds of formula IV-6, i.e., compounds wherein both R_{20} and R_{21} are H.

Other compounds of formula IV-5 include those wherein R_{21} is H and R_{20} is $-N(H$ or C_1-C_4 alkyl)phenyl or $-N(H$ or C_1-C_4 alkyl)SO_2-phenyl wherein the phenyl is optionally substituted with C_1-C_6 alkyl. More preferably, the phenyl is substituted with C_2-C_5 alkyl. Even more preferably with n-butyl. Still more preferably, it is substituted at the four position.

Preferred compounds of Formula I include those where the A ring is phenyl substituted as specified above. In this preferred aspect, the phenyl is substituted with at least one aryl or heteroaryl group, e.g., phenyl or benzofuryl, where the

aryl or heteroaryl group is optionally mono-, di- or trisubstituted as specified above.

A preferred "A ring-L_3-Q" group within Formula I is biphenyl, i.e., where the A ring is phenyl, L_3 is a bond, and Q is phenyl that is optionally substituted as specified above.

Other preferred compounds of Formula I include those where the A ring is thiazolyl, preferably 2- or 4-thiazolyl, and more preferably a 2- or 4-thiazolyl group substituted with at least one phenyl or pyridinyl group (from either Z or Q), where the phenyl and pyridinyl groups are optionally mono-, di- or trisubstituted as specified above. Particularly preferred compounds of this aspect include those where the A ring is 2- or 4-thiazolyl disubstituted as specified above.

Other preferred compounds of Formula I include those where the A ring is pyrazolyl, preferably 1-pyrazolyl, and more preferably a 1-pyrazolyl group substituted with at least one phenyl or pyridinyl group (from either Z or Q), where the phenyl and pyridinyl groups are optionally mono-, di- or trisubstituted as specified above. In this aspect, the at least one phenyl or pyridinyl group is preferably in the 3- or 5-position of the pyrazole A ring. Particularly preferred compounds include those where the A ring is pyrazolyl disubstituted in the 3- and 5- or 3- and 4-positions of the pyrazole A ring.

Still other preferred compounds of Formula I are those where L_2 is -NHC(O)- or -N[$(C_1$-$C_6)$alkyl]C(O)-, more preferably -NHC(O)-.

Still other preferred compounds of Formula I are those where L_2 is -C(O)-. Other preferred compounds of Formula I include those where L_2 is -$S(O)_2$N[$(C_1$-$C_6)$alkyl]-.

Another preferred L_2 group is -[$(C_1$-$C_3)$alkylene]N(R_9)-. Preferably R_9 in this aspect is -SO_2-phenyl where the phenyl is optionally substituted as specified above. More preferably, the phenyl groups within the scope of R_9 are substituted with haloalkyl or halogen and even more preferably disubstituted where at least one of the substituents is haloalkyl or halogen.

Other preferred compounds of Formula I are those where n is 0. In this aspect, more preferred compounds are those where R_2 is phenyl or benzyl, most preferably benzyl. In certain aspects R_2 is benzyl optionally substituted with one or two C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, or trifluoromethyl.

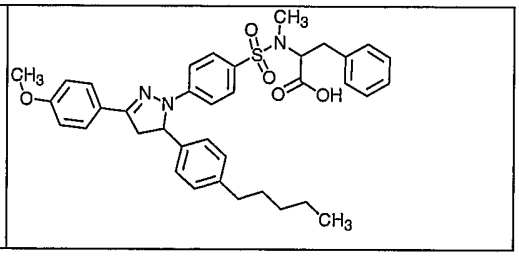
In another aspect, the invention provides a method of treating diabetes, comprising administering to a patient in need of such treatment a pharmaceutically acceptable amount of a compounds of formula I.

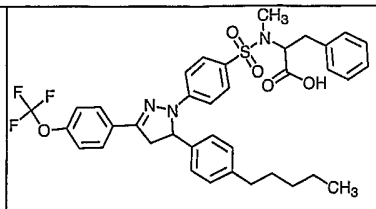
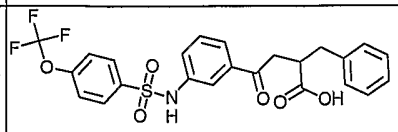
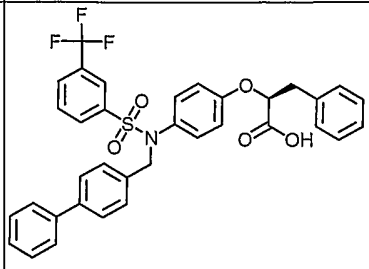
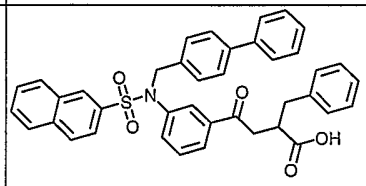
In another aspect, the invention encompasses a method of treating diabetes comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of formula I or a pharmaceutical composition comprising a compound or salt of formula I.

In another aspect, the invention encompasses a method of inhibiting TPT-1B comprising administering to a patient in need thereof, 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 cancer or neurodegenerative diseases comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of formula I or a pharmaceutical composition comprising a compound or salt of formula I.

Illustrative compounds of the invention include the following, which were named using ChemDraw v. 6.02, which is sold by Cambridgesoft.com in Cambridge, MA.

N-({4-[3-(4-methoxyphenyl)-5-(4-pentylphenyl)-4,5-dihydro-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine	

N-methyl-N-[(4-{5-(4-pentylphenyl)-3-[4-(trifluoromethoxy)phenyl]-4,5-dihydro-1H-pyrazol-1-yl}phenyl)sulfonyl]phenylalanine	
2-benzyl-4-oxo-4-[3-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]butanoic acid	
(2S)-2-[4-((biphenyl-4-ylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid	
2-benzyl-4-{3-[(biphenyl-4-ylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoic acid	

As noted above, compounds of the invention bind to and preferably, inhibit PTP-1B. As a result, compounds of the invention are useful in the treatment of various diseases, including controlling or treating Type 2 diabetes, improving glucose tolerance, and in improving insulin sensitivity in patients in need thereof. Compounds or their pharmaceutically acceptable salts are also useful in treating or controlling other PTP-1B mediated diseases, such as the treatment of cancer, neurodegenerative diseases and the like.

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, isopropoxy and hexyloxy.

As used herein, the term "alkyl" includes those alkyl groups of a designed number of carbon atoms. Alkyl groups may

be straight, or branched. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like.

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 C_3-C_8 cyclic hydrocarbon. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

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

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-tetrahydroisoquinoline, piperazine, morpholine, piperidine, tetrahydrofuran, pyrrolidine, pyridinonyl, and pyrazole. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, pyridinonyl, dihydropyrrolidinyl, and pyrrolidinonyl.

The term "heteroaryl" refers to an aromatic ring containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heteroaryl ring may be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings. Examples of

heteroaryl groups include, for example, pyridine, furan, thienyl, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl.

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic or diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included.

The compounds 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 and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile,

fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I 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 general Formula I 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, 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 antiinflammatory 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.

As noted above, the invention also provides methods and compositions for combination therapy of Type I and Type II diabetes. In one such aspect, the invention provides methods of using compounds of formula I in combination with one or more

angiotensin converting enzyme (ACE) inhibitors for improving the cardiovascular risk profile in patients experiencing or subject to Syndrome X or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic.

These methods include the reduction of hyperlipidemia in a patients experiencing or subject to Syndrome X or type II diabetes. These methods include methods lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. The methods herein may further be characterized as useful for inhibiting, preventing or reducing atherosclerosis in a type II diabetics, or for reducing the risk factors thereof.

These methods also include the lowering of free fatty acid blood levels and triglyceride levels in type II diabetics.

Among the ACE inhibitors which may be utilized with the invention described herein are quinapril, ramipril, verapamil, captopril, diltiazem, clonidine, hydrochlorthiazide, benazepril, prazosin, fosinopril, lisinopril, atenolol, enalapril, perindropril, perindropril tert-butylamine, trandolapril and moexipril, or a pharmaceutically acceptable salt form of one or more of these compounds.

The invention also provides methods of using PTPase 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), preferably in human type II diabetics or a patient experiencing or subject to Syndrome X. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic or a patient experiencing or subject to Syndrome X.

The invention also provides methods of using a pharmacological combination of one or more PTPase inhibiting

agents, one or more biguanide agents, and, optionally one or more sulfonylurea agents for treatment of type II diabetes or Syndrome X in a patient in need of such treatment. Also provided are methodS of using these agents to treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia in a patient in need thereof. Further included in this invention is a method of modulating blood glucose levels in a patient in need thereof.

Each of these methods comprises administering to a patient in need thereof pharmaceutically effective amounts of:

a) a PTPase inhibiting agent of formula I; and

b) a biguanide agent; and

c) optionally, a sulfonylurea agent.

Biguanide agents useful with this invention include metformin and its pharmaceutically acceptable salt forms. Sulfonylurea agents useful for the methods and combinations of this invention may be selected from the group of glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form of these agents.

This invention also provides pharmaceutical compositions and methods of using PTPase inhibitors of formula I in combination with one or more alpha-glucosidase inhibitors, such as miglitol or acarbose, for improving the cardiovascular risk profile in patients experiencing or subject to Syndrome X or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the reduction of risk factors for heart disease, stroke or heart attack in a patient in such need.

These methods include the reduction of hyperlipidemia in type II diabetics, including methods in type II diabetics for lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. The methods herein may further be characterized as useful for inhibiting, preventing or reducing atherosclerosis in a type II

diabetic or a patient experiencing or subject to Syndrome X, or the risk factors of either.

These methods also include the lowering free fatty acid blood levels and triglyceride levels in type II diabetics, or a patient experiencing or subject to Syndrome X.

Among the alpha-glucosidase inhibitors which may be utilized with the invention described herein are miglitol or acarbose, or a pharmaceutically acceptable salt form of one or more of these compounds.

This invention further provides methods for using a PTPase inhibitor of the invention and a sulfonylurea agent for the management of Syndrome X or type 2 diabetes and for improving the cardiovascular risk profile in patients experiencing or subject to those maladies. These methods may also be characterized as the reduction of risk factors in such patients for heart disease, stroke or heart attack in a type II diabetic. Such methods include the reduction of hyperlipidemia in a patients experiencing or subject to Syndrome X or type II diabetes and include methods for lowering low density lipoprotein (LDL) blood levels, high density lipoprotein (HDL) blood levels, and overall blood lipoprotein levels. The methods herein may further be characterized as inhibiting, preventing or reducing atherosclerosis in patients subject to or experiencing Syndrome X or type II diabetes, or the risk factors thereof. Such methods further include the lowering of free fatty acid blood levels and triglyceride levels in such patients.

Representative sulfonylurea agents include glipizide, glyburide (glibenclamide), chlorpropamide, tolbutamide, tolazamide and glimepriride, or the pharmaceutically acceptable salt forms thereof.

In addition, the invention provides combinations of a PTPase inhibitor of the invention and at least one thiazolidinedione agents. Such combinations are useful for treatment, inhibition or maintenance of Syndrome X or type II diabetes in patients in need of such treatment. Accordingly,

methods of using such combinations are provided by the invention. Thus, the invention provides methods of using these agents to treat or inhibit metabolic disorders mediated by insulin resistance or hyperglycemia in patients in need thereof. Further included in this invention are methods of modulating blood glucose levels in a patient in need thereof.

Each of these methods comprises administering to a patient in need thereof pharmaceutically effective amounts of:

a) a thiazolidinedione agent, such as selected from the group of pioglitizone and rosiglitazone, or a pharmaceutically acceptable salt form of these agents; and

b) a compound of formula I.

The invention also provides pharmaceutical compositions and methods of using PTPase inhibitors in combination with one or more antilipemic agents. Such methods and compositions are useful for improving the cardiovascular risk profile in patients experiencing or subject to type II diabetes (non-insulin-dependent diabetes mellitus), preferably in type II diabetics or Syndrome X. These methods also include reducing the risk factors for heart disease, stroke or heart attack in a type II diabetic or a patient experiencing or subject to Syndrome X. Such methods further include the reduction of hyperlipidemia in type II diabetics, including such methods in type II diabetics for lowering low density lipoprotein (LDL) blood levels and to increase high density lipoprotein (HDL) blood levels. These compositions and methods are also useful for inhibiting, preventing or reducing atherosclerosis in a type II diabetic or a patient experiencing or subject to Syndrome X, or the risk factors thereof. In this aspect, the compositions and methods are useful for lowering of free fatty acid blood levels and triglyceride levels in type II diabetics, or patients experiencing or subject to Syndrome X.

Representative antilipemic or agents, also known as antihyperlipidemic agents, suitable for use in the invention are bile acid sequestrants, fibric acid derivatives, HMG-CoA

reductase inhibitors and nicotinic acid compounds. Bile acid sequestrant agents useful with this invention include colestipol and colesevelam, and their pharmaceutically acceptable salt forms. Fibric acid derivatives which may be used with the present invention include clifofibrate, gemfibrozil and fenofibrate. HMG-CoA reductase inhibitors, also known as statins, useful with this invention include cerivastatin, fluvastatin, atorvastatin, lovastatin, pravastatin and simvastatin, or the pharmaceutically acceptable salt forms thereof. Niacin is an example of a nicotinic acid compound which may be used with the methods of this invention. Also useful are lipase inhibiting agents, such as orlistat.

This invention also provides pharmaceutical compositions that are a combination of a compound of Formula I and an aldose reductase inhibitor (ARI). Such combinations are useful in methods for treating, inhibiting or preventing type II diabetes, or its related and associated symptoms, disorders and maladies. These methods comprise administering to a patient in need of such therapy a pharmaceutically effective amount of a composition comprising a combination of pharmaceutically effective amounts of a compound of formula I and an ARI. These compositions and methods are useful for the treatment, prevention or inhibition of diabetic neuropathy, diabetic nephropathy, retinopathy, keratopathy, diabetic uveitis, cataracts.

Representative suitable ARIs are disclosed in U.S. Patent Nos. 6,420,426 and 6,214,991.

