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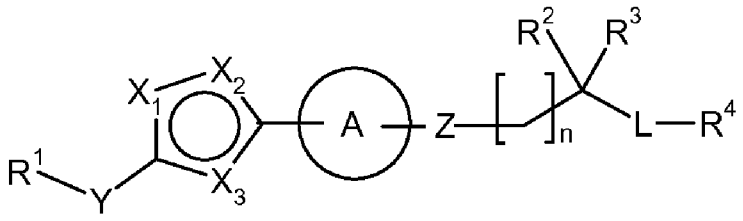

(57) Abstract: Disclosed is a method of treating a B-cell lymphoma by administering a compound having the formula wherein X1; X2, X3, R1, R2, R3, R4, Y, A, Z, L and n are as defined herein.

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METHODS OF TREATMENT

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a method of treating a B-cell lymphoma, particularly B-cell lymphomas associated with deacetylases, particularly Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, and Waldenström Macroglobulinemia (lymphoplasmacytic lymphoma), by administering to a patient in need thereof a compound that inhibits HDAC activity.

Background of the Invention

Chromatin organization involves DNA wound around histone octamers that form nucleosomes. Core histones with N-terminal tails extending from compact nucleosomal core particles can be acetylated or deacetylated at epsilon lysine residues affecting histone–DNA and histone–non-histone protein interactions. Histone deacetylases (HDACs) catalyze the deacetylation of histone and non-histone proteins and play an important role in epigenetic regulation. There are currently 18 known HDACs that are organized into three classes: class I HDACs (HDAC1, HDAC2, HDAC3, HDAC8 and HDAC11) are mainly localized to the nucleus; class II HDACs (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10), which shuttle between the nucleus and the cytoplasm; and class III HDACs (SIRT1–7), whose cellular localization includes various organelles.

Class II HDACs are further characterized as class IIa HDACs and class IIb HDACs.

HDAC9 is a class IIa histone deacetylase highly expressed in human B cells. Relative to normal B cells, expression of HDAC9 is deregulated in cell lines derived from B cell tumours and HDAC9 is highly overexpressed in cells derived from patients with non-Hodgkin's lymphoma (http://icr.ac.uk/research/team_leaders/Zelent_Arthur/Zelent_Arthur_RI/index.shtml). HDAC4 and HDAC9 have booth been reported to be overexpressed in CD19+ cells from patients with Waldenström Macroglobulinemia (Sun *et al.*, Clinical Lymphoma, Myeloma & Leukemia, 2011, p. 152)

Class IIa HDACs (HDAC4, HDAC5, HDAC7 and HDAC9) have been reported to associate with Bcl-6, a transcription factor implicated in the pathogenesis of B-cell malignancies (Lemercier *et al*, Journal of Biological Chemistry, 2002,p. 22045, and Petrie

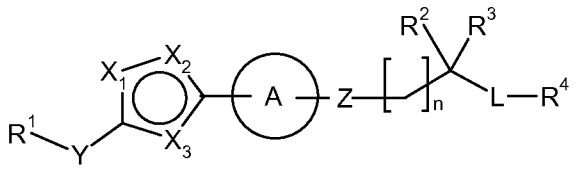
et al, Journal of Biological Chemistry, 2003, p. 16059). Due to these interactions class IIa HDACs have been suggested to modulate the transcriptional repression of BCL6 and participate in its role in B-cell activation and differentiation, inflammation, and cell-cycle regulation (Verdin *et al*. TRENDS in Genetics, 2003, p. 286) .

HDAC6, a class IIb HDAC, has been reported to play an important role in aggresomal protein degradation, making it a target for the treatment of B cell malignancies (Simms-Waldrip *et al.*, Molecular Genetics and Metabolism, 2008, p. 283)

Based on the above evidence, a small molecule selective inhibitor of HDAC activity (more specifically, an inhibitor of HDAC4 and/or HDAC5 and/or HDAC6 and/or HDAC7 and/or HDAC8 and/or HDAC9 activity) is expected to be beneficial in the treatment of B-cell malignancies by targeting one or several of the above enzymes..

SUMMARY OF THE INVENTION

The invention is directed to a method of treatment of a B-cell lymphoma comprising administering, to a patient in need thereof, a compound of Formula I:



I

wherein:

R^1 is halo(C_1-C_4)alkyl, wherein said halo(C_1-C_4)alkyl contains at least 2 halo groups;

Y is a bond and X_1 is O, N or NH, X_2 is N or CH and X_3 is N or NH,

or Y is –C(O)- and X_1 and X_2 are CH or N, X_3 is O or S,

or Y is –C(O)- and X_1 is O, X_2 is CH or N, and X_3 is CH or N;

A is optionally substituted (C_3-C_6)cycloalkyl, phenyl, naphthyl, 4-7 membered heterocycloalkyl, 5-6 membered heteroaryl, or 9-10 membered heteroaryl,

wherein any optionally substituted cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl is optionally substituted by 1-3 groups independently selected from (C_1-C_4)alkyl, halogen, cyano, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl)NR^AR^A;

Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, $-NR^XC(=O)-$, $-SO_2-$, $-SO_2NR^X-$, $-NR^XSO_2-$, $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1$-$C_4)$alkyl-, $-NR^X-$, or $-(C_1$-$C_3)$alkyl-NR^X-;

n is 0-4;

when n is 0, R^2 and R^3 are independently selected from H and optionally substituted $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl-,

when n is 1-4, R^2 and R^3 are independently selected from H, fluoro, and optionally substituted $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl-, wherein,

when n is 1, R^2 is F and R^3 is H, then Z is $-C(=O)NR^X$-, $-NR^XC(=O)NR^X$, $-SO_2NR^X$-, $-NHCH(CF_3)$-, $-CH(CF_3)NH$-, $-CH(CF_3)$-, $-(C_1\text{-}C_4)$alkyl-, $-NR^X$-, or $-(C_1\text{-}C_3)$alkyl-NR^X-, and

when n is 1-4, R^2 is selected from $-NR^AR^B$, $-(C_1\text{-}C_4)$alkyl-NR^AR^B, $-CONR^AR^B$, $-(C_1\text{-}C_4)$alkyl-$CONR^AR^B$, $-CO_2H$, $-(C_1\text{-}C_4)$alkyl-CO_2H, hydroxyl, hydroxy$(C_1\text{-}C_4)$alkyl-, $(C_1\text{-}C_3)$alkoxy, and $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_4)$alkyl-, and R^3 is selected from H and optionally substituted $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl-,

wherein the aryl, cycloalkyl and each of the $(C_1\text{-}C_4)$alkyl moieties of said optionally substituted $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl- of any R^2 and R^3 are optionally substituted by 1, 2 or 3 groups independently selected from halogen, cyano, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, $-NR^AR^A$, $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$, and hydroxyl;

or R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, 6, or 7 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 or 2 heteroatoms independently selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by 1, 2 or 3 substituents independently selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, halogen, cyano, aryl$(C_1\text{-}C_4)$alkyl-, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl-, $-OR^Y$, $-NR^YR^Y$, $-C(=O)OR^Y$, $-C(=O)NR^YR^Y$, $-NR^YC(=O)R^Y$, $-SO_2NR^YR^Y$, $-NR^YSO_2R^Y$, $-OC(=O)NR^YR^Y$, $-NR^YC(=O)OR^Y$, and $-NR^YC(=O)NR^YR^Y$; and

L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted,

wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and $(C_1\text{-}C_4)$alkyl;

R^4 is H, $(C_1\text{-}C_4)$alkyl, halo, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $((C_1\text{-}C_4)\text{alkyl})((C_1\text{-}C_4)\text{alkyl})N(C_1\text{-}C_4)$alkoxy, $((C_1\text{-}C_4)\text{alkyl})((C_1\text{-}C_4)\text{alkyl})N(C_1\text{-}C_4)$alkyl-, $(C_1\text{-}C_4)$haloalkoxy-, $(C_1\text{-}C_4)$alkylamino, optionally substituted $(C_3\text{-}C_6)$cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl,

wherein said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkylthio-, halo$(C_1\text{-}C_4)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^C$;

or L-R^4 , taken together, form a 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group wherein said benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group is optionally substituted by 1, 2 or 3 groups independently selected from (C_1-C_4)alkyl, halogen, cyano, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio-, halo(C_1-C_4)alkoxy, hydroxyl, -NR^AR^C and -((C_1-C_4)alkyl)NR^AR^C;

wherein each R^A is independently selected from H and (C_1-C_4)alkyl;

R^B is H, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, –C(=O)(C_1-C_4)alkyl, -C(=O)O(C_1-C_4)alkyl, -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), -SO_2(C_1-C_4)alkyl, or R^A and R^B taken together with the atom to which they are attached form a 4-6 membered heterocyclic ring, optionally containing one additional heteroatom selected from N, O and S and optionally substituted by (C_1-C_4)alkyl;

R^C is H, (C_1-C_4)alkyl, phenyl, 5-6 membered heterocycloalkyl, or 5-6 membered heteroaryl, or R^A and R^C taken together with the atom to which they are attached form a 4-8 membered heterocyclic ring, optionally containing one additional heteroatom selected from N, O and S and optionally substituted by (C_1-C_4)alkyl;

each R^X is independently selected from H, (C_1-C_6)alkyl, and optionally substituted (C_2-C_6)alkyl, where said optionally substituted (C_2-C_6)alkyl is optionally substituted by hydroxyl, cyano, amino, (C_1-C_4)alkoxy, (C_1-C_4)alkyl)NH-, or ((C_1-C_4)alkyl)((C_1-C_4)alkyl)N-; and

each R^Y is independently selected from H, (C_1-C_4)alkyl, phenyl, and -(C_1-C_4)alkylphenyl;

or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

The invention is further directed to the use of a compound of Formula I, or a salt thereof, particularly a pharmaceutically acceptable salt, thereof in therapy, particularly the use of a compound of Formula I, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, to treat a B-cell lymphoma, particularly a B-cell lymphoma associated with deacetylases, particularly Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, and Waldenström Macroglobulinemia (lymphoplasmacytic lymphoma).

The invention is still further directed to the manufacture of a medicament containing a compound of Formula I, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, for use in therapy, particularly for use to treat a B-cell lymphoma, particularly a B-cell lymphoma associated with deacetylases, particularly Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse

large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, and Waldenström Macroglobulinemia (lymphoplasmacytic lymphoma).

DETAILED DESCRIPTION OF THE INVENTION

The alternative definitions for the various groups and substituent groups of Formula I provided throughout the specification are intended to particularly describe each compound species disclosed herein, individually, as well as groups of one or more compound species. The scope of this invention includes any combination of these group and substituent group definitions.

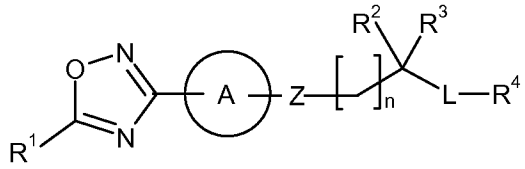
In one embodiment of the compound or salt of Formula I, R^1 is a fluoro- alkyl group containing at least 2 fluoro groups (atoms). In another embodiment, R^1 is a $(C_1$-$C_2)$alkyl group containing at least 2 fluoro groups. In a specific embodiment, R^1 is CHF_2 or CF_3; more specifically, R^1 is CF_3

In selected embodiments of the compound or salt of Formula I, when Y is a bond, X_1, X_2, and X_3, taken together with the atoms to which they are attached, form an oxadiazolyl (X_1 is O, X_2 and X_3 are N), oxazolyl (X_1 is O, X_2 is CH, X_3 is N), imidazolyl (X_1 is N or NH, X_2 is CH, X_3 is N or NH); or a triazolyl (X_1 is N or NH, X_2 is N, X_3 is N or NH) ring moiety. In specific embodiments, when Y is a bond, X_1, X_2, and X_3, taken together with the atoms to which they are attached form an oxadiazolyl ring moiety.

