THIAZOLE AND THIADIAZOLE COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES

The invention relates to compounds of structural formula (I) or a pharmaceutically acceptable salt, solvate, clathrate, or produrg thereof, wherein R1, X, X’, L, and Y are defined herein. These compounds are useful as immunosuppressive agents and for treating and preventing inflammatory conditions, allergic disorders, and immune disorders.
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RELATED APPLICATIONS
This application claims the benefit of U.S. Provisional Application No. 60/761,974, filed January 25, 2006 and U.S. Provisional Application No. 60/761,933, filed January 25, 2006, the entire teachings of which are incorporated herein by reference.

FIELD OF THE INVENTION
This invention relates to biologically active chemical compounds, namely thiazole and [1,3,4]thiadiazole derivatives that may be used for immunosuppression or to treat or prevent inflammatory conditions and immune disorders.

BACKGROUND OF THE INVENTION
Inflammation is a mechanism that protects mammals from invading pathogens. However, while transient inflammation is necessary to protect a mammal from infection, uncontrolled inflammation causes tissue damage and is the underlying cause of many illnesses. Inflammation is typically initiated by binding of an antigen to T-cell antigen receptor. Antigen binding by a T-cell initiates calcium influx into the cell via calcium ion channels, such as Ca\(^{2+}\)-release-activated Ca\(^{2+}\) channels (CRAC). Calcium ion influx in turn initiates a signaling cascade that leads to activation of these cells and an inflammatory response characterized by cytokine production.

Interleukin 2 (IL-2) is a cytokine that is secreted by T cells in response to calcium ion influx into the cell. IL-2 modulates immunological effects on many cells of the immune system. For example, it is a potent T cell mitogen that is required for the T cell proliferation, promoting their progression from G1 to S phase of the cell cycle; it stimulates the growth of NK cells; and it acts as a growth factor to B cells and stimulates antibody synthesis.
IL-2, although useful in the immune response, can cause a variety of problems. IL-2 damages the blood-brain barrier and the endothelium of brain vessels. These effects may be the underlying causes of neuropsychiatric side effects observed under IL-2 therapy, e.g. fatigue, disorientation and depression. It also alters the electrophysiological behaviour of neurons.

Due to its effects on both T and B cells, IL-2 is a major central regulator of immune responses. It plays a role in inflammatory reactions, tumour surveillance, and hematopoiesis. It also affects the production of other cytokines, inducing IL-1, TNF-α and TNF-β secretion, as well as stimulating the synthesis of IFN-γ in peripheral leukocytes.

T cells that are unable to produce IL-2 become inactive (anergic). This renders them potentially inert to any antigenic stimulation they might receive in the future. As a result, agents which inhibit IL-2 production can be used for immunosuppression or to treat or prevent inflammation and immune disorders. This approach has been clinically validated with immunosuppressive drugs such as cyclosporin, FK506, and RS61443. Despite this proof of concept, agents that inhibit IL-2 production remain far from ideal. Among other problems, efficacy limitations and unwanted side effects (including dose-dependant nephrotoxicity and hypertension) hinder their use.

Over production of proinflammatory cytokines other than IL-2 has also been implicated in many autoimmune diseases. For example, Interleukin 5 (IL-5), a cytokine that increases the production of eosinophils, is increased in asthma. Overproduction of IL-5 is associated with accumulation of eosinophils in the asthmatic bronchial mucosa, a hallmark of allergic inflammation. Thus, patients with asthma and other inflammatory disorders involving the accumulation of eosinophils would benefit from the development of new drugs that inhibit the production of IL-5.

Interleukin 4 (IL-4) and interleukin 13 (IL-13) have been identified as mediators of the hypercontractility of smooth muscle found in inflammatory bowel disease.
and asthma. Thus, patients with asthma and inflammatory bowel disease would benefit from the development of new drugs that inhibit IL-4 and IL-13 production.

Granulocyte macrophage-colony stimulating factor (GM-CSF) is a regulator of maturation of granulocyte and macrophage lineage population and has been implicated as a key factor in inflammatory and autoimmune diseases. Anti-GM-CSF antibody blockade has been shown to ameliorate autoimmune disease. Thus, development of new drugs that inhibit the production of GM-CSF would be beneficial to patients with an inflammatory or autoimmune disease.

There is therefore a continuing need for new drugs which overcome one or more of the shortcomings of drugs currently used for immunosuppression or in the treatment or prevention of inflammatory disorders, allergic disorders and autoimmune disorders. Desirable properties of new drugs include efficacy against diseases or disorders that are currently untreatable or poorly treatable, new mechanism of action, oral bioavailability and/or reduced side effects.
SUMMARY OF THE INVENTION

This invention meets the above-mentioned needs by providing certain thiazole and [1,3,4]thiadiazole derivatives that inhibit the activity of CRAC ion channels and inhibit the production of IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, and IFNγ. These compounds are particularly useful for immunosuppression and/or to treat or prevent inflammatory conditions and immune disorders.

The invention relates to compounds of formula (I):

\[
\begin{align*}
R'_{1} & \quad \text{or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:} \\
Y & \quad \text{is an optionally substituted alkyl, an optionally substituted cycloalkyl,} \\
& \quad \text{an optionally substituted cycloalkenyl, an optionally substituted alkenyl, an} \\
& \quad \text{optionally substituted heterocyclyl, an optionally substituted aryl, or an} \\
& \quad \text{optionally substituted heteroaryl;} \\
R'_{1} & \quad \text{is an optionally substituted aryl or an optionally substituted heteroaryl, provided that } R'_{1} \text{ is not a pyrazolyl;} \\
X \text{ and } X' & \quad \text{are each independently CH, CZ, or N; provided that at least one} \\
& \quad \text{of } X \text{ or } X' \text{ is N;} \\
L & \quad \text{is a linker; and} \\
Z & \quad \text{is a substituent.}
\end{align*}
\]

A compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof is particularly useful inhibiting immune cell (e.g., T-cells and/or B-cells) activation (e.g., activation in response to an antigen). In particular, a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof can inhibit the production of certain cytokines that regulate immune cell activation. For example, a compound of
the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof can inhibit the production of IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, INF-γ or combinations thereof. Moreover, a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels.

A compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof is particularly useful for immunosuppression or for treating or preventing inflammatory conditions, allergic disorders, and immune disorders.

The invention also encompasses pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for immunosuppression and treating or preventing inflammatory conditions, allergic disorders and immune disorders.

The invention further encompasses methods for treating or preventing inflammatory conditions, allergic disorders, and immune disorders, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, or a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof. These methods may also comprise administering to the subject an additional agent separately or in a combination composition with the compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

The invention further encompasses methods for suppressing the immune system of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a pharmaceutically
acceptable salt, solvate, clathrate, or prodrug thereof, or a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof. These methods may also comprise administering to the subject an additional agent separately or in a combination composition with the compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

The invention further encompasses methods for inhibiting immune cell activation, including inhibiting proliferation of T cells and/or B cells, in vivo or in vitro comprising administering to the cell an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof or a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

The invention further encompasses methods for inhibiting cytokine production in a cell, (e.g., IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, and/or INF-γ production) in vivo or in vitro comprising administering to a cell an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof or a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

The invention further encompasses methods for modulating ion channel activity (e.g., CRAC) in vivo or in vitro comprising administering an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof or a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

All of the methods of this invention may be practice with a compound of the invention alone, or in combination with other agents, such as other
immunosuppressive agents, anti-inflammatory agents, agents for the treatment of allergic disorders or agents for the treatment of immune disorders.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

Unless otherwise specified, the below terms used herein are defined as follows:

As used herein, the term an "aromatic ring" or "aryl" means a monocyclic or polycyclic-aromatic ring or ring radical comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted with one or more substituents (including without limitation alkyl (preferably, lower alkyl or alkyl substituted with one or more halo), hydroxy, alkoxy (preferably, lower alkoxy), alkylthio, cyano, halo, amino, and nitro. In certain embodiments, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms.

As used herein, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon typically having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl,
3,3-diethylhexyl and the like. Alkyl groups included in compounds of this invention may be optionally substituted with one or more substituents, such as amino, alkylamino, alkoxy, alkylthio, oxo, halo, acyl, nitro, hydroxyl, cyano, aryl, alkyaryl, aryloxy, arythio, arylamino, carbocyclyl, carbocyclyloxy, carbocyclythio, carbocyclylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclythio, and the like. In addition, any carbon in the alkyl segment may be substituted with oxygen (=O), sulfur (=S), or nitrogen (=NR₂³, wherein R₂³ is –H, an alkyl, acetyl, or aralkyl). Lower alkyls are typically preferred for the compounds of this invention.

The term alkylene refers to an alkyl group that has two points of attachment to two moieties (e.g., {–CH₂⁻}, {–CH₂–CH₂⁻},

\[ \text{CH₃} \quad \text{, etc., wherein the brackets indicate the points of attachment}. \]

Alkylene groups may be substituted or unsubstituted.

An aralkyl group refers to an aryl group that is attached to another moiety via an alkylene linker. Aralkyl groups can be substituted or unsubstituted.

The term "alkoxy," as used herein, refers to an alkyl group which is linked to another moiety though an oxygen atom. Alkoxy groups can be substituted or unsubstituted.

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group in which the alkyl portion is substituted with another alkoxy group.

The term "alkyl sulfanyl," as used herein, refers to an alkyl group which is linked to another moiety though a divalent sulfur atom. Alkyl sulfanyl groups can be substituted or unsubstituted.
The term "alkylamino," as used herein, refers to an amino group in which one hydrogen atom attached to the nitrogen has been replaced by an alkyl group. The term "dialkylamino," as used herein, refers to an amino group in which two hydrogen atoms attached to the nitrogen have been replaced by alkyl groups, in which the alkyl groups can be the same or different. Alkylamino groups and dialkylamino groups can be substituted or unsubstituted.

As used herein, the term "alkenyl" means a straight chain or branched, hydrocarbon radical typically having from 2 to 10 carbon atoms and having at least one carbon-carbon double bond. Representative straight chain and branched alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylene, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonanyl, 2-nonanyl, 3-nonanyl, 1-decenyl, 2-decenyl, 3-decenyl and the like. Alkenyl groups can be substituted or unsubstituted.

As used herein, the term "alkynyl" means a straight chain or branched, hydrocarbons radical typically having from 2 to 10 carbon atoms and having at least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyynyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-methyl-1-butylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonynyl, 2-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl, 3-decynyl and the like. Alkynyl groups can be substituted or unsubstituted.

As used herein, the term "cycloalkyl" means a saturated, mono- or polycyclic alkyl radical typically having from 3 to 10 carbon atoms. Representative cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, decahydroquinaphthyl, octahydropentalene, bicycle[1.1.1]pentany, and the like. Cycloalkyl groups can be substituted or unsubstituted.
As used herein, the term "cycloalkenyl" means a cyclic non-aromatic alkenyl radical having at least one carbon-carbon double bond in the cyclic system and typically having from 5 to 10 carbon atoms. Representative cycloalkenyls include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclodecenyl, cyclodecadienyl and the like. Cycloalkenyl groups can be substituted or unsubstituted.

As used herein, the term "heterocycle" or "heterocyclyl" means a monocyclic or polycyclic heterocyclic ring (typically having 3- to 14-members) which is either a saturated ring or an unsaturated non-aromatic ring. A 3-membered heterocycle can contain up to 3 heteroatoms, and a 4- to 14-membered heterocycle can contain from 1 to about 8 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholiny1, thiomorpholiny1, pyrrolidiny1, pyrrolidiny1, piperdiny1, pipereziny1, hydantoiny1, valerolactamy1, oxirany1, oxetany1, tetrahydrofurany1, tetrahydropyrrany1, tetrahydropyrindiny1, tetrahydropyririmidiny1, tetrahydrothiopheny1, tetrahydrothiopyrrany1, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl may be optionally substituted with one or more substituents (including without limitation a halogen atom, an alkyl radical, or aryl radical). Only stable isomers of such substituted heterocyclic groups are contemplated in this definition. Heterocyclyl groups can be substituted or unsubstituted.

As used herein, the term "heteroaromatic" or "heteroaryl" means a monocyclic or polycyclic heteroaromatic ring (or radical thereof) comprising carbon atom ring members and one or more heteroatom ring members (such as, for example, oxygen, sulfur or nitrogen). Typically, the heteroaromatic ring has
from 5 to about 14 ring members in which at least 1 ring member is a heteroatom selected from oxygen, sulfur and nitrogen. In another embodiment, the heteroaromatic ring is a 5 or 6 membered ring and may contain from 1 to about 4 heteroatoms. In another embodiment, the heteroaromatic ring system has a 7 to 14 ring members and may contain from 1 to about 7 heteroatoms. Representative heteroaryl groups include pyridyl, furyl, thiényl, pyrrolyl, oxazolyl, imidazolyl, indolizinyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, pyridinyl, thiadiazolyl, pyrazinyl, quinolyl, isoquinolyl, indazolyl, benzoazolyl, benzofuryl, benzothiazolyl, indolizinyl, imidazopyridinyl, isothiazolyl, tetrazolyl, benzimidazolyl, benzoazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidyl, pyrazolo[3,4]pyrimidyl or benzo(b)thiienyl and the like. These heteroaryl groups may be optionally substituted with one or more substituents.

A heteroaralkyl group refers to a heteroaryl group that is attached to another moiety via an alkylene linker. Heteroaralkyl groups can be substituted or unsubstituted.

As used herein, the term "halogen" or "halo" means -F, -Cl, -Br or -I.

As used herein, the term "haloalkyl" means an alkyl group in which one or more –H is replaced with a halo group. Examples of haloalkyl groups include –CF₃, –CHF₂, –CCl₃, –CH₂CH₂Br, –CH₂CH(CH₂CH₂Br)CH₃, –CHICH₃, and the like.

As used herein, the term "haloalkoxy" means an alkoxy group in which one or more –H is replaced with a halo group. Examples of haloalkoxy groups include –OCF₃ and –OCHF₂.

As used herein, the term "contiguous linear connectivity" means connected together so as to form an uninterrupted linear array or series of atoms. For example, a linker of the compounds described herein having a specified
number of atoms in contiguous linear connectivity has at least that number of atoms connected together so as to form an uninterrupted chain, but may also include additional atoms that are not so connected (e.g., branches or atoms contained within a ring system).

As used herein, the term "linker" means a diradical having from 1-6 atoms in contiguous linear connectivity (i.e., as defined above and excluding atoms present in any side chains and branches), that covalently connects the thiazole or thiadiazole portion of a compound of this invention to the Y or Y' group of the compound, as illustrated in formulas (I) and (III). The atoms of the linker in contiguous linear connectivity may be connected by saturated or unsaturated covalent bonds. Linkers include, but are not limited to, alkylidene, alkenylidene, alkynylidene and cycloalkylidene (such as lower alkylidene, cycloalkylidene, alkylcycloalkylidene and alkyl-substituted alkylidene) linkers wherein one or more (e.g., between 1 and 4, (e.g., 1 or 2)) carbon atoms may be optionally replaced with O, S, or N and wherein two or more (e.g., 2-4 (e.g., 2 or 3)) adjacent atoms may be optionally linked together to form a carbocyclic or heterocyclic moiety within the linker (which may be monocyclic, polycyclic and/or fused, and which may be saturated, unsaturated, or aromatic).

Examples of specific linkers useful in the compounds of the invention include (without limitation) diradicals of alkyl, alkenyl, alynyl, alkoxy, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, alkylcycloalkyl, and alkyl-substituted alkylcycloalkyl (wherein one or more carbon atoms in any of these linkers may be optionally replaced with O, S, or N).

The terms "bioisostere" and "bioisosteric replacement" have the same meanings as those generally recognized in the art. Bioisosteres are atoms, ions, or molecules in which the peripheral layers of electrons can be considered substantially identical. The term bioisostere is usually used to mean a portion of an overall molecule, as opposed to the entire molecule itself. Bioisosteric replacement involves using one bioisostere to replace another with the expectation of maintaining or slightly modifying the biological activity of the first bioisostere. The bioisosteres in this case are thus atoms or groups of atoms.
having similar size, shape and electron density. Preferred bioisosteres of esters, amides or carboxylic acids are compounds containing two sites for hydrogen bond acceptance. In one embodiment, the ester, amide or carboxylic acid bioisostere is a 5-membered monocyclic heteroaryl ring, such as an optionally substituted 1H-imidazolyl, an optionally substituted oxazolyl, 1H-tetrazolyl, [1,2,4]triazolyl, or an optionally substituted [1,2,4]oxadiazolyl.

As used herein, the terms "subject", "patient" and "animal", are used interchangeably and include, but are not limited to, a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human. The preferred subject, patient or animal is a human.

As used herein, the term "lower" refers to a group having up to four carbon atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, and a "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms, respectively. A lower alkoxy or a lower alkyl sulfanyl refers to an alkoxy or a alkyl sulfanyl having from 1 to 4 carbon atoms. Lower substituents are typically preferred.

Where a particular substituent, such as an alkyl substituent, occurs multiple times in a given structure or moiety, the identity of the substituent is independent in each case and may be the same as or different from other occurrences of that substituent in the structure or moiety. Furthermore, individual substituents in the specific embodiments and exemplary compounds of this invention are preferred in combination with other such substituents in the compounds of this invention, even if such individual substituents are not expressly noted as being preferred or not expressly shown in combination with other substituents.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.
Suitable substituents for an alkyl, alkoxy, alkyl sulfanyl, alkylamino, dialkylamino, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycyl, aryl, aralkyl, heteroaryl, and heteroarylatedkyl groups include any substituent which will form a stable compound of the invention. Examples of substituents for an alkyl, alkoxy, alkylsulfanyl, alkylamino, dialkylamino, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycyl, aryl, aralkyl, heteroaryl, and heteroarylatedkyl include an alkyl, alkoxy, alkyl sulfanyl, alkylamino, dialkylamino, an alkenyl, an alkynyl, an cycloalkyl, an cycloalkenyl, an heterocycyl, an aryl, an heteroaryl, an aralkyl, an heteroarylatedkyl, a haloalkyl, -C(O)NR_{13}R_{14}, -NR_{15}C(O)R_{16}, halo, -OR_{15}, cyano, nitro, haloalkoxy, -C(O)R_{15}, -NR_{13}R_{14}, -SR_{15}, -C(O)OR_{15}, -OC(O)R_{15}, -NR_{15}C(O)NR_{13}R_{14}, -OC(O)NR_{13}R_{14}, -NR_{15}C(O)OR_{16}, -S(O)_{2}R_{15}, or -S(O)_{2}NR_{13}R_{14}, wherein R_{13} and R_{14}, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroarylatedkyl; or R_{13} and R_{14} taken together with the nitrogen to which they are attached is optionally substituted heterocycyl or optionally substituted heteroaryl; and R_{15} and R_{16} for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroarylatedkyl;

In addition, alkyl, cycloalkyl, alkylene, a heterocycyl, and any saturated portion of a alkenyl, cycloalkenyl, alkynyl, aralkyl, and heteroarylatedkyl groups, may also be substituted with =O, =S, =N-R_{15}.

When a heterocycyl, heteroaryl, or heteroarylatedkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the
aromatic ring of a heteroary1 group has a substituent the nitrogen may be a quaternary nitrogen.

Choices and combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject). Typically, such compounds are stable at a temperature of 40°C or less, in the absence of excessive moisture, for at least one week. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

Unless indicated otherwise, the compounds of the invention containing reactive functional groups (such as, without limitation, carboxy, hydroxy, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one or more protecting groups. Suitable protecting groups for carboxy moieties include benzyl, tert-butyl, and the like. Suitable protecting groups for amino and amido groups include acetyl, tert-butoxycarbonyl, benzyloxy carbonyl, and the like. Suitable protecting groups for hydroxy include benzyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the entire teachings of which are incorporated herein by reference.

As used herein, the term "compound(s) of this invention" and similar terms refers to a compound of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof and also include protected derivatives thereof.
As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide a compound of this invention. Prodrugs may only become active upon such reaction under biological conditions, but they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of any one of formulas (I) through (XI), or Table 1 that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds of any one of formulas (I) through (XI), or of Table 1 that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed), the entire teachings of which are incorporated herein by reference.

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide", "biohydrolyzable ester", "biohydrolyzable carbamate", "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable phosphate analogue" mean an amide, ester, carbamate, carbonate, ureide, or phosphate analogue, respectively, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is itself biologically inactive but is converted in vivo to a biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids,
hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from an acid and a basic group of one of the compounds of any one of formulas (I) through (XI) or of Table 1. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of formulas (I) through (XI) or Table 1 having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethyamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)-amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-,N-(2-hydroxyethyl)-amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of formulas (I) through (XI) or Table 1 having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include, but are not limited to, hydrogen sulfate, citric acid, acetic acid,
oxalic acid, hydrochloric acid, hydrogen bromide, hydrogen iodide, nitric acid, phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid.

As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more solvent molecules to one or more molecules of a compound of any one of formulas (I) through (X11) or Table 1. The term solvate includes hydrates (e.g., hemi-hydrate, mono-hydrate, dihydrate, trihydrate, tetrahydrate, and the like).

As used herein, the term "clathrate" means a compound of the present invention or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

As used herein, the term "asthma" means a pulmonary disease, disorder or condition characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to a variety of stimuli.

"Immunosuppression" refers to impairment of any component of the immune system resulting in decreased immune function. This impairment may be measured by any conventional means including whole blood assays of lymphocyte function, detection of lymphocyte proliferation and assessment of the expression of T cell surface antigens. The antisheep red blood cell (SRBC) primary (IgM) antibody response assay (usually referred to as the plaque assay) is one specific method. This and other methods are described in Luster, M.I., Portier, C., Pait, D.G., White, K.L., Jr., Gennings, C., Munson, A.E., and Rosenthal, G.J. (1992). "Risk Assessment in Immunotoxicology I: Sensitivity and Predictability of Immune Tests." Fundam. Appl. Toxicol., 18, 200-210. Measuring the immune response to a T-cell dependent immunogen is another

The compounds of this invention can be used to treat subjects with immune disorders. As used herein, the term "immune disorder" and like terms means a disease, disorder or condition caused by the immune system of an animal, including autoimmune disorders. Immune disorders include those diseases, disorders or conditions that have an immune component and those that are substantially or entirely immune system-mediated. Autoimmune disorders are those wherein the animal's own immune system mistakenly attacks itself, thereby targeting the cells, tissues, and/or organs of the animal's own body. For example, the autoimmune reaction is directed against the nervous system in multiple sclerosis and the gut in Crohn's disease. In other autoimmune disorders such as systemic lupus erythematosus (lupus), affected tissues and organs may vary among individuals with the same disease. One person with lupus may have affected skin and joints whereas another may have affected skin, kidney, and lungs. Ultimately, damage to certain tissues by the immune system may be permanent, as with destruction of insulin-producing cells of the pancreas in Type 1 diabetes mellitus. Specific autoimmune disorders that may be ameliorated using the compounds and methods of this invention include without limitation, autoimmune disorders of the nervous system (e.g., multiple sclerosis, myasthenia gravis, autoimmune neuropathies such as Guillain-Barré, and autoimmune uveitis), autoimmune disorders of the blood (e.g., autoimmune hemolytic anemia, pernicious anemia, and autoimmune thrombocytopenia), autoimmune disorders of the blood vessels (e.g., temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, and Behcet's disease), autoimmune disorders of the skin (e.g., psoriasis, dermatitis herpetiformis, pemphigus vulgaris, and vitiligo), autoimmune disorders of the gastrointestinal system (e.g., Crohn's disease, ulcerative colitis, primary biliary cirrhosis, and autoimmune hepatitis), autoimmune disorders of the endocrine glands (e.g., Type 1 or
immune-mediated diabetes mellitus, Grave's disease. Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, and autoimmune disorder of the adrenal gland; and autoimmune disorders of multiple organs (including connective tissue and musculoskeletal system diseases) (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies such as ankylosing spondylitis, and Sjogren's syndrome). In addition, other immune system mediated diseases, such as graft-versus-host disease and allergic disorders, are also included in the definition of immune disorders herein. Because a number of immune disorders are caused by inflammation, there is some overlap between disorders that are considered immune disorders and inflammatory disorders. For the purpose of this invention, in the case of such an overlapping disorder, it may be considered either an immune disorder or an inflammatory disorder. "Treatment of an immune disorder" herein refers to administering a compound or a composition of the invention to a subject, who has an immune disorder, a symptom of such a disease or a predisposition towards such a disease, with the purpose to cure, relieve, alter, affect, or prevent the autoimmune disorder, the symptom of it, or the predisposition towards it.

As used herein, the term "allergic disorder" means a disease, condition or disorder associated with an allergic response against normally innocuous substances. These substances may be found in the environment (such as indoor air pollutants and aeroallergens) or they may be non-environmental (such as those causing dermatological or food allergies). Allergens can enter the body through a number of routes, including by inhalation, ingestion, contact with the skin or injection (including by insect sting). Many allergic disorders are linked to atopy, a predisposition to generate the allergic antibody IgE. Because IgE is able to sensitize mast cells anywhere in the body, atopic individuals often express disease in more than one organ. For the purpose of this invention, allergic disorders include any hypersensitivity that occurs upon re-exposure to the sensitizing allergen, which in turn causes the release of inflammatory mediators. Allergic disorders include without limitation, allergic rhinitis (e.g., hay fever), sinusitis, rhinosinusitis, chronic or recurrent otitis media, drug
reactions, insect sting reactions, latex reactions, conjunctivitis, urticaria, anaphylaxis and anaphylactoid reactions, atopic dermatitis, asthma and food allergies.

The compounds of this invention can be used to prevent or to treat subjects with inflammatory disorders. As used herein, an "inflammatory disorder" means a disease, disorder or condition characterized by inflammation of body tissue or having an inflammatory component. These include local inflammatory responses and systemic inflammation. Examples of such inflammatory disorders include: transplant rejection, including skin graft rejection; chronic inflammatory disorders of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung disorders such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory disorders of the eye including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disorders of the gums, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney including uremic complications, glomerulonephritis and nephrosis; inflammatory disorders of the skin including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematoses; systemic lupus erythematosus (SLE); and inflammatory diseases of the heart such as cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis); as well as various other diseases with significant inflammatory components, including pre eclampsia; chronic liver failure, brain and spinal cord trauma, cancer). There may also be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by
cancer chemotherapy in response to pro-inflammatory cytokines, e.g., shock associated with pro-inflammatory cytokines. Such shock can be induced, e.g., by a chemotherapeutic agent used in cancer chemotherapy. "Treatment of an inflammatory disorder" herein refers to administering a compound or a composition of the invention to a subject, who has an inflammatory disorder, a symptom of such a disorder or a predisposition towards such a disorder, with the purpose to cure, relieve, alter, affect, or prevent the inflammatory disorder, the symptom of it, or the predisposition towards it.

An "effective amount" is the quantity of compound in which a beneficial outcome is achieved when the compound is administered to a subject or alternatively, the quantity of compound that possess a desired activity in-vivo or in-vitro. In the case of inflammatory disorders and autoimmune disorders, a beneficial clinical outcome includes reduction in the extent or severity of the symptoms associated with the disease or disorder and/or an increase in the longevity and/or quality of life of the subject compared with the absence of the treatment. The precise amount of compound administered to a subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of inflammatory disorder or autoimmune disorder or the degree of immunosuppression sought. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective amounts of the disclosed compounds typically range between about 1 mg/mm² per day and about 10 grams/mm² per day, and preferably between 10 mg/mm² per day and about 1 gram/mm².

The compounds of the invention may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. According to this invention, the chemical structures depicted herein, including the compounds of this invention, encompass all of the corresponding compounds' enantiomers and stereoisomers, that is, both the stereomerically pure form
(e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric, diastereomeric, and geometric isomeric mixtures. In some cases, one enantiomer, diastereomer, or geometric isomer will possess superior activity or an improved toxicity or kinetic profile compared to others. In those cases, such enantiomers, diastereomers, and geometric isomers of a compound of this invention are preferred.

The term "inhibit production of IL-2" and like terms means inhibiting IL-2 synthesis (e.g. by inhibiting transcription (mRNA expression), or translation (protein expression)) and/or inhibiting IL-2 secretion in a cell that has the ability to produce and/or secrete IL-2 (e.g., T lymphocyte). Likewise, the term "inhibiting production of IL-4, IL-5, IL-13, GM-CSF, TNF-α or INF-γ means inhibiting the synthesis (e.g. by inhibiting transcription, or translation) and/or inhibiting the secretion in a cell that has the ability to produce and/or secrete these cytokines.

As used herein, a composition that "substantially" comprises a compound means that the composition contains more than about 80% by weight, more preferably more than about 90% by weight, even more preferably more than about 95% by weight, and most preferably more than about 97% by weight of the compound.

As used herein, a composition that is "substantially free" of a compound means that the composition contains less than about 20% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight, and most preferably less than about 3% by weight of the compound.

As used herein, a reaction that is "substantially complete" means that the reaction contains more than about 80% by weight of the desired product, more preferably more than about 90% by weight of the desired product, even more preferably more than about 95% by weight of the desired product, and most preferably more than about 97% by weight of the desired product.
As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to all chiral centers in the molecule. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of the compounds of any one of formulas (I) through (XI) or Table 1.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

When administered to a patient, e.g., to a non-human animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are typically administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, via conventional techniques, the compounds of the invention are purified. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a single compound of the invention by weight of the isolate.

Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.
The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

5 SPECIFIC EMBODIMENTS

The invention relates to compounds and pharmaceutical compositions that are particularly useful for immunosuppression or to treat or prevent inflammatory conditions, immune disorders, and allergic disorders.

One embodiment of the invention relates to compounds of Formula (I):

\[ \text{(I)} \]

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

- Y is an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted alkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, or an optionally substituted heteroaryl;
- \( R_1' \) is an optionally substituted aryl or an optionally substituted heteroaryl, provided that \( R_1' \) is not a pyrazolyl;
- \( X \) and \( X' \) are each independently \( \text{CH}, \text{CZ}, \text{or N} \); provided that at least one of \( X \) or \( X' \) is \( N \);
- \( L \) is a linker; and
- \( Z \) is a substituent.

In another embodiment, the invention relates to compounds of formula (II):
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

Y' is optionally substituted aryl or an optionally substituted heterocaryl;
L' is \(-\text{NRCH}_2-, \text{-CH}_2\text{NR}-, \text{-C(O)-}, \text{-NR-C(O)-}, \text{-C(O)-NR-}, \text{C(S)-}, \text{-NR-C(S)-}, \text{-C(S)-NR-}, \text{-NRS(O)z-}, \text{-S(O)zNR-}, \text{-NRC(O)CH}_2-, \text{-NRC(O)CH=CH-}, \text{-NRC(O)NR-}, \text{-NRC(NR)NR-}, \text{-NRC(S)NR-}, \text{NRS(O)zNR-}, \text{-NR-CH}2-\text{NR-}, \text{-CH=CH-}, \text{-C(O)OR}_7;\)

\(R, \text{for each occurrence, is independently } -\text{H, alkyl, -C(O)-R}, \text{or -C(O)OR}_7;\)

\(R, \text{for each occurrence, is } -\text{H or alkyl; } R, \text{for each occurrence, is independently } -\text{H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteraryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; } \)

\(R, \text{for each occurrence, is independently } -\text{H, lower alkyl, -CH}_2\text{CH}_2\text{OH, or (CH}_2)_3\text{NMe; }\)

\(Z, \text{is } -\text{H, halo, or a lower alkyl which is optionally substituted with halo, } \text{-NH}_2, \text{lower alkyl amino, lower dialkyl amino, or cycloalkyl; } Z \text{ is a substituent, provided that } Z \text{ is not } -\text{S(O)zCH}_3,\)

\(-\text{SO}_2\text{Cl or S(O)zNR}_6R; \text{and } t \text{ is an integer } 1-5;\)
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In one embodiment of compounds of formula (II), there applies one or more (including all) of the following provisos:

a) provided that when \( R'_1 \) is methoxyphenyl, \( Y' \) is not a substituted naphthalene;

b) provided that when \( R'_1 \) is chlorophenyl, \( Y' \) is not [(pyrazinyl)oxy)methyl]fluorophenyl;

c) provided that when \( R'_1 \) is chlorophenyl, \( Y' \) is not cyanobenzoic acid;

and

d) provided that when \( L' \) is \(-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{-CH}_2^-\), \( R'_1 \) is not methoxyphenyl.

Another embodiment of the invention relates to compounds of formula (III):

\[
\text{(III)}
\]

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

\( X_2 \) is \( \text{CH} \) or \( \text{CZ}_2 \);

\( L_1 \) is \(-\text{NRCH}_2^-,\text{-CH}_2\text{NR}^-,\text{-C}(\text{O})^-,\text{-NR}-\text{C}(\text{O})^-,\text{-C}(\text{O})^-\text{NR}^-,\text{C}(\text{S})^-,
\text{NR-C}(\text{S})^-\text{-C}(\text{S})^-\text{-NR}^-\text{-NRS(O)}_2^-,\text{-S(O)}_2\text{NR}^-\text{-NRC(O)CH}_2^-,\text{-NRC(O)CH}^=\text{-CH}^-\text{-NRC(O)NR}^-,\text{-NRC}(\text{NR})\text{NR}^-,\text{-NRC(S)NR}^-,\text{NRS(O)}_2\text{NR}^-\text{-NR-CH}_2^\text{-NR}^-\text{-NR-NR-C(O)}^-\text{-N=CR}^-\text{-CR=N}^-\text{-CH=CH}^-\text{-C=CN}^-\text{NNR}^-=\text{-C(NR)}^-\text{or-CR}_3=\text{NNR}^-;\)
Y₁ is an optionally substituted phenyl or an optionally substituted pyridinyl;

Z₂ and Z₄ are each independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted arylalkenyl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, -C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)ₚR₄, or -S(O)ₚNR₁R₂;

R, for each occurrence, is independently -H, alkyl, -C(O)-R₇, or -C(O)OR₇;

R₁ and R₂, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

m is 0, 1, 2, 3, or 4; and

p is 0, 1, or 2.

Another embodiment of the invention relates to compounds of formula (IV):
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein, \( Z_5 \) and \( Z_6 \) are each independently a substituent; and \( L' \), \( Y' \), and \( Z_1 \) are defined as for formula (II).

Another embodiment of the invention relates to compounds of formula (V):

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

\( Z_6, Z_7 \) and \( Z_8 \) are each independently a substituent; and \( L' \) and \( Z_1 \) are defined as for formula (II).