Combinations of the compounds of Formula I and an ARI are also useful for inhibition or reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic. Therefore, in this aspect the invention is useful for reducing hyperlipidemia and/or low density lipoprotein (LDL) blood levels in type II diabetics. Also included in this aspect are methods for inhibiting, preventing or reducing atherosclerosis or the risk factors thereof in type II diabetics. This aspect includes

lowering of free fatty acid blood levels and triglyceride levels.

This invention also provides methods of using a compound of formula I and insulin(s) for the management of type I or type II diabetes. Accordingly, the invention provides for combination therapy, i.e., where a compound of Formula I is administered in combination with insulin. Such combination therapy encompasses simultaneous or sequential administration of the compound of Formula I and insulin. The insulins useful in this aspect include both naturally occurring and synthetic insulins.

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

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

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

Also useful with the methods and formulations of this invention are intermediate and rapid acting insulin combinations, such as the HUMALOG® Mix 75/25 (75% Insulin Lispro Protamine Suspension and 25% Insulin Lispro Injection), HUMULIN® 50/50 (50% Human Insulin Isophane Suspension and 50% Human Insulin Injection) and HUMULIN® 70/30 (70% Human Insulin Isophane Suspension and 30% Human Insulin Injection), each available from Eli Lilly and Company. Also useful are the NOVALIN® 70/30 (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection) line of combination products available from Novo Nordisk Pharmaceuticals.

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

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

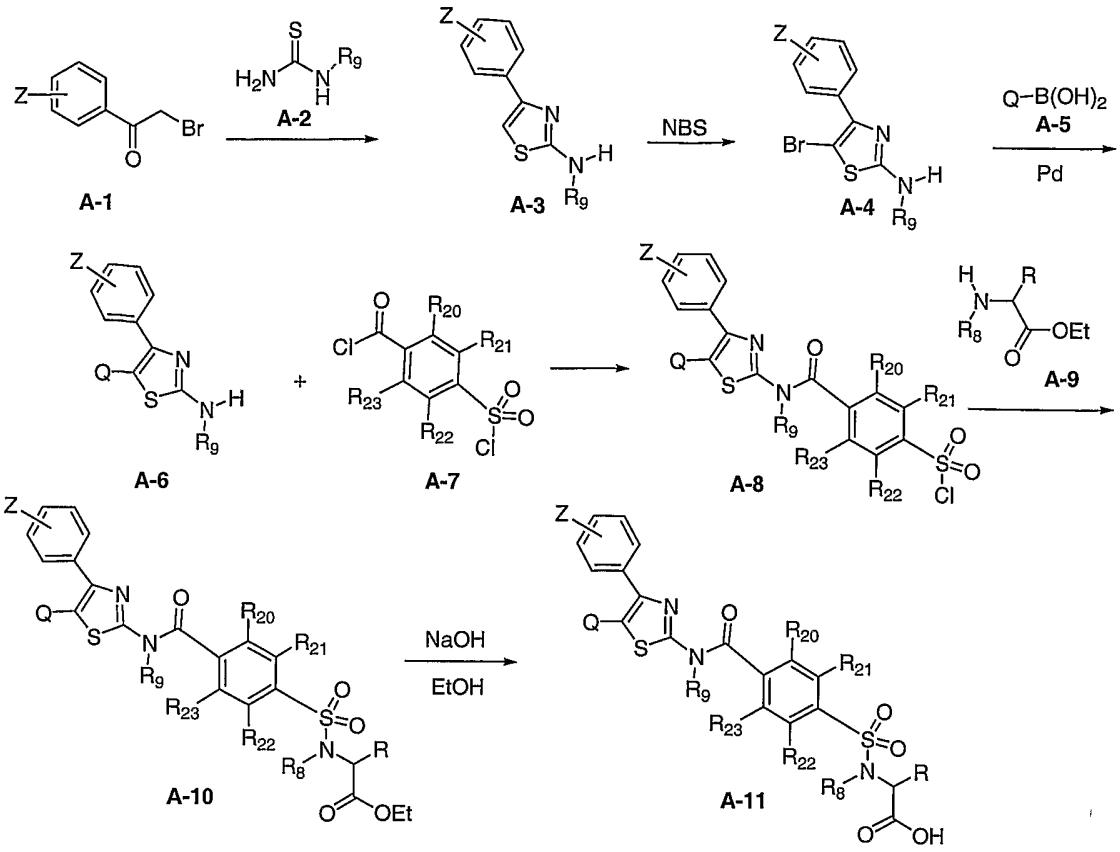
Each of these insulin products can be administered as directed by a medical professional using administrations, dosages and regimens known in the art, such as those published for each product in the Physicians' Desk Reference, 55 Edition, 2001, published by Medical Economics Company, Inc. at Montvale, N.J., the relevant sections of which are incorporated herein by reference. In this aspect, the invention includes, for example, methods for improving the cardiovascular and cerebrovascular risk profiles in patients experiencing or subject to type I or type II diabetes (non-insulin-dependent diabetes mellitus), preferably in human type II diabetics. These methods may also be characterized as the inhibition or reduction of risk factors for heart disease, stroke or heart attack in a type II diabetic.

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. Representative methods for synthesizing compounds of the invention are presented below. It is understood that the nature of the

substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below.

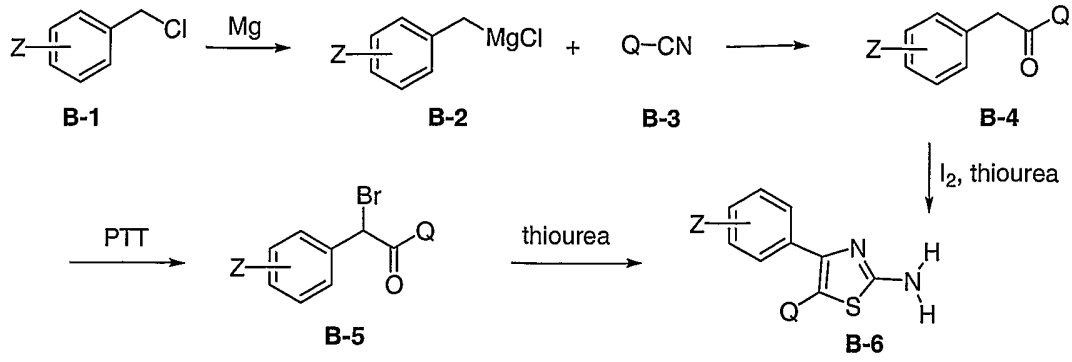
Methods of Preparation

Compounds of the invention where A in Formula I is a thiazole, L_2 is $-C(O)N(R_9)-$ and L_1 is $-SO_2N(R_8)$alkyl can be conveniently prepared from a substituted 2-bromoacetophenone using general Scheme A set forth below. In this method, the desired 2-bromoacetophenone A-1 is cyclized with thiourea A-2 in an alcoholic solvent to form the thiazole product A-3. Subsequent bromination with NBS followed by coupling with a Q-boronic acid provides intermediate A-6. If the boronic acid is not readily available, other metallic intermediates such as the tin or zinc reagent may be used. The 2-aminothiazole can then be coupled to the desired acid chloride A-7 using standard conditions. The resulting sulfonyl chloride A-8 can subsequently be coupled to the amino acid ester A-9 by treatment with a base like triethylamine or pyridine in DMF or dichloromethane. The coupled product A-10 can then be hydrolyzed to give the target compound, A-11, by treatment with aqueous NaOH in a solvent like THF or ethanol.



Scheme A

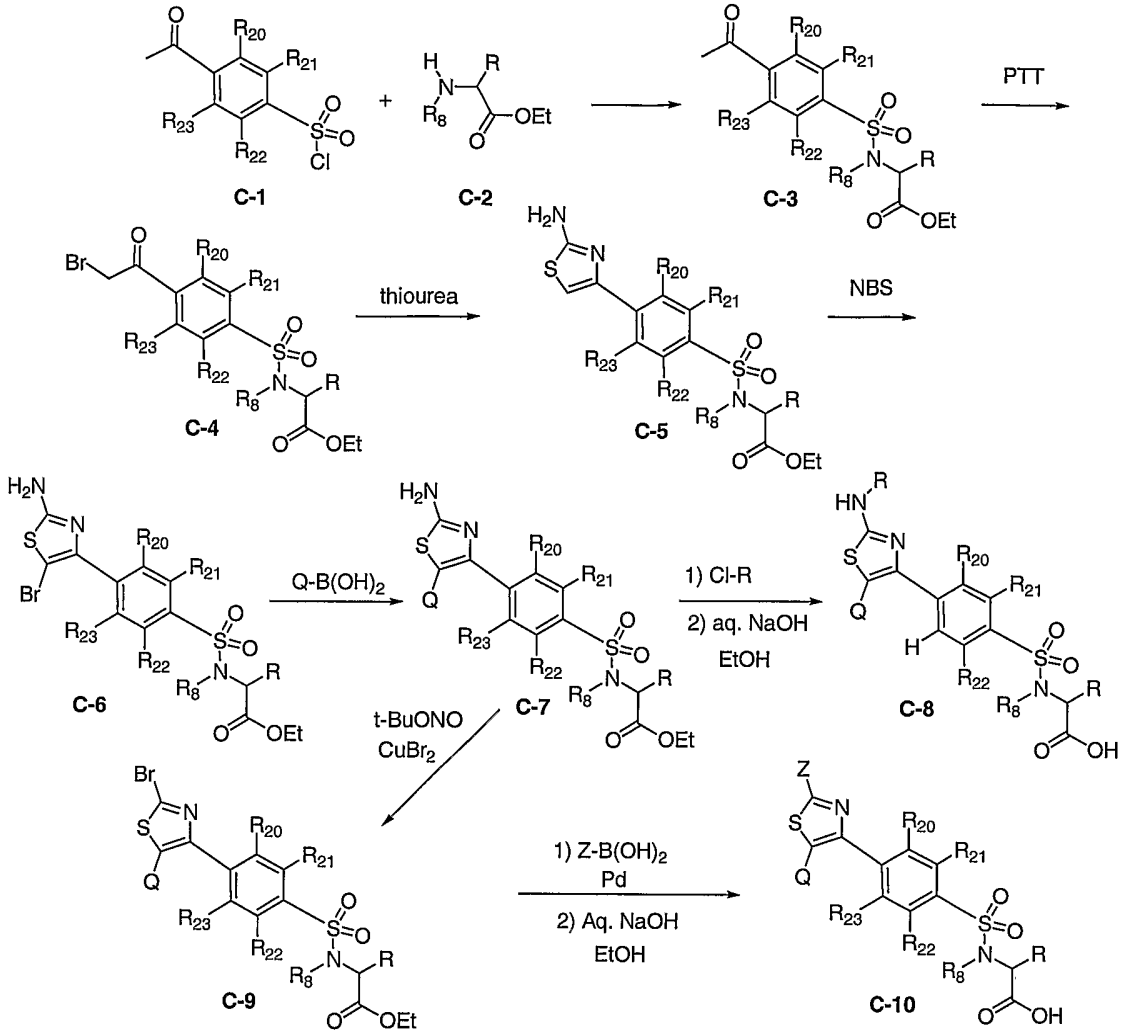
An alternate method for preparing the 4,5-disubstituted-2-amino thiazole intermediate is outlined in scheme B. Here a substituted benzyl chloride or bromide B-1 is treated with magnesium to form the corresponding Grignard reagent B-2. Subsequent treatment with nitrile B-3 followed by an acid hydrolysis gives ketone B-4. Bromination with PTT and subsequent cyclization with thiourea gives the desired aminothiazole intermediate B-6. Alternatively, ketone B-4 can be converted directly to thiazole B-6 by treatment with iodine and thiourea.



Scheme B

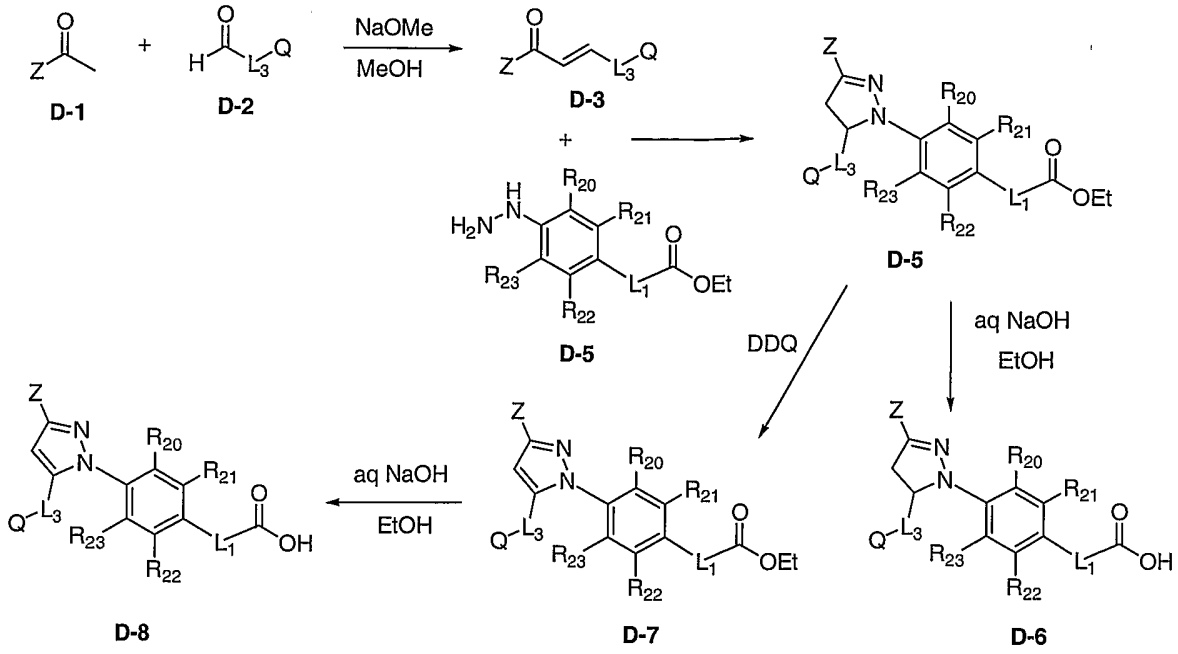
Compounds of the invention where A in Formula I is a thiazole, L_2 and L_3 are bonds and -L-C(R_2)(R_3)- is -SO_2N(R_8)alkyl can be prepared from a substituted 2-bromoacetophenone using general Scheme C set forth below.