In selected embodiments of the compound or salt of Formula I, when Y is –C(O)-, X_1, X_2, and X_3, taken together with the atoms to which they are attached, form an thiazolyl (X_3 is S, X_1 is CH and X_2 is N or X_3 is S, X_1 is N and X_2 is CH), oxazolyl (X_3 is O, X_1 is CH and X_2 is N or X_3 is O, X_1 is N and X_2 is CH), thienyl (X_1 and X_2 are CH, X_3 is S) or furanyl (X_1 and X_2 are CH, X_3 is O) ring moiety. In specific embodiments, when Y is –C(O)-, X_1, X_2, and X_3, taken together with the atoms to which they are attached form a thienyl, thiazolyl or oxazolyl ring moiety, more specifically a thienyl moiety.

In selected embodiments of the compound or salt of Formula I, when Y is –C(O)-, X_1, X_2, and X_3, taken together with the atoms to which they are attached, form a furanyl or furyl (X_1 is O, X_2 and X_3 are CH), oxazolyl (X_1 is O, X_2 is CH, and X_3 is N), isoxazolyl (X_1 is O, X_2 is N, and X_3 is CH), or oxadiazolyl (X_1 is O, X_2 and X_3 are N) ring moiety. In specific embodiments, when Y is –C(O)-, X_1, X_2, and X_3, taken together with the atoms to which they are attached form a furanyl (furyl) ring moiety.

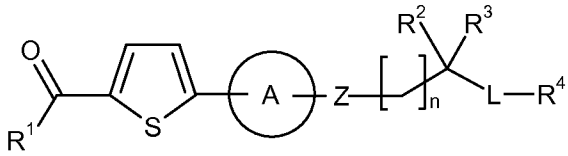
The invention is further directed to methods of treatment and uses of a compound of Formula (I-a):



(I-a),

wherein R^1, R^2, R^3,R^4, A, Z, n and L are as defined herein.

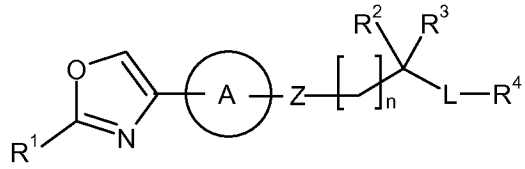
The invention is still further directed to a compound of Formula (I-b):



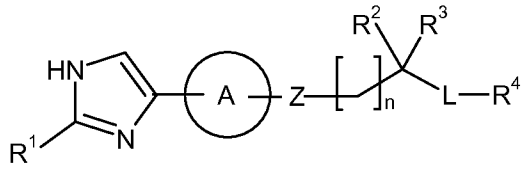
(I-b),

wherein R^1, R^2, R^3,R^4, A, Z, n and L are as defined herein.

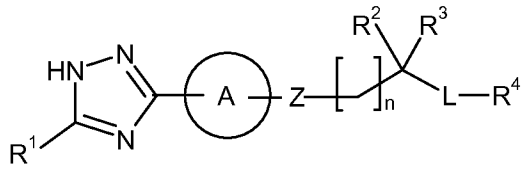
The invention is further directed to methods of treatment and uses of a compound of Formula (I-c), (I-d) or (I-e):



(I-c),



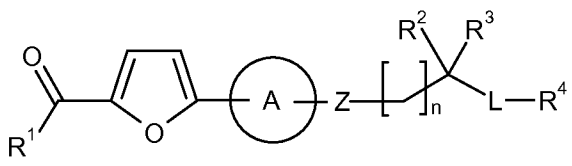
(I-d),



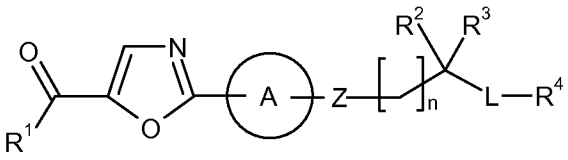
(I-e),

wherein R^1, R^2, R^3,R^4, A, Z, n and L are as defined herein.

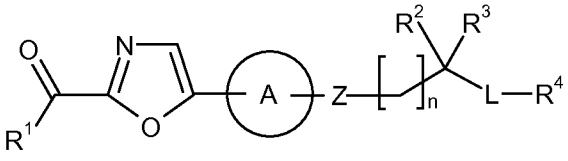
The invention is still further directed to methods of treatment and uses of a compound of Formula (I-f), (I-g), (I-h), (I-i) or (I-j):



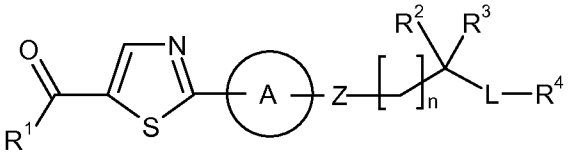
(I-f),



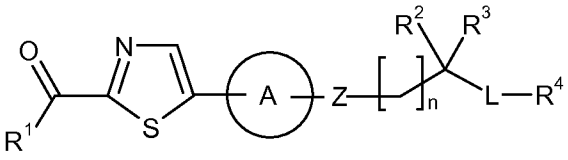
(I-g),



(I-h),



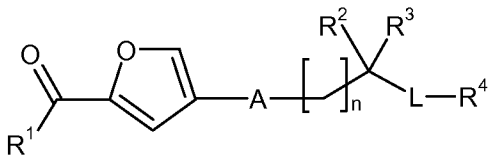
(I-i),



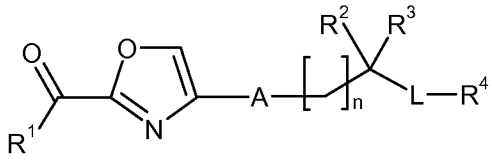
(I-j),

wherein R^1, R^2, R^3,R^4, A, Z, n and L are as defined herein.

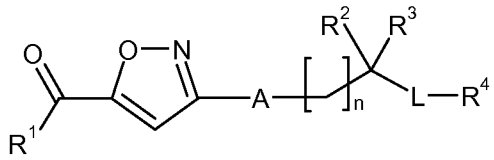
The invention is still further directed to methods of treatment and uses of a compound of Formula (I-k), (I-l), (I-m), or (I-n):



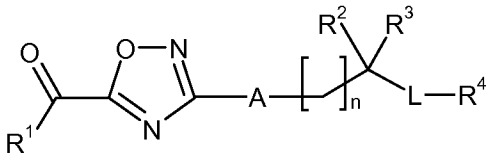
(I-k),



(I-l),



(I-m),



(I-n),

wherein R^1, R^2, R^3,R^4, A, n and L are as defined herein.

In another embodiment of the compound or salt of Formula I, A is a phenyl group optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$. In further embodiments, A is a phenyl group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$, where each R^A is independently H or methyl. In specific embodiments of the compound or salt of Formula I, A is an unsubstituted phenyl group or a phenyl group substituted by an ethyl, fluoro, cyano or methoxy group.

In yet another embodiment of the compound or salt of Formula I, A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$. In further embodiments, A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from methyl, ethyl, tert-butyl, methoxy, ethoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$, where each R^A is independently H or methyl. In selected embodiments of the compound or salt of Formula I, A is a cyclopropyl, cyclopentyl or cyclohexyl group.

In another embodiment of the compound or salt of Formula I, A is naphthyl, optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$.

In another embodiment of the compound or salt of Formula I, A is a 4-7 membered heterocycloalkyl group optionally substituted by 1-3 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, oxo, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$.

In another embodiment of the compound or salt of Formula I, A is a 9-10 membered heteroaryl optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, oxo, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$. In selected embodiments, A is isoquinolyl, indazolyl, tetrahydroisoquinolinonyl, isoindolinonyl, and indolinyl.

In further embodiments of the compound or salt of Formula I, A is a 5-6 membered heteroaryl optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$. In still further embodiments, A is a 5-6 membered heteroaryl optionally substituted by 1 group selected from methyl, ethyl, fluoro, trifluoromethyl, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$, where each R^A is independently H or methyl and the

5-6 membered heteroaryl contains 1 ring heteroatom selected form N, O and S and optionally contains 1 additional ring nitrogen atom. In selected embodiments, A is oxazolyl, pyrazolyl, or thienyl optionally substituted by a methyl group. In other selected embodiments, A is pyrazolyl or thienyl, optionally substituted by a methyl group. In specific embodiments, A is thienyl. In other specific embodiments, A is oxazolyl.

In yet other embodiments, A is a pyridyl or pyridyl-N-oxide group optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$. In further embodiments, A is a pyridyl or pyridyl-N-oxide group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, $-NR^AR^A$ and $-((C_1$-$C_4)$alkyl$)NR^AR^A$, where each R^A is independently H or methyl. In selected embodiments of the compound or salt of Formula I, A is pyridyl or pyridyl-N-oxide. In specific embodiments, A is pyridyl.

In another embodiment of the compound or salt of Formula I, Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, or $-NR^XC(=O)-$; particularly $-C(=O)NR^X-$ or $-NR^XC(=O)-$. In another embodiment, Z is $-SO_2NR^X-$ or $-NR^XSO_2-$. In another embodiment of the compound or salt of Formula I, Z is $-NHCH(CF_3)-$ or $-CH(CF_3)NH-$. In another embodiment, Z is $-CH(CF_3)-$ or $-(C_1$-$C_4)$alkyl-. In another embodiment of the compound or salt of Formula I, Z is $-NR^X-$ or $-(C_1$-$C_3)$alkyl-NR^X-.

For each of the above embodiments of Z, R^X, or for $-NR^XC(=O)NR^X$, each R^X, may be independently selected from H, $(C_1$-$C_4)$alkyl, and optionally substituted $(C_2$-$C_4)$alkyl, where said optionally substituted $(C_2$-$C_4)$alkyl is optionally substituted by hydroxyl, cyano, amino, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl)NH-, or $((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl)N-. For each of the above embodiments of Z, R^X, or for $-NR^XC(=O)NR^X$, each R^X, may be independently selected from H, methyl, ethyl, tert-butyl, hydroxyethyl-, methoxymethyl-, cyanoethyl-, N-methylaminoethyl- and dimethylaminoethyl-. In specific embodiments of the compound or salt of Formula I, each R^X is independently H, methyl or cyanoethyl, more specifically, R^X is H or methyl.

In particular embodiments, Z is $-C(=O)NR^X-$, $-SO_2-$, $-SO_2NR^X-$, $-CH(CF_3)NH-$, methyl (methylenyl), ethyl (ethylenyl), $-NR^X-$, or $-(C_1$-$C_3)$alkyl-NR^X-, where each R^X is independently H, methyl or ethyl. In specific embodiments, each R^X is H. In selected embodiments of the compound or salt of Formula I, Z is $-C(=O)NH-$, $-SO_2NH-$, $-CH(CF_3)NH-$, ethyl (ethylenyl), $-CH_2NH-$, $-CH_2N(CH_2CH_3)-$, $-CH(CH_3)N(CH_2CH_3)-$, or $-CH(CH_3)NH-$. In specific embodiments, Z is $-C(=O)NH-$ or $-CH_2NH-$.

In another embodiment of the compound or salt of Formula I, n is 0-4; particularly 0-3. In specific embodiments, n is 1 or n is 0.

In another embodiment, one of R^2 and R^3 is other than hydrogen. In yet another embodiment, both R^2 and R^3 are C_{1-4} alkyl (e.g., methyl). In a still further embodiment, one of R^2 and R^3 is H and the other of R^2 and R^3 is C_{1-4} alkyl (e.g., methyl). In a further embodiment of the compound or salt of Formula I, R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, halogen, cyano, aryl$(C_1\text{-}C_2)$alkyl-, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_2)$alkyl-, $-OR^{Ya}$, $-NR^{Ya}R^{Yb}$, $-C(=O)OR^{Ya}$, $-C(=O)NR^{Ya}R^{Yb}$, $-NR^{Yb}C(=O)R^{Ya}$, $-SO_2NR^{Ya}R^{Yb}$, and $-NR^{Yb}SO_2R^{Ya}$, where R^{Ya} is selected from H, $(C_1\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_2)$alkyl- and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_2)$alkyl-, and each R^{Yb} is independently selected from H and $(C_1\text{-}C_4)$alkyl, specifically H and methyl.

