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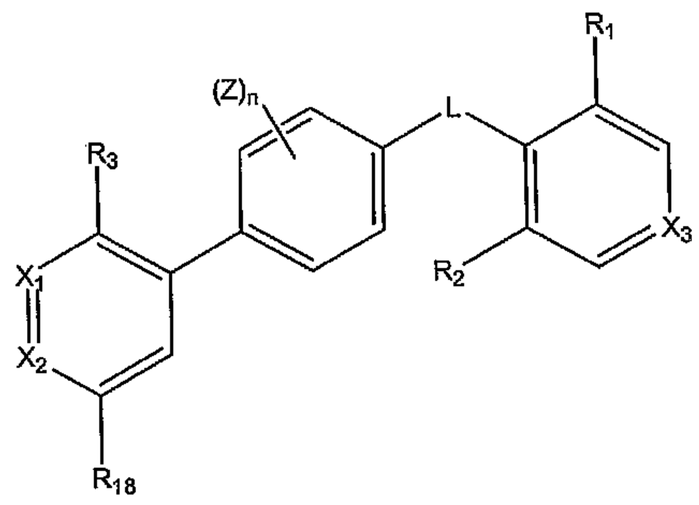
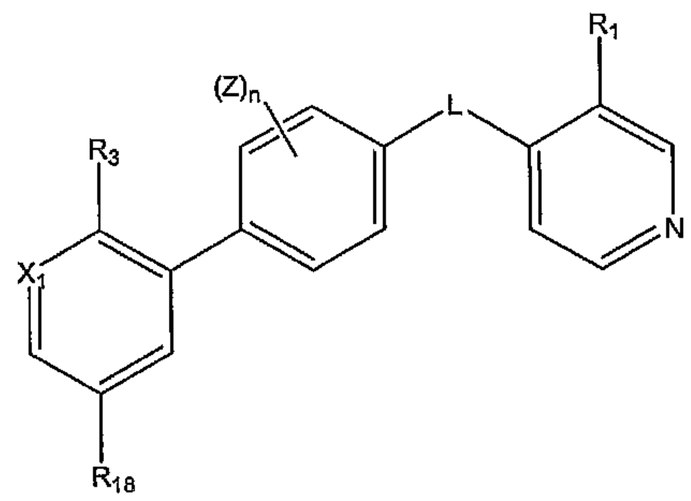
(54) Titre : COMPOSES UTILISES POUR DES ETATS INFLAMMATOIRES ET IMMUNITAIRES
(54) Title: COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES



(I)



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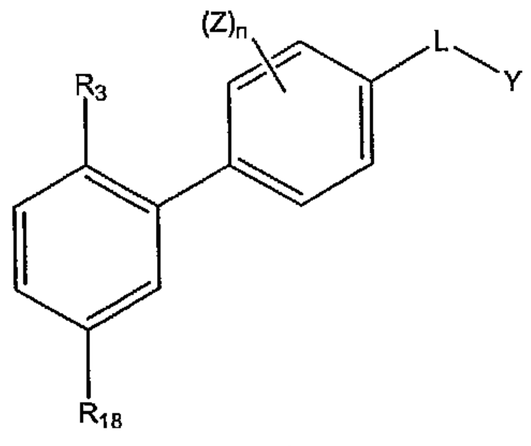

(XI)

(57) Abrégé/Abstract:
The invention relates to compounds of structural formulas (I), (VII) and (XI): or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein X_1, X_2, X_3. Y, Z, L, R_1, R_2, R_3, R_{18} and n 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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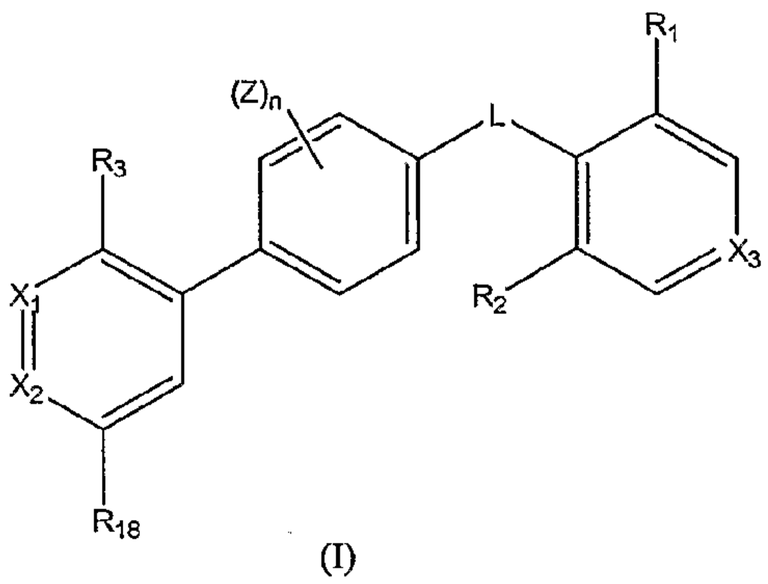
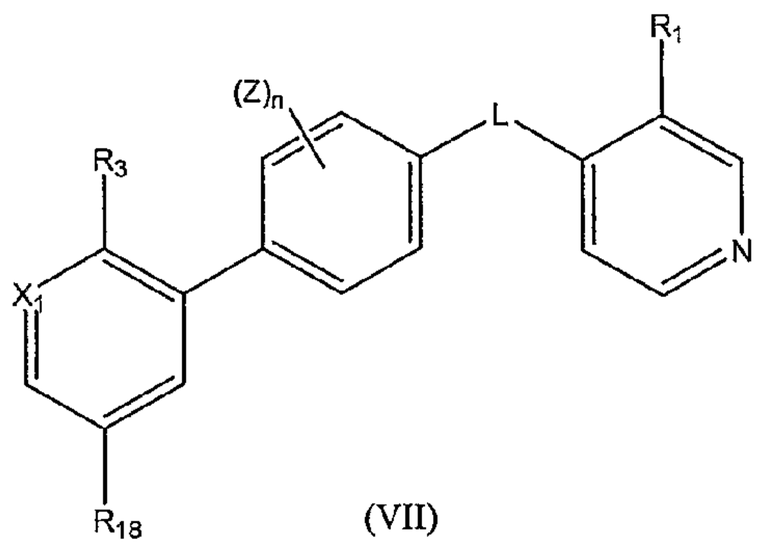
(54) Title: COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES



(I)



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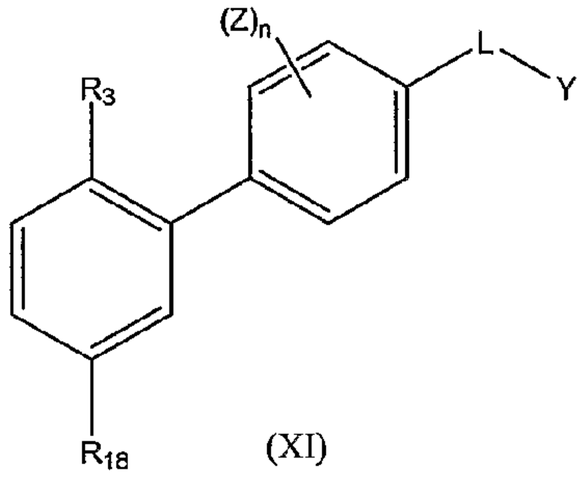

(XI)

(57) Abstract: The invention relates to compounds of structural formulas (I), (VII) and (Xl): or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein X_I, X_2, X_3. Y, Z, L, R_1, R_2, R_3, R_{18} and n 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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COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 60/642,179, filed on January 7, 2005 and U.S. Provisional Patent Application No. 60/707,845, filed on August 12, 2005. The entire teachings of each of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to biologically active chemical compounds, namely biphenyl and pyridylphenyl derivatives that may be used for immunosuppression or to treat or prevent inflammatory conditions, immune disorders, and allergic 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 immunosupression 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 hall mark 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 athsma and inflammatory bowel disease would benefit from the development of new drugs that inhibit IL-4 and IL-13 production.

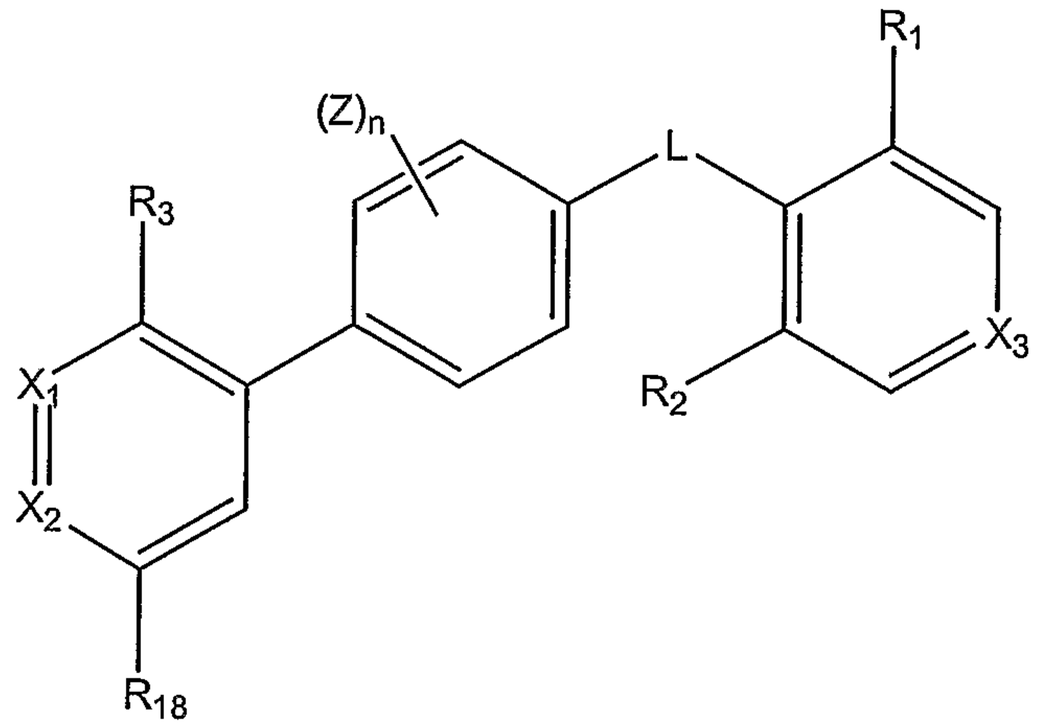
Granulocyte macrophage-colony stimulating factor (GM-CSF) is a regulator of maturation of granulocyte and macrophage lineage population and has been implicated as a key factor in inflammatory and autoimmune diseases. Anti-GM-CSF antibody blockade has been shown to ameliorate autoimmune disease. Thus, 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 biphenyl and phenylpyridyl 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.

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



(I)

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

L is a linker selected from the group consisting of a covalent bond, –$NRCH_2$-, -CH_2NR-, –C(O)-, –NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, –NR-C(S)-, -C(S)-NR-;

X_1 and X_3 are each, independently, CH or N;

X_2 is CH, CR_{10} or N;

each Z is independently selected from the group consisting of a lower alkyl, a lower haloalkyl, a halo, a lower alkoxy, a lower alkyl sufanyl, cyano, nitro, or lower haloalkoxy;

R, for each occurrence is independently selected from -H, an alkyl, -$C(O)R_5$, or -$C(O)OR_5$;

R_1 and R_2 are each, independently, a halo, a haloalkyl, a lower alkyl, a lower alkoxy, or a haloalkoxy;

R_3 is an alkyl, a haloalkyl, a halo, a haloalkoxy, -OR_5, -SR_5, or -NR_6R_7;

R_{18} is a halo, cyano, nitro, -$C(O)R_5$, -$C(O)OR_5$, -$C(O)SR_5$, -$C(O)NR_6R_7$, -$C(S)R_5$, -$C(S)OR_5$, -$C(S)SR_5$, -$C(S)NR_6R_7$, -$C(NR_8)R_5$, -$C(NR_8)OR_5$, -$C(NR_8)SR_5$, -$C(NR_8)NR_6R_7$, -$S(O)_pR_5$, -$S(O)_pNR_5$, -$S(O)_pOR_5$, -$P(O)(OR_5)_2$, -$OP(O)(OR_5)_2$, -$P(O)(R_5)_2$, a five or six membered optionally substituted heterocycloalkyl, a five or six membered optionally substituted heterocyclyl, or a five or six membered optionally substituted heteroaryl;

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;

R_6 and R_7, 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

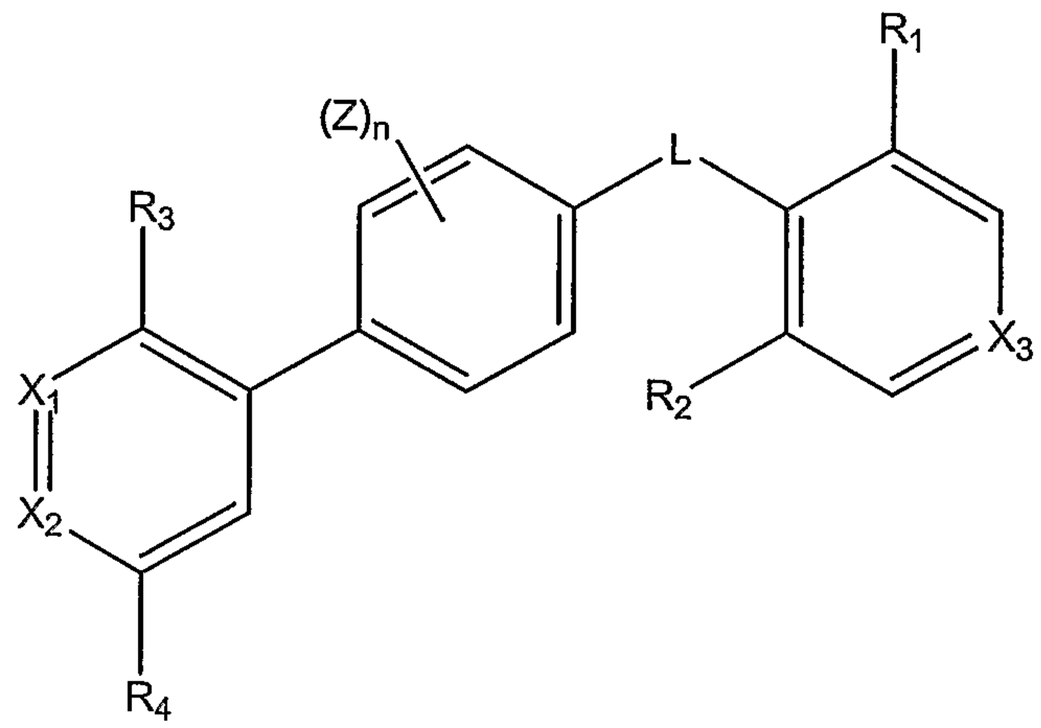
heteraralkyl; or R_6 and R_7 taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_8, for each occurrence, is independently –H, a halo, an alkyl, $-OR_5$, $-NR_6R_7$, $-C(O)R_5$, $-C(O)OR_5$, or $-C(O)NR_6R_7$;

R_{10} is a lower alkyl, a lower alkoxy, a halo, a lower haloalkyl, a lower haloalkoxy, a cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, or $-P(O)(R_5)_2$;n is zero or an integer from 1 to 4; and

p, for each occurrence, is independently 1 or 2.

In one embodiment, the invention relates to compounds of formula (II):



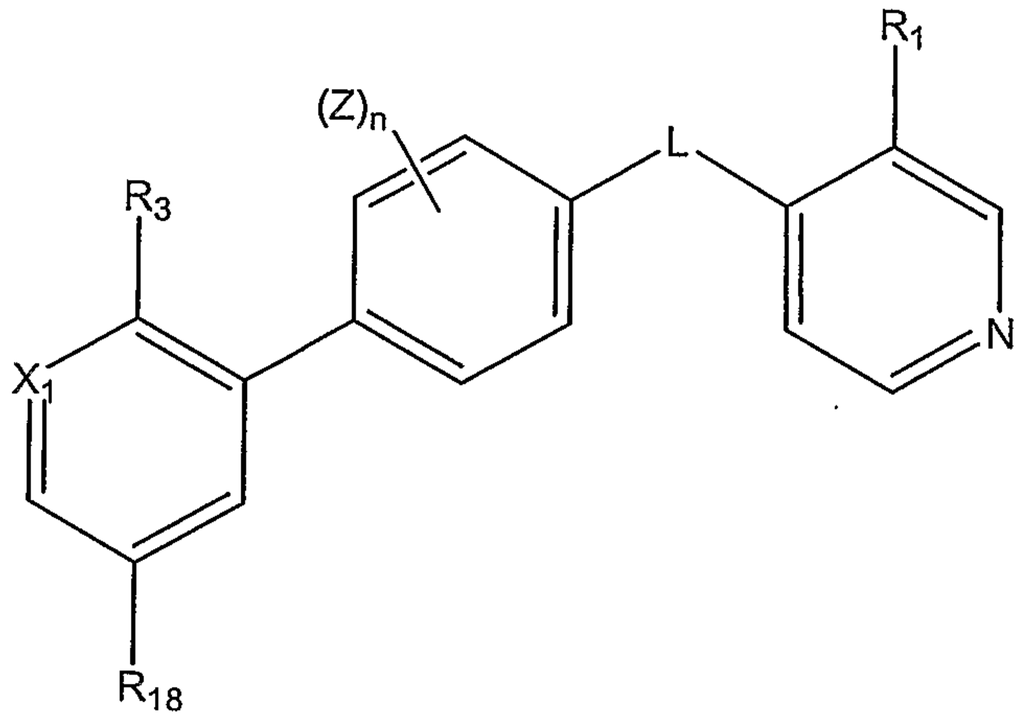
(II)

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

L, X_1, X_2, X_3, Z, R_1, R_2, R_3 and n are defined as for formula (I); and

R_4 is a halo, cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, $-P(O)(R_5)_2$, or an ester, amide or carboxylic acid bioisostere.

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

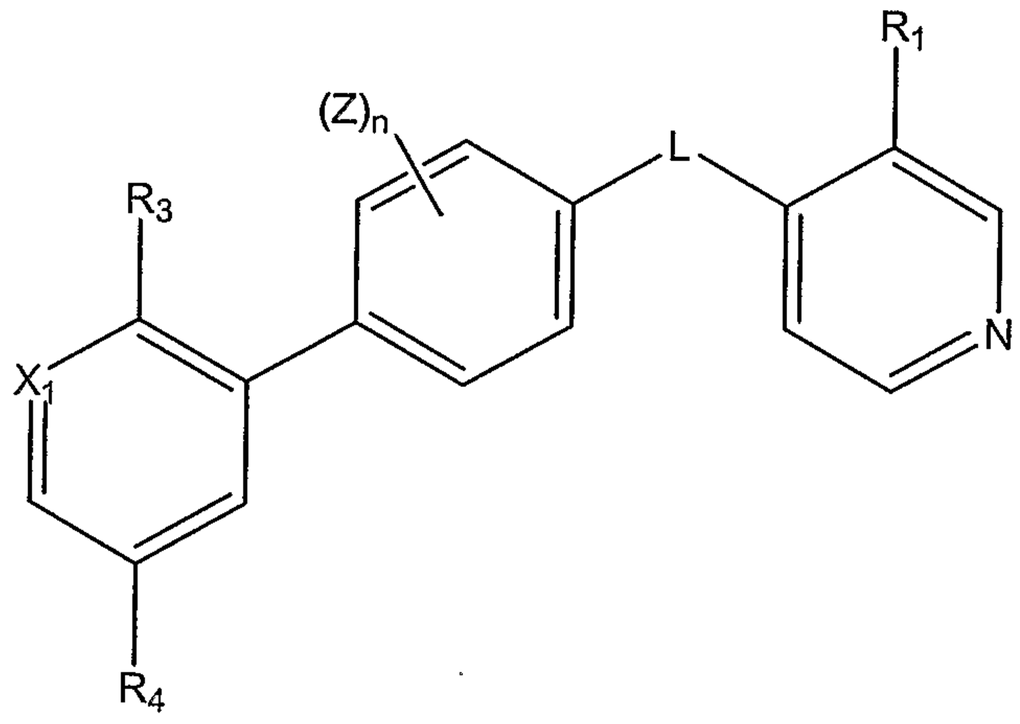


(VII)

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

X_1, L, Z, R_1, R_3, R_{18} and n are defined as for formula (I).

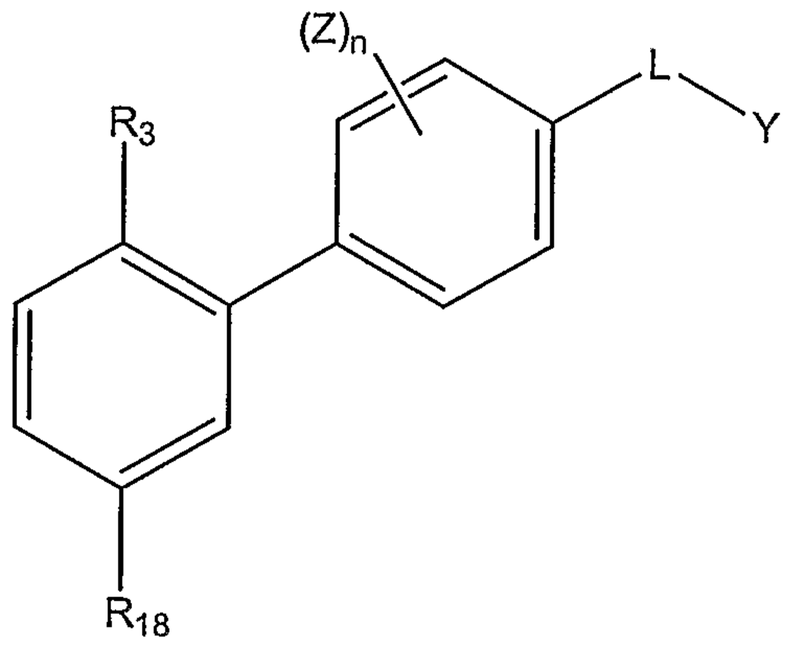
In another embodiment, the invention relates to compounds represented by formula (VIII):



(VIII)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein L, X_1, Z, R_1, R_3, R_4, and n are defined as for formula (I).

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



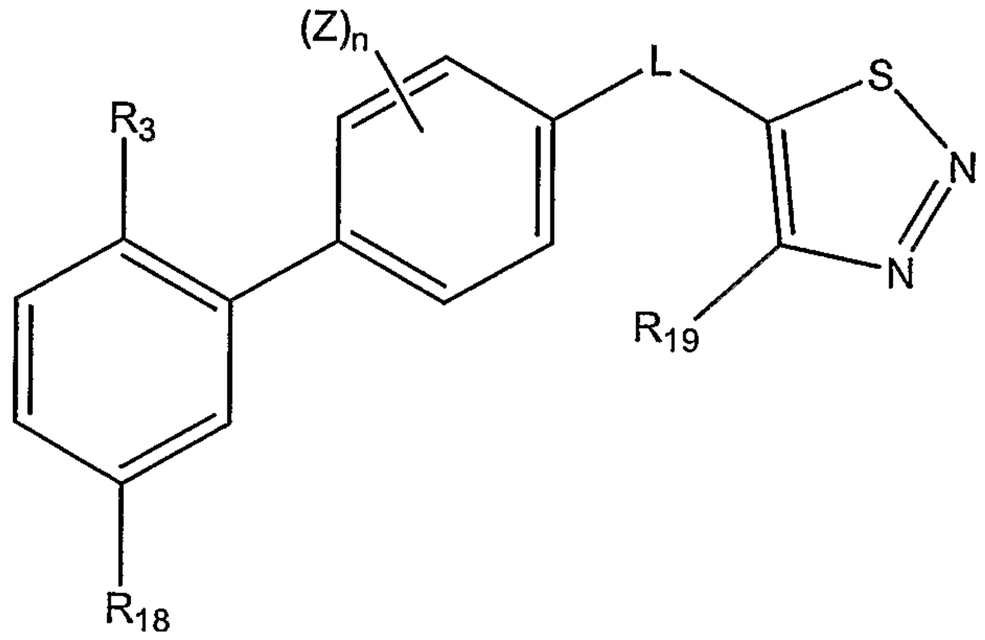
(XI)

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

Z, R_3, R_{18} and n are defined as for formula (I); and

Y is an optionally substituted 5- or 6-membered heteroaryl.

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



(XII)

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

Z, R_3, R_{18} and n are defined as for formula (I); and

R_{19} is H, a halo, an optionally substituted alkyl, an optionally substituted alkoxy, or an optionally substituted alkyl sulfanyl.

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, B-cells and/or mast 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 in need thereof, 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. In one embodiment, the subject in need of immune system suppression is an organ transplant recipient, such as a recipient of a heart, kidney, lung, liver, skin graft, islet of Langerhans, and the like. 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 mast cell degranulation, *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.

Description of the Drawing

Figure 1 is a graph showing the inhibition of chemotaxis in human and mini pig T cells after exposure to Compound 1.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

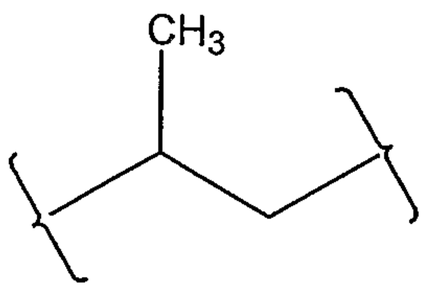
Unless otherwise specified, the below terms used herein are defined as follows:

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, anthacenyl, 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-dimtheylpentyl, 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, alkylaryl, aryloxy, arylthio, arylamino, carbocyclyl, carbocyclyloxy, carbocyclylthio, carbocyclylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylthio, and the like. In addition, any carbon in the alkyl segment may be substituted with oxygen (=O), sulfur (=S), or nitrogen ($=NR^{23}$, wherein R^{23} 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., {-CH_2-}, -{CH_2CH_2-},



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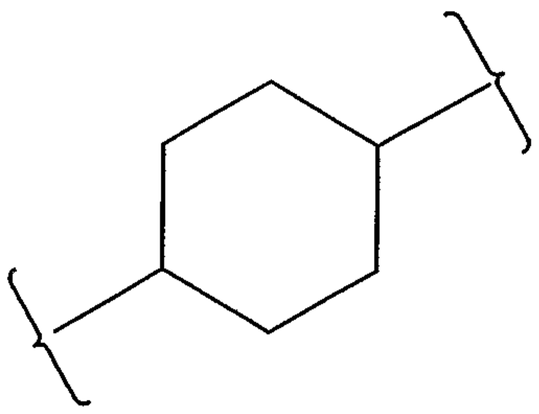


, etc., wherein the brackets indicate the points of attachement). Alkylene groups may be substituted or unsubstituted.