In this method sulfonyl chloride C-1 is coupled to aminoalkyl acid C-2 to give the sulfonamide. Treatment of methyl ketone C-3 with PTT followed by thiourea give 2-aminothiazole C-5. Bromination at the 5-position with NBS gives bromide C-6, which can be coupled to a variety of Q groups (C-7). Many possible methods can be used for this coupling reaction. Some of the most common methods use an aryl or heteroaryl boronic acid, tin or zinc reagent with a palladium catalyst. The amino group on the thiazole intermediate C-7 can be functionalized using a variety of alkylation or acylation reactions. Subsequent hydrolysis of these intermediates gives target compounds C-8. Alternatively, Intermediate C-7 can be treated with t-BuONO and $CuBr_2$ to give the corresponding bromide (C-9), which can be modified, as previously described to give target compounds C-10.



Scheme C

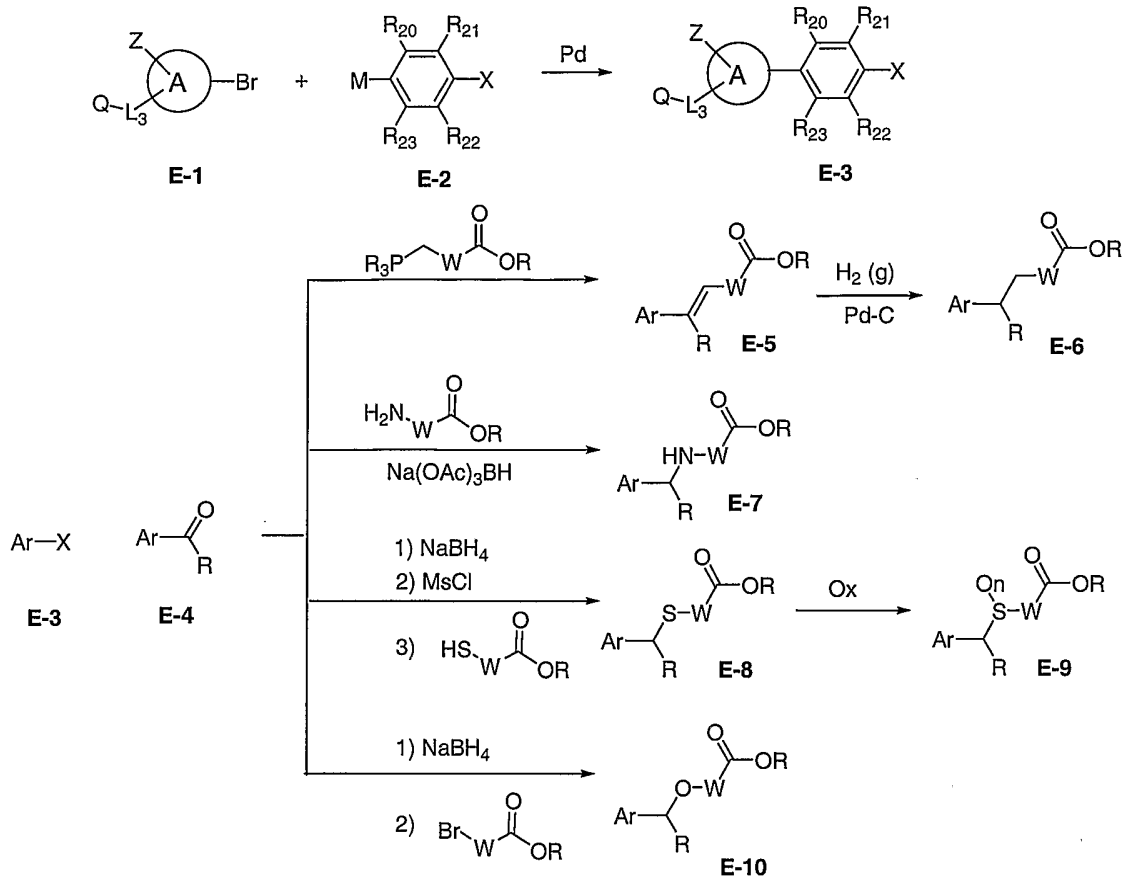
Compounds of the invention where A is a substituted pyrazole or pyrazoline and L_2 is a bond can typically be prepare using the chemistry described in scheme D. Here methyl ketone D-1 and aldehyde D-2 undergo an aldol condensation and form an α, β-unsaturated ketone D-3 when they are treated with a sodium alkoxide in an alcohol solvent. Intermediate D-3 can subsequently be cyclized with an appropriately substituted hydrazine D-4 to give the pyrazoline product D-5. Hydrolysis gives the pyrazoline product D-6. Alternatively, intermediate D-5 may be oxidized with DDQ to give ester intermediate D-7. Hydrolysis gives the desired pyrazole target compound D-8.



Scheme D

Compounds with a variety of L_1 linkers (Formula I) can be prepared using the chemistry described in general scheme E. Here aryl or heteroaryl bromide E-1 is coupled to intermediate E-2 containing a functional group X that can be modified to provide the desired L_1-CO_2R substituent. The initial coupling reaction between intermediates E-1 and E-2 can often be carried out using a transition metal coupling reaction. Some of the most useful reactions of this type include the Suzuki, Stille and Negishi reactions. Alternatively, for some examples, it may be more convenient to reverse the coupling functional groups such that metal-M is on the E-1 intermediate and the halogen, preferable Br or I, is on the E-2 intermediate. A variety of X substituents may be useful for preparing compounds with a specific L_1-CO_2R group. Some useful X substituents include sulfonamides, acids, esters, aldehydes, ketones, amides, nitro groups, anilino groups, hydroxyl groups, sulfides and halides. Some examples of targets compounds prepared from intermediate E-

3 with X equal to aldehyde or ketone are illustrated in scheme E.



Scheme E

Treatment of carbonyl compound E-4 with a Wittig type reagent provides the unsaturated derivative E-5. If the saturated compound E-6 is required, simple hydrogenation with, for example, palladium on carbon can be used. In some cases the carboxylic acid moiety (R = H) may need to be protected as an ester to facilitate the reactions in the scheme. Carbonyl compound E-4 can also be coupled with an amine derivative using a reducing agent like sodium triacetoxyborohydride in a reductive amination reaction to give the corresponding amine E-7. Reduction of aldehyde or ketone E-4 with sodium borohydride gives the corresponding alcohol. Subsequent conversion of this alcohol to a leaving group such as a mesylate or halide followed be displacement with a nucleophile such as a thiol gives sulfide

E-8, which if desired can be oxidized to form the sulfoxide or sulfone. Similarly, the same mesylate or halogen leaving group can be displaced by other nucleophiles like amines or alcohols to give the corresponding amine and ether linkers. The sodium borohydride reduction product can also be coupled directly to an alkyl halide or substituted phenol using simple alkylation or Mitsunobu conditions respectively.

Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the sequence of the reactions altered, and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups as well as the conditions necessary to attach and remove such groups will be apparent to those skilled in the art of organic synthesis.

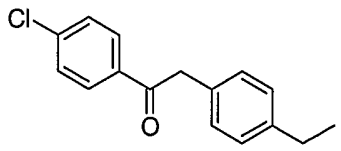
The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference in their entirety.

The preparation of the compounds of the present invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. In all cases, unless otherwise specified, the column chromatography is performed using a silica gel solid phase.

Example 1

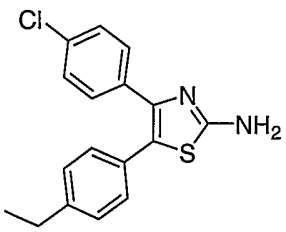
Preparation of 2-{4-[4-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid

Step 1: Preparation of 1-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-ethanone



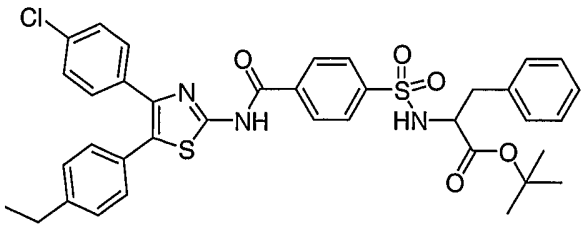
In an oven dried 50 mL round-bottomed flask under an atmosphere of dry nitrogen, a solution of magnesium turnings (2.92 g, 120 mmol) in anhyd THF (10 mL) is treated with 4-ethylbenzylchloride (17.7g, 114 mmol) in anhyd THF (60 mL) and then stirred for 30 min. While stirring, the temperature is maintained between 30 and 38 °C using an ice-bath. The resulting purple solution is stirred at room temperature for an additional 3 h, cooled to -10 °C (NaCl-ice water bath) and then a solution of 4-chlorobenzyl nitrile (13.0 g, 94.6 mmol) in anhyd THF (50 mL) is added over 10 min. During the addition the temperature is maintained between -10 and -15 °C. After the addition is complete, the ice bath is removed and the resulting solution is stirred for an additional 4 h. Once complete, the reaction mixture is cooled to 0 °C degree (ice-bath), and acidified with 5% aq H_2SO_4 to a pH < 7. After stirring an additional 15 min without the ice-bath, the solution is extracted with diethyl ether (2 x 200 mL) and the combined organic extracts are washed sequentially with water (150 mL) and sat'd aq NaCl (100 mL). The resulting solution is dried over $MgSO_4$, filtered, concentrated under reduced pressure, and then purified by flash column chromatography (0-15% ethyl acetate in heptane) to give 1-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-ethanone as a yellow oil (13.1 g, 54%).

Step 2: Preparation of 4-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylamine



In an oven dried 100 mL round-bottomed flask under an atmosphere of dry nitrogen, 1-(4-chloro-phenyl)-2-(4-ethyl-phenyl)-ethanone (13.1 g, 50.6 mmol), thiourea (7.71 g, 101 mmol) and iodine (12.8 g, 50.6 mmol) are combined and the neat mixture is heated to 90 °C. After stirring for about 72 h, 50 mL of H_2O is added and the mixture is then heated in a 120 °C oil bath for 30 min. After cooling to room temperature, the reaction mixture is poured into water (300 mL), basified with 1 N aq NaOH to a pH >8 and then extracted with dichloromethane (2 x 350 mL). The combined organic extracts are washed successively with water (200 mL) and sat'd aq NaCl (100 mL), dried over $MgSO_4$, filtered and concentrated. The concentrate is purified by flash column chromatography (10-30% ethyl acetate in heptane) to afford 4-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylamine (5.32 g, 33%).

Step 3: Preparation of 2-{4-[4-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid tert-butyl ester



In an oven dried 50 mL round-bottomed flask under an atmosphere of dry nitrogen, a solution of 4-chlorosulfonyl-benzoic acid (350 mg, 1.59 mmol) in dry 1,2-dichloroethane (10

mL) is treated with thionyl chloride (0.35 mL, 4.0 mmol), and then heated to reflux in a 100 °C oil bath for 4 h. After cooling to room temperature, the solution is concentrated under reduced pressure. The resulting residue is dissolved in anhyd. dichloromethane (15 mL), cooled to 0 °C, and then a solution of 4-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylamine (500 mg, 1.59 mmol) in dichloromethane (15 mL) is added over a time period of approximately 2 min. After stirring for about 1h at 0 °C, diisopropylethylamine (0.30 mL, 1.6 mmol) is added, and the solution is stirred for an additional 3 h. Next, H-Phe-Ot-Bu.HCl (652 mg, 1.59 mmol) and diisopropylethylamine (0.69 mL, 4.0 mmol) are added, and the solution is stirred for 1 h. The reaction mixture is then allowed to warm to room temperature, stirring is continued for 1 h, and then the reaction mixture is concentrated under reduced pressure. The resulting residue is purified by flash column chromatography (20-30% ethyl acetate in heptane) to give 2-{4-[4-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid tert-butyl ester (610 mg, 55%) as a yellow solid.

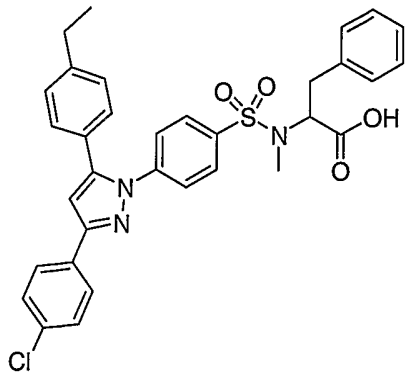
Step 4: Preparation of 2-{4-[4-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid

2-{4-[4-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid tert-butyl ester (1.20 g, 1.71 mmol) is treated with trifluoroacetic acid (6 mL) at room temperature. After stirring for 3 h. the solution is concentrated under reduced pressure and triturated with diethyl ether (3 mL). The yellow precipitate is filtered and washed with diethyl ether (2 x 3 mL), to give 2-{4-[4-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-thiazol-2-ylcarbamoyl]-

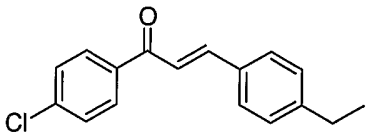
benzenesulfonylamino}-3-phenyl-propionic acid (750 mg, 68%) as a pale yellow solid.

Example 2

Preparation of 2-({4-[3-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid

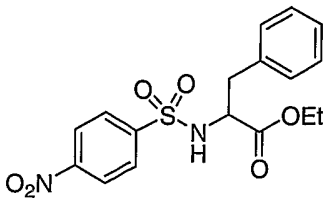


Step 1: Preparation of 1-(4-Chloro-phenyl)-3-(4-ethyl-phenyl)-propenone



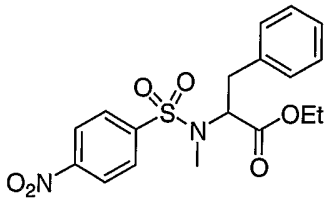
A solution of 4-chloroactophenone (6.18 g, 10 mmol) and 4-ethylbenzaldehyde (5.76 mL, 10.5 mmol) in dry methanol (25 mL) is treated with sodium methoxide (0.568 g, 10.5 mmol) and stirred at room temperature for 16 h. After the reaction is complete, the solution is acidified with 0.5 N HCl (25 mL) and the resulting precipitate is collected by filtration. The crude product is washed with a 50% methanol in water solution (3 X 25 mL) to give 1-(4-chloro-phenyl)-3-(4-ethyl-phenyl)-propenone (10.6 g, 98%) No further purification is required.