In another embodiment of the compound or salt of Formula I, when n is 0, R^2 and R^3 are independently selected from H and optionally substituted $(C_1\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_2)$alkyl-, and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_2)$alkyl-.

In another embodiment, when n is 1, R^2 and R^3 are independently selected from H and optionally substituted $(C_1\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_2)$alkyl-, and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_2)$alkyl-.

In another embodiment of the compound or salt of Formula I, when n is 1, R^2 is F and R^3 is H, then Z is $-C(=O)NH$-, -NHC(=O)NH, $-SO_2NH$-, $-NHCH(CF_3)$-, $-CH(CF_3)NH$-, $-CH(CF_3)$-, -$(C_1\text{-}C_4)$alkyl-, -NH-, or $-CH_2NH$-; more specifically, Z is $-C(=O)NH$- or $-CH_2NH$-.

In another embodiment, when n is 2-4, R^2 and R^3 are independently selected from H, fluoro, and optionally substituted $(C_1\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_4)$alkyl-.

In another embodiment of the compound or salt of Formula I, when n is 1-4, R^2 is selected from amino, $(C_1\text{-}C_4)$alkylamino, $((C_1\text{-}C_3)$alkyl$)((C_1\text{-}C_3)$alkyl)amino, amino$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_3)$alkylamino$(C_1\text{-}C_4)$alkyl, $((C_1\text{-}C_3)$alkyl$)((C_1\text{-}C_3)$alkyl)amino$(C_1\text{-}C_4)$alkyl, (substituted$(C_1\text{-}C_3)$alkyl$)((C_1\text{-}C_3)$alkyl)amino$(C_1\text{-}C_4)$alkyl (where said (substituted $(C_1\text{-}C_3)$alkyl moiety is substituted by $-C(=O)OH$, -C(=O)O$(C_1\text{-}C_4)$alkyl, or 1-8 fluoro groups), aminocarbonyl$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_3)$alkylaminocarbonyl$(C_1\text{-}C_4)$alkyl, $((C_1\text{-}C_3)$alkyl$)((C_1\text{-}C_3)$alkyl)aminocarbonyl$(C_1\text{-}C_4)$alkyl, hydroxyl, hydroxy$(C_1\text{-}C_4)$alkyl-, $(C_1\text{-}C_4)$alkoxy, and $(C_1\text{-}C_4)$alkoxy$(C_1\text{-}C_4)$alkyl- and R^3 is selected from H and optionally substituted $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl-, and $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_4)$alkyl-.

In another embodiment of the compound or salt of Formula I, when n is 1-4, R^2 is selected from amino, hydroxyl, and $(C_1$-$C_4)$alkoxy, and R^3 is selected from H and optionally substituted $(C_1$-$C_4)$alkyl, phenyl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-. In another embodiment, n is 1-3, R^2 is hydroxyl and R^3 is H or methyl; more specifically, n is 1, R^2 is hydroxyl and R^3 is H or methyl. In another embodiment, (for any value of n) R^2 and R^3 are independently selected from H and optionally substituted $(C_1$-$C_4)$alkyl, phenyl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-.

In another embodiment of the compound or salt of Formula I, (for any value of n) R^2 is selected from H and optionally substituted $(C_1$-$C_4)$alkyl, phenyl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl- and R^3 is selected from H and methyl.

In specific embodiments of the compound or salt of Formula I (for any value of n), R^2 and R^3 are independently selected from H and methyl. In more specific embodiments, both R^2 and R^3 are H or both R^2 and R^3 are methyl.

In another embodiment, the aryl, phenyl, cycloalkyl and each of the $(C_1$-$C_4)$alkyl or $(C_1$-$C_2)$alkyl moieties of said optionally substituted $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$alkyl-, phenyl $(C_1$-$C_4)$alkyl-, $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_4)$alkyl- and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl- of any R^2 and R^3 are optionally substituted by 1, 2 or 3 halogen (specifically fluorine) groups and/or 1 or 2 groups independently selected from cyano, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, NR^AR^A, -$((C_1$-$C_4)$alkyl$)NR^AR^A$, and hydroxyl.

In another embodiment of the compound or salt of Formula I, R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, halogen, cyano, aryl$(C_1$-$C_2)$alkyl-, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-, $-OR^{Ya}$, $-NR^{Ya}R^{Yb}$, $-C(=O)OR^{Ya}$, $-C(=O)NR^{Ya}R^{Yb}$, $-NR^{Yb}C(=O)R^{Ya}$, $-SO_2NR^{Ya}R^{Yb}$, and $-NR^{Yb}SO_2R^{Ya}$, where R^{Ya} is selected from H, $(C_1$-$C_4)$alkyl phenyl$(C_1$-$C_2)$alkyl- and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-, and each R^{Yb} is independently selected from H and $(C_1$-$C_4)$alkyl, specifically H and methyl.

In specific embodiments of the compound or salt of Formula I, R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5 or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N and O and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-.

In selected embodiments of the compound or salt of Formula I, R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl, cyclopropyl, cyclohexyl, 1-ethyl-piperidinyyl, tetrahydrofuranyl, piperidinyl, 1-methyl-pyrrolidinyl, 1-benzyl-pyrrolidinyl, 1-cyclopropylmethyl-pyrrolidinyl, oxetanyl, azetidinyl, 1-methyl-azetidinyl, 1-benzyl-azetidinyl, or 1-cyclopropylmethyl-azetidinyl group.

In specific embodiments, R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl group.

In another embodiment of the compound or salt of Formula I, L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and methyl.

In another embodiment, L is a 5-membered heteroaryl, pyridyl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 substituent selected from chloro, fluoro, cyano and methyl.

In selected embodiments of the compound or salt of Formula I, L is pyrazolyl, oxadiazolyl, 1-methyl-imidazolyl, thiazolyl, thienyl, triazolyl, pyridyl, phenyl, oxazolyl or isoxazolyl, any of which is substituted by a methyl group.

In specific embodiments, L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl, any of which is substituted by a methyl group.

In another embodiment of the compound or salt of Formula I, R^4 is H, halogen, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_2)$alkoxy, $((C_1\text{-}C_2)\text{alkyl})((C_1\text{-}C_2)\text{alkyl})N(C_1\text{-}C_3)$alkoxy-, $((C_1\text{-}C_2)\text{alkyl})((C_1\text{-}C_2)\text{alkyl})N(C_1\text{-}C_3)$alkyl-, $(C_1\text{-}C_2)$haloalkyl, $(C_1\text{-}C_3)$alkylamino, optionally substituted $(C_3\text{-}C_6)$cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl, where said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1 or 2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_2)$alkoxy, halo$(C_1\text{-}C_2)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^C$.

In a selected embodiments, R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, dimethylaminopropyl-, and optionally substituted pyridyl, cyclohexyl, piperidinyl, piperazinyl, imidazolyl, thienyl, or phenyl, where the pyridyl, cyclohexyl, piperidinyl, piperizinyl, imidazolyl, thienyl, or phenyl are optionally substituted

by 1-2 substituents independently selected from methyl, chloro, bromo, fluoro, trifluoromethyl, methoxy, and cyano.

In a selected embodiments, of the compound or salt of Formula I R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, phenyl, 4-chlorophenyl, 2-bromophenyl-,4-fluorophenyl, 4-cyanophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, cyclohexyl, imidazolyl, thienyl, pyrid-2-yl, pyrid-3-yl, or pyrid-4-yl.

In other embodiments of the compound or salt of Formula I, L-R^4 , taken together, form a 1,3-benzodioxolyl, thienopyrimidinyl , benzo-isothiazolyl, 2,3-dihydro-1,4-benzodioxinyl, benzofuranyl, benzimidazolyl, benzimidazolonyl, tetrahydroisoquinolyl, indolinyl or isoindolinyl group, optionally substituted with 1 or 2 groups independently selected from methyl, trifluoromethyl, chloro, fluoro, cyano, methoxy, phenyl, and morpholinylpropyl-.

In selected embodiments, L-R^4 , taken together, form a 1,3-benzodioxolyl, tetrahydroisoquinolyl or isoindolinyl group.

In another embodiment of the compound or salt of Formula I, each R^A and R^C is independently selected from H and (C_1-C_4)alkyl; specifically each R^A and R^C is independently selected from H, methyl and ethyl.

In another embodiment, each R^Y is independently selected from H, (C_1-C_4)alkyl, phenyl, and -(C_1-C_4)alkylphenyl; specifically each R^Y is independently selected from H, methyl, ethyl, phenyl, benzyl and -ethylphenyl.

As used herein, the term "alkyl" represents a saturated, straight or branched hydrocarbon moiety, which may be unsubstituted or substituted by one, or more of the substituents defined herein. Exemplary alkyls include, but are not limited to methyl (Me), ethyl (Et), *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, iso-pentyl (3-methyl-butyl), *neo*-pentyl (2,2-dimethylpropyl), etc. The term "C_1-C_4" refers to an alkyl containing from 1 to 4 carbon atoms.

When the term "alkyl" is used in combination with other substituent groups, such as "haloalkyl" or "cycloalkyl-alkyl" or "arylalkyl", the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical. For example, "arylalkyl" is intended to mean the radical –alkylaryl, wherein the alkyl moiety thereof is a divalent straight or branched-chain carbon radical and the aryl moiety thereof is as defined herein, and is represented by the bonding arrangement present in a benzyl group (-CH_2-phenyl).

In addition, the term "alkyl" may be used to define a divalent substituent, such as a group bonded to two other groups. In this instance, the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical. For example, "pentyl" is intended to represent a pentylene diradical –wherein the pentyl moiety is any

one of a divalent straight ($-CH_2CH_2CH_2CH_2CH_2-$) or branched ($-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)-$, $-CH_2CH_2C(CH_3)_2-$) chain 5-carbon radical.

As used herein, the term "cycloalkyl" refers to a non-aromatic, saturated, cyclic hydrocarbon ring. The term "(C_3-C_8)cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to eight ring carbon atoms. Exemplary "(C_3-C_8)cycloalkyl" groups useful in the present invention include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

"Alkoxy" refers to a group containing an alkyl radical attached through an oxygen linking atom. The term "(C_1-C_4)alkoxy" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 4 carbon atoms attached through an oxygen linking atom. Exemplary "(C_1-C_4)alkoxy" groups useful in the present invention include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *s*-butoxy, and *t*-butoxy.

"Aryl" represents a group or moiety comprising an aromatic, monovalent monocyclic or bicyclic hydrocarbon radical containing from 6 to 10 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents defined herein, and to which may be fused one or more cycloalkyl rings, which may be unsubstituted or substituted by one or more substituents defined herein.

Generally, in the compounds of Formula I, aryl is phenyl.

Heterocyclic groups may be heteroaryl or heterocycloalkyl groups.