Another embodiment of the invention relates to compounds of formula (VI):
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

5 $Z_5$, $Z_6$, $Z_7$ and $Z_8$ are each independently a substituent; and $L'$ and $Z_1$ are defined as for formula (II).

Another embodiment of the invention relates to compounds of formula (VII):

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

10 $Z_9$ is a substituent; and $L'$, $Z_1$, $Z_3$, and $m$ are defined as for formula (II).

In another embodiment, the invention relates to compounds of formula (VIII):

- 30 -
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

Z\textsubscript{10} is \(-\text{H}, \) an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, 
-\text{C}(\text{O})\text{NR}_1\text{R}_2, -\text{NR}_4\text{C}(\text{O})\text{R}_5, \) halo, -\text{OR}_4, \) cyano, \) nitro, \) haloalkoxy, \text{-C}(\text{O})\text{R}_4, \text{-NR}_1\text{R}_2, -\text{SR}_4, -\text{C}(\text{O})\text{OR}_4, -\text{OC}(\text{O})\text{R}_4, -\text{NR}_4\text{C}(\text{O})\text{NR}_1\text{R}_2, -\text{OC}(\text{O})\text{NR}_1\text{R}_2, 
-\text{NR}_4\text{C}(\text{O})\text{OR}_5, -\text{S}((\text{O})_p\text{R}_4, \text{or } -\text{S}(\text{O})_p\text{NR}_1\text{R}_2;

Z\textsubscript{11} is \(-\text{H}, \) an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, 
-\text{C}(\text{O})\text{NR}_1\text{R}_2, -\text{NR}_4\text{C}(\text{O})\text{R}_5, \) halo, -\text{OR}_4, \) cyano, \) nitro, \) haloalkoxy, \text{-C}(\text{O})\text{R}_4, 
-\text{NR}_1\text{R}_2, -\text{SR}_4, -\text{C}(\text{O})\text{OR}_4, -\text{OC}(\text{O})\text{R}_4, -\text{NR}_4\text{C}(\text{O})\text{NR}_1\text{R}_2, -\text{OC}(\text{O})\text{NR}_1\text{R}_2, 
-\text{NR}_4\text{C}(\text{O})\text{OR}_5, -\text{S}((\text{O})_p\text{R}_4, \text{or } -\text{S}(\text{O})_p\text{NR}_1\text{R}_2;

Z is defined as for formula (I), \( L_1 \) is defined as for formula (III) and \( Y' \) is defined as for formula (II).

In one embodiment of compounds of formula (VIII), there applies one or more (including all) of the following provisos:

1) when \( Z = -\text{OCH}_3 \) and \( Z_{10} = -\text{H}, Z_{11} \) is not furanyl;
2) when \( Z = -\text{CF}_3 \) and \( Z_{10} \) is \(-\text{H}, \) \( Y \) is not a bromophenol;
3) when $Z$ is $-\text{OCH}_3$ and $Z_{10}$ is $-\text{H}$, $L_1$ is not $-\text{N}(\text{n-Pr})\text{-CH}_2$; 
4) when $Z$ is $-\text{CF}_3$ and $Z_{10}$ is $-\text{H}$, $Z_{11}$ is not $-\text{CF}_3$; 
5) when $Z$ is $-\text{Cl}$ and $Z_{10}$ is $-\text{H}$, $Y$ is not a cyanobenzoic acid; and 
6) when $Z$ is $-\text{OCH}_3$, $Z_{10}$ is $-\text{OCH}_3$ and $Z_{11}$ is a methoxyphenyl, $Y'$ is not 
an indole.

In another embodiment, the invention relates to compounds of formula (IX):

![Chemical structure](image)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

$Z_{12}$ is a substituent;

one of $X_3$ or $X_4$ is $-\text{S}$- and the other is $-\text{CH}$- or $-\text{CZ}$-;

$w$ is 0, 1, or 2;

$Z_{11}$ is defined as for formula (VIII), $L_1$ and $Y_1$ are defined as formula (III).

In one embodiment of compounds of formula (IX), there applies one or more

including all) of the following provisos:

1) when $X_4$ is $-\text{S}$-, $X_3$ is $-\text{C(Br)}$-, and $Z_{11}$ is $-\text{H}$, $Y_1$ is not

$(2,4\text{-dioxo-5-thiazolidinyl})\text{methylphenyl}$; and

2) when $X_4$ is $-\text{S}$-, $X_3$ is $-\text{CH}$-, and $Z_{11}$ is $-\text{H}$, $Y_1$ is not an unsubstituted

phenyl.

In another embodiment, the invention relates to compounds of formula (X):
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein:

\( Z_{13} \) is a substituent:

\( v \) is 0, 1, 2, or 3;

\( Z_{11} \) is defined as for formula (VIII), \( L_1 \) is defined as for formula (III) and

\( Y' \) is defined as for formula (II).

In another embodiment, the invention relates to compounds of formula (XI):

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof wherein \( Z, Z_{10}, \) and \( Z_{11} \) are defined as for formula (VIII), \( L_1 \) is defined as for formula (III) and \( Y' \) is defined as for formula (II).

In one embodiment of compounds of formula (XI), there applies one or more (including all) of the following provisos:

1) when \( Z \) is \(-\text{Cl}, -\text{CH}_3, \) or \(-\text{CF}_3 \), \( Z_{10} \) is \(-\text{H} \) and \( L_1 \) is \(-\text{C(O)NH}^- \), \( Y' \) is not
a methoxy phenyl, a –C(O)phenyl substituted phenyl or an unsubstituted phenyl;
2) when Z is –Cl, Z₁₀ is –H and L₁ is –NHC(O)₁⁻, Y’ is not an unsubstituted phenyl; and
3) when Z is –CH₃, Z₁₀ is –H and L₁ is -CR₆=NNR₂, Y’ is not a dinitrophenyl.

In one embodiment, in compounds represented by formula (I), L is –NRCH₂₁, -CH₂NR₂, -C(O)₁⁻, -NR-C(O)₁⁻, -C(O)-NR₁⁻, C(S)₁⁻,
-NR-C(S)₁⁻, -C(S)-NR₁⁻, -NRS(O)₂₁⁻, -S(O)₂NR₁⁻, -NRC(O)(CH₂)₃₁⁻,
-NRC(O)CH=CH₁⁻, -NRC(O)NR₁⁻, -NRC(NR₁⁻)NR₁⁻, -NRC(S)NR₁⁻, NRS(O)₂NR₁⁻,
-NR-CH₂NR₁⁻, -NR-NR-C(O)₁⁻, -N=CR₁⁻, -CR=NR₁⁻, -CH=CH₁⁻, -C≡C₁⁻, NNR=CR₆₁⁻,
-C(NR₁⁻), or -CR₆=NNR₂₁⁻. In another aspect, L is –NRCH₂₁, -CH₂NR₂,
-NR-C(O)₁⁻, or -C(O)-NR₁⁻. In one aspect, L is –NHCH₂₁⁻. In one aspect, L is
-NR-C(O)₁⁻). In one aspect, R is –H. In one aspect, L is –NH-C(O)₁⁻.

In one embodiment, in compounds represented by formula (I), Y is optionally substituted alkyl or an optionally substituted cycloalkyl. In one aspect, Y is optionally substituted lower alkyl or an optionally substituted lower cycloalkyl. In one aspect, Y is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or methylcyclohexyl.

In one embodiment, in compounds represented by formula (I), Y is optionally substituted cycloalkenyl, an optionally substituted alkenyl, or an optionally substituted heterocyclyl. In one aspect, Y is optionally substituted lower cycloalkenyl, an optionally substituted lower alkenyl, or an optionally substituted lower heterocyclyl. In one aspect, Y is optionally substituted ethenyl.

In one embodiment, in compounds represented by formula (I), Y is an optionally substituted aryl or an optionally substituted heteroaryl. In one aspect, Y is an optionally substituted phenyl or an optionally substituted pyridinyl. In one aspect, Y is substituted with one to two substituents. In one aspect, the one to two substituents are each independently a lower alkyl or a
halo. In one aspect, Y is an optionally substituted thiadiazolyl. In one aspect, Y is 2,6-difluorophenyl.

In one embodiment, in compounds represented by formula (I), R'₁ is an optionally substituted phenyl or an optionally substituted pyridinyl. In one aspect, R'₁ is substituted with one to two substituents. In one aspect, the one to two substituents are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl;

R₄ , for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

In one embodiment, in compounds represented by formula (I), X is N. In one aspect, X' is N. In one aspect, X' is CH or CZ.

In one embodiment, in compounds represented by formula (I), X' is N. In one aspect, X is N. In one aspect, X is CH or CZ.

In one embodiment, in compounds represented by formula (I), X' is N; X is CZ; Z is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,

-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄,
-NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂,
-NR₄C(O)OR₅, -S(O)₝R₄, or -S(O)₝NR₁R₂;

R₁ and R₂, for each occurrence are, independently, H, an optionally
substituted alkyl; an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and p is 0, 1, or 2.

In one aspect, R'₁ is an optionally substituted phenyl or an optionally substituted pyridinyl; and Y is an optionally substituted phenyl or an optionally substituted pyridinyl. In one aspect, Y is substituted with one to two substituents and the one to two substituents are each independently a lower alkyl or a halo. In one aspect, R'₁ is substituted with one to two substituents and the one to two substituents are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In one aspect, L is -NRCH₂-, -CH₂NR-, -C(O)-, -NR-C(O)-, -C(O)-NR-, C(S)-, -NR-C(S)-, -C(S)-NR-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)(CH₂)₉-, -NRC(O)CH=CH-, -NRC(O)NR-, -NRC(NR)NR-, -NRC(S)NR-, NRS(O)₂NR-, -NR-CH₂-NR-, -CH=CH-, -C≡C-, NRN=CR₆-, -C(NR) -, or -CR₆=NNR-. In one aspect, L is -NRC(O)-. In one aspect, R is -H. In one aspect, L is -NHC(O)−.

In one embodiment, in compounds represented by formula (I), Z is an alkyl, -C(O)R₄, or -C(O)OR₄. In one aspect, R'₁ is an optionally substituted phenyl or an optionally substituted pyridinyl; and Y is an optionally substituted phenyl or an optionally substituted pyridinyl. In one aspect, Y is substituted
with one to two substituents; and wherein the one to two substituents are each independently a lower alkyl or a halo.

In one aspect, R’1 is substituted with one to two substituents; and wherein the one to two substituents are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR4, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl; and

\[ R_4, \] for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl. In one aspect, L is \(-\text{NRCH}_2\text{-}, \text{-CH}_2\text{NR}-, \text{-C(O)-}, \text{-NR-C(O)-}, \text{-C(O)-NR-}, \text{-C(S)-}, \text{-NR-C(S)-}, \text{-C(S)-NR-}, \text{-NRS(O)NR-}, \text{-S(O)NR-}, \text{-NR-C(O)(CH}_2\text{)-}, \text{-NR(C(O)CH=CH}-, \text{-NRC(O)NR-}, \text{-NRC(NR)NR-}, \text{-NRC(S)NR-}, \text{-NRS(O)NR-}, \text{-H-}, \text{-NR-CH}_2\text{NR}-, \text{-N=CR-}, \text{-NR-NR-C(O)-}, \text{-CH=CH-}, \text{-C≡C-}, \text{NRN=CR}_5\text{-}, \text{-C(NR)-}, \text{or -CR}_5\text{=NNR-}. In one aspect, L is \(-\text{NRCH}_2\text{-}, \text{-CH}_2\text{NR}-, \text{-C(O)-}, \text{-NR-C(O)-}, \text{-C(O)-NR-}, \text{C(S)-}, \text{-NR-C(S)-}, \text{-C(S)-NR-}, \text{-NRS(O)NR-}, \text{-S(O)NR-}, \text{-NR-C(O)(CH}_2\text{)-}, \text{-NR(C(O)CH=CH}-, \text{-NRC(O)NR-}, \text{-NRC(NR)NR-}, \text{-NRC(S)NR-}, \text{-NRS(O)NR-}, \text{-H-}, \text{-NR-CH}_2\text{NR}-, \text{-N=CR-}, \text{-NR-NR-C(O)-}, \text{-CH=CH-}, \text{-C≡C-}, \text{NRN=CR}_5\text{-}, \text{-C(NR)-}, \text{or -CR}_5\text{=NNR-}. In one aspect, L is \(-\text{NRC(O)-}. In one aspect, R is \(-H-. In one aspect, L is \(-\text{NHC(O)-}.\n
In one embodiment, in compounds represented by formula (III), Z_2 and Z_4 are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl; cyano, an optionally substituted tetrazolyl, -C(O)OR_4, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl; and m is 0 or 1. In one aspect, L is \(-\text{NRC(O)-}. In one aspect, Z_4 is halo, a lower alkyl, morpholinyl, or cyano; and m is 1. In one aspect, m is 0. In one aspect, Z_2 is lower alkyl.
In one embodiment, in compounds represented by formula (II), (IV), (VIII), (X),
or (XI), Y' is an optionally substituted phenyl or an optionally substituted
pyridinyl. In one aspect, Y' is substituted with one to two substituents. In one
aspect, the one to two substituents are each independently a lower alkyl or a
halo. In one aspect, Y' is a 2,6-disubstituted phenyl. In one aspect, Y' is
2,6-difluorophenyl.

In one embodiment, in compounds represented by formula (II), (IV), (V), (VI),
or (VII), L' is -NRCH₂₋, -CH₂NR₋, -C(O)₋, -NR-C(O)₋, -C(O)-NR₋, -C(S)₋,
-NR-C(S)₋, or -C(S)-NR₋. In another aspect, L' is -NRCH₂₋, -CH₂NR₋,
-NR-C(O)₋, or -C(O)-NR₋. In one aspect, L' is -NHCH₂₋. In one aspect, L' is
-NH-C(O)₋. In one aspect, R is -H.

In one embodiment, in compounds represented by formula (II), (IV), (V), (VI),
or (VII), L' is -NRS(O)₂₋, -S(O)₂NR₋, -NRS(O)₂NR₋, -NRC(O)CH₂₋,
-NRC(O)CH=CH₋, -NRC(O)NR₋, -NRC(NR)NR₋, -NRC(S)NR₋, -NRCH₂NR₋,
-NRN=CR₋, -C(NR)₋, -CR₋=NNR₋; -CH=CH₋ or -C≡C₋. In one aspect, R is -H.

In one embodiment, in compounds represented by formula (II), (IV), (V), (VI),
or (VII), Z₁ is lower alkyl or -H. In one aspect, Z₁ is lower alkyl. In one aspect,
Z₁ is methyl. In one aspect, Z₁ is -H.

In one embodiment, in compounds represented by formula (II) or (VII), Z₃ is an
optionally substituted alkyl, an optionally substituted alkenyl, an optionally
substituted alkynyl, an optionally substituted cycloalkyl, an optionally
substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally
substituted aryl, an optionally substituted heteroaryl, an optionally substituted
aryl, an optionally substituted heteraralkyl, a haloalkyl,
-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄,
-NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂,
-NR₄C(O)OR₅, -S(O)₂R₄, or -S(O)₂NR₁R₂;

R₁ and R₂, for each occurrence are, independently, H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted
alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and p is 0, 1, or 2.

In one aspect, each Z₃ is independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl; and t is 1 or 2. In one aspect, each Z₃ is independently chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl.

In one embodiment, in compounds represented by formula (IV) or (VI), Z₅ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,

-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)ₖR₄, or -S(O)ₖNR₁R₂;

R₁ and R₂, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted heteroaryl,
aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an
optionally substituted heteraralkyl; or R₁ and R₂ taken together with the
nitrogen to which they are attached is optionally substituted heterocyclyl or
optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted
alkynyl, an optionally substituted cycloalkyl, an optionally substituted
cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted
aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an
optionally substituted heteraralkyl; and p is 0, 1, or 2.

In one aspect, Z₅ is halo, an optionally substituted lower alkyl, an
optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally
substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an
optionally substituted oxazolyl, or an optionally substituted morpholinyl. In
another aspect, Z₅ is halo or lower alkoxy. In one aspect, Z₅ is chloro.

In one embodiment, in compounds represented by formula (IV), (V), or (VI), Z₆
is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally
substituted alkynyl, an optionally substituted cycloalkyl, an optionally
substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally
substituted aryl, an optionally substituted heteroaryl, an optionally substituted
aralkyl, an optionally substituted heteraralkyl, a haloalkyl,
-C(O)NR₁R₂, -NR₂C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄,
-NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂,
-NR₄C(O)OR₅, -S(O)ₙR₄, or -S(O)ₙNR₁R₂;

R₁ and R₂, for each occurrence are, independently, H, an optionally
substituted alkyl, an optionally substituted alkenyl, an optionally substituted
alkynyl, an optionally substituted cycloalkyl, an optionally substituted
cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted
aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an
optionally substituted heteraralkyl; or R₁ and R₂ taken together with the
nitrogen to which they are attached is optionally substituted heterocyclyl or
optionally substituted heteroaryl;
R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and p is 0, 1, or 2.

In one aspect, Z₆ is halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In another aspect, Z₆ is chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl. In one aspect, Z₆ is trifluoromethyl. In one aspect, Z₆ is cyano. In one aspect, Z₆ is -C(O)CH₃. In one aspect, Z₆ is methoxy. In one aspect, Z₆ is 2-methyl-2H-tetrazolyl.

In one embodiment, in compounds represented by formula (IV), (V), or (VI), Z₆ is a biostere of an ester, amide, or carboxylic acid.

In one embodiment, in compounds represented by formula (IV), Y' is a phenyl substituted with one to two substituents or a pyridinyl substituted with one to two substituents, wherein the one to two substituents are each independently a lower alkyl or a halo; L' is –NR-(C(O))--; Z₁ is lower alkyl or –H; and Z₅ and Z₆ are each independently chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl.

In one embodiment, in compounds represented by formula (V) or (VI), Z₇ and Z₈ are each independently halo. In one aspect, Z₇ and Z₈ are each fluoro.

In one embodiment, in compounds represented by formula (V), Z₆ is chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl,
methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl; and Z₇ and Z₈ are each independently halo.

In one aspect, Z₁ is lower alkyl or –H. In one aspect, L’ is –NR-C(O)–. In one aspect, R is –H.

In one embodiment, in compounds represented by formula (VI), Z₅ is halo or lower alkoxy; Z₆ is chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl; and Z₇ and Z₈ are each independently halo. In one aspect, Z₁ is lower alkyl or –H. In one aspect, L’ is –NR-C(O)–. In one aspect, R is –H.

In one embodiment, in compounds represented by formula (VII), each Z₃ is independently chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, oxazol-2-yl, or methyl; and Z₉ is a lower alkyl or halo. In one aspect, Z₁ is lower alkyl or –H. In one aspect, L’ is –NR-C(O)–. In one aspect, R is –H. In one aspect, t is 1 or 2.

In one embodiment, in compounds represented by formula (III), (VIII), (IX), (X), or (XI), L₁ is –NRCH₂–, -CH₂NR–, -C(O)–, –NR-C(O)–, -C(O)-NR–, -C(S)–, –NR-C(S)–, or -C(S)-NR–. In another aspect, L₁ is –NRCH₂–, -CH₂NR–, -NR-C(O)–, or -C(O)-NR–. In one aspect, L₁ is –NHCH₂–. In one aspect, L₁ is –NH-C(O)–. In one aspect, R is –H.

In one embodiment, in compounds represented by formula (III), (VIII), (IX), (X), or (XI), L₁ is -NRS(O)₂–, -S(O)₂NR–, -NRS(O)₂NR–, -NRC(O)CH₂–, -NRC(O)CH=CH–, -NRC(O)NR–, -NRC(NR)NR–, -NRC(S)NR–, -NRCH₂NR–, -NRN=CR₆–, -C(NR)–, -CR₆=NNR–; -CH=CH– or –C≡C–. In one aspect, R is –H.

In one embodiment, in compounds represented by formula (III) or (IX), Y₁ is substituted with one to two substituents. In one aspect, the one to two
substituents are each independently a lower alkyl or a halo. In one aspect, Y$_1$ is a 2,6-disubstituted phenyl. In one aspect, Y$_1$ is 2,6-difluorophenyl.

In one embodiment of the compounds represented by formula (VIII) or (XI), Z is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,

\[-C(O)NR$_1$R$_2$, -NR$_4$C(O)R$_5$, halo, -OR$_4$, cyano, nitro, haloalkoxy, -C(O)R$_4$, -NR$_1$R$_2$, -SR$_4$, -C(O)OR$_4$, -OC(O)R$_4$, -NR$_4$C(O)NR$_1$R$_2$, -OC(O)NR$_1$R$_2$, -NR$_4$C(O)OR$_5$, -S(O)$_p$R$_4$, or -S(O)$_p$NR$_1$R$_2$;\]

R$_1$ and R$_2$, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R$_1$ and R$_2$ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R$_4$ and R$_5$, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and p is 0, 1, or 2.

In one embodiment of the compounds represented by formula (VIII) or (XI), Z is halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR$_4$, nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In another aspect, Z is chloro, bromo, fluoro, cyano, trifluoromethyl, -OCH$_3$, -C(O)CH$_3$. 

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2-methyl-2H-tetrazolyl, methoxy, nitro, dimethlamino, thiazol-2-yl, oxazol-2-yl, or methyl. In another aspect, Z is trifluoromethyl or -OCH₃. In one aspect, Z is trifluoromethyl. In one aspect, Z is cyano. In one aspect, Z is -C(O)CH₃. In one aspect, Z is methoxy. In one aspect, Z is 2-methyl-2H-tetrazolyl.

In one embodiment, in compounds represented by formula (VIII) or (XI), Z is a biostere of an ester, amide, or carboxylic acid.

In one embodiment of the compounds represented by formula (VIII) or (XI), Z₁₀ is -H, -OR₄, halo, or an optionally substituted lower alkyl. In another aspect, Z₁₀ is -H, -OCH₃, halo, or methyl. In one aspect, Z₁₀ is halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In another aspect, Z₁₀ is halo or lower alkoxy. In one aspect, Z₁₀ is chloro.

In one embodiment of the compounds represented by formula (VIII), (IX), (X), or (XI), Z₁₁ is -H, an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted lower alkynyl, an optionally substituted cycloalkyl, -C(O)OR₄, -C(O)R₄, -C(O)NR₄R₂, -NR₄R₂, cyano, halo, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted oxadiazolyl, an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, or an optionally substituted phenyl. In one aspect, Z₁₁ is -H, optionally substituted lower alkyl, cyclopropyl, -C(O)OH, -C(O)CH₃, -C(O)OCH₃, optionally substituted oxazol-5-yl, optionally substituted 1H-imidazol-2-yl, or optionally substituted thiazol-2-yl. In one aspect, Z₁₁ is -H or methyl. In another aspect, Z₁₁ is lower alkyl or -H. In one aspect, Z₁₁ is lower alkyl. In one aspect, Z₁₁ is methyl. In one aspect, Z₁₁ is -H.

In one embodiment of the compounds represented by formula (IX), Z₁₂ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally
substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,

-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄,
-NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂,
-NR₄C(O)OR₅, -S(O)ₚR₄, or -S(O)ₚNR₁R₂. In one aspect, Z₁₂ is halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In another aspect, Z₁₂ is halo or lower alkoxy. In one aspect, Z₁₂ is halo.

In one embodiment of the compounds represented by formula (IX), w is 0. In one embodiment of the compounds represented by formula (IX), w is 1. In one embodiment of the compounds represented by formula (IX), w is 2.

In one embodiment of the compounds represented by formula (IX), X₃ is -S-. In one embodiment of the compounds represented by formula (IX), X₄ is -S-.

In one embodiment of the compounds represented by formula (X), Z₁₃ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,

-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄,
-NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂,
-NR₄C(O)OR₅, -S(O)ₚR₄, or -S(O)ₚNR₁R₂. In one aspect, Z₁₃ is halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted oxazolyl, or an optionally substituted morpholinyl. In another aspect, Z₁₃ is halo or lower alkoxy. In a further aspect, Z₁₃ is halo or cyano.
In one embodiment of the compounds represented by formula (X), v is 0 or 1.
In one aspect, v is 0. In another aspect, v is 1.

In one embodiment of the compounds represented by formula (VIII), L₁ is
-\text{N}-C(O)- or -C(O)-NH--; Y' is 2,6-difluorophenyl; Z is chloro, bromo, fluoro,
cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy,
nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl; Z₁₀ is -H, -OCH₃, halo,
or methyl; and Z₁₁ is -H, optionally substituted lower alkyl, cyclopropyl,
-C(O)OH, -C(O)CH₃, -C(O)OCH₃, optionally substituted oxazol-5-yl, optionally
substituted 1H-imidazol-2-yl, or optionally substituted thiazol-2-yl.

In one embodiment of the compounds represented by formula (XI), L₁ is
-\text{N}-C(O)- or -C(O)-NH--; Y' is 2,6-difluorophenyl; Z is chloro, bromo, fluoro,
cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy,
nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl; Z₁₀ is -H, -OCH₃, halo,
or methyl; and Z₁₁ is -H or methyl.

In another embodiment, the invention relates to compounds selected from the
group consisting of:

N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-difluoro-N-[5-(3-(trifluoromethyl)phenyl)thiazol-2-yl]benzamide;
N-[5-(3-Cyano-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide;
3-[2-(2,6-Difluoro-benzoylamino)-4-methyl-thiazol-5-yl]-benzoic acid methyl ester;
2,6-Difluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzamide;
3-Fluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide;
3-Methyl-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide;
4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid
[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-amide;
N-[5-(3-Cyano-phenyl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-benzamide;
3-Methyl-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-isonicotinamide;
2,6-Difluoro-N-(4-methyl-5-pyridin-3-yl-thiazol-2-yl)-benzamide;
2,6-Difluoro-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-benzamide;
3-Methyl-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-isonicotinamide;
2,6-Difluoro-N-[4-methyl-5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide;
N-(5-(4-(dimethylamino)phenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-[5-(4-Dimethylamino-phenyl)-4-methyl-thiazol-2-yl]-3-methyl-isonicotinamide;
N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(2-bromo-4,5-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-difluoro-N-(5-(3-methoxyphenyl)-4-methylthiazol-2-yl)benzamide;
N-(5-(3,4-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-difluoro-N-(4-methyl-5-(2-methyl-5-(oxazol-2-yl)phenyl)thiazol-2-yl)benzamide;
N-[5-(2-Bromo-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-difluoro-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl)benzamide;
3-Methyl-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl)isonicotinamide;
N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-3-methylisonicotinamide hydrochloride;
N-[5-(2-Cyano-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[4-methyl-5-(2-morpholin-4-yl-pyridin-4-yl)-thiazol-2-yl]-benzamide;
N-[4-Ethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
Methyl 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl) phenyl)thiazole-4-carboxylate;
Methyl 2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate;
Methyl 2-(2,6-difluorobenzamido)-5-(3-fluorophenyl)thiazole-4-carboxylate;
Methyl 5-(3-fluorophenyl)-2-(3-methylisonicotinamido)thiazole-4-carboxylate;
2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(fluoro)phenyl)thiazol-2-yl)benzamide;
(2-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid
2,6-difluoro-phenyl)-amide;
4-Methyl-5-(3-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid (2,6-difluoro-phenyl)-amide;
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-2,6-difluoro-
benzamide;
N-(5-(2,5-dimethylcyclohex-1-enyl)thiazol-2-yl)-3-methylisonicotinamide;
5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid(3-methyl-pyridin-4-yl)-
amide;
2-(2-Chloro-5-trifluoromethyl-phenyl)-4-methyl-thiazole-5-carboxylic acid
(2,6-difluoro-phenyl)-amide;
Sodium (2,6-difluorobenzoyl)(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)
amide;
Sodium (4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)(3-methyl
isonicotinoyl)amide;
2-Fluoro-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide;
2-Methyl-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide;
N-(4-Cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-3-methylisonicotinamide;
2,6-Difluoro-N-(4-(methyl-5-(pyridin-4-yl)thiazol-2-yl)benzamide hydrobromide;
N-(5-(2,5-Dimethoxyphenyl)-4-methythiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(7-Bromobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(Benzod[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(7-Cyanobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(5-Bromothiophen-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-methyl-5-(thiophen-2-yl)thiazol-2-yl)benzamide;
N-(5-(2,5-Dibromothiophen-3-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-methyl-5-(thiophen-3-yl)thiazol-2-yl)benzamide;
Methyl 5-(2-(allyloxy)-5-(trifluoromethyl)phenyl)-2-(2,6-difluorobenzamido)thiazole-4-
carboxylate;
N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)-4-(prop-1-en-2-yl)thiazol-2-yl)-2,6-
difluorobenzamide;
N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid;
2,6-Difluoro-N-(4-formyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(2-hydroxypropan-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-difluoro-N-(4-(prop-1-en-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-isopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(Chloromethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-((Dimethylamino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
(Z)-2,6-difluoro-N-(4-((hydroxyimino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
N-(4-Cyano-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-(1-hydroxyethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-vinylthiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(oxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(4,5-Dihydro-1H-imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-(1H-Imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluoro benzamide hydrochloride;
2,6-Difluoro-N-(4-(4-methyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-Difluoro-N-(4-(1-methyl-1H-imidazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
N-(4-(2,4-dimethyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-difluoro-N-(4-(hydroxyl(pyridin-2-yl)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-Acetyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide
N-(4-(2-Bromoacetyl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(2'-methyl-5-(3-trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)benzamide;
N-(2'-amino-5-(3-trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide;
Ethyl 2'-(2,6-difluorobenzamido)-5'-(3-trifluoromethyl)phenyl)-4,4'-bithiazole-2-carboxylate;
N-(4-(4,5-dihydrooxazol-2-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide
N-(4-(1,3,4-oxadiazol-2-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-difluoro-N-(4-oxazol-2-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-difluoro-N-(4-(3-methyl-1,2,4-oxadiazol-5-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2-(2,6-difluorobenzamido)-N-methoxy-N-methyl-5-(3-trifluoromethyl)phenyl)thiazole-4-carboxamide;
2,6-difluoro-N-(4-propionyl-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(2',5'-dimethyl-5-(3-trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide;
Ethyl 2'-(2,6-difluorobenzamido)-5-methyl-5'-(3-trifluoromethyl)phenyl)-4,4'-bithiazole-2-carboxylate;
N-(2,6-Difluorobenzamido)-5-(3-trifluoromethyl)phenyl)thiazole-4-carboxamide;
N-(2,2-diethoxyethyl)-2-(2,6-difluorobenzamido)-5-(3-trifluoromethyl)phenyl)thiazole-4-carboxamide;
2,6-Difluoro-N-(4-propiolooyl-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(1H-Pyrazol-3-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-(1-methyl-1H-pyrazol-3-yl)-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-amino-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-Chloro-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-ethynyl-5-(3-trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-(5-(trimethylsilyl)isoxazol-3-yl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(isoxazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(pyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(6-methylpyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(3,4-Dimethoxyphenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-(4-(Dimethylamino)phenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate hydrochloride;
2-(3-Methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid;
Methyl 2-(2,6-difluorobenzamido)-5-(3-methoxyphenyl)thiazole-4-carboxylate;
Methyl 2-(2,6-difluorobenzamido)-5-(3-(methoxycarbonyl)phenyl)thiazole-4-carboxylate;
Ethyl 2'-(2,6-difluorobenzamido)-4'-methyl-4,5'-bithiazole-2-carboxylate;
N-(2,4'-Dimethyl-4,5'-bithiazol-2'-yl)-2,6-difluorobenzamide;
N-(2,6-Difluorobenzyl)-4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-amine;
N-(2,6-difluorophenyl)-4-methyl-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide;
methyl 3-(2-(2,6-difluorophenyl)carbamoyl)-4-methylthiazol-5-yl)benzoate;
5-(3-(1,3,4-oxadiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide;
5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide;
4-methyl-N-(3-methylpyridin-4-yl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide;
N-(2,6-difluorophenyl)-2-(2-methyl-5-(oxazol-2-yl)phenyl)thiazole-5-carboxamide;
N-(2,6-difluorophenyl)-2-(2-methyl-5-(thiazol-2-yl)phenyl)thiazole-5-carboxamide;
N-(2,6-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)thiazole-5-carboxamide;
N-(2,6-difluorophenyl)-2-(3-(oxazol-2-yl)phenyl)thiazole-5-carboxamide;
2-(2-chloro-5-(thiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide;
2-(5-chloro-2-methoxypyrirdin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide;
2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide; N-(2,6-difluorophenyl)-2-(2-methyl-5-(1,3,4-oxadiazol-2-yl)phenyl)thiazole-5-carboxamide; 5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)thiazole-2-carboxamide; N-(2,6-difluorophenyl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide; N-(2,6-difluorophenyl)-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide; 5-(2-methyl-5-(oxazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide; or 5-(2-methyl-5-(thiazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide; or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

All of the features, specific embodiments and particular substituents disclosed herein may be combined in any combination. Each feature, embodiment or substituent disclosed in this specification may be replaced by an alternative feature, embodiment or substituent serving the same, equivalent, or similar purpose. In the case of chemical compounds, specific values for variables (e.g., values shown in the exemplary compounds disclosed herein) in any chemical formula disclosed herein can be combined in any combination resulting in a stable structure. Furthermore, specific values (whether preferred or not) for substituents in one type of chemical structure may be combined with values for other substituents (whether preferred or not) in the same or different type of chemical structure. Thus, unless expressly stated otherwise, each feature, embodiment or substituent disclosed is only an example of a generic series of equivalent or similar features, embodiments or substituents.

In another embodiment, the invention relates to pharmaceutical compositions that comprise a compound of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, as an active ingredient, and a pharmaceutically acceptable carrier or vehicle. The compositions are useful for immunosuppression or to treat or prevent inflammatory conditions, allergic conditions and immune disorders.
In another embodiment, the invention relates to methods for immunosuppression or for treating or preventing inflammatory conditions, immune disorders, or allergic disorders in a patient in need thereof comprising administering an effective amount of a compound represented by any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, the invention relates to methods for immunosuppression or for treating or preventing inflammatory conditions, immune disorders, or allergic disorders in a patient in need thereof comprising administering an effective amount of a pharmaceutical composition that comprises a compound represented by any one of formulas (I) through (XI), or in or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, compounds of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, are particularly useful inhibiting immune cell (e.g., T-cells and/or B-cells) activation (e.g., activation in response to an antigen) and/or T cell and/or B cell proliferation. Indicators of immune cell activation include secretion of IL-2 by T cells, proliferation of T cells and/or B cells, and the like. In one embodiment, a compound of any one of formulas (I) through (XI) or Table 1, inhibits immune cell activation and/or T cell and/or B cell proliferation in a mammal (e.g., a human).