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, isobutylenyl, 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-nonenyl, 2-nonenyl, 3-nonenyl, 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, hydrocarbonon radical typically having from 2 to 10 carbon atoms and having at lease one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl,-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, 9-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, adamantly, decahydronaphthyl, octahydropentalene, bicycle[1.1.1]pentanyl, 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 a 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 morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, 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 heteroaryls include pyridyl, furyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, indolizinyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, pyridinyl, thiadiazolyl, pyrazinyl, quinolyl, isoquniolyl, indazolyl, benzoxazolyl, benzofuryl, benzothiazolyl, indolizinyl, imidazopyridinyl, isothiazolyl, tetrazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, qunizaolinyl, purinyl,

pyrrolo[2,3]pyrimidyl, pyrazolo[3,4]pyrimidyl or benzo(b)thienyl 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 $-CF_3$, $-CHF_2$, $-CCl_3$, $-CH_2CH_2Br$, $-CH_2CH(CH_2CH_2Br)CH_3$, $-CHICH_3$, 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 $-OCF_3$ and $-OCHF_2$.

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, an optionally substituted thiazolyl, 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 substitutent 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, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroarylalkyl 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, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroarylalkyl include an

alkyl, alkoxy, alkyl sulfanyl, alkylamino, dialkylamino, an alkenyl, an alkynyl, an cycloalkyl, an cycloalkenyl, an heterocyclyl, an aryl, an heteroaryl, an aralkyl, an heteraralkyl, a haloalkyl, $-C(O)NR_{13}R_{14}$, $-NR_{15}C(O)R_{16}$, halo, $-OR_{15}$, cyano, nitro, haloalkoxy, $-C(O)R_{15}$, $-NR_{13}R_{14}$, $-SR_{15}$, $-C(O)OR_{15}$, $-OC(O)OR_{15}$, $-OC(O)R_{15}$, $-NR_{15}C(O)NR_{13}R_{14}$, $-NR_{15}C(NR_{16})NR_{13}R_{14}$, $-OC(O)NR_{13}R_{14}$, $-NR_{15}C(O)OR_{16}$, $-S(O)_pR_{15}$, , $-NR_{16}S(O)_pR_{15}$, or $-S(O)_pNR_{13}R_{14}$, 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 heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{13} and R_{14} taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl 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 heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.

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

When a heterocyclyl, heteroaryl, or heteroaralkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic ring of a heteroaryl 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 ore 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, benzyloxycarbonyl, and the like. Suitable proetecting 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 (XII), 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 (XII), 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 (XII), or of Table 1 that comprise -NO, -NO_2, -ONO, or -ONO_2 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 (XII) 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, glucaronate, 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 (XII) 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-ethylamine; 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 (XII) 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 (XII) 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 particularly useful assay (Dean, J.H., House, R.V., and Luster, M.I. (2001). "Immunotoxicology: Effects of, and Responses to, Drugs and Chemicals." In Principles and Methods of Toxicology: Fourth Edition (A.W. Hayes, Ed.), pp. 1415-1450, Taylor & Francis, Philadelphia, Pennsylvania).

A subject in need of immune system suppression, as used herein, is a subject that is about to undergo or has had an organ transplant or a subject that has an inflammatory disorder, an immune disorder or an allergic disorder or is at risk of the reoccurrence of inflammatory disorder, an immune disorder or an allergic disorder. In one embodiment, a subject in need of immune system suppression is at risk of aquiring or developing an inflammatory disorder, an immune disorder or an allergic disorder based on, for example, the subject's medical history or genetic background. The risk of the reoccurrence of or of aquiring or developing an inflammatory disorder, an immune disorder or an allergic disorder is within the judgement of a physician skilled in the art.

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 erythematodes; 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 preeclampsia; 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 immune 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/mm^2 per day and about 10 $grams/mm^2$ per day, and preferably between 10 mg/mm^2 per day and about 1 $gram/mm^2$.

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 is 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 (XII) 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.

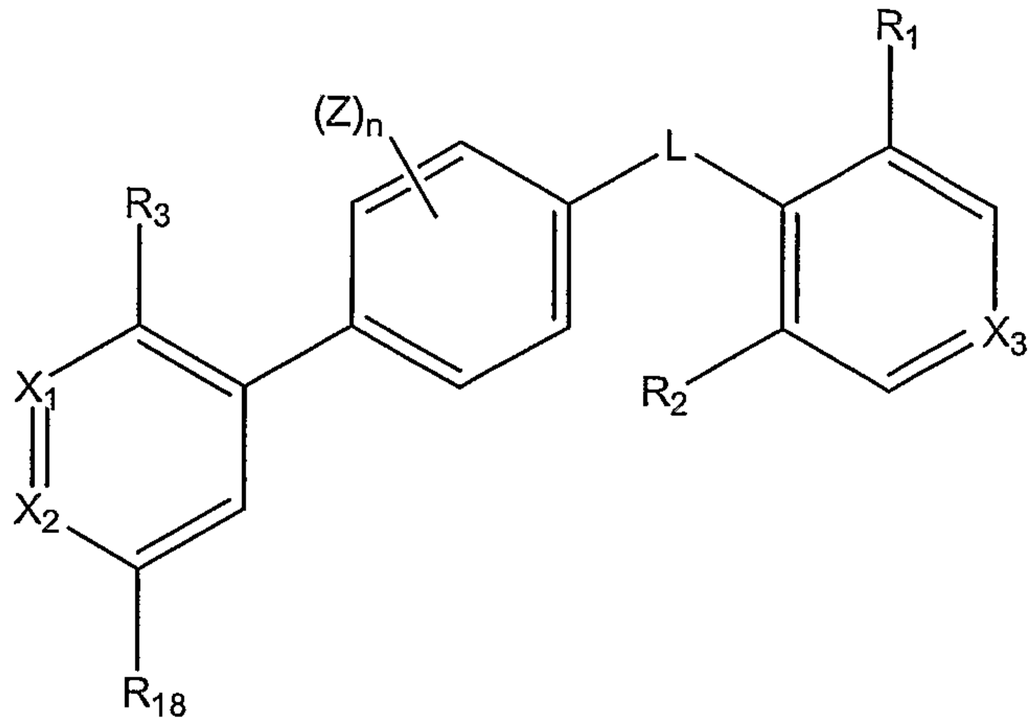
Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

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.

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):



(I)

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

L is a linker selected from the group consisting of a covalent bond, –NRCH$_2$-, -CH$_2$NR-, –C(O)-, –NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, –NR-C(S)-, -C(S)-NR-;

X_1 and X_3 are each, independently, CH or N;

X_2 is CH, CR_{10} or N;

each Z is independently selected from the group consisting of a lower alkyl, a lower haloalkyl, a halo, a lower alkoxy, a lower alkyl sufanyl, cyano, nitro, or lower haloalkoxy;

R, for each occurrence is independently selected from -H, an alkyl, -C(O)R_5, or -C(O)OR_5;

R_1 and R_2 are each, independently, a halo, a haloalkyl, a lower alkyl, a lower alkoxy, or a haloalkoxy;

R_3 is an alkyl, a haloalkyl, a halo, a haloalkoxy, -OR_5, -SR_5, or -NR_6R_7;

R_{18} is a halo, cyano, nitro, -C(O)R_5, -C(O)OR_5, -C(O)SR_5, -C(O)NR_6R_7, -C(S)R_5, -C(S)OR_5, -C(S)SR_5, -C(S)NR_6R_7, -C(NR_8)R_5, -C(NR_8)OR_5, -C(NR_8)SR_5, -C(NR_8)NR_6R_7, -S(O)$_p$$R_5$, -S(O)$_pNR_5$, -S(O)$_pOR_5$, -P(O)(O$R_5$)$_2$, -OP(O)(O$R_5$)$_2$, -P(O)($R_5$)$_2$, a five or six membered optionally substituted heterocycloalkyl, a five or six membered optionally substituted heterocyclyl, or a five or six membered optionally substituted heteroaryl;

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;

R_6 and R_7, 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_6 and R_7 taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_8, for each occurrence, is independently –H, a halo, an alkyl, $-OR_5$, $-NR_6R_7$, $-C(O)R_5$, $-C(O)OR_5$, or $-C(O)NR_6R_7$;

R_{10} is a lower alkyl, a lower alkoxy, a halo, a lower haloalkyl, a lower haloalkoxy, a cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, or $-P(O)(R_5)_2$;n is zero or an integer from 1 to 4; and

p, for each occurrence, is independently 1 or 2.

In one embodiment of the compounds represented by formula (I), R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. Preferably, R_{18} is unsubstituted or substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

In another embodiment of the compounds represented by formula (I), R_{18} is an ester, amide or carboxylic acid bioisostere. Preferably, when R_{18} is an ester, amide or carboxylic acid bioisostere, it is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

In another embodiment of the compounds represented by formula (I), R_{18} is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

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

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-3-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-4-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-isoxazole-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-1*H*-pyrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1*H*-pyrrol-2-yl)-biphenyl-4-yl]- benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(5-oxo-4,5-dihydro-[1,2,4]- oxadiazol-3-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(morpholino-4-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide;

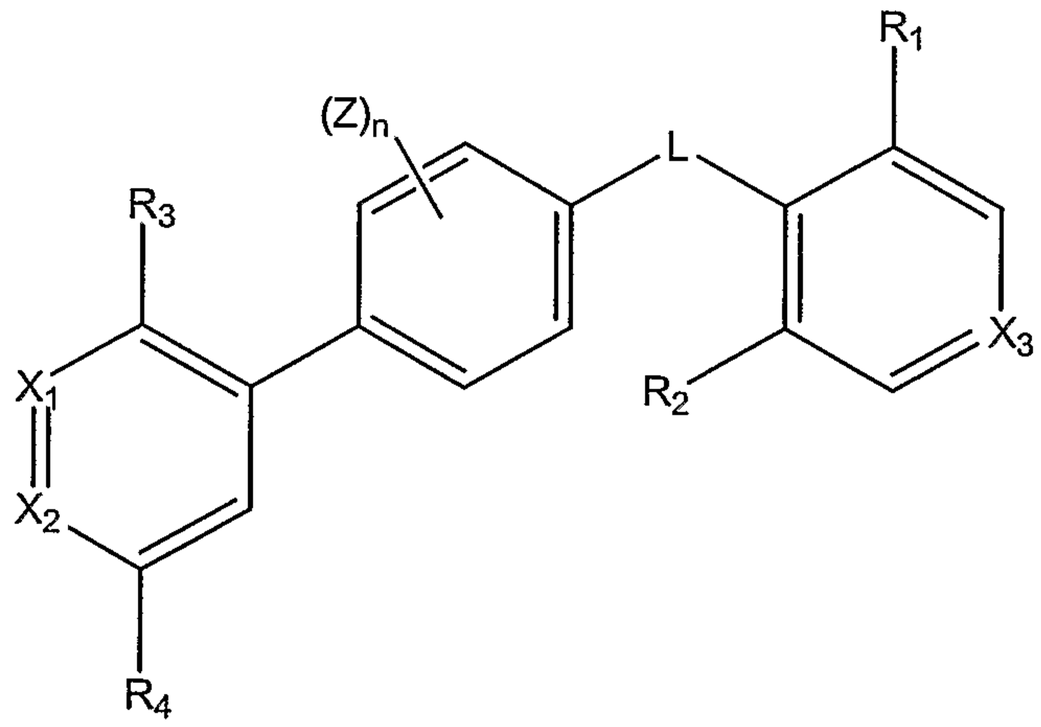
2,6-Difluoro-N-[2'-methyl-5'-(5-amino-[1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl- 4-yl}-N-methyl-benzamide;

2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl- 4-yl}-benzamide;

and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

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



(II)

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

L, X_1, X_2, X_3, Z, R_1, R_2, R_3 and n are defined as for formula (I); and

R_4 is a halo, cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, $-P(O)(R_5)_2$, or an ester, amide or carboxylic acid bioisostere.

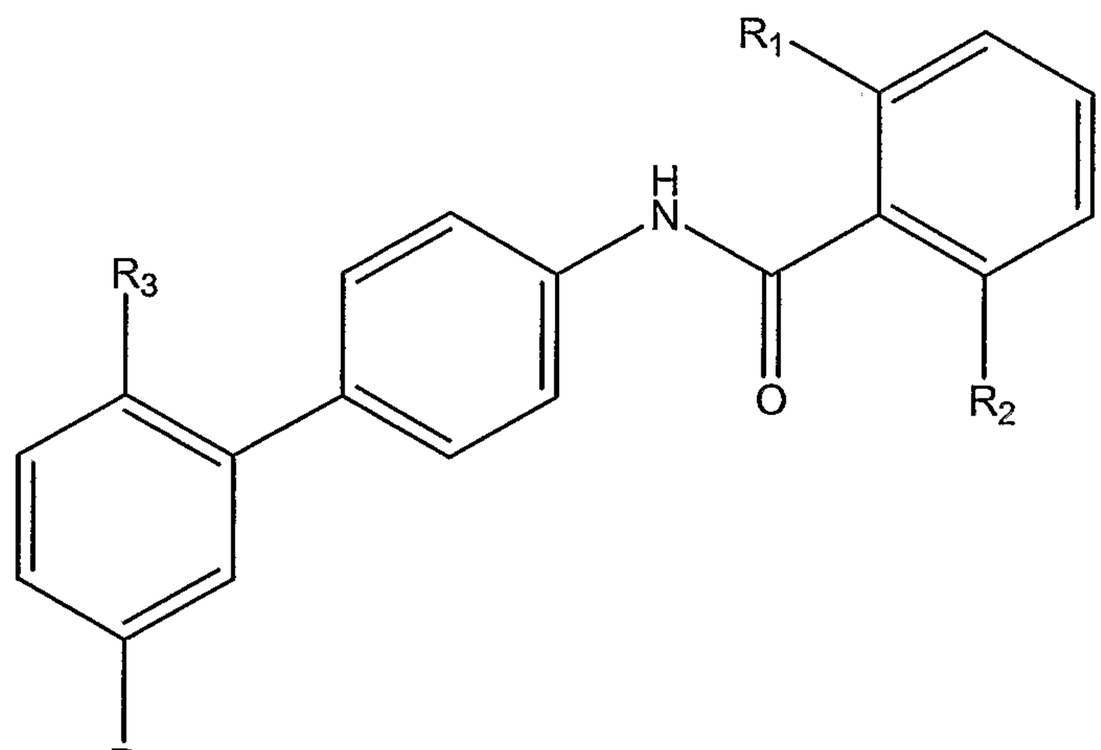
In one embodiment of the compounds represented by formula (I) or (II), n is 0. In another embodiment, n is 1. In another embodiment, n is 2.

In another embodiment of the compounds represented by formula (I) or (II), Z, for each occurrence, is independently, a lower alkyl, a lower alkoxy, a lower haloalkoxy, a halo, cyano, or haloalkyl and n is 1 or 2.

In another embodiment of the compounds represented by formula (I) or (II), L is –NHC(O)-.

In another embodiment of the compounds represented by formula (I) or (II), L is -$NHCH_2$-.

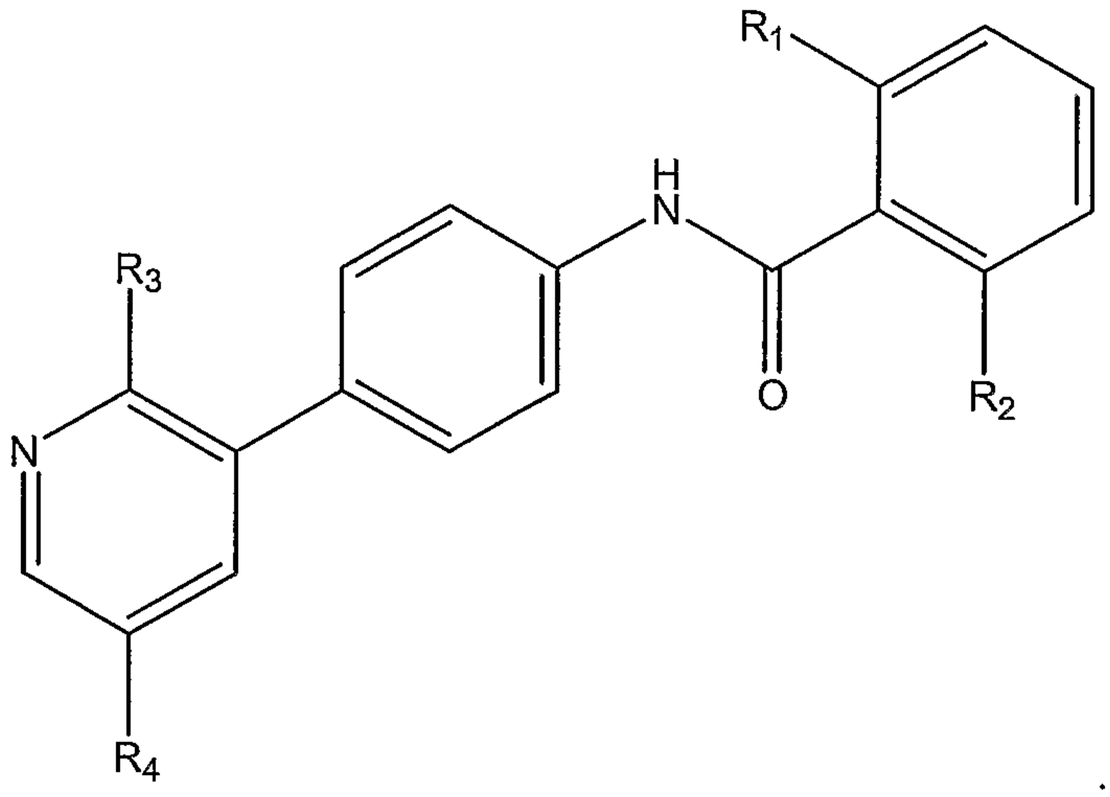
In another embodiment, the invention relates to compounds of formula (III):



(III)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_2, R_3, and R_4 are defined as above.

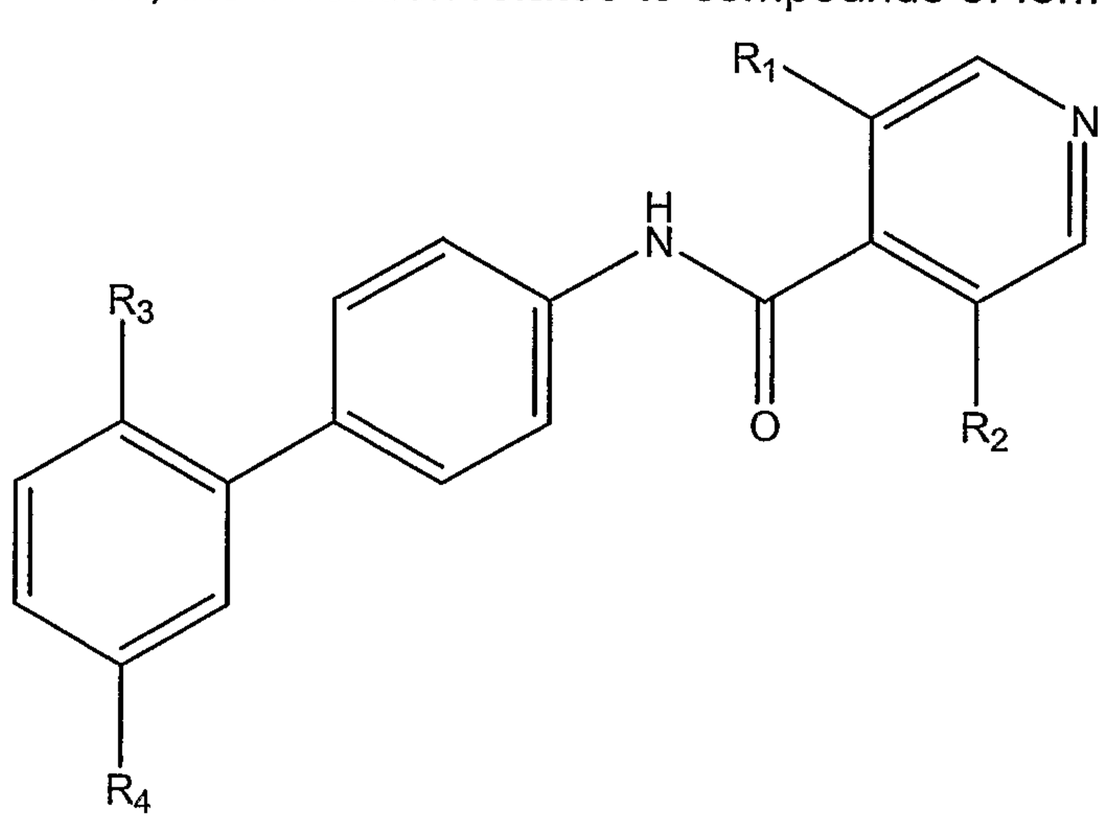
In another embodiment, the invention relates to compounds of formula (IV):



(IV)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_2, R_3, and R_4 are defined as above.

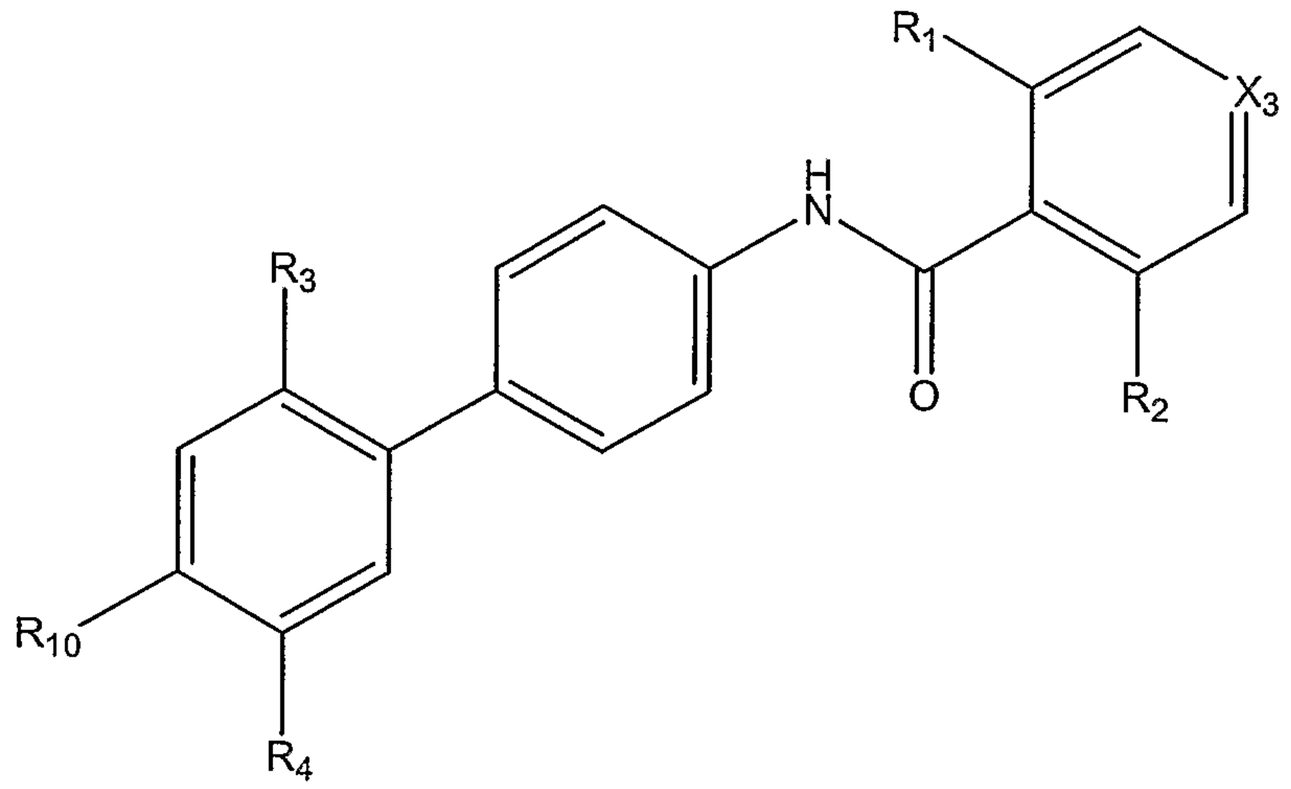
In another embodiment, the invention relates to compounds of formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_2, R_3, and R_4 are defined as above.

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



(VI)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_2, R_3, R_4 and R_{10} are defined as above, and

In another embodiment of the compounds represented by formula (I), (II), (III), (IV), (V), or (VI), R_1 and R_2 are each, independently, a halo.

In another embodiment of the compounds represented by formula (I), (II), (III), (IV), (V), or (VI), R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, or a halo.

In another embodiment of the compounds represented by formula (II), (III), (IV), (V), or (VI), R_4 is a bioisostere of an ester, amide, or carboxylic acid. For example, R_4 is a 5-membered heteroaryl, such as, an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

In another embodiment of the compounds represented by formula (II), (III), (IV), (V), or (VI), R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

In another embodiment of the compounds represented by formula (I), (II), (III), (IV), (V), or (VI), R_1 and R_2 are each a fluoro group.