"Heterocycloalkyl" represents a group or moiety comprising a stable, non-aromatic, monovalent monocyclic or bicyclic radical, which is saturated or partially unsaturated, containing 3 to 10 ring atoms, which includes 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents defined herein. The heterocycloalkyl may be attached by any atom of the monocyclic or bicyclic radical which results in the creation of a stable structure. This term encompasses bicyclic heterocycloalkyl moieties where the rings are joined at two atoms per ring, as exemplified by the bonding arrangement in 2,5-diazabicyclo[2.2.1]heptyl, 2-azabicyclo[2.2.1]heptyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 7-oxa-2-azabicyclo[2.2.1]heptyl, 2-thia-5-azabicyclo[2.2.1]heptyl,7-azabicyclo[2.2.1]heptyl, 2,6-diazatricyclo[3.3.1.13,7]decyl, 2-azatricyclo[3.3.1.13,7]decyl, 2,4,9-triazatricyclo[3.3.1.13,7]decyl, 8-azabicyclo[3.2.1]octyl, 2,5-diazabicyclo[2.2.2]octyl, 2-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]octyl, octahydro-1*H*-pyrrolo[3,2-*b*]pyridyl group. This term specifically excludes bicyclic heterocycloalkyl moieties where the rings are joined at a single atom per ring (spiro), as exemplified by the bonding arrangement in a 1-oxa-2-azaspiro[4.5]dec-2-en-3-yl group. Illustrative examples of heterocycloalkyls include, but are not limited to, azetidinyl, pyrrolidyl (or pyrrolidinyl),

piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), dihydrofuryl, oxazolinyl, thiazolinyl, pyrazolinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl and 1,5,9-triazacyclododecyl.

Generally, in the compounds of Formula I, heterocycloalkyl groups are 5-membered and/or 6-membered heterocycloalkyl groups, such as pyrrolidyl (or pyrrolidinyl), tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, dihydrofuryl, oxazolinyl, thiazolinyl or pyrazolinyl, piperidyl (or piperidinyl), piperazinyl, morpholinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxanyl, tetrahydro-2H-1,4-thiazinyl, 1,4-dioxanyl, 1,3-oxathianyl, and 1,3-dithianyl.

"Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. This term is also intended to encompass heterocyclic groups containing nitrogen and/or sulfur where the nitrogen or sulfur heteroatoms are optionally oxidized. Illustrative examples of heteroaryls include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl (or furanyl), isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl (or pyridinyl), pyridyl-N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, tetrazolyl, benzo[b]thienyl, isobenzofuryl, 2,3-dihydrobenzofuryl, chromenyl, chromanyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthridinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, isoindolinyl, indolinyl, cinnolinyl, pteridinyl, isothiazolyl.

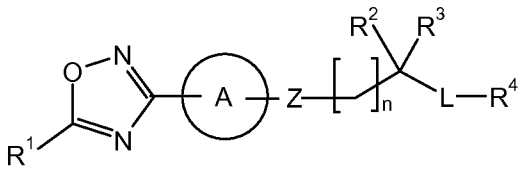
Some of the heteroaryl groups present in the compounds of Formula I are 5-6 membered monocyclic heteroaryl groups. Selected 5-membered heteroaryl groups contain one nitrogen, oxygen or sulfur ring heteroatom, and optionally contain 1, 2 or 3 additional nitrogen ring atoms. Selected 6-membered heteroaryl groups contain 1, 2, 3 or 4 nitrogen ring heteroatoms. Selected 5- or 6-membered heteroaryl groups include thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, triazolyl, and tetrazolyl or pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and thiadiazolyl.

Some of the heteroaryl groups present in the compounds of Formula I are 9-10 membered bicyclic heteroaryl groups. Selected 9-membered heteroaryl groups contain one nitrogen, oxygen or sulfur ring heteroatom, and optionally contain 1, 2 or 3 additional nitrogen ring atoms. Selected 10-membered heteroaryl groups contain one nitrogen, oxygen or sulfur ring heteroatom, and optionally contain 1, 2, 3 or 4 additional nitrogen ring atoms. Selected 9-10 membered heteroaryl groups include benzo[b]thienyl, isobenzofuryl, 2,3-dihydrobenzofuryl, chromenyl, chromanyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthridinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl.

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Hydroxy" or “hydroxyl” is intended to mean the radical –OH. The term “oxo” is intended to mean a keto diradical (=O), such as present on a pyrrolidin-2-one ring.

The compounds of Formula I are only those which are contemplated to be “chemically stable” as will be appreciated by those skilled in the art.

Specifically, the compound of Formula I is a compound according to Formula (I-a):



(I-a)

wherein:

R^1 is $-CF_3$;

A is optionally substituted (C_3-C_6)cycloalkyl, phenyl, naphthyl, 4-7 membered heterocycloalkyl, 5-6 membered heteroaryl, or 9-10 membered heteroaryl,

wherein any optionally substituted cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl is optionally substituted by 1-3 groups independently selected from (C_1-C_4)alkyl, halogen, cyano, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, $-NR^AR^A$ and $-(($C_1$-$C_4$)alkyl)$NR^AR^A$;

Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, $-NR^XC(=O)-$, $-SO_2-$, $-SO_2NR^X-$, $-NR^XSO_2-$, $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1$-$C_4)$alkyl-, $-NR^X-$, or $-(C_1$-$C_3)$alkyl-NR^X-;

n is 0-4;

when n is 0, R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-,

when n is 1-4, R^2 and R^3 are independently selected from H, fluoro, and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-, wherein, when n is 1, R^2 is F and R^3 is H, then Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, $-SO_2NR^X-$, $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1$-$C_4)$alkyl-, $-NR^X-$, or $-(C_1$-$C_3)$alkyl-NR^X-, and

when n is 1-4, R^2 is selected from amino, hydroxyl, and $(C_1$-$C_4)$alkoxy, and R^3 is selected from H and optionally substituted $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$alkyl-, and $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_4)$alkyl-,

wherein the aryl, cycloalkyl and each of the $(C_1$-$C_4)$alkyl moieties of said optionally substituted $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$alkyl-, and $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_4)$alkyl- of any R^2 and R^3 are optionally substituted by 1, 2 or 3 groups independently selected from halogen, cyano, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, halogen, $-NR^AR^A$, $-((C_1$-$C_4)$alkyl$)NR^AR^A$, $(C_1$-$C_4)$alkoxy, hydroxyl, cyano, halo$(C_1$-$C_4)$alkyl, and halo$(C_1$-$C_4)$alkoxy;

or R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, 6, or 7 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 or 2 heteroatoms independently selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by 1, 2 or 3 substituents independently selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, halogen, cyano, aryl$(C_1$-$C_4)$alkyl-, $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_4)$alkyl-, $-OR^Y$, $-NR^YR^Y$, $-C(=O)OR^Y$, $-C(=O)NR^YR^Y$, $-NR^YC(=O)R^Y$, $-SO_2NR^YR^Y$, $-NR^YSO_2R^Y$, $-OC(=O)NR^YR^Y$, $-NR^YC(=O)OR^Y$, and $-NR^YC(=O)NR^YR^Y$; and

L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted,

wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and $(C_1$-$C_4)$alkyl;

R^4 is H, $(C_1$-$C_4)$alkyl, halo, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl$)N(C_1$-$C_4)$alkoxy, $((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl$)N(C_1$-$C_4)$alkyl-, $(C_1$-$C_4)$haloalkoxy-, $(C_1$-$C_4)$alkylamino, optionally substituted $(C_3$-$C_6)$cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl,

wherein said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylthio-, halo$(C_1$-$C_4)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1$-$C_4)$alkyl$)NR^AR^C$;

or L-R^4 , taken together, form a 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group wherein said benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylthio-, halo$(C_1$-$C_4)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1$-$C_4)$alkyl$)NR^AR^C$;

wherein each R^A is independently selected from H and $(C_1$-$C_4)$alkyl;

R^C is H, (C_1-C_4)alkyl, phenyl, 5-6 membered heterocycloalkyl, or 5-6 membered heteroaryl, or R^A and R^C taken together with the atom to which they are attached form an optionally substituted 4-8 membered heterocyclic ring, optionally containing one additional heteroatom selected from N, O and S;

each R^X is independently selected from H, (C_1-C_6)alkyl, and optionally substituted (C_2-C_6)alkyl, where said optionally substituted (C_2-C_6)alkyl is optionally substituted by hydroxyl, cyano, amino, (C_1-C_4)alkoxy, (C_1-C_4)alkyl)NH-, or ((C_1-C_4)alkyl)((C_1-C_4)alkyl)N-; and

each R^Y is independently selected from H, (C_1-C_4)alkyl, phenyl, and -(C_1-C_4)alkylphenyl;

or a salt, particularly a pharmaceutically acceptable salt, thereof.

In one embodiment of this invention, the method excludes treatment with the following compounds:

N-[(4-fluorophenyl)methyl]-4-[5-(2,2,2-trifluoroacetyl)-2-thienyl]-benzamide,

N-[(4-fluorophenyl)methyl]-3-[5-(2,2,2-trifluoroacetyl)-2-thienyl]-benzamide,

or a salt thereof.

Accordingly, the invention is further directed to a method of treatment or use of a compound according to Formula I, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N, or

Y is –C(O)-, X_1 and X_2 are CH, and X_3 is S, or

Y is –C(O)-, X_1 is O, and X_2 and X_3 are CH;

A is a phenyl group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, -NR^AR^A and -((C_1-C_4)alkyl)NR^AR^A, or

A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from methyl, ethyl, tert-butyl, methoxy, ethoxy, -NR^AR^A and -((C_1-C_4)alkyl)NR^AR^A, or

A is a 5-6 membered heteroaryl or a 9-10 membered heteroaryl optionally substituted by 1 group selected from methyl, ethyl, fluoro, trifluoromethyl, -NR^AR^A and -((C_1-C_4)alkyl)NR^AR^A, where the 5-6 membered heteroaryl or 9-10 membered heteroaryl contains 1 ring heteroatom selected form N, O and S and optionally contains 1 additional ring nitrogen atom,

where each R^A is independently H or methyl;

Z is –C(=O)NR^X-, -NR^XC(=O)NR^X, -NR^XC(=O)-, -NHCH(CF_3)-, -CH(CF_3)NH-, -CH(CF_3)-, -(C_1-C_4)alkyl-, or -(C_1-C_4)alkylNR^X-, where R^X is H, (C_1-C_4)alkyl, or optionally substituted (C_2-C_4)alkyl, where said optionally substituted (C_2-C_4)alkyl is optionally substituted by hydroxyl, cyano, amino, (C_1-C_4)alkoxy, (C_1-C_4)alkyl)NH-, or (((C_1-C_4)alkyl)((C_1-C_4)alkyl)N-;

n is 0-3 and R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-, or

n is 1-3 and R^2 is hydroxyl and R^3 is H or methyl, or

n is 0-3 and R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, halogen, cyano, aryl(C_1-C_2)alkyl-, (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-, –OR^{Ya}, -$NR^{Ya}R^{Yb}$, –C(=O)OR^{Ya}, -C(=O)$NR^{Ya}R^{Yb}$, -NR^{Yb}C(=O)R^{Ya}, -$SO_2NR^{Ya}R^{Yb}$, and -$NR^{Yb}SO_2R^{Ya}$, where R^{Ya} is selected from H, (C_1-C_4)alkyl phenyl(C_1-C_2)alkyl- and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-, and each R^{Yb} is independently selected from H and (C_1-C_4)alkyl;

L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and methyl; and

R^4 is H, halogen, (C_1-C_4)alkyl, halo(C_1-C_2)alkyl, (C_1-C_2)alkoxy, (((C_1-C_2)alkyl)((C_1-C_2)alkyl)N(C_1-C_3)alkoxy-, (((C_1-C_2)alkyl)((C_1-C_2)alkyl)N(C_1-C_3)alkyl-, (C_1-C_2)haloalkyl, (C_1-C_3)alkylamino, optionally substituted (C_3-C_6)cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl, where said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1 or 2 groups independently selected from (C_1-C_4)alkyl, halogen, cyano, halo(C_1-C_2)alkyl, (C_1-C_2)alkoxy, halo(C_1-C_2)alkoxy, hydroxyl, -NR^AR^C and -(((C_1-C_4)alkyl)NR^AR^C;

or a salt, particularly a pharmaceutically acceptable salt, thereof.