In another embodiment, compounds of any one of formula (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, can inhibit the production of certain cytokines that regulate immune cell activation. For example, compounds of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, can inhibit the production of IL-2, IL-4, IL-5, IL-13, GM-CSF, IFN-γ, TNF-α and combinations thereof. In one embodiment, a compound of any one
of formulas (I) through (XI), or Table 1, inhibits cytokine production in a mammal (e.g., a human).

In another embodiment, compounds of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels. In one embodiment, a compound of any one of formulas (I) through (XI) or Table 1 can inhibit the influx of calcium ions into an immune cell (e.g., T cells and/or B cells) by inhibiting the action of CRAC ion channels. In general, a decrease in $I_{\text{CRAC}}$ current upon contacting a cell with a compound is one indicator that the compound inhibitions CRAC ion channels. $I_{\text{CRAC}}$ current can be measured, for example, using a patch clamp technique, which is described in more detail in the examples below. In one embodiment, a compound of any one of formulas (I) through (XI) or Table 1 modulates an ion channel in a mammal (e.g., a human).

**EXEMPLARY COMPOUNDS OF THE INVENTION**

Exemplary compounds of the invention are depicted in Table 1 below.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Structure</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure" /></td>
<td>N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>3</td>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>N-[5-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td>N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>5</td>
<td><img src="image4.png" alt="Chemical Structure 4" /></td>
<td>2,6-difluoro-N-(5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5.png" alt="Chemical Structure 5" /></td>
<td>N-[5-(3-Cyano-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>7</td>
<td><img src="image6.png" alt="Chemical Structure 6" /></td>
<td>2,6-Difluoro-N-[5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide</td>
</tr>
<tr>
<td>No.</td>
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<td>8</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>3-[(2,6-Difluoro-benzoylamino)-4-methyl-thiazol-5-yl]-benzoic acid methyl ester</td>
</tr>
<tr>
<td>9</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2,6-Difluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzamide</td>
</tr>
<tr>
<td>10</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>3-Fluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide</td>
</tr>
<tr>
<td>11</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>3-Methyl-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide</td>
</tr>
<tr>
<td>12</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid [4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-amide</td>
</tr>
<tr>
<td>13</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>N-[5-(3-Cyano-phenyl)-4-methyl-thiazol-2-yl]-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>14</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>2,6-Difluoro-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-benzamide</td>
</tr>
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<td>15</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>3-Methyl-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-isonicotinamide</td>
</tr>
<tr>
<td>16</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-methyl-5-pyridin-3-yl-thiazol-2-yl)-benzamide</td>
</tr>
<tr>
<td>17</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-benzamide</td>
</tr>
<tr>
<td>18</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>3-Methyl-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-isonicotinamide</td>
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<td><img src="image5" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-[4-methyl-5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide</td>
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<tr>
<td>20</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>N-(5-(4-(dimethylamino)phenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
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<td>21</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>N-[5-(4-Dimethylamino-phenyl)-4-methyl-thiazol-2-yl]-3-methyl-isonicotinamide</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
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<tr>
<td>23</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(5-(2-bromo-4,5-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(5-(3-methoxyphenyl)-4-methylthiazol-2-yl)benzamide</td>
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<tr>
<td>25</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(5-(3,4-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
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<td>26</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-methyl-5-(2-methyl-5-(oxazol-2-yl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-[5-(2-Bromo-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluorobenzamide</td>
</tr>
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<td>28</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>29</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>3-Methyl-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl)isonicotinamide</td>
</tr>
<tr>
<td>30</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>31</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-3-methylisonicotinamide hydrochloride</td>
</tr>
<tr>
<td>32</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-[5-(2-Cyano-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>33</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>2,6-Difluoro-N-[4-methyl-5-(2-morpholin-4-yl-pyridin-4-yl)-thiazol-2-yl]-benzamide</td>
</tr>
<tr>
<td>34</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>N-[4-Ethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>35</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Methyl 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
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</tr>
<tr>
<td>36</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Methyl 2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate</td>
</tr>
<tr>
<td>37</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Methyl 2-(2,6-difluorobenzamido)-5-(3-fluorophenyl)thiazole-4-carboxylate</td>
</tr>
<tr>
<td>38</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Methyl 5-(3-fluorophenyl)-2-(3-methylisonicotinamido)thiazole-4-carboxylate</td>
</tr>
<tr>
<td>39</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-(hydroxymethyl)5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
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<td>40</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-(hydroxymethyl)5-(3-(fluoro)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>41</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(2-(2-Chloro-5-trifluoromethylphenyl)thiazole-5-carboxylic acid 2,6-difluoro-phenyl)-amide</td>
</tr>
<tr>
<td>42</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>4-Methyl-5-(3-trifluoromethylphenyl)thiazole-2-carboxylic acid (2,6-difluoro-phenyl)-amide</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Description</td>
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</tr>
<tr>
<td>43</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>44</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>N-[5-(2-Chloro-5-trifluoromethyl-phenyl)[1,3,4]thiadiazol-2-yl]-2,6-difluoro-benzamide</td>
</tr>
<tr>
<td>45</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>N-(5-(2,5-dimethylcyclohex-1-enyl)thiazol-2-yl)-3-methylisonicotinamide</td>
</tr>
<tr>
<td>46</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid(3-methyl-pyridin-4-yl)-amide</td>
</tr>
<tr>
<td>47</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2-(2-Chloro-5-trifluoromethyl-phenyl)-4-methyl-thiazole-5-carboxylic acid (2,6-difluoro-phenyl)-amide</td>
</tr>
<tr>
<td>48</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Sodium (2,6-difluorobenzoyl)(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)amide</td>
</tr>
<tr>
<td>49</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>Sodium (4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)(3-methylisonicotinoyl)amide</td>
</tr>
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<td></td>
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<td>Description</td>
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<tr>
<td>50</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2-Fluoro-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide</td>
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<td>51</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2-Methyl-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide</td>
</tr>
<tr>
<td>52</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>N-(4-Cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>53</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>N-(4-cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-3-methylisonicotinamide</td>
</tr>
<tr>
<td>54</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-methyl-5-(pyridin-4-yl)thiazol-2-yl)benzamide hydrobromide</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Description</td>
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</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Structure 55" /></td>
<td>N-(5-(2,5-Dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>56</td>
<td><img src="image" alt="Structure 56" /></td>
<td>N-(5-(7-Bromobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>57</td>
<td><img src="image" alt="Structure 57" /></td>
<td>N-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
<td>N-(5-(7-Cyanobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>59</td>
<td><img src="image" alt="Structure 59" /></td>
<td>N-(5-(5-Bromothiophen-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
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<td>Description</td>
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</tr>
<tr>
<td>60</td>
<td><img src="image" alt="Structure 60" /></td>
<td>2,6-Difluoro-N-(4-methyl-5-(thiophen-2-yl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>61</td>
<td><img src="image" alt="Structure 61" /></td>
<td>N-(5-(2,5-Dibromothiophen-3-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>62</td>
<td><img src="image" alt="Structure 62" /></td>
<td>2,6-Difluoro-N-(4-methyl-5-(thiophen-3-yl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>63</td>
<td><img src="image" alt="Structure 63" /></td>
<td>Methyl 5-(2-(allyloxy)-5-(trifluoromethyl)phenyl)-2-(2,6-difluorobenzamido)thiazole-4-carboxylate</td>
</tr>
<tr>
<td>64</td>
<td><img src="image" alt="Structure 64" /></td>
<td>N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)-4-(prop-1-en-2-yl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>65</td>
<td><img src="image" alt="Structure 65" /></td>
<td>N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
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<td>Description</td>
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</tr>
<tr>
<td>66</td>
<td><img src="image1" alt="Molecular Structure" /></td>
<td>2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid</td>
</tr>
<tr>
<td>67</td>
<td><img src="image2" alt="Molecular Structure" /></td>
<td>2,6-Difluoro-N-(4-formyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
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<td>68</td>
<td><img src="image3" alt="Molecular Structure" /></td>
<td>2,6-Difluoro-N-(4-(2-hydroxypropan-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>68a</td>
<td><img src="image4" alt="Molecular Structure" /></td>
<td>2,6-difluoro-N-(4-(prop-1-en-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>69</td>
<td><img src="image5" alt="Molecular Structure" /></td>
<td>2,6-Difluoro-N-(4-isopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>70</td>
<td><img src="image6" alt="Molecular Structure" /></td>
<td>N-(4-(Chloromethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>71</td>
<td><img src="image7" alt="Molecular Structure" /></td>
<td>N-(4-((Dimethylamino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>Number</td>
<td>Structure</td>
<td>Chemical Formula</td>
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</tr>
<tr>
<td>72</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>(Z)-2,6-difluoro-N-(4-((hydroxylimino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>73</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>N-(4-Cyano-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>74</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>2,6-Difluoro-N-(4-(1-hydroxyethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>75</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-vinylthiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>76</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>2,6-Difluoro-N-(4-(oxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>77</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>N-(4-(4,5-Dihydro-1H-imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>78</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>N-(4-(1H-Imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide hydrochloride</td>
</tr>
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<td></td>
<td>Chemical Structure</td>
<td>Description</td>
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<tr>
<td>79</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-(4-methyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>80</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-(1-methyl-1H-imidazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>81</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>N-(4-(2,4-dimethyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>82</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(4-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide</td>
</tr>
<tr>
<td>83</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-(hydroxyl(pyridin-2-yl)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>84</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>N-(4-Acetyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>85</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(4-(2-Bromoacetyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>----</td>
<td>-----------------------------</td>
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</tr>
<tr>
<td>86</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2,6-Difluoro-N-(2'-methyl-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>87</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(2'-amino-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>88</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Ethyl 2'(2,6-difluorobenzamido)-5'(3-(trifluoromethyl)phenyl)-4',4'-bithiazole-2-carboxylate</td>
</tr>
<tr>
<td>89</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(4-(4,5-dihydrooxazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>90</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>N-(4-(1,3,4-oxadiazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>91</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-(oxazol-2-yl))-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
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</tr>
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<td><img src="image2" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-(3-methyl-1,2,4-oxadiazol-5-yl))-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>93</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>2-(2,6-difluorobenzamido)-N-methoxy-N-methyl-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide</td>
</tr>
<tr>
<td>94</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2,6-difluoro-N-(4-propionyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
</tr>
<tr>
<td>95</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>N-(2',5'-dimethyl-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>96</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Ethyl 2'-(2,6-difluorobenzamido)-5-methyl-5'-(3-(trifluoromethyl)phenyl)-4,4'-bithiazole-2-carboxylate</td>
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| 97 | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{N} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{CF}_3 \\
\end{array}
\] |
<table>
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<tbody>
<tr>
<td>2-(2,6-Difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide</td>
<td></td>
</tr>
</tbody>
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| 98 | \[
\begin{array}{c}
\text{EtO} \\
\text{NH} \\
\text{N} \\
\text{N} \\
\text{F} \\
\text{F} \\
\text{CF}_3 \\
\end{array}
\] |
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<tr>
<td>N-(2,2-diethoxyethyl)-2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide</td>
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| 99 | \[
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{N} \\
\text{F} \\
\text{F} \\
\text{CF}_3 \\
\end{array}
\] |
<table>
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<tr>
<td>2,6-Difluoro-N-(4-propioloyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide</td>
<td></td>
</tr>
</tbody>
</table>

| 100 | \[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{F} \\
\text{F} \\
\text{F} \\
\text{CF}_3 \\
\end{array}
\] |
<table>
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<tbody>
<tr>
<td>N-(4-(1H-Pyrazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
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<tr>
<td>-----</td>
<td>--------------------</td>
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<tr>
<td>101</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>102</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>103</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>104</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
105  

![Chemical Structure](image1)  

2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-(5-(trimethylsilyl)isoxazol-3-yl)thiazol-2-yl)benzamide

106  

![Chemical Structure](image2)  

2,6-Difluoro-N-(4-(isoxazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

107  

![Chemical Structure](image3)  

2,6-Difluoro-N-(4-(pyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

108  

![Chemical Structure](image4)  

2,6-Difluoro-N-(4-(6-methylpyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide
<table>
<thead>
<tr>
<th></th>
<th>Molecular Structure</th>
<th>Description</th>
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<tr>
<td>109</td>
<td><img src="image" alt="Molecule" /></td>
<td>N-(4-(3,4-Dimethoxyphenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>110</td>
<td><img src="image" alt="Molecule" /></td>
<td>N-(4-(4-(Dimethylamino)phenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>111</td>
<td><img src="image" alt="Molecule" /></td>
<td>2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate hydrochloride</td>
</tr>
<tr>
<td>112</td>
<td><img src="image" alt="Molecule" /></td>
<td>2-(3-Methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid</td>
</tr>
<tr>
<td>113</td>
<td><img src="image" alt="Molecule" /></td>
<td>Methyl 2-(2,6-difluorobenzamido)-5-(3-methoxyphenyl)thiazole-4-carboxylate</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>114</td>
<td><img src="image1" alt="Structure" /></td>
<td>Methyl 2-(2,6-difluorobenzamido)-5-(3-(methoxycarbonyl)phenyl) thiazole-4-carboxylate</td>
</tr>
<tr>
<td>114a</td>
<td><img src="image2" alt="Structure" /></td>
<td>Ethyl 2'- (2,6-difluorobenzamido)-4'-methyl-4,5'-bithiazole-2-carboxylate</td>
</tr>
<tr>
<td>114b</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(2,4'-Dimethyl-4,5'-bithiazol-2'-yl)-2,6-difluorobenzamide</td>
</tr>
<tr>
<td>115</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-(2,6-Difluorobenzyl)-4-methyl-5-(3-(trifluoromethyl)phenyl) thiazol-2-amine</td>
</tr>
<tr>
<td>116</td>
<td><img src="image5" alt="Structure" /></td>
<td>N-(2,6-difluorophenyl)-4-methyl-5-(3-(oxazol-2-y1)phenyl)thiazole-2-carboxamide</td>
</tr>
<tr>
<td>117</td>
<td><img src="image6" alt="Structure" /></td>
<td>Methyl 3-(2-(2,6-difluorophenyl carbamoyl)-4-methylthiazol-5-y1) benzoate</td>
</tr>
<tr>
<td>No.</td>
<td>Formula</td>
<td>Description</td>
</tr>
<tr>
<td>-----</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>118</td>
<td><img src="image1.png" alt="Structure 118" /></td>
<td>5-(3-(1,3,4-oxadiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide</td>
</tr>
<tr>
<td>119</td>
<td><img src="image2.png" alt="Structure 119" /></td>
<td>5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide</td>
</tr>
<tr>
<td>120</td>
<td><img src="image3.png" alt="Structure 120" /></td>
<td>4-methyl-N-(3-methylpyridin-4-yl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide</td>
</tr>
<tr>
<td>121</td>
<td><img src="image4.png" alt="Structure 121" /></td>
<td>N-(2,6-difluorophenyl)-2-(2-methyl-5-(oxazol-2-yl)phenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td>122</td>
<td><img src="image5.png" alt="Structure 122" /></td>
<td>N-(2,6-difluorophenyl)-2-(2-methyl-5-(thiazol-2-yl)phenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Formula</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>123</td>
<td><img src="image1.png" alt="Image" /></td>
<td>N-(2,6-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td>124</td>
<td><img src="image2.png" alt="Image" /></td>
<td>N-(2,6-difluorophenyl)-2-(3-(oxazol-2-yl)phenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td>125</td>
<td><img src="image3.png" alt="Image" /></td>
<td>2-(2-chloro-5-(thiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td>126</td>
<td><img src="image4.png" alt="Image" /></td>
<td>2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide</td>
</tr>
<tr>
<td>127</td>
<td><img src="image5.png" alt="Image" /></td>
<td>2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide</td>
</tr>
</tbody>
</table>
128
N-(2,6-difluorophenyl)-2-(2-methyl-5-(1,3,4-oxadiazol-2-yl)phenyl)thiazole-5-carboxamide

129
5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)thiazole-2-carboxamide

130
N-(2,6-difluorophenyl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide

131
N-(2,6-difluorophenyl)-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide

132
5-(2-methyl-5-(oxazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide
MECHANISM OF ACTION

Activation of T-lymphocytes in response to an antigen is dependent on calcium ion oscillations. Calcium ion oscillations in T-lymphocytes are triggered through stimulation of the T-cell antigen receptor, and involve calcium ion influx through the stored-operated Ca\(^{2+}\)-release-activated Ca\(^{2+}\) (CRAC) channel. Although the molecular structure of the CRAC ion channel has not been identified, a detailed electrophysiological profile of the channel exist. Thus, inhibition of CRAC ion channels can be measured by measuring inhibition of the I\(_{\text{CRAC}}\) current. Calcium ion oscillations in T-cells have been implicated in the activation of several transcription factors (e.g., NFAT, Oct/Oap and NFκB) which are critical for T-cell activation (Lewis, *Biochemical Society Transactions* (2003), 31:925-929, the entire teachings of which are incorporated herein by reference). Without wishing to be bound by any theory, it is believed that because the compounds of the invention inhibit the activity of CRAC ion channels, they inhibit immune cell activation.

METHODS OF TREATMENT AND PREVENTION

In accordance with the invention, an effective amount of a compound of any one of formulas (I) through (XI) or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, or a pharmaceutical composition comprising a compound of any one of formulas (I) through (XI) or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, is administered to a patient in need of immunosuppression or in need of treatment or prevention of an inflammatory condition, an immune disorder, or
an allergic disorder. Such patients may be treatment naive or may experience partial or no response to conventional therapies.

Responsiveness of a particular inflammatory condition, immune disorder, or allergic disorder in a subject can be measured directly (e.g., measuring blood levels of inflammatory cytokines (such as IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, IFN-γ and the like) after administration of a compound of this invention), or can be inferred based on an understanding of disease etiology and progression. The compounds of any one of formulas (I) through (XI), or Table 1, or pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof can be assayed in vitro or in vivo, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, known animal models of inflammatory conditions, immune disorders, or allergic disorders can be used to demonstrate the safety and efficacy of compounds of this invention.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

Pharmaceutical compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form can be used for immunosuppression or to treat or prevent inflammatory conditions, immune disorders, and allergic disorders. Preferred pharmaceutical compositions and dosage forms comprise a compound of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable prodrug, salt, solvate, or clathrate thereof, optionally in combination with one or more additional active agents.

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for
oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form suitable for mucosal administration may contain a smaller amount of active ingredient(s) than an oral dosage form used to treat the same indication. This aspect of the invention will be readily apparent to those skilled in the art. See, e.g., Remington’s Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms.

The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines (e.g., N-desmethylvenlafaxine and N,N-didesmethylvenlafaxine) are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions of the
invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopoeia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen (1995) Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically
sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizer” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise a compound of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof in an amount of from about 1 mg to about 1000 mg, preferably in an amount of from about 50 mg to about 500 mg, and most preferably in an amount of from about 75 mg to about 350 mg. The typical total daily dosage of a compound of any one of formulas (I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof can range from about 1 mg to about 5000 mg per day, preferably in an amount from about 50 mg to about 1500 mg per day, more preferably from about 75 mg to about 1000 mg per day. It is within the skill of the art to determine the appropriate dose and dosage form for a given patient.

**ORAL DOSAGE FORMS**

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.
Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic
acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. One specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103J and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical
compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

CONTROLLED RELEASE DOSAGE FORMS

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer
matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

A particular extended release formulation of this invention comprises a therapeutically or prophylactically effective amount of a compound of formula
(I) through (XI), or Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, in spheroids which further comprise microcrystalline cellulose and, optionally, hydroxypropylmethyl-cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Such extended release formulations can be prepared according to U.S. Patent No. 6,274,171, the entire teachings of which are incorporated herein by reference.

A specific controlled-release formulation of this invention comprises from about 6% to about 40% a compound of any one of formulas (I) through (XI), or Table 1 by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

PARENTERAL DOSAGE FORMS

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene
glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

**TRANSDERMAL, TOPICAL, AND MUCOSAL DOSAGE FORMS**

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, e.g., Remington’s Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA and Introduction to Pharmaceutical Dosage Forms (1985) 4th ed., Lea, & Febiger, Philadelphia. Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofurfuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

**COMBINATION THERAPY**

The methods for immunosuppression or for treating or preventing inflammatory conditions and immune disorders in a patient in need thereof can further comprise administering to the patient being administered a compound of this invention, an effective amount of one or more other active agents. Such active agents may include those used conventionally for immunosuppression or for
inflammatory conditions or immune disorders. These other active agents may also be those that provide other benefits when administered in combination with the compounds of this invention. For example, other therapeutic agents may include, without limitation, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, immunosuppressive agents and suitable mixtures thereof. In such combination therapy treatment, both the compounds of this invention and the other drug agent(s) are administered to a subject (e.g., humans, male or female) by conventional methods. The agents may be administered in a single dosage form or in separate dosage forms. Effective amounts of the other therapeutic agents and dosage forms are well known to those skilled in the art. It is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range.

In one embodiment of the invention where another therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount when the other therapeutic agent is not administered. In another embodiment, the effective amount of the conventional agent is less than its effective amount when the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In one embodiment relating to autoimmune and inflammatory conditions, the other therapeutic agent may be a steroid or a non-steroidal anti-inflammatory agent. Particularly useful non-steroidal anti-inflammatory agents, include, but are not limited to, aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramprofen, muroprofen, trixaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, buclocic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam; salicylic
acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenbutazone); and alkanones, including nabumetone and pharmaceutically acceptable salts thereof and mixtures thereof. For a more detailed description of the NSAIDs, see Paul A. Insel, *Analgesic-Antipyretic and Anti-Inflammatory Agents and Drugs Employed in the Treatment of Gout*, in *Goodman & Gilman’s The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entirety.

Of particular relevance to allergic disorders, the other therapeutic agent may be an antihistamine. Useful antihistamines include, but are not limited to, loratadine, cetirizine, fexofenadine, desloratadine, diphenhydramine, chlorpheniramine, chlorcyclizine, pyrilamine, promethazine, terfenadine, doxepin, carboxamine, clemastine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, cyproheptadine, phenindamine, acrivastine, azelastine, levocabastine, and mixtures thereof. For a more detailed description of antihistamines, see *Goodman & Gilman’s The Pharmacological Basis of Therapeutics* (2001) 651-57, 10th ed).

Immunosuppressive agents include glucocorticoids, corticosteroids (such as Prednisone or Solumedrol), T cell blockers (such as cyclosporin A and FK506), purine analogs (such as azathioprine (Imuran)), pyrimidine analogs (such as cytosine arabinoside), alkylating agents (such as nitrogen mustard, phenylalanine mustard, busulfan, and cyclophosphamide), folic acid antagonists
(such as aminopterin and methotrexate), antibiotics (such as rapamycin, actinomycin D, mitomycin C, puramycin, and chloramphenicol), human IgG, antilymphocyte globulin (ALG), and antibodies (such as anti-CD3 (OKT3), anti-CD4 (OKT4), anti-CD5, anti-CD7, anti-IL-2 receptor, anti-alpha/beta TCR, anti-ICAM-1, anti-CD20 (Rituxan), anti-IL-12 and antibodies to immunotoxins).

The foregoing and other useful combination therapies will be understood and appreciated by those of skill in the art. Potential advantages of such combination therapies include a different efficacy profile, the ability to use less of each of the individual active ingredients to minimize toxic side effects, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

OTHER EMBODIMENTS

The compounds of this invention may be used as research tools (for example, as a positive control for evaluating other potential CRAC inhibitors, or IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, and/or INF-γ inhibitors). These and other uses and embodiments of the compounds and compositions of this invention will be apparent to those of ordinary skill in the art.

The invention is further defined by reference to the following examples describing in detail the preparation of compounds of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention. The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.
EXAMPLES

EXPERIMENTAL RATIONALE
Without wishing to be bound by theory, it is believed that the compounds of this invention inhibit CRAC ion channels, thereby inhibiting production of IL-2 and other key cytokines involved with inflammatory and immune responses. The examples that follow demonstrate these properties.

MATERIALS AND GENERAL METHODS

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Varian 300MHz NMR spectrometer. Significant peaks are tabulated in the order: δ (ppm): chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons.

Patch clamp experiments were performed in the tight-seal whole-cell configuration at 21-25°C. High resolution current recordings were acquired by a computer-based patch clamp amplifier system (EPC-9, HEKA, Lambrecht, Germany). Patch pipettes had resistances between 2-4 MΩ after filling with the standard intracellular solution. Immediately following establishment of the whole-cell configuration, voltage ramps of 50-200 ms duration spanning the voltage range of -100 to +100 mV were delivered at a rate of 0.5 Hz over a period of 300-400 seconds. All voltages were corrected for a liquid junction potential of 10 mV between external and internal solutions when using glutamate as the intracellular anion. Currents were filtered at 2.9 kHz and digitized at 10 μs intervals. Capacitive currents and series resistance were determined and corrected before each voltage ramp using the automatic capacitance compensation of the EPC-9. The low resolution temporal development of membrane currents was assessed by extracting the current amplitude at -80 mV or +80 mV from individual ramp current records.
Compounds of the invention can also be prepared as in U.S. Application No. 10/897,681, filed July 22, 2004 and U.S. Application No. --- entitled "Compounds for Inflammation and Immune-Related Uses," by Lijun Sun, et al., filed on January 6, 2006, the entire teachings of which are incorporated herein by reference.

EXAMPLE 1: SYNTHESIS OF REPRESENTATIVE EXEMPLARY COMPOUNDS OF THIS INVENTION

**Compound 1: N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide**

(1). 4-(2,4-dichlorophenyl)thiazol-2-amine: To a solution of thiourea (1.52g, 20.0mmol) in ETOH (20.0mL) at room temperature was added the 2-chloro-1-(2,4-dichlorophenyl)ethanone (2.23g, 10.0mmol). The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The desired product 4-(2,4-dichlorophenyl)thiazol-2-amine (2.12g) was collected by filtration. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.50 (d, J = 9 Hz, 1H), 7.43 (d, J = 2 Hz, 1H), 7.28 (dd, J = 9, 2 Hz, 1H), 6.75 (s, 1H).

(2). N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide:
To a solution of 4-(2,4-dichlorophenyl)thiazol-2-amine (100mg, 0.4mmol), Et$_3$N (101 mg, 1.0mmol) and DMAP (10.0mg, 0.08mmol) in CH$_2$Cl$_2$ (3.0mL) at room temperature was added 2,6-difluorobenzoylchloride (89mg, 0.50mmol) in CH$_2$Cl$_2$ (1.0 mL). The mixture was stirred at room temperature overnight, taken up with additional CH$_2$Cl$_2$, then washed with a solution of saturated NaHCO$_3$. The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated. The residue
was purified on silica gel (eluted with CH₂Cl₂) to give pure
N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide (115mg). ¹H
NMR (300 MHz, CDCl₃)  δ 7.80 (d, J = 9 Hz, 1H), 7.68 (s, 1H), 7.47 (d, J = 2 Hz,
1H), 7.33-7.26 (m, 2H), 7.04 (t, J = 9 Hz, 2H ). MS (ESI) [MH⁺]: 385

Compound 2 below was synthesized in a similar manner:

**Compound 2:**
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

¹H NMR (300 MHz, CDCl₃)  δ  10.25 (s, 1H), 7.68 (s, 1H), 7.60 (d, J = 8 Hz, 1H),
7.26-7.43 (m, 1H), 6.80-7.01 (m, 4H), 3.90 (s, 3H), 3.80 (s, 3H)ppm. MS (ESI)
[MH⁺]: 377.1.

**Compound 3:**
N-[5-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

Into a solution of (methoxymethyl)triphenylphosphoniumchloride (4.14g,
12.0mmol) in THF (60.0mL) at -78°C was added n-BuLi (7.50mL of 1.6M in
hexane, 12.0mmol). The mixture was stirred at -78°C for 2 hours, then at 0°C
for 30 minutes. The mixture was cooled to -78°C. Into the reaction mixture, a solution of aldehyde 1a (1.66g, 10.0mmol) in THF (20.0mL) was added. The mixture was kept at 0°C for 1 hour, then at room temperature for 3 hours. Into the reaction mixture a solution of saturated NH₄Cl was added. The mixture was taken up in EtOAc. The organic layer was washed with brine and dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:9 EtOAc:Hexanes) to give 1b as a 3:2 mixture of isomers (1.25g).

1H NMR (300 MHz, CDCl₃) δ 7.63 (d, J = 3 Hz, 0.4H), 7.13 (d, J = 14 Hz, 0.6H), 6.82-6.62 (m, 2.4H), 6.18 (d, J = 8 Hz, 0.4H), 5.99 (d, J = 14 Hz, 0.6H), 5.61 (d, J = 8 Hz, 0.4H), 3.79 (s, 1.2H), 3.77 (s, 1.6H), 3.76 (s, 1.6H), 3.70 (s, 1.2H).

Into a solution of the enol ether 2 (1.25g, 6.40mmol) in ether (100mL) at 0°C was added bromine (1.15g, 6.40mmol) in CH₂Cl₂ (10.0mL). The mixture was stirred at 0°C for 15 minutes, then was poured into a solution of saturated NaHCO₃. The resulting mixture was stirred at 0°C for 1 hour. The layers were separated. The organic layer was washed with water then with brine and dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the crude aldehyde 1c (1.58g), which was used directly in the subsequent step.

Into a solution of the crude aldehyde 1c (1.58g, 6.10mmol) in EtOH (20.0mL) at room temperature was added thiourea (1.52g, 20.0mmol). The mixture was stirred at room temperature for 30 minutes then at 80°C overnight. The mixture was poured into a solution of saturated NaHCO₃. The precipitate was collected by filtration and air-dried to give 1d (1.25g).

1H NMR (300 MHz, CDCl₃) δ 7.50 (s, 1H), 7.02 (d, J = 3 Hz, 1H), 6.86 (d, J = 9 Hz, 1H), 6.74 (dd, J = 9, 3 Hz, 1H), 4.90 (bs, 2H), 3.85 (s, 3H), 3.79 (s, 3H).

Into a solution of 1d (100 mg, 0.42 mmol) in CH₂Cl₂ (2.0 mL) at room temperature were added DMAP (10.0 mg, 0.08 mmol), triethylamine (101 mg, 1.00 mmol), and 2,6-difluorobenzoyl chloride (89.0 mg, 0.50 mmol). The
mixture was stirred at room temperature overnight, diluted with CH₂Cl₂, washed with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give the title Compound 3.

¹H NMR (300 MHz, CDCl₃) δ 7.60-7.50 (m, 1H), 7.09 (t, J = 8 Hz, 2H), 7.01 (s, 1H), 6.97 (d, J = 3 Hz, 1H), 6.91 (d, J = 9 Hz, 1H), 6.83 (dd, J = 9, 3 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H).

MS (ESI) [M+H⁺]: 377

Compound 4 through Compound 6 below were synthesized in a similar manner as Compound 3:

**Compound 4:**

N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

¹H NMR (300 MHz, CDCl₃) δ 7.63-7.52 (m, 4H), 7.10 (t, J = 8 Hz, 2H), 6.88 (s, 1H).

MS (ESI) [M+H⁺]: 419

**Compound 5:**

2,6-difluoro-N-(5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

¹H NMR (300 MHz, CDCl₃) δ 8.16(s, 1H), 8.00 (s, 1H), 7.96-7.92 (m, 1H), 7.70-7.61 (m, 3H), 7.28 (t, J=8.1Hz, 2H). MS (ESI) [MH⁺] 385.0

**Compound 6:** N-[5-(3-Cyano-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

¹H NMR (300 MHz, CDCl₃) δ 7.80 (dd, J = 1, 1 Hz, 1H), 7.73 (ddd, J = 8, 1, 1 Hz, 1H), 7.58-7.45 (m, 4H), 7.04 (t, J = 8 Hz, 2H).

MS (ESI) [M+H⁺]: 342

**Compound 7:**

2,6-Difluoro-N-[5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide

A solution of Compound 6 (50mg, 0.15mmol), sodium azide (52mg, 0.75mmol),
triethylammonium hydrochloride (21mg, 0.15mmol) in DMF (1mL) was heated to 110°C overnight. The mixture was cooled to room temperature, diluted with CH₂Cl₂. The mixture was eluted through a plug of silica (initially with CH₂Cl₂, then with 1:9, MeOH: CH₂Cl₂) provided the crude tetrazole upon solvent removal. Methylation of the crude tetrazole was accomplished by treating the residue with a freshly prepared solution of CH₂N₂ in ether. The reaction mixture was concentrated under reduced pressure. The residue was purified on silica gel to give Compound 7 (20mg).

1H NMR (300 MHz, CDCl₃) δ 8.37 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.80 (s, 1H), 7.70-7.50 (m, 2H), 7.25-7.17 (m, 1H), 6.57-6.41 (m, 2H).

**Compound 8:** 3-[2-(2,6-Difluoro-benzoylamino)-4-methyl-thiazol-5-yl]-benzoic acid methyl ester
A mixture of aldehyde 9 (1.64g, 10.0mmol), ammonium acetate (0.77g, 10.0mmol), nitroethane (0.75g, 10.0mmol) in glacial acetic acid (10.0mL) was heated to 80°C overnight. The mixture was cooled to room temperature, diluted with CH₂Cl₂, washed with water, then with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated to give crude 10 (2.11g), which was used directly without further purification.

Partial 'H NMR for 10 (300 MHz, CDCl₃) δ 8.10 (s, 1H), 3.94 (s, 3H), 2.46 (s, 3H).

Into a solution of the crude 10 (2.11g, 9.50mmol) in glacial acetic acid (20.0mL) at room temperature was added zinc powder (1.30g, 20.0mmol). The mixture was stirred at room temperature for 30 minutes then heated to 80°C for 1 hour. The mixture was cooled to room temperature, diluted with CH₂Cl₂, washed with water, then with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue was filtered through a short plug of silica gel (eluted with 1:9, EtOAC:Hexanes) to give 11 (1.42g)

'¹H NMR (300 MHz, CDCl₃) δ 8.00-7.40 (m, 4H), 3.76 (s, 2H), 2.18 (s, 3H).