Step 2: Preparation of 2-(4-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid ethyl ester



A solution of phenylalanine ethyl ester hydrochloride (3.0 g, 10 mmol) and N,N-diisopropylethylamine (3.8 mL, 22 mmol) in dichloromethane (50 mL) is cooled to 0 °C (ice-water bath) and treated with 4-nitrobenzensulfonyl chloride (2.33 g, 10.5 mmol). After 30 min the solution is warmed to room temperature and stirring is continued for an additional 4 h. After the reaction is complete, the reaction mixture is diluted with water (100 mL), and the organic layer is extracted with dichloromethane (3 x 50 mL). The combined organic extracts are dried over MgSO4, filtered and concentrated. Purification by flash column chromatography (10% ethyl acetate in heptane) gives 2-(4-nitro-benzenesulfonylamino)-3-phenyl-propionic acid ethyl ester (3.56 g, 94%) as a white crystalline solid.

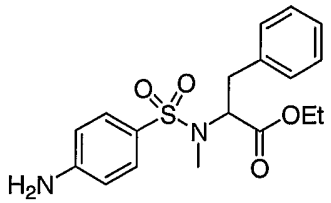
Step 3: Preparation of 2-[Methyl-(4-nitro-benzenesulfonyl)-amino]-3-phenyl-propionic acid ethyl ester



A solution of N-(4-nitrobenznesulfonyl)-phenylalanine ethyl ester (3.8 g, 10 mmol) and cesium carbonate (3.58 g, 11 mmol) in DMF (25 mL) is stirred for 10 min, then treated with methyl iodide (0.75 mL, 12 mmol). After stirring an additional 16 h, the reaction mixture is filtered; the filtrate is diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extracts are dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (10%

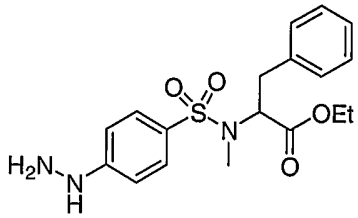
ethyl acetate in heptane) gave 2-[methyl-(4-nitro-benzenesulfonyl)-amino]-3-phenyl-propionic acid ethyl ester (3.5 g, 90%) as a white crystalline solid.

Step 4: Preparation of 2-[(4-Amino-benzenesulfonyl)-methyl-amino]-3-phenyl-propionic acid ethyl ester



A solution of 2-[methyl-(4-nitro-benzenesulfonyl)-amino]-3-phenyl-propionic acid ethyl ester (3.5 g, 9.0 mmol) and palladium on carbon (0.4 g) in ethyl acetate (25 mL), is treated with hydrogen gas at 20 psi for 4 h at room temperature. The resulting solution is filtered and concentrated. No further purification is necessary.

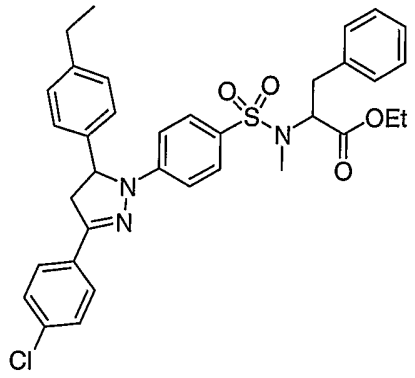
Step 5: Preparation of 2-[(4-Hydrazino-benzenesulfonyl)-methyl-amino]-3-phenyl-propionic acid ethyl ester hydrochloride



A solution of 2-[(4-amino-benzenesulfonyl)-methyl-amino]-3-phenyl-propionic acid ethyl ester in conc HCl (12 mL) is cooled to 0 °C (ice-bath) and carefully treated with aq $NaNO_2$ (0.69 g in 5 mL water, 10 mmol) at a rate such that the temperature does not rise above 5 °C. Stirring is continued for 1.5 h. Once complete, the solution is transferred to a separate ice-cooled solution of $SnCl_2$ (7.11 g, 37.5 mmol) in conc HCl (12 mL) and slowly warmed to room temperature with continued stirring for 2 h. The resulting precipitate is collected by filtration and

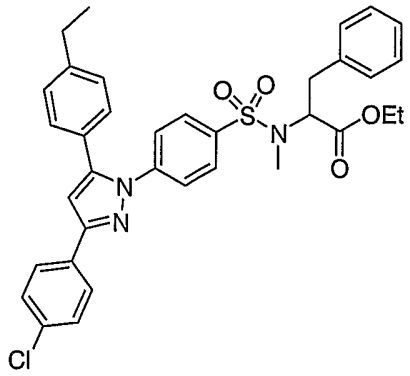
washed with benzene (3 x 100 mL) to give 2-[(4-hydrazino-benzenesulfonyl)-methyl-amino]-3-phenyl-propionic acid ethyl ester hydrochloride (xx g, 98%) as a white solid.

Step 6: Preparation of 2-({4-[3-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester



A solution of 1-(4-Chloro-phenyl)-3-(4-ethyl-phenyl)-propenone (0.270 g, 1 mmol) and 2-[(4-hydrazino-benzenesulfonyl)-methyl-amino]-3-phenyl-propionic acid ethyl ester hydrochloride (0.452 g, 1.1 mmol) in ethanol (50 mL) is heated to reflux for 4 h. After cooling to room temperature, the solution is concentrated, diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extracts are dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (10% ethyl acetate in heptane) provides 2-({4-[3-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester (0.49 g, 78%)

Step 7: Preparation of 2-({4-[3-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester



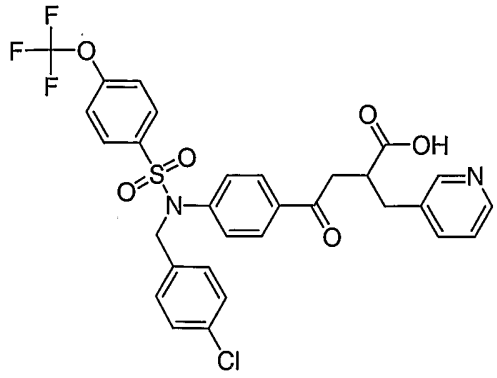
A solution of 2-({4-[3-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester (0.25 g, 0.4 mmol) in benzene (20 mL) is treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.136 g, 0.6 mmol) and refluxed for 6 h. After cooling to room temperature, the resulting solution is concentrated and purified by flash column chromatography (10% ethyl acetate in heptane) to give 2-({4-[3-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester (0.232 g, 95%).

Step 8: Preparation of 2-({4-[3-(4-Chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid

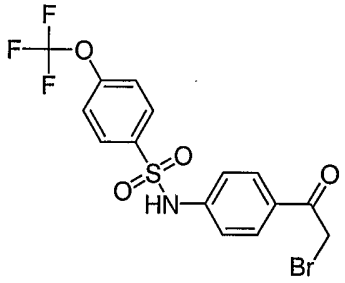
A solution of 2-({4-[3-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid ethyl ester in anhyd THF (2 mL) and methanol (6 mL) is treated with 10% v/v aq KOH (1 mL, 1 mmol). After stirring for 2 h, the solution is acidified to pH 2-3 with 0.5 N HCl, extracted with ethyl acetate (3 x 15 mL) and concentrated. Purification by flash column chromatography (50% ethyl acetate in heptane) gives 2-({4-[3-(4-chloro-phenyl)-5-(4-ethyl-phenyl)-pyrazol-1-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid (0.160 g, 85%) as a white solid.

Example 3

4-{4-[(-Chlorobenzyl)-(4-trifluoromethoxybenzenesulfonyl)-amino]-phenyl}-4-oxo-2-pyridin-3-ylmethyl-butyric acid.



Step 1: *N*-[4-(2-Bromoacetyl)-phenyl]-4-trifluoromethoxybenzenesulfonamide

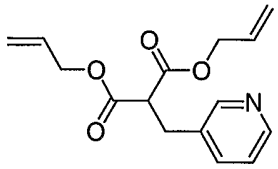


4-Trifluoromethoxybenzenesulfonyl chloride (3.18 g, 2.07 mL, 1.22 mmol) was added to a solution of 4'-aminoacetophenone (1.5 g, 1.11 mmol) and triethylamine (3.1 mL, 2.22 mmol) in anhydrous methylene chloride (50 mL). The reaction was stirred for 16 hours and then poured into water (50 mL), and extracted with diethyl ether (3 x 30 mL). The combined extract was washed with 0.5 N hydrochloric acid (2 x 10 mL), water and finally brine. The ethereal solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The product methyl ketone was used in the subsequent bromination step without further purification.

Phenyltrimethylammonium tribromide (4.68 g, 1.22 mmol) was added to a solution of the methyl ketone (prepared in the previous step) in anhydrous dioxan (50 mL). The reaction eas stirred at room temperature for 3 hours and then poured into water (50 mL), and extracted with diethyl ether (3 x 30 mL).

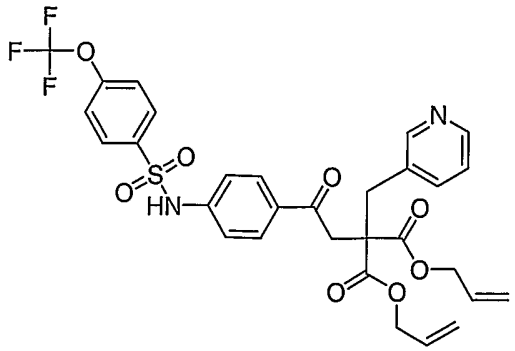
The combined extract was washed with 0water and brine. The ethereal solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the title compound has a white solid (4.36 g, 89%); 1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (4H, d, J = 8 Hz, Ar-H), 7.38 (2H, d, J = 8 Hz, Ar-H), 7.20 (3H, m, Ar-H, NH), 4.38 (2H, s, CH_2Br).

Step 2: 2-Pyridin-3-ylmethyl-malonic acid diallyl ester



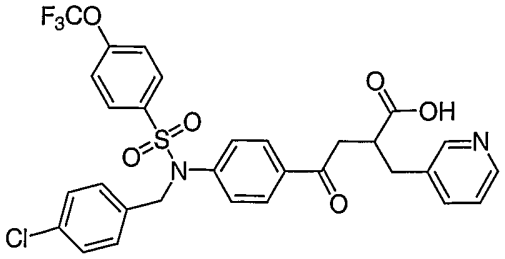
A solution of diallyl malonate (3.0 g, 16.3 mmol) in anhydrous THF (30 mL) was added cautiously to a stirred suspension of sodium hydride (95%, 900 mg, 36 mmol) in anhydrous THF (25 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of 3-(iodomethyl)pyridine hydroiodide (6.24 g, 18 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at room temperature for 16-24 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trituration and filtration from MeOH afforded the title compound as a white solid (4.03g, 90%); 1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (2H, m), 7.38 (1H, td, J = 8, 2 Hz, Ar-H), 7.20 (2H, dd, J = 8, 5 Hz), 5.82 (2H, m), 5.26 (4H, m), 4.60 (4H, m), 3.88 (1H, t, J = 7 Hz), 3.21 (2H, d, J = 7 Hz).

Step 3: 2-{2-oxo-2-[4-(4-trifluoromethoxybenzenesulfonylamino]-ethyl}-2-pyridin-3-ylmethyl-malonic acid diallyl ester



A solution of 2-pyridin-3-ylmethyl-malonic acid diallyl ester (1.15g, 4.18 mmol) in anhydrous THF (30 mL) was added to a stirred suspension of sodium hydride (95%, 232 mg, 9.2 mmol) in anhydrous THF (25 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of N-[4-(2-Bromoacetyl)-phenyl]-4-trifluoromethoxy-benzenesulfonamide (2.01 g, 4.6 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at 50°C for 5 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the title compound has a white solid (4.36 g, 89%); 1H NMR ($CDCl_3$, 300 MHz): δ 8.48 (1H, d, J = 3 Hz), 8.20 (1H, s), 7.90 (2H, d, J = 8 Hz), 7.78 (2H, d, J = 8 Hz), 7.42 (1H, d, J = 7 Hz), 7.32 (3H, m), 7.20 (1H, m), 7.12 (2H, d, J = 8 Hz), 5.88 (2H, m), 5.29 (4H, m), 4.62 (4H, s), 3.58 (2H, s), 3.50 (2H, s); ESI-LCMS e/z calcd for $C_{30}H_{27}F_3N_2O_8S$: 632.610, found 633 $(M+H)^+$.

Step 4: 4-{4-[(-Chlorobenzyl)-(4-trifluoromethoxybenzenesulfonyl)-amino]-phenyl}-4-oxo-2-pyridin-3-ylmethyl-butyric acid.



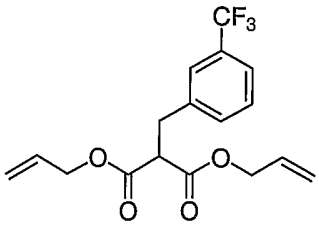
A solution of 2-{2-oxo-2-[4-(4-trifluoromethoxybenzenesulfonylamino]-ethyl}-2-pyridin-3-ylmethyl-malonic acid diallyl ester (1.06g, 1.67 mmol) in anhydrous THF (15 mL) was added to a stirred suspension of sodium hydride (95%, 47 mg, 1.84 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at room temperature for 1 hr. A solution of 4-chlorobenzyl chloride (0.3 g, 1.84 mmol) in anhydrous THF (25 mL) was added dropwise, and the resultant solution was stirred at 50°C for 5 hrs (TLC control). The reaction mixture was poured into water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The combined extract was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* affording the N-alkylated diallyl ester.