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

4'-(2,6-Difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid methyl ester;

6-Chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-(carboxylic acid 2-methoxyethyl ester);

2,6-Difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-bezamide;

4'-[(3,5-Difluoro-pyridine-4-cabonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester;

N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-(2'-methyl-5'- oxazol-2-yl-biphenyl-4-yl)- isonicotinamide;

2,6-Difluoro-N-(2'-methoxy-5'- oxazol-2-yl-biphenyl-4-yl)- benzamide;

2,6-Difluoro-N-[2'-methyl-5'- (oxazol-5-yl)-biphenyl-4-yl]- benzamide;

3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-chloro-5'-(oxazol-2-yl)-biphenyl-4-yl]- benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(4-trifluoromethyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-chloro-5'- (thiazol-2-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide

2,6-Difluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-benzamide;

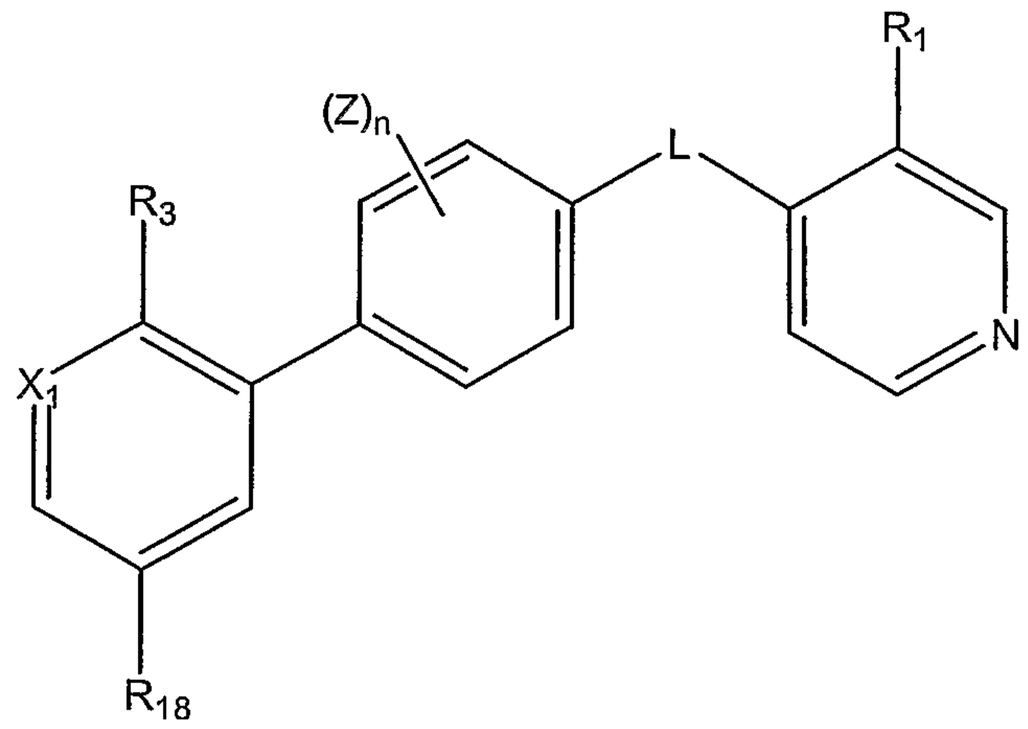
2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

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



(VII)

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

X_1, L, Z, R_1, R_3, R_{18} and n are defined as for formula (I).

In one embodiment of the compounds represented by formula (VII), R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. Preferably, R_{18} is unsubstituted or substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

In another embodiment of the compounds represented by formula (VII), R_{18} is an ester, amide or carboxylic acid bioisostere. Preferably, when R_{18} is an ester, amide or carboxylic acid bioisostere, it is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

In another embodiment of the compounds represented by formula (VII), R_{18} is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

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

3-Methyl-N-[5'-(pyridin-3-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]- isonicotinamide;

3-Methyl-N-[5'-(3-methyl-isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methoxy-5'-(furan-2-yl)-biphenyl-4-yl]-isonicotinamide;

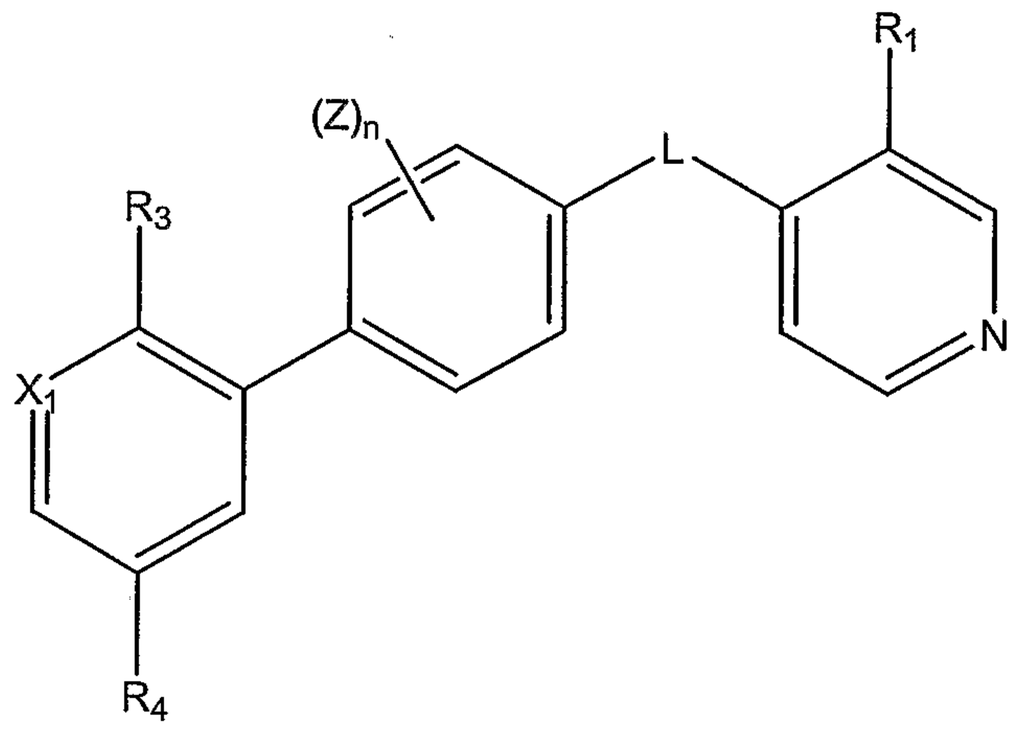
3-Methyl-N-[5'-(thien-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

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



(VIII)

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

X_1, L, Z, R_1, R_3, R_4 and n are defined as for formula (I).

In another embodiment of the compounds represented by formula (VII) or (VIII), n is 0.

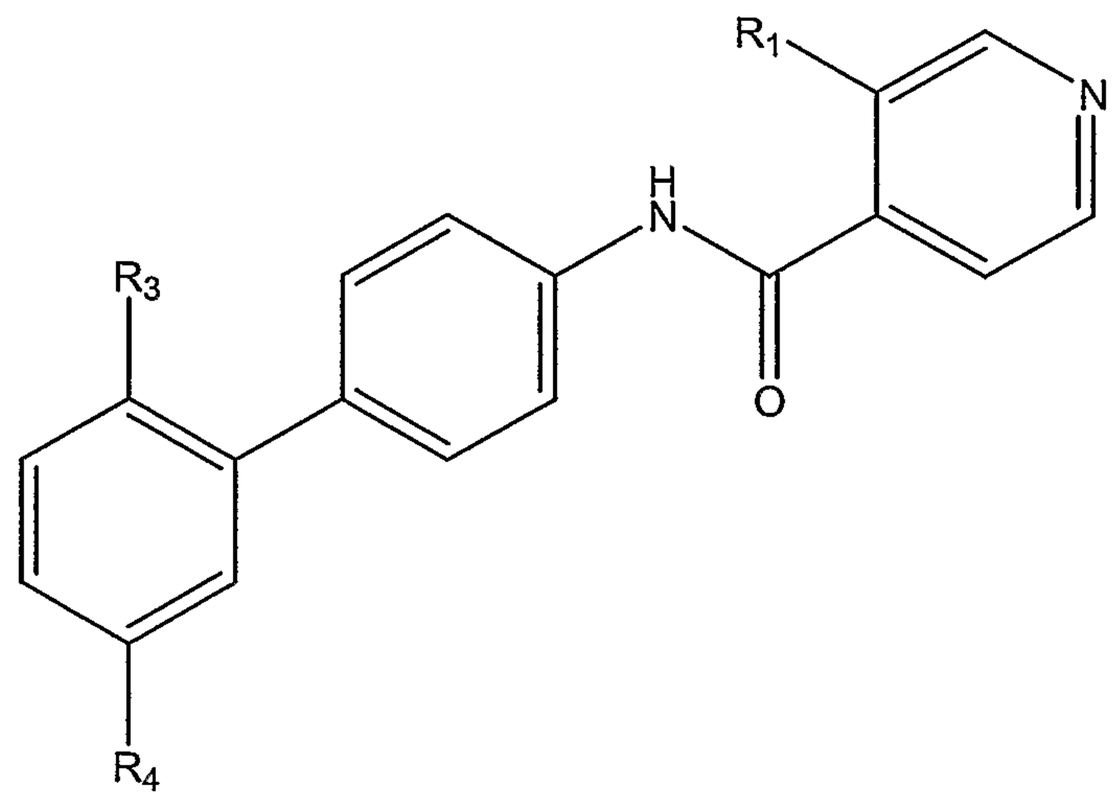
In another embodiment of the compounds represented by formula (VII) or (VIII), X_1 is CH.

In another embodiment of the compounds represented by formula (VII) or (VIII), X_1 is N.

In another embodiment of the compounds represented by formula (VII) or (VIII), Z, for each occurrence, is independently, a lower alkyl, a lower alkoxy, a lower haloalkoxy, a halo, cyano, or haloalkyl and n is 1 or 2.

In another embodiment of the compounds represented by formula (VII) or (VIII), L is –NHC(O)-.

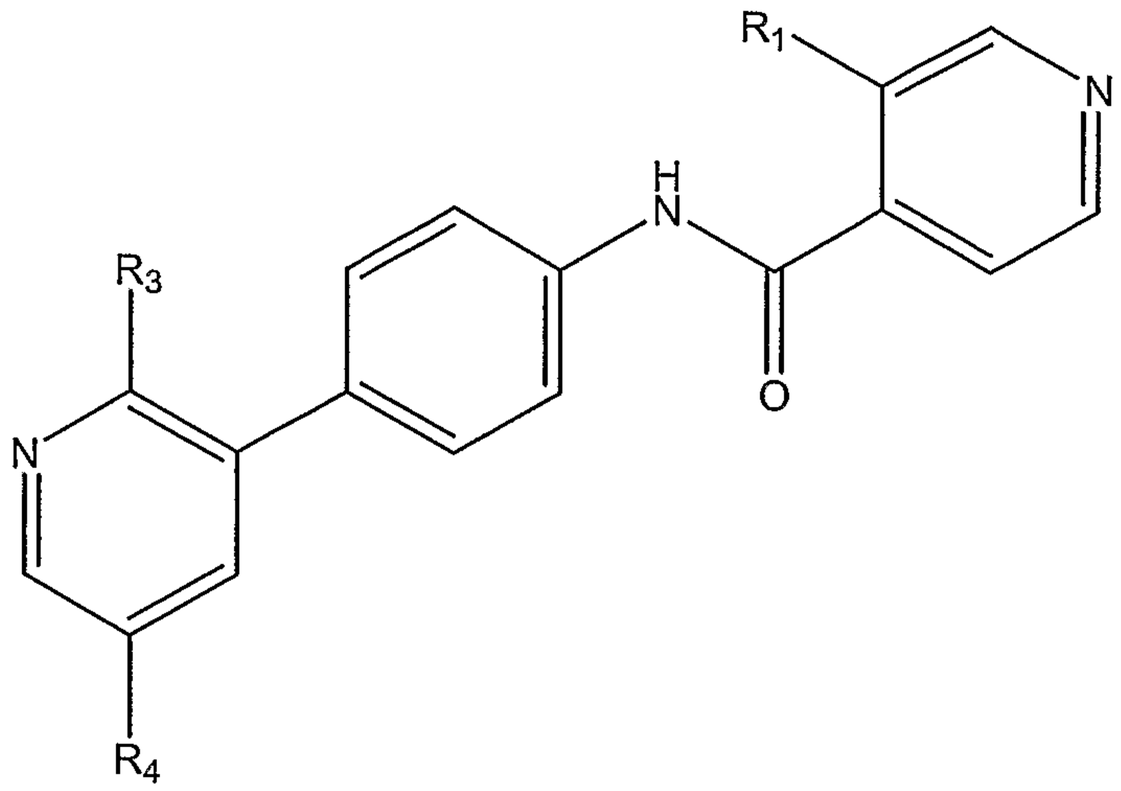
In another embodiment, the invention relates to compounds of formula (IX):



(IX)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_3, and R_4 are defined as above.

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



(X)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein R_1, R_3, and R_4 are defined as above.

In another embodiment of the compounds represented by formula (VII), (VIII), (IX) or (X), R_1 is a lower alkyl or a halo.

In another embodiment of the compounds represented by formula (VII), (VIII), (IX) or (X), R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

In another embodiment of the compounds represented by formula (VII), (VIII), (IX) or (X), R_3 is a lower alkyl.

In another embodiment of the compounds represented by formula (VIII), (IX) or (X), R_4 is a bioisostere of an ester, amide, or carboxylic acid.

In another embodiment of the compounds represented by formula (VIII), (IX) or (X), R_4 is a 5-membered heteroaryl.

In another embodiment of the compounds represented by formula (VIII), (IX) or (X), R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an

optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

In another embodiment of the compounds represented by formula (VIII), (IX) or (X), R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

In another embodiment of the compounds represented by formula (VII), (VIII), (IX) or (X), R_1 is fluoro or methyl.

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

3-Methyl-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)- isonicotinamide;

3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)- isonicotinamide;

3-Fluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)- isonicotinamide;

4'-[(3-Fluoro-pyridine-4- carbonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester;

3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotin- amide;

3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotin- amide;

3-Methyl-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(4-methyl-thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-2-yl)-2'- (N,N-dimethylamino)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

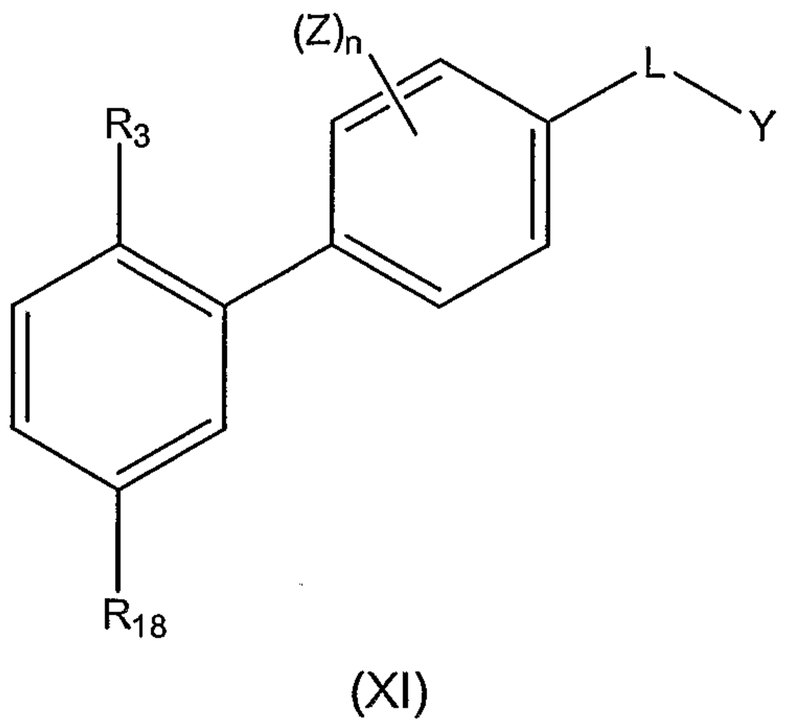
3-Fluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

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



(XI)

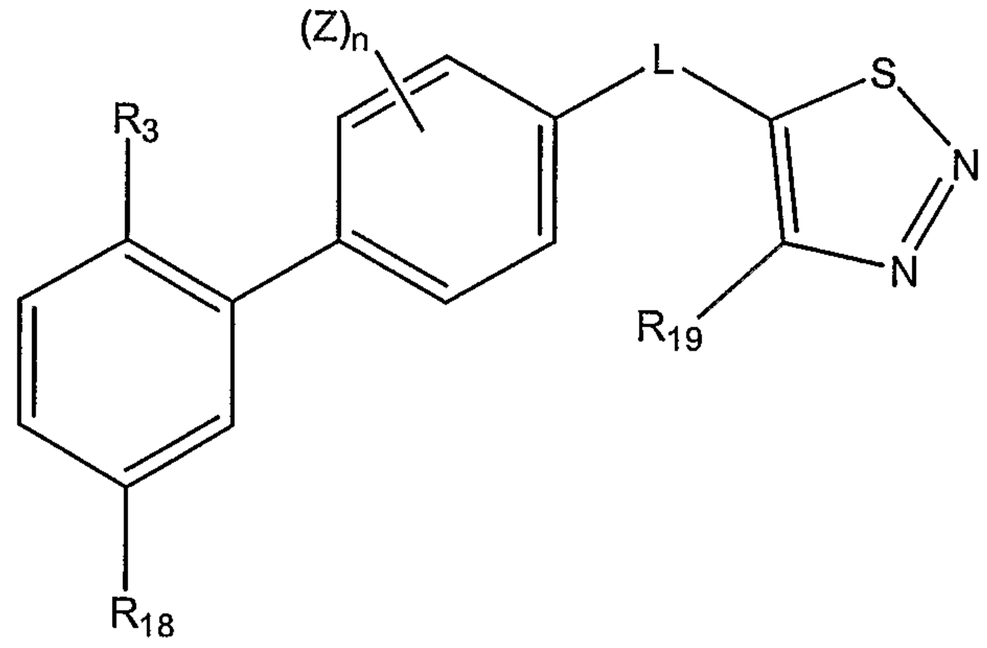
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

Z, R_3, R_{18} and n are defined as for formula (I); and

Y is an optionally substituted 5- or 6-membered heteroaryl.

In one embodiment of the compounds represented by formula (XI), Y is an optionally substituted 5-membered heteroaryl. For example, Y may be an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. Preferably, Y is an optionally substituted [1,2,3]thiadiazolyl.

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



(XII)

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

Z, R_3, R_{18} and n are defined as for formula (I); and

R_{19} is H, a halo, an optionally substituted alkyl, an optionally substituted alkoxy, or an optionally substituted alkyl sulfanyl.

In another embodiment of the compounds represented by formula (XII), R_{19} is a halo or a lower alkyl. Preferably, R_{19} is a lower alkyl.

In another embodiment of the compounds represented by formula (X) or (XII), n is 0.

In another embodiment of the compounds represented by formula (X) or (XII), Z, for each occurrence, is independently, a lower alkyl, a lower alkoxy, a lower haloalkoxy, a halo, cyano, or haloalkyl and n is 1 or 2.

In another embodiment of the compounds represented by formula (X) or (XII), L is –NHC(O)-.

In another embodiment of the compounds represented by formula (XI) or (XI), R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

In another embodiment of the compounds represented by formula (XI) or (XI), R_3 is a lower alkyl.

In one embodiment of the compounds represented by formula (XI), R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. Preferably, R_{18} is unsubstituted or

substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

In another embodiment of the compounds represented by formula (XI) or (XI), R_{18} is a bioisostere of an ester, amide, or carboxylic acid.

In another embodiment of the compounds represented by formula (XI) or (XI), R_{18} is a 5-membered heteroaryl.

In another embodiment of the compounds represented by formula (XI) or (XI), R_{18} is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

In another embodiment of the compounds represented by formula (XI) or (XI), R_{18} is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

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

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-3-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-2-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid [2'-methoxy-5'-(oxazol-5-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(isoxazol-5-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(thiazol-2-yl)-biphenyl-4-yl]-amide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs 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 (XII), 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 (XII), 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 (XII), 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 (XII), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, are particularly useful inhibiting immune cell (e.g., T-cells, B-cells, and/or mast cell) 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. The compounds of the invention inhibit IL-2 secretion by T-cells and/or B-cells. In one embodiment, a compound of any one of formulas (I) through (XII) 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, the compounds of the invention inhibit mast cell degranulation in response to an antigen.

In another embodiment, compounds of of any one of formulas (I) through (XII), 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 (XII), 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 (XII), or Table 1, inhibits cytokine production in a mammal (e.g., a human).

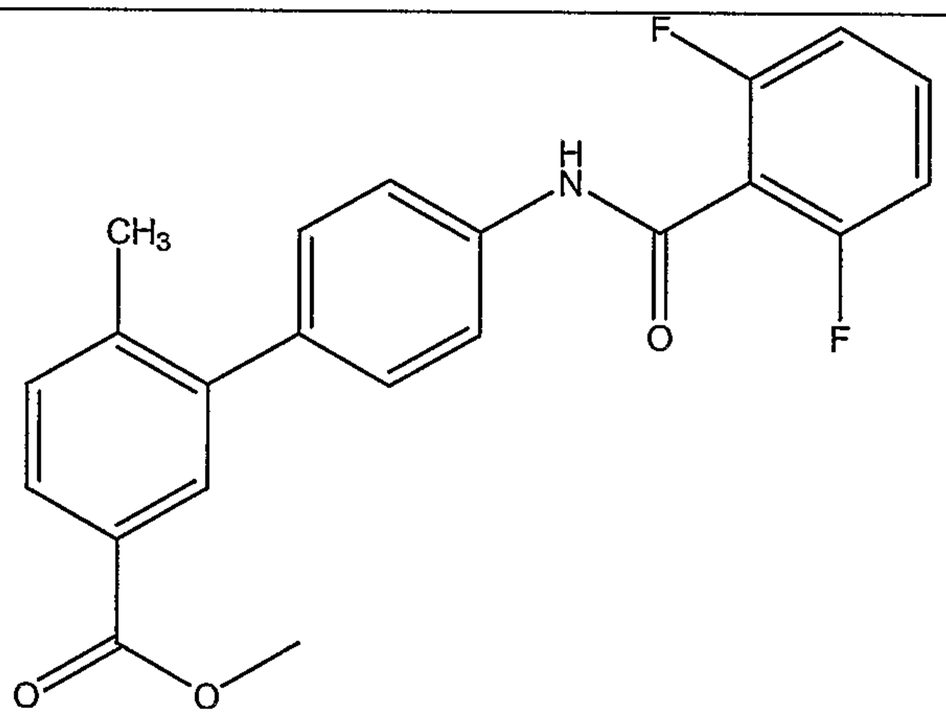
In another embodiment, compounds of any one of formulas (I) through (XII), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels. In one embodiment, a compound of any one of

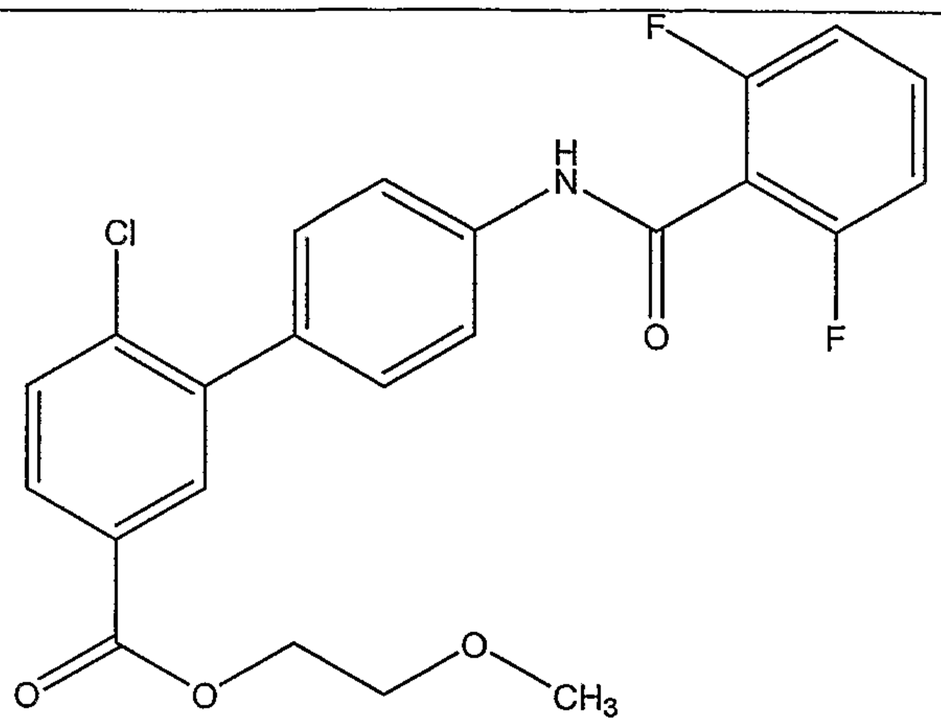
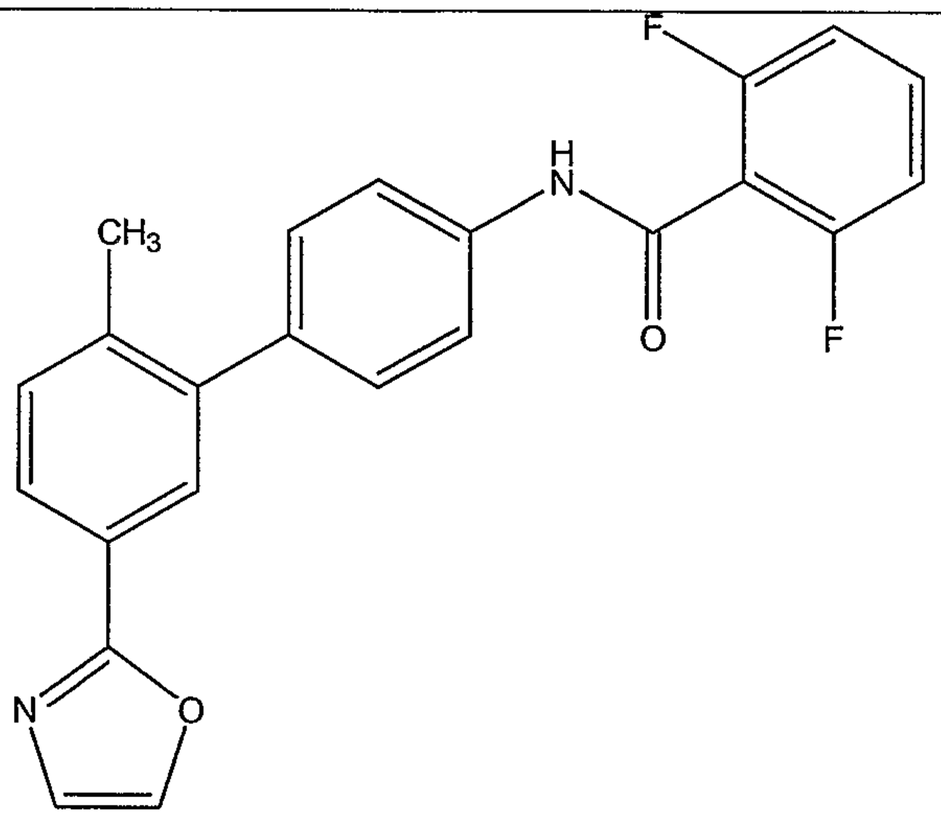
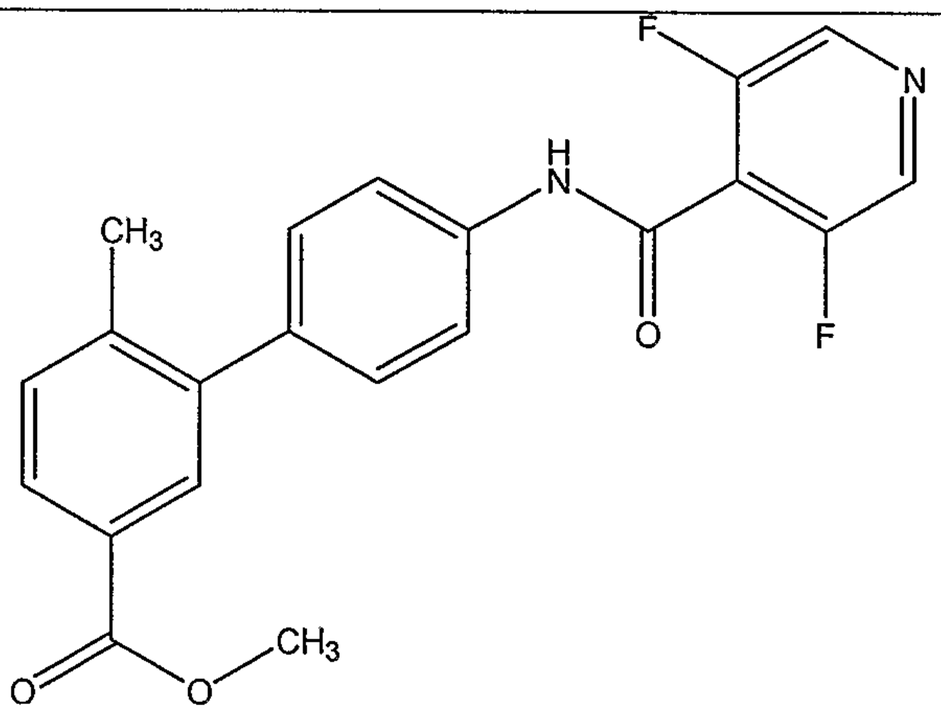
formulas (I) through (XII) or Table 1 can inhibit the influx of calcium ions into an immune cell (e.g., T cells and/or B cells and/or mast cells) by inhibiting the action of CRAC ion channels. The inhibition of the CRAC channel may be directed or indirect inhibition of the channel activity. In general, a decrease in I_{CRAC} current upon contacting a cell with a compound is one indicator that the compound inhibitions CRAC ion channels. I_{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 (XII) or Table 1 modulates an ion channel (e.g., CRAC channels) in a mammal (e.g., a human).