The invention is further directed to a method of treatment or use of a compound according to Formula I, as defined herein wherein:

n is 0-3 and R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-, or

n is 1-3 and R2 is hydroxyl and R^3 is H or methyl, or

n is 0-3 and R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5 or 6 membered cycloalkyl or heterocycloalkyl group,

wherein said heterocycloalkyl group contains 1 heteroatom selected from N and O and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from (C_1-C_4)alkyl, aryl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-;

R^X is H, methyl or cyanoethyl;

L is a 5-membered heteroaryl, pyridyl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 substituent selected from chloro, fluoro, cyano and methyl; and

R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, dimethylaminopropyl-, and optionally substituted pyridyl, cyclohexyl, piperidinyl, piperazinyl, imidazolyl, thienyl, or phenyl, where the pyridyl, cyclohexyl, piperidinyl, piperizinyl, imidazolyl, thienyl, or phenyl are optionally substituted by 1-2 substituents independently selected from methyl, chloro, bromo, fluoro, trifluoromethyl, methoxy, and cyano;

or a salt, particularly a pharmaceutically acceptable salt, thereof.

The invention is further directed to a method of treatment or use of a compound according to Formula I, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N, or

Y is –C(O)-, X_1 and X_2 are CH, and X_3 is S, or

Y is –C(O)-, X_1 is O, and X_2 and X_3 are CH;

A is an unsubstituted phenyl group or a phenyl group substituted by an ethyl, fluoro, cyano or methoxy group, or a thienyl, pyridyl, cyclopropyl, cyclopentyl or cyclohexyl group;

Z is -C(=O)NH- or $–CH_2NH$-;

n is 0 or 1 and both R^2 and R^3 are H or both R^2 and R^3 are methyl, or

n is 1 and R^2 is hydroxyl and R^3 is H or methyl, or

n is 0 or 1 and R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl group;

L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl, any of which is optionally substituted by a methyl group;

R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, phenyl, 4-chlorophenyl, 2-bromophenyl-,4-fluorophenyl, 4-cyanophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, cyclohexyl, imidazolyl, thienyl, pyrid-2-yl, pyrid-3-yl, or pyrid-4-yl; or

L-R^4 , taken together, form a 1,3-benzodioxolyl, tetrahydroisoquinolyl or isoindolinyl group;

or a salt, particularly a pharmaceutically acceptable salt, thereof.

The invention is more specifically directed to a method of treatment or use of a compound according to Formula I, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N;

A is an unsubstituted phenyl or pyridyl group;

Z is -C(=O)NH- or $-CH_2NH-$;

n is 1;

R^2 and R^3 are both methyl, or

R^2 is hydroxyl and R^3 is methyl, or

R^2 and R^3 are both hydrogen, or

R^2 is methyl and R^3 is hydrogen, or

R^2 is hydroxyl and R^3 is hydrogen, or

R^2 is dimethylamino and R^3 is H, or

R^2 is N,N-dimethylaminoethyl and R^3 is H, or

R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, or a 1-methyl-piperidinyl group;

L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl, any of which is optionally substituted by a methyl group;

R^4 is phenyl, optionally substituted by halo (chloro or fluoro), cyano, halo(C_1-C_2)alkyl, or (C_1-C_2)alkoxy;

or a salt, particularly a pharmaceutically acceptable salt, thereof.

As used herein, the term “optionally substituted” means unsubstituted groups or rings (e.g., cycloalkyl, heterocycle, and heteroaryl rings) and groups or rings substituted with one or more specified substituents.

The compounds of Formula I that are useful in the method of this invention (as well as methods for the preparation of such compounds) are described in WO2011/088181, the disclosure of which is incorporated herein by reference.

Representative compounds of Formula I include:

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(2-(dimethylamino)ethoxy)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(dimethylamino)ethoxy)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(1*H*-imidazol-1-yl)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-cyanoethyl)-*N*-(pyridin-3-ylmethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-((4-(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-4-yl)methyl)benzamide ,

1-(4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)methanamine,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(4-phenylthiophen-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-(4-phenylthiazol-2-yl)cyclopentyl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(3-phenyl-1*H*-1,2,4-triazol-5-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-phenylthiazol-4-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-methoxyphenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-chlorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide ,

N-(2-methyl-2-(4-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-methyl-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-fluorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(5-methyl-4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-cyclohexylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(pyridin-2-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(pyridin-4-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophene-2-carboxamide,

N-((4-(4-(thiophen-2-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-fluoro-*N*-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-cyano-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-methoxy-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-cyanophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-fluorophenyl)thiazol-2-yl)-2,2-dimethyltetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzenesulfonamide,

3-ethyl-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(3-bromophenyl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-((4-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)benzamide,

N-(2-methyl-2-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxamide,

N-((1-methyl-4-(2-phenylthiazol-4-yl)piperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)isonicotinamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)picolinamide,

N-(2-(dimethylamino)-2-(4-phenylthiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-(4-phenylthiazol-2-yl)cyclopropyl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(4-(4-fluorophenyl)thiazol-2-yl)-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)propanamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-phenylthiazol-2-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(3,4-dihydroisoquinolin-2(1*H*)-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-methyl-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

2,2,2-trifluoro-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanamine,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-6-methyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(3-(4-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(5-phenylthiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(3-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-2-methyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-methyl-2-(5-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((2-(4-fluorophenyl)oxazol-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-(4-fluorophenyl)oxazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(2-phenyloxazol-4-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methyl-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)propan-1-amine,

3-(3-(4-(4-phenylthiazol-2-yl)butyl)phenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole,

N-(2-methyl-2-(5-phenyloxazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenylthiazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(2-phenylthiazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

2-fluoro-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)oxazole-4-carboxamide,

N-(2-(1-methyl-2-phenyl-1*H*-imidazol-5-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxyethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

5-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)nicotinamide,

N-(2-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide hydrochloride,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-2-methoxy-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)butyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)butyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxyethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)oxazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

2-(2-(4-chlorophenyl)oxazol-4-yl)-2-methyl-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)propan-1-amine,

N-(2-(2-(4-fluorophenyl)oxazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-methoxyphenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

2-chloro-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(3-(2-(4-fluorophenyl)oxazol-4-yl)-3-hydroxypropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-cyanophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(2-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

3-(5-(2,2-difluoroacetyl)thiophen-2-yl)-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiazol-2-yl)benzamide,

N-(2-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)furan-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methoxyethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-([1,1'-biphenyl]-3-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4'-fluoro-[1,1'-biphenyl]-3-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(3,5-difluorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(3,5-difluorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenyloxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenyloxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-methyl-2-(2-phenyloxazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-pyrazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-([1,1'-biphenyl]-3-yl)-1-methylpiperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(4-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxypropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)furan-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)-1,2,4-oxadiazol-3-yl)benzamide,

and salts, particularly pharmaceutically acceptable salts, thereof.

Particular compounds of Formula I include:

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2H-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(2-phenyloxazol-4-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-fluorophenyl)-1H-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxyethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-Fluorophenyl)-1H-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)nicotinamide,

N-(4-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)butyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiazol-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxypropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

(3-(5-(4-fluorophenyl)oxazol-2-yl)piperidin-1-yl)(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)methanone,

and salts, particularly pharmaceutically acceptable salts, thereof.

As used herein, the term "compound(s) of Formula I " means a compound of Formula I, including any stereoisomer thereof (e.g., including any enantiomer or diastereomer of a compound recited above), in any form, for example, any salt or non-salt form (e.g., as a free acid or base form, or as a pharmaceutically acceptable salt thereof), any solvate form (particularly a hydrate thereof (including mono-, di- and hemi- hydrates and including any hydrate of a salt thereof) and any physical form thereof (e.g., including non-solid forms (e.g., liquid or semi-solid forms), and solid forms (e.g., amorphous or crystalline forms, specific polymorphic forms of any of the above)), and mixtures of various forms. Compound names were generated using the software naming program ChemDraw 11.0 available from CambridgeSoft Corporation., 100 CambridgePark Drive, Cambridge, MA 02140, USA (http://www.cambridgesoft.com).

The invention also includes the use of various deuterated forms of the compounds of Formula I. Each available hydrogen atom attached to a carbon atom may be independently replaced with a deuterium atom. A person of ordinary skill in the art will know how to synthesize deuterated forms of the compounds of Formula I. The invention further includes the use of various radio-labelled or other isotopically enriched forms of the compounds of Formula I, such as compounds that contain a ^{2}H, ^{3}H, ^{14}C, ^{11}C, or ^{18}F atom. Similarly, a person of ordinary skill in the art will know how to synthesize such radio-labelled or isotopically enriched forms of the compounds of Formula I.

The present invention is directed to a method of treating a B-cell lymphoma, particularly a B-cell lymphoma associated with deacetylases, which comprises administering to a patient in need thereof, a compound of Formula I or a salt thereof, particularly a pharmaceutically acceptable salt thereof. More specifically, this invention is

directed to a method of treatment of Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, and Waldenström Macroglobulinemia (lymphoplasmacytic lymphoma), comprising administering a therapeutically effective amount of the compound of Formula I or a salt thereof, particularly a pharmaceutically acceptable salt thereof, to a patient, specifically a human, in need thereof. As used herein, "patient" refers to a mammal, specifically, a human. A therapeutically "effective amount" is intended to mean that amount of a compound that, when administered to a patient in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, e.g., a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, is a quantity of an inventive agent that, when administered to a human in need thereof, is sufficient to inhibit the activity of HDAC such that a disease condition which is mediated by that activity is reduced, alleviated or prevented. The amount of a given compound that will correspond to such an amount will vary depending upon factors such as the particular compound (e.g., the potency (pXC_{50}), efficacy (EC_{50}), and the biological half-life of the particular compound), disease condition and its severity, the identity (e.g., age, size and weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in the art. Likewise, the duration of treatment and the time period of administration (time period between dosages and the timing of the dosages, e.g., before/with/after meals) of the compound will vary according to the identity of the mammal in need of treatment (e.g., weight), the particular compound and its properties (e.g., pharmaceutical characteristics), disease or condition and its severity and the specific composition and method being used, but can nevertheless be determined by one of skill in the art.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a patient, where the disease condition is caused or mediated by HDAC. The methods of treatment for mitigation of a disease condition include the use of the compounds in Formula I in any conventionally acceptable manner, for example for prevention, retardation, prophylaxis, therapy or cure of a disease.

Examples of B-cell lymphomas associated with deacetylases that may be treated using the method of this invention include Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, and Waldenström Macroglobulinemia (lymphoplasmacytic lymphoma).

In another embodiment, this invention is directed to inhibitors of HDAC and their use to stop or reduce the growth of neoplastic cells, e.g., cancer cells and tumor cells.

The compounds of Formula I may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin.

The compounds of Formula I may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of Formula I depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of Formula I depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Treatment of a B-cell lymphoma may be achieved using the compounds of Formula I as a monotherapy, or in dual or multiple combination therapy, such as in combination with other agents, for example, in combination with one or more of the following agents: antibodies (such as rituxumab, alone or in combination with cyclophosphamide), chemotherapeutic regimens, proteasome inhibitors (such as bortezomib), HDAC inhibitors (such as vorinostat, romidepsin, valproic acid, panobinostat, mocetinostat, givinostat, belinostat and entinostat), mTOR inhibitors (such as temsirolimus, deforolimus, everolimus,and rapamycin), DNA methyltransferase inhibitors, acetyl transferase enhancers, proteasome or HSP90 inhibitors, which are administered in effective amounts as is known in the art.

The compounds of Formula I will normally, but not necessarily, be formulated into a pharmaceutical composition prior to administration to a patient. Accordingly, in another aspect, the invention is directed to the administration of a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically-acceptable excipient to treat B cell lymphomas.

The pharmaceutical compositions useful in the invention may be prepared and packaged in bulk form wherein an effective amount of a compound of the invention can be extracted and then given to the patient such as with powders, syrups, and solutions for injection. Alternatively, the pharmaceutical compositions may be prepared and packaged in unit dosage form. For oral application, for example, one or more tablets or capsules may be administered. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of a compound of Formula I or a salt, particularly a pharmaceutically acceptable salt, thereof. When prepared in unit dosage form, the pharmaceutical compositions may contain from 1 mg to 1000 mg of a compound of Formula I.