Into a solution of 11 (1.42g, 7.40mmol) in CH₂Cl₂ (30.0mL) at room temperature was added Br₂ (1.77g, 10.0mmol). The mixture was stirred at
room temperature for 2 hours. The reaction was quenched by addition of an aqueous solution of 10% NaHSO₃. The mixture was taken up in additional CH₂Cl₂. The organic layer was washed with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated to give crude bromide 12 (1.35g).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \[ \delta \ 8.09 \text{ (s, 1H), 8.04 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.48 (dd, J = 8, 8 Hz, 1H), 5.45 (s, 1H), 2.34 (s, 3H).} \]

The crude bromide 12 (1.35g, 4.98mmol) was taken up in EtOH (20.0mL).

Thiourea (0.76g, 10.0mmol) was added. The mixture was heated to 80°C for 2 hours, cooled to room temperature, poured over a solution of saturated NaHCO₃. The precipitate was collected by filtration to give 13 (1.01g).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \[ \delta \ 8.02 \text{ (s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.46 (dd, J = 8, 8 Hz, 1H), 3.93 (s, 3H), 2.32 (s, 3H).} \]

Compound 8 was prepared from 13 as described for the preparation of Compound 3.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \[ \delta \ 8.07 \text{ (s, 1H), 8.04 (d, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8, 8 Hz, 1H), 7.44-7.32 (m, 1H), 6.92 (t, J = 8 Hz, 2H), 3.94 (s, 3H), 2.30 (s, 3H).} \]

Compound 9 through Compound 15 were synthesized in a similar manner as Compound 8:

**Compound 9:**
2,6-Difluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzamide

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \[ \delta7.64 \text{ (s, 1H), 7.63-7.44 (m, 4H), 7.00 (t, J = 8 Hz, 2H), 2.06 (s, 3H). MS (ESI) [MH]^+: 399} \]
**Compound 10:** 3-Fluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.72 (d, $J = 2.7$ Hz, 1H), 8.69 (dd, $J = 5.1, 1.5$ Hz, 1H), 8.05 (dd, $J = 6.0, 5.1$ Hz, 1H), 7.71-7.51 (m, 4H), 2.45 (s, 3H). MS (ESI) [MH$^+$]: 382

**Compound 11:** 3-Methyl-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.58 (s, 1H), 8.55 (d, $J = 8$ Hz, 1H), 7.71 (s, 1H), 7.68-7.56 (m, 3H), 7.48 (d, $J = 8$ Hz, 1H), 2.52 (s, 3H), 2.42 (s, 3H)ppm. MS (ESI) [MH$^+$]: 378

**Compound 12:** 4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid [4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-amide

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.64-7.52 (m, 4H), 2.99 (s, 3H), 2.36 (s, 3H)ppm; MS (ESI) [MH$^+$]: 385

**Compound 13:**
N-[5-(3-Cyano-phenyl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.70-7.43 (m, 4H), 7.38-7.26 (m, 1H), 7.08 (t, $J = 8$ Hz, 2H), 2.10 (bs, 3H). MS (ESI) [MH$^+$]: 356

**Compound 14:**
2,6-Difluoro-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-benzamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.30 (d, $J = 7$ Hz, 2H), 7.61 (d, $J = 7$ Hz, 2H), 7.37-7.26 (m, 1H), 7.06 (t, $J = 8$ Hz, 2H), 2.39 (s, 3H). MS (ESI) [MH$^+$]: 376

**Compound 15:**
3-Methyl-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-isonicotinamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.56 (s, 1H), 8.55 (d, $J = 5.1$ Hz, 1H), 8.27 (d, $J = 7$ Hz, 2H), 7.61 (d, $J = 7$ Hz, 2H), 7.43 (d, $J = 5.1$ Hz, 1H), 2.50 (s, 3H), 2.45 (s, 3H). MS (ESI) [MH$^+$]: 355
Compound 16: 2,6-Difluoro-N-(4-methyl-5-pyridin-3-yl-thiazol-2-yl)-benzamide

Compound 16 was prepared as described for the preparation of Compound 52 (below) using 3-pyridylacetic acid and methylmagnesium bromide. The bromination step was carried out directly on the methyl ketone. Formation of silylenol ether was not necessary. It was necessary that the bromination product was isolated as a hydrobromide salt, which was accomplished by evaporation of excess Br₂ and solvent under reduced pressure. Other transformation was carried out as described.

¹H NMR (300 MHz, CDCl₃) δ 8.63 (dd, J = 1, 2.4 Hz, 1H), 8.49 (dd, J = 1.8, 5.1 Hz, 1H), 7.74 (ddd, J = 1.8, 2.4, 8.1 Hz, 1H), 7.50-7.34 (m, 2H), 7.00 (t, J = 8 Hz, 2H), 2.34 (s, 3H).
MS (ESI) [M+H⁺]: 332

Compound 17: 2,6-Difluoro-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-benzamide

Compound 17 was prepared as described for the preparation of Compound 16 using commercially available (4-pyridyl)acetone.

¹H NMR (300 MHz, CDCl₃) δ 8.59 (dd, J = 1.5, 6 Hz, 2H), 7.50-7.40 (m, 1H), 7.37 (d, J = 6 Hz, 2H) 7.03 (t, J = 8.7 Hz, 2H), 2.44 (s, 3H).
MS (ESI) [M+H⁺]: 332

Compound 18:
3-Methyl-N-(4-methyl-5-pyridin-4-yl-thiazol-2-yl)-isonicotinamide

Compound 18 was prepared as described for the preparation of Compound 17 using corresponding acid chloride.

¹H NMR (300 MHz, CDCl₃) δ 8.62-8.57 (m, 4H), 7.49-7.42 (m, 3H), 2.53 (s, 3H), 2.52 (s, 3H)
MS (ESI) [M+H⁺]: 311
Compound 19:
2,6-Difluoro-N-(4-methyl-5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide

To a solution of

N-[5-(3-Cyano-phenyl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide (0.23mmol), and triethylamine hydrochloride (32.0mg, 0.23mmol) in DMF (1mL) was added excess azidotrimethylsilane (0.20mL). The mixture was sealed and heated to 100 °C overnight, cooled to room temperature. The mixture was diluted with CH₂Cl₂. The resulting solution was eluted through a short plug of silica (eluted first with CH₂Cl₂ then with MeOH). The polar portion was concentrated to give the tetrazole product, which was directly methylated with a freshly prepared solution of CH₂N₂ in ether. Upon solvent removal, the title compound was obtained as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.22 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 7.55-7.46 (m, 3H), 7.02 (t, , J = 8 Hz, 2H), 4.41 (s, 3H), 2.26 (s, 3H). MS (ESI) [MH⁺]: 413

Compound 20: N-(5-(4-(dimethylamino)phenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

To a solution of

2,6-Difluoro-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-benzamide (50mg) in EtOH (5mL) at room temperature were added a solution of 37% formaldehyde in water (0.1 mL), 6N HCl (0.1mL), and 10% Pd/C (10mg). The mixture was stirred under an atmosphere of hydrogen gas for 3 hours. The mixture was neutralized with a solution of saturated NaHCO₃, extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound (45mg).

¹H NMR (300 MHz, CDCl₃) δ 7.50-7.43 (m, 1H), 7.31 (d, J = 9 Hz, 2H), 7.01 (t, J = 8 Hz, 2H), 6.76 (d, J = 9 Hz, 2H), 3.00 (s, 6H), 2.32 (s, 3H), 2.06 (s, 3H). MS (ESI) [MH⁺]: 374

Compound 21 was synthesized in a similar manner as Compound 20:
Compound 21: N-[5-(4-Dimethylamino-phenyl)-4-methyl-thiazol-2-yl]-3-methylisonicotinamide

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.57 (s, 1H), 8.53 (d, $J = 5.4$ Hz, 1H), 7.38 (d, $J = 5.4$ Hz, 1H), 7.29 (d, $J = 8.7$ Hz, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 2.99 (s, 6H), 2.51 (s, 3H), 2.21 (s, 3H). MS (ESI) [MH$^+$]: 353

Compound 22: N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

![Chemical structure diagram]

(1). 1-bromo-1-(3-methoxyphenyl)propan-2-one: To the solution of 1-(3-methoxyphenyl)propan-2-one (20 mmol) in 50 mL of CH$_2$Cl$_2$ at 0 °C was added bromine (40 mmol) dropwise. The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was treated with saturated NaHCO$_3$ solution and extracted with chloroform. The combined extracts were concentrated. The residue was purified by flash chromatography (20-100% ethyl acetate in hexanes) to give the title compound as a yellow liquid.

(2). 5-(3-methoxyphenyl)-4-methylthiazol-2-amine: To the solution of 1-bromo-1-(3-methoxyphenyl)propan-2-one prepared above in 50 mL of EtOH was added thiourea (1.55g, 20 mmol) at room temperature. The resulting solution was heated to 65 °C for 1 hour. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate. The solution was washed with saturated solution of NaHCO$_3$ and extracted with ethyl acetate. The combined extracts were dried over Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel (20-100% EtOAc) gave 4.1
g of title compound as a white solid. Yield: 68%. MS (ESI) [M+H]+ 299. (3).

N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide:
Using 5-(3-methoxyphenyl)-4-methylthiazol-2-amine as the raw materials, the
same operation as for Compound 1(3) gave the title compound. Yield: 71%.

H-NMR(CDCl₃): 7.60-6.80 (6H, m), 3.80 (3H, s), 2.05 (3H, s). MS (ESI) [M+H]+
441.

Compound 23 below was synthesized in a similar manner as Compound 22.

**Compound 23:** N-(5-(2-bromo-4,5-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-
difluorobenzamide
Yield: 52%. H-NMR(CDCl₃): 7.42 (1H, m), 7.08 (1H, s), 6.96 (2H, t), 6.78 (1H, s), 3.88 (3H, s), 3.81 (3H, s), 2.12 (3H, s). MS (ESI) [M+H]+ 469.

**Compound 24:**
2,6-difluoro-N-(5-(3-methoxyphenyl)-4-methylthiazol-2-yl)benzamide
The title compound was prepared from
N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2-fluorobenzamide by
hydrogenation with Pd/C at under 1 atm H₂ atmosphere in EtOH. Yield: 94%.

H-NMR(CDCl₃): 7.57 (1H, m), 7.40 (1H, t, J = 8.0), 7.10-6.95 (5H, m), 3.85
(3H, s), 2.45 (3H, s). MS (ESI) [M+H]+ 361.

Compound 25 below was synthesized in a similar manner as Compound 24.

**Compound 25:** N-(5-(3,4-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-
difluorobenzamide
Yield: 91%. H-NMR(CDCl₃): 7.50 (1H, m), 7.10-6.80 (5H, m) 3.95 (3H, s), 3.92
(3H, s), 2.57 (3H, s). MS (ESI) [M+H]+ 391.

**Compound 26:**
2,6-difluoro-N-(4-methyl-5-(2-methyl-5-(oxazol-2-yl)phenyl)thiazol-
2-yl)benzamide
(1). \( N-(5\text{-bromo-4-methylthiazol-2-yl})-2,6\text{-difluorobenzamide} \):  
2-Amino-5-bromo-4-trifluoromethylthiazole (0.8 g) was dissolved in 3 mL of 1:1 mixture of THF and pyridine. 2,6-difluorobenzoylchloride (0.6 g) was added at room temperature with stirring. The mixture was stirred for 3 hours at room temperature. The mixture was poured into ice water and acidified with aqueous hydrochloric acid then extracted with chloroform. The organic layer was dried over \( \text{Na}_2\text{SO}_4 \) and the solvent was removed under reduced pressure. Flash chromatography on silica gel gave the title compound as a white solid. Yield 83%.

(2). 2,6-difluoro-\( N-(4\text{-methyl-5-(2-methyl-5-(oxazol-2-yl)phenyl})\text{thiazol-2-yl)} \) benzamide:  
\( N-(5\text{-bromo-4-methylthiazol-2-yl})-2,6\text{-difluorobenzamide} \) (60 mg), 2-(4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazole (70 mg), 2 M NaHCO\(_3\) solution (0.5 mL), dichlorobis(benzonitrile)palladium (5 mg) and 1,4-Bis(diphenyl-phosphino)butane (10 mg) were mixed together in 2 mL of toluene in a sealed tube. The resulting suspension was stirred in microwave oven at 170 °C for 1 hour. After the reaction, the mixture was extracted with \( \text{Et}_2\text{O} \). The organic phases were removed under reduced pressure and the residue was chromatographed to give the title compound as a white solid. Yield 27%.

\(^{1}\text{HNMR (300 MHz)}\) 7.98 (1H, d, \( J = 8.0 \)), 7.96 (1H, s), 7.74 (1H, s), 7.50 (1H, m), 7.42 (1H, d, \( J = 8.0 \)), 7.33 (1H, s), 7.24 (1H, s), 7.05 (1H, t, \( J = 8.3 \)), 2.32 (3H, s), 2.18 (3H, s). MS (ESI) (MH\(^+\)) 412.
**Compound 27:** N-[5-(2-Bromo-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide

Into a solution of LDA (2M in THF, 10.0mL, 20.0mmol) in THF (30.0mL) at -78°C was added slowly a solution 2-bromo-4-methylpyridine (3.44g, 20.0mmol) in THF (10.0mL). The resulting mixture was stirred at -78°C for 2 hours. A solution of N-methoxy-N-methyl-acetamide (2.06g, 20.0mmol) in THF (10.0mL) was added. The mixture was stirred at 0°C for 1 hour then at room temperature for 30 minutes. The mixture was acidified with 2N HCl and stirred at room temperature for 30 minutes. After neutralization with a solution of saturated NaHCO₃, the mixture was extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica to give pure 19 (3.10g).

1H NMR (300 MHz, CDCl₃) δ 8.31 (d, J = 5 Hz, 1H), 7.33 (s, 1H), 7.09 (d, J = 5 Hz, 1H), 3.70 (s, 2H), 2.23 (s, 3H).

Into a solution of 19 (3.10g, 14.5mmol) in CH₂Cl₂ (30.0mL) at room temperature was added a solution of Br₂ (3.54g, 20.0 mmol) in CH₂Cl₂ (10.0mL). The mixture was stirred at room temperature for 15 minutes, quenched by addition of an aqueous solution of 10% NaHSO₃. The resulting
solution was neutralized with a solution of saturated NaHCO₃, extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a crude product 20 (4.10g).

\[ ^1H \text{NMR (300 MHz, CDCl}_3) \delta 8.40 \ (d, J = 5 \text{ Hz, 1H}), 7.56 \ (s, 1H), 7.32 \ (d, J = 5 \text{ Hz, 1H}), 5.24 \ (s, 1H), 2.40 \ (s, 3H). \]

Into a solution of crude 20 (4.10g, 14.0mmol) in EtOH (30.0mL) was added thiourea (2.28g, 30.0mmol). The mixture was stirred at room temperature for 3 hours. A solution of saturated NaHCO₃ was added. Pure 21 (2.95g) was collected as a solid precipitate.

\[ ^1H \text{NMR (300 MHz, CDCl}_3) \delta 8.26 \ (d, J = 5 \text{ Hz, 1H}), 7.40 \ (s, 1H), 7.18 \ (d, J = 5 \text{ Hz, 1H}), 2.37 \ (s, 3H). \]

MS (ESI) [M+H⁺]: 272

Compound 27 was prepared from 21 as described for the preparation of Compound 9.

\[ ^1H \text{NMR (300 MHz, CDCl}_3) \delta 8.70 \ (d, J = 5 \text{ Hz, 1H}), 7.75 \ (s, 1H), 7.55 \ (d, J = 5 \text{ Hz, 1H}), 7.51-7.46 \ (m, 1H), 7.04 \ (t, J = 8 \text{ Hz, 3H}), 2.42 \ (s, 3H). \]

MS (ESI) [M+H⁺]: 412

Compound 28 through Compound 31 were synthesized in a similar manner:

**Compound 28**: 2,6-difluoro-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl) benzamide
Yield: 72%. H-NMR (CDCl₃+CD₃OD): 8.40 (1H, d, J = 5.2), 7.43-7.20 (3H, m), 7.00-6.90 (2H, m), 2.40 (3H, s), 2.38 (3H, s). MS (ESI) [MH+] 346.

**Compound 29**: 3-Methyl-N-(4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl) isonicotinamide
Yield: 35%. H-NMR(CDCl₃+CD₃OD): 8.56-8.43 (3H, m), 7.50 (1H, d, J = 5.0),
7.39 (1H, s), 7.06 (1H, d, J = 5.0), 2.60 (3H, s), 2.52 (3H, s), 2.43 (3H, s). MS (ESI) [MH+] 325.

**Compound 30: N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide**

Yield: 69%. H-NMR (CDCl₃+CD₃OD): 8.51 (1H, d, J = 5.5), 7.51-7.42 (1H, m), 7.48 (1H, s), 7.18 (1H, d, J = 5.5), 7.03 (2H, t), 2.37 (3H, s). MS (ESI) [MH+] 366.

**Compound 31: N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-3-methylisonicotinamide hydrochloride**

Yield 41%. H-NMR (CDCl₃+CD₃OD) 8.57 (1H, s), 8.56 (1H, d, J = 5.5), 8.51 (1H, d, J = 5.0), 7.57 (1H, d, J = 2.2), 7.48 (1H, d, J = 5.5), 7.22 (1H, dd, J = 5.0, 2.2), 2.47 (3H, s), 2.38 (3H, s). MS (ESI). [MH+] 345.

**Compound 32: N-[5-(2-Cyano-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluorobenzamide**

A solution of N-[5-(2-Bromo-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluorobenzamide (100mg, 0.24mmol), Zn(CN)₂ (43.0mg, 0.36mmol), and Pd(PPh₃)₄ (20.0mg, 0.02mmol) in DMF (4.0mL) was degassed by purging with a stream of nitrogen for 10 minutes. The mixture was heated to 110 °C overnight, cooled to room temperature, diluted with CH₂Cl₂, washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give the title compound (45mg).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J = 5.1$ Hz, 1H), 7.76 (s, 1H), 7.57-7.45 (m, 2H), 7.04 (t, $J = 8$ Hz, 2H), 2.48 (s, 3H). MS (ESI) [M+H$^+$]: 357

**Compound 33**: 2,6-Difluoro-N-[4-methyl-5-(2-morpholin-4-yl-pyridin-4-yl)-thiazol-2-yl]-benzamide

A mixture of 28c (100mg, 0.37mmol) in excess morpholine (0.5mL) was heated to 110°C overnight, cooled to room temperature, taken up in CH$_2$Cl$_2$, washed with water, dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to 31a (85mg).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.15 (d, $J = 5$ Hz, 1H), 6.67 (d, $J = 5$ Hz, 1H), 6.54 (s, 1H), 5.15 (bs, 2H), 3.85-3.76 (m, 4H), 3.52-3.46 (m, 4H), 2.36 (s, 3H).

Compound 33 was prepared from 31a as described for the preparation of Compound 9.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.22 (d, $J = 5$ Hz, 1H), 7.58-7.42 (m, 1H), 7.02 (t, $J = 8$ Hz, 2H), 6.72 (d, $J = 5$ Hz, 1H), 6.64 (s, 1H), 3.86-3.83 (m, 4H), 3.56-3.53 (m, 4H), 2.23 (s, 3H).

MS (ESI) [M+H$^+$]: 417
Compound 34: N-[4-Ethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

Into a solution of 2-(3-(trifluoromethyl)phenyl)acetic acid (2.04g, 10.0mmol), N,O-Dimethylhydroxylamine hydrochloride (0.98g, 10.0 mmol), and triethylamine (2.02g, 20.0 mmol) in CH$_2$Cl$_2$ (20.0mL) at room temperature was added N-(3-Dimethylaminopropyl)-N'-ethylecarbodiimide hydrochloride (3.00g, 15.6 mmol). The mixture was stirred at room temperature overnight, diluted with additional CH$_2$Cl$_2$, washed with a solution of saturated NaHCO$_3$, dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was filtered through a short plug of silica gel (eluted with EtOAc) to give pure 23 (1.85g).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.54-7.43 (m, 4H), 3.83 (s, 2H), 3.65 (s, 3H), 3.21 (s, 3H).

Into a solution of 23 (1.85g, 7.49mmol) in THF (20.0mL) at 0°C was added ethylmagnesium bromide (5.0mL of 3M solution in ether, 15.0mmol). The mixture was stirred at room temperature for 2 hours, cooled to 0°C. The cooled solution was poured over an ice-cooled solution of 1N HCl. The acidified
solution was stirred at room temperature for 30 minutes, extracted with CH₂Cl₂. The extract was washed with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give pure 24 (1.50g).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \text{)} \delta \ 7.54-7.37 \text{ (m, 4H), 3.76 (s, 2H), 2.51 (q, } J = 7.3 \text{ Hz, 2H), 1.07 (t, } J = 7.3 \text{ Hz, 3H).} \]

Into a solution of 24 (1.50g; 6.94mmol) in 1,2-dichloroethane (40.0 mL) at room temperature was added NBS (1.48g, 8.33mmol) and benzoyl peroxide (24mg, 0.1mmol). The mixture was heated to 80°C for 2 hours, cooled to room temperature, diluted with CH₂Cl₂, washed with an aqueous solution of 10% NaHSO₃, the with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude 25, which was taken up in EtOH (20.0mL). Into the alcoholic solution, thiourea (1.52g, 20.0mmol) was added the mixture was heated to 80°C for 2 hours, cooled to room temperature. A solution of saturated NaHCO₃ was added. The precipitate was collected by filtration and air-dried to give 26 (1.55g).

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \text{)} \delta \ 7.56-7.32 \text{ (m, 4H), 2.54 (q, } J = 7.3 \text{ Hz, 2H), 1.22 (t, } J = 7.3 \text{ Hz, 3H)} \]

MS (ESI) [M+H⁺]: 273

Compound 34 was prepared from 26 as described for the preparation of Compound 9.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \text{)} \delta \ 7.67-7.48 \text{ (m, 5H), 7.05 (t, } J = 8 \text{ Hz, 2H), 2.62 (q, } J = 7 \text{ Hz, 2H), 1.26 (t, } J = 7 \text{ Hz, 3H)} \]

MS (ESI) [M+H⁺]: 413

Compound 35: Methyl 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate
(1). Methyl 3-chloro-2-oxo-3-(3-(trifluoromethyl)phenyl)propanoate: A mixture of NaOMe (20 mmol, 25% in MeOH) and 30 mL of THF cooled to -78 °C. Then methyl dichloroacetate (2.0 mL, 20 mmol) and 3-(trifluoromethyl)benzaldehyde (3.48 g, 20 mmol) was added under N₂. The mixture was stirred at the same temperature for 3 hours and allowed to stand overnight at room temperature. After concentration the reaction mixture was extracted with ethyl acetate. The extracts were dried over Na₂SO₄, concentrated and purified by flash chromatography on silica gel (3-10% ethyl acetate in hexanes) to give 5.2 g of the title compound as a yellow oil. Yield: 93%. H-NMR (CDCl₃): 7.70-7.50 (4H, m), 4.58 (1H, s), 3.95 (3H, s).

(2). Methyl 2-amino-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate: To the solution of methyl 3-chloro-2-oxo-3-(3-(trifluoromethyl)phenyl)propanoate prepared above in 50 mL of EtOH was added thiourea (2.0 g, 26.3 mmol) at room temperature. The resulting solution was heated to 65 °C for 4 hours. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate. The solution was treated with saturated solution of NaHCO₃ and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (20-100% EtOAc in hexanes) gave 4.8 g of title compound as a white solid. Yield: 92%. H-NMR (CDCl₃): 7.70-7.50 (4H, m), 3.76 (3H, s). MS (ESI) [MH⁺] 303.
(3). Methyl 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate:

A solution of 2,6-difluorobenzoyl chloride (1.5 mmol), methyl 2-amino-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate (1.0 mmol) and NEt$_3$ (3 mmol) in 30 mL of THF was stirred at room temperature for 4 hours. The reaction mixture was treated with 20 mL of saturated NaHCO$_3$ solution and the resulting mixture was extracted with ethyl acetate. The organic extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (10%-100% ethyl acetate in hexanes) to give 318 mg of the title compound as a pale solid. Yield: 72%. H-NMR (CDCl$_3$+CD$_3$OD): 7.71 (1H, s), 7.63 (2H, m), 7.53 (1H, m), 3.75 (3H, s). MS (ESI) [MH$^+$] 443.

Compound 36 through Compound 38 below were synthesized in a similar manner as in Compound 35.

**Compound 36:** Methyl 2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate

Yield: 64%. H-NMR (CDCl$_3$): 8.63 (1H, s), 8.54 (1H, d, J = 4.9), 7.77 (1H, s), 7.71-7.68 (2H, m), 7.59 (1H, dd, J = 8.0, 7.4), 7.35 (1H, d, J = 4.9), 3.65 (3H, s), 2.55 (3H, s). MS (ESI) [MH$^+$] 422.

**Compound 37:** Methyl 2-(2,6-difluorobenzamido)-5-(3-fluorophenyl)thiazole-4-carboxylate

Yield: 78%. H-NMR (CDCl$_3$): 10.93 (1H, br s, NH), 7.6-6.8 (m, 7 H), 3.68 (3H, s). MS (ESI) [MH$^+$] 393.

**Compound 38:** Methyl 5-(3-fluorophenyl)-2-(3-methylisonicotinamido)
thiazole-4-carboxylate
Yield: 66%. H-NMR(CDC$_3$ + CD$_3$OD): 8.59 (1H, s), 7.55-7.13 (6H, m), 3.80 (3H, s), 2.50 (3H, s). MS (ESI) [MH$^+$] 372.

5 Compound 39: 2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide
Into a solution of Compound 63 (442 mg, 1.0 mmol) in THF (5.0 mL) at 0°C was added dropwise a solution of 1M Lithium aluminum hydride in THF (2.0 mL, 2.0 mmol). The mixture was stirred at room temperature for 1 hour, cooled to 0°C. Into the mixture ice was added followed by 2N NaOH. The mixture was extracted with methylene chloride. The extracts were washed with water, dried (Na$_2$SO$_4$) and concentrated to give Compound 39 (380 mg). MS (ESI) [M+H$^+$]: 415.

15 Compound 40: 2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(fluoro)phenyl)thiazol-2-yl)benzamide
The title compound was prepared by reducing Methyl 2-(2,6-difluorobenzamido)-5-(3-fluorophenyl)thiazole-4-carboxylate with lithium aluminum hydride (2 equiv) in THF. Yield: 92%. H-NMR(CDC$_3$)

7.50-6.90 (7H, m), 4.60 (2H, s). MS (ESI) [MH$^+$] 365.

Compound 41: 2-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (2,6-difluoro-phenyl)-amide
(1). 2-Chloro-5-(trifluoromethyl)benzothioamide: To a solution of 2-chloro-5-(trifluoromethyl)benzonitrile (1.03g, 5.0mmol) in 2M NH₃ in EtOH (10.0mL) at 0 °C was introduced a gentle stream of H₂S gas. Upon saturation a yellow solution was observed. The reaction mixture was sealed and stirred at room temperature for 1 hour. Excess H₂S gas was removed by purging the reaction mixture with a steady stream of N₂ gas. The solvent was removed under reduced pressure to give 2-chloro-5-(trifluoromethyl)benzothioamide in quantitative yield.

(2). Ethyl 2-(2-chloro-5-(trifluoromethyl)phenyl)thiazole-5-carboxylate: 2-chloro-5-(trifluoromethyl)benzothioamide was taken up in THF (20.0mL). To the mixture, ethyl 2-chloro-3-oxopropanoate (1.01g, 0.67mmol) was added. The mixture was heated to 65 °C overnight, cooled to room temperature, diluted with ethyl acetate, washed with a solution of saturated NaHCO₃, with brine and dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:19, EtOAc:Hexanes) to give pure ethyl 2-(2-chloro-5-(trifluoromethyl)phenyl)thiazole-5-carboxylate (450mg). ¹H NMR (300 MHz, CDCl₃) δ 8.68 (s, 1H), 8.52 (s, 1H), 7.72-7.56 (m, 2H), 4.40 (q, J = 7 Hz, 2H), 1.44 (t, J = 7 Hz, 3H).
(3). 2-(2-Chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide: To a solution of ethyl 2-(2-chloro-5-(trifluoromethyl)phenyl)thiazole-5-carboxylate (106mg, 0.32mmol), 2,6-difluoroaniline (50.0mg, 0.38mmol) in toluene (4.0mL) was added a solution of Al(Me)$_3$ (2M in toluene, 0.30mL, 0.60mmol). The mixture was sealed and heated to 80 °C for 2 hours, cooled to room temperature, quenched by addition of a solution of saturated NH$_4$Cl. The resulting aqueous solution was extracted with CH$_2$Cl$_2$. The combined extracts were washed with 1N HCl, with a solution of saturated NaHCO$_3$, then dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:9, EtOAc:hexanes) to give the title compound (95mg). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.69 (s, 1H), 8.47 (s, 1H), 7.70-7.63 (m, 2H), 7.36 (bs, 1H), 7.34-7.25 (m, 1H), 7.02 (t, J = 8 Hz, 2H).

Compound 42: 4-Methyl-5-(3-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid (2,6-difluoro-phenyl)-amide

(1). Ethyl 4-methyl-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxylate: To the solution of ethyl 2-amino-2-thiooxoacetate (0.67 mmol) was added 1-bromo-1-(3-(trifluoromethyl)phenyl)propan-2-one (0.67mmol) at room temperature. The mixture was heated to 65 °C overnight, cooled to room temperature, diluted with ethyl acetate, washed with a solution of saturated NaHCO$_3$, with brine and dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:19, EtOAc:Hexanes) to give pure ethyl 4-methyl-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxylate (450mg). $^1$H NMR
(300 MHz, CDCl₃) δ 7.74-7.52 (m, 4H), 4.50 (q, J = 7 Hz, 2H), 2.57 (s, 3H), 1.43 (t, J = 7 Hz, 3H).

(2). 4-Methyl-5-(3-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid

5 (2,6-difluoro-phenyl)-amide: Into a solution of ethyl 4-methyl-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxylate (0.32mmol), 2,6-difluoroaniline (50.0mg, 0.38mmol) in toluene (4.0mL) was added a solution of Al(Me)₃ (2M in toluene, 0.30mL, 0.60mmol). The mixture was sealed and heated to 80 °C for 2 hours, cooled to room temperature, quenched by addition of a solution of saturated NH₄Cl. The resulting aqueous solution was extracted with CH₂Cl₂. The combined extracts were washed with 1N HCl, with a solution of saturated NaHCO₃, then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:9, EtOAc:hexanes) to give the title compound (95mg). ¹H NMR (300 MHz, CDCl₃) δ 8.61 (bs, 1H), 7.73-7.60 (m, 4H), 7.30-7.25 (m, 1H), 7.03 (t, J = 8 Hz, 2H), 2.57 (s, 3H).

Compound 43:
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide

¹H NMR (300 MHz, CDCl₃) δ 10.25 (s, 1H), 7.68 (s, 1H), 7.60 (d, J = 8 Hz, 1H), 7.26-7.43 (m, 1H), 6.80-7.01 (m, 4H), 3.90 (s, 3H), 3.80 (s, 3H)ppm; MS (ESI) [M+H⁺]: 377.1.

Compound 44: N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-2,6-difluoro-benzamide

¹H NMR (300 MHz, CD₃OD) δ8.55 (s, 1H), 7.85-7.95 (m, 2H), 7.62-7.75 (m, 1H), 7.25 (t, J = 8, 2H)ppm; MS (ESI) [M+H⁺]: 420.

Compound 45: N-(5-(2,5-dimethylcyclohex-1-etyl)thiazol-2-yl)-3-methylisonicotinamide

Aminothiazole (1g, 9.9mmol) was dissolved in THF and was cooled to -78°C and stirred vigorously. n-BuLi (2eq, 19.8mmol) was added to the solution and stirred for 30 minutes followed by the addition of TMSCl (2eq, 19.8mmol) which
was warmed to -30 °C then cooled to -78 °C and the ketone (19.9 mmol) was added. This was stirred for 15 minutes then quenched with 1N HCl solution. After aqueous work-up it was purified by flash chromatography give 111mg of the amine, 5-(2,5-Dimethyl-cyclohex-1-enyl)-thiazol-2-ylamine, in the pure form. This amine was then subjected to the standard amide formation procedure with 3-Methyl-isonicotinic acid to form the title compound as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.64 (s, 1H), 8.60 (d, J=5.1 Hz, 1H), 7.43 (d, J=5.1 Hz, 1H), 5.99 (s, 1H), 2.52 (s, 3H), 2.33-2.05 (m, 3H), 1.79-1.90 (m, 2H), 1.75 (s, 3H), 1.03 (d, J=6.0 Hz, 3H) ppm.

ESMS calcd. (C18H21N3OS): 327.1; found: 328.1(M + H).

**Compound 48**: Sodium

(2,6-difluorobenzoyl)(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)amide

Into a solution of Compound 9 (398 mg, 1.00 mmol) in methanol (2.0 mL) at 0°C was added dropwise a solution of 1M NaOMe in methanol (1.00 mL, 1.00 mmol). The mixture was stirred at 0°C for 30 minutes. The solvent was removed under reduced pressure to give compound 48 in quantitative yield.

$^1$H NMR (300 MHz, CD$_3$OD) δ 7.73-7.52 (m, 4H), 7.37-7.27 (m, 1H), 6.95 (dd, J = 8, 8 Hz, 2H), 2.38 (s, 3H).

MS (ESI) [M-Na+2H$^+$]: 399

**Compound 49**: Sodium (4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) (3-methylisonicotinoyl)amide

Compound 49 was prepared from Compound 11 as described for the preparation of Compound 48.

MS (ESI) [M-Na+2H$^+$]: 378

**Compound 50**: 2-Fluoro-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) nicotinamide
Compound 50 was prepared as described for the preparation of Compound 9 with the corresponding acid chloride.

MS (ESI) [M+H⁺]: 382.

**Compound 51:** 2-Methyl-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) nicotinamide

Compound 51 was prepared as described for the preparation of Compound 9 with the corresponding acid chloride.

**1H NMR (300 MHz, CDCl₃)** δ 8.65 (dd, J = 1.6, 4.8 Hz, 1H), 7.80 (dd, J = 1.6, 7.0 Hz, 1H), 7.64-7.54 (m, 5H), 7.18 (dd, J = 5.0, 7.7 Hz, 1H), 2.76 (s, 3H), 1.78 (s, 3H).  

MS (ESI) [M+H⁺]: 378.

**Compound 52:** N-(4-Cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

![Chemical structure diagram](attachment:image.png)
23a was prepared similarly as described for the preparation of 22b using cyclopropylmagnesium bromide.