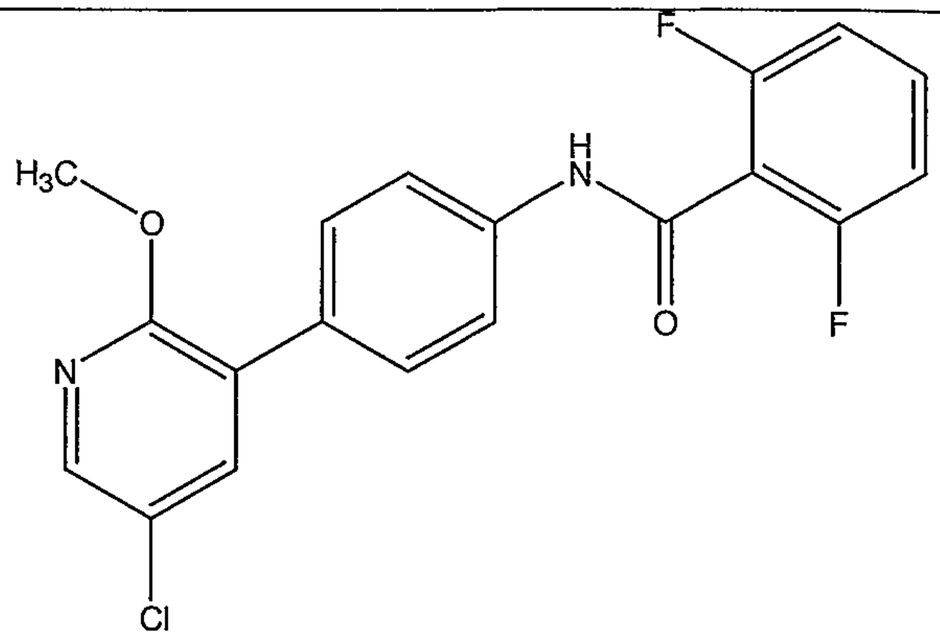
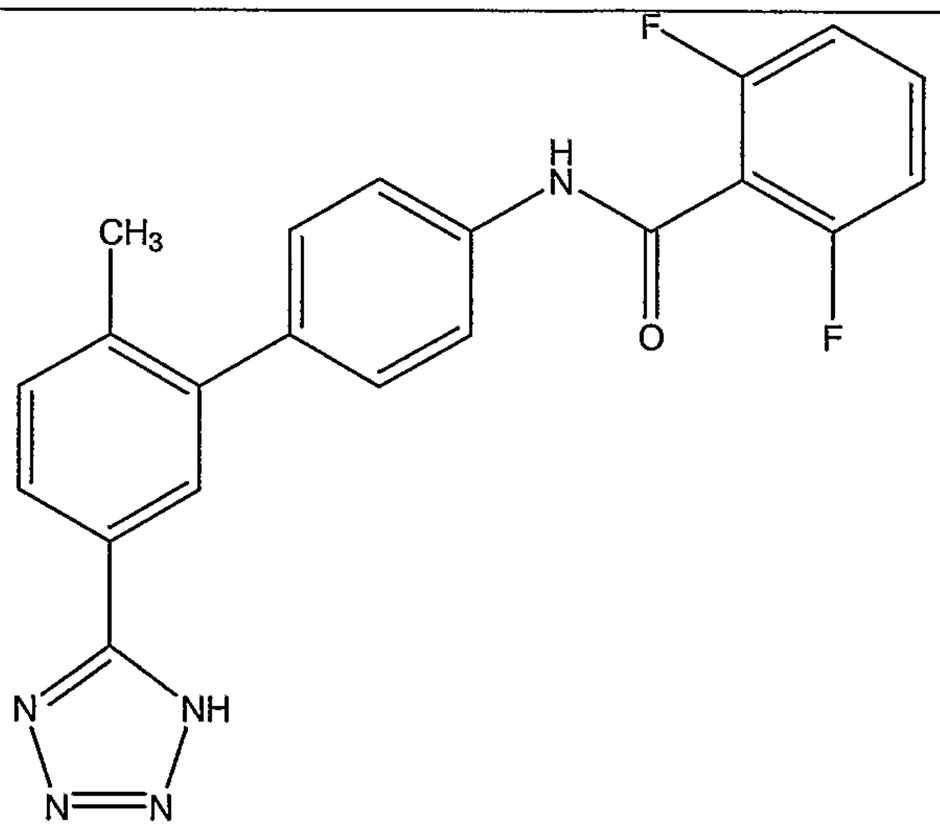
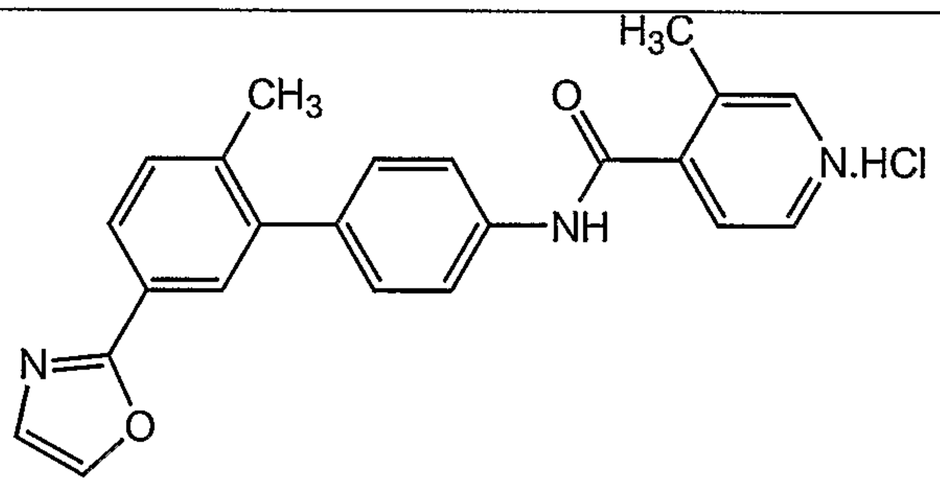
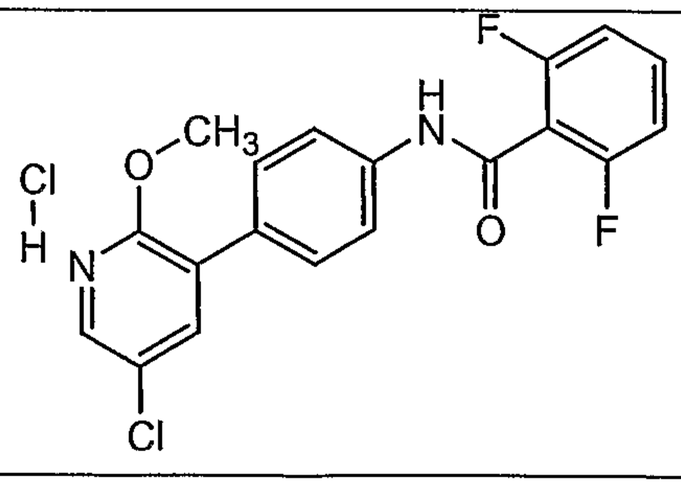
EXEMPLARY COMPOUNDS OF THE INVENTION

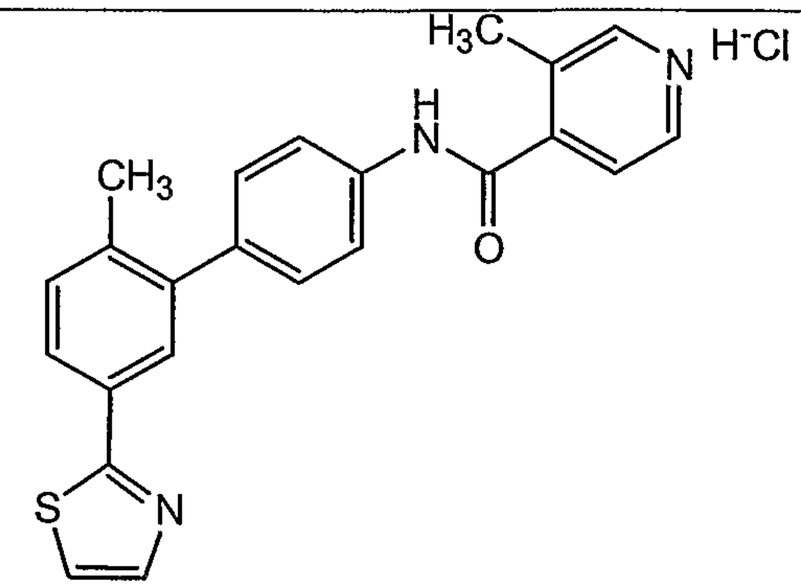
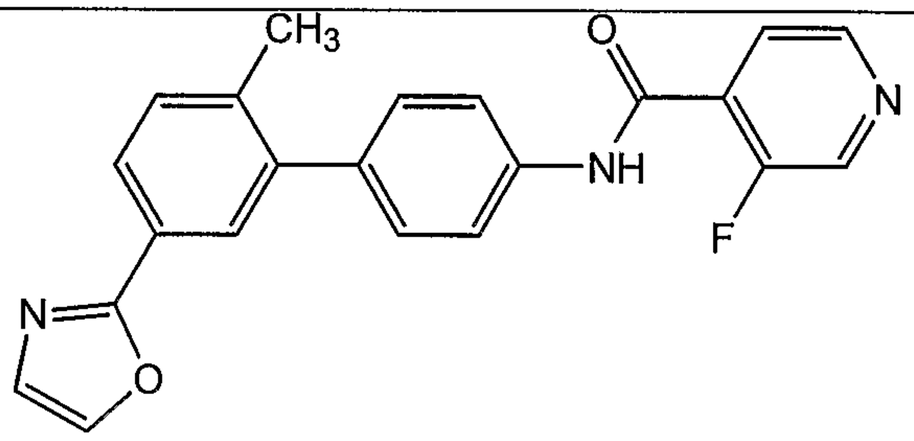
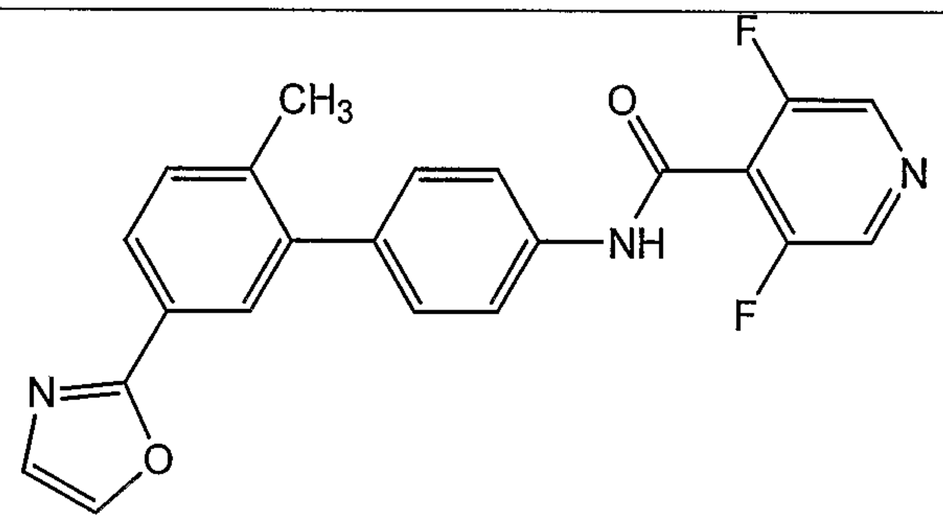
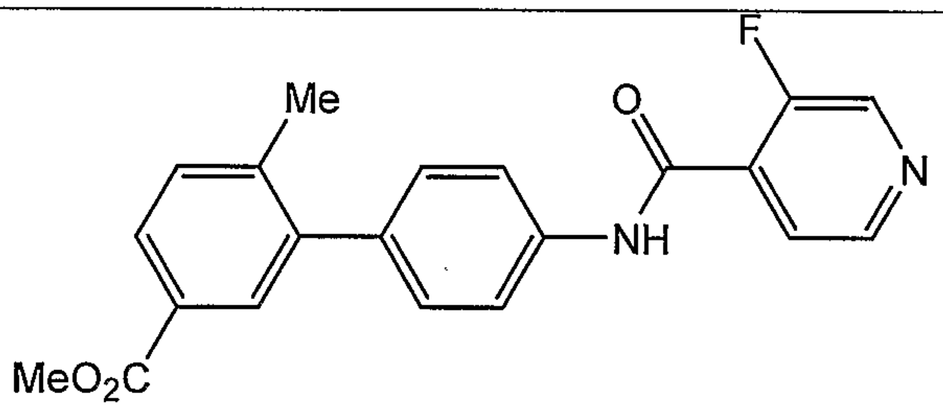
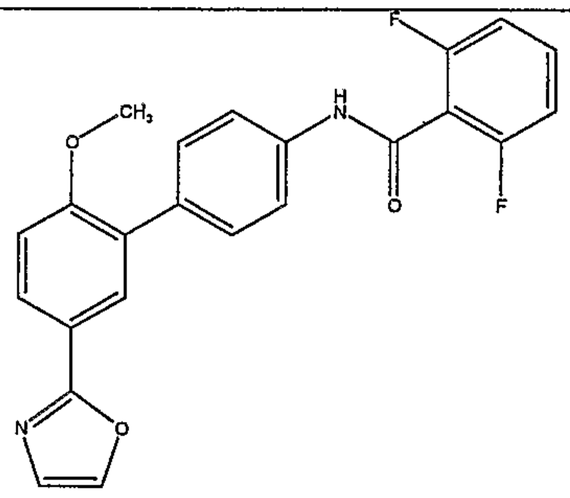
Exemplary compounds of the invention are depicted in Table 1 below.

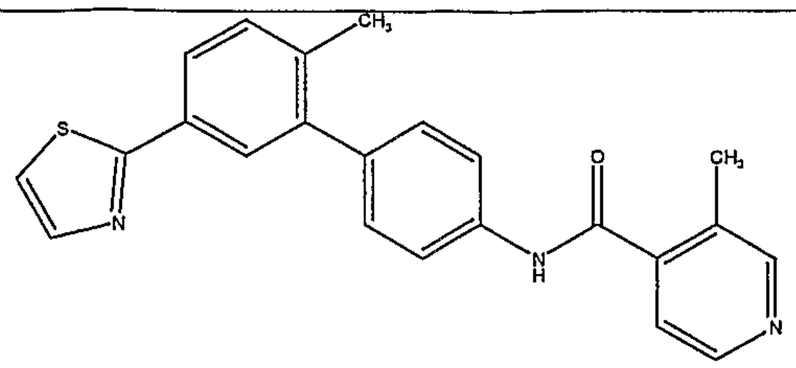
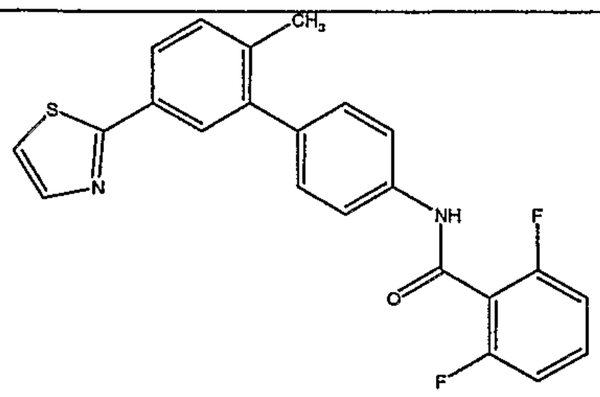
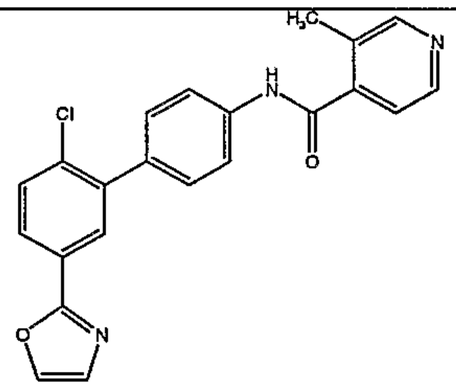
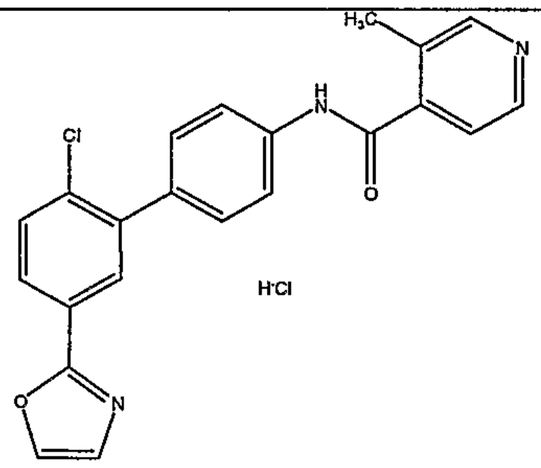
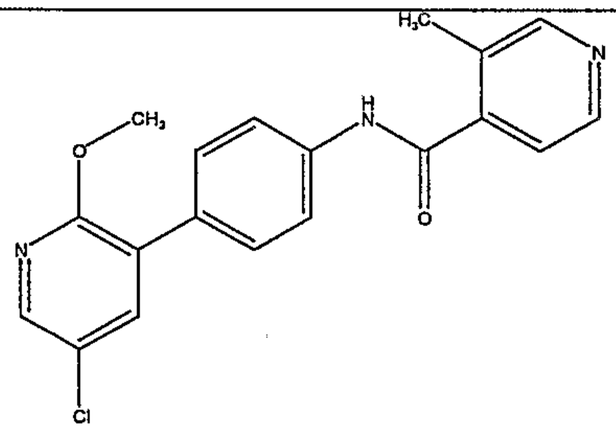
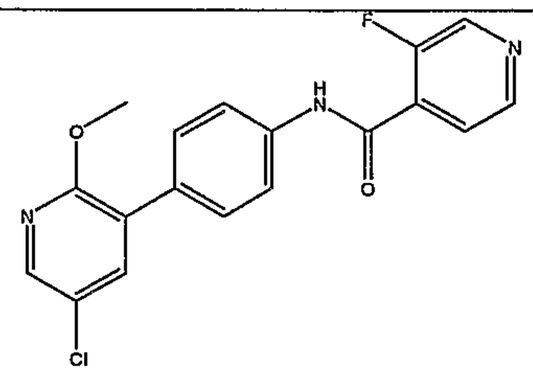
Table 1

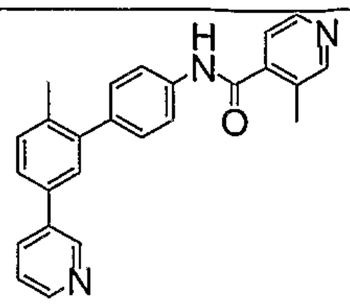
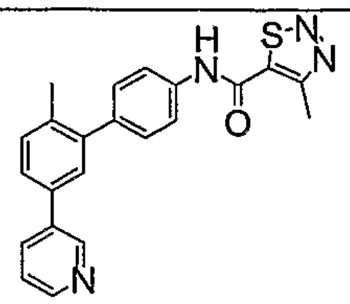
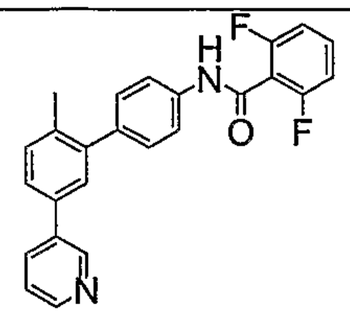
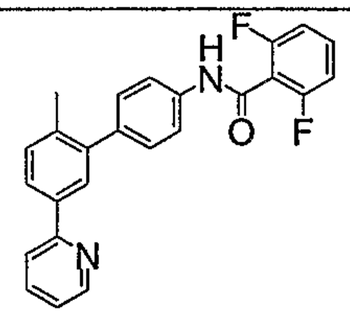
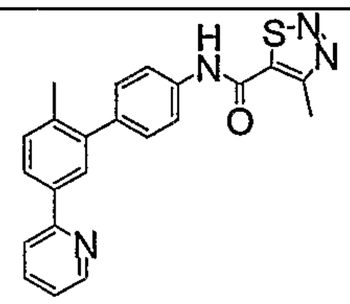
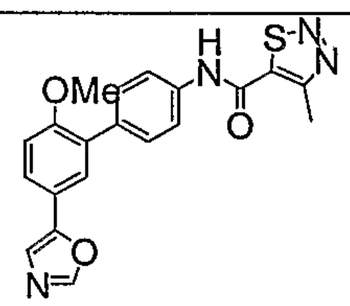
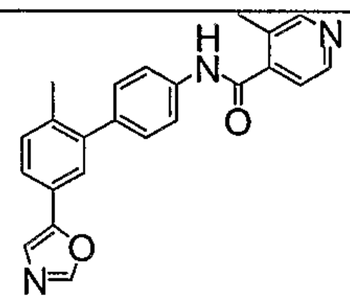
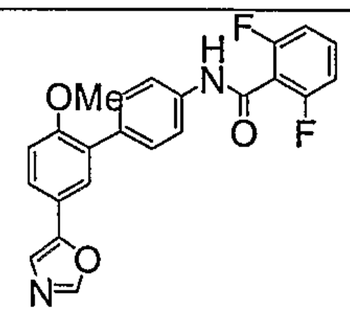
Compound No.	Structure	Chemical Name
1		4'-(2,6-Difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid methyl ester