The diallyl ester was redissolved in dioxan (15 mL). *Tetrakis*-(Triphenylphospine)-palladium(0) (5 mg) and triethylamine (0.1 mL) was added to the stirred solution, and then the reaction was heated to 100°C for 30 mins, cooled to room temperature and concentrated *in vacuo*. Purification of the product by flash column chromatography, using 20 % ethyl acetate/heptane as eluent, afforded the title compound has a white solid (846 mg, 80%); Rf 0.30 (10% methanol in dichloromethane)1H NMR (MeOH-d4, 300 MHz): δ 8.42 (1H, s), 8.36 (1H, d, J = 3 Hz), 7.84 (2H, d, J = 8 Hz), 7.76 (3H, m), 7.42 (2H, d, J = 8 Hz), 7.35 (1H, dd, J = 8, 3 Hz), 7.20 (5H, m), 4.82 (2H, s), 3.42 (1H, m), 3.20 (1H, m), 3.02 (2H, m), 2.92 (2H, m); ESI-LCMS e/z calcd for $C_{30}H_{24}ClF_3N_2O_6S$: 633.041, found 633 $[M+H(^{35}Cl)]^+$, 635 $[M+H(^{37}Cl)]^+$.

Example 5

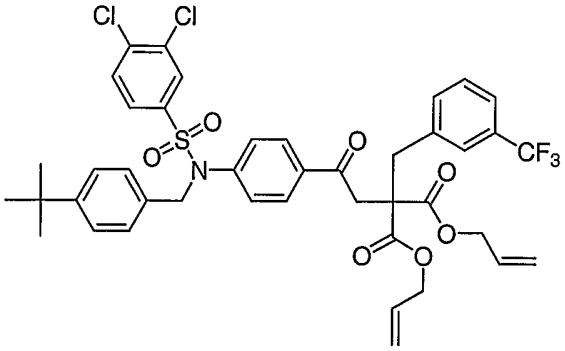
4-{4-[(4-tert-Butylbenzyl)-(3,4-dichlorobenzenesulfonyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.

Step 1: 2-(3-Trifluoromethylbenzyl)-malonic acid diallyl ester



2-(3-Trifluoromethylbenzyl)-malonic acid diallyl ester was prepared in analogous fashion to 2-Pyridin-3-ylmethyl-malonic acid diallyl ester, using malonic acid diallyl ester (4.5 g, 24.5 mmol), sodium hydride (95%, 680 mg, 27 mmol) and 3-trifluoromethylbenzyl bromide (6.45 g, 27 mmol), to yield the title compound as a colorless oil (6.87 g, 82%), 1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (2H, d, J = 8 Hz), 7.32 (2H, d, J = 8 Hz), 5.82 (2H, m), 5.24 (4H, m), 4.59 (4H, m), 3.72 (1H, t, J = 7 Hz), 3.31 (2H, d, J = 7 Hz).

Step 2: 2-(2-{4-[(4-*tert*-Butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester

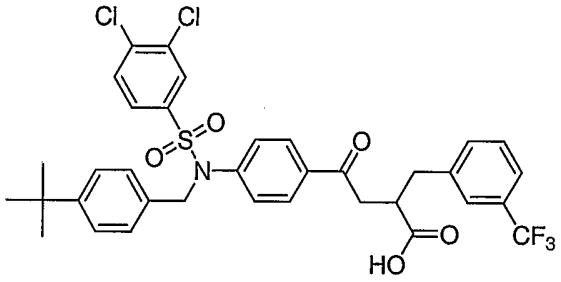


2-(2-{4-[(4-*tert*-Butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester was synthesized in similar fashion to that reported previously using *N*-{4-(2-bromoacetyl)phenyl]-3,4-

dichlorobenzene-sulfonamide as the second step alkylating reagent, to afford the *N*-alkylated product 2-{2-[4-(3,4-dichlorobenzenesulfonylamino)-phenyl]-2-oxoethyl}-2-(3-trifluoromethyl-benzyl}-malonic acid diallyl ester.

N-Alkylation of this intermediate with 4-*tert*-butylbenzyl bromide, under the conditions reported previously, afforded the N,N-dialkylated product. 1H NMR ($CDCl_3$, 300 MHz): δ 7.73 (1H, d, J = 8 Hz), 7.69 (1H, d, J = 2 Hz), 7.56 (2H, m), 7.47 (1H, m), 7.39 (1H, m), 7.32 (2H, m), 7.26 (4H, m), 7.10 (3H, m), 5.88 (2H, m), 5.26 (4H, m), 4.72 (2H, s), 4.64 (4H, m), 3.58 (2H, s), 3.42 (2H, s), 1.26 (9H, s).

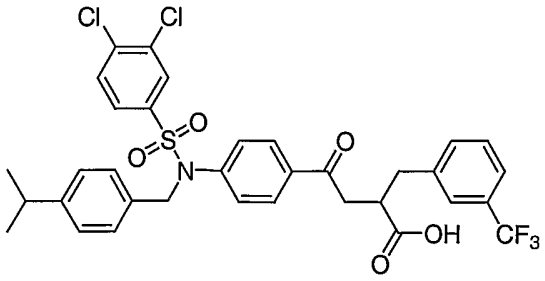
Step 3: 4-{4-[(4-tert-Butylbenzyl)-(3,4-dichlorobenzenesulfonyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.



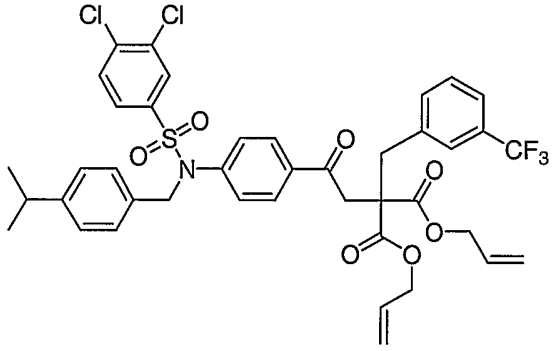
The title compound was prepared by saponification and decarboxylation of 2-(2-{4-[(4-*tert*-butylbenzyl)-(3,4-dichlobenzenesulfonyl)-amino]phenyl}-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester. Purification of the product by flash column chromatography, using 5 % methanol in dichloromethane as eluent, afforded the title compound has a beige solid; Rf 0.62 (10% methanol in dichloromethane): 1H NMR ($CDCl_3$, 300 MHz): δ 7.77 (1H, d, J = 8 Hz), 7.66 (2H, m), 7.28 - 7.54 (8H, m), 7.24 (2H, d, J = 9 Hz), 7.10 (2H, d, J = 9 Hz), 4.71 (2H, s), 3.16 - 3.38 (3H, m), 2.93 (2H, m), 1.25 (9H, s); ESI-LCMS e/z calcd for $C_{35}H_{32}Cl_2F_3NO_5S$: 706.606, found 706 $(M+H, {}^{35}Cl, {}^{35}Cl)^+$.

Example 6

4-{4-[(3,4-dichlorobenzenesulfonyl)-(4-isopropylbenzyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.



Step 1: 2-(2-{4-[(3,4-Dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester



2-(2-{4-[(3,4-Dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester was synthesized i via alkylation of 2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester with *N*-{4-(2-bromoacetyl)-phenyl]-3,4-dichlorobenzene-sulfonamide, with subsequent *N*-alkylation of this intermediate with 4-isopropylbenzyl bromide to afford the N,N-dialkylated product. 1H NMR ($CDCl_3$, 300 MHz): δ 7.73 (1H, d, J = 8 Hz), 7.69 (1H, s), 7.56 (2H, m), 7.47 (1H, m), 7.36 (3H, m), 7.26 (4H, m), 7.10 (3H, m), 5.89 (2H, m), 5.30 (4H, m), 4.71 (2H, s), 4.66 (4H, m), 3.56 (2H, s), 3.43 (2H, s), 2.83 (1H, sept, J = 7 Hz), 1.20 (3H, s), 1.18 (3H, s).

Step 2: 4-{4-[(3,4-dichlorobenzenesulfonyl)-(4-isopropylbenzyl)-amino]-phenyl}-4-oxo-2-(3-trifluoromethylbenzyl)-butyric acid.

The title compound prepared by saponification and decarboxylation of 2-(2-{4-[(3,4-dichlorobenzenesulfonyl-(4-isopropylbenzyl)-amino]-phenyl-2-oxoethyl)-2-(3-trifluoromethylbenzyl)-malonic acid diallyl ester. Purification of the product by flash column chromatography, using 5 % methanol in dichloromethane as eluent, afforded the title compound has a cream solid; Rf 0.60 (10% methanol in dichloromethane): 1H NMR ($CDCl_3$, 300 MHz): δ 7.76 (1H, d, J = 8 Hz), 7.70 (2H, m), 7.28 – 7.62 (8H, m), 7.24 (2H, m), 7.10 (2H, m), 4.70 (2H, s), 3.34 (1H, m), 3.20 (2H, m), 2.89 (2H, m), 2.81 (1H, sept, J = 7Hz), 1.19 (3H, s), 1.17 (3H, s); ESI-LCMS e/z calcd for $C_{34}H_{30}Cl_2F_3NO_5S$: 692.579, found 692 (M+H, ^{35}Cl, $^{35}Cl)^+$.

Example 7

The following compounds were prepared essentially according to the methods and procedures described above in the schemes and examples 1 to 6.

Still other compounds of the invention are the following, which were named using ChemDraw v. 6.02, which is sold by Cambridgesoft.com in Cambridge, MA.

Cmpnd. No.	Name
1	N-{[4-({[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;
2	N-({4-[3-(4-methoxyphenyl)-5-(4-pentylphenyl)-4,5-dihydro-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;
3	N-{[4-({[4-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

4 N-methyl-N-[(4-{5-(4-pentylphenyl)-3-[4-(trifluoromethoxy)phenyl]-4,5-dihydro-1H-pyrazol-1-yl}phenyl)sulfonyl]phenylalanine;

5 N-({4-[3-(4-methoxyphenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

6 N-methyl-N-[(4-{5-(4-pentylphenyl)-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]phenylalanine;

7 N-({4-[5-(4-butoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

8 2-benzyl-4-oxo-4-[3-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]butanoic acid;

9 N-{[4-({[4-(3-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

10 N-({4-[5-(4-isopropylphenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

11 N-{[4-({[4-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

12 N-{[4-({[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}-N-methylphenylalanine;

13 methyl (2S)-2-[4-((biphenyl-4-ylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoate;

14 N-{[4-({[4-(4-bromophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

15 N-{[4-({[4-(4-chlorophenyl)-5-(4-ethylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

16 (2S)-2-[4-((biphenyl-4-ylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

17 N-[(4-{[4,6-bis(4-methoxyphenyl)pyrimidin-2-yl]amino}phenyl)sulfonyl]-N-methyl-L-phenylalanine;

18 N-methyl-N-({4-[5-(4-pentylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)phenylalanine;

19 2-benzyl-4-[4-({[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

20 2-[3-[(4-butylphenyl)amino]-4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

21 2-[3-[(4-butylphenyl)amino]-4-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

22 (2S)-2-[3-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

23 2-{4-{[(4-bromophenyl)sulfonyl]amino}-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

24 N-({4-[2-[(4-chlorobenzoyl)amino]-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methylphenylalanine

25 (2S)-2-[4-((2-naphthylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

26 N-[(4-{4-bromo-3-(4-methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

27 N-({4-[5-(4-bromophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

28 2-{4-[(4-bromobenzoyl)amino]-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

29 N-({4-[(6-bromo-4-phenylquinazolin-2-yl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

30 N-({4-[2-[(cyclopentylacetyl)amino]-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

31 N-({4-[2-(4-chlorophenyl)-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

32 N-({4-[5-(4-ethylphenyl)-2-(6-methoxypyridin-3-yl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

33 2-(3-[(4-butylphenyl)amino]-4-{[(4-chloro-3-nitrophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

34 N-[(4-{[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}phenyl)sulfonyl]-N-methyl-L-phenylalanine;

35 2-[3-[(4-butylphenyl)amino]-4-({[5-(dimethylamino)-1-naphthyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

36 2-(3-[(4-butylphenyl)amino]-4-{[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

37 2-benzyl-4-[3-((2-naphthylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

38 N-[(4-{3-(4-chlorophenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

39 N-({4-[3-(4-chlorophenyl)-5-(4-ethylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

40 N-[(4-{4-bromo-3-(4-chlorophenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

41 N-({4-[4-bromo-3-(4-chlorophenyl)-5-(4-ethylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

42 N-({4-[5-(4-bromophenyl)-3-(4-chlorophenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

43 N-({4-[3-(4-chlorophenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

44 N-({4-[4-bromo-3-(4-chlorophenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

45 2-{4-{[(4-bromo-3-fluorophenyl)sulfonyl]amino}-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

46 2-{4-({[4-bromo-3-(trifluoromethyl)phenyl]sulfonyl}amino)-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

47 2-benzyl-4-[3-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

48 2-{4-({[4-bromo-2-(trifluoromethoxy)phenyl]sulfonyl}amino)-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

49 2-(3-[(4-butylphenyl)amino]-4-{[(3,4-dichlorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

50 diallyl {2-oxo-2-[4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]ethyl}[4-(trifluoromethyl)benzyl]malonate;

51 N-({4-[(6-isopropyl-4-phenylquinazolin-2-yl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

52 N-({4-[5-(4-chlorophenyl)-2-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-ethyl-L-phenylalanine;

53 N-({4-[5-(4-chlorophenyl)-2-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)phenylalanine;

54 N-({4-[2,5-bis(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)phenylalanine;

55 2-(3-[(4-butylphenyl)amino]-4-{[(3,4-dibromophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

56 2-benzyl-4-(4-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

57 methyl 2-benzyl-4-(3-{(biphenyl-4-ylmethyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

58 methyl 2-benzyl-4-(3-{(3,4-dichlorobenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

59 methyl 2-benzyl-4-{3-[[4-chloro-3-(trifluoromethyl)benzyl](2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

60 methyl 2-benzyl-4-{3-[(biphenyl-4-ylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

61 2-benzyl-4-{3-[(biphenyl-4-ylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoic acid;

62 2-(3-[(4-bromophenyl)amino]-4-{[(4-butylphenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

63 methyl 2-benzyl-4-{3-[(2-naphthylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

64 2-benzyl-4-{3-[(2-naphthylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoic acid;

65 4-{3-[(2-anthrylsulfonyl)(2-naphthylmethyl)amino]phenyl}-2-benzyl-4-oxobutanoic acid;

66 methyl 2-benzyl-4-{3-[{[4-(dimethylamino)-3-fluorophenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

67 methyl 2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoate;

68 methyl 2-benzyl-4-{3-[{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

69 2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

70 methyl 2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-difluorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate; or

71 methyl 2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-fluorophenyl]sulfonyl}amino)phenyl]-4-oxobutanoate.