The pharmaceutical compositions typically contain one compound of Formula I. However, in certain embodiments, the pharmaceutical compositions may contain more than one compound of Formula I. In addition, the pharmaceutical compositions may optionally further comprise one or more additional pharmaceutically active compounds.

As used herein, "pharmaceutically-acceptable excipient" means a material, composition or vehicle involved in giving form or consistency to the composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of Formula I when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically-acceptable are avoided. In addition, each excipient must of course be of sufficiently high purity to render it pharmaceutically-acceptable.

The compounds of Formula I and the pharmaceutically-acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. Conventional dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols and solutions; and

(6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting the compound or compounds of Formula I once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions useful in the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to the use of a solid oral dosage form ,such as a tablet or capsule, comprising an effective amount of a compound of Formula I and a

diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

Pharmaceutical Compositions

Example A

Tablets are prepared using conventional methods and are formulated as follows:

Ingredient	Amount per tablet
Compound	5mg
Microcrystalline cellulose	100mg
Lactose	100mg
Sodium starch glycollate	30mg
Magnesium stearate	2mg
Total	237mg

Example B

Capsules are prepared using conventional methods and are formulated as follows:

Ingredient	Amount per tablet
Compound	15mg
Dried starch	178mg
Magnesium stearate	2mg
Total	195mg

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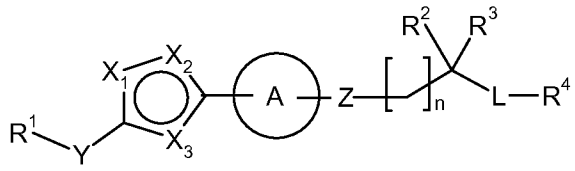
What is claimed is:

1. A method of treatment of a B-cell lymphoma associated with deacetylases comprising administering, to a patient in need thereof, a compound of Formula I:



I

wherein:

R^1 is halo(C_1-C_4)alkyl, wherein said halo(C_1-C_4)alkyl contains at least 2 halo atoms;

Y is a bond and X_1 is O, N or NH, X_2 is N or CH and X_3 is N or NH,

or Y is –C(O)- and X_1 and X_2 are CH or N, X_3 is O or S,

or Y is –C(O)- and X_1 is O, X_2 is CH or N, and X_3 is CH or N;

A is optionally substituted (C_3-C_6)cycloalkyl, phenyl, naphthyl, 4-7 membered heterocycloalkyl, 5-6 membered heteroaryl, or 9-10 membered heteroaryl,

wherein any optionally substituted cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl is optionally substituted by 1-3 groups independently selected from (C_1-C_4)alkyl, halogen, cyano, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, -NR^AR^A and -((C_1-C_4)alkyl)NR^AR^A;

Z is –C(=O)NR^X-, -NR^XC(=O)NR^X, -NR^XC(=O)-, -SO_2-, -SO_2NR^X-, -NR^XSO_2-, -NHCH(CF_3)-, -CH(CF_3)NH-, -CH(CF_3)-, -(C_1-C_4)alkyl-, -NR^X-, or -(C_1-C_3)alkyl-NR^X-;

n is 0-4;

when n is 0, R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-,

when n is 1-4, R^2 and R^3 are independently selected from H, fluoro, and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-, wherein, when n is 1, R^2 is F and R^3 is H, then Z is –C(=O)NR^X-, -NR^XC(=O)NR^X, -SO_2NR^X-, -NHCH(CF_3)-, -CH(CF_3)NH-, -CH(CF_3)-, -(C_1-C_4)alkyl-, -NR^X-, or -(C_1-C_3)alkyl-NR^X-, and

when n is 1-4, R^2 is selected from -NR^AR^B, -(C_1-C_4)alkyl-NR^AR^B, -$CONR^AR^B$, -(C_1-C_4)alkyl-$CONR^AR^B$, -CO_2H, -(C_1-C_4)alkyl-CO_2H, hydroxyl, hydroxy(C_1-C_4)alkyl-, (C_1-C_3)alkoxy, and (C_1-C_3)alkoxy(C_1-C_4)alkyl-, and R^3 is selected from H and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-,

wherein the aryl, cycloalkyl and each of the (C_1-C_4)alkyl moieties of said optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl- of any R^2 and R^3 are optionally substituted by 1, 2 or 3 groups independently selected from halogen,

cyano, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, $-NR^AR^A$, $-((C_1$-$C_4)$alkyl$)NR^AR^A$, and hydroxyl;

or R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, 6, or 7 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 or 2 heteroatoms independently selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by 1, 2 or 3 substituents independently selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, halogen, cyano, aryl$(C_1$-$C_4)$alkyl-, $(C_3$-$C_7)$cycloalkyl$(C_1$-$C_4)$alkyl-, $-OR^Y$, $-NR^YR^Y$, $-C(=O)OR^Y$, $-C(=O)NR^YR^Y$, $-NR^YC(=O)R^Y$, $-SO_2NR^YR^Y$, $-NR^YSO_2R^Y$, $-OC(=O)NR^YR^Y$, $-NR^YC(=O)OR^Y$, and $-NR^YC(=O)NR^YR^Y$; and

L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted,

wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and $(C_1$-$C_4)$alkyl;

R^4 is H, $(C_1$-$C_4)$alkyl, halo, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl$)N(C_1$-$C_4)$alkoxy, $((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl$)N(C_1$-$C_4)$alkyl-, $(C_1$-$C_4)$haloalkoxy-, $(C_1$-$C_4)$alkylamino, optionally substituted $(C_3$-$C_6)$cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl,

wherein said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylthio-, halo$(C_1$-$C_4)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1$-$C_4)$alkyl$)NR^AR^C$;

or L-R^4 , taken together, form a 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group wherein said benzofuranyl, tetrahydroisoquinolyl or isoindolinyl group is optionally substituted by 1, 2 or 3 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylthio-, halo$(C_1$-$C_4)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1$-$C_4)$alkyl$)NR^AR^C$;

wherein each R^A is independently selected from H and $(C_1$-$C_4)$alkyl;

R^B is H, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $-C(=O)(C_1$-$C_4)$alkyl, $-C(=O)O(C_1$-$C_4)$alkyl, $-C(=O)NH_2$, $-C(=O)NH(C_1$-$C_4)$alkyl, $-C(=O)N((C_1$-$C_4)$alkyl$)((C_1$-$C_4)$alkyl$)$, $-SO_2(C_1$-$C_4)$alkyl, or R^A and R^B taken together with the atom to which they are attached form a 4-6 membered heterocyclic ring, optionally containing one additional heteroatom selected from N, O and S and optionally substituted by $(C_1$-$C_4)$alkyl;

R^C is H, $(C_1$-$C_4)$alkyl, phenyl, 5-6 membered heterocycloalkyl, or 5-6 membered heteroaryl, or R^A and R^C taken together with the atom to which they are attached form a

4-8 membered heterocyclic ring, optionally containing one additional heteroatom selected from N, O and S and optionally substituted by $(C_1\text{-}C_4)$alkyl;

each R^X is independently selected from H, $(C_1\text{-}C_6)$alkyl, and optionally substituted $(C_2\text{-}C_6)$alkyl, where said optionally substituted $(C_2\text{-}C_6)$alkyl is optionally substituted by hydroxyl, cyano, amino, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl)NH-, or $((C_1\text{-}C_4)$alkyl)$((C_1\text{-}C_4)$alkyl)N-; and

each R^Y is independently selected from H, $(C_1\text{-}C_4)$alkyl, phenyl, and -$(C_1\text{-}C_4)$alkylphenyl;

or a salt thereof.

2. The method according to claim 1, wherein R^1 is a fluoro-alkyl group containing at least 2 fluoro atoms.

3. The method according to claim 1, wherein R^1 is a $(C_1\text{-}C_2)$alkyl group containing at least 2 fluoro atoms.

4. The method according to claim 1, wherein R^1 is CHF_2 or CF_3.

5. The method according to claim 1, wherein R^1 is CF_3.

6. The method according to any one of claims 1-5, wherein when Y is a bond, X_1 is O, X_2 and X_3 are N, or X_1 is O, X_2 is CH, X_3 is N, or X_1 is N or NH, X_2 is CH, X_3 is N or NH; or X_1 is N or NH, X_2 is N, X_3 is N or NH.

7. The method according to any one of claims 1-5, wherein when Y is a bond, X_1 is O, X_2 and X_3 are N.

8. The method according to any one of claims 1-5, wherein when Y is -C(O)-, X_3 is S, X_1 is CH and X_2 is N, or X_3 is S, X_1 is N and X_2 is CH, or X_3 is O, X_1 is CH and X_2 is N, or X_3 is O, X_1 is N and X_2 is CH, or X_1 and X_2 are CH, X_3 is S or X_1 and X_2 are CH, X_3 is O.

9. The method according to any one of claims 1-5, wherein when Y is -C(O)-, X_3 is S, X_1 is CH and X_2 is N, or X_3 is S, X_1 is N and X_2 is CH, or X_3 is O, X_1 is CH and X_2 is N, or X_3 is O, X_1 is N and X_2 is CH, or X_1 and X_2 are CH, X_3 is S.

10. The method according to any one of claims 1-5, wherein when Y is –C(O)-, X_1 and X_2 are CH, X_3 is S.

11. The method according to any one of claims 1-5, wherein when Y is –C(O)-, X_1 is O, X_2 and X_3 are CH, or X_1 is O, X_2 is CH, and X_3 is N, or X_1 is O, X_2 is N, and X_3 is CH, or X_1 is O, X_2 and X_3 are N.

12. The method according to any one of claims 1-5, wherein when Y is –C(O)-, X_1 is O, X_2 and X_3 are CH.

13. The method according to any one of claims 1-12, wherein A is a phenyl group optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, halogen, cyano, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, -NR^AR^A and -$((C_1$-$C_4)$alkyl)NR^AR^A.

14. The method according to any one of claims 1-12, wherein A is a phenyl group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, -NR^AR^A and -$((C_1$-$C_4)$alkyl)NR^AR^A, where each R^A is independently H or methyl.

15. The method according to any one of claims 1-12, wherein A is an unsubstituted phenyl group or a phenyl group substituted by an ethyl, fluoro, cyano or methoxy group.

16. The method according to any one of claims 1-12, wherein A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, -NR^AR^A and -$((C_1$-$C_4)$alkyl)NR^AR^A.

17. The method according to any one of claims 1-12, wherein A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from methyl, ethyl, tert-butyl, methoxy, ethoxy, -NR^AR^A and -$((C_1$-$C_4)$alkyl)NR^AR^A, where each R^A is independently H or methyl.

18. The method according to any one of claims 1-12, wherein A is a cyclopropyl, cyclopentyl or cyclohexyl group.

19. The method according to any one of claims 1-12, wherein A is naphthyl, optionally substituted by 1-2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$.

20. The method according to any one of claims 1-12, wherein A is a 4-7 membered heterocycloalkyl group optionally substituted by 1-3 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, oxo, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$.

21. The method according to any one of claims 1-12, wherein A is a 9-10 membered heteroaryl optionally substituted by 1-2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, oxo, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$.

22. The method according to any one of claims 1-12, wherein A is isoquinolyl, indazolyl, tetrahydroisoquinolinonyl, isoindolinonyl, and indolinyl.

23. The method according to any one of claims 1-12, wherein A is a 5-6 membered heteroaryl optionally substituted by 1-2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$.

24. The method according to any one of claims 1-12, wherein A is a 5-6 membered heteroaryl optionally substituted by 1 group selected from methyl, ethyl, fluoro, trifluoromethyl, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$, where each R^A is independently H or methyl and the 5-6 membered heteroaryl contains 1 ring heteroatom selected form N, O and S and optionally contains 1 additional ring nitrogen atom.