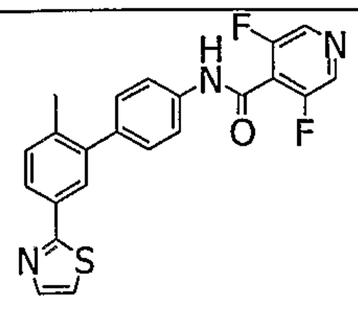
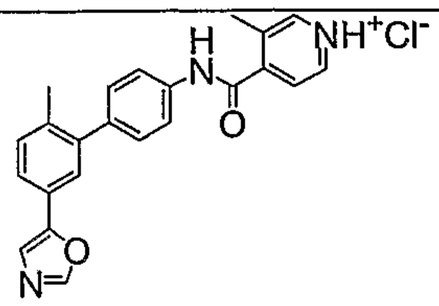
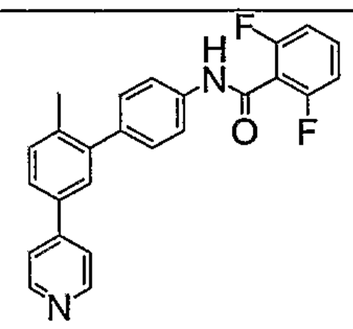
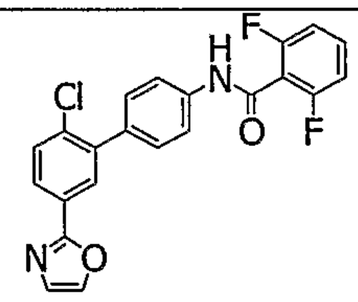
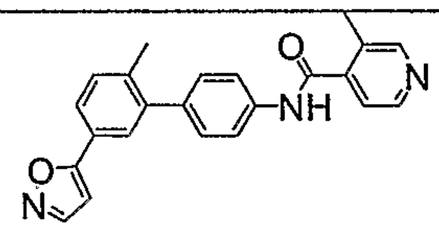
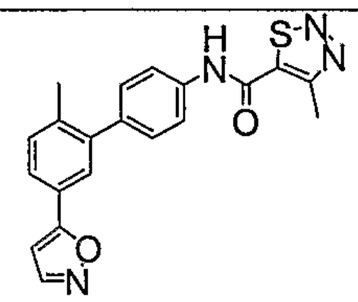
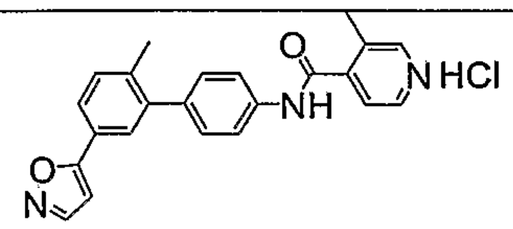
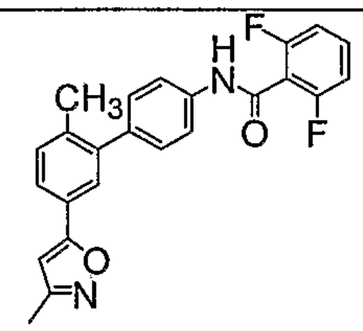
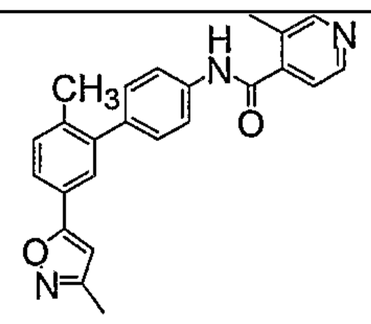
2		6-Chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-(carboxylic acid 2-methoxyethyl ester)
3		2,6-Difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-bezamide
4		4'-[(3,5-Difluoro-pyridine-4-cabonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester

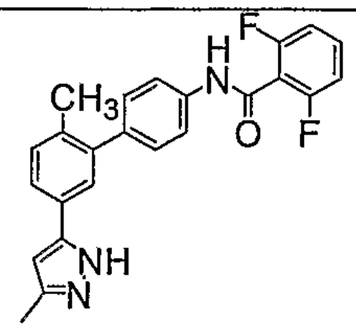
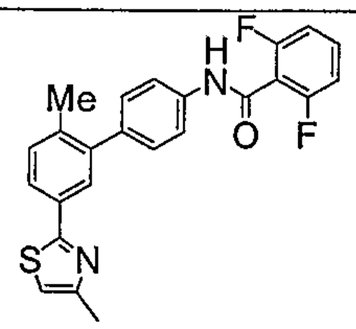
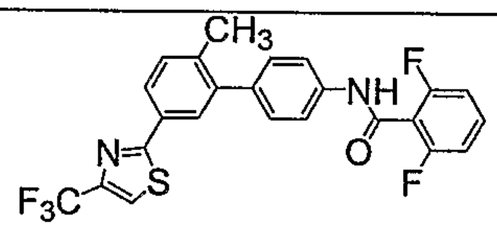
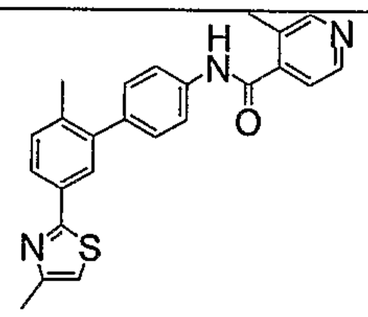
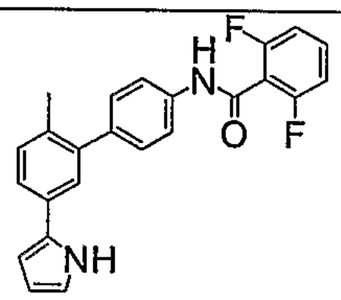
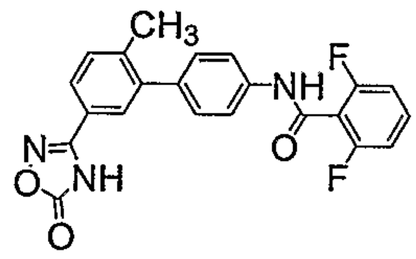
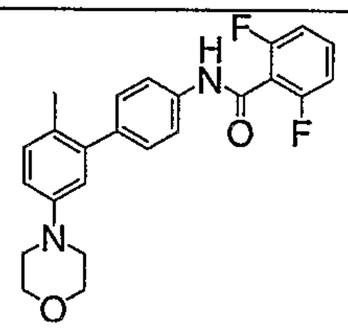
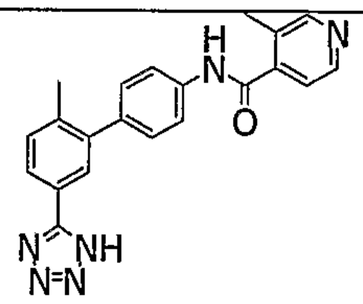
5		N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide
6		2,6-Difluoro-N-[2'-methyl-5'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-benzamide
7		3-Methyl-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide, hydrochloride
8		N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide, hydrochloride

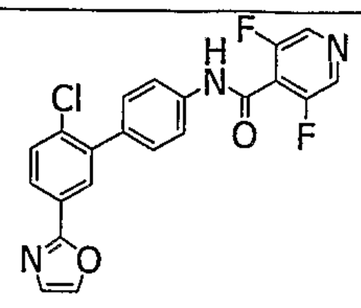
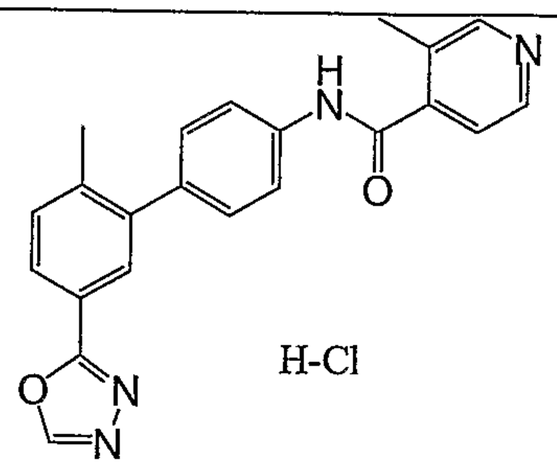
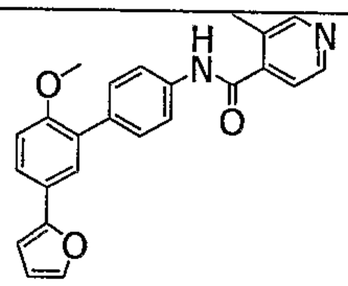
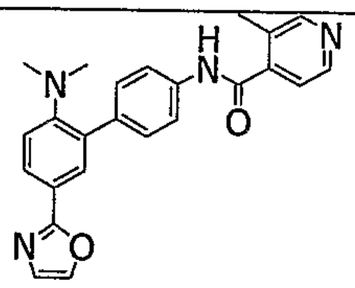
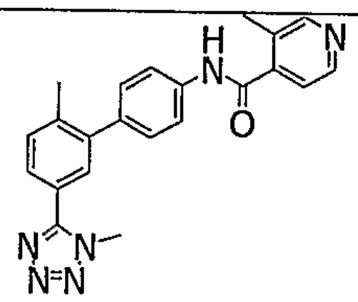
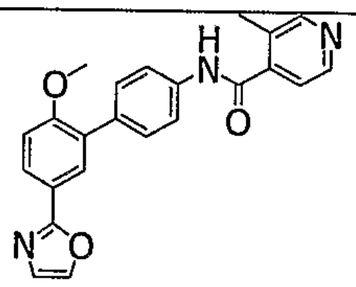
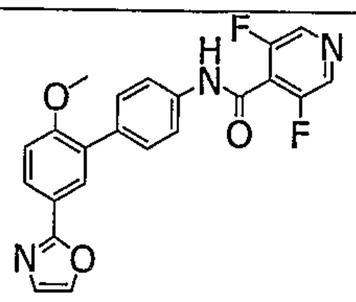
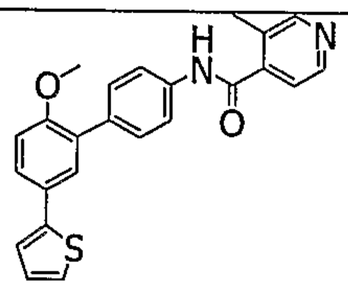
9		3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotinamide, HCl salt
10		3-Fluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide
11		3,5-Difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide
12		4'-[(3-Fluoro-pyridine-4-carbonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester
13		2,6-Difluoro-N-(2'-methoxy-5'-oxazol-2-yl-biphenyl-4-yl)-benzamide

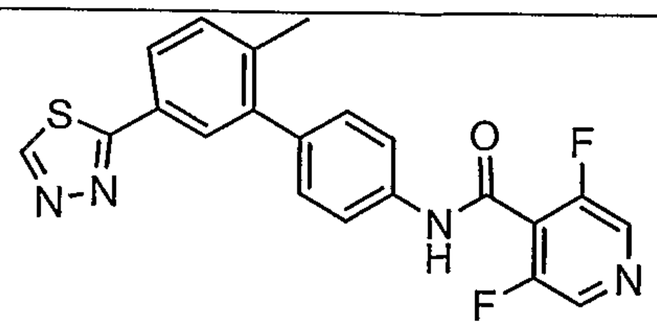
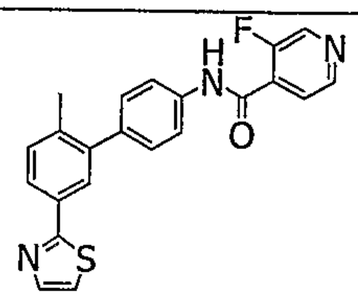
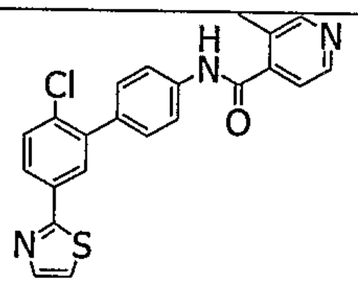
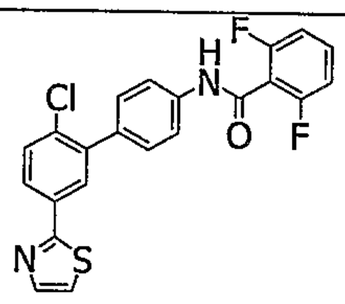
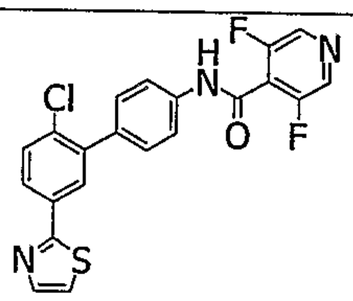
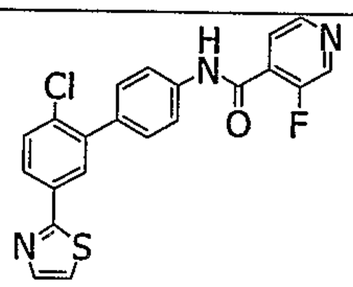
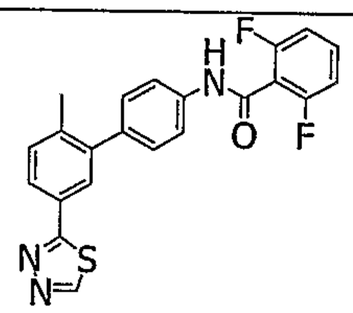
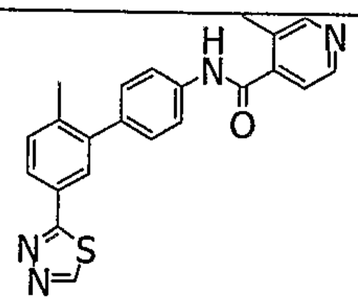
14		3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotin-amide
15		2,6-Difluoro-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-benzamide
16		3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotin-amide
17		3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotin-amide, hydrochloride
18		3-Methyl-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide
19		3-Fluoro-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide

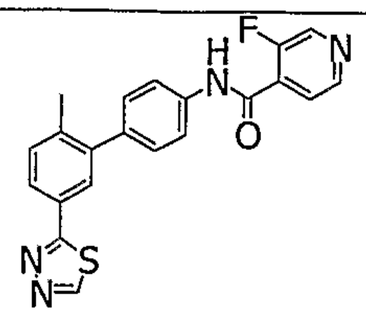
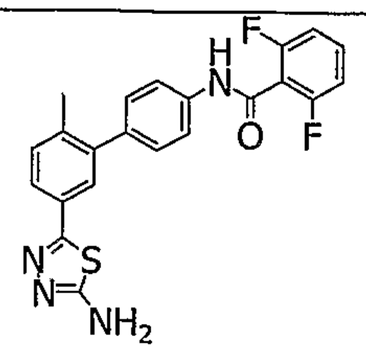
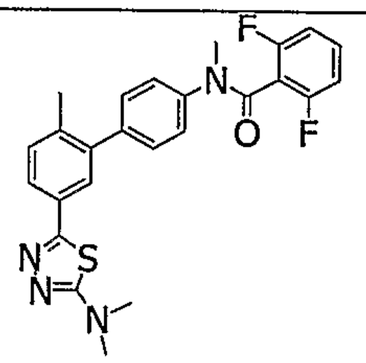
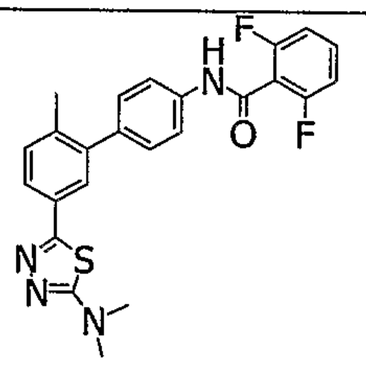
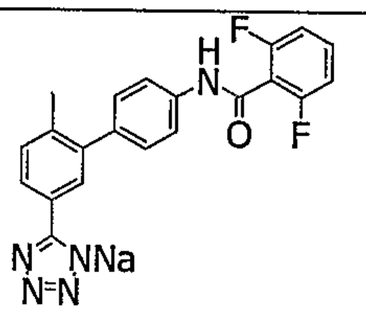
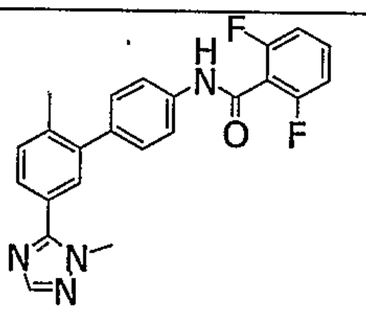
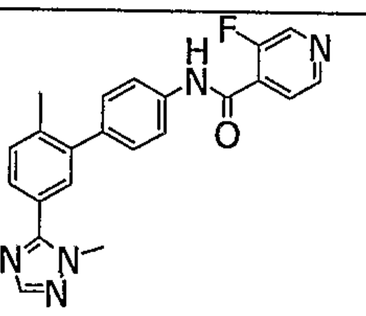
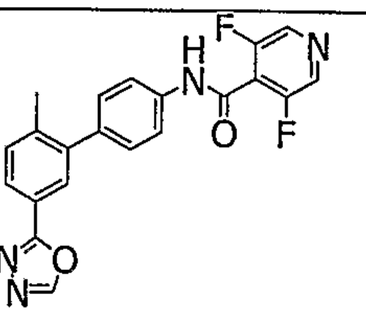
20		3-Methyl-N-[5'-(pyridin-3-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
21		4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-3-yl)-biphenyl-4-yl]-amide
22		2,6-Difluoro-N-[2'-methyl-5'-(pyridine-3-yl)-biphenyl-4-yl]-benzamide
23		2,6-Difluoro-N-[2'-methyl-5'-(pyridine-2-yl)-biphenyl-4-yl]-benzamide
24		4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-2-yl)-biphenyl-4-yl]-amide
25		4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid [2'-methoxy-5'-(oxazol-5-yl)-biphenyl-4-yl]-amide
26		3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
27		2,6-Difluoro-N-[2'-methyl-5'-(oxazol-5-yl)-biphenyl-4-yl]-benzamide

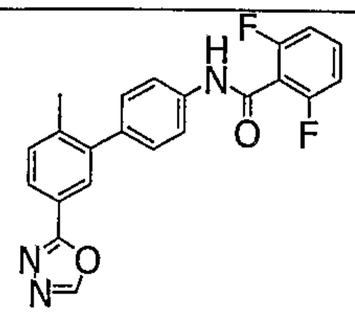
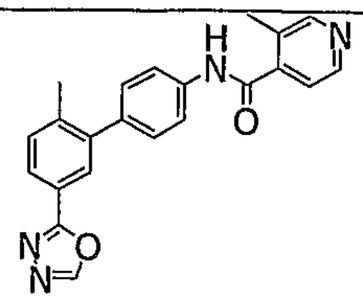
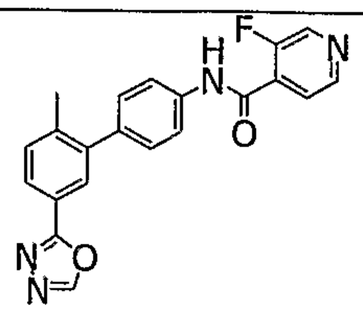
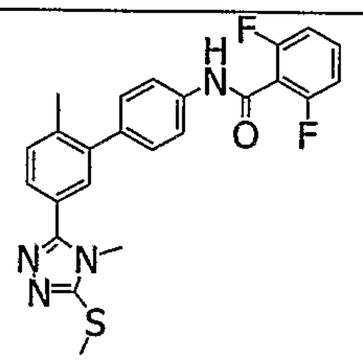
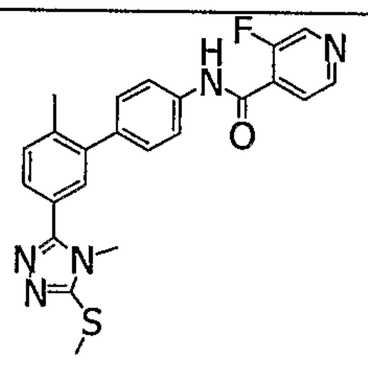
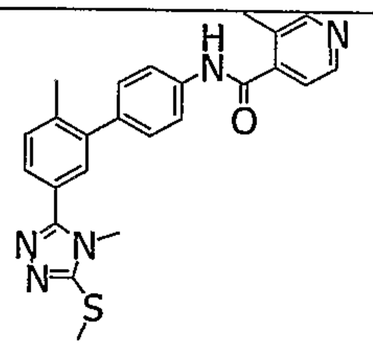
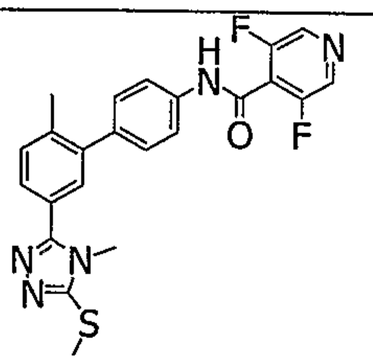
28		3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
29		3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide, HCl salt
30		2,6-Difluoro-N-[2'-methyl-5'-(pyridine-4-yl)-biphenyl-4-yl]-benzamide
31		2,6-Difluoro-N-[2'-chloro-5'-(oxazol-2-yl)-biphenyl-4-yl]-benzamide
32		3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
33		4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(isoxazol-5-yl)-biphenyl-4-yl]-amide
34		3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide, HCl salt
35		2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-isoxazole-5-yl)-biphenyl-4-yl]-benzamide
36		3-Methyl-N-[5'-(3-methyl-isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide

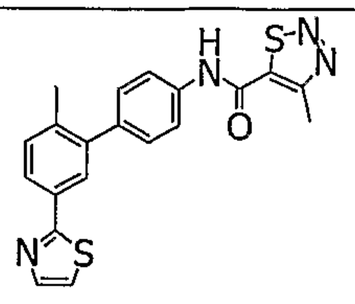
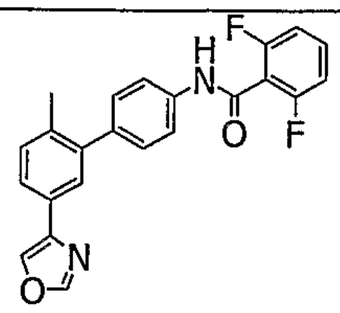
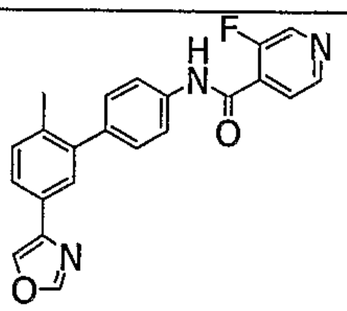
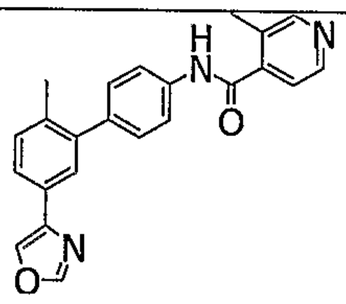
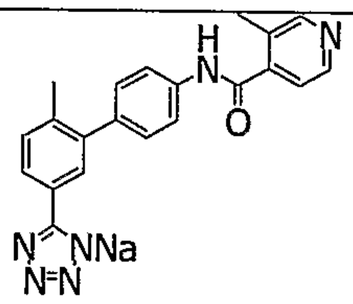
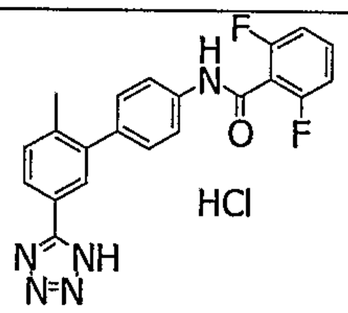
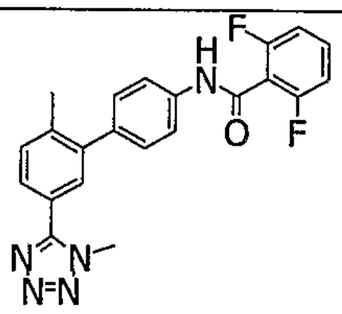
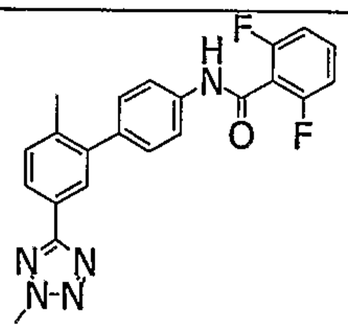
37		2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-1*H*-pyrazol-5-yl)-biphenyl-4-yl]-benzamide
38		2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide
39		2,6-Difluoro-N-[2'-methyl-5'-(4-trifluoromethyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide
40		3-Methyl-N-[5'-(4-methyl-thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
41		2,6-Difluoro-N-[2'-methyl-5'-(1*H*-pyrrol-2-yl)-biphenyl-4-yl]-benzamide
42		2,6-Difluoro-N-[2'-methyl-5'-(5-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)-biphenyl-4-yl]-benzamide
43		2,6-Difluoro-N-[2'-methyl-5'-(morpholino-4-yl)-biphenyl-4-yl]-benzamide
44		3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide

45		3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide
46	 H-Cl	3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide, HCl salt
47		3-Methyl-N-[2'-methoxy-5'-(furan-2-yl)-biphenyl-4-yl]-isonicotinamide
48		3-Methyl-N-[5'-(oxazol-2-yl)-2'-(N,N-dimethylamino)-biphenyl-4-yl]-isonicotinamide
49		3-Methyl-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide
50		3-Methyl-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide
51		3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide
52		3-Methyl-N-[5'-(thien-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide

53		3,5-Difluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
54		3-Fluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
55		3-Methyl-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide
56		2,6-Difluoro-N-[2'-chloro-5'-(thiazol-2-yl)-biphenyl-4-yl]-benzamide
57		3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide
58		3-Fluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide
59		2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide
60		3-Methyl-N-[5'-([1,3,4]thiadiazol-2-yl)- 2'-methyl-biphenyl-4-yl]-isonicotinamide

61		3-Fluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide
62		2,6-Difluoro-N-[2'-methyl-5'-(5-amino-[1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide
63		2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl-4-yl}-N-methyl-benzamide
64		2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl-4-yl}-benzamide
65		2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide, sodium salt
66		2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide
67		3-Fluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide
68		3,5-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide

69		2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-benzamide
70		3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide
71		3-Fluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide
72		2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide
73		3-Fluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide
74		3-Methyl-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide
75		3,5-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide

76		4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(thiazol-2-yl)-biphenyl-4-yl]-amide
77		2,6-Difluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-benzamide
78		3-Fluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide
79		3-Methyl-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide
80		3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide, sodium salt
81		2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide, HCl salt
82		2,6-Difluoro-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide
83		2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide

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 exists. Thus, inhibition of CRAC ion channels can be measured by measuring inhibition of the I_{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 (XII) 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 (XII) 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 naïve or may experience partial or no response to conventional therapies.