Into a solution of 23a (1.61g, 7.05 mmol) in THF (30 mL) at -78°C was added dropwise a solution of 2M LDA (5.00 mL, 10.0 mmol). The mixture was stirred at -78°C for 2 hours. Into the reaction mixture as solution of TBSCI (1.28g, 8.50 mmol) in THF (5.00 mL) was added. The mixture was stirred at 0°C for 1 hour, recooled to -78°C. A solution of saturated ammonium chloride was added. The mixture was extracted with ethyl acetate. The extract was washed with brine and dried ((Na₂SO₄), filtered and concentrated. The residue was purified on silica to give 23b (570 mg) and recovered 23a (1.20 g).

Into a solution of 23b (570 mg, 1.66 mmol) in CH₂Cl₂ (15 mL) at 0°C was added a solution of bromine (288 mg, 1.80 mmol) in CH₂Cl₂ (5 mL) dropwise. Upon completion of bromine addition, the solvent was removed under reduced pressure to give crude 23c. The crude 23c was taken up in EtOH (10.0 mL). Thiourea (380 mg, 5.00 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was taken up in CH₂Cl₂, washed with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give 23d (470 mg).

¹H NMR (300 MHz, CDCl₃) δ 7.73 (s, 1H), 7.54-7.49 (m, 1H), 7.48-7.46 (m, 2H), 2.03-1.86 (m, 1H), 1.10-0.85 (m, 4H).
MS (ESI) [M+H⁺]: 285

Compound 52 was prepared from 23d as described for the preparation of Compound 9.

¹H NMR (300 MHz, CDCl₃) δ 7.83-7.38 (m, 5H), 7.01 (dd, J = 8, 8 Hz, 2H), 2.05-1.88 (m, 1H), 0.95-0.86 (m, 4H).
MS (ESI) [M+H⁺]: 425

Compound 53: N-(4-cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-3-methylisonicotinamide
Compound 53 was prepared from 23d and the corresponding acid chloride as described for the preparation of compound 9.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.56 (s, 1H), 8.55 (d, $J = 6.3$ Hz, 1H), 7.85 (s, 1H), 7.76 (bd, $J = 6.9$Hz, 1H), 7.62-7.54 (m, 2H), 7.46 (d, $J = 5.1$Hz, 1H), 2.53 (s, 3H), 2.11-2.02 (m, 1H), 1.00-0.94 (m, 4H).

MS (ESI) [M+H$^+$]: 404

**Compound 54**: 2,6-Difluoro-N-(4-methyl-5-(pyridin-4-yl)thiazol-2-yl)benzamide hydrobromide

Into a solution of Compound 27 (21.0 mg, 0.05 mmol) in ethanol (2.0 mL) was added 10% Pd/C (10.0 mg). The mixture was stirred under 1 atmosphere of hydrogen for overnight. The mixture was filtered through a short plug of silica to give Compound 54, 19.4 mg, 92%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.64 (d, $J = 5.7$ Hz, 2H), 7.56-7.46 (m, 1H), 7.38 (d, $J = 5.7$ Hz, 2H), 7.04 (t, $J = 8.5$ Hz, 2H).

MS (ESI) [M+H$^+$]: 332

**Compound 55**: N-(5-(2,5-Dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

![Chemical structure](image)

Into a slurry of N,O-dimethylhydroxylamine hydrochloride (732 mg, 7.5 mmol) in CH$_2$Cl$_2$ (10.0 mL) at room temperature was added triethylamine (1.52g, 15.0 mmol). The mixture was stirred at room temperature for 10 minutes, cooled to
-78°C. Into the reaction mixture a solution of 2-(2,5-dimethoxyphenyl)acetyl chloride (1.08 g, 5.0 mmol) in CH₂Cl₂ (5.0 mL) was added dropwise. The mixture was gradually warm to room temperature. After 30 minutes at room temperature, the reaction mixture was quenched by slow addition of a solution of saturated NaHCO₃, extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated to the crude 32a (950 mg). The crude amide was taken up in THF (10.0 mL). Into the resulting solution at 0°C was added dropwise a solution of 3M methylmagnesium bromide in ether (2.00 mL, 6.00 mmol). The mixture was stirred at room temperature for 3 hours, cooled to 0°C, quenched with ice. The mixture was acidified with 6N HCl. After 1 hour at room temperature, the mixture was neutralized with a solution of saturated NaHCO₃, extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated. The resulting methyl ketone was used directly without purification to prepare Compound 55 in the similar manner as described for the preparation of Compound 27.

¹H NMR (300 MHz, CDCl₃) δ 7.50-7.40 (m, 1H), 7.00 (dd, J = 8, 8 Hz, 2H), 6.92-6.84 (m, 3H), 3.79 (s, 6H), 2.04 (s, 3H).

MS (ESI) [M+H⁺]: 391

Compound 56: N-(5-(7-Bromobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

Compound 56 was prepared from 2-(benzo[d][1,3]dioxol-5-yl)acetyl chloride in the similar manner as described for the preparation of Compound 55 with the exception that 2 equivalents of bromine was used.

¹H NMR (300 MHz, CDCl₃) δ 7.53-7.42 (m, 1H), 7.11 (s, 1H), 7.00 (dd, J = 8.4, 8.4 Hz, 2H), 6.77 (s, 1H), 6.04 (s, 2H), 1.85 (s, 3H).

MS (ESI) [M+H⁺]: 455

Compound 57: N-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

A mixture of Compound 56 (50 mg) and 10% Pd/C (10 mg) in EtOH (2.0 mL)
was stirred under an atmosphere of hydrogen gas overnight. The mixture was filtered through a short plug of celite. The filtrate was concentrated under reduced pressure to give Compound 57 (37mg).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \[ \delta \] 7.60-7.50 (m, 1H), 7.08 (dd, J = 8.4, 8.4 Hz, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.87 (s, 1H), 6.06 (s, 2H), 2.54 (s, 3H).

MS (ESI) [M+H\textsuperscript{+}]: 374

**Compound 58**: N-(5-(7-Cyanobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

A degassed mixture of Compound 56 (80 mg, 0.18 mmol), zinc cyanide (26 mg, 0.22 mmol) and tetrakis(triphenylphosphine)palladium (20.0 mg, 0.017 mmol) in DMF (2.0 mL) was heated to 100°C overnight. The mixture was cooled to room temperature, diluted with ethyl acetate. The mixture was washed with a solution of saturated NaHCO\textsubscript{3} then with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated. The residue was purified on silica to provide Compound 58 (55 mg).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \[ \delta \] 7.52-7.44 (m, 1H), 7.02 (dd, J = 8.4, 8.4 Hz, 2H), 6.87 (s, 1H), 6.12 (s, 2H), 2.19 (s, 3H).

MS (ESI) [M+H\textsuperscript{+}]: 400

**Compound 59**: N-(5-(5-Bromothiophen-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

Compound 59 was prepared from 2-(thiophen-2-yl)acetic acid in the similar manner as described for the preparation of compound 22a and with further modifications as described for the preparation of Compound 56.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \[ \delta \] 7.53-7.43 (m, 1H), 7.03 (d, J = 3.9 Hz, 1H), 6.98 (dd, J = 8, 8 Hz, 2H), 6.84 (d, J = 3.9 Hz, 1H), 2.03 (s, 3H).

MS (ESI) [M+H\textsuperscript{+}]: 417
Compound 60: 2,6-Difluoro-N-(4-methyl-5-(thiophen-2-yl)thiazol-2-yl) benzamidem

Compound 60 was prepared from Compound 59 as described for the preparation of Compound 57.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.59-7.51 (m, 1H), 7.47 (d, $J = 5.1$ Hz, 1H), 7.22-7.08 (m, 4H), 2.54 (s, 3H).
MS (ESI) [M+H$^+$]: 337

Compound 61: N-(5-(2,5-Dibromothiophen-3-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide

Compound 61 was prepared from 3-(thiophen-2-yl)acetic acid in the similar manner as described for the preparation of 23 (see prep of Compound 34) and with further modifications as described for the preparation of Compound 56 and with the exception that 3 equivalents of bromine was used.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.52-7.42 (m, 1H), 7.00 (dd, $J = 8.4, 8.4$ Hz, 2H), 6.89 (s, 1H), 1.86 (s, 3H).
MS (ESI) [M+H$^+$]: 495

Compound 62: 2,6-Difluoro-N-(4-methyl-5-(thiophen-3-yl)thiazol-2-yl) benzamide

Compound 62 was prepared from was prepared from Compound 61 as described for the preparation of Compound 57.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62-7.53 (m, 2H), 7.49 (s, 1H), 7.11 (dd, $J = 8.7, 8.4$ Hz, 2H), 2.62 (s, 3H).
MS (ESI) [M+H$^+$]: 337

Compound 63: Methyl 5-(2-(allyloxy)-5-(trifluoromethyl)phenyl)-2-(2,6-difluorobenzamido)thiazole-4-carboxylate
Into a solution of 2-fluoro-5-(trifluoromethyl)benzaldehyde (3.00g, 15.6 mmol) in allyl alcohol was added K₂CO₃ (2.80g, 20.0 mmol). The mixture was heated to 60°C for 5 hours, cooled to room temperature, taken up in ethyl acetate, washed with water, then with brine and dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with a solution of ethyl acetate: hexane, 1:19) to give 40a (2.15g, 60% yield).

^1H NMR (300 MHz, CDCl₃) δ 10.52 (s, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.76 (dd, J = 1.5, 8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 6.18-5.84 (m, 1H), 5.36-5.16 (m, 2H), 4.75 (d, J = 6 Hz, 2H).

Into a mixture of 25% NaOMe in MeOH (2.30 mL, 10.0 mmol) and THF (40 mL) at -78°C was added dropwise a solution of 40a (2.15g, 9.34 mmol) and methyl dichloroacetate (1.43 g, 10.0 mmol) in THF (10 mL). The mixture was stirred at -78°C for 3 hours, then at room temperature overnight. The reaction mixture was quenched with the addition of ice, extracted with methylene chloride. The extract was washed with water, dried (Na₂SO₄), filtered and concentrated. The residue was taken up MeOH (40.0 mL). Thiourea (1.52g, 20.0 mmol) was added. The mixture was stirred at room temperature for 8 hours, neutralized with a saturated solution of NaHCO₃, extracted with CH₂Cl₂ (2X). The extracts were washed with water, dried (Na₂SO₄), filtered and concentrated to give 40b (2.05g, 61% yield).
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.58 (d, \(J = 8\) Hz, 1H), 7.57 (s, 1H), 6.96 (d, \(J = 8\) Hz, 1H), 5.92 (tdd, \(J = 5.4, 10.5, 17\) Hz, 1H), 5.31 (d, \(J = 17\) Hz, 1H), 5.23 (d, \(J = 10.5\) Hz, 1H), 4.58 (d, \(J = 5.4\), 2H), 3.70 (s, 3H).

MS (ESI) [M+H\(^+\)]: 359

Into a solution of 40b (2.00g, 5.60 mmol), triethylamine (1.01g, 10.0 mmol), and catalytic amount of DMAP (20.0 mg, 0.16 mmol) in methylene chloride (20.0 mL) at room temperature was added 2,6-difluorobenzoylchloride. The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in MeOH (20.0 mL). K\(_2\)CO\(_3\) (1.38g, 10.0 mmol) was added. The mixture was stirred at room temperature for 1 hour, diluted with methylene chloride, washed with water, dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride) to give Compound 63 (2.21g, 79% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 10.07 (bs, 1H), 7.63 (d, \(J = 8.4\) Hz, 1H), 7.60 (s, 1H), 7.56-7.46 (m, 1H), 7.07-7.01 (m, 3H), 5.94 (tdd, \(J = 5.4, 10, 17\) Hz, 1H), 5.32 (d, \(J = 17\) Hz, 1H), 5.26 (d, \(J = 10\) Hz, 1H), 4.61 (d, \(J = 5.4\), 2H), 3.71 (s, 3H).

MS (ESI) [M+H\(^+\)]: 499

Compounds 64: N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)-4-(prop-1-en-2-yl))thiazol-2-yl)-2,6-difluorobenzamides

Into a solution of Compound 63 (1.00g, 2.00 mmol) at -78\(^\circ\)C was added a solution of 3M methylmagnesium bromide in ether (4.00 mL, 12.0 mmol). The mixture was gradually warmed to room temperature. After 30 minutes at room temperature, the mixture was cooled to 0\(^\circ\)C, quenched by addition of saturated NH\(_4\)Cl, extracted with CH\(_2\)Cl\(_2\). The extract was dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was taken up in trifluoroacetic acid (6.00 mL), heated to 40\(^\circ\)C for 2 hours, concentrated. The residue was diluted with CH\(_2\)Cl\(_2\), washed with a solution of saturated NaHCO\(_3\), dried (Na\(_2\)SO\(_4\)), filtered and concentrated to give the titled Compound 64.
\( ^1H \text{NMR (300 MHz, CDCl}_3 \delta 7.60-7.40 \text{ (m, 3H), 7.05-6.95 (m, 3H), 6.00 (ddt, J = 15.0, 10.5, 5.1, 1H), 5.35 (d, J = 15.0 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 5.13 (bs, 1H), 4.99 (bs, 1H), 4.65 (d, J = 5.1 Hz, 2H).} \)

MS (ESI) [M+H\(^+\)]: 481

**Compound 65**: N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 63 (30 mg, 0.06 mmol) in 2 mL MeOH was added NaOH (50 mg). The solution was heated to reflux for 30 minutes. After cooling to room temperature, the solvent was removed, and the residue was dissolved in 4 mL of DMF and 1 mL of water. The mixture was heated to 150°C for 16 hours. The mixture was diluted with 20 mL of Et\(_2\)O and the solution was washed with brine, dried and concentrated. The residue was purified on silica (eluted with 10-50% of ethyl acetate in hexanes) to give Compound 65 (7.9 mg, 30%) as a white solid.

\( ^1H \text{NMR (300 MHz, CDCl}_3 \delta 7.65 \text{ (s, 1H), 7.50 \text{ (m, 2H), 7.10-7.00 \text{ (m, 4H), 6.12 \text{ (m, 1H), 5.44 \text{ (d, J = 16.0 Hz, 1H), 5.36 \text{ (d, J =10.4 Hz, 1H), 4.75 \text{ (d, J = 5.3 Hz, 2H).} \)} \)

MS (ESI) [M+H\(^+\)]: 441

**Compound 66**: 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid

Into a solution of Compound 35 (884 mg, 2 mmol) in 20 mL of MeOH was added NaOH (400 mg, 10 mmol). The solution was heated to reflux for 1 hour and cooled down to room temperature. The reaction was neutralized with 2N HCl and extracted with Et\(_2\)O. The combined extracts were washed with water, dried (Na\(_2\)SO\(_4\)), filtered and concentrated. Recrystallization from Et\(_2\)O gave Compound 66 (810mg, 95%) as a white solid.

\( ^1H \text{NMR (300 MHz, CDCl}_3 \delta 7.71 \text{ (1H), 7.69 (d, J = 8.0 Hz, 1H), 7.43-7.34 \text{ (m, 2H), 6.78 (t, J = 8.2Hz, 2H).} \)}
MS (ESI) [M+H⁺]: 429.

**Compound 67:**
2,6-Difluoro-N-(4-formyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide

Into a solution of Compound 39 (100 mg, 0.24 mmol) in 2 mL of CH₂Cl₂ was added Dess-Martin periodinane (127 mg, 0.3 mmol) at 0 °C. The solution was stirred at 0 °C for 1 hour and warmed to room temperature. The reaction was concentrated. The residue was purified by column chromatography on silica gel (1-5% MeOH in CH₂Cl₂) to give Compound 67 (93 mg, 94%) as a white solid.

**¹H NMR (300 MHz, CDCl₃)** δ 9.72 (s, 1H), 7.80 (s, 1H), 7.80-7.64 (m, 3H), 7.52 (m, 1H), 7.05 (t, J = 8.2 Hz, 2H).

MS (ESI) [M+H⁺]: 413.

**Compound 68:** 2,6-Difluoro-N-(4-(2-hydroxypropan-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide

Into a solution of Compound 35 (100 mg, 0.24 mmol) in 5 mL of Et₂O was added dropwise MeMgBr (1.0 M solution in THF, 1.2 mL) at 0°C. The mixture was stirred at room temperature for 1 hour and quenched with 10 mL of H₂O. The solution was extracted with Et₂O. The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (10-70% EtOAc in hexanes) to give Compound 68 (91 mg, 91%) as a white solid.

**¹H NMR (300 MHz, CDCl₃)** δ 10.5 (brs, 1H, NH), 7.68-7.45 (m, 5H), 7.02 (t, J = 8.2 Hz, 2H), 4.22 (brs, 1H, OH), 1.33 (s, 6H).

MS (ESI) [M+H⁺]: 443.

**Compound 68a:** 2,6-difluoro-N-(4-(prop-1-en-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide

Into a solution of Compound 68 (22 mg, 0.05 mmol) in 5 mL of toluene was added dropwise of 0.2 mL of TFA. The mixture was heated to reflux for 30 minutes. After cooled down to room temperature, the reaction was
concentrated. The residue was purified by column chromatography on silica
gel (10-20% EtOAc in hexanes) to give Compound 68a (20 mg, 95%) as a
white solid.

\[^{1}H\ NMR\ (300\ MHz,\ CDCl\_3)\ \delta\ 7.72\ (s,\ 1H),\ 7.65-7.40\ (m,\ 4H),\ 7.00\ (t,\ J = 8.0\ Hz,
2H),\ 5.08\ (brs,\ 1H),\ 5.06\ (t,\ 1H),\ 1.85\ (s,\ 3H)\]

MS (ESI) [M+H\(^{+}\)]: 425.

**Compound 69**: 2,6-Difluoro-N-(4-isopropyl-5-(3-(trifluoromethyl)phenyl)
thiazol-2-yl)benzamide

Into a solution of Compound 68a (63.6 mg, 0.15 mmol) in EtOAc (2.0 mL) was
added 5% Pd/C (50 mg). The mixture was stirred at room temperature under
1 atmosphere of hydrogen for 2 hours. The mixture was filtered through a short
plug of silica, the filtrate was concentrated, the residue was purified by column
chromatography on silica gel (eluted with 10-70% ethyl acetate in hexanes) to
give Compound 69 (46 mg, 72%) as a white solid.

\[^{1}H\ NMR\ (300\ MHz,\ CDCl\_3)\ \delta\ 7.61\ (1H,\ s),\ 7.63-7.46\ (m,\ 4H),\ 7.06\ (t,\ J = 8.0\ Hz,
2H),\ 3.13\ (m,\ 1H),\ 1.26\ (d,\ J = 6.9\ Hz,\ 6H)\]

MS (ESI) [M+H\(^{+}\)]: 427.

**Compound 70**: N-(4-(Chloromethyl)-5-(3-(trifluoromethyl)phenyl)
thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 39 (123 mg, 0.3 mmol) in 5 mL of CH\(_2\)Cl\(_2\) was
added SOCl\(_2\) (0.4 mmol) and NEt\(_3\) (0.5 mmol) at room temperature. The
solution was stirred at room temperature for 2 hours. The solution was treated
with 10 mL of water and extracted with CH\(_2\)Cl\(_2\). The combined extracts were
washed with water, dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was
purified on silica (eluted with 5-50% ethyl acetate in hexane) to give Compound
70 (114 mg, 88%) as a white solid.
1H NMR (300 MHz, CDCl₃) δ 9.60 (brs, 1H), 7.79 (s, 1H), 7.75-7.59 (m, 3H), 7.57-7.48 (m, 1H), 7.04 (t, J = 8.5 Hz, 2H), 4.54 (s, 2H).
MS (ESI) [M+H⁺]: 433.

**Compound 71**: N-(4-((Dimethylamino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 70 (50 mg, 0.12 mmol) in 5 mL of THF was added NH(Me)₂ (40% solution in water, 0.1 mL) and NEt₃ (0.1 mL) at room temperature. The solution was stirred at room temperature for 1 hour. The solution was washed with 5 mL of water and dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with 5-100% ethyl acetate in hexane) to give Compound 71 (44 mg, 84%) as a white solid.

1H NMR (300 MHz, CDCl₃) δ 7.91 (s, 1H), 7.71-7.45 (m, 4H), 7.04 (t, J = 8.5 Hz, 2H), 3.38 (s, 2H), 2.24 (s, 6H).
MS (ESI) [M+H⁺]: 442.

**Compound 72**: (Z)-2,6-difluoro-N-(4-((hydroxyimino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

Into a solution of Compound 67 (180 mg, 0.44 mmol) in 3 mL of EtOH was added hydroxylamine hydrochloride (60 mg, 0.9 mmol) and pyridine (0.5 mL). The solution was stirred at room temperature for 2 hours. The reaction was diluted with 20 mL of CH₂Cl₂ and the solution was washed with 10 mL of water and dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with 5-100% ethyl acetate in hexane) to give Compound 72 (98 mg, 52%) as a white solid.

1H NMR (300 MHz, CDCl₃) δ 8.02 (brs, 1H), 7.71-7.54 (m, 4H), 7.35-7.25 (m, 1H), 6.78 (t, J = 8.0 Hz, 2H).
MS (ESI) [M+H⁺]: 428.

**Compound 73**: N-(4-Cyano-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 72 (90 mg, 0.21 mmol) in 10 mL of CH₂Cl₂ was
added 2-chloro-1-methylpyridium iodide (128 mg, 0.5 mmol) and NEt₃ (0.1 mL). The solution was stirred at room temperature for 2.5 hours. The solution was washed with saturated NH₄Cl, dried (Na₂SO₄) and concentrated. The residue was purified on silica (eluted with 1% MeOH in CH₂Cl₂) to give Compound 73 (74 mg, 86%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 9.59 (brs, 1H, NH), 7.98 (d, J = 7.7 Hz, 1H), 7.96 (s, 1H), 7.75-7.53 (m, 3H), 7.11 (t, J = 8.5 Hz, 2H).
MS (ESI) [M+H⁺]: 410.

**Compound 74**: 2,6-Difluoro-N-(4-(1-hydroxyethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

Compound 74 was prepared from Compound 67 and MeMgBr similarly as described for the preparation of Compound 68.

¹H NMR (300 MHz, CDCl₃) δ 9.90 (brs, 1H, NH), 7.68-7.54 (m, 4H), 7.53-7.44 (m, 1H), 7.02 (t, J = 8.2 Hz, 2H), 4.91 (q, J = 6.6 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H).
MS (ESI) [M+H⁺]: 429.

**Compound 75**: 2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-vinylthiazol-2-yl)benzamide

Compound 75 was prepared from Compound 74 similarly as described for the preparation of Compound 68a.

¹H NMR (300 MHz, CDCl₃) δ 7.70 (s, 1H), 7.65-7.44 (m, 4H), 7.05 (t, J = 8.0 Hz, 2H), 6.61 (dd, J = 10.7, 17.0 Hz, 1H), 6.02 (dd, J = 1.7, 17.0 Hz, 1H), 5.36 (dd, J = 1.7, 10.7 Hz, 1H).
MS (ESI) [M+H⁺]: 411.

**Compound 76**: 2,6-Difluoro-N-(4-(oxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

Into a solution of Compound 67 (62 mg, 0.15 mmol) in 5 mL of dry methanol
was added tosyilmethyl isocyanide (35 mg, 0.18 mmol), followed by dry potassium carbonate (25 mg, 0.18 mmol). The reaction mixture was heated to 65 °C for 2 hours. The reaction mixture was dissolved in ethyl acetate, washed each with water and brine; dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-50% ethyl acetate in hexanes) to give Compound 76 (49 mg, 72%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 10.97 (brs, 1H, NH), 7.74-7.51 (m, 4H), 7.73 (s, 1H), 7.46 (m, 1H), 7.16 (s, 1H), 6.99 (t, J = 8.2 Hz, 2H).

MS (ESI) [M+H⁺]: 452.

**Compound 77**: N-(4-(4,5-Dihydro-1H-imidazol-2-yl)-1,5-difluorobenzamide phenyl)thiazol-2-yl)-2,6-difluorobenzamide

To the solution of aldehyde Compound 67 (206 mg, 0.5 mmol) in 10 mL of dried CH₂Cl₂ was added ethylenediamine (0.55 mmol). The mixture was stirred at 0 °C for 20 min, and NBS (100 mg, 0.55 mmol) was added to the mixture and the resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was treated with 10% NaOH aq. solution. The mixture was extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 5-15% MeOH in CH₂Cl₂) to give the free base. Treatment with HCl in Et₂O gave Compound 77 (165 mg, 73%) as a white solid.

MS (ESI) [M+H⁺]: 453.

**Compound 78**: N-(4-(1H-Imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide hydrochloride

Into a solution of aldehyde Compound 67 (412 mg, 1 mmol) in 2 mL of MeOH at 0 °C was added a solution of 40% glyoxal in water (0.2 mL) and ammonium hydroxide (2.0 M in MeOH, 3 mL). The reaction mixture was stirred for 30 minutes at 0 °C and then at room temperature overnight. The reaction mixture was concentrated and the residue was purified by column chromatography on basic Al₂O₃ (eluted with
ethyl acetate) to give a colorless solid. Treatment with HCl in Et₂O gave the salt Compound 78 (242 mg, 50%) as a white solid. MS (ESI) [M+H⁺]: 451.

**Compound 79:** 2,6-Difluoro-N-(4-(4-methyloxazol-5-yl)-5-(3-(trifluoromethyl phenyl)thiazol-2-yl)benzamide

Compound 79 was prepared from Compound 67 similarly as described for the preparation of Compound 76 using 1-methyl-1-tosylethylisocyanide MS (ESI) [M+H⁺]: 482.

**Compound 80:** 2,6-Difluoro-N-(4-(1-methyl-1H-imidazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

Into a solution of Compound 67 (206 mg, 0.5 mmol) and MeNH₂ (2.0 M in MeOH, 1.25 mL) in 10 mL of EtOH was added HOAc (0.15 mL). The solution was heated under reflux for 2 hours, cooled to room temperature. The solution was treated with tosylmethyl isocyanide (0.75 mmol) and K₂CO₃ (2 mmol). The mixture was stirred under reflux for 2 hours. The reaction mixture was concentrated and partitioned between ethyl acetate and 1 N NaOH aq. solution. The organic phase was washed with water, dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel (eluted with MeOH in CH₂Cl₂) to give Compound 80 (125 mg, 54%) as a yellow solid.

^1H NMR (300 MHz, CDCl₃) δ 7.60-7.53 (m, 2H), 7.51-7.43 (m, 4H), 7.03 (t, J = 8.2 Hz, 2H), 6.88 (s, 1H), 3.50 (s, 3H).

**MS (ESI) [M+H⁺]:** 465.

**Compound 81:** N-(4-(2,4-dimethyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of the aldehyde Compound 67 (123 mg, 0.3 mmol) in 1.5 mL of pyridine was added 2-acetamidoacrylic acid (65 mg, 0.5 mmol). The solution was heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up with CH₂Cl₂, washed with a solution of saturated NH₄Cl and brine, dried (Na₂SO₄), filtered and
concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-100% ethyl acetate in hexane) to give Compound 81 (103 mg, 72%) as a yellow solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.3 (brs, 1H, NH), 7.67 (s, 1H), 7.60 (d, $J$ = 7.8 Hz, 1H), 7.58 (d, $J$ = 7.8 Hz, 2H), 7.50 (t, $J$ = 7.8 Hz, 1H), 7.49 (m, 1H), 7.04 (t, $J$ = 8.3 Hz, 2H), 2.36 (s, 3H), 1.98 (s, 3H).

MS (ESI) [M+H$^+$]: 480.

**Compound 82**: 2,6-Difluoro-N-(4-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

A solution of aldehyde Compound 67 (206 mg, 0.5 mmol), ammonium acetate (300 mg, 3 mmol) and nitroethane (2 mL) in 2 mL of HOAc was stirred under N$_2$ for 48 hours. The mixture was cooled to room temperature, basified with 1 N NaOH and extracted with Et2O. The organic phase was dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-100% ethyl acetate in hexane) to give Compound 82 (79 mg, 34%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.0 (brs, 1H, NH), 7.82 (s, 1H), 7.74 (d, $J$ = 7.7 Hz, 1H), 7.68 (d, $J$ = 7.7 Hz), 7.56 (t, $J$ = 7.7 Hz, 1H), 7.49-7.39 (m, 1H), 6.96 (t, $J$ = 8.5 Hz, 2H), 2.55 (s, 3H).

MS (ESI) [M+H$^+$]: 467.

**Compound 83**: 2,6-difluoro-N-(4-(hydroxy(pyridin-2-yl)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

To a stirred solution of 2-bromopyridine (2 mmol) in 10 mL of anhydrous THF was added n-BuLi (2.0 M in hexane, 1.1 mL) at -78°C under N$_2$. After 5 minutes, the reaction was treated with the solution of aldehyde Compound 67 (62 mg, 0.15 mmol) in 2 mL of THF. The mixture was stirred at -78°C for 30 minutes and warmed to room temperature over 1 hour. The reaction was quenched with water and extracted with ether. The organic phase was dried
(Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-100% ethyl acetate in hexanes) to give Compound 83 (57 mg, 77%) as a white solid.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 10.2 \text{ (brs, 1H, NH)}, 8.49 \text{ (d, } J = 5.0 \text{ Hz, 1H)}, 7.90 \text{ (s, 1H)}, 7.85 \text{ (d, } J = 7.4 \text{ Hz, 1H)}, 7.67-7.38 \text{ (m, 5H)}, 7.19-7.10 \text{ (m, 2H)}, 6.98 \text{ (t, } J = 8.2 \text{ Hz, 2H)}, 5.86 \text{ (s, 1H)}. \]

MS (ESI) [M+H⁺]: 492.

10 Compound 84: N-(4-Acetyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

To the solution of Compound 74 (22 mg, 0.05 mmol) in CH₂Cl₂ (2 mL) was added Dess-Martin periodinate (22 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The solvent was removed and the residue was purified by column chromatography on silica gel (eluted with 10-70% ethyl acetate in hexanes) gave Compound 84 (17.5 mg, 82%) as a white solid.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 7.82 \text{ (s, 1H)}, 7.75 \text{ (d, } J = 7.7 \text{ Hz, 1H)}, 7.68 \text{ (d, } J = 7.7 \text{ Hz, 1H)}, 7.57-7.52 \text{ (m, 2H)}, 7.08 \text{ (t, } J = 8.5 \text{ Hz, 2H)}, 2.53 \text{ (s, 3H)}. \]

MS (ESI) [M+H⁺]: 452.

Compound 85: N-(4-(2-Bromoacetyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 84 (132 mg, 0.33 mmol) in THF (10 mL) at 0°C was added phenyltrimethylammonium tribromide (125 mg, 0.33 mmol). The mixture was stirred at 0°C for 1 hour, quenched by ice addition, extracted with methylene chloride. The combined extracted was dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride) to give Compound 85 (128 mg, 85%) as a white solid.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 10.90 \text{ (brs, 1H, NH)}, 7.83 \text{ (s, 1H)}, 7.79 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 7.68 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 7.56 \text{ (t, } J = 8.0 \text{ Hz, 1H)}, 5.8-7.48 \text{ (m, 1H)}, 7.06 \]
(t, J = 8.5 Hz, 1H), 4.57 (s, 2H).
MS (ESI) [M+H⁺]: 507, 505.

**Compound 86:** 2,6-Difluoro-N-(2'-methyl-5-(3-(trifluoromethyl)phenyl)-
4,4'-bithiazol-2-yl)benzamide

To the solution of Compound 85 (51 mg, 0.1 mmol) in 5 mL of EtOH was added
ethanethioamide (0.2 mmol) at room temperature. The resulting solution was
stirred at room temperature for 4 hours. The solvent was removed under
reduced pressure and the residue was redissolved in ethyl acetate. The
solution was treated with saturated solution of NaHCO₃ and extracted with ethyl
acetate. The combined extracts were dried (Na₂SO₄) and concentrated.
Column chromatography on silica gel (eluted with ethyl acetate) gave
Compound 86 (41 mg, 86%) as a yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 11.1 (brs, 1H, NH), 7.68 (s, 1H), 7.58 (d, J = 8.0
Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.40 (m, 1H), 7.00 (s,
1H), 6.89 (t, J = 8.2 Hz, 2H), 2.67 (s, 3H).
MS (ESI) [M+H⁺]: 482.

**Compound 87:** N-(2'-amino-5-(3-(trifluoromethyl)phenyl)-4,4'-
bithiazol-2-yl)-2,6-difluorobenzamide

Compound 87 was prepared from Compound 85 and thiourea similarly as
described for the preparation of Compound 86.

¹H NMR (300 MHz, CDCl₃) δ 7.74 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.62 (d, J =
8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.50 (m, 1H), 7.06 (t, J = 8.3 Hz, 2H), 6.29
(s, 1H).
MS (ESI) [M+H⁺]: 483.

**Compound 88:** Ethyl 2'-(2,6-difluorobenzamido)-5'-(3-(trifluoromethyl)phenyl)-
4,4'-bithiazole-2-carboxylate

Compound 88 was prepared from Compound 85 and ethyl thiooxamate
similarly as described for the preparation of Compound 86.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.78 (s, 1H), 7.68 (d, \(J = 8.0\) Hz, 1H), 7.66 (d, \(J = 8.0\) Hz, 1H), 754 (t, \(J = 8.0\) Hz, 1H), 7.52 (s, 1H), 7.49 (m, 1H), 7.03 (t, \(J = 8.3\) Hz, 2H), 4.45 (q, \(J = 7.2\) Hz, 2H), 1.40 (t, \(J = 7.2\) Hz, 3H).

MS (ESI) [M+H\(^+\)]: 540.

**Compound 89**: N-(4-(4,5-dihydrooxazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

\[ \text{Compound 66} \rightarrow \text{69a} \rightarrow \text{Compound 89} \]

**69a** was prepared from Compound 66 by stirring in excess oxalyl chloride in methylene chloride and catalytic amount of DMF for 2 hours at room temperature. Removal of solvent and excess reagent provided **69a** in quantitative yield.