Yet still other compounds of the invention are the following, which were named using ChemDraw v. 6.02, which is sold by Cambridgesoft.com in Cambridge, MA.

Ex. No.	Name
72	(2S)-2-[4-([4-(methoxycarbonyl)benzyl]{[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;
73	2-benzyl-4-oxo-4-[4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl] butanoic acid;
74	2-[3-[(4-butylphenyl)amino]-4-({[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

75 N-{[4-[(4-butylphenyl)amino]-3-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl] sulfonyl}-N-methyl-L-phenylalanine;

76 benzyl (2S)-2-[4-([(5-nitro-2-furyl)methyl]{[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoate;

77 (2R)-2-[4-({[4-chloro-2-(trifluoromethyl)quinolin-5-yl]methyl}{[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

78 2-(4-[(4-butylphenyl)amino]-3-{[4-(trifluoromethoxy)benzoyl]amino}phenoxy)-3-phenylpropanoic acid;

79 2-(3-[(4-butylphenyl)amino]-4-{[(4-chlorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

80 N-({4-[(6-bromo-4-phenylquinazolin-2-yl)(carboxymethyl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

81 2-(3-[(4-butylphenyl)amino]-4-{[(3-cyano-4-fluorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

82 4-[4-((4-chlorobenzyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxo-2-(pyridin-3-ylmethyl)butanoic acid;

83 2-benzyl-4-[4-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

84 2-benzyl-4-{4-[{[4-methoxy-3-(trifluoromethyl)phenyl]sulfonyl}(1-naphthylmethyl)amino]phenyl}-4-oxobutanoic acid;

85 2-benzyl-4-(4-{[(3,4-dichlorophenyl)sulfonyl][4-(trifluoromethoxy)benzyl]amino}phenyl)-4-oxobutanoic acid;

86 2-benzyl-4-(4-{[4-chloro-3-(trifluoromethyl)benzyl][(3-fluoro-4-methoxyphenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

87 methyl 2-benzyl-4-{3-[[(3,4-dichlorophenyl)sulfonyl](2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

88 methyl 2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

89 2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

90 2-benzyl-4-(3-{(biphenyl-4-ylmethyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

91 methyl 4-(3-{(4-benzoylbenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-2-benzyl-4-oxobutanoate;

92 2-benzyl-4-{3-[[(3,4-dichlorophenyl)sulfonyl](4-isopropylbenzyl)amino]phenyl}-4-oxobutanoic acid;

93 4-(4-dibenzo[b,d]furan-4-ylphenyl)-4-oxo-2-[3-(trifluoromethyl)benzyl]butanoic acid;

94 2-benzyl-4-{3-[{[4-methoxy-3-(trifluoromethyl)phenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoic acid;

95 methyl 2-benzyl-4-{3-[[(3,4-difluorophenyl)sulfonyl](2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

96 N-{[4-(2-bromo-5-dibenzo[b,d]furan-4-yl-1,3-thiazol-4-yl)phenyl]sulfonyl}phenylalanine;

97 N-{[4-(5-bromo-2-dibenzo[b,d]furan-4-yl-1,3-thiazol-4-yl)phenyl]sulfonyl}phenylalanine;

98 2-[4-(5-Bromo-2-dibenzofuran-4-yl-thiazol-4-yl)-benzenesulfonylamino]-3-phenyl-propionic acid

99 2-[4-(2-Dibenzofuran-4-yl-thiazol-4-yl)-benzenesulfonylamino]-3-phenyl-propionic acid

100 (4-{2-[(8-Chloro-dibenzofuran-4-carbonyl)-amino]-5-ethyl-thiazol-4-yl}-phenoxy)-phenyl-acetic acid

101 [4-(2-Benzo[b]thiophen-3-yl-5-ethyl-thiazol-4-yl)-phenoxy]-phenyl-acetic acid

102 [4-(2-Dibenzofuran-4-yl-5-ethyl-thiazol-4-yl)-phenoxy]-phenyl-acetic acid.

Still other compounds of the invention are

2-{4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;	R_f 0.66 (20% methanol in dichloromethane) ^1H NMR (CD_3OD, 300 MHz) δ 8.03 (d, J = 8.4 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 2 H), 7.49 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.24-7.15 (m, 9 H), 4.13-4.05 (m, 1 H), 3.12-3.06 (m, 1 H), 2.90-2.82 (m, 1 H), 2.38 (s, 3 H) ; ESI-LCMS *m/z* calcd for $C_{32}H_{26}ClN_3O_5S_3$: 631; found 630 $(M - 1)^+$.
2-{4-[4-(3-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;	R_f 0.63 (20% methanol in dichloromethane), ^1H NMR (CD_3OD, 300 MHz) δ 8.03 (d, J = 8.4 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 2 H), 7.58 (br s, 1 H), 7.40-7.37 (m, 1 H), 7.27-7.12 (m, 11 H), 4.11 (dd, J1 = 9.0 Hz, J2 = 5.4 Hz, 1 H), 3.09 (dd (J1 = 13.8 Hz, J2 = 5.4 Hz, 1 H), 2.85 (dd, J1 = 13.8 Hz, J2 = 9.9 Hz, 1 H), 2.39 (s, 3 H); ESI-LCMS *m/z* calcd for $C_{32}H_{26}ClN_3O_5S_3$: 631; found 630 $(M - 1)^+$.
2-{4-[4-(2-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;	R_f 0.64 (20% methanol in dichloromethane), ^1H NMR (CD_3OD, 300 MHz) δ 8.03 (d (J = 8.4 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.47-7.23 (m, 2 H), 7.18-7.04 (m, 11 H), 4.11 (dd, J1 = 8.7 Hz, J2 = 5.1 Hz, 1 H), 3.09 (dd, J1 = 13.8 Hz, J2 = 4.8 Hz, 1 H), 2.85 (dd, J1 = 13.8 Hz, J2 = 9.3 Hz, 1 H), 2.30 (s, 3 H); ESI-LCMS *m/z* calcd for $C_{32}H_{26}ClN_3O_5S_3$: 631; found 630 $(M - 1)^+$.

2-({4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;	R_f 0.67 (20% methanol in dichloromethane), ^1H NMR (CD_3OD, 300 MHz) δ 8.02 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 8.7 Hz, 2 H), 7.49 (d J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.23-7.19 (m, 9 H), 4.94 (dd, J1 = 10.5 Hz, J2 = 5.4 Hz, 1 H), 3.30-3.23 (m, 1 H), 2.95 (dd, J1 = 14.4 Hz, J2 = 10.5 Hz, 1 H), 2.93 (s, 3 H), 2.38 (s, 3 H); ESI-LCMS *m/z* calcd for $C_{33}H_{28}ClN_3O_5S_3$: 645; found 646 $(M + 1)^+$.
2-({4-[2-(2-Cyclopentyl-acetylamino)-5-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;	R_f 0.82 (20% methanol in dichloromethane), ^1H NMR (CD_3OD, 300 MHz) δ 7.5 (d, J = 8.4 Hz, 2 H), 7.26-7.17 (m, 11 H), 3.32-3.25 (m, 1 H), 2.85 (dd, J1 = 14.4 Hz, J2 = 10.5 Hz, 1 H), 2.83 (s, 3 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.50 (d, J = 7.5 Hz, 2 H), 2.37-2.76 (m, 1 H), 1.90-1.83 (m, 3 H), 1.74-1.57 (m, 6 H), 1.30-1.26 (m, 3 H); ESI-LCMS *m/z* calcd for $C_{34}H_{37}ClN_3O_5S_2$: 631; found 632 $(M + 1)^+$.
2-({4-[2-(4-Chloro-benzoylamino)-5-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;	R_f 0.60 (20% methanol in ethyl acetate), ^1H NMR (DMSO-d_6, 300 MHz) δ 8.02 (d, J = 8.7 Hz, 2 H), 7.55 (dd, J1 = 8.1 Hz, J2 = 6.6 Hz, 4 H), 7.293-7.10 (m, 11 H), 3.66 (s, 1 H), 3.30-3.25 (m, 1 H), 2.93-2.84 (m, 1 H), 2.72 (q, J = 7.5 Hz, 2 H), 1.28 (t, J = 7.5 Hz, 3 H); ESI-LCMS *m/z* calcd for $C_{34}H_{30}ClN_3O_5S_2$: 659; found 660 $(M + 1)^+$.
2-({4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylamino]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;	R_f 0.67 (20% methanol in ethyl acetate), ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 9.3 Hz, 2 H), 7.51 (d, J = 9.3 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H), 7.31-7.15 (m, 11 H), 3.29-3.25 (m, 1 H), 2.95-2.85 (m, 2 H), 2.85 (s, 3 H), 2.36 (s, 3 H); ESI-LCMS *m/z* calcd for $C_{32}H_{28}ClN_3O_4S_2$: 617; found 618 $(M + 1)^+$.

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.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

Example 9

Male Wistar rats were fed a High Fat Diet for at least 4 weeks. Jugular vein and carotid artery cannulations were performed one week prior to the clamp experiment. Test compound (Compound 15) is administered p.o. 4 hrs before the clamp and labeled 3-3H-glucose is infused 1 hr prior to calculated endogenous glucose production (EGP). Insulin is infused at a rate of 0.75U/kg/hr raising plasma insulin levels to ~200 mU/ml. To maintain euglycemia (80 mg/dl), unlabeled glucose is infused at a variable rate and adjusted every 10 minutes.

Treatment with Compound 15 (30mg/kg) significantly increased the glucose infusion rate (GIR). This effect reflects enhanced suppression of endogenous glucose production (EGP) and augmented stimulation of glucose utilization (GU).

The results of this study indicate that the test compound improves insulin action in insulin resistant rats *in vivo*. This improvement affects both hepatic glucose production as well as

2-({4-[5-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-ethyl-amino)-3-phenyl-propionic acid;	R_f 0.79 (20% methanol in ethyl acetate), ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.86 (m, 2 H), 7.63-7.53 (m, 6 H), 7.35-7.12 (m, 9 H), 4.79 (dd, J1 = 8.4 Hz, J2 = 6.6 Hz, 1 H), 3.41-3.28 (m, 3 H), 2.91 (dd, J1 = 14.4 Hz, J2 = 8.7 Hz, 2 H), 2.74-2.64 (m, 2 H), 1.29-1.21 (m, 6 H); ESI-LCMS *m/z* calcd for $C_{34}H_{31}ClN_2O_4S_2$: 630; found 631 $(M + 1)^+$.
2-{4-[5-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonylamino}-3-phenyl-propionic acid; or	R_f 0.89 (20% methanol in ethyl acetate), ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 8.4 Hz, 2 H), 7.64-7.56 (m, 4 H), 7.41-7.33 (m, 4 H), 7.27-7.14 (m, 7 H), 4.06 (dd, J1 = 8.3 Hz, J2 = 5.4 Hz, 1 H), 3.06 (dd, J1 = 13.5 Hz, J2 = 5.4 Hz, 1 H), 2.86 (dd, J1 = 13.5 Hz, J2 = 8.3 Hz, 1 H), 2.73 (q, J = 7.4 Hz, 2 H), 1.29 (t, J = 7.4 Hz, 3 H); ESI-LCMS *m/z* calcd for $C_{32}H_{27}ClN_2O_4S_2$: 602; found 603 $(M + 1)^+$.
2-({4-[2-(4-Chloro-phenyl)-5-(6-methoxy-pyridin-3-yl)-thiazol-4-yl]-benzenesulfonyl}-ethyl-amino)-3-phenyl-propionic acid;	R_f 0.86 (20% methanol in dichloromethane)

or pharmaceutically acceptable salts thereof.

Example 8

Method for measuring PTP-1B activity

The test compounds are evaluated for their in vitro inhibitory activity against recombinant human PTP1B with phosphotyrosyl dodecapeptide TRDI(P)YETD(P)Y(P)YRK [SEQ ID NO:1]. 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

peripheral glucose utilization. The results demonstrate that compounds of the invention are useful as insulin potentiators for the treatment of insulin resistance in diabetes mellitus.

Effects of a single oral dose of Compound 15 on insulin action in insulin resistant rats

Dose	N	N GIR	EGP	GU
0 mg/kg	6	19.4±2.5	4.0±1.3	15.5±3.6
10 mg/kg	3	29.6±5.0	1.4±1.8	28.3±6.6
30 mg/kg	5	30.8±2.2**	0.16±0.5*	30.7±2.00**
60 mg/kg	4	38.0±2.2**	0.77±0.4	37.3±2.3**

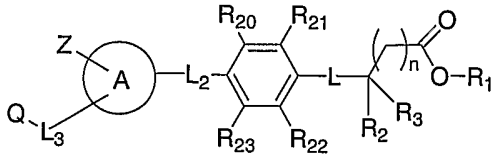
*P<0.05

** P<0.01 vs. control; GIR, EGP and GU are mean ± sem in mg/kg/min

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound according to claim 1 of the formula:



or a pharmaceutically acceptable salt thereof, wherein,

n is 0, 1, 2, or 3;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-$C(O)NH_2$, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-heterocycloalkyl, -(C_1-C_4) alkyl-heteroaryl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H or -CO_2R_1,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, arylalkoxy, arylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-aryl, -N(C_1-C_4 alkyl)C(O)aryl, -NHC(O)aryl, NHarylalkyl, NHC(O)-(C_1-C_4) alkyl-aryl, N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-aryl, N(C_1-C_4)alkyl-aryl, -$NHSO_2$-aryl, -N(C_1-C_4alkyl)SO_2aryl, or -N(C_1-C_4alkyl)arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, $-NHSO_2-$, -O-, -C(O)NH-, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, $-N(C_1-C_4)$ alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy;

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl-$C(O)NR_9-$, $-(C_1-C_4)$alkyl-$N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-N(R_9)C(O)-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl-$C(O)N(R_9)-(C_1-C_4)$alkyl-, $-(C_1-C_4)$alkyl-$N(R_9)C(O)-(C_1-C_4)$alkyl-, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, -N(R9)-, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-O-, or $-(C_1-C_4)$alkyl-$N(R_9)-$,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, $-SO_2$aryl, arylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, $-(C_1-C_4)$alkyl-O-, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$ alkyl-, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, CN, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, aryl, -aryl-carbonyl-aryl, -aryl-alkyl-aryl, -aryl-heteroaryl, -aryl-heterocycloalkyl, -heteroaryl, -heteroaryl-alkyl-aryl, -heterocycloalkyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted

with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, aryl(C_1-C_6)alkyl, alkanoyl, arylalkanoyl, alkoxycarbonyl, arylalkoxycarbonyl, heteroarylcarbonyl, heteroaryl, heterocycloalkylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-aryl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl or haloalkoxy, and

Z is absent, H, -NHC(O)aryl, -N(C_1-C_4 alkyl)C(O)aryl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

provided that when L2 is a bond, the A ring is not phenyl.