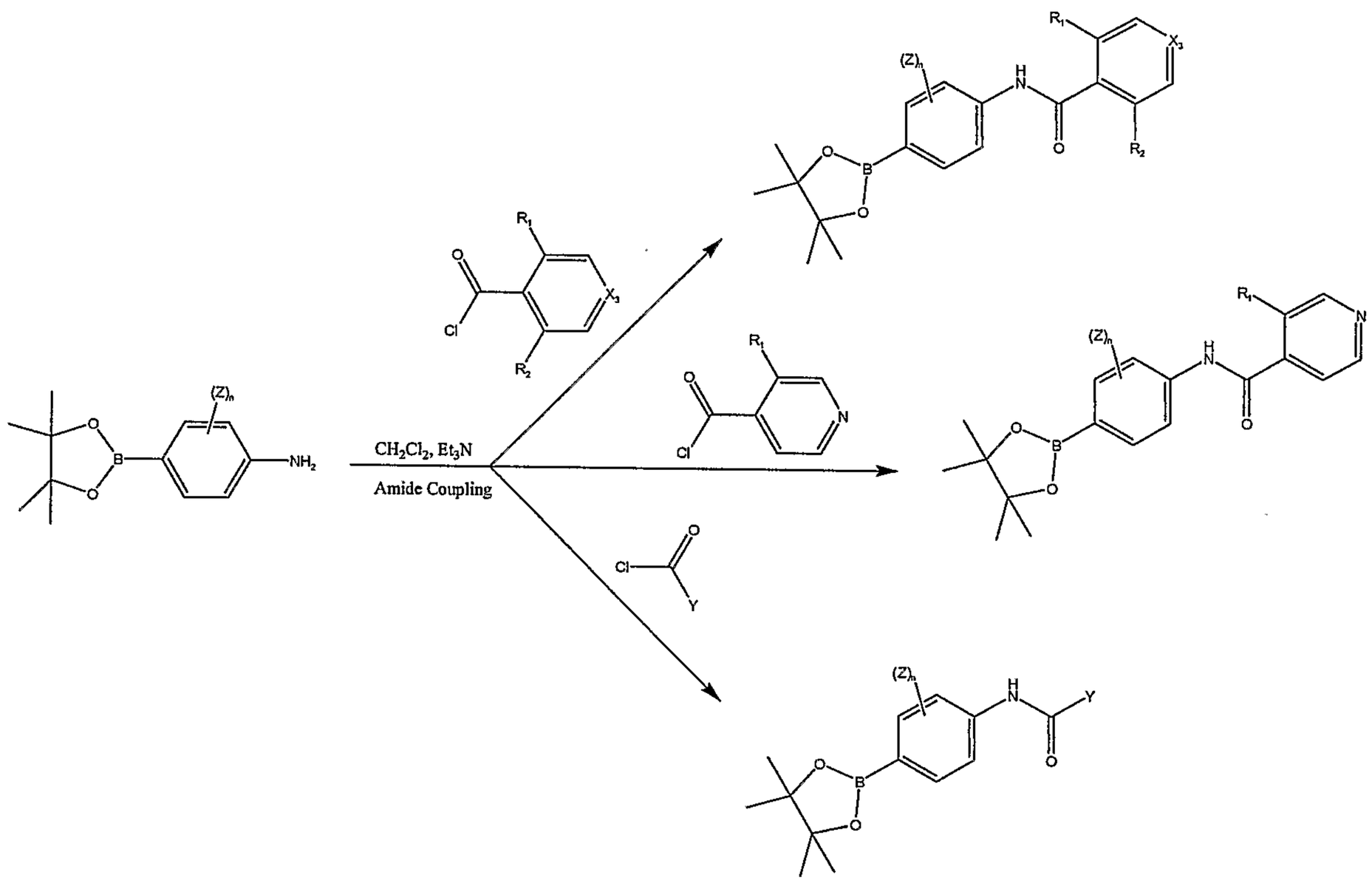
Responsiveness of a particular inflammatory condition, immune disorder, or allergic disorder in a subject can be measured directly (e.g., measuring blood levels of inflammatory cytokines (such as IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, IFN-γ and the like) after administration of a compound of this invention), or can be inferred based on an understanding of disease etiology and progression. The compounds of any one of formulas (I) through (XII), or Table 1, or pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof can be assayed *in vitro* or *in vivo*, for

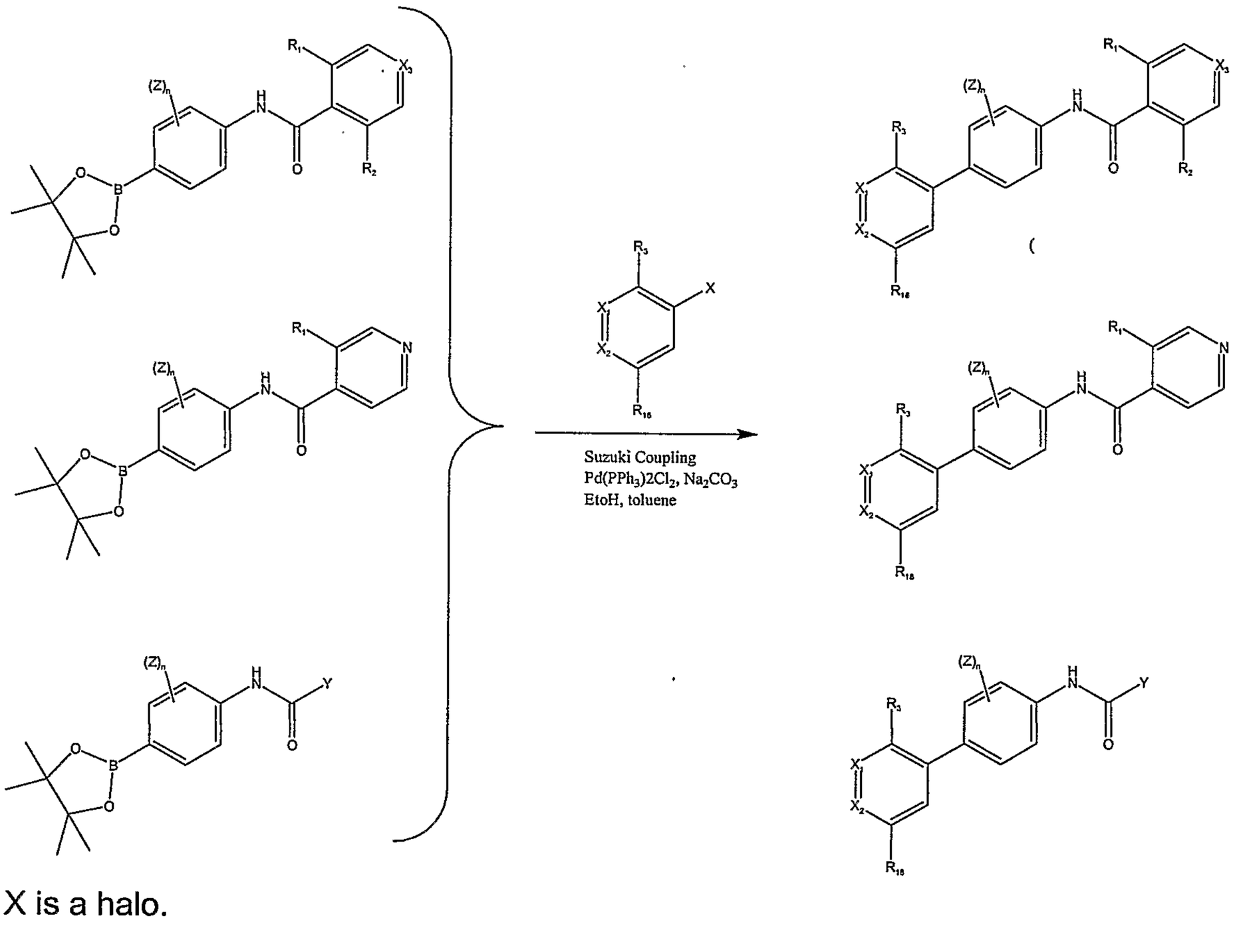
the desired therapeutic or prophylactic activity, prior to use in humans. For example, known animal models of inflammatory conditions, immune disorders, or allergic disorders can be used to demonstrate the safety and efficacy of compounds of this invention.

SYNTHESIS OF COMPOUNDS OF THE INVENTION

In general, compounds of the invention that have an amide linker can be prepared via an amide coupling reaction, followed by a Suzuki coupling reaction (see Scheme A).

Scheme A

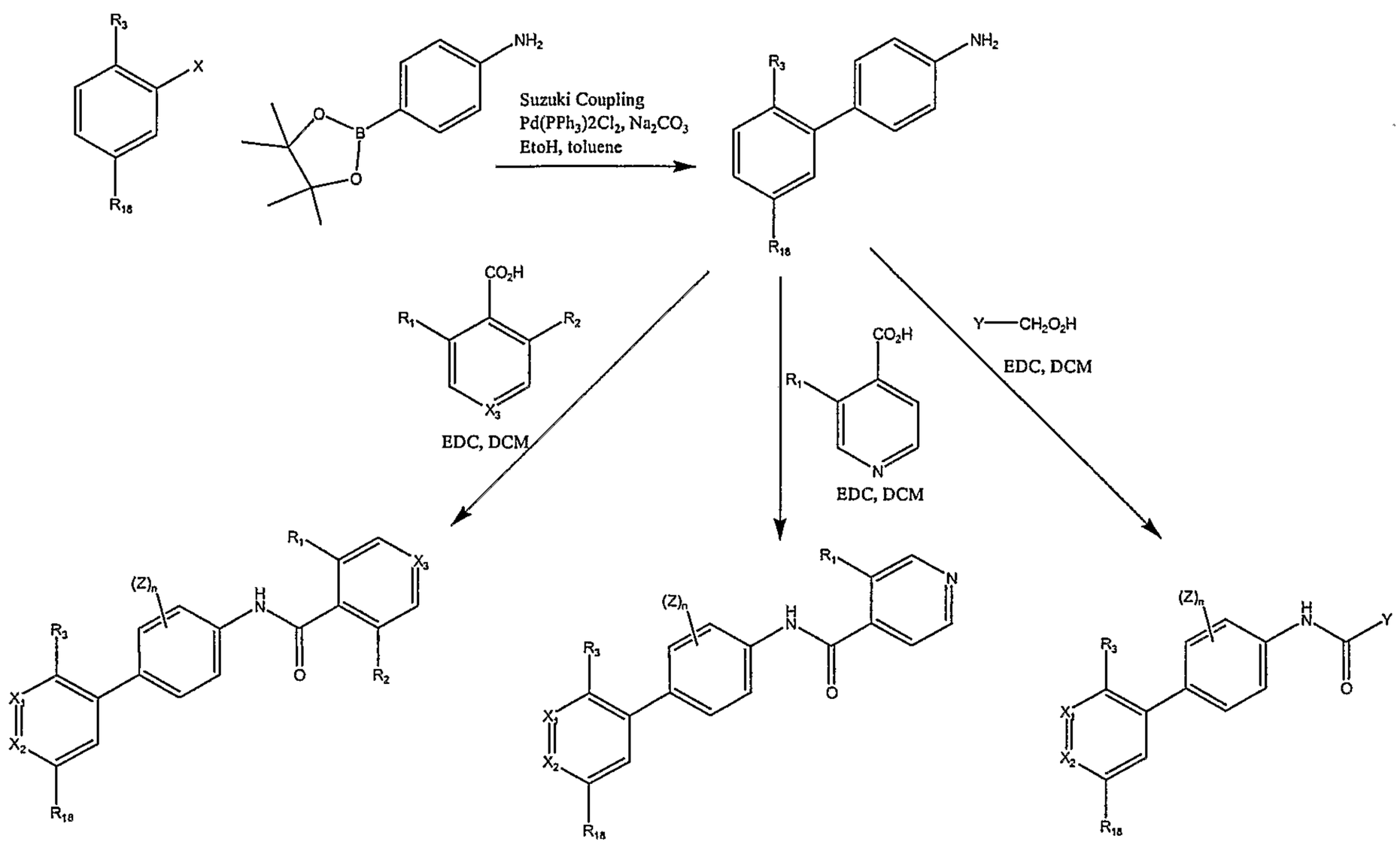




X is a halo.

Alternatively, the Suzuki coupling reaction can be done first, followed by an amide coupling reaction (see Scheme B).

Scheme B



The amide coupling reaction can be accomplished by contacting an acid chloride with an amine in the presence of a base as shown in Scheme A or by contacting a carboxylic acid with an amine in the presence of a an dialkylcarbodiimide, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), as shown in Schem B.

Compounds that have an amide group in the reverse direction (i.e., the carbonyl portion of the amide is attached to the biphenyl or pyridinyl-phenyl group) can be synthesized by analogous methods as those shown in Schemes A and B.

In general methods for preparing compounds in which L is $-NRCH_2-$, $-CH_2NR-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-C(S)-$, $-NR-C(S)-$, or $-C(S)-NR-$ are known in the art and can be found, for example, in March, *Advanced Organic Chemistry, third edition*, (1985), John Wiley & Sons, the entire teachings of which are incorporated herein by reference. Examples of such methods are described briefly below.

Compounds in which L is $-NRCH_2-$ or $-CH_2NR-$ can be prepared from compounds that have amide linkers by reducing the amide group with sodium borohydride.

Typically, the reaction is carried out in an alcohol solvent, such as ethanol, and the reaction is heated.

Compounds in which L is –C(O)O- or –OC(O)- can be prepared by a method analogous to the amide coupling reaction except that the -NH_2 group is replaced with a hydroxyl group.

Compounds in which L is –C(S)NR- or –NRC(S)- can be prepared by treating compounds that have an amide linker with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfied (see Pedersen, *et al., Bul. Soc. Chim. Belges* (1978), *87*:223, the entire teachings of which are incorporated herein by reference). Compounds in which L is –C(S)- can be prepared from compounds that have a –C(O)- linker by a similar method.

Methods of preparing the compounds of the invention are described in more detail below in the example. Additional methods for preparing compounds of the invention can be found in U.S. Patent Application No. 10/897,681, filed on July 22, 2004, the entire teachings of which are incorporated herein by reference.

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 (XII), 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. Pharmocopia (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 (XII), 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 (XII), 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 algins, 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 formulas (I) through (XII), 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 (XII), 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 known in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA.

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 tetrahydrofuryl; 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, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic 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-aminophennol 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, oxyphenthartazone); 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 Antiinflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff 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 entireties.

Of particular relevance to allergic disorders, the other therapeutic agent may be an anthihistamine. Useful antihistamines include, but are not limited to, loratadine, cetirizine, fexofenadine, desloratadine, diphenhydramine, chlorpheniramine, chlorcyclizine, pyrilamine, promethazine, terfenadine, doxepin, carbinoxamine, clemastine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, cyproheptadine, phenindamine, acrivastine, azelastine, levocabastine, and mixtures thereof. For a more detailed description of anthihistamines, *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, buslfan, and cyclophosphamide), folic acid antagonsists (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

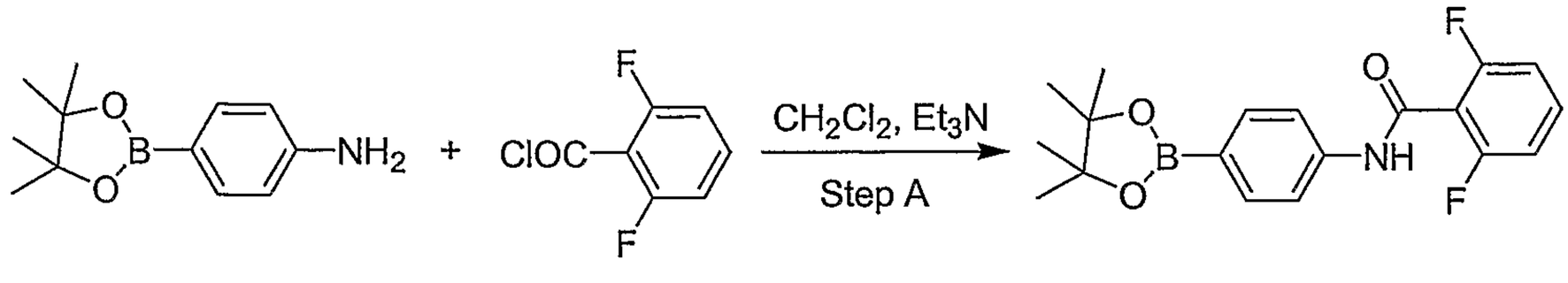
Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 300MHz NMR spectrometer. Significant peaks are tabulated in the order: δ (ppm): chemical shift, multiplicity (s,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

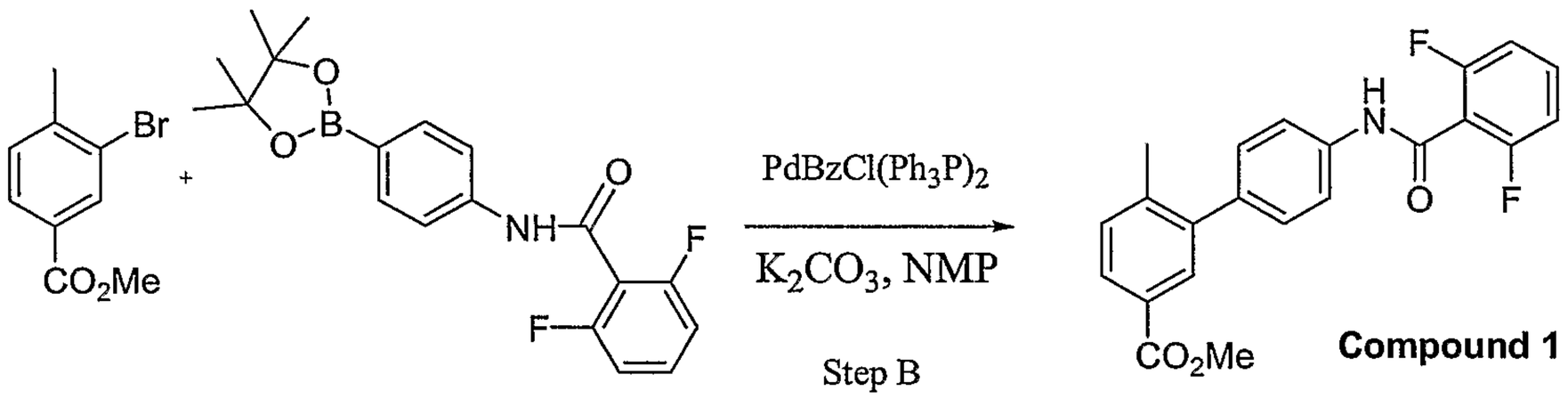
Patch clamp experiments were performed in the tight-seal whole-cell configuration at 21-25°C. High resolution current recordings were acquired by a computer-based patch clamp amplifier system (EPC-9, HEKA, Lambrecht, Germany). Patch pipettes had resistances between 2-4 MΩ after filling with the standard 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.

EXAMPLE 1: SYNTHESIS OF REPRESENTATIVE EXEMPLARY COMPOUNDS OF THIS INVENTION

Compound 1: 4'-(2,6-difluro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid methyl ester

Scheme I





Compound 1

Step A: To a stirred solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (5.2 g, 24 mmol), TEA (5 mL) in dry DCM (50 mL) at 0°C was added 2,6-difluoro-benzoyl chloride (3.0 mL, 24 mmol) dropwise. The mixture was allowed to warm to to room temperature over 2 h before it was washed with water (2 x 100 mL) and dried. Removal of solvents gave 2,6-difluoro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide (8.4 g, 23 mmol) as white solid.

^{1}H-NMR ($CDCl_3$) δ (ppm) 7.8 (d, 2H, J = 8), 7.7 (br, 1H), 7.6 (m, 2H), 7.4 (m, 1H), 7.0 (t, 2H, J = 9), 1.35 (s, 12H); ESMS clcd for $C_{19}H_{20}BF_2NO_3$: 359.1; Found: 360.1 $(M+H)^+$.

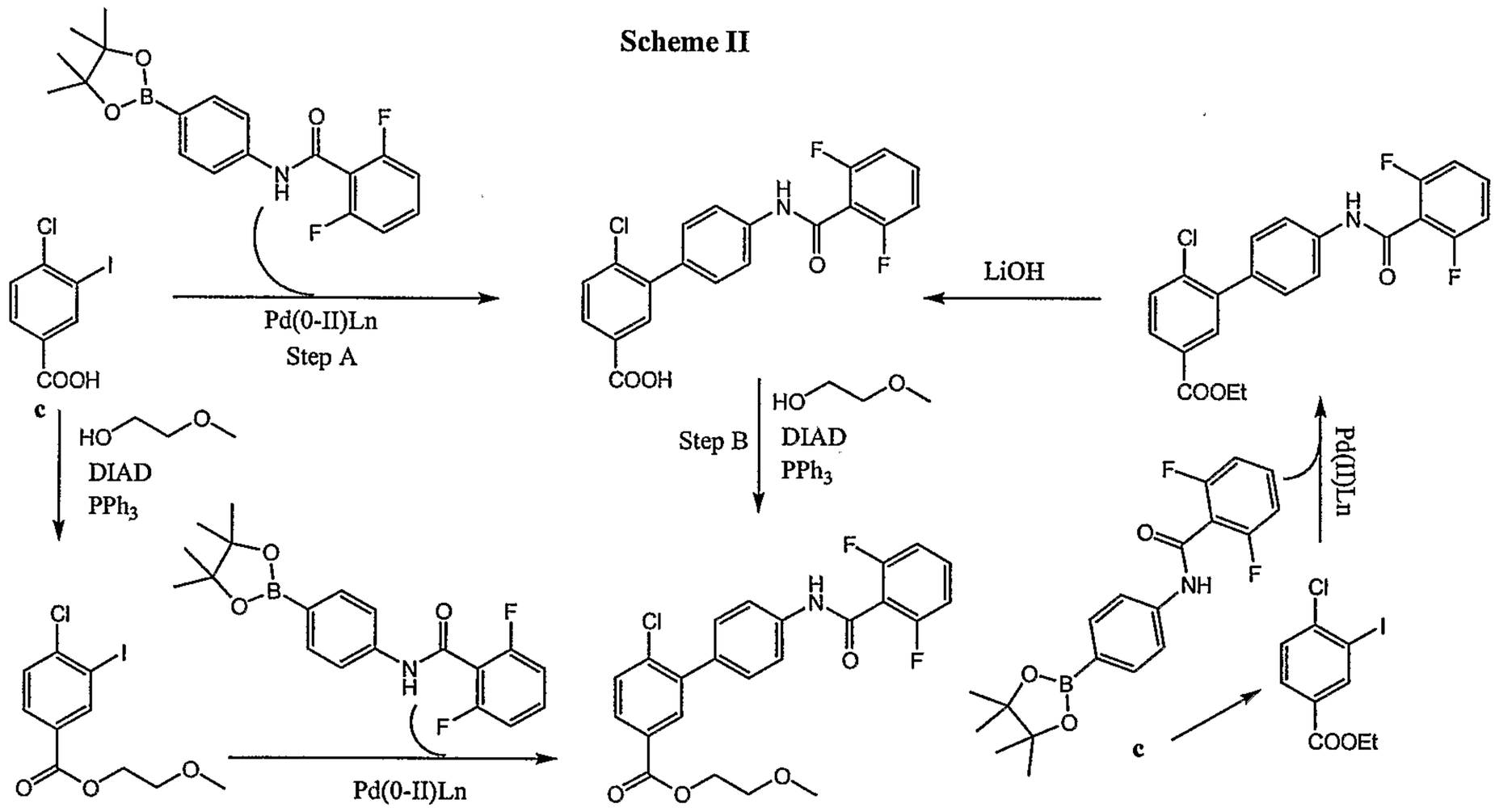
Step B: A suspension of 2,6-difluoro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide (359 mg, 1mmol), 3-bromo-4-methyl-benzoic acid methyl ester (228 mg, 1mmol), benzyl(chloro)bis(triphenylphosphine)palladium (38 mg, 0.05mmol) and K_2CO_3 (690mg, 5 mmol) in 1-methyl pyrrolidinone (NMP) (5 ml) was degassed with vacuum and heated at 120°C for 10 hr. After cooling down to room temperature, ethyl acetate (EtOAc) (200ml) was added and the mixture was washed with water (60 ml x 3). The EtOAc was evaporated and the residue was purified by column chromatography on silica gel (Hexanes:EtOAc) to give Compound 1 (286 mg,

yield 75%).

^{1}H NMR (300MHz, $CDCl_3$): 7.96-6.95 (m, 10H), 3.88(s, 3H), 2.32(s, 3H). ESMS cacld ($C_{22}H_{17}F_2NO_3$):381.12; found: 382.1 (M+H).

Compound 2: 6-Chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-carboxylic acid 2-methoxy-ethyl ester

Scheme II



Compound 2

Step A: A mixture of 2,6-difluoro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide (0.35 g, 1 mmol), 4-chloro-3-iodo-benzoic acid (**c**) (0.28 g, 1 mmol), $PdCl_2(PPh_3)_2$ (80 mg, 0.1 mmol), and K_2CO_3 (0.14g, 1 mmol) in NMP (4 mL) was stirred at 130 °C under nitrogen for 24 h. After being cooled, the mixture was poured into ice-water (50 mL). The resultant precipitation was collected by filtration, then washed with water. The solid material was dried and dissolved in DCM, undissolved material was filtered off. 0.12 g (30%) of pure product, 6-chloro-4'-(2,6-difluoro- benzoylamino)-biphenyl-3-carboxylic acid, was obtained by silica gel chromatography (hexane/EtOAc to EtOAc/MeOH).