Into a solution of acid chloride **69a** (100 mg, 0.22 mmol) in 5 mL of CH\(_2\)Cl\(_2\) was added a solution of ethanolamine (153 mg, 0.25 mmol) and NEt\(_3\) (0.1 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The residue was partitioned between CH\(_2\)Cl\(_2\) and 2N HCl. The organic phase was washed with brine, dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was dissolved in 5 mL of CHCl\(_3\). Into the solution thionyl chloride (0.2 mL) was added. The mixture was heated to reflux for 1 hour, cooled and poured onto saturated NaHCO\(_3\) solution. The mixture was extracted with ether, and the organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was dissolved in 5 mL of THF. Into the solution was added NaH (60% in mineral oil, 15 mg) at room temperature. The mixture was stirred at 50°C for 30 minutes, diluted with water and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-100% ethyl acetate in hexanes).
gave Compound 89 (33mg, 32%) as yellow solid.
MS (ESI) [M+H+]: 454.

**Compound 90:** N-(4-(1,3,4-oxadiazol-2-yl)-5-(3-(trifluoromethyl)phenyl)
thiazol-2-yl)-2,6-difluorobenzamide

![Chemical Structure 69a](image)

![Chemical Structure Compound 90](image)

Into a solution of hydrazine hydrate (25 mg, 0.5 mmol) and NEt3 (0.1 mL) in 5 mL of dimethoxyethane was added acid chloride 69a (112 mg, 0.25 mmol) at 0°C. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue was taken up in 5 mL of THF. To the solution was added 0.5 mL of triethyl orthoformate. The mixture was stirred under reflux for 4 hours, cooled and concentrated. The residue was purified by column chromatography on silica gel (10-100% ethyl acetate in hexanes) to give Compound 90 (24 mg, 21%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.25 (bs, 1H, NH), 8.36 (s, 1H), 7.83 (s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.53 (m, 1H), 7.06 (t, $J = 8.3$ Hz, 2H).
MS (ESI) [M+H$^+$]: 453.

**Compound 91:** 2,6-difluoro-N-(4-(oxazol-2-yl)-5-(3-(trifluoromethyl)
phenyl)thiazol-2-yl)benzamide

![Chemical Structure 69a](image)

![Chemical Structure Compound 91](image)
Into a solution of acid chloride 69a (100 mg, 0.22 mmol) in 5 mL of sulfolane was added 1,2,3-triazole (83 mg, 0.26 mmol) and K₂CO₃ (70 mg, 0.5 mmol). The solution was stirred under N₂ at 110°C for 5 hours, cooled and concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ and water. The organic phase was dried (Na₂SO₄), concentrated under reduced pressure. Column chromatography on silica gel (10-100% ethyl acetate in hexanes) gave Compound 91 (74 mg, 73%) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 10.8 (brs, 1H, NH), 7.83 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.52 (brs, 1H), 7.45 (m, 1H), 7.11(brs, 1H), 7.96 (t, J = 8.3 Hz, 2H).

MS (ESI) [M+H⁺]: 452.

**Compound 92**: 2,6-difluoro-N-(4-(3-methyl-1,2,4-oxadiazol-5-yl)-5-(3-( trifluoromethyl)phenyl)thiazol-2-yl)benzamide

![Diagram of compound 69a and compound 92]

Into a solution of acid chloride 69a (100 mg, 0.22 mmol) in 5 mL of toluene was added acetamidoxime (100 mg, 1.35 mmol) and pyridine (0.3 mL). The solution was heated to reflux for 4 hours, cooled and concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ and water. The organic phase was dried (Na₂SO₄) and concentrated. Chromatography on silica gel (10-70% ethyl acetate in hexanes) gave Compound 92 (29 mg, 28%) as a white solid.
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.88 (s, 1H), 7.76 (d, \( J = 8.0 \) Hz, 1H), 7.74 (d, \( J = 8.0 \) Hz, 1H), 7.62 (t, \( J = 8.0 \) Hz, 1H), 7.53 (m, 1H), 7.05 (t, \( J = 8.5 \) Hz, 2H), 2.40 (s, 3H).

MS (ESI) [M+H\textsuperscript{+}]: 467.

**Compound 93**: 2-(2,6-difluorobenzamido)-N-methoxy-N-methyl-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide

Into a solution of acid chloride 69a (200 mg, 0.44 mmol) in 10 mL of CH\textsubscript{2}Cl\textsubscript{2} was added N,O-dimethylhydroxylamine hydrochloride (50 mg, 0.51 mmol) and NEt\textsubscript{3} (0.2 mL). The solution was stirred at room temperature for 10 minutes. The solution was washed with water and dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated. Recrystallization from CH\textsubscript{2}Cl\textsubscript{2} gave Compound 93 (200 mg, 95%) as a white solid.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 10.2 (brs, 1H), 7.70 (s, 1H), 7.68 (d, \( J = 8.0 \) Hz, 1H), 7.59 (d, \( J = 8.0 \) Hz, 1H), 7.51 (t, \( J = 8.0 \) Hz, 1H), 7.50 (m, 1H), 7.02 (t, \( J = 8.5 \) Hz, 2H), 3.48 (s, 3H), 3.20 (s, 3H).

MS (ESI) [M+H\textsuperscript{+}]: 472.

**Compound 94**: 2,6-difluoro-N-(4-propionyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

To the solution of Compound 93 (220 mg, 0.47 mmol) in 10 mL of anhydrous
THF was added MeMgBr (3.0 M in Et$_2$O, 0.5 mL) at −78 °C. The solution was slowly warmed to room temperature over 2 hours. The reaction mixture was treated with 10 mL of water. The mixture was extracted with Et$_2$O, the combined organic phases were dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (eluted with 10-100% ethyl acetate in hexanes) to give Compound 94 (184 mg, 83%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.60 (s, 1H, NH), 7.80 (s, 1H), 7.76 (d, $J = 7.7$ Hz, 1H), 7.67 (d, $J = 7.7$ Hz, 1H), 7.59-7.50 (m, 2H), 7.08 (t, $J = 8.5$ Hz, 2H), 2.97 (q, $J = 7.0$ Hz, 2H), 1.11 (t, $J = 7.0$ Hz, 3H).

MS (ESI) [M+H$^+$]: 441.

**Compound 95**: N-(2',5'-dimethyl-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 94 (145 mg, 0.33 mmol) in THF (10 mL) at 0 °C was added phenyltrimethylammonium tribromide (125 mg, 0.33 mmol). The mixture was stirred at 0 °C for 1 hour, quenched by ice addition, extracted with methylene chloride. The combined extracted was dried (Na$_2$SO$_4$), filtered and concentrated to give crude 75a (200 mg).

Into a solution of 75a (52 mg, 0.1 mmol) in 3 mL of EtOH was added ethanethioamide (0.2 mmol) at room temperature. The resulting solution was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue was taken up with ethyl acetate. The solution was treated with saturated solution of NaHCO$_3$ and extracted with ethyl
acetate. The combined extracts were dried (Na$_2$SO$_4$) and concentrated. Column chromatography on silica gel (eluted with 10-70% ethyl acetate in hexanes) gave Compound 95 (40 mg).

5 $^1$H NMR (300 MHz, CDCl$_3$) δ 10.40 (brs, 1H), 7.54-7.42 (m, 5H), 7.02 (t, $J = 8.5$ Hz, 2H), 2.65 (s, 3H), 1.90 (s, 3H).
MS (ESI) [M+H$^+$]: 496.

**Compound 96: Ethyl**

2'-((2,6-difluorobenzamido)-5-methyl-5'-((3-(trifluoromethyl)
phenyl)-4,4'-bithiazole-2-carboxylate

![Chemical Structure 75a](image)

Compound 96 was prepared from 75a and ethyl thiooxamate similarly as described for the preparation of Compound 95.

15 $^1$H NMR (300 MHz, CDCl$_3$) δ 9.86 (brs, 1H, NH), 7.58-7.42 (m, 5H), 7.06 (t, $J = 8.5$ Hz, 2H), 4.45 (q, $J = 7.0$ Hz, 2H), 2.12 (s, 3H), 1.41 (t, $J = 7.0$ Hz, 3H).
MS (ESI) [M+H$^+$]: 554.

**Compound 97: 2-(2,6-Difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide

![Chemical Structure 66](image)  

Compound 66

![Chemical Structure 97](image)  

Compound 97
Into a solution of Compound 66 (50.0 mg, 0.12 mmol) and DMF (2 drops) in CH₂Cl₂ (2.00 mL) at room temperature was added oxalyl chloride (0.10 mL, 1.20 mmol). The mixture was stirred at room temperature for 1 hour. The solvent and excess reagent was removed under reduced pressure. The residue was taken up CH₂Cl₂ (1.00 mL). The resulting solution was added dropwise to a solution of 2M NH₃ in MeOH at 0°C. The mixture was stirred at room temperature for 10 minutes, then concentrated. The residue was purified on silica to give the titled Compound 97 (11.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 7.81-7.75 (m, 2H), 7.60-7.43 (m, 2H). 6.94 (dd, J = 8, 8 Hz, 2H).
MS (ESI) [M+H⁺]: 428

**Compound 98:** N-(2,2-diethoxyethyl)-2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide

![Image of Compound 66 and Compound 98](image)

Compound 98 was prepared as described for the preparation of Compound 97 using the corresponding amine.
MS (ESI) [M+H⁺]: 544

**Compound 99:** 2,6-Difluoro-N-(4-propionyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide
Into a solution of Compound 93 (175 mg, 0.37 mmol) in THF (1.0 mL) at room temperature was added a solution of 0.5M lithium acetylide (2.0 mL, 1.0 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was cooled to 0°C. Ice was added. The mixture was acidified by 6N HCl, stirred at 0°C for 1 hour, neutralized with a solution of saturated NaHCO₃, extracted with CH₂Cl₂ (2X). The combined extracts were dried (Na₂SO₄), filtered and concentrated to give the crude Compound 99 (141 mg).

MS (ESI) [M+H⁺]: 437

**Compound 100**: N-(4-(1H-Pyrazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of crude Compound 99 (70 mg) in ethanol (1.0 mL) was added hydrazine monohydrate (2 drops). The mixture was stirred at room temperature for 2 hours, diluted with CH₂Cl₂, washed with water (3X), dried
(Na₂SO₄), filtered and concentrated. With CH₂Cl₂ volume reduction, precipitation was observed. Compound 100 (45 mg) was collected by filtration.

³¹H NMR (300 MHz, CDCl₃) δ 7.80 (s, 1H), 7.75-7.68 (m, 2H), 7.62 (d, J = 8.1 Hz, 1H), 7.58-7.46 (m, 1H), 7.07 (dd, J = 8, 8 Hz, 2H), 6.91 (d, J = 2, 1H), 5.87 (d, J = 2 Hz, 1H).

MS (ESI) [M+H⁺]: 451

**Compound 101**: 2,6-Difluoro-N-(4-(1-methyl-1H-pyrazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

![Compound 99](image1)

![Compound 101](image2)

Into a solution of crude Compound 99 (70 mg) in ethanol (1.0 mL) was added methylhydrazine (23 mg, 0.50 mmol). The mixture was stirred at room temperature for 2 hours, diluted with CH₂Cl₂, washed with water (2X), dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give Compound 101 (38 mg) as a 4:1 isomeric mixture.

³¹H NMR (300 MHz, CDCl₃) δ 7.67-7.00 (m, 7H), 6.16 (bs, 1H), 3.72 (s, 3H).

MS (ESI) [M+H⁺]: 465

**Compound 102**: N-(4-amino-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide
Into a solution of Compound 66 (500 mg, 1.17 mmol), t-BuOH (173 mg, 2.37 mmol) and triethylamine (355 mg, 3.51 mmol) in THF (6.0 mL) at room temperature was added diphenylphosphorylazide (644 mg, 2.34 mmol). The mixture was heated to 60°C overnight. The mixture was cooled to room temperature, diluted with CH$_2$Cl$_2$, washed with a solution of saturated NaHCO$_3$, dried (Na$_2$SO$_4$), filtered and concentrated. The residue was taken up in a 1:1 mixture of CH$_2$Cl$_2$ and TFA (5.0 mL). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was taken up in CH$_2$Cl$_2$, washed with a solution of saturated NaHCO$_3$, dried (Na$_2$SO$_4$), filtered and concentrated. The residue was purified on silica to give the titled Compound 102 (280 mg).

MS (ESI) [M+H$^+$]: 400

**Compound 103**: N-(4-Chloro-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a suspension of Compound 102 (40.0 mg, 0.10 mmol) and Cu powder
(40.0 mg, 0.68 mmol) at 0°C was added slowly NaNO₂ (40.0 mg, 0.58 mmol). The mixture was stirred at 0°C for 1 hour then gradually warmed to room temperature then heated to 60°C overnight. Ice was added. The resulting mixture was extracted with CH₂Cl₂ (2X). The combined extracts were washed with a solution of saturated NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give the Compound 103 (12.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 10.06 (s, 1H), 7.92 (s, 1H), 7.83 (d, J = 7.5, 1H), 7.65-7.50 (m, 3H), 7.07 (dd, J = 8.7, 8.7 Hz, 2H).
MS (ESI) [M+H⁺]: 419

**Compound 104:** N-(4-ethynyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Into a solution of Compound 67 (50.0 mg, 0.12 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (46.0 mg, 0.24 mmol) in MeOH (1.00 mL) was added K₂CO₃ (50.0 mg, 0.36 mmol) was added. The mixture was stirred at room temperature overnight, diluted with CH₂Cl₂, washed with water, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give Compound 104 (10.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 8.12 (s, 1H), 7.96 (d, J = 7.6, 1H), 7.66-7.43 (m, 3H), 7.04 (dd, J = 8, 8 Hz, 2H), 3.26 (s, 1H).
MS (ESI) [M+H⁺]: 409
Compound 105:
2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-(5-(trimethylsilyl)isoxazol-3-yl)thiazol-2-yl)benzamide

Into a solution of Compound 67 (206 mg, 0.50mmol) in 2-propanol (1.0mL) was added hydroxylamine hydrochloride (35 mg, 0.50mmol). Water was added (4 drops). The mixture was heated to 80°C for 1 hour, cooled to room temperature, concentrated under reduced pressure. The residue was taken up in ethyl acetate (4.0mL). The mixture was cooled to 0°C. Into the mixture, water (4 drops), NaHCO₃ (84 mg, 1.0 mmol), trimethylsilyl acetylene (0.50mL, 3.60 mmol), and N-chlorosuccinimide (134 mg, 1.00 mmol) were added sequentially. The mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with water then with brine, and dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give Compound 105 (110 mg).

¹H NMR (300 MHz, CDCl₃) δ 7.77-7.48 (m, 5H), 7.02 (dd, J = 8, 8 Hz, 2H), 6.39 (s, 1H), 0.29 (s, 9H).

MS (ESI) [M+H⁺]: 524

Compound 106: 2,6-Difluoro-N-(4-(isoxazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide
Into a solution of Compound 105 (55.0 mg, 0.10 mmol) in ethanol (2.0 mL) at room temperature was added cesium fluoride (152 mg, 1.0 mmol). The mixture was stirred at room temperature for 1 hour, diluted with CH$_2$Cl$_2$, washed with water (2X), dried (Na$_2$SO$_4$), filtered and concentrated. The residue was purified on silica to give Compound 106 (39 mg).

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.33 (bs, 1H), 7.77-7.45 (m, 5H), 7.02 (dd, $J = 8.4, 9.0$ Hz, 2H), 6.23 (s, 1H).

MS (ESI) [M+H$^+$]: 452

**Compound 107**: 2,6-Difluoro-N-(4-(pyridin-2-yl)-5-(3-(trifluoromethyl)phenyl) thiazol-2-yl)benzamide
Into a solution of 2-bromopyridine (1.58g, 10.0 mmol) in THF (20.0 mL) at -78°C was added dropwise a solution of 1.6M n-BuLi (6.25 mL, 10.0 mmol). The mixture was stirred at -78°C for 30 minutes. Into the reaction mixture, a solution of 22a (1.00g, 4.05 mmol) in THF (10.0 mL) was added. The mixture was stirred at 0°C for 1 hour then at room temperature for 30 minutes. The mixture was poured over ice. The resulting solution was acidified with 6N HCl, stirred at 0°C for 1 hour, neutralized with a solution of saturated NaHCO₃, extracted with CH₂Cl₂. The extract was dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give 87a (475 mg). MS (ESI) [M+H⁺]: 266

Into a solution of 87a (475 mg, 1.79 mmol) in CH₂Cl₂ (20.0 mL) at 0°C was added Br₂ (288 mg, 1.80 mmol). The mixture was stirred at 0°C for 30 minutes then at room temperature for 2 hours. The solvent and excess reagent was removed under reduced pressure. The residue was taken up in ethanol (10.0
mL). Thiourea (304 mg, 4.00 mmol) was added. The mixture was stirred at room temperature overnight. Ethanol was removed under reduced pressure. The residue was neutralized with a solution of saturated NaHCO$_3$, extracted with CH$_2$Cl$_2$. The extract was dried (Na$_2$SO$_4$), filtered and concentrated. The residue was purified on silica to give 87b (450 mg).

MS (ESI) [M+H$^+$]: 322

Compound 107 was prepared from 87b as described for the preparation of Compound 9.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.53 (bs, 1H), 7.65 (s, 1H), 7.62-7.55 (m, 3H), 7.48-7.37 (m, 3H), 7.20-7.16 (m, 1H), 7.01-6.92 (m, 2H).

MS (ESI) [M+H$^+$]: 462

**Compound 108**: 2,6-Difluoro-N-(4-(6-methylpyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide

![Chemical Structure of Compound 108]

Compound 108 was prepared from 22a and 2-bromo-6-methylpyridine as described for the preparation of Compound 107.

MS (ESI) [M+H$^+$]: 476

**Compound 109**: N-(4-(3,4-Dimethoxyphenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

- 152 -
Compound 109 was prepared from 22a and 3,4-dimethoxyphenylimagnesium bromide as described for the preparation of Compound 107.

MS (ESI) [M+H⁺]: 521

**Compound 110**: N-(4-(4-(Dimethylamino)phenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide

Compound 110 was prepared from 22a and N,N-dimethyl-4-aminophenylimagnesium bromide as described for the preparation of Compound 107.

MS (ESI) [M+H⁺]: 504
Compound 111: Methyl 2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl) thiazole-4-carboxylate hydrochloride

A solution of Compound 36 (21 mg, 0.05 mmol) in 1 mL of Et₂O was treated with 0.1 mL of 2M HCl in Et₂O. The precipitate formed was collected, washed with Et₂O and dried to give Compound 111 (20 mg) as a white solid.

\(^1\)H NMR (300 MHz, CDCl₃ + CD₃OD) δ 8.87 (s, 1H), 8.88 (d, J = 6.1 Hz, 1H), 8.12 (d, J = 6.1 Hz, 1H), 7.79-7.41 (m, 4H), 3.79 (s, 3H), 2.71 (s, 3H).
MS (ESI) [M+H\(^+\)]: 422.

Compound 112: 2-(3-Methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl) thiazole-4-carboxylic acid

Compound 112 was prepared from Compound 111 by hydrolysis similarly as described for the preparation of Compound 66.

\(^1\)H NMR (300 MHz, CD₃OD) δ 8.59-8.56 (m, 2H), 7.88-7.61 (m, 5H), 2.50 (s, 3H).
MS (ESI) [M+H\(^+\)]: 408.
Compound 113: Methyl 2-(2,6-difluorobenzamido)-5-(3-methoxyphenyl) thiazole-4-carboxylate

Compound 113 was prepared as from 3-methoxybenzaldehyde as described for the preparation of Compound 63.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 11.3 \text{ (brs, 1H, NH), 7.45 (m, 1H), 7.34 (t, } J = 8.0 \text{ Hz, 1H), 7.08-6.90 (m, 5H), 3.81 (s, 3H), 3.64 (s, 3H).} \]

MS (ESI) [M+H\(^{+}\)]: 405.

Compound 114: Methyl 2-(2,6-difluorobenzamido)-5-(3-(methoxycarbonyl) phenyl)thiazole-4-carboxylate

Compound 114 was prepared as from methyl 3-formylbenzoate as described for the preparation of Compound 63.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 11.0 \text{ (brs, 1H, NH), 8.19 (s, 1H), 8.10 (d, } J = 7.8 \text{ Hz, 1H), 7.70 (d, } J = 8.0 \text{ Hz, 1H), 7.55-7.45 (m, 2H), 7.02 (t, } J = 8.0 \text{ Hz, 2H), 3.94 (s, 3H), 3.71 (s, 3H).} \]

MS (ESI) [M+H\(^{+}\)]: 433.

N-(5-Acetyl-4-methylthiazol-2-yl)-2,6-difluorobenzamide

\[
\begin{align*}
\text{CON} & + \text{H}_2\text{N-S} & \text{CON} \\
\text{O} & \text{O} & \text{S} & \text{N} & \text{N} \\
\text{F} & \text{F} & \text{F} & \text{F} & \text{F} \\
\text{Cl} & \text{CON} & \text{CON} & \text{CON} & \text{CON} \\
\end{align*}
\]

The solution of 3-chloro-2,4-pentanedione (670 mg, 4.88 mmol), N-carbamothioyl-2,6-difluorobenzamide (1.08 g, 5.0 mmol) and K\(_2\)CO\(_3\) (0.8 g) in 20 mL of MeOH was stirred at reflux for 5 hours. The reaction was cooled to room temperature, and concentrated under reduced pressure. The residue was taken up with EtOAc. The solution was washed with water, dried (Na\(_2\)SO\(_4\)), filtered and concentrated. Purification on silica gel gave N-(5-Acetyl-4-methylthiazol-2-yl)-2,6-difluorobenzamide (1.0 g, 71%) as a white solid.
\(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 9.86 (\text{brs}, 1\text{H}, \text{NH}), 7.58-7.42 (\text{m}, 5\text{H}), 7.06 (\text{t}, J = 8.5 \text{ Hz}, 2\text{H}), 4.45 (\text{q}, J = 7.0 \text{ Hz}, 2\text{H}), 2.12 (\text{s}, 3\text{H}), 1.41 (\text{t}, J = 7.0 \text{ Hz}, 3\text{H}). \text{MS (ESI) [M+H]}^+\): 297.

**Compound 114a:** Ethyl 2'-\((2,6\text{-difluorobenzamido})\)-4'-methyl-4,5'-bithiazole-2-carboxylate

\[
\begin{align*}
\text{95} & \quad \text{Br} \quad \text{96a} \quad \text{EtO}_2\text{C} \\
\text{O} & \quad \text{N} & \quad \text{F} & \quad \text{Br} & \quad \text{N} & \quad \text{O} & \quad \text{F} & \quad \text{Compound 114a}
\end{align*}
\]

Into a solution of N-(5-Acetyl-4-methylthiazol-2-yl)-2,6-difluorobenzamide (132 mg, 0.33 mmol) in THF (10 mL) at 0 \text{°C} was added phenyltrimethylammonium tribromide (125 mg, 0.33 mmol). The mixture was stirred at 0 \text{°C} for 1 hour, quenched by ice addition, extracted with methylene chloride. The extract was dried (Na\text{$_2$}SO\text{$_4$}), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride) to give 96a (100 mg, 80%) as a white solid. \text{MS (ESI) [M+H]}^+\): 377, 375.

Into the solution of 96a (76 mg, 0.2 mmol) in 5 mL of EtOH was added ethyl thiooxamate (53 mg, 0.4 mmol) at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluted with 10-70% ethyl acetate in hexanes) to give Compound 114a (49 mg, 60%) as a yellow solid.

\(^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 11.5 (\text{brs}, 1\text{H}, \text{NH}), 7.46 (\text{s}, 1\text{H}), 7.45 (\text{m}, 1\text{H}), 6.97 (\text{t}, J = 8.5 \text{ Hz}, 2\text{H}), 4.49 (\text{q}, J = 7.2 \text{ Hz}, 2\text{H}), 2.16 (\text{s}, 3\text{H}), 1.46 (\text{t}, J = 7.2 \text{ Hz}, 3\text{H}). \text{MS (ESI) [M+H]}^+\): 410.

**Compound 114b:** N-(2,4'-Dimethyl-4,5'-bithiazol-2'-yl)-2,6-
difluorobenzamid

\[
\begin{array}{c}
\text{Br} \\
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{F}
\end{array} \\
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{H}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{F}
\end{array}
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\rightarrow
\begin{array}{c}
\text{N} \\
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\text{F}
\end{array} \\
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{H}
\end{array} \\
\begin{array}{c}
\text{F}
\end{array}
\]

\text{Compound 114b}

To the solution of 96a (38 mg, 0.1 mmol) in 3 mL of EtOH was added ethanethioamide (15 mg, 0.2 mmol) at room temperature. The resulting solution was stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate. The solution was washed with NaHCO₃, dried (Na₂SO₄) and concentrated. Column chromatography on silica gel (eluted with 10-70% ethyl acetate in hexanes) gave Compound 114b (20 mg).

\(^1\text{H NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 7.50-7.40 (m, 1H), 7.02 (s, 1H), 6.96 (t, J = 8.5 \text{ Hz}, 2H), 2.75 (s, 3H), 2.12 (s, 3H).
\]
\[
\text{MS (ESI)} \ [\text{M+H}^+] : 352.
\]

**Compound 115**: N-(2,6-Difluorobenzyl)-4-methyl-5-(3-(trifluoromethyl)phenyl) thiazol-2-amine

\[
\begin{array}{c}
\text{CF}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{CF}_3
\end{array}
\]

Into solution of Compound 9 (75.0 mg, 0.19 mmol) at room temperature was added a solution of 1.0M borane-dimethylsulfide complex in THF (1.0 mL, 1.0 mmol). The mixture was heated to 60°C overnight, cooled to room temperature, quenched by addition of water, extracted with CH₂Cl₂. The extracts were dried (Na₂SO₄), filtered and concentrated. The residue was
purified on silica to give Compound 115 (25.0 mg).
MS (ESI) [M+H]+: 385

**Compound 116:** N-(2,6-difluorophenyl)-4-methyl-5-(3-(oxazol-2-yl)phenyl) thiazole-2-carboxamide

\[^1\text{H-NMR (CDCl}_3\text{) }\delta\text{ (ppm)}\] 8.6 (br, 1H), 8.17 (s, 1H), 8.1 (m, 1H), 7.76 (s, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 7.0 (t, 2H, J=8), 2.60 (s, 3H); ESMS clcd for C\text{\textsubscript{20}}H\text{\textsubscript{13}}F\text{\textsubscript{2}}N\text{\textsubscript{2}}O\text{\textsubscript{3}}S: 397.1; Found: 398.2 (M+H)+.

**Compound 117:** methyl 3-(2-(2,6-difluorophenylcarbamoyl)-4-methylthiazol-5-yl) benzoate

\[^1\text{H-NMR (CDCl}_3\text{) }\delta\text{ (ppm)}\] 8.6 (br, 1H), 8.1 (m, 2H), 7.6 (m, 2H), 7.3 (m, 1H), 7.0 (t, 2H, J=8), 3.96 (s, 3H), 2.57 (s, 3H); ESMS clcd for C\text{\textsubscript{19}}H\text{\textsubscript{14}}F\text{\textsubscript{2}}N\text{\textsubscript{2}}O\text{\textsubscript{3}}S: 388.1; Found: 389.1 (M+H)+.

**Compound 118:** 5-(3-(1,3,4-oxadiazol-2-yl)phenyl))-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide

\[^1\text{H-NMR (CDCl}_3\text{) }\delta\text{ (ppm)}\] 8.6 (br, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 8.1 (m, 1H), 7.6 (m, 2H), 7.3 (m, 1H), 7.0 (t, 2H, J=8), 2.60 (s, 3H); ESMS clcd for C\text{\textsubscript{19}}H\text{\textsubscript{12}}F\text{\textsubscript{2}}N\text{\textsubscript{3}}O\text{\textsubscript{2}}S: 398.1; Found: 399.1 (M+H)+.

**Compound 119:**
5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide

\[^1\text{H-NMR (CDCl}_3\text{) }\delta\text{ (ppm)}\] 8.6 (br, 1H), 7.7 (m, 3H), 7.3 (m, 1H), 7.0 (t, 2H, J=8), 2.38 (s, 3H); ESMS clcd for C\text{\textsubscript{19}}H\text{\textsubscript{10}}ClF\text{\textsubscript{5}}N\text{\textsubscript{2}}OS: 432.0; Found: 433.1 (M+H)+.

**Compound 120:** 4-methyl-N-(3-methylpyridin-4-yl)-5-(3-(trifluoromethyl)phenyl)
thiazole-2-carboxamide

\(^1\)H-NMR (CDCl\(_3\)) δ (ppm) 9.1 (br, 1H), 8.5 (d, 1H, J=5), 8.43 (s, 1H), 8.3 (d, 1H, J=5), 7.7 (m, 2H), 7.5 (m, 2H), 2.54 (s, 3H), 2.38 (s, 3H); ESMS clcd for C\(_{18}\)H\(_{14}\)F\(_3\)N\(_2\)OS: 377.1; Found: 378.2 (M+H\(^+\)).

Compound 121:
N-(2,6-difluorophenyl)-2-(2-methyl-5-(oxazol-2-yl)phenyl)thiazole-5-carboxamide

\(^1\)H-NMR (CDCl\(_3\)) δ (ppm) 8.4 (m, 2H), 8.1 (d, 1H, J=8), 7.74 (s, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 7.0 (t, 2H, J=8), 2.67 (s, 3H); ESMS clcd for C\(_{20}\)H\(_{13}\)F\(_2\)N\(_2\)O\(_2\)S: 397.1; Found: 398.2 (M+H\(^+\)).

Compound 122: N-(2,6-difluorophenyl)-2-(2-methyl-5-(thiazol-2-yl)phenyl)

thiazole-5-carboxamide

\(^1\)H-NMR (CDCl\(_3\)) δ (ppm) 8.45 (s, 1H), 8.0 (d, 1H, J=2), 8.0 (m, 1H), 7.9 (d, 1H, J=3), 7.3-7.4 (m, 4H), 7.0 (t, 2H, J=8), 2.67 (s, 3H); ESMS clcd for C\(_{20}\)H\(_{13}\)F\(_2\)N\(_2\)OS\(_2\): 413.1; Found: 414.1 (M+H\(^+\)).

Compound 123: N-(2,6-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)

thiazole-5-carboxamide

\(^1\)H-NMR (CDCl\(_3\)) δ (ppm) 8.38 (s, 1H), 8.29 (s, 1H), 8.1 (d, 1H, J=8), 7.8 (d, 1H, J=8), 7.6 (m, 1H), 7.4 (br, 1H), 7.3 (m, 1H), 7.0 (t, 2H, J=8); ESMS clcd for C\(_{17}\)H\(_{9}\)F\(_3\)N\(_2\)OS: 384.0; Found: 385.1 (M+H\(^+\)).

Compound 124: N-(2,6-difluorophenyl)-2-(3-(oxazol-2-yl)phenyl)thiazole-

5-carboxamide

\(^1\)H-NMR (CDCl\(_3\)) δ (ppm) 8.6 (m, 1H), 8.40 (s, 1H), 8.2 (m, 1H), 8.1 (m, 1H), 7.78 (s; 1H), 7.6 (t, 1H, J=8), 7.4 (br, 1H), 7.3 (m, 2H), 7.0 (t, 2H, J=8); ESMS clcd for C\(_{19}\)H\(_{11}\)F\(_2\)N\(_2\)O\(_2\)S: 383.1; Found: 384.1 (M+H\(^+\)).
**Compound 125:** 2-(2-chloro-5-(thiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide

\[ ^1H-NMR \text{ (CDCl}_3 \text{) } \delta \text{ (ppm) 8.9 (d, 1H, J=2), 8.49 (s, 1H), 8.1 (m, 1H), 7.9 (d, 1H, J=3), 7.6 (d, 1H, J=8), 7.4 (d, 1H, J=3), 7.3 (br, 1H), 7.2 (m, 1H), 7.0 (t, 2H, J=8); ESMS clcd for C\textsubscript{19}H\textsubscript{10}Cl\textsubscript{2}F\textsubscript{2}N\textsubscript{3}O\textsubscript{2}S: 433.0; Found: 434.1 (M+H)^+ .} \]

**Compound 126:** 2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide

\[ ^1H-NMR \text{ (CDCl}_3 \text{) } \delta \text{ (ppm) 8.7 (d, 1H, J=3), 8.42 (s, 1H), 8.2 (d, 1H, J=3), 7.3 (m, 2H), 7.0 (t, 2H, J=8), 4.19 (s, 3H); ESMS clcd for C\textsubscript{16}H\textsubscript{10}Cl\textsubscript{2}F\textsubscript{2}N\textsubscript{3}O\textsubscript{2}S: 381.0; Found: 382.1 (M+H)^+ .} \]

**Compound 127:**
2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl) thiazole-5-carboxamide

\[ ^1H-NMR \text{ (CDCl}_3 \text{) } \delta \text{ (ppm) 8.49 (s, 1H), 8.33 (s, 1H), 7.69 (s, 1H), 7.3 (m, 2H), 7.0 (t, 2H, J=8), 3.99 (s, 3H); ESMS clcd for C\textsubscript{16}H\textsubscript{10}Cl\textsubscript{2}F\textsubscript{2}N\textsubscript{3}O\textsubscript{2}S: 381.0; Found: 382.1 (M+H)^+ .} \]

**Compound 128:** N-(2,6-difluorophenyl)-2-(2-methyl-5-(1,3,4-oxadiazol-2-yl)phenyl)thiazole-5-carboxamide

\[ ^1H-NMR \text{ (CDCl}_3 \text{) } \delta \text{ (ppm) 8.5 (m, 3H), 8.1 (d, 1H, J=8), 7.5 (d, 1H, J=8), 7.4 (br, 1H), 7.3 (m, 1H), 7.0 (t, 2H, J=8), 2.71 (s, 3H); ESMS clcd for C\textsubscript{19}H\textsubscript{12}F\textsubscript{2}N\textsubscript{4}O\textsubscript{2}S: 398.1; Found: 399.1 (M+H)^+ .} \]

**Compound 129:** 5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)thiazole-2-carboxamide
$^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 8.7 (br, 1H), 8.14 (s, 1H), 7.8 (m, 1H), 7.7 (m, 2H), 7.3 (m, 1H), 7.0 (t, 2H, J=8); ESMS clcd for C$_{17}$H$_8$ClF$_5$N$_2$OS: 418.0; Found: 419.1 (M+H)$^+$.  

5 Compound 130: N-(2,6-difluorophenyl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide  

$^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 8.6 (br, 1H), 8.15 (s, 1H), 7.6-7.9 (m, 4H), 7.3 (m, 1H), 7.0 (t, 2H, J=8); ESMS clcd for C$_{17}$H$_8$F$_5$N$_2$OS: 384.0; Found: 385.1 (M+H)$^+$.  