25. The method according to any one of claims 1-12, wherein A is oxazolyl, pyrazolyl, or thienyl, optionally substituted by a methyl group.

26. The method according to any one of claims 1-12, wherein A is a pyridyl or pyridyl-N-oxide group optionally substituted by 1-2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, $-NR^AR^A$ and $-((C_1\text{-}C_4)\text{alkyl})NR^AR^A$.

27. The method according to any one of claims 1-12, wherein A is a pyridyl or pyridyl-N-oxide group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, $-NR^AR^A$ and $-((C_1-C_4)alkyl)NR^AR^A$, where each R^A is independently H or methyl.

28. The method according to any one of claims 1-12, wherein A is thienyl, oxazolyl, or pyridyl.

29. The method according to any one of claims 1-28, wherein Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, $-NR^XC(=O)-$, $-NR^XSO_2-$, $-SO_2NR^X-$, $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1-C_4)alkyl-$, or $-(C_1-C_3)alkylNR^X-$.

30. The method according to claim 29, wherein R^X, or for $-NR^XC(=O)NR^X$, each R^X, may be independently selected from H, $(C_1-C_4)alkyl$, and optionally substituted $(C_2-C_4)alkyl$, where said optionally substituted $(C_2-C_4)alkyl$ is optionally substituted by hydroxyl, cyano, amino, $(C_1-C_4)alkoxy$, $(C_1-C_4)alkyl)NH-$, or $((C_1-C_4)alkyl)((C_1-C_4)alkyl)N-$.

31. The method according to claim 29, wherein R^X is H, methyl or cyanoethyl.

32. The method according to claim 29, wherein R^X is H.

33. The method according to any one of claims 1-28, wherein Z is $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1-C_4)alkyl-$ or $-CH_2NH-$.

34. The method according to any one of claims 1-28, wherein Z is $-C(=O)NH-$ or $-CH_2NH-$.

35. The method according to any one of claims 1-34, wherein n is 0-3.

36. The method according to any one of claims 1-35, wherein n is 0 or 1.

37. The method according to any one of claims 1-36, wherein one of R^2 and R^3 is other than hydrogen.

38. The method according to any one of claims 1-36, wherein both R^2 and R^3 are C_{1-4}alkyl.

39. The method according to any one of claims 1-36, wherein one of R^2 and R^3 is H and the other of R^2 and R^3 is C_{1-4} alkyl.

40. The method according to any one of claims 1-34, wherein when n is 1-4, R^2 is selected from amino, (C_1-C_4)alkylamino, ((C_1-C_3)alkyl)((C_1-C_3)alkyl)amino, amino(C_1-C_4)alkyl, (C_1-C_3)alkylamino(C_1-C_4)alkyl, ((C_1-C_3)alkyl)((C_1-C_3)alkyl)amino(C_1-C_4)alkyl, (substituted(C_1-C_3)alkyl)((C_1-C_3)alkyl)amino(C_1-C_4)alkyl (where said (substituted (C_1-C_3)alkyl moiety is substituted by –C(=O)OH, -C(=O)O(C_1-C_4)alkyl, or 1-8 fluoro groups), aminocarbonyl(C_1-C_4)alkyl, (C_1-C_3)alkylaminocarbonyl(C_1-C_4)alkyl, ((C_1-C_3)alkyl)((C_1-C_3)alkyl)aminocarbonyl(C_1-C_4)alkyl, hydroxyl, hydroxy(C_1-C_4)alkyl-, (C_1-C_4)alkoxy, and (C_1-C_4)alkoxy(C_1-C_4)alkyl- and R^3 is selected from H and optionally substituted (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl-, and (C_3-C_7)cycloalkyl(C_1-C_4)alkyl-.

41. The method according to any one of claims 1-34, wherein when n is 1-4, R^2 is selected from amino, hydroxyl, and (C_1-C_4)alkoxy, and R^3 is selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-.

42. The method according to any one of claims 1-36, wherein R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-.

43. The method according to any one of claims 1-36, wherein R^2 is selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl- and R^3 is selected from H and methyl.

44. The method according to any one of claims 1-36, wherein R^2 and R^3 are independently selected from H and optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl-; wherein the phenyl, cycloalkyl and each of the (C_1-C_4)alkyl or (C_1-C_2)alkyl moieties of said optionally substituted (C_1-C_4)alkyl, phenyl(C_1-C_2)alkyl-, and (C_3-C_6)cycloalkyl(C_1-C_2)alkyl- are optionally substituted by 1, 2 or 3 halogen groups and/or 1 or 2 groups independently selected from cyano, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, NR^AR^A, -((C_1-C_4)alkyl)NR^AR^A, and hydroxyl.

45. The method according to any one of claims 1-36, wherein both R^2 and R^3 are H or both R^2 and R^3 are methyl.

46. The method according to any one of claims 1-34, wherein R^2 is hydroxyl and R^3 is H or methyl.

47. The method according to any one of claims 1-34, wherein n is 1, R^2 is hydroxyl and R^3 is H or methyl.

48. The method according to any one of claims 1-36, wherein R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, halogen, cyano, aryl$(C_1$-$C_2)$alkyl-, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-, $-OR^{Ya}$, $-NR^{Ya}R^{Yb}$, $-C(=O)OR^{Ya}$, $-C(=O)NR^{Ya}R^{Yb}$, $-NR^{Yb}C(=O)R^{Ya}$, $-SO_2NR^{Ya}R^{Yb}$, and $-NR^{Yb}SO_2R^{Ya}$, where R^{Ya} is selected from H, $(C_1$-$C_4)$alkyl phenyl$(C_1$-$C_2)$alkyl- and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-, and each R^{Yb} is independently selected from H and $(C_1$-$C_4)$alkyl.

49. The method according to claim 48, wherein R^Y is independently selected from H, $(C_1$-$C_4)$alkyl, phenyl, and $-(C_1$-$C_4)$alkylphenyl.

50. The method according to claim 46, wherein each R^Y is independently selected from H, methyl, ethyl, phenyl, benzyl and -ethylphenyl.

51. The method according to any one of claims 1-36, wherein R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5 or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N and O and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-.

52. The method according to any one of claims 1-36, wherein R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl, cyclopropyl, cyclohexyl, 1-

ethyl-piperidinyyl, tetrahydrofuranyl, piperidinyl, 1-methyl-pyrrolidinyl, 1-benzyl-pyrrolidinyl, 1-cyclopropylmethyl-pyrrolidinyl, oxetanyl, azetidinyl, 1-methyl-azetidinyl, 1-benzyl-azetidinyl, or 1-cyclopropylmethyl-azetidinyl group.

53. The method according to any one of claims 1-36, wherein R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl group.

54. The method according to any one of claims 1-53, wherein L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and methyl.

55. The method according to any one of claims 1-53, wherein L is a 5-membered heteroaryl, pyridyl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 substituent selected from chloro, fluoro, cyano and methyl.

56. The method according to any one of claims 1-53, wherein L is pyrazolyl, oxadiazolyl, 1-methyl-imidazolyl, thiazolyl, thienyl, triazolyl, pyridyl, phenyl, oxazolyl or isoxazolyl which is substituted by optionally further substituted by a methyl group.

57. The method according to any one of claims 1-53, wherein L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl which is substituted by a methyl group.

58. The method according to any one of claims 1-57, wherein R^4 is H, halogen, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_2)$alkoxy, $((C_1\text{-}C_2)$alkyl$)((C_1\text{-}C_2)$alkyl$)N(C_1\text{-}C_3)$alkoxy-, $((C_1\text{-}C_2)$alkyl$)((C_1\text{-}C_2)$alkyl$)N(C_1\text{-}C_3)$alkyl-, $(C_1\text{-}C_2)$haloalkyl, $(C_1\text{-}C_3)$alkylamino, optionally substituted $(C_3\text{-}C_6)$cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl, where said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1 or 2 groups independently selected from $(C_1\text{-}C_4)$alkyl, halogen, cyano, halo$(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_2)$alkoxy, halo$(C_1\text{-}C_2)$alkoxy, hydroxyl, $-NR^AR^C$ and $-((C_1\text{-}C_4)$alkyl$)NR^AR^C$.

59. The method according to any one of claims 1-57, wherein R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, dimethylaminopropyl-, and optionally

substituted pyridyl, cyclohexyl, piperidinyl, piperazinyl, imidazolyl, thienyl, or phenyl, where the pyridyl, cyclohexyl, piperidinyl, piperizinyl, imidazolyl, thienyl, or phenyl are optionally substituted by 1-2 substituents independently selected from methyl, chloro, bromo, fluoro, trifluoromethyl, methoxy, and cyano.

60. The method according to any one of claims 1-57, wherein R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, phenyl, 4-chlorophenyl, 2-bromophenyl-,4-fluorophenyl, 4-cyanophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, cyclohexyl, imidazolyl, thienyl, pyrid-2-yl, pyrid-3-yl, or pyrid-4-yl.

61. The method according to any one of claims 1-53, wherein L-R^4 , taken together, form a 1,3-benzodioxolyl, thienopyrimidinyl , benzo-isothiazolyl, 2,3-dihydro-1,4-benzodioxinyl, benzofuranyl, benzimidazolyl, benzimidazolonyl, tetrahydroisoquinolyl, indolinyl or isoindolinyl group, optionally substituted with 1 or 2 groups independently selected from methyl, trifluoromethyl, chloro, fluoro, cyano, methoxy, phenyl, and morpholinylpropyl-.

62. The method according to any one of claims 1-53, wherein L-R^4 , taken together, form a 1,3-benzodioxolyl, tetrahydroisoquinolyl or isoindolinyl group.

63. The method according to any one of claims 1-62, wherein each R^A and R^B is independently selected from H and (C_1-C_4)alkyl.

64. The method according to any one of claims 1-62, wherein each R^A and R^B is independently selected from H, methyl and ethyl.

65. The method according to claim 1, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N, or

Y is –C(O)-, X_1 and X_2 are CH, and X_3 is S, or

Y is –C(O)-, X_1 is O, and X_2 and X_3 are CH;

A is a phenyl group optionally substituted by 1 group selected from methyl, ethyl, fluoro, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, cyano, -NR^AR^A and -((C_1-C_4)alkyl)NR^AR^A, or

A is a cyclopropyl, cyclopentyl or cyclohexyl group, optionally substituted by 1-2 groups independently selected from methyl, ethyl, tert-butyl, methoxy, ethoxy, $-NR^AR^A$ and $-((C_1-C_4)alkyl)NR^AR^A$, or

A is a 5-6 membered heteroaryl or a 9-10 membered heteroaryl optionally substituted by 1 group selected from methyl, ethyl, fluoro, trifluoromethyl, $-NR^AR^A$ and $-((C_1-C_4)alkyl)NR^AR^A$, where the 5-6 membered heteroaryl or 9-10 membered heteroaryl contains 1 ring heteroatom selected form N, O and S and optionally contains 1 additional ring nitrogen atom,

where each R^A is independently H or methyl;