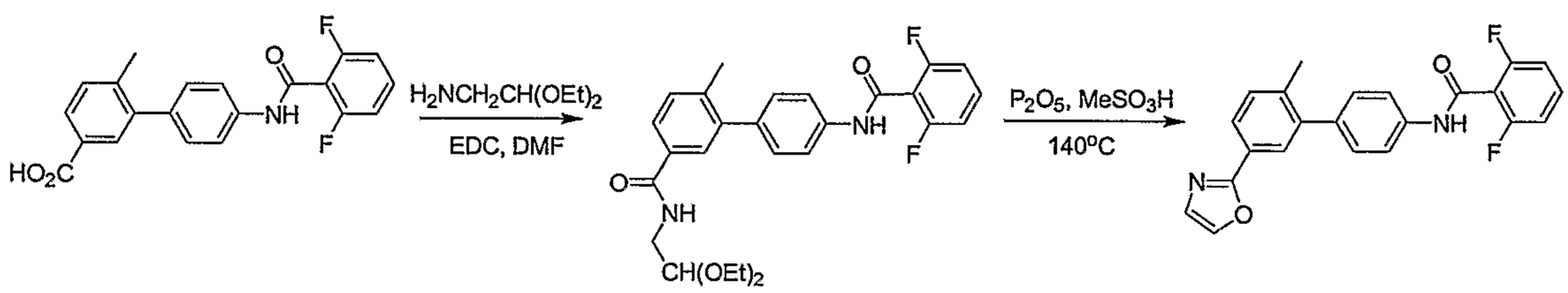
^{1}H-NMR ($CDCl_3$) δ ppm 7.30 (t, 2H, J = 7), 7.40-8.15 (m, 9H); ESMS calcd for $C_{20}H_{12}ClF_2NO_3$: 387.0; found: 388.0 (M + H).

Step B: To a stirred solution of 6-chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-carboxylic acid (13 mg, 36 umol), 2-methoxy-ethanol (2.6 mg, 36 umol), and triphenylphosphine (PPh_3) (10 mg, 38 umol) in dry THF (0.5 mL) was added diisopropyl azodicarboxylate (DIAD) (8 mg, 38 umol). The resultant yellow solution was stirred at room temperature for 4 h. After removal of the solvent, the crude material was purified by silica gel chromatography (hexane to 30% Hexane/EtOAc) to afford 13.4 mg (90% yield) of the desired product, 6-chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-carboxylic acid 2-methoxy-ethyl ester, as an off-white powder.

^{1}H-NMR ($CDCl_3$) δ ppm 3.40 (s, 3H), 3.70 (t, 2H, J = 6), 4.45 (t, 2H, J = 6), 7.01 (t, 2H, J = 8), 7.38-7.62 (m, 4H), 7.75 (d, 2H, J = 8), 7.85 (s, 1H), 7.95 (d, 1H, J = 8), 8.05 (s, 1H); ESMS calcd for $C_{23}H_{18}ClF_2NO_4$: 445.2; found: 446.2 (M + H).

Compound 3: 2,6-Difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-benzamide

Scheme III



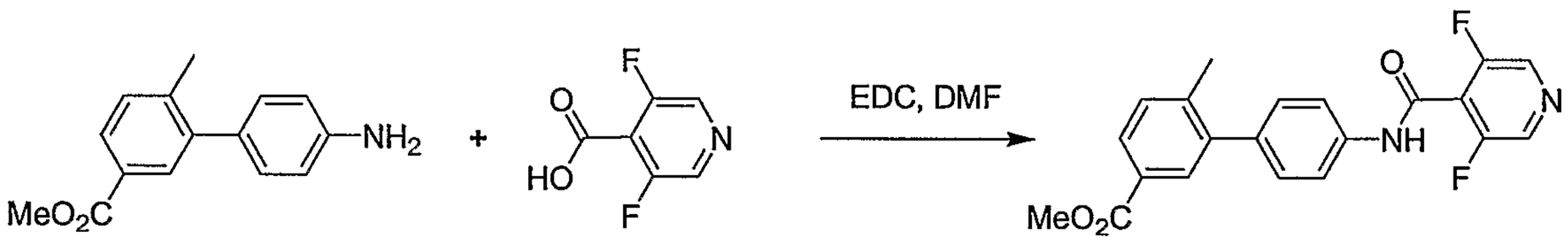
Compound 1 was hydrolyzed by heating it in a solution of LiOH to yield 4'-(2,6-difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid. A mixture of 4'-(2,6-difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid (800 mg, 2.2 mmol), 2,2-diethoxy-ethylamine (0.32 mL, 2.2. mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (5 mmol) in dry DMF (5 mL) was stirred at room temperature for 24 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (EtOAc) (2 x 20 mL). The organic extract was washed with water and dried. The oil obtained on concentration of the organic layer was purified by flash chromatograghed on silica gel to give 4'-(2,6-difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid (2,2-diethoxy-ethyl)-amide as colorless oil (0.68g).

The oil of above was treated with a solution of P_2O_5 (1 g) in $MeSO_3H$ (6 mL) and was kept at 140 °C for 4 h. The mixture was poured onto ice, neutralized with Na_2CO_3 and extracted with EtOAc (2 x 50 mL). The oil obtained on concentration of the organic layer was purified by flash chromatograghed on silica gel to give 2,6-difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-benzamide as yellowish solid (0.50 g).

^{1}H-NMR (DMSO-d_6) δ (ppm) 10.96 (br, 1H), 8.22 (s, 1H), 7.9 (m, 1H), 7.8 (m, 3H), 7.6 (m, 1H), 7.4 (m, 4H), 7.2 (t, 2H, J = 9), 2.32 (s, 3H); ESMS clcd for $C_{23}H_{16}F_2N_2O_2$: 390.1; Found: 391.1 $(M+H)^+$.

Compound 4: 4'-[(3,5-Difluoro-pyridine-4-carbonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester

Scheme IV



A mixture of 4'-amino-6-methyl-biphenyl-3-carboxylic acid methyl ester (0.50 g), 3,5-difluoro-isonicotinic and EDC (0.80 g) in dry dimethylformamide (DMF) (12 mL) was stirred at room temperature for 3 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (2 x 50 mL). The oil obtained on concentration of the organic layer was flash chromatograghed on silica gel to give 4'-[(3,5-difluoro-pyridine-4-carbonyl)-amino]-6-methyl- biphenyl-3-carboxylic acid methyl ester (0.45 g) as white solid.

^{1}H-NMR ($CDCl_3$) δ (ppm) 8.6 (br, 1H), 8.41 (s, 2H), 7.9 (d, 2H, J = 8), 7.7 (d, 2H, J = 8), 7.4 (m, 3H), 3.85 (s, 3H), 2.32 (s, 3H); ESMS clcd for $C_{21}H_{16}F_2N_2O_3$: 382.1; Found: 383.2 $(M+H)^+$.

Compound 5: N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide

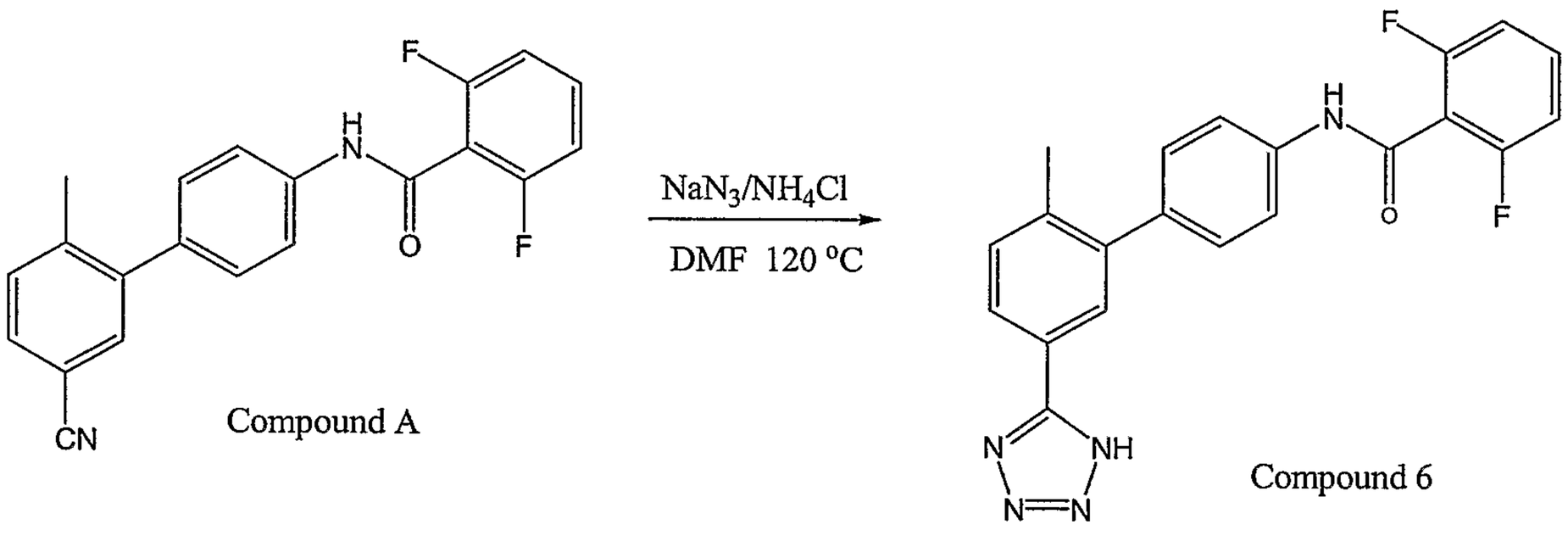
Compound 5 was prepared by an analogous method as Compound 1 except that

3-bromo-4-methyl-benzoic acid methyl ester was replaced with 3-bromo-5-chloro-2-methoxypyridine.

^{1}H NMR (300MHz, $CDCl_3$): 8.21(s, 1H), 7.88-6.95 (m, 7H), 6.73 (s, 1H), 3.93(s, 3H). ESMS cacld($C_{19}H_{13}ClF_2N_2O_2$):374.06; found: 375.1 (M+H).

Compound 6: 2,6-Difluro-N-[2'-methyl-5'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-benzamide

Scheme V



Compound A

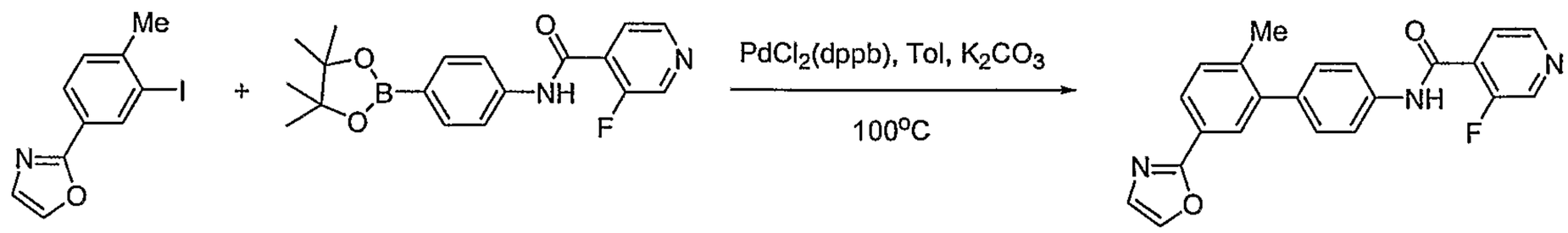
Compound 6

N-(5'-cyano-2'-methyl-biphenyl-4yl)-2,6-difluoro-benzamide (Compound A) was prepared by an analogous method as Compound 1 except that 3-bromo-4-methyl-benzoic acid methyl ester was replaced with 2-bromo-4-cyano-toluene. A mixture of Compound A (348 mg 1 mmol), sodium azide (78mg 1.2mmol), and ammonium chloride (65mg, 1.2mmol) in DMF (5ml) was stirred and heated at 120°C for 10 hr. After cooling the reaction mixture to room temperature, EtOAc (200ml) was added, and the mixture was washed with water (60 ml x 3). The EtOAc layer was concentrated and the residue was subjected to silica gel chromatography (Hexanes:EtOAc, EtOAc:MeOH) to give the product, 2,6-difluro-N-[2'-methyl-5'-(1H-tetrazol-5yl)-biphenyl-4-yl]- benzamide (313mg, yield 80%) as a off-white solid.

^{1}H NMR (300MHz, $CDCl_3$): 7.96-6.97 (m, 10H), 2.37(s, 3H). ESMS cacld($C_{21}H_{15}F_2N_5O$):391.12; found: 392.1 (M+H).

Compound 10: 3-Fluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)- isonicotinamide

Scheme VI

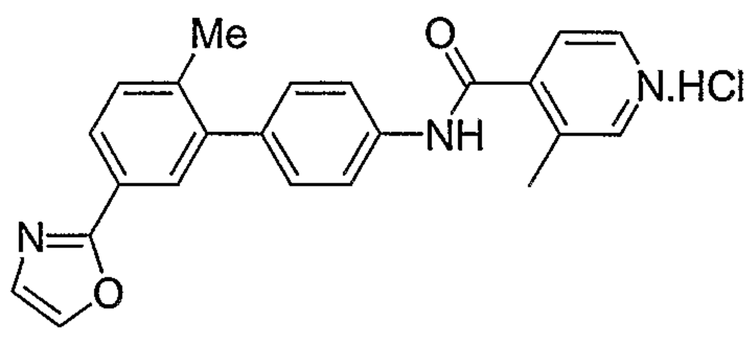


a b Compound 10

Bis(benzonitrile)dichloropalladium (0.03 mmol) and 1,4-bis(diphenylphosphino)-butane (dppb, 0.03 mmol) in toluene (5 mL) were stirred under N_2 for 30 min. 2-(3-Iodo-4-methyl-phenyl)-oxazole (**a**, 1.0 mmol) and 3-fluoro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-isonicotinamide (**b**, 1.0 mmol) was added followed by potassium carbonate solution (1M, 1.0 mL) and ethanol (0.2 mL) and the mixture was heated at 90°C for 12 h. The mixture was loaded onto silica gel and purified by was flash chromatography to give 3-fluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide (Compound 10) as white solid (0.8 mmol).

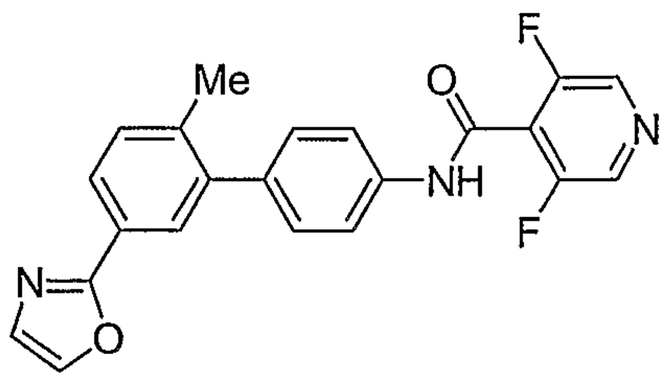
^{1}H-NMR ($CDCl_3$) δ (ppm) 8.7 (m, 2H), 8.4 (br, 1H), 8.1 (t, 1H, J = 6), 8.0 (m, 2H), 7.7 (m, 3H), 7.4 (m, 2H), 7.2 (m, 2H), 2.34 (s, 3H); ESMS clcd for $C_{22}H_{16}FN_3O_2$: 373.1; Found: 374.1 $(M+H)^+$.

Compound 7: 3-Methyl-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)- isonicotinamide, hydrochloride



^{1}H-NMR (DMSO-d_6) δ (ppm) *δ* 10.65 (br, 1H), 8.6 (m, 2H), 8.22 (s, 1H), 7.8 (m, 4H), 7.4 (m, 5H), 2.39 (s, 3H), 2.32 (s, 3H); ESMS clcd for $C_{23}H_{20}ClN_3O_2$: 405.1; Found: 370.1 $(M-Cl)^+$.

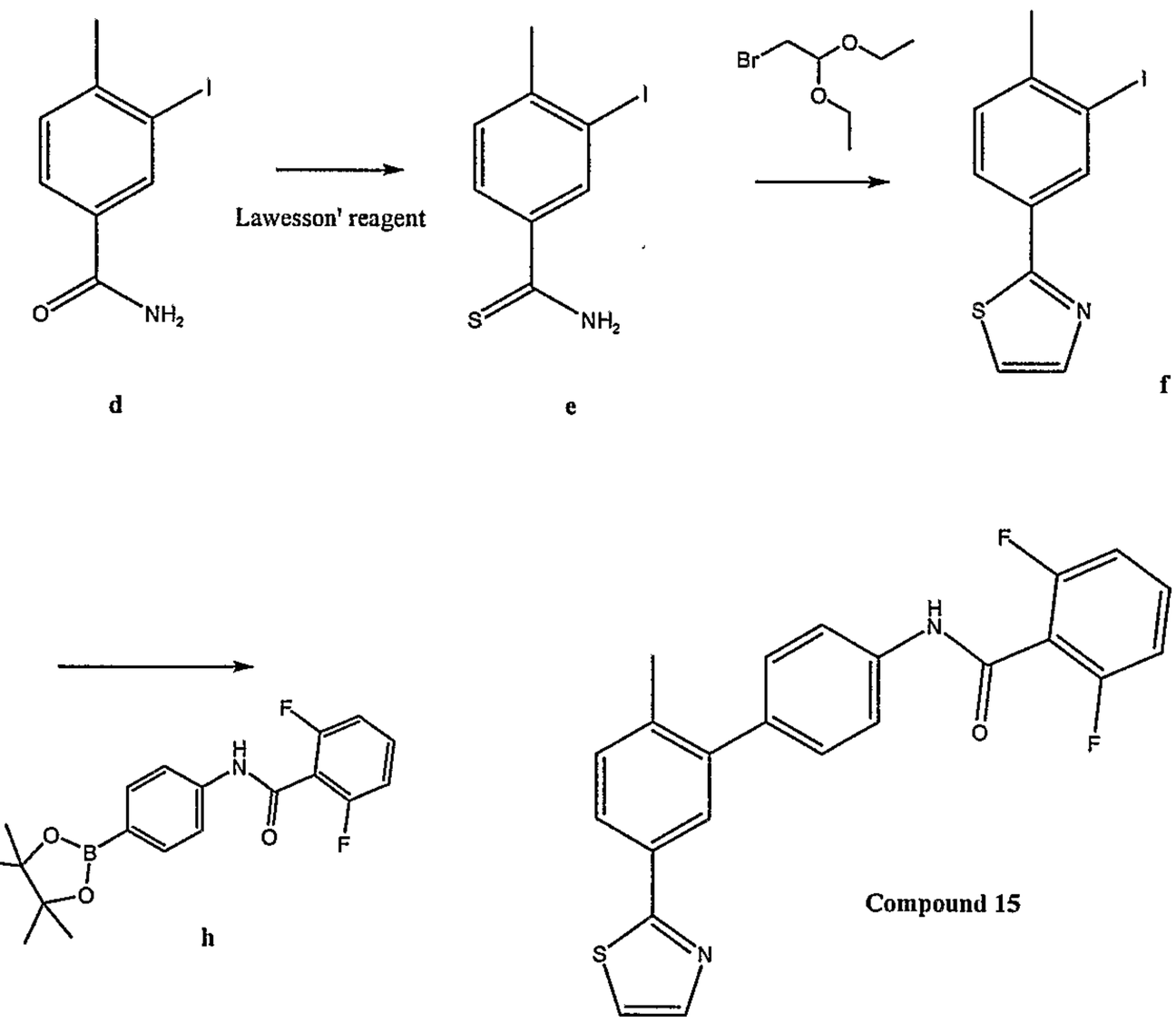
Compound 11: 3,5-Difluoro-N-(2'-methyl-5'- oxazol-2-yl-biphenyl-4-yl)- isonicotin-amide



^{1}H-NMR ($CDCl_3$) δ (ppm) 9.47 (s, 2H), 8.2 (br, 1H), 7.9 (m, 2H), 7.7 (m, 3H), 7.4 (m, 3H), 7.19 (s, 1H), 2.33 (s, 3H); ESMS clcd for $C_{22}H_{15}F_2N_3O_2$: 391.1; Found: 392.1 $(M+H)^+$.

Compound 15: 2,6-Difluoro-N-(2'-methyl-5'- thiazol-2-yl-biphenyl-4-yl)- benzamide

Scheme VII



To a suspension of compound **d** (10g) in benzene (700ml), lawesson's reagent (20 g) was added, the reaction was refluxed for 8 min in 100°C oil bath. The mixture was filtered with silica gel funnel, and eluted with CH_2Cl_2/ EtOAc (1:1), and subjected to silical gel column chromatography (5:1 Hexanes:Ethyl acetate) to give compound **e** (5.3 g).

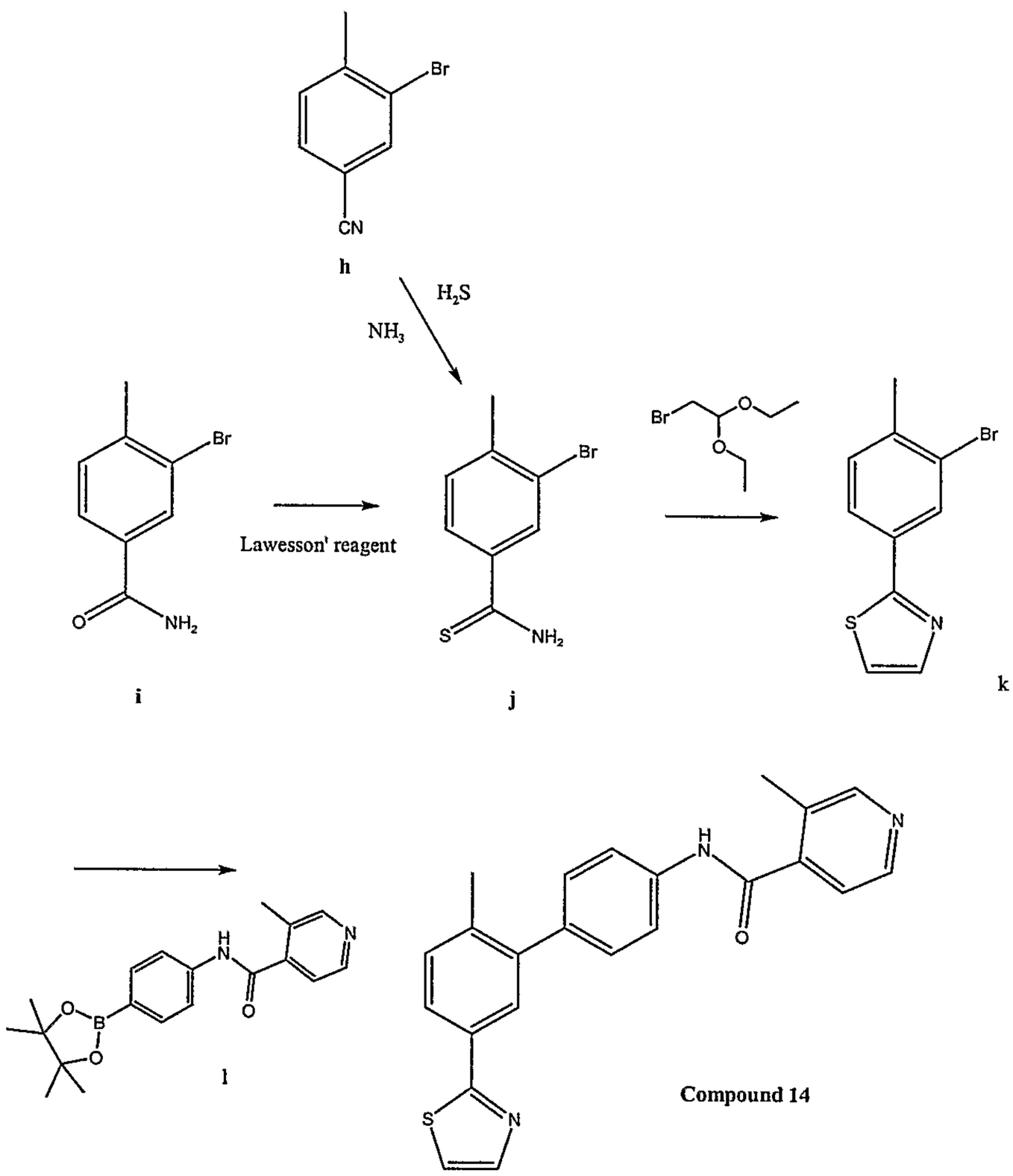
To a solution of compound **e** (5.3 g) in THF (anhydrous) (50 ml) was added bromoacetaldehyde diethyl acetal (10 ml), the mixture was refluxed for 24m hr. (Check by TLC). The solvents were evaporated and the residue was purified with silica gel column chromatography to give **f** (2.8 g).

To a suspension of compound **f** (300mg) toluene (100ml) was added compound **h** (360mg), dichlorobis(triphenylphosphine)palladium(II) (160 mg), 1M Na_2CO_3 (900 μl), and ethanol (150 μl). The reaction was at 100°C for 10 hours (check by TLC). The mixture was directly applied to silica gel column chromatography to give **compound 15** (315 mg).

^{1}H-NMR ($CDCl_3$) δ (ppm), 7.79-6.92 (m, 12H), 2.32 (s, 3H). ESMS clcd for $C_{23}H_{16}F_2N_2OS$: 406.10; Found: 407.1 $(M+H)^+$.

Compound 14: 3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotinamide

Scheme VIII



To a solution of **h** (2g) in methanol (100ml) containing NH_3 (3eq) was bubbled with H_2S for 2hr, after standing for another 10 hr, the solvent was evaporated to give crude **j**, which was used directly for the next step.

Alternatively, **j** can be prepared as follows. To a stirred suspension of **i** (10g) in benzene (700ml) was added lawesson's reagent (20 g). The reaction was refluxed for 8 min in 100^0C oil bath. The mixture was filtered with silica gel funnel, and eluted with CH_2Cl_2/ EtOAc (1:1), and subjected to silical gel column chromatography (5:1 Hexanes:Ethyl acetate) to give **j** (5.3 g).