2. A compound according to claim 1, wherein

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-S(O)$_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -$(C_1$-$C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, benzofuranyl, benzothienyl, pyrrolyl, imidazolyl, -pyridyl-$(C_1$-$C_4)$alkyl-phenyl, -pyrimidyl-$(C_1$-$C_4)$alkyl-phenyl, morpholinyl, thiomorpholinyl, dibenzofuranyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_6)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_6)$alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1$-$C_6)$alkyl, $-C(O)N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

3. A compound according to claim 2, wherein

L is -SO_2NH-, -SO_2N(C_1-C_4) alkyl-, -NHSO_2-, -O-, -C(O)NH-, -C(O)N(C_1-C_4)alkyl-, -SO_2-, -C(O)-(C_1-C_4) alkyl-, -(C_1-C_4) alkyl-C(O)-, -NH-, or -N(C_1-C_4) alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O) -(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-C(O)N(R_9)-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-N(R_9)C(O) -(C_1-C_4)alkyl-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, anthracenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-; and

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl,

NH-phenyl, -NHC(O)-(C_1-C_4) alkyl-phenyl, -N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

4. A compound according to claim 3, wherein

L is -SO_2NH-, -SO_2N(C_1-C_4) alkyl-, -C(O)NH-, -C(O)N(C_1-C_4)alkyl-, -NH-, or -N(C_1-C_4) alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -(C_1-C_4)alkyl-C(O)NR_9-, -(C_1-C_4)alkyl-N(R_9)C(O)-, -C(O)N(R_9)-(C_1-C_4)alkyl-, -N(R_9)C(O)-(C_1-C_4)alkyl-,-N(R_9)SO_2-, -SO_2N(R_9)-, -N(R9)-, -N(R_9)-(C_1-C_4)alkyl-, -O-(C_1-C_4)alkyl-, -(C_1-C_4)alkyl-O-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenyl(C_1-C_4)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, -C(O)-;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-C(O)NH_2, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the

heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

wherein b is 0, 1, or 2;

R_3 is H;

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenyl(C_1-C_4)alkoxy, phenyl(C_1-C_4)alkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, N(C_1-C_4)alkyl-phenyl, NHbenzyl, or -N(C_1-C_6)alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl, pyrimidyl, or triazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl;

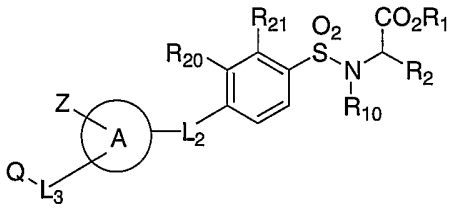
Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, imidazolidinyl, dibenzofuranyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

5. A compound according to claim 4 of the formula



wherein,

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

R_{10} is H, C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, benzyloxy, benzyl, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, NH-phenyl, $N(C_1$-$C_4)$alkyl-phenyl, NHbenzyl, or $-N(C_1$-$C_6)$alkylbenzyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy.

6. A compound according to claim 5, wherein

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1$-$C_4)$alkyl$-C(O)NR_9-$, $-(C_1$-$C_4)$alkyl$-N(R_9)C(O)-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1$-$C_4)$alkyl-, or $-(C_1$-$C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, benzyl, phenethyl, naphthyl-CH_2-, anthracenyl-CH_2-, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy;

L_3 is a bond, $-(C_1$-$C_4)$alkyl$-O-$, $-O-(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$ alkyl-, $-C(O)-$;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl-pyridyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl,

pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, dibenzofuranyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_4)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_4)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, pyridylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3, and

Z is -NHC(O)phenyl, -NHC(O)naphthyl, -N(C_1-C_4 alkyl)C(O)phenyl, -N(C_1-C_4 alkyl)C(O)naphthyl, naphthyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

7. A compound according to claim 6, wherein

R_1 is H, C_1-C_4 alkyl, or benzyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6

alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, C_1-C_2 haloalkyl, or C_1-C_2 haloalkoxy; and

R_{20}, and R_{21}, are independently selected from H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, or $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl,

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1$-$C_4)$alkyl$-C(O)NR_9-$, $-(C_1$-$C_4)$alkyl$-N(R_9)C(O)-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1$-$C_4)$alkyl-, or $-(C_1$-$C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3;

L_3 is a bond, $-(C_1$-$C_4)$alkyl$-O-$, $-O-(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$ alkyl-, or $-C(O)-$;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, C_1-C_2 haloalkoxy, C_1-C_2 haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is -NHC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, or -N(C_1-C_4)alkylC(O)-(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

8. A compound according to claim 7, wherein

R_1 is H, or C_1-C_4 alkyl;

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, wherein the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or -SO_2-(C_1-C_4) alkyl;

R_{10} is H, C_1-C_4 alkyl, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, CF_3, or OCF_3; and

At least one of R_{20} and R_{21}, is H, while the other is H, halogen, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl,

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, benzyl, phenethyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, or -C(O)-;

the A ring is thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, imidazolyl, isothiazolyl, pyrrolyl, pyrimidyl, or oxazolyl, each of which is optionally substituted with 1, or 2 groups that are independently,

halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl;

Q is H, phenyl, naphthyl, pyridyl, pyrimidyl, furanyl, thienyl, piperidinyl, pyrrolidinyl, or piperazinyl each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1$-$C_6)$alkyl, $N(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, CF_3, or OCF_3, and

Z is -NHC(O)phenyl, $-N(C_1$-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2, or

Z is $-NHC(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl, or $-N(C_1$-$C_4)$alkyl$C(O)-(C_1$-$C_4)$alkyl$-(C_3$-$C_7)$cycloalkyl.

9. A compound according to claim 8, wherein

L_2 is a bond;

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or $-SO_2-(C_1$-$C_4)$ alkyl;

Q is phenyl, or pyridyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, or NR_6R_7; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl$(C_1$-$C_4)$alkyl, C_2-C_6 alkanoyl, phenyl$(C_1$-$C_4)$alkanoyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4

alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, CF_3, or OCF_3, and

Z is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, or NO_2.

10. A compound according to claim 1, wherein

n is 0, 1, 2, or 3;

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

R_2 is phenyl, phenyl(C_1-C_4) alkyl, C_1-C_6 alkyl, -(C_1-C_4) alkyl-$C(O)NH_2$, -(C_1-C_4) alkyl-C(O)NH(C_1-C_4)alkyl, -(C_1-C_4) alkyl-C(O)N(C_1-C_4)alkyl(C_1-C_4)alkyl, -(C_1-C_4) alkyl-$S(O)_b$-(C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, -(C_1-C_4) alkyl-pyridinyl, -(C_1-C_4) alkyl-piperidinyl, -(C_1-C_4) alkyl-pyrrolidinyl, or -(C_1-C_4) alkyl-tetrahydrofuranyl, wherein the heterocycloalkyl group is optionally fused to a phenyl ring and wherein the heterocycloalkyl portion, the phenyl portion, or both are optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2$-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; wherein b is 0, 1, or 2;

R_3 is H or $-CO_2R_1$,

R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, phenylalkyl, halogen, alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, NHC(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4 alkyl)C(O)-(C_1-C_4) alkyl-phenyl, N(C_1-C_4)alkyl-phenyl, $-NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenylalkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy; and

L is $-SO_2NH$-, $-SO_2N$(C_1-C_4) alkyl-, $-NHSO_2$-, -O-, -C(O)NH-, -C(O)N(C_1-C_4)alkyl-, $-SO_2$-, -C(O)-(C_1-C_4) alkyl-, -(C_1-C_4) alkyl-C(O)-, -NH-, -N(C_1-C_4) alkyl-, wherein the alkyl group

is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy.

11. A compound according to claim 10, wherein

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl$-C(O)NR_9-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-(C_1-C_4)$alkyl$-C(O)N(R_9)-(C_1-C_4)$alkyl$-$, $-(C_1-C_4)$alkyl$-N(R_9)C(O)-(C_1-C_4)$alkyl$-$, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl$-$, $-O-(C_1-C_6)$alkyl$-$, $-(C_1-C_6)$alkyl$-O-$, or $-(C_1-C_4)$alkyl$-N(R_9)-$,

R_9 is H, C_1-C_6 alkyl optionally substituted with CO_2H, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl$-O-$, $-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkyl$-$, -alkenyl-, C(O);

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, furanyl, isothiazolyl, pyrrolyl, oxazolyl, triazolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl $-(C_1-C_4)$alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-oxazolyl, -phenyl-thiazolyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperidinyl, -phenyl-pyrrolidinyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl, -phenyl-thiomorpholinyl dioxide,

-phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, pyridyl, pyrimidyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, -C(O)NH_2, -C(O)NH(C_1-C_6)alkyl, -C(O)N(C_1-C_6)alkyl(C_1-C_6)alkyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, -NHC(O)phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, or phenyl, wherein the phenyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

12. A compound according to claim 11, wherein R_{20}, R_{21}, R_{22}, and R_{23} are independently selected from H, phenylalkoxy, benzyl, phenethyl, halogen, C_1-C_6 alkyl, OH, alkoxy, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally

substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy;

L is $-SO_2NH-$, $-SO_2N(C_1-C_4)$ alkyl-, $-NHSO_2-$, -O-, $-C(O)NH-$, $-C(O)N(C_1-C_4)$alkyl-, $-SO_2-$, $-C(O)-(C_1-C_4)$ alkyl-, $-(C_1-C_4)$ alkyl-C(O)-, -NH-, $-N(C_1-C_4)$ alkyl-, wherein the alkyl group is optionally substituted with phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, or haloalkoxy; or

L_2 is a bond or $-C(O)NR_9-$, $-N(R_9)C(O)-$, $-(C_1-C_4)$alkyl-$C(O)NR_9-$, $-(C_1-C_4)$alkyl-$N(R_9)C(O)-$, $-C(O)N(R_9)-(C_1-C_4)$alkyl-, $-N(R_9)C(O)-(C_1-C_4)$alkyl-, $-N(R_9)SO_2-$, $-SO_2N(R_9)-$, $-N(R_9)-$, $-N(R_9)-(C_1-C_4)$alkyl-, $-O-(C_1-C_6)$alkyl-, $-(C_1-C_6)$alkyl-O-, or $-(C_1-C_4)$alkyl-$N(R_9)-$,

R_9 is H, C_1-C_6 alkyl, $-SO_2$phenyl, phenylalkyl, naphthylalkyl, or anthracenylalkyl, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is absent, a bond, $-(C_1-C_4)$alkyl-O-, -O-(C_1-C_4)alkyl, $-(C_1-C_4)$ alkyl-, -alkenyl-, C(O);

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

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, $-(C_1-C_4)$ alkyl-pyridinyl, (C_1-C_4) hydroxyalkyl, wherein the phenyl ring is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-SO_2-(C_1-C_4)$ alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, or pyrrolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl,

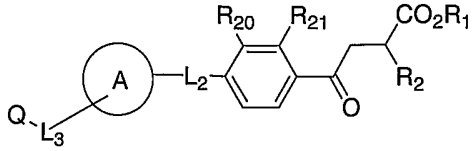
haloalkyl, haloalkoxy, NO_2, NH_2, $NH(C_1-C_6)$alkyl, or $N(C_1-C_6)$alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-carbonyl-phenyl, -phenyl -(C_1-C_4)alkyl- phenyl, -phenyl-pyridyl, -phenyl-pyrimidyl, -phenyl-imidazolyl, -phenyl-pyrrolyl, -phenyl-piperazinyl, -phenyl-morpholinyl, -phenyl-thiomorpholinyl dioxide, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, -pyrimidyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, piperidinylcarbonyl, pyrrolidinylcarbonyl, $-C(O)NH_2$, $-C(O)NH(C_1-C_6)$alkyl, $-C(O)N(C_1-C_6)$alkyl(C_1-C_6)alkyl, or $-SO_2$-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, $NH(C_1-C_6)$alkyl, $N(C_1-C_6)$alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy, and

Z is absent, H, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or NO_2.

13. A compound according to claim 12, of the formula



wherein

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

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, -CH_2-pyridyl, or (C_1-C_4) hydroxyalkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -$NHSO_2$-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

14. A compound according to claim 13, wherein

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dibenzofuranyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, pyrimidyl, furanyl, thienyl, pyrrolyl, imidazolyl, -pyridyl-(C_1-C_4)alkyl-phenyl, morpholinyl, thiomorpholinyl, thiomorpholinyl dioxide, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, piperazinyl, C_1-C_6 alkyl, halogen, haloalkoxy, haloalkyl, or C_1-C_6 alkoxycarbonyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6

alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, C_1-C_6 alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, pyridylcarbonyl, furanylcarbonyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

15. A compound according to claim 14, wherein

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, C(O);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, -CH_2-pyridyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

16. A compound according to claim 15, wherein

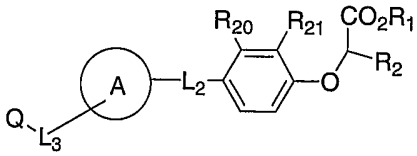
L_3 is a bond;

R_2 is phenyl, benzyl, phenethyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, or phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; and

the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, dihydropyrazolyl, quinazolinyl, and benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl.