10 Compound 131: N-(2,6-difluorophenyl)-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide  

$^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 8.6 (br, 1H), 8.3 (m, 1H), 8.19 (s, 1H), 8.1 (m, 1H), 7.78 (s, 1H), 7.7 (m, 1H), 7.6 (t, 1H, J=8), 7.3 (m, 2H), 7.0 (t, 2H, J=8); ESMS clcd for C$_{19}$H$_{11}$F$_2$N$_3$O$_2$S: 383.1; Found: 384.1 (M+H)$^+$.  

20 Compound 132: 5-(2-methyl-5-(oxazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide  

$^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 8.6 (m, 2H), 8.39 (s, 1H), 7.4-8.0 (m, 6H), 7.2 (s, 1H), 2.40 (s, 3H), 2.16 (s, 3H); ESMS clcd for C$_{20}$H$_{15}$N$_4$O$_2$S: 376.1; Found: 377.3 (M+H)$^+$.  

25 Compound 133: 5-(2-methyl-5-(thiazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide  

$^1$H-NMR (CDCl$_3$) $\delta$ (ppm) 8.6 (m, 2H), 8.40 (s, 1H), 7.9 (m, 1H), 7.8 (m, 3H), 7.6 (m, 1H), 7.3 (m, 2H), 2.40 (s, 3H), 2.15 (s, 3H); ESMS clcd for C$_{20}$H$_{15}$N$_4$OS$_2$: 392.1; Found: 393.3 (M+H)$^+$.  

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Compounds of the invention in which \( L \) is \(-\text{NHC(S)-} \) or \(-\text{C(S)NH-} \) can be prepared by treating compounds having an amide linker with Lawesson's reagent.

Compounds having \(-\text{CH}_2-\text{NH-} \) or \(-\text{NH-CH}_2-\) linkers can be prepared by contacting compounds having \(-\text{NHC(S)-} \) or \(-\text{C(S)NH-} \) linkers with Raney Ni. Alternatively, compounds of the invention having a \(-\text{CH}_2-\text{NH-} \) or \(-\text{NH-CH}_2-\) linker can be prepared by reducing a compound having a \(-\text{C(O)-NH-} \) or \(-\text{NH-C(O)-} \) linker, respectively, with, for example, sodium borohydride (see U.S. Patent Application No. 10/897,681, filed on July 22, 2004, the entire teachings of which are incorporated herein by reference).

Compounds of the invention having \(-\text{C(O)-} \) linkers can be prepared by a Friedel-Craft acylation reaction, similar to Scheme IV. Scheme IV shows a pyridinyl derivative (XXIII) being reacted with an acid chloride (XXIV) in the presence of \( \text{AlCl}_3 \) to form an intermediate which can then be reacted with an \([1,3,2]\)dioxaborolan-2-yl-aryl or \(-\text{heteroaryl} \) (XXV) in the presence of a palladium catalyst and a base to form a compound having a carbonyl linker (XXVI) (see Scheme IV).

\[
\text{Scheme IV}
\]

\[
(\text{XXIII}) + \text{ClC}(\text{XXIV}) \xrightarrow{\text{AlCl}_3} (\text{XXV}) + (\text{XXVI})\]

\[
(\text{XXII}) + \text{Pd(PPh)_3}_2, \text{DMF, K}_2\text{CO}_3 \xrightarrow{} (\text{XXVII})
\]

Compounds of the invention that have \(-\text{C(S)-} \) can be prepared from compounds that have carbonyl linkers by treating them with Lawesson's reagent or \( \text{P}_2\text{S}_5 \) in pyridine.
Compounds having \(-\text{C=C-}\) linkers can in general be prepared as in the scheme below:

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{P(OEt)}_3} \quad \text{Br} \quad \xrightarrow{\text{NaHMDS}} \quad \text{Br} \quad \xrightarrow{\text{Suzuki}} \quad \text{Br}
\end{align*}
\]

5. Compounds having \(-\text{N(R)-}\) linkers can in general be prepared as in the scheme below:

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

Compounds having \(-\text{NRC(O)NR-}\) linkers can in general be prepared as in the scheme below:

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

Compounds having \(-\text{NRN=CR}_6\) linkers can in general be prepared as in the scheme below:
Compounds of the invention having -CH₂-NH- or -NH-CH₂- linkers can be prepared by contacting compounds having -NHC(S)- or -C(S)NH- linkers with Raney Ni. Alternatively, compounds of the invention having a -CH₂-NH- or -NH-CH₂- linker can be prepared by reducing a compound having a -C(O)-NH- or -NH-C(O)- linker, respectively, with, for example, sodium borohydride. Alternatively, compounds that have -NHCH₂- linkers can be prepared by reacting aldehyde (f) with amine (XX) followed by reduction of the shift base with sodium borohydride as shown in Scheme Vla (see U.S. Patent Application No. 10/897,681, filed on July 22, 2004, the entire teachings of which are incorporated herein by reference).

**Scheme Vla**

**EXAMPLE 2: INHIBITION OF IL-2 PRODUCTION**

Jurkat cells were placed in a 96 well plate (0.5 million cells per well in 1% FBS medium) then a test compound of this invention was added at different concentrations. After 10 minutes, the cells were activated with PHA (final concentration 2.5 μg/mL) and incubated for 20 hours at 37°C under CO₂. The final volume was 200 μL. Following incubation, the cells were centrifuged and the supernatants collected and stored at -70°C prior to assaying for IL-2 production. A commercial ELISA kit (IL-2 Eli-pair, Diaclone Research,
Besancon, France) was used to detect production of IL-2, from which dose response curves were obtained. The IC\textsubscript{50} value was calculated as the concentration at which 50% of maximum IL-2 production after stimulation was inhibited versus a non-stimulation control.

<table>
<thead>
<tr>
<th>Compound #</th>
<th>IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>107, 129</td>
<td>&lt; 30 nM</td>
</tr>
<tr>
<td>9, 11, 122</td>
<td>30 nM &lt; and &lt; 50 nM</td>
</tr>
<tr>
<td>4, 48, 52, 53, 68a, 76, 91, 94, 116, 131</td>
<td>50 nM &lt; and &lt; 100 nM</td>
</tr>
<tr>
<td>3, 13, 59, 108, 117, 121, 130</td>
<td>100 nM &lt; and &lt; 200 nM</td>
</tr>
<tr>
<td>8, 49, 50, 55, 56, 57, 58, 60, 61, 69, 73, 75, 84, 86, 89, 90, 92, 100, 103, 118, 119, 125, 128</td>
<td>200 nM &lt; and &lt; 500 nM</td>
</tr>
<tr>
<td>5, 19, 41, 79, 82, 101, 102, 104, 108, 111, 113, 115</td>
<td>500 nM &lt; and &lt; 1 \mu M</td>
</tr>
<tr>
<td>2, 6, 7, 10, 12, 44, 51, 54, 62, 63, 64, 65, 66, 67, 68, 70, 72, 74, 77, 78, 80, 81, 83, 87, 93, 95, 96, 97, 98, 109, 110, 112, 114, 114a, 114b, 120, 123, 124, 126, 127, 132, 133</td>
<td>1 \mu M &lt;</td>
</tr>
</tbody>
</table>

Inhibition of other cytokines, such as IL-4, IL-5, IL-13, GM-CSF, TNF-\alpha, and INF-\gamma, can be tested in a similar manner using a commercially available ELISA kit for each cytokine.

**EXAMPLE 3: PATCH CLAMP STUDIES OF INHIBITION OF I\textsubscript{CRAC} CURRENT IN RBL CELLS, JURKAT CELLS, AND PRIMARY T CELLS**
In general, a whole cell patch clamp method is used to examine the effects of a compound of the invention on a channel that mediates $I_{\text{crac}}$. In such experiments, a baseline measurement is established for a patched cell. Then a compound to be tested is perfused (or puffed) to cells in the external solution and the effect of the compound on $I_{\text{crac}}$ is measured. A compound that modulates $I_{\text{crac}}$ (e.g., inhibits) is a compound that is useful in the invention for modulating CRAC ion channel activity.

1) **RBL cells**

**Cells**

Rat basophilic leukemia cells (RBL-2H3) were grown in DMEM media supplemented with 10% fetal bovine serum in an atmosphere of 95% air/5% CO$_2$. Cells were seeded on glass coverslips 1-3 days before use.

**Recording Conditions**

Membrane currents of individual cells were recorded using the whole-cell configuration of the patch clamp technique with an EPC10 (HEKA Electronik, Lambrecht, Germany). Electrodes (2-5 MΩ in resistance) were fashioned from borosilicate glass capillary tubes (Sutter Instruments, Novato, Ca). The recordings were done at room temperature.

**Intracellular pipette solution**

The intracellular pipette solution contained Cs-Glutamate 120mM; CsCl 20mM; CsBAPTA 10mM; CsHEPES 10mM; NaCl 8mM; MgCl$_2$ 1mM; IP$_3$ 0.02mM; pH=7.4 adjusted with CsOH. The solution was kept on ice and shielded from light before the experiment was preformed.

**Extracellular solution**

The extracellular solution contained NaCl 138mM; NaHEPES, 10mM; CsCl 10mM; CaCl$_2$ 10mM; Glucose 5.5mM; KCl 5.4mM; KH$_2$PO$_4$ 0.4mM; Na$_2$HPO$_4$H$_2$O 0.3mM at pH=7.4 adjusted with NaOH.
**Compound treatment**

Each compound was diluted from a 10 mM stock in series using DMSO. The final DMSO concentration was always kept at 0.1 %.

**Experimental procedure**

IC\textsubscript{CRAC} currents were monitored every 2 seconds using a 50 msec protocol, where the voltage was ramped from -100 mV to +100 mV. The membrane potential was held at 0 mV between the test ramps. In a typical experiment, the peak inward currents would develop within 50-100 seconds. Once the IC\textsubscript{CRAC} currents were stabilized, the cells were perfused with a test compound in the extracellular solution. At the end of an experiment, the remaining IC\textsubscript{CRAC} currents were then challenged with a control compound (SKF96365, 10 \mu M) to ensure that the current could still be inhibited.

**Data analysis**

The IC\textsubscript{CRAC} current level was determined by measuring the inward current amplitude at -80 mV of the voltage ramp in an off-line analysis using MATLAB. The IC\textsubscript{CRAC} current inhibition for each concentration was calculated using peak amplitude in the beginning of the experiment from the same cell. The IC\textsubscript{50} value and Hill coefficient for each compound was estimated by fitting all the individual data points to a single Hill equation.

**Results**

The table below shows the concentration of compounds of the invention which inhibits 50 % of the IC\textsubscript{CRAC} current in RBL cells.

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>220 nM</td>
</tr>
<tr>
<td>3</td>
<td>400 nM</td>
</tr>
<tr>
<td>SKF96365</td>
<td>4 \mu M</td>
</tr>
</tbody>
</table>
2) **Jurkat cells**

**Cells**

Jurkat T cells are grown on glass coverslips, transferred to the recording chamber and kept in a standard modified Ringer's solution of the following composition: NaCl 145mM, KCl 2.8mM, CsCl 10mM, CaCl$_2$ 10mM, MgCl$_2$ 2mM, glucose 10mM, HEPES-NaOH 10mM, pH 7.2.

**Extracellular Solution**

The external solution contains 10 mM CaNaR, 11.5 mM glucose and a test compound at various concentrations.

**Intracellular Pipette Solution**

The standard intracellular pipette solution contains: Cs-glutamate 145 mM, NaCl 8 mM, MgCl$_2$ 1 mM, ATP 0.5 mM, GTP 0.3 mM, pH 7.2 adjusted with CsOH. The solution is supplemented with a mixture of 10 mM Cs-BAPTA and 4.3-5.3 mM CaCl$_2$ to buffer [Ca$^{2+}$]i to resting levels of 100-150 nM.

**Patch-clamp recordings**

Patch-clamp experiments are performed in the tight-seal whole-cell configuration at 21-25 °C. High-resolution current recordings are acquired by a computer-based patch-clamp amplifier system (EPC-9, HEKA, Lambrecht, Germany). Sylgard®-coated patch pipettes have resistances between 2-4 MΩ after filling with the standard intracellular solution. Immediately following establishment of the whole-cell configuration, voltage ramps of 50 ms duration spanning the voltage range of −100 to +100 mV are delivered from a holding potential of 0 mV at a rate of 0.5 Hz over a period of 300 to 400 seconds. All voltages are corrected for a liquid junction potential of 10 mV between external and internal solutions. Currents are filtered at 2.3 kHz and digitized at 100 μs intervals. Capacitive currents and series resistance are determined and corrected before each voltage ramp using the automatic capacitance compensation of the EPC-9.
Data analysis
The very first ramps before activation of I_{CRAC} (usually 1 to 3) are digitally filtered at 2 kHz, pooled and used for leak-subtraction of all subsequent current records. The low-resolution temporal development of inward currents is extracted from the leak-corrected individual ramp current records by measuring the current amplitude at -80 mV or a voltage of choice.

3) Primary T Cells

Preparation of Primary T Cells
Primary T cells are obtained from human whole blood samples by adding 100μL of RosetteSep® human T cell enrichment cocktail to 2 mL of whole blood. The mixture is incubated for 20 minutes at room temperature, then diluted with an equal volume of PBS containing 2% FBS. The mixture is layered on top of RosetteSep® DM-L density medium and then centrifuged for 20 minutes at 1200 g at room temperature. The enriched T cells are recovered from the plasma/density medium interface, then washed with PBS containing 2% FBS twice, and used in patch clamp experiments following the procedure described for RBL cells.

EXAMPLE 4: INHIBITION OF MULTIPLE CYTOKINES IN PRIMARY HUMAN PBMCs
Peripheral blood mononuclear cells (PBMCs) are stimulated with phytohemagglutinin (PHA) in the presence of varying concentrations of compounds of the invention or cyclosporine A (CsA), a known inhibitor of cytokine production. Cytokine production is measured using commercially available human ELISA assay kits (from Cell Science, Inc.) following the manufacturers instructions.

The compounds of the invention are expected to be potent inhibitors of IL-2, IL-4, IL-5, IL-13, GM-CSF, INF-γ and TNF-α in primary human PBMC cells. In addition, compounds of the invention are not expected to inhibit the anti-inflammatory cytokine, IL-10.
EXAMPLE 5: INHIBITION OF DEGRANULATION IN RBL CELLS

Procedure:
5 The day before the assay is performed, RBL cells, that have been grown to confluence in a 96 well plate, are incubated at 37°C for at least 2 hours. The medium is replaced in each well with 100 μL of fresh medium containing 2μLg/mL of anti-DNP IgE.

10 On the following day, the cells are washed once with PRS (2.6 mM glucose and 0.1% BSA) and 160μL of PRS is added to each well. A test compound is added to a well in a 20μL solution at 10X of the desired concentration and incubated for 20 to 40 minutes at 37°C. 20μL of 10X mouse anti-IgE (10 μL/mL) is added. Maximum degranulation occurs between 15 to 40 minutes after addition of anti-IgE.

Compounds of the invention are expected to inhibit degranulation.

EXAMPLE 6: INHIBITION OF CHEMOTAXIS IN T CELLS

T-cell isolation:
Twenty ml aliquots of heparinized whole blood (2 pig, 1 human) are subjected to density gradient centrifugation on Ficoll Hypaque. The buffy coat layers representing peripheral blood mononuclear cells (PBMCs) containing lymphocytes and monocytes are washed once, resuspended in 12 ml of incomplete RPMI 1640 and then placed in gelatin-coated T75 culture flasks for 1 hr at 37°C. The non-adherent cells, representing peripheral blood lymphocytes (PBLs) depleted of monocytes, are resuspended in complete RPMI media and placed in loosely packed activated nylon wool columns that have been equilibrated with warm media. After 1 hr at 37°C, the non-adherent T cell populations are eluted by washing of the columns with additional media. The T cell preparations are centrifuged, resuspended in 5 ml of incomplete RPMI, and counted using a hemocytometer.
Cell migration assay:
Aliquots of each T cell preparation are labeled with Calciend AM (TefLabs) and suspended at a concentration of 2.4 x10^6/ml in HEPES-buffered Hank's Balanced Salt Solution containing 1.83 mM CaCl2 and 0.8 mM MgCl2, pH 7.4 (HBBSS). An equal volume of HBBSS containing 0, 20 nM, 200 nM or 2000 nM of compound 1 or 20 nM EDTA is then added and the cells incubated for 30 min at 37 °C. Fifty µl aliquots of the cell suspensions (60,000 cells) are placed on the membrane (pore size 5 µm) of a Neuroprobe ChemoTx 96 well chemotaxis unit that have been affixed over wells containing 10 ng/ml MIP-1α in HBBSS. The T cells are allowed to migrate for 2 hr at 37 °C, after which the apical surface of the membrane is wiped clean of cells. The chemotaxis units are then placed in a CytoFlour 4000 (PerSeptive BioSystems) and the fluorescence of each well measured (excitation and emission wavelengths of 450 and 530 nm, respectively). The number of migrating cells in each well is determined from a standard curve generated from measuring the fluorescence of serial two-fold dilutions of the labeled cells placed in the lower wells of the chemotaxis unit prior to affixing the membrane.

Compounds of the invention are expected to inhibit chemotactic response of T cells.

All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting in any way.

From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein. Such embodiments are also within the scope of the following claims.
WE CLAIM:

1. A compound represented by formula (I):

   \[
   \begin{array}{c}
   \text{R}_1 \\
   \text{S} \\
   \text{L} \\
   \text{Y} \\
   \text{X} \\
   \text{X'}
   \end{array}
   \]

   or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:
   - Y is an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted alkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, or an optionally substituted heteroaryl;
   - \text{R}_1 is an optionally substituted aryl or an optionally substituted heteroaryl, provided that \text{R}_1 is not a pyrazoly;
   - \text{X} and \text{X'} are each independently CH, CZ, or N; provided that at least one of \text{X} or \text{X'} is N;
   - \text{L} is a linker; and
   - \text{Z} is a substituent.

2. The compound of Claim 1, wherein
   - \text{L} is \(-\text{NRCH}_2\text{-}, \text{-CH}_2\text{NR}_-\text{-}, \text{-C(O)-}, \text{-NR-C(O)-}, \text{-C(O)-NR-}, \text{C(S)-}, \text{-NR-C(S)-}, \text{-C(S)-NR-}, \text{-NRS(O)}_2\text{-}, \text{-S(O)}_2\text{NR-}, \text{-NR-C(O)(CH}_2\text{)}_2\text{-}, \text{-NRC(O)CH=CH-}, \text{-NRC(O)NR-}, \text{-NRC(NR)NR-}, \text{-NRC(S)NR-}, \text{NRS(O)}_2\text{NR-}, \text{-NR-CH}_2\text{-NR-}, \text{-N=CR-}, \text{-CR=N-}, \text{-NR-NR-C(O)-}, \text{-CH=CH-}, \text{-C≡C-}, \text{NRN=CR}_6\text{-}, \text{-C(NR)-}, \text{or -CR}_6\text{=NNR-};
   - \text{R}, for each occurrence, is independently \(-\text{H}, \text{alkyl}, \text{-C(O)-R}_7\), or \(-\text{C(O)OR}_7\); 
   - \text{R}_6, for each occurrence, is \(-\text{H} or \text{alkyl};
   - \text{R}_7, for each occurrence is, independently, \text{H}, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted alkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, or an optionally substituted heteroaryl;
substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

q is an integer 1-6.

3. The compound of Claim 1, wherein L is \(-NRCH_2-, -CH_2NR-, -NR-C(O)-,\)
   or \(-C(O)-NR-.\)

4. The compound of Claim 3, wherein L is \(-NH-C(O)-.\)

5. The compound of Claim 1, wherein Y is an optionally substituted aryl or an optionally substituted heteroaryl.

6. The compound of Claim 5, wherein Y is an optionally substituted phenyl or an optionally substituted pyridinyl.

7. The compound of Claim 6, wherein Y is substituted with one to two substituents.

8. The compound of Claim 7, wherein the one to two substituents are each independently a lower alkyl or a halo.

9. The compound of Claim 1, wherein R\(_1\) is an optionally substituted phenyl or an optionally substituted pyridinyl.

10. The compound of Claim 9, wherein R\(_1\) is substituted with one to two substituents.

11. The compound of Claim 10, wherein the one to two substituents are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally
substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl;

R₄, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.

12. The compound of Claim 1, wherein X is N.

13. The compound of Claim 12, wherein X' is N.

14. The compound of Claim 12, wherein X' is CH or CZ.

15. The compound of Claim 1, wherein X' is N.

16. The compound of Claim 15, wherein X is N.

17. The compound of Claim 15, wherein X is CH or CZ.

18. The compound of Claim 1, wherein

X' is N;

X is CZ;

Z is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, -C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂.
-NR₄C(O)OR₅, -S(O)ₓR₄, or -S(O)ₓNR₃R₂;

R₁ and R₂, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroary1, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroary1, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 0, 1, or 2.

19. The compound of Claim 18, wherein R₁ is an optionally substituted phenyl or an optionally substituted pyridinal; and Y is an optionally substituted phenyl or an optionally substituted pyridinal.

20. The compound of Claim 19, wherein Y is substituted with one to two substituents; and wherein the one to two substituents are each independently a lower alkyl or a halo.

21. The compound of Claim 20, wherein R₁ is substituted with one to two substituents; and wherein the one to two substituents are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally
substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl.

22. The compound of Claim 21, wherein:

L is \(-\text{NRCH}_2\), \(-\text{CH}_2\text{NR},\) \(-\text{C(O)},\) \(-\text{NR-C(O)},\) or \(-\text{C(O)-NR};\)
R, for each occurrence, is independently \(-\text{H, alkyl, -C(O)-R}_7\) or \(-\text{C(O)OR}_7;\)
R\(_6\), for each occurrence, is \(-\text{H or alkyl;}
R\(_7\), for each occurrence is, independently, \(-\text{H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.}

23. The compound of Claim 22, wherein L is \(-\text{NHC(O)}-.\)

24. The compound of Claim 1, wherein the compound is represented by formula (III):

\[
\begin{align*}
(Z_4)_m & \quad \text{N} \quad \text{S} \\
\text{X}_2 & \quad \text{L}_1 \quad \text{Y}_1
\end{align*}
\]

(III)

wherein:

X\(_2\) is \text{CH or CZ}.

L\(_1\) is \(-\text{NRCH}_2\), \(-\text{CH}_2\text{NR},\) \(-\text{C(O)},\) \(-\text{NR-C(O)},\) \(-\text{C(O)-NR},\) \text{C(S)},
\(-\text{NR-C(S)},\) \(-\text{C(S)-NR},\) \(-\text{NRS(O)}_2\), \(-\text{S(O)}_2\text{NR},\) \(-\text{NRC(O)CH}_2-,\)
-NRC(O)CH=CH-, -NRC(O)NR-, -NRC(NR)NR-, -NRC(S)NR-, 
NRS(O)2NR-, -NR-CH2-NR-, -NR-NR-C(O)-, -N=CR-, -CR=N-, 
-CH=CH-, -C≡C-, NRN=CR6-, -C(NR)-, or -CR6=NNR-;

Y1 is an optionally substituted phenyl or an optionally substituted pyridinyl;

Z2 and Z4 are each independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, a haloalkyl,

-C(O)NR1R2, -NR4C(O)R5, halo, -OR4, cyano, nitro, haloalkoxy,
-C(O)R4, -NR4R2, -SR4, -C(O)OR4, -OC(O)R4, -NR4R4C(O)NR4R2,
-OC(O)NR1R2, -NR4C(O)OR5, -S(O)R4, or -S(O)R4NR4R2;

R, for each occurrence, is independently -H, alkyl, -C(O)-R7, or
-C(O)OR7;

R1 and R2, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl; or R1 and R2 taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R4 and R5, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteroaralkyl;

R6, for each occurrence, is -H or alkyl;
R₂, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; m is 0, 1, 2, 3, or 4; and p is 0, 1, or 2.

25. The compound of Claim 24, wherein
   Z₂ and Z₄ are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl; and m is 0 or 1.

26. The compound of Claim 24, wherein L₁ is -NRCH₂-, -CH₂NR-, -NR-C(O)-, or -C(O)-NR-.

27. The compound of Claim 26, wherein L₁ is -NHC(O)-.

28. The compound of Claim 27, wherein Z₄ is halo, a lower alkyl, morpholinyl, or cyano; and m is 1.

29. The compound of Claim 27, wherein m is 0.

30. The compound of Claim 28 or Claim 29, wherein Z₂ is lower alkyl.

31. A compound represented by formula (II):
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

Y' is an optionally substituted aryl or an optionally substituted heteroaryl;

L' is \(-\text{NRCH}_2\), \(-\text{CH}_2\text{NR}\), \(-\text{C(O)}\), \(-\text{NR-C(O)}\), \(-\text{C(O)-NR}\), \(-\text{S(O)}\), \(-\text{NR-C(S)}\), \(-\text{S(O)-NR}\), \(-\text{C(S)}\), \(-\text{NR-S(O)}\), \(-\text{NRS(O)}\), \(-\text{S(O)NR}\), \(-\text{NR-CCH}_2\), \(-\text{NR-C(O)CH}_2\), \(-\text{NRC(O)CH}=\text{CH}\), \(-\text{NRC(O)NR}\), \(-\text{NRC(NR)}\), \(-\text{NRC(S)NR}\), \(-\text{NRS(O)NR}\), \(-\text{NR-CH}_2\text{-NR}\), \(-\text{CH}=\text{CH}\), \(-\text{C}==\text{C}\), \(-\text{NRN=CR}_6\), \(-\text{C(NR)}\), or \(-\text{CR}_6\text{=NNR}\);

R, for each occurrence, is independently \(-\text{H}, \text{alkyl}, \text{C(O)-R}_7\), or \(-\text{C(O)OR}_7\);

R, for each occurrence, is \(-\text{H}\) or alkyl;

R, for each occurrence, is independently \(-\text{H}, \text{an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;\)}

R, for each occurrence, is independently \(-\text{H}, \text{lower alkyl, -CH}_2\text{CH}_2\text{OH, or (CH}_2\text{)_2NMe};\)

Z, is \(-\text{H}, \text{halo, or a lower alkyl which is optionally substituted with halo, -NH}_2\), lower alkyl amino, lower dialkyl amino, or cycloalkyl;

Z, is a substituent, provided that Z is not \(-\text{S(O)}\), \(-\text{S(O)}\text{Cl or S(O)}\text{NR}_6\text{R}_6\);
t is an integer 1-5; and
provided that when \( Z_3 \) is methoxy, \( Y' \) is not a substituted naphthalene;
provided that when \( Z_3 \) is chloro, \( Y' \) is not

\[ \text{[(pyrazinylxyloxy)methyl]fluorophenyl}; \]
provided that when \( Z_3 \) is chloro, \( Y' \) is not cyanobenzoic acid; and
provided that when \( L' \) is \(-\text{N(CH}_2\text{CH}_2\text{CH}_3)-\text{CH}_2^-\), \( Z_3 \) is not methoxy.

32. The compound of Claim 31, wherein \( Y' \) is an optionally substituted phenyl or an optionally substituted pyridinyl.

33. The compound of Claim 32, wherein \( Y' \) is substituted with one to two substituents.

34. The compound of Claim 33, wherein the one to two substituents are each independently a lower alkyl or a halo.

35. The compound of Claim 31, wherein

\( Z_3 \) is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aralkyl, an optionally substituted heteroaryl, a haloalkyl, \(-\text{C(O)NR}_1\text{R}_2, \text{-NP}_2\text{C(O)R}_5, \text{-OR}_4, \text{-NR}_4\text{C(O)OR}_5, \text{-OC(O)R}_4, \text{-NR}_4\text{C(O)NR}_1\text{R}_2, \text{-OC(O)NR}_1\text{R}_2, \text{-NR}_4\text{C(O)OR}_5, \text{-S(O)NR}_1\text{R}_2; \)

\( R_1 \) and \( R_2 \), for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted...
heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocycl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 0, 1, or 2.

36. The compound of Claim 35, wherein:

each Z₃ is independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, -C(O)OR₄, nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholiny; and

t is 1 or 2.

37. The compound of Claim 35, wherein each Z₃ is independently chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl.

38. The compound of Claim 31, wherein L' is -NRCH₂-, -CH₂NR-, -C(O)-, -NR-C(O)-, -C(O)-NR-, -C(S)-, -NR-C(S)-, or -C(S)-NR-.

39. The compound of Claim 38, wherein L' is -NH-C(O)-.
40. The compound of Claim 31, wherein \( L' \) is \(-NRS(O)_2\), \(-S(O)_2NR\), \(-NRS(O)_2NR\), \(-NRC(O)CH_2\), \(-NRC(O)CH=CH_2\), \(-NRC(O)NR\), \(-NRC(NR)NR\), \(-NRC(S)NR\), \(-NRCH_2NR\), \(-NRN=CR_5\), \(-C(NR)\), \(-CR_6=NNR\); \(-CH=CH\) or \(-C\equiv C\).

41. The compound of Claim 31, wherein \( Z_1 \) is lower alkyl.

42. The compound of Claim 31, wherein the compound is represented by formula (IV):

![Formula (IV)](image)

(IV)

wherein, \( Z_5 \) and \( Z_6 \) are each independently a substituent.

43. The compound of Claim 42, wherein \( Y' \) is an optionally substituted phenyl or an optionally substituted pyridinyl.

44. The compound of Claim 43, wherein \( Y' \) is substituted with one to two substituents.

45. The compound of Claim 44, wherein the one to two substituents are each independently a lower alkyl or a halo.

46. The compound of Claim 45, wherein \( Y' \) is 2,6-difluorophenyl.
47. The compound of Claim 42, wherein

\[ Z_5 \text{ and } Z_6 \text{ are each independently an optionally substituted alkyl, an} \]
\[ \text{optionally substituted alkenyl, an optionally substituted alkynyl, an} \]
\[ \text{optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an} \]
\[ \text{optionally substituted heterocyclyl, an optionally substituted aryl, an} \]
\[ \text{optionally substituted heteroaryl, an optionally substituted aralkyl, an} \]
\[ \text{optionally substituted heteraralkyl, a haloalkyl,} \]
\[ -\text{C(O)NR}_1R_2, -\text{NR}_4\text{C(O)R}_5, \text{halo, -OR}_4, \text{cyano, nitro, haloalkoxy,} \]
\[ -\text{C(O)R}_4, -\text{NR}_1R_2, -\text{SR}_4, -\text{C(O)OR}_4, -\text{OC(O)R}_4, -\text{NR}_4\text{C(O)NR}_1R_2, \]
\[ -\text{OC(O)NR}_1R_2, -\text{NR}_4\text{C(O)OR}_5, -\text{S(O)}_p\text{R}_4, \text{or -S(O)}_p\text{NR}_1R_2; \]

\[ R_1 \text{ and } R_2, \text{ for each occurrence are, independently, H, an} \]
\[ \text{optionally substituted alkyl, an optionally substituted alkenyl, an} \]
\[ \text{optionally substituted alkynyl, an optionally substituted cycloalkyl, an} \]
\[ \text{optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an} \]
\[ \text{optionally substituted aryl, an optionally substituted heteroaryl, an} \]
\[ \text{optionally substituted heteroaryl, an optionally substituted aralkyl, or an} \]
\[ \text{optionally substituted heteraralkyl; or } R_1 \text{ and } R_2 \text{ taken together with the} \]
\[ \text{nitrogen to which they are attached is optionally substituted heterocyclyl or} \]
\[ \text{optionally substituted heteroaryl;} \]

\[ R_4 \text{ and } R_5, \text{ for each occurrence are, independently, H, an} \]
\[ \text{optionally substituted alkyl, an optionally substituted alkenyl, an} \]
\[ \text{optionally substituted alkynyl, an optionally substituted cycloalkyl, an} \]
\[ \text{optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an} \]
\[ \text{optionally substituted aryl, an optionally substituted heteroaryl, an} \]
\[ \text{optionally substituted heteroaryl, an optionally substituted aralkyl, or an} \]
\[ \text{optionally substituted heteraralkyl; and} \]

\[ p \text{ is } 0, 1, \text{ or } 2. \]
48. The compound of Claim 47, wherein
   \[ Z_5 \text{ and } Z_6 \text{ are each independently halo, an optionally substituted lower alkyl, an optionally substituted lower alkoxy, a halo alkyl, cyano, an optionally substituted tetrazolyl, } -C(O)OR_4, \text{ nitro, a dialkyl amino, an alkyl amino, an optionally substituted thiazolyl, an optionally substituted oxazolyl, or an optionally substituted morpholinyl.} \]

49. The compound of Claim 48, wherein \( Z_5 \) is halo or lower alkoxy.

50. The compound of Claim 48, wherein \( Z_6 \) is chloro, bromo, fluoro, cyano, trifluoromethyl, \(-C(O)CH_3\), 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl.

51. The compound of Claim 42, wherein \( L' \) is \(-NRCH_2-\), \(-CH_2NR-\), \(-C(O)-\), \(-NR-C(O)-\), \(-C(O)-NR-\), \(-OC(O)-\), \(-C(O)O-\), \(-C(S)-\), \(-NR-C(S)-\), \(-S=SNR-\), \(-CH=CH-\), or \(-C=C-\).

52. The compound of Claim 51, wherein \( L' \) is \(-NH-C(O)-\).

53. The compound of Claim 42, wherein \( L' \) is \(-NRS(O)R-\), \(-S(O)_2NR-\), \(-NRS(O)_2NR-\), \(-NRC(O)CH_2-\), \(-NRCH(O)CH=CH-\), \(-NRCH(NR)NR-\), \(-NRCH(NR)NR-\), \(-NRCH(NR)=NR-\), \(-NR=CR_5\), \(-C=N-\), \(-NR=CR_5\), \(-S-NR=CR_5\), \(-NH-\), or \(-C=C-\).

54. The compound of Claim 42, wherein \( Z_1 \) is lower alkyl.

55. The compound of Claim 42, wherein \( Z_1 \) is \(-H\).

56. The compound of Claim 42, wherein
   \( Y' \) is a phenyl substituted with one to two substituents or a pyridinyl substituted with one to two substituents, wherein the one to two substituents are each independently a lower alkyl or a halo;
   \( L' \) is \(-NR-C(O)-\);
$Z_1$ is lower alkyl or $-\text{H}$; and

$Z_5$ and $Z_6$ are each independently chloro, bromo, fluoro, cyano, trifluoromethyl, $-\text{C(O)}\text{CH}_3$, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl.