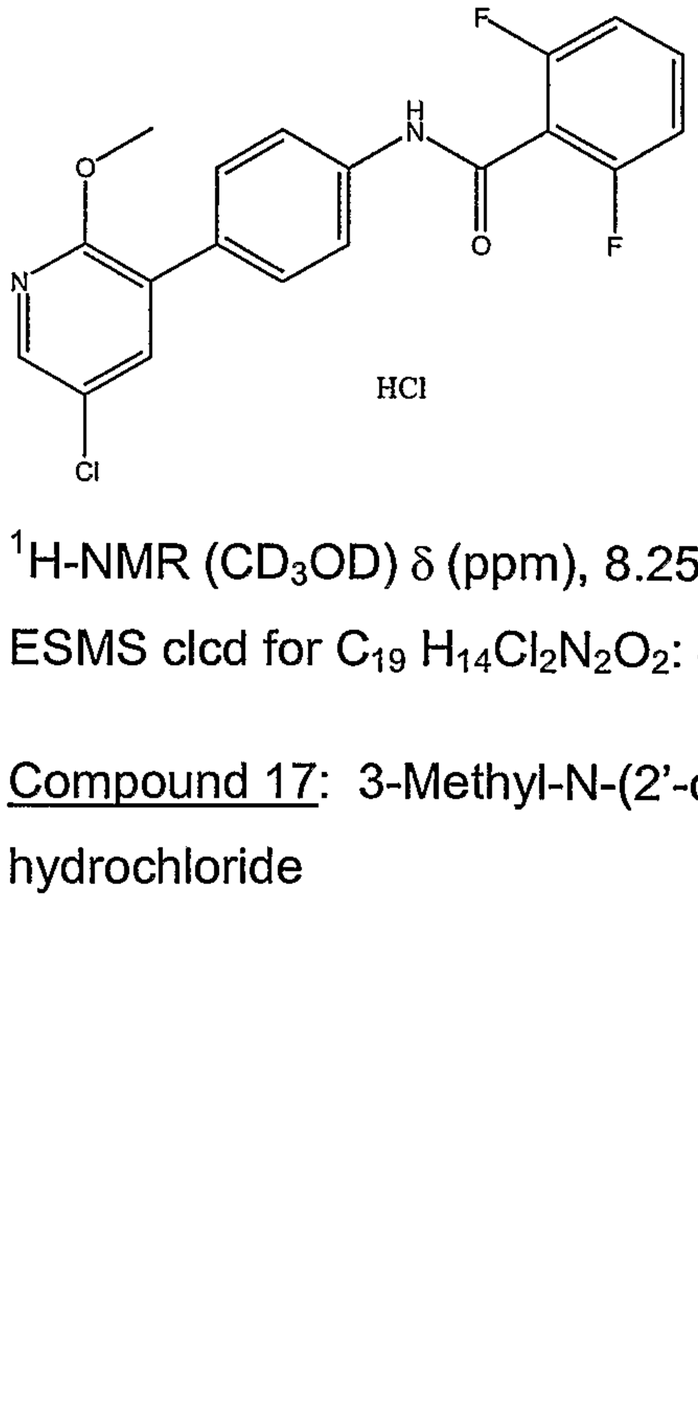
To a stirred solution of **j** (5.3 g) in THF (anhydrous, 50 ml) was added bromoacetaldehyde diethyl acetal (10 ml). The mixture was refluxed and followed by

TLC to determine when the reaction had gone to completion. After 24 hrs, the solvents were evaporated and the residue was purified with silica gel column chromatography to give **k** (3.5 g).

To a stirred suspension of **k** (2.5g) in toluene (500ml) was added **l** (3.4 g), dichlorobis(triphenylphosphine)- palladium(II) (1.6g), 1M Na_2CO_3 (7.5ml), and ethanol (12.5 ml). The reaction mixture was stirred at 115^{0}C for 10 hours (check by TLC). After being cooled to room temperature, the mixture was directly applied to silica gel column chromatography to give **compound 14** (3.1g).

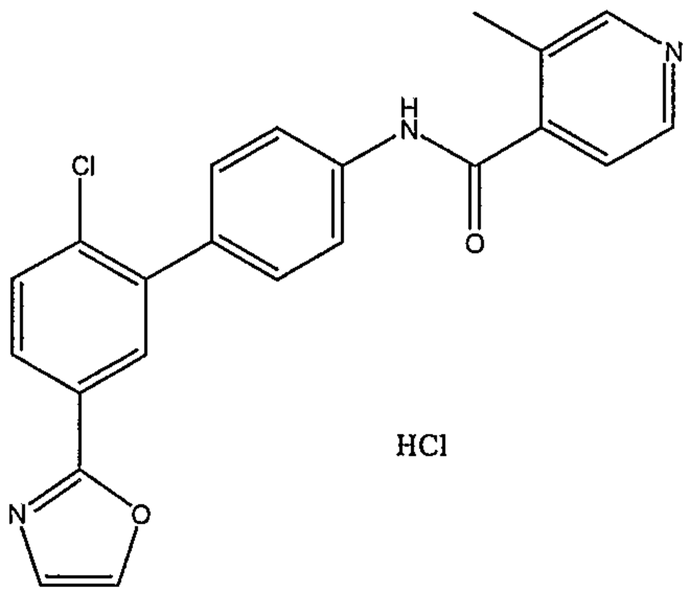
^{1}H-NMR (CD_3Cl) δ (ppm), 8.53(s, 1H), 8.49(d, , J=4.2, 1H), 8.11(s, 1H), 7.82-7.22(m, 10H), 2.50 (s, 3H), 2.32(s, 3H). ESMS clcd for $C_{23}H_{19}N_3OS$: 385.12; Found: 386.1. $(M+H)^+$.

Compound 8: N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide, hydrochloride



^{1}H-NMR (CD_3OD) δ (ppm), 8.25 (s, 1H), 8.84-7.13 (m, 7H), 7.01(s, 1H), 4.02 (s, 3H). ESMS clcd for C_{19} $H_{14}Cl_2N_2O_2$: 410.04; Found: 375.1 $(M+H-HCl)^+$.

Compound 17: 3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotin- amide, hydrochloride

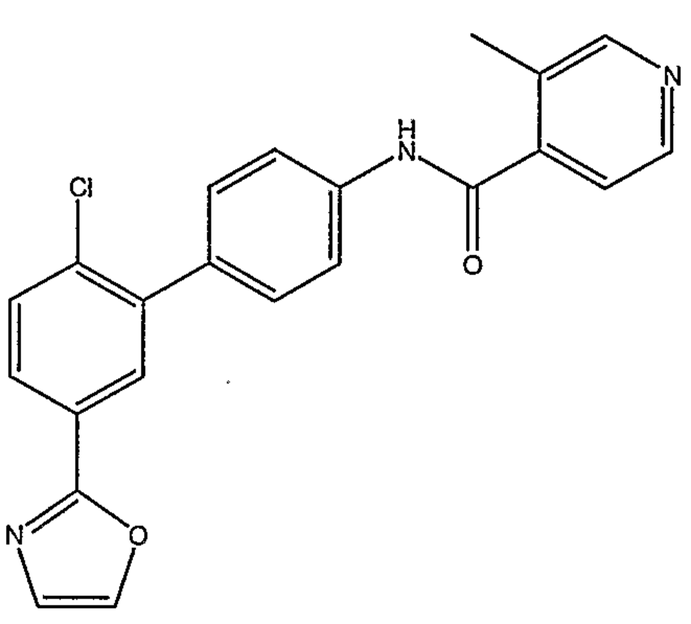


HCl

^{1}H-NMR (CD_3OD) δ (ppm), 8.95(s, 1H), 8.87-7.51 (m, 10H), 2.63 (s, 3H). ESMS clcd for $C_{22}H_{17}Cl_2N_3O_2$: 425.07; Found: 390.1 $(M+H-HCl)^+$.

^{1}H-NMR ($DMSOd_6$) δ (ppm), 10.95(s, 1H), 8.87-8.73(m, 2H), 8.26 (s, 1H), 8.01-7.42 (m, 8H), 7.41(s, 1H), 2.50 (s, 3H).

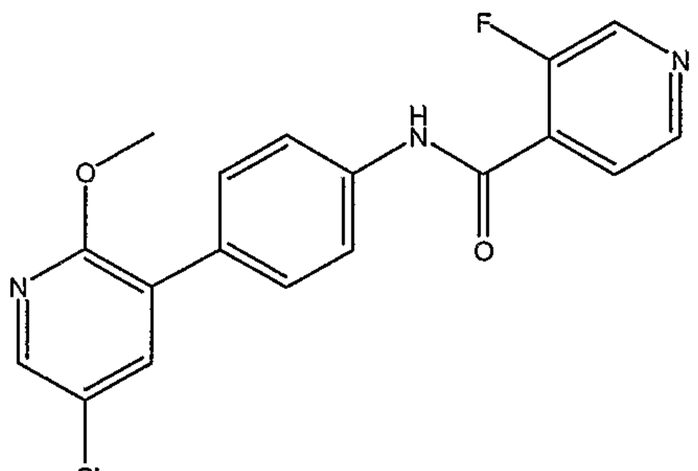
Compound 16: 3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide



^{1}H-NMR ($DMSO\text{-}d_6$) δ (ppm), 10.62(s, 1H), 8.60-7.43 (m, 10H), 7.41 (s, 1H), 2.39 (s, 1H),. ESMS clcd for $C_{22}H_{16}ClN_3O_2$: 389.09; Found: 390.1 $(M+H)^+$.

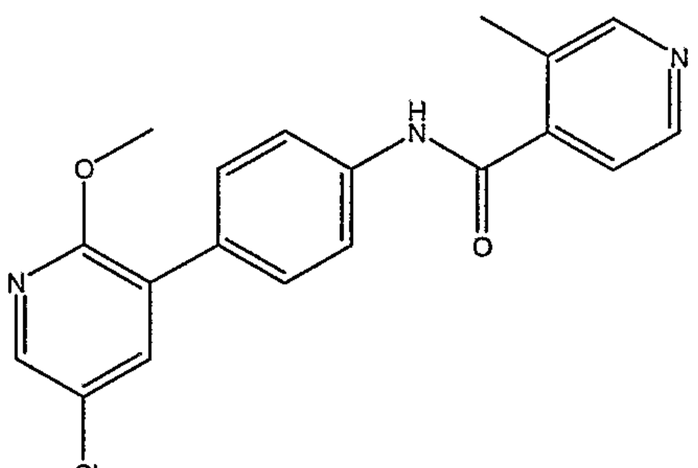
^{1}H-NMR (CD_3Cl) δ (ppm), 10.67(s, 1H), 8.58 (s, 1H), 8.46(d, , J =4.1, 1H), 8.22(s, 1H), 7.96-7.42(m, 8H), 7.40(s, 1H), 2.39 (s, 3H). ESMS clcd for $C_{22}H_{16}ClN_3O_2$: 389.09; Found: 390.1. $(M+H)^+$.

Compound 19: 3-Fluoro-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide



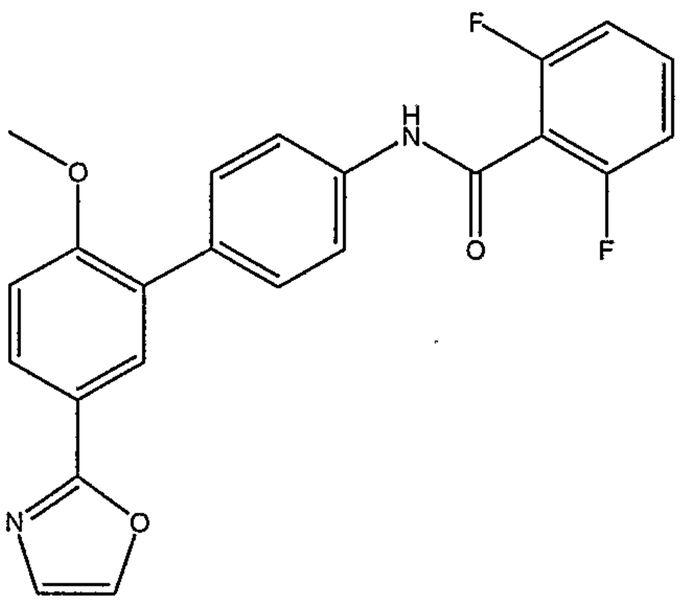
^{1}H-NMR ($CDCl_3$) δ (ppm), 8.69-7.40(m, 8H), 6.76 (s, 1H), 3.89 (s, 3H). ESMS clcd for $C_{18}H_{13}ClFN_3O_2$: 357.07.; Found: 358.1 $(M+H)^+$.

Compound 18: 3-Methyl-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide



^{1}H-NMR ($CDCl_3$) δ (ppm), 8.569-7.27(m, 8H), 6.765(s, 1H), 3.92 (s, 3H), 2.22 (s, 3H). ESMS clcd for $C_{19}H_{16}ClN_3O_2$: 353.09.; Found: 354.1 $(M+H)^+$.

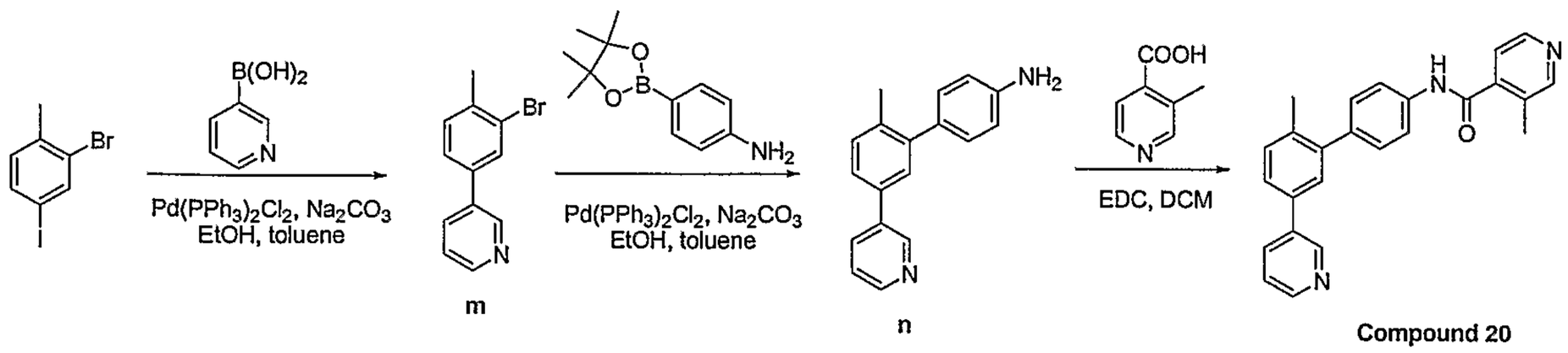
Compound 13: 2,6-Difluoro-N-(2'-methoxy-5'- oxazol-2-yl-biphenyl-4-yl)- benzamide



^{1}H-NMR ($CDCl_3$) δ (ppm), 8.02 (s, 1H), 7.73-6.93 (m, 11H), 3.84 (s, 3H). ESMS clcd for $C_{23}H_{16}F_2N_2O_3$: 406.11; Found: 407.1 $(M+H)^+$.

Compound 20: 3-Methyl-N-[5'-(pyridin-3-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide

Scheme IX



To a solution of 2-bromo-4-iodo-toluene (500 mg, 1.68 mmol), dichlorobis (triphenylphosphine)palladium (II) ($Pd(PPh_3)_2Cl_2$, 175 mg, 0.25 mmol), and 3-pyridineboronic acid (200 mg, 1.62 mmol) in toluene (8 mL) was added Na_2CO_3 (2 N, 1.0 mL) and ethanol (1.0 mL). The stirred mixture was heated up to 80 °C in the sealed tube for 24 hr. The solution was cooled to room temperature and diluted with H_2O (20 mL) and EtOAc (20 mL). The organic phase was dried over Na_2SO_4, concentrated, and chromatographied to give the pure product **m** (265 mg, 64%).

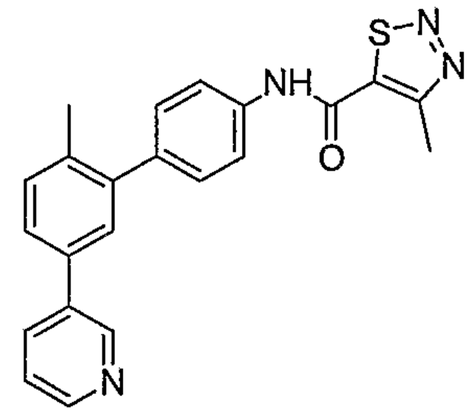
Suzuki Coupling Reaction: To a solution of 3-(3-bromo-4-methylphenyl)-pyridine **m** (145 mg, 0.58 mmol), dichlorobis (triphenylphosphine)palladium (II) ($Pd(PPh_3)_2Cl_2$, 60 mg, 0.09 mmol), and 4-aminophenylboronic acid pinacol ester (130 mg, 0.58 mmol) in toluene (4 mL) was added Na_2CO_3 (2 N, 0.3 mL) and ethanol (0.5 mL). The stirred mixture was heated up to 80 °C for 6 hr. The solution was cooled to room temperature and diluted with H_2O (10 mL) and EtOAc (10 mL). The organic phase was dried over Na_2SO_4, concentrated, and chromatographied to give **n** (90 mg, 60%).

Amide Coupling Reaction: To a solution of 2'-methyl-5'-(pyridin-3-yl)biphenyl-4-amine **n** (40 mg, 0.15 mmol) in DCM (3 mL) was added EDC (85 mg, 0.45 mmol) and 3-methylisonicotinic acid (40 mg, 0.3 mmol). The solution was stirred at room temperature for 6 hr before it was concentrated and chromatographied to give Compound 20 (50 mg, 88%).

^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.79-8.77 (m, 1 H), 8.47-8.41 (m, 3 H),

7.90-7.86 (m, 1 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.49-7.26 (m, 7 H), 2.47 (s, 3 H), 2.34 (s, 3 H). ESMS cacld ($C_{25}H_{21}N_3O$): 379.1; found: 380.4 (M+H).

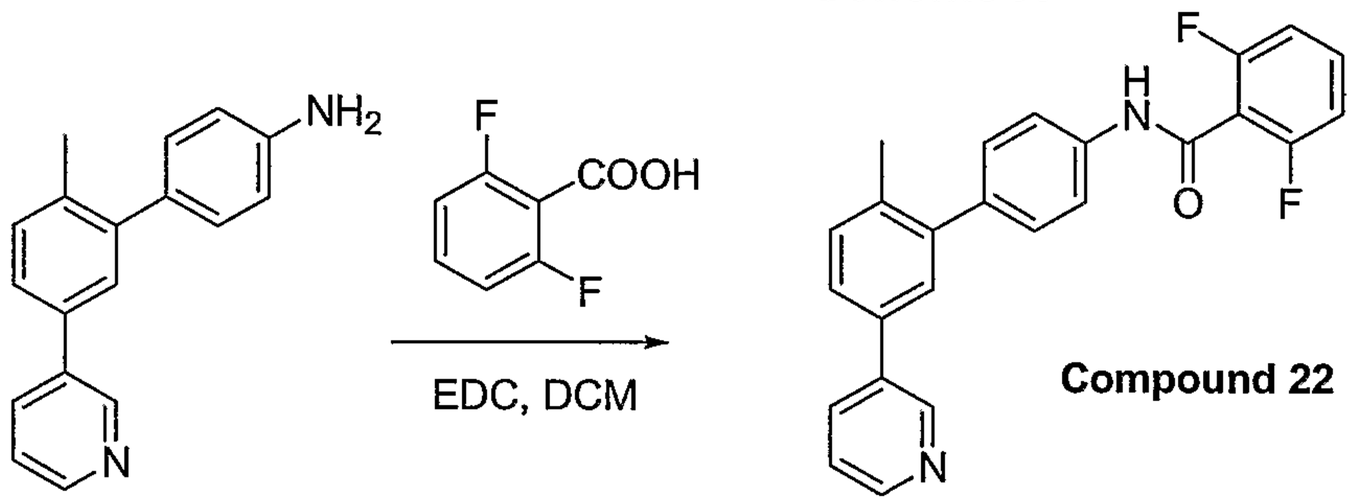
Compound 21: 4-Methyl-[1,2,3]thiadazole-5- carboxylic acid [2'-methyl-5'-(pyridin-3-yl)-biphenyl-4-yl]- amide



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, J = 2.4 Hz, 1 H), 8.57-8.54 (m, 1 H), 7.91-7.87 (m, 2 H), 7.68-7.65 (m, 2 H), 7.52-7.34 (m, 6 H), 3.00 (s, 3 H), 2.33 (s, 3 H). ESMS cacld ($C_{22}H_{18}N_4OS$): 386.1; found: 387.2 (M+H).

Compound 22: 2,6-Difluoro-N-[2'-methyl-5'- (pyridine-3-yl)-biphenyl-4-yl]-benzamide

Scheme X

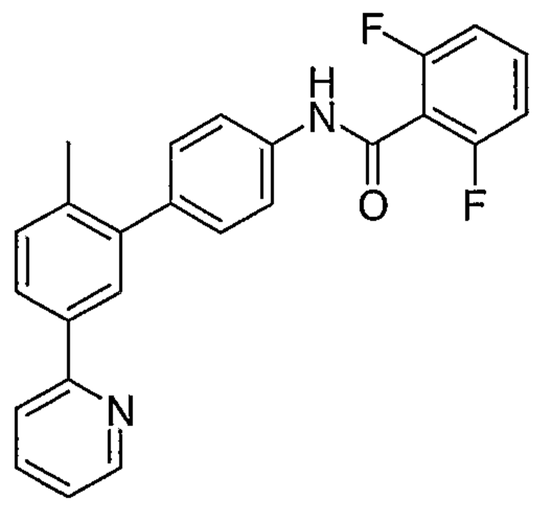


n **Compound 22**

Compound 22 was prepared by a method analogous to that described for the amide coupling reaction of Compound 20.

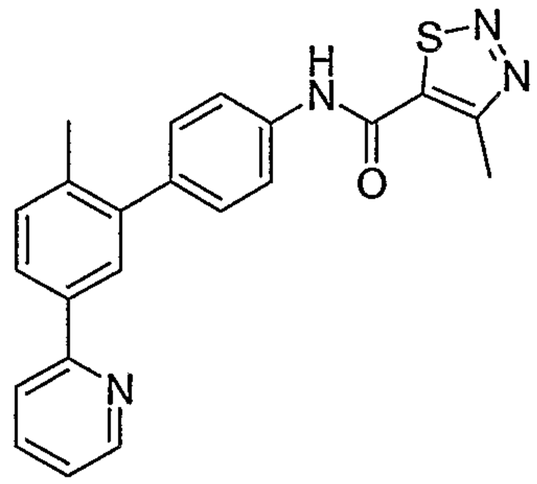
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 8.55-8.50 (m, 1 H), 8.24 (s, 1 H), 7.91-7.85 (m, 1 H), 7.76-7.71 (m, 2 H), 7.51-7.31 (m, 7 H), 7.02-6.93 (m, 2 H), 2.32 (s, 3 H); ESMS cacld ($C_{25}H_{18}F_2N_2O$): 400.1; found: 401.1 (M+H).

Compound 23: 2,6-Difluoro-N-[2'-methyl-5'-(pyridine-2-yl)-biphenyl-4-yl]-benzamide



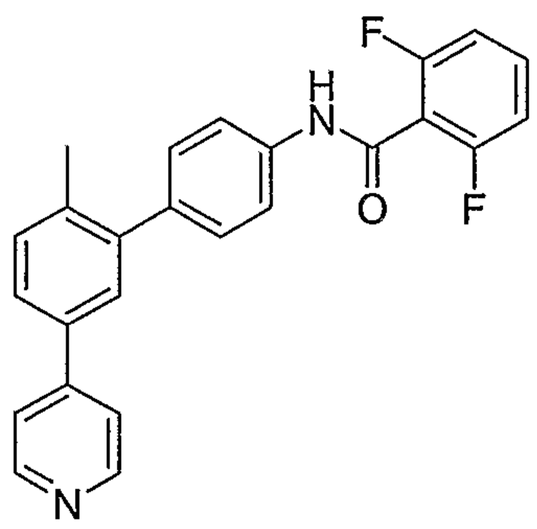
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68-8.62 (m, 1 H), 8.11 (s, 1 H), 7.82-7.64 (m, 6 H), 7.41-7.16 (m, 5 H), 6.99-6.86 (m, 2 H), 2.33 (s, 3 H); ESMS cacld ($C_{25}H_{18}F_2N_2O$): 400.1; found: 401.0 (M+H).

Compound 24: 4-Methyl-[1,2,3]thiadazole-5- carboxylic acid [2'-methyl-5'-(pyridin-2-yl)-biphenyl-4-yl]- amide



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.64 (m, 1 H), 8.17 (s, 1 H), 7.84-7.63 (m, 5 H), 7.39-7.36 (m, 3 H), 7.26-7.20 (m, 1 H), 2.94 (s, 3 H), 2.33 (s, 3 H); ESMS cacld ($C_{22}H_{18}N_4OS$): 386.1; found: 387.2 (M+H).

Compound 30: 2,6-Difluoro-N-[2'-methyl-5'-(pyridine-4-yl)-biphenyl-4-yl]- benzamide

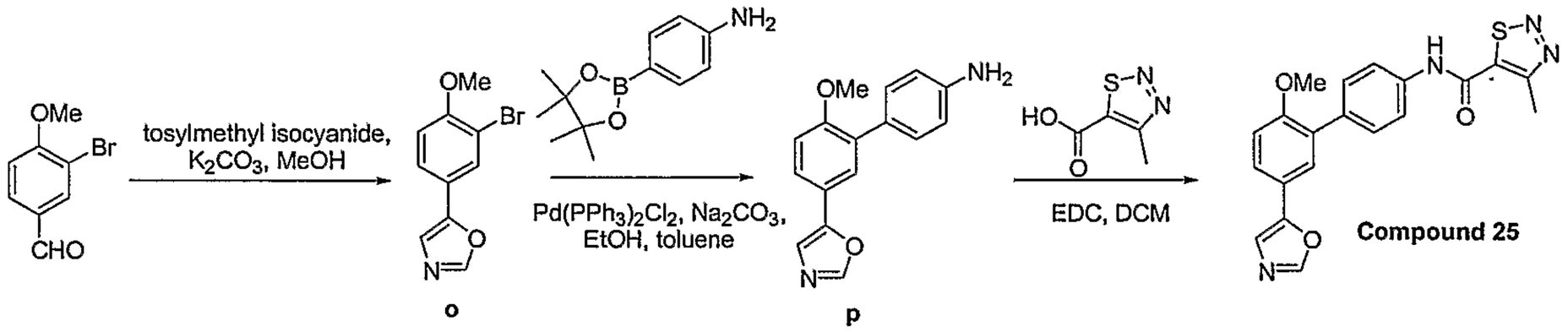


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63-8.58 (m, 2 H), 8.13 (s, 1 H), 7.