Z is $-C(=O)NR^X-$, $-NR^XC(=O)NR^X$, $-NR^XC(=O)-$, $-NHCH(CF_3)-$, $-CH(CF_3)NH-$, $-CH(CF_3)-$, $-(C_1-C_4)alkyl-$, or $-(C_1-C_4)alkylNR^X-$, where R^X is H, $(C_1-C_4)alkyl$, or optionally substituted $(C_2-C_4)alkyl$, where said optionally substituted $(C_2-C_4)alkyl$ is optionally substituted by hydroxyl, cyano, amino, $(C_1-C_4)alkoxy$, $(C_1-C_4)alkyl)NH-$, or $((C_1-C_4)alkyl)((C_1-C_4)alkyl)N-$;

n is 0-3 and R^2 and R^3 are independently selected from H and optionally substituted $(C_1-C_4)alkyl$, $phenyl(C_1-C_2)alkyl-$, and $(C_3-C_6)cycloalkyl(C_1-C_2)alkyl-$, or

n is 1-3 and R^2 is hydroxyl and R^3 is H or methyl, or

n is 0-3 and R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5, or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N, O and S and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1-C_4)alkyl$, $halo(C_1-C_4)alkyl$, halogen, cyano, $aryl(C_1-C_2)alkyl-$, $(C_3-C_6)cycloalkyl(C_1-C_2)alkyl-$, $-OR^{Ya}$, $-NR^{Ya}R^{Yb}$, $-C(=O)OR^{Ya}$, $-C(=O)NR^{Ya}R^{Yb}$, $-NR^{Yb}C(=O)R^{Ya}$, $-SO_2NR^{Ya}R^{Yb}$, and $-NR^{Yb}SO_2R^{Ya}$, where R^{Ya} is selected from H, $(C_1-C_4)alkyl$ $phenyl(C_1-C_2)alkyl-$ and $(C_3-C_6)cycloalkyl(C_1-C_2)alkyl-$, and each R^{Yb} is independently selected from H and $(C_1-C_4)alkyl$;

L is 5-6 membered heteroaryl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 or 2 substituents independently selected from halogen, cyano and methyl; and

R^4 is H, halogen, $(C_1-C_4)alkyl$, $halo(C_1-C_2)alkyl$, $(C_1-C_2)alkoxy$, $((C_1-C_2)alkyl)((C_1-C_2)alkyl)N(C_1-C_3)alkoxy-$, $((C_1-C_2)alkyl)((C_1-C_2)alkyl)N(C_1-C_3)alkyl-$, $(C_1-C_2)haloalkyl$, $(C_1-C_3)alkylamino$, optionally substituted $(C_3-C_6)cycloalkyl$, optionally substituted phenyl, optionally substituted 5-6 membered heterocycloalkyl, or optionally substituted 5-6 membered heteroaryl, where said optionally substituted cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted by 1 or 2 groups independently selected from $(C_1-C_4)alkyl$, halogen, cyano, $halo(C_1-C_2)alkyl$, $(C_1-C_2)alkoxy$, $halo(C_1-C_2)alkoxy$, hydroxyl, $-NR^AR^C$ and $-((C_1-C_4)alkyl)NR^AR^C$.

66. The method according to claim 65, wherein:

n is 0-3 and R^2 and R^3 are independently selected from H and optionally substituted $(C_1$-$C_4)$alkyl, phenyl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-, or

n is 1-3 and R^2 is hydroxyl and R^3 is H or methyl, or

n is 0-3 and R^2 and R^3 taken together with the atom to which they are connected form an optionally substituted 4, 5 or 6 membered cycloalkyl or heterocycloalkyl group, wherein said heterocycloalkyl group contains 1 heteroatom selected from N and O and said optionally substituted cycloalkyl or heterocycloalkyl group is optionally substituted by a substituent selected from $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_2)$alkyl-, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_2)$alkyl-;

R^X is H, methyl or cyanoethyl;

L is a 5-membered heteroaryl, pyridyl or phenyl which is substituted by R^4 and is optionally further substituted, wherein when L is further substituted, L is substituted by 1 substituent selected from chloro, fluoro, cyano and methyl; and

R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, dimethylaminopropyl-, and optionally substituted pyridyl, cyclohexyl, piperidinyl, piperazinyl, imidazolyl, thienyl, or phenyl, where the pyridyl, cyclohexyl, piperidinyl, piperizinyl, imidazolyl, thienyl, or phenyl are optionally substituted by 1-2 substituents independently selected from methyl, chloro, bromo, fluoro, trifluoromethyl, methoxy, and cyano.

67. The method according to claim 1, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N, or

Y is –C(O)-, X_1 and X_2 are CH, and X_3 is S, or

Y is –C(O)-, X_1 is O, and X_2 and X_3 are CH;

A is an unsubstituted phenyl group or a phenyl group substituted by an ethyl, fluoro, cyano or methoxy group, or a thienyl, pyridyl, cyclopropyl, cyclopentyl or cyclohexyl group;

Z is -C(=O)NH- or $–CH_2NH$-;

n is 0 or 1 and both R^2 and R^3 are H or both R^2 and R^3 are methyl, or

n is 1 and R^2 is hydroxyl and R^3 is H or methyl, or

n is 0 or 1 and R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, cyclopentyl, 1-methyl-piperidinyl group;

L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl, any of which is optionally substituted by a methyl group;

R^4 is H, methyl, bromo, trifluoromethyl, dimethylaminoethoxy-, phenyl, 4-chlorophenyl, 2-bromophenyl-,4-fluorophenyl, 4-cyanophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, cyclohexyl, imidazolyl, thienyl, pyrid-2-yl, pyrid-3-yl, or pyrid-4-yl; or

L-R^4 , taken together, form a 1,3-benzodioxolyl, tetrahydroisoquinolyl or isoindolinyl group.

68. The method according to claim 1, wherein the compound of Formula I, or salt thereof is selected from:

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(2-(dimethylamino)ethoxy)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(dimethylamino)ethoxy)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(1*H*-imidazol-1-yl)benzyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-cyanoethyl)-*N*-(pyridin-3-ylmethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-((4-(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-4-yl)methyl)benzamide ,

1-(4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)methanamine,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(4-phenylthiophen-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-(4-phenylthiazol-2-yl)cyclopentyl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(3-phenyl-1*H*-1,2,4-triazol-5-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-phenylthiazol-4-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-methoxyphenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-chlorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide ,

N-(2-methyl-2-(4-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-methyl-4-(4-phenylthiazol-2-yl)piperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-fluorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(5-methyl-4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-cyclohexylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(pyridin-2-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(pyridin-4-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)thiophene-2-carboxamide,

N-((4-(4-(thiophen-2-yl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-fluoro-*N*-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-cyano-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-methoxy-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-cyanophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(4-fluorophenyl)thiazol-2-yl)-2,2-dimethyltetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzenesulfonamide,

3-ethyl-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(3-bromophenyl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-((4-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)benzamide,

N-(2-methyl-2-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxamide,

N-((1-methyl-4-(2-phenylthiazol-4-yl)piperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)isonicotinamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)picolinamide,

N-(2-(dimethylamino)-2-(4-phenylthiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((1-(4-phenylthiazol-2-yl)cyclopropyl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

3-(4-(4-fluorophenyl)thiazol-2-yl)-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)propanamide,

N-(2-(2-(4-chlorophenyl)thiazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-phenylthiazol-2-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(3,4-dihydroisoquinolin-2(1*H*)-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-methyl-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)thiazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

2,2,2-trifluoro-*N*-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanamine,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-6-methyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(3-(4-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(5-phenylthiazol-2-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(3-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-2-methyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-methyl-2-(5-phenylthiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((2-(4-fluorophenyl)oxazol-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-(4-fluorophenyl)oxazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(2-phenyloxazol-4-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methyl-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)propan-1-amine,

3-(3-(4-(4-phenylthiazol-2-yl)butyl)phenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole,

N-(2-methyl-2-(5-phenyloxazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenylthiazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(2-phenylthiazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)thiazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

2-fluoro-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)oxazole-4-carboxamide,

N-(2-(1-methyl-2-phenyl-1*H*-imidazol-5-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxyethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

5-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)nicotinamide,

N-(2-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide hydrochloride,

N-(2-(3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)-2-methylpropyl)-5-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-2-methoxy-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-5-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)butyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(4-(dimethylamino)-2-(2-(4-fluorophenyl)oxazol-4-yl)butyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxyethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-(2-(4-chlorophenyl)oxazol-4-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

2-(2-(4-chlorophenyl)oxazol-4-yl)-2-methyl-*N*-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)propan-1-amine,

N-(2-(2-(4-fluorophenyl)oxazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-([1,1'-biphenyl]-3-yl)-1-methylpiperidin-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-methoxyphenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

2-chloro-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(3-(2-(4-fluorophenyl)oxazol-4-yl)-3-hydroxypropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-cyanophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(2-fluorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

3-(5-(2,2-difluoroacetyl)thiophen-2-yl)-*N*-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiazol-2-yl)benzamide,

N-(2-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)furan-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methoxyethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(4-fluorophenyl)thiazol-2-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-([1,1'-biphenyl]-3-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4'-fluoro-[1,1'-biphenyl]-3-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-((4-(4-(3,5-difluorophenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(4-(3,5-difluorophenyl)thiazol-2-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenyloxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-phenyloxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)ethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-methyl-2-(2-phenyloxazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-chlorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-methyl-2-(3-phenyl-1*H*-pyrazol-5-yl)propyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)propyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(4-(4-chlorophenyl)thiazol-2-yl)-2-methylpropyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-((4-([1,1'-biphenyl]-3-yl)-1-methylpiperidin-4-yl)methyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)nicotinamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(4-(2,2,2-trifluoroacetyl)thiophen-2-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-hydroxypropyl)-3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)furan-3-yl)benzamide,

N-(2-(2-(4-fluorophenyl)oxazol-4-yl)-2-methylpropyl)-3-(5-(2,2,2-trifluoroacetyl)thiophen-3-yl)benzamide, and

N-((4-(4-phenylthiazol-2-yl)tetrahydro-2*H*-pyran-4-yl)methyl)-3-(5-(2,2,2-trifluoroacetyl)-1,2,4-oxadiazol-3-yl)benzamide.

69. The method according to claim 1, wherein:

R^1 is CHF_2 or CF_3;

Y is a bond, X_1 is O, and X_2 and X_3 are N;

A is an unsubstituted phenyl or pyridyl group;

Z is -C(=O)NH- or $-CH_2NH-$; n is 1;

R^2 and R^3 are both methyl, or

R^2 is hydroxyl and R^3 is methyl, or

R^2 and R^3 are both hydrogen, or

R^2 is methyl and R^3 is hydrogen, or

R^2 is hydroxyl and R^3 is hydrogen, or

R^2 is dimethylamino and R^3 is H, or

R^2 is N,N-dimethylaminoethyl and R^3 is H, or

R^2 and R^3 taken together with the atom to which they are connected form a tetrahydropyranyl, 2,2-dimethyl-tetrahydropyranyl, or a 1-methyl-piperidinyl group;

L is thiazolyl, thienyl, triazolyl, pyridyl, phenyl, or oxazolyl, any of which is optionally substituted by a methyl group;

R^4 is phenyl, optionally substituted by halo (chloro or fluoro), cyano, halo(C_1-C_2)alkyl, or (C_1-C_2)alkoxy.

70. The method according to any one of claims 1-69, wherein the B-cell lymphoma is Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, or Waldenström Macroglobulinemia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/046201

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 25/28 (2012.01)
USPC - 514/364
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/00, 31/44, 31/497, 31/502, 31/506, 38/00, 38/45; A61P 9/00, 25/00, 25/28, 35/00, 37/02 (2012.01)
USPC - 424/94.5; 514/236.8, 248, 340, 350, 364, 372, 374; 548/125, 134

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent, Google Patents, STN International, WIPO, Public AppFT and PatFT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2001/018045 A1 (PAVLETICH et al) 15 March 2001 (15.03.2001) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1-12, 65-69
A	US 2005/0256153 A1 (DHANOA et al) 17 November 2005 (17.11.2005) entire document	1-12, 65-69
A	US 2009/0048228 A1 (ATTENNI et al) 19 February 2009 (19.02.2009) entire document	1-12, 65-69
A	US 2010/0197723 A1 (GHOSH et al) 05 August 2010 (05.08.2010) entire document	1-12, 65-69
A	US 2011/0117073 A1 (SINGH et al) 19 May 2011 (19.05.2011) entire document	1-12, 65-69
A, P	WO 2011/088187 A1 (BALOGLU et al) 21 July 2011 (21.07.2011) entire document	1-12, 65-69

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September 2012	19 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/046201

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 13-64, 70
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.