57. The compound of Claim 31, wherein the compound is represented by formula (V):

![Chemical Structure](image)

(V)

wherein:

$Z_6$, $Z_7$ and $Z_8$ are each independently a substituent.

58. The compound of Claim 57, wherein

$Z_6$ is chloro, bromo, fluoro, cyano, trifluoromethyl, $-\text{C(O)}\text{CH}_3$, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl; and

$Z_7$ and $Z_8$ are each independently halo.

59. The compound of Claim 58, wherein $Z_1$ is lower alkyl or $-\text{H}$.

60. The compound of Claim 59, wherein $L'$ is $-\text{NH-C(O)}\cdot$.

61. The compound of Claim 31, wherein the compound is represented by formula (VI):
wherein $Z_5$, $Z_6$, $Z_7$ and $Z_8$ are each independently a substituent.

5 62. The compound of Claim 61, wherein:
   $Z_5$ is halo or lower alkoxy;
   $Z_6$ is chloro, bromo, fluoro, cyano, trifluoromethyl, -C(O)CH$_3$,
   2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl,
   oxazol-2-yl, or methyl; and
   $Z_7$ and $Z_8$ are each independently halo.

10 63. The compound of Claim 62, wherein $Z_1$ is lower alkyl or $-H$.

64. The compound of Claim 63, wherein $L'$ is $-NH-C(O)-$.

15 65. The compound of Claim 31, wherein the compound is represented by
   formula (VII):

wherein $Z_9$ is a substituent.
66. The compound of Claim 65, wherein
   each Z₃ is independently chloro, bromo, fluoro, cyano,
   trifluoromethyl, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro,
   dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl;
   Z₉ is a lower alkyl or halo; and
   t is 1 or 2.

67. The compound of Claim 66, wherein Z₁ is lower alkyl or –H.

68. The compound of Claim 67, wherein L¹ is –NH–C(O)–.

69. The compound of Claim 1, wherein the compound is represented by
   formula (VIII):

   ![Chemical Structure](attachment:image.png)

   where:
   L₁ is –NRCH₂–, –CH₂NR–, –C(O)–, –NR–C(O)–, –C(O)–NR–, C(S)–,
   –NR–C(S)–, –C(S)–NR–, –NRS(O)₂–, –S(O)₂NR–, –NRC(O)CH₂–,
   -NRC(O)CH=CH–, -NRC(O)NR–, -NRC(NR)NR–, -NRC(S)NR–,
   NRS(O)₂NR–, -NR–CH₂–NR–, -NR–NR–C(O)–, -N=CR–, -CR=N–,
   -CH=CH–, -C≡C–, NRN=CR₉–, -C(NR)–, or -CR₆=NNR–;
   Y¹ is an optionally substituted aryl or an optionally substituted
   heteroaryl;
   Z is a substituent;
   Z₁₀ is –H, an optionally substituted alkyl, an optionally substituted
   alkenyl, an optionally substituted alkynyl, an optionally substituted
   cycloalkyl, an optionally substituted cycloalkenyl, an optionally
substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloaryl, -C(O)NR_{1}R_{2}, -NR_{4}C(O)R_{5},
halo, -OR_{4}, cyano, nitro, haloalkoxy, -C(O)R_{4}, -NR_{1}R_{2}, -SR_{4},
-C(O)OR_{4}, -OC(O)R_{4}, -NR_{4}C(O)NR_{1}R_{2}, -OC(O)NR_{1}R_{2},
-NR_{4}C(O)OR_{5}, -S(O)_{p}R_{4}, or -S(O)_{p}NR_{1}R_{2};

Z_{11} is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloaryl, -C(O)NR_{1}R_{2}, -NR_{4}C(O)R_{5},
halo, -OR_{4}, cyano, nitro, haloalkoxy, -C(O)R_{4}, -NR_{1}R_{2}, -SR_{4},
-C(O)OR_{4}, -OC(O)R_{4}, -NR_{4}C(O)NR_{1}R_{2}, -OC(O)NR_{1}R_{2},
-NR_{4}C(O)OR_{5}, -S(O)_{p}R_{4}, or -S(O)_{p}NR_{1}R_{2};

R, for each occurrence, is independently -H, alkyl, -C(O)-R_{7}, or
-C(O)OR_{7};

R_{1} and R_{2}, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl; or R_{1} and R_{2} taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_{4} and R_{5}, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;
R₆, for each occurrence, is –H or alkyl;
R₇, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, or an optionally substituted heteraralkyl;
p is 0, 1, or 2; and
provided that when Z is –OCH₃ and Z₁₀ is –H, Z₁₁ is not furanyl;
provided that when Z is –CF₃ and Z₁₀ is –H, Y is not a bromophenol;
provided that when Z is –OCH₃ and Z₁₀ is –H, L₁ is not –N(n-Pr)-CH₂-;
provided that when Z is –CF₃ and Z₁₀ is –H, Z₁₁ is not –CF₃;
provided that when Z is –Cl and Z₁₀ is –H, Y is not a cyanobenzoic acid; and
provided that when Z is –OCH₃, Z₁₀ is –OCH₃ and Z₁₁ is a methoxyphenyl, Y’ is not an indole.

70. The compound of Claim 69, wherein L₁ is –NRCH₂–, –CH₂NR–,
–NR-C(O)–, or C(O)-NR–.

71. The compound of Claim 70, wherein L₁ is –NH-C(O)– or -C(O)-NH–.

72. The compound of Claim 69, wherein Y’ is an optionally substituted phenyl or an optionally substituted pyridinyl.

73. The compound of Claim 72, wherein Y’ is substituted with one to two substituents.

74. The compound of Claim 73, wherein the one to two substituents are each independently a lower alkyl or a halo.
75. The compound of Claim 74, wherein \( Y' \) is 2,6-difluorophenyl.

76. The compound of Claim 69, wherein \( Z \) is chloro, bromo, fluoro, cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl.

77. The compound of Claim 69, wherein \( Z_{10} \) is \(-H, -OR_t, \) halo, or an optionally substituted lower alkyl.

78. The compound of Claim 69, wherein \( Z_{11} \) is \(-H, \) an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted lower alkynyl, an optionally substituted cycloalkyl, -C(O)OR₄, -C(O)R₄, -C(O)NR₄R₄, -NR₄R₂, cyano, halo, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted oxadiazolyl, an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted phenyl, or an optionally substituted phenyl.

79. The compound of Claim 69, wherein
\[
L_1 \text{ is } -\text{NH-C(O)- or } -\text{C(O)-NH-};
\]
\( Y' \) is 2,6-difluorophenyl;
\( Z \) is chloro, bromo, fluoro, cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl;
\( Z_{10} \) is \(-H, -OCH₃, \) halo, or \( \text{methyl} \); and
\( Z_{11} \) is \(-H, \) optionally substituted lower alkyl, cyclopropyl, -C(O)OH, -C(O)CH₃, -C(O)OCH₃, optionally substituted oxazol-5-yl, optionally substituted 1H-imidazol-2-yl, or optionally substituted thiazol-2-yl.

80. The compound of Claim 1, wherein the compound is represented by formula (IX):
wherein:

- $L_1$ is $-\text{NRCH}_2$, $-\text{CH}_2\text{NR}$, $-\text{C(O)}$, $-\text{NR-C(O)}$, $-\text{C(O)-NR}$, $\text{C(S)}$, $-\text{NR-C(S)}$, $-\text{C(S)-NR}$, $-\text{NRS(O)}_2$, $-\text{S(O)}_2\text{NR}$, $-\text{NRC(O)CH}_2$, $-\text{NRC(O)CH}=\text{CH}$, $-\text{NRC(O)NR}$, $-\text{NRC(NR)NR}$, $-\text{NRC(S)NR}$, $\text{NRS(O)}_2\text{NR}$, $-\text{NR-CH}_2\text{NR}$, $-\text{NR-NR-C(O)}$, $-\text{N=CR}$, $-\text{CR=NR}$, $-\text{CR=CH}$, $-\text{C=CR}$, $\text{NRN=CR}_2$, $-\text{C(NR)}$, or $-\text{CR=NR}$;

- $Y_1$ is an optionally substituted phenyl or an optionally substituted pyridinyl;

- one of $X_3$ or $X_4$ is $-\text{S}$ and the other is $-\text{CH}$ or $-\text{CZ}$;

- $Z$ is a substituent;

- $Z_11$ is $-\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heteroalkyl, a haloalkyl, $-\text{C(O)}\text{NR}_4\text{R}_2$, $-\text{NR}_4\text{C(O)}\text{R}_5$, $\text{hala}$, $-\text{OR}_4$, $\text{cyan}$, $\text{nitro}$, $\text{hala}$,$\text{alkox}$, $-\text{C(O)}\text{R}_4$, $-\text{NR}_4\text{R}_2$, $-\text{SR}_4$, $-\text{C(O)}\text{OR}_4$, $-\text{OC(O)}\text{R}_4$, $-\text{NR}_4\text{C(O)}\text{NR}_4\text{R}_2$, $-\text{OC(O)}\text{NR}_4\text{R}_2$, $-\text{NR}_4\text{C(O)}\text{OR}_5$, $-\text{S(O)}_p\text{R}_4$, or $-\text{S(O)}_p\text{NR}_4\text{R}_2$;

- $Z_{12}$ is a substituent;

- $R$, for each occurrence, is independently $-\text{H}$, alkyl, $-\text{C(O)-R}_7$, or $-\text{C(O)OR}_7$;

- $R_1$ and $R_2$, for each occurrence are, independently, $\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an
optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R₁ and R₂ taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R₆, for each occurrence, is –H or alkyl;
R₇, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

p is 0, 1, or 2;
w is 0, 1, or 2; and
provided that when X₄ is –S–, X₃ is –C(SR)–, and Z₁₁ is –H, Y₁ is not (2,4-dioxo-5-thiazolidinyl)methylphenyl; and

provided that when X₄ is –S–, X₃ is –CH₂–, and Z₁₁ is –H, Y₁ is not an unsubstituted phenyl.

81. The compound of Claim 80, wherein L₁ is –NRCH₂–, –CH₂NR–, –NR-C(O)–, or –C(O)-NR–.

82. The compound of Claim 81, wherein L₁ is –NH-C(O)– or –C(O)-NH–.
83. The compound of Claim 82, wherein Y' is 2,6-difluorophenyl.

84. The compound of Claim 83, wherein Z₁₁ is –H, an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted lower alkynyl, an optionally substituted cycloalkyl, -C(O)OR₄, -C(O)R₄, -C(O)NR₄R₂, -NR₄R₂, cyano, halo, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted oxadiazolyl, an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, or an optionally substituted phenyl.

85. The compound of Claim 84, wherein Z₁₂ is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, -C(O)NR₄R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₄R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₄R₂, -OC(O)NR₄R₂, -NR₄C(O)OR₅, -S(O)₉R₄, or -S(O)₉NR₄R₂.

86. The compound of Claim 85, wherein Z₁₂ is halo.

87. The compound of Claim 84, wherein X = 0.

88. The compound of Claim 1, wherein the compound is represented by formula (X):
wherein:

$L_1$ is $-\text{NRCH}_2^-, -\text{CH}_2\text{NR}^-, -\text{C}(\text{O})^-, -\text{NR}-\text{C}(\text{O})^-, -\text{C}(\text{O})^-\text{NR}^-, \text{C}(\text{S})^-, -\text{NR}-\text{C}(\text{S})^-, -\text{C}(\text{S})^-\text{NR}^-, -\text{NR}-\text{S}(\text{O})_2^-, -\text{S}(\text{O})_2\text{NR}^-, -\text{NR}-\text{C}(\text{O})\text{CH}_2^-, -\text{NR}(\text{C}(\text{O})\text{NR}^-, -\text{NR}(\text{NR})\text{NR}^-, -\text{NR}(\text{S})\text{NR}^-, -\text{NR}(\text{S})_2\text{NR}^-, -\text{NR}-\text{CH}_2\text{NR}^-, -\text{NR}-\text{NR}-\text{C}(\text{O})^-, -\text{N}^-=\text{CR}^-, -\text{CR}^-=\text{N}^-$

$Y'$ is an optionally substituted aryl or an optionally substituted heteroaryl;

$Z_{11}$ is $-\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteroalkyl, a haloalkyl, $-\text{OR}_4$, $-\text{NR}^1\text{R}^2$, $-\text{N}^=\text{C}(\text{O})\text{R}^4$, $-\text{C}(\text{O})\text{R}^4$, $-\text{OC}(\text{O})\text{R}^4$, $-\text{NR}^4\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^1\text{R}^2$, $-\text{NR}^4\text{C}(\text{O})\text{OR}_5$, $-\text{S}(\text{O})_2\text{R}_4$, or $-\text{S}(\text{O})_2\text{NR}^1\text{R}^2$;

$Z_{13}$ is a substituent:

$R$, for each occurrence, is independently $-\text{H}$, alkyl, $-\text{C}(\text{O})^-\text{R}^7$, or $-\text{C}(\text{O})\text{OR}^7$;

$R^1$ and $R^2$, for each occurrence are, independently, $\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an
optionally substituted cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or \( R_1 \) and \( R_2 \) taken together with the nitrogen to which they are attached is optionally substituted heterocycloalkyl or optionally substituted heteroaryl;

\( R_4 \) and \( R_5 \), for each occurrence are, independently, \( H \), an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

\( R_6 \), for each occurrence, is \( -H \) or alkyl;

\( R_7 \), for each occurrence is, independently, \( H \), an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

\( p \) is 0, 1, or 2; and

\( v \) is 0, 1, 2, or 3.

89. The compound of Claim 88, wherein \( L_1 \) is \(-\text{NR}(-\text{C(O)}-)\), \(-\text{NR}(-\text{C(O)})\text{-NR}-\), or \(-\text{C(O)}\text{-NR}-\).

90. The compound of Claim 89, wherein \( L_1 \) is \(-\text{NH}(-\text{C(O)})\text{-NH}-\).

91. The compound of Claim 90, wherein \( Y' \) is 2,6-difluorophenyl.

92. The compound of Claim 91, wherein \( Z_{11} \) is \(-H\), an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted lower alkynyl, an optionally substituted lower cycloalkyl, an optionally substituted lower cycloalkenyl, an optionally substituted lower heterocycloalkyl, an optionally substituted lower aryl, an optionally substituted lower heteroaryl, an optionally substituted lower aralkyl, or an optionally substituted lower heteraralkyl;
cycloalkyl, -C(O)OR₄, -C(O)R₄, -C(O)NR₁R₂,
-NR₁R₂, cyano, halo, an optionally substituted oxazolyl, an optionally
substituted imidazolyl, an optionally substituted oxadiazolyl, an
optionally substituted thiazolyl, an optionally substituted pyrazolyl, an
optionally substituted pyridinyl, or an optionally substituted phenyl.

93. The compound of Claim 92, wherein Z₁₃ is an optionally substituted
alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl,
an optionally substituted cycloalkyl, an optionally substituted
cycloalkenyl, an optionally substituted heterocyclyl, an optionally
substituted aryl, an optionally substituted heteroaryl, an optionally
substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl,
-C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy,
-C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂,
-OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)₆R₄, or -S(O)₆NR₁R₂.

94. The compound of Claim 93, wherein Z₁₃ is halo or cyano.

95. The compound of Claim 92, wherein v is 0 or 1.

96. The compound of Claim 1, wherein the compound is represented by
formula (XI):

![Chemical Structure](attachment:image)

(XI)

wherein:

L₁ is -NRCH₂-, -CH₂NR-, -C(O)-, -NR-C(O)-, -C(O)-NR-, C(S)-,
-NR-C(S)-, -C(S)-NR-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)CH₂-,
-NRC(O)CH=CH-, -NRC(O)NR-, -NRC(NR)NR-, -NRC(S)NR-. 

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\[ \text{NRS(O)}_2\text{NR}, \text{-NR-CH}_2\text{-NR}, \text{-NR-NR-C(O)}_-, \text{-N=CR}, \text{-CR=N}, \]
\[ \text{-CH=CH}, \text{-C≡C}, \text{NRN=CR}_5, \text{-C(NR)}, \text{or -CR}_5\text{=NNR}; \]
\[ Y' \text{ is an optionally substituted aryl or an optionally substituted heteroaryl;} \]
\[ Z \text{ is a substituent;} \]
\[ Z_{10} \text{ is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, a haloalkyl, \ -C(O)NR}_1\text{R}_2, \text{-NR}_4\text{C(O)R}_5, \]
\[ \text{halo, -OR}_4, \text{cyano, nitro, haloalkoxy, -C(O)R}_4, \text{-NR}_1\text{R}_2, \text{-SR}_4, \]
\[ \text{-C(O)OR}_4, \text{-OC(O)R}_4, \text{-NR}_4\text{C(O)NR}_1\text{R}_2, \text{-OC(O)NR}_1\text{R}_2, \]
\[ \text{-NR}_4\text{C(O)OR}_5, \text{-S(O)}_p\text{R}_4, \text{or -S(O)}_p\text{NR}_1\text{R}_2; \]
\[ Z_{11} \text{ is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, a haloalkyl, \ -C(O)NR}_1\text{R}_2, \text{-NR}_4\text{C(O)R}_5, \]
\[ \text{halo, -OR}_4, \text{cyano, nitro, haloalkoxy, -C(O)R}_4, \text{-NR}_1\text{R}_2, \text{-SR}_4, \]
\[ \text{-C(O)OR}_4, \text{-OC(O)R}_4, \text{-NR}_4\text{C(O)NR}_1\text{R}_2, \text{-OC(O)NR}_1\text{R}_2, \]
\[ \text{-NR}_4\text{C(O)OR}_5, \text{-S(O)}_p\text{R}_4, \text{or -S(O)}_p\text{NR}_1\text{R}_2; \]
\[ R, \text{ for each occurrence, is independently -H, alkyl, -C(O)-R}_7, \text{or -C(O)OR}_7; \]
\[ R_1 \text{ and } R_2, \text{ for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocycl, an optionally substituted aralkyl, an optionally substituted heteroaralkyl, or } R_1 \text{ and } R_2 \text{ taken together with the nitrogen to which they are attached is optionally substituted heterocycl or optionally} \]
substituted heteroaryl;

R₄ and R₅, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkylnyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R₆, for each occurrence, is –H or alkyl;

R₇, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkylnyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

p is 0, 1, or 2; and

provided that when Z is –Cl, –CH₃, or –CF₃, Z₁₀ is –H and L₁ is –C(O)NH-, Y’ is not a methoxy phenyl, a –C(O)phenyl substituted phenyl or an unsubstituted phenyl;

provided that when Z is –Cl, Z₁₀ is –H and L₁ is –NHC(O)-, Y’ is not  a dinitrophenyl.

97. The compound of Claim 96, wherein L₁ is –NRCH₂-, –CH₂NR-, –NR-C(O)-, or -C(=O)-NR-.

98. The compound of Claim 97, wherein L₁ is –NH-C(O)- or -C(O)-NH-.

99. The compound of Claim 96, wherein Y’ is an optionally substituted phenyl or an optionally substituted pyridinyl.
100. The compound of Claim 99, wherein Y' is substituted with one to two substituents.

101. The compound of Claim 100, wherein the one to two substituents are each independently a lower alkyl or a halo.

102. The compound of Claim 101, wherein Y' is 2,6-difluorophenyl.

103. The compound of Claim 96, wherein Z is chloro, bromo, fluoro, cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl.

104. The compound of Claim 96, wherein Z₁₀ is -H, -OR₄, halo, or an optionally substituted lower alkyl.

105. The compound of Claim 96, wherein Z₁₁ is -H, an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted lower alkylnyl, an optionally substituted cycloalkyl, -C(O)OR₄, -C(O)R₄, -C(O)NR₁R₂, -NR₁R₂, cyano, halo, an optionally substituted oxazolyl, an optionally substituted imidazolyl, an optionally substituted oxadiazolyl, an optionally substituted thiazolyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, or an optionally substituted phenyl.

106. The compound of Claim 96, wherein

L₁ is -NH-C(O)- or -C(O)-NH-;
Y' is 2,6-difluorophenyl;
Z is chloro, bromo, fluoro, cyano, trifluoromethyl, -OCH₃, -C(O)CH₃, 2-methyl-2H-tetrazolyl, methoxy, nitro, dimethylamino, thiazol-2-yl, oxazol-2-yl, or methyl;
Z₁₀ is -H, -OCH₃, halo, or methyl; and
Z₁₁ is -H or methyl.
107. The compound of Claim 1, wherein the compound is selected from the group consisting of:
N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-difluoro-N-(5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-[5-(3-Cyano-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide;
3-[2-(2,6-Difluoro-benzoylamino)-4-methyl-thiazol-5-yl]-benzoic acid methyl ester;
2,6-Difluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzamide;
3-Fluoro-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide;
3-Methyl-N-[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-isonicotinamide;
4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid
[4-methyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-amide;
N-[5-(3-Cyano-phenyl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-benzamide;
3-Methyl-N-[4-methyl-5-(4-nitro-phenyl)-thiazol-2-yl]-isonicotinamide;
2,6-Difluoro-N-[4-methyl-5-pyridin-3-yl-thiazol-2-yl]-benzamide;
2,6-Difluoro-N-[4-methyl-5-pyridin-4-yl-thiazol-2-yl]-benzamide;
3-Methyl-N-[4-methyl-5-pyridin-4-yl-thiazol-2-yl]-isonicotinamide;
2,3-Difluoro-N-[4-methyl-5-[3-(2-methyl-2H-tetrazol-5-yl)-phenyl]-thiazol-2-yl]-benzamide;
N-(5-(4-(dimethylamino)phenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-[5-(4-Dimethylamino-phenyl)-4-methyl-thiazol-2-yl]-3-methyl-isonicotinamide;
N-(5-(2-bromo-5-methoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(2-bromo-4,5-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-difluoro-N-(5-(3-methoxyphenyl)-4-methylthiazol-2-yl)benzamide;
N-(5-(3,4-dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
2,6-difluoro-N-[4-methyl-5-(2-methyl-5-(oxazol-2-yl)phenyl)thiazol-2-yl]benzamide;
N-[5-(2-Bromo-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-difluoro-N-[4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl]benzamide;
3-Methyl-N-[4-methyl-5-(2-methylpyridin-4-yl)thiazol-2-yl]isonicotinamide;
N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide;
N-(5-(4-chloropyridin-2-yl)-4-methylthiazol-2-yl)-3-methylisonicotinamide hydrochloride;
N-[5-(2-Cyano-pyridin-4-yl)-4-methyl-thiazol-2-yl]-2,6-difluoro-benzamide;
2,6-Difluoro-N-[4-methyl-5-(2-morpholin-4-yl-pyridin-4-yl)-thiazol-2-yl]-benzamide;
N-[4-Ethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
Methyl 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl) phenyl)thiazole-4-carboxylate;
Methyl 2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate;
Methyl 2-(2,6-difluorobenzamido)-5-(3-fluorophenyl)thiazole-4-carboxylate;
Methyl 5-(3-fluorophenyl)-2-(3-methylisonicotinamido)thiazole-4-carboxylate;
2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-difluoro-N-(4-(hydroxymethyl)-5-(3-(fluoro)phenyl)thiazol-2-yl) benzamide;
(2-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid
2,6-difluoro-phenyl)-amide;
4-Methyl-5-(3-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid
(2,6-difluoro-phenyl)-amide;
N-[4-(2,5-Dimethoxy-phenyl)-thiazol-2-yl]-2,6-difluoro-benzamide;
N-[5-(2-Chloro-5-trifluoromethyl-phenyl)-[1,3,4]thiadiazol-2-yl]-2,6-difluoro-
benzamide;
N-(5-(2,5-dimethylcyclohex-1-enyl)thiazol-2-yl) 3-methylisonicotinamide;
5-(2-Chloro-5-trifluoromethyl-phenyl)-thiazole-2-carboxylic acid(3-methyl-pyridin-4-y1)-
amide;
2-(2-Chloro-5-trifluoromethyl-phenyl)-4-methyl-thiazole-5-carboxylic acid
(2,6-difluoro-phenyl)-amide;
Sodium (2,6-difluorobenzoyl)(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)
amide;
Sodium (4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)(3-methyl isonicotinoyl)amide;
2-Fluoro-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide;
2-Methyl-N-(4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)nicotinamide;
N-(4-Cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-cyclopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-3-methylisonicotinamide; 2,6-Difluoro-N-(4-methyl-5-(pyridin-4-yl)thiazol-2-yl)benzamide hydrobromide; N-(5-(2,5-Dimethoxyphenyl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; N-(5-(7-Bromobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; N-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; N-(5-(7-Cyanobenzo[d][1,3]dioxol-5-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; N-(5-(5-Bromothiophen-2-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; 2,6-Difluoro-N-(4-methyl-5-(thiophen-2-yl)thiazol-2-yl)benzamide; N-(5-(2,5-Dibromothiophen-3-yl)-4-methylthiazol-2-yl)-2,6-difluorobenzamide; 2,6-Difluoro-N-(4-methyl-5-(thiophen-3-yl)thiazol-2-yl)benzamide; Methyl 5-(2-(allyloxy)-5-(trifluoromethyl)phenyl)-2-(2,6-difluorobenzamido)thiazole-4-carboxylate; N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)-4-(prop-1-en-2-yl)thiazol-2-yl)-2,6-difluorobenzamide; N-(5-(2-(Allyloxy)-5-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide; 2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid; 2,6-Difluoro-N-(4-formyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; 2,6-Difluoro-N-(4-(2-hydroxypropan-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; 2,6-difluoro-N-(4-(prop-1-en-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; 2,6-Difluoro-N-(4-isopropyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; N-(4-((Chloromethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide; N-(4-((Dimethylamino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide; (Z)-2,6-difluoro-N-(4-((hydroxyimino)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; N-(4-Cyano-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide; 2,6-Difluoro-N-(4-(1-hydroxyethyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide; 2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-vinylthiazol-2-yl)benzamide; 2,6-Difluoro-N-(4-(oxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(4,5-Dihydro-1H-imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6difluorobenzamide;
N-(4-(1H-Imidazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluoro benzamide hydrochloride;
2,6-Difluoro-N-(4-(4-methyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-Difluoro-N-(4-(1-methyl-1H-imidazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
N-(4-(2,4-dimethyloxazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6difluorobenzamide;
2,6-Difluoro-N-(4-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol2-yl)benzamide;
2,6-difluoro-N-(4-(hydroxyl(pyridin-2-yl)methyl)-5-(3-(trifluoromethyl)phenyl)thiazol2-yl)benzamide;
N-(4-Acetyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-(2-Bromoacetyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6difluorobenzamide;
2,6-Difluoro-N-(2'-methyl-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)benzamide;
N-(2'-amino-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide;
Ethyl 2'-((2,6-difluorobenzamido)-5'-3-(trifluoromethyl)phenyl)-4,4'-bithiazole2-carboxylate;
N-(4-(4,5-dihydrooxazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6difluorobenzamide
N-(1,3,4-oxadiazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl) benzamide;
2,6-difluoro-N-(4-(oxazol-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-difluoro-N-(4-(3-methyl-1,2,4-oxadiazol-5-yl)-5-(3-(trifluoromethyl)phenyl)thiazol2-yllbenzamide;
2-(2,6-difluorobenzamido)-N-methoxy-N-methyl-5-(3-(trifluoromethyl)phenyl)thiazole4-carboxamide;
2,6-difluoro-N-(4-propionyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(2',5'-dimethyl-5-(3-(trifluoromethyl)phenyl)-4,4'-bithiazol-2-yl)-2,6-difluorobenzamide;
Ethyl 2'-(2,6-difluorobenzamido)-5-methyl-5'-(3-(trifluoromethyl)phenyl)-4,4'-bithiazole-2-carboxylate;
2-(2,6-Difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide;
N-(2,2-diethoxyethyl)-2-(2,6-difluorobenzamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxamide;
2,6-Difluoro-N-(4-propioloyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(1H-Pyrazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(4-(1-methyl-1H-pyrazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-amino-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-Chloro-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-ethynyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
2,6-Difluoro-N-(5-(3-(trifluoromethyl)phenyl)-4-(5-(trimethylsilyl)isoxazol-3-yl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(isoxazol-3-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(pyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
2,6-Difluoro-N-(4-(6-methylpyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide;
N-(4-(3,4-Dimethoxyphenyl)-5-(3-(trifluoromethyl)phenyl)thiazol-2-yl)-2,6-difluorobenzamide;
N-(4-(1-(1-(3-(trifluoromethyl)phenyl)thiazol-2-yl))-3-(trimethylsilyl)isoxazol-4-yloxy-2,6-difluorobenzamide;
2-(3-methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylate hydrochloride;
2-(3-Methylisonicotinamido)-5-(3-(trifluoromethyl)phenyl)thiazole-4-carboxylic acid;
Methyl 2-(2,6-difluorobenzamido)-5-(3-methoxyphenyl)thiazole-4-carboxylate;
Methyl 2-(2,6-difluorobenzamido)-5-(3-(methoxycarbonyl)phenyl)thiazole-4-carboxylate;
Ethyl 2'-(2,6-difluorobenzamido)-4'-methyl-4,5'-bithiazole-2-carboxylate;
N-(2,4'-Dimethyl-4,5'-bithiazol-2-yl)-2,6-difluorobenzamide;
N-(2,6-Difluorobenzyl)-4-methyl-5-(3-(trifluoromethyl)phenyl)thiazol-2-amine;  
N-(2,6-difluorophenyl)-4-methyl-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide;  
methyl 3-(2-(2,6-difluorophenyl)carbamoyl)-4-methylthiazol-5-yl)benzoate;  
5-(3-(1,3,4-oxadiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide;  
5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)-4-methylthiazole-2-carboxamide;  
4-methyl-N-(3-methylpyridin-4-yl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide;  
N-(2,6-difluorophenyl)-2-(2-methyl-5-(oxazol-2-yl)phenyl)thiazole-5-carboxamide;  
N-(2,6-difluorophenyl)-2-(2-methyl-5-(thiazol-2-yl)phenyl)thiazole-5-carboxamide;  
N-(2,6-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)thiazole-5-carboxamide;  
N-(2,6-difluorophenyl)-2-(3-(oxazol-2-yl)phenyl)thiazole-5-carboxamide;  
2-(2-chloro-5-(thiazol-2-yl)phenyl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide;  
2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide;  
2-(5-chloro-2-methoxypyridin-3-yl)-N-(2,6-difluorophenyl)thiazole-5-carboxamide;  
N-(2,6-difluorophenyl)-2-(2-methyl-5-(1,3,4-oxadiazol-2-yl)phenyl)thiazole-5-carboxamide;  
5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(2,6-difluorophenyl)thiazole-2-carboxamide;  
N-(2,6-difluorophenyl)-5-(3-(trifluoromethyl)phenyl)thiazole-2-carboxamide;  
N-(2,6-difluorophenyl)-5-(3-(oxazol-2-yl)phenyl)thiazole-2-carboxamide;  
5-(2-methyl-5-(oxazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide; or  
5-(2-methyl-5-(thiazol-2-yl)phenyl)-N-(3-methylpyridin-4-yl)thiazole-2-carboxamide;  

A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of Claims 1 through 107.

The pharmaceutical composition of Claim 108, further comprising one or more additional therapeutic agents.
110. The pharmaceutical composition according to Claim 109, wherein the additional therapeutic agent is selected from the group consisting of immunosuppressive agents, anti-inflammatory agents and suitable mixtures thereof.

111. The pharmaceutical composition of Claim 110, wherein the additional therapeutic agent is selected from the group consisting of steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and suitable mixtures thereof.

112. A method of inhibiting immune cell activation comprising administering to the cell a compound of any one of Claims 1 through 107.

113. The method of Claim 112, wherein immune cell activation is inhibited in a subject by administering the compound to the subject.

114. The method of Claim 113, wherein the subject is human.

115. A method of inhibiting cytokine production in a cell, comprising administering to the cell a compound of any one of Claims 1 through 107.

116. The method of Claim 115, wherein cytokine production is inhibited in a subject by administering the compound to the subject.

117. The method of Claim 116, wherein the subject is human.

118. The method of Claim 116, wherein the cytokine is selected from the group consisting of IL-2, IL-4, IL-5, IL-13, GM-CSF, IFN-γ, TNF-α, and combinations thereof.

119. The method of Claim 118, wherein the cytokine is IL-2.
120. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of any one of Claims 1 through 107.

121. The method of Claim 120, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.

122. The method of Claim 121, wherein the subject is human.

123. The method of Claim 121, wherein the ion channel is a Ca_{2+}-release-activated Ca_{2+} channel (CRAC).

124. A method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to the cell a compound of any one of Claims 1 through 107.

125. The method of Claim 124, wherein T-cell and/or B-cell proliferation is inhibited in a subject by administering the compound to the subject.

126. The method of Claim 125, wherein the subject is human.

127. A method for treating or preventing an immune disorder in a subject in need thereof, comprising administering to the subject a compound of any one of Claims 1 through 107.

128. The method of Claim 127, wherein the subject is human.

129. The method of Claim 127, wherein the disorder is selected from the group consisting of multiple sclerosis, myasthenia gravis, Guillain-Barré, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo,
Crohn's disease, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease. Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, ankylosing spondylitis, and Sjogren's syndrome.

130. A method for treating or preventing an inflammatory condition in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 107.

131. The method of Claim 130, wherein the subject is human.

132. The method according to Claim 130, wherein the disorder is selected from transplant rejection, skin graft rejection, arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel disease, ileitis, ulcerative colitis, Barrett's syndrome, Crohn's disease; asthma, adult respiratory distress syndrome, chronic obstructive airway disease; corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis, endophthalmitis; gingivitis, periodontitis; tuberculosis; leprosy; uremic complications, glomerulonephritis, nephrosis; scleroderma, psoriasis, dermatomyositis; chronic idiopathic pulmonary fibrosis, multiple sclerosis, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, viral or autoimmune encephalitis; autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematosus; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer.
133. A method for suppressing the immune system of a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 107.

134. The method of Claim 133, wherein the subject is human.

135. A method for treating or preventing an allergic disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 107.

136. The method of Claim 135, wherein the subject is human.

137. The method of Claim 135, wherein the disorder is allergic rhinitis, sinusitis, rhinosinusitis, chronic otitis media, recurrent otitis media, drug reactions, insect sting reactions, latex reactions, conjunctivitis, urticaria, anaphylaxis reactions, anaphylactoid reactions, atopic dermatitis, asthma, or food allergies.