17. A compound according to claim 11, of the formula



wherein

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

R_2 is phenyl, phenyl(C_1-C_4)alkyl, C_1-C_6 alkyl, or (C_1-C_4) hydroxyalkyl, wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are

independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

18. A compound according to claim 17, wherein the A ring is phenyl, naphthyl, thiazolyl, pyrazolyl, quinolinyl, dihydropyrazolyl, benzofuranyl, pyrimidyl, quinazolinyl, furanyl, or benzo[b]thiophene, each of which is optionally substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkoxycarbonyl, CF_3, OCF_3, CN, NO_2, NH_2, NH(C_1-C_6)alkyl, or N(C_1-C_6)alkyl(C_1-C_6)alkyl; and

R_{20} and R_{21}, are independently selected from H, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NH-phenyl, -N(C_1-C_4 alkyl)C(O)phenyl, -NHC(O)phenyl, NHphenylalkyl, N(C_1-C_4)alkyl-phenyl, -NHSO_2-phenyl, -N(C_1-C_4alkyl)SO_2phenyl, or -N(C_1-C_4alkyl)phenyl(C_1-C_6)alkyl, wherein the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, OH, NO_2, haloalkyl, haloalkoxy.

19. A compound according to claim 18, wherein

L_2 is a bond or -C(O)NR_9-, -N(R_9)C(O)-, -N(R_9)SO_2-, -SO_2N(R_9)-, -N(R_9)-, -N(R_9)-(C_1-C_4)alkyl-, or -(C_1-C_4)alkyl-N(R_9)-,

R_9 is H, C_1-C_6 alkyl, -SO_2phenyl, phenylalkyl, naphthyl-CH_2-, or anthracenyl-CH_2-, wherein the aryl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, OH, NO_2, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, haloalkyl, or haloalkoxy;

L_3 is a bond, -(C_1-C_4)alkyl-O-, -O-(C_1-C_4)alkyl, -(C_1-C_4) alkyl-, C(O);

R_2 is phenyl, phenyl(C_1-C_4)alkyl, or C_1-C_6 alkyl wherein the phenyl portion is optionally substituted with a total of 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_2-(C_1-C_4) alkyl, CF_3, or OCF_3;

Q is H, phenyl, naphthyl, -phenyl-pyridyl, -phenyl-, pyridyl, piperidinyl, pyrrolidinyl, or piperazinyl, wherein the aforementioned cyclic groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkoxycarbonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, NR_6R_7, or phenyl; wherein

R_6 and R_7 are independently H, C_1-C_6 alkyl, phenyl(C_1-C_6)alkyl, C_2-C_6 alkanoyl, phenyl(C_1-C_6)alkanoyl, or -SO_2-phenyl, wherein the cyclic groups are optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, OH, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, C_1-C_2 haloalkyl or C_1-C_2 haloalkoxy.

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

21. A method of treating diabetes, comprising administering to a patient in need of such treatment a pharmaceutically acceptable amount of a compound of claim 1.

22. A compound according to claim 1 that is

N-{[4-({[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

N-({4-[3-(4-methoxyphenyl)-5-(4-pentylphenyl)-4,5-dihydro-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-{[4-({[4-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

N-methyl-N-[(4-{5-(4-pentylphenyl)-3-[4-(trifluoromethoxy)phenyl]-4,5-dihydro-1H-pyrazol-1-yl}phenyl)sulfonyl]phenylalanine;

N-({4-[3-(4-methoxyphenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-methyl-N-[(4-{5-(4-pentylphenyl)-3-[4-(trifluoromethoxy)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]phenylalanine;

N-({4-[5-(4-butoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

2-benzyl-4-oxo-4-[3-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]butanoic acid;

N-{[4-({[4-(3-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

N-({4-[5-(4-isopropylphenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-{[4-({[4-(3-chloro-4-methylphenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

N-{[4-({[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}-N-methylphenylalanine;

methyl (2S)-2-[4-((biphenyl-4-ylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoate;

N-{[4-({[4-(4-bromophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

N-{[4-({[4-(4-chlorophenyl)-5-(4-ethylphenyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}phenylalanine;

(2S)-2-[4-((biphenyl-4-ylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

N-[(4-{[4,6-bis(4-methoxyphenyl)pyrimidin-2-yl]amino}phenyl)sulfonyl]-N-methyl-L-phenylalanine;

N-methyl-N-({4-[5-(4-pentylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)phenylalanine;

2-benzyl-4-[4-({[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

2-[3-[(4-butylphenyl)amino]-4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

2-[3-[(4-butylphenyl)amino]-4-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

(2S)-2-[3-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

2-{4-{[(4-bromophenyl)sulfonyl]amino}-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

N-({4-[2-[(4-chlorobenzoyl)amino]-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methylphenylalanine

(2S)-2-[4-((2-naphthylmethyl){[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

N-[(4-{4-bromo-3-(4-methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

N-({4-[5-(4-bromophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

2-{4-[(4-bromobenzoyl)amino]-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

N-({4-[(6-bromo-4-phenylquinazolin-2-yl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

N-({4-[2-[(cyclopentylacetyl)amino]-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

N-({4-[2-(4-chlorophenyl)-5-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

N-({4-[5-(4-ethylphenyl)-2-(6-methoxypyridin-3-yl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-methyl-L-phenylalanine;

2-(3-[(4-butylphenyl)amino]-4-{[(4-chloro-3-nitrophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

N-[(4-{[4-(4-chlorophenyl)-5-(4-methylphenyl)-1,3-thiazol-2-yl]amino}phenyl)sulfonyl]-N-methyl-L-phenylalanine;

2-[3-[(4-butylphenyl)amino]-4-({[5-(dimethylamino)-1-naphthyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

2-(3-[(4-butylphenyl)amino]-4-{[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

2-benzyl-4-[3-((2-naphthylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

N-[(4-{3-(4-chlorophenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

N-({4-[3-(4-chlorophenyl)-5-(4-ethylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-[(4-{4-bromo-3-(4-chlorophenyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}phenyl)sulfonyl]-N-methylphenylalanine;

N-({4-[4-bromo-3-(4-chlorophenyl)-5-(4-ethylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-({4-[5-(4-bromophenyl)-3-(4-chlorophenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-({4-[3-(4-chlorophenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

N-({4-[4-bromo-3-(4-chlorophenyl)-5-(4-pentylphenyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)-N-methylphenylalanine;

2-{4-{[(4-bromo-3-fluorophenyl)sulfonyl]amino}-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

2-{4-({[4-bromo-3-(trifluoromethyl)phenyl]sulfonyl}amino)-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

2-benzyl-4-[3-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

2-{4-({[4-bromo-2-(trifluoromethoxy)phenyl]sulfonyl}amino)-3-[(4-butylphenyl)amino]phenoxy}-3-phenylpropanoic acid;

2-(3-[(4-butylphenyl)amino]-4-{[(3,4-dichlorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

diallyl {2-oxo-2-[4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]ethyl}[4-(trifluoromethyl)benzyl]malonate;

N-({4-[(6-isopropyl-4-phenylquinazolin-2-yl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

N-({4-[5-(4-chlorophenyl)-2-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)-N-ethyl-L-phenylalanine;

N-({4-[5-(4-chlorophenyl)-2-(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)phenylalanine;

N-({4-[2,5-bis(4-ethylphenyl)-1,3-thiazol-4-yl]phenyl}sulfonyl)phenylalanine;

2-(3-[(4-butylphenyl)amino]-4-{[(3,4-dibromophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

2-benzyl-4-(4-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

methyl 2-benzyl-4-(3-{(biphenyl-4-ylmethyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

methyl 2-benzyl-4-(3-{(3,4-dichlorobenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

methyl 2-benzyl-4-{3-[[4-chloro-3-(trifluoromethyl)benzyl](2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

methyl 2-benzyl-4-{3-[(biphenyl-4-ylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

2-benzyl-4-{3-[(biphenyl-4-ylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoic acid;

2-(3-[(4-bromophenyl)amino]-4-{[(4-butylphenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

methyl 2-benzyl-4-{3-[(2-naphthylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoate;

2-benzyl-4-{3-[(2-naphthylmethyl)(2-naphthylsulfonyl)amino]phenyl}-4-oxobutanoic acid;

4-{3-[(2-anthrylsulfonyl)(2-naphthylmethyl)amino]phenyl}-2-benzyl-4-oxobutanoic acid;

methyl 2-benzyl-4-{3-[{[4-(dimethylamino)-3-fluorophenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

methyl 2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoate;

methyl 2-benzyl-4-{3-[{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

methyl 2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-difluorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

methyl 2-benzyl-4-[3-([4-chloro-3-(trifluoromethyl)benzyl]{[4-(dimethylamino)-3-fluorophenyl]sulfonyl}amino)phenyl]-4-oxobutanoate;

(2S)-2-[4-([4-(methoxycarbonyl)benzyl]{[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

2-benzyl-4-oxo-4-[4-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl] butanoic acid;

2-[3-[(4-butylphenyl)amino]-4-({[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

N-{[4-[(4-butylphenyl)amino]-3-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenyl] sulfonyl}-N-methyl-L-phenylalanine;

benzyl (2S)-2-[4-([(5-nitro-2-furyl)methyl]{[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoate;

(2R)-2-[4-({[4-chloro-2-(trifluoromethyl)quinolin-5-yl]methyl}{[3-(trifluoromethyl)phenyl]sulfonyl}amino)phenoxy]-3-phenylpropanoic acid;

2-(4-[(4-butylphenyl)amino]-3-{[4-(trifluoromethoxy)benzoyl]amino}phenoxy)-3-phenylpropanoic acid;

2-(3-[(4-butylphenyl)amino]-4-{[(4-chlorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

N-({4-[(6-bromo-4-phenylquinazolin-2-yl)(carboxymethyl)amino]phenyl}sulfonyl)-N-methylphenylalanine;

2-(3-[(4-butylphenyl)amino]-4-{[(3-cyano-4-fluorophenyl)sulfonyl]amino}phenoxy)-3-phenylpropanoic acid;

4-[4-((4-chlorobenzyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxo-2-(pyridin-3-ylmethyl)butanoic acid;

2-benzyl-4-[4-((biphenyl-4-ylmethyl){[4-(trifluoromethoxy)phenyl]sulfonyl}amino)phenyl]-4-oxobutanoic acid;

2-benzyl-4-{4-[{[4-methoxy-3-(trifluoromethyl)phenyl]sulfonyl}(1-naphthylmethyl)amino]phenyl}-4-oxobutanoic acid;

2-benzyl-4-(4-{[(3,4-dichlorophenyl)sulfonyl][4-(trifluoromethoxy)benzyl]amino}phenyl)-4-oxobutanoic acid;

2-benzyl-4-(4-{[4-chloro-3-(trifluoromethyl)benzyl][(3-fluoro-4-methoxyphenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

methyl 2-benzyl-4-{3-[[(3,4-dichlorophenyl)sulfonyl](2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

methyl 2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoate;

2-benzyl-4-(3-{[4-chloro-3-(trifluoromethyl)benzyl][(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

2-benzyl-4-(3-{(biphenyl-4-ylmethyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-4-oxobutanoic acid;

methyl 4-(3-{(4-benzoylbenzyl)[(3,4-dichlorophenyl)sulfonyl]amino}phenyl)-2-benzyl-4-oxobutanoate;

2-benzyl-4-{3-[[(3,4-dichlorophenyl)sulfonyl](4-isopropylbenzyl)amino]phenyl}-4-oxobutanoic acid;

4-(4-dibenzo[b,d]furan-4-ylphenyl)-4-oxo-2-[3-(trifluoromethyl)benzyl]butanoic acid;

2-benzyl-4-{3-[{[4-methoxy-3-(trifluoromethyl)phenyl]sulfonyl}(2-naphthylmethyl)amino]phenyl}-4-oxobutanoic acid;

methyl 2-benzyl-4-{3-[[(3,4-difluorophenyl)sulfonyl](2-naphthylmethyl)amino]phenyl}-4-oxobutanoate;

N-{[4-(2-bromo-5-dibenzo[b,d]furan-4-yl-1,3-thiazol-4-yl)phenyl]sulfonyl}phenylalanine;

N-{[4-(5-bromo-2-dibenzo[b,d]furan-4-yl-1,3-thiazol-4-yl)phenyl]sulfonyl}phenylalanine;

2-{4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;

2-{4-[4-(3-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;

2-{4-[4-(2-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonylamino}-3-phenyl-propionic acid;

2-({4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylcarbamoyl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;

2-({4-[2-(2-Cyclopentyl-acetylamino)-5-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;

2-({4-[2-(4-Chloro-benzoylamino)-5-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;

2-({4-[4-(4-Chloro-phenyl)-5-p-tolyl-thiazol-2-ylamino]-benzenesulfonyl}-methyl-amino)-3-phenyl-propionic acid;

2-({4-[5-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonyl}-ethyl-amino)-3-phenyl-propionic acid;

2-{4-[5-(4-Chloro-phenyl)-2-(4-ethyl-phenyl)-thiazol-4-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

2-({4-[2-(4-Chloro-phenyl)-5-(6-methoxy-pyridin-3-yl)-thiazol-4-yl]-benzenesulfonyl}-ethyl-amino)-3-phenyl-propionic acid;

2-[4-(5-Bromo-2-dibenzofuran-4-yl-thiazol-4-yl)-benzenesulfonylamino]-3-phenyl-propionic acid

2-[4-(2-Dibenzofuran-4-yl-thiazol-4-yl)-benzenesulfonylamino]-3-phenyl-propionic acid

(4-{2-[(8-Chloro-dibenzofuran-4-carbonyl)-amino]-5-ethyl-thiazol-4-yl}-phenoxy)-phenyl-acetic acid

[4-(2-Benzo[b]thiophen-3-yl-5-ethyl-thiazol-4-yl)-phenoxy]-phenyl-acetic acid

[4-(2-Dibenzofuran-4-yl-5-ethyl-thiazol-4-yl)-phenoxy]-phenyl-acetic acid; or pharmaceutically acceptable salts thereof.

SEQUENCE LISTING

<110> Van Zandt, Michael

<120> Substituted Phenylalkanoic Acids For The Treatment Of Diabetes

<130> 03-334-B

<140> tba
<141> 2004-04-14

<150> 60/463,102
<151> 2003-04-14

<160> 1

<170> PatentIn version 3.0

<210> 1
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> phosphotyrosine

<220>
<221> MISC_FEATURE
<222> (9)..(10)
<223> phosphotyrosine

<400> 1

Thr Arg Asp Ile Tyr Glu Thr Asp Tyr Tyr Arg Lys
1 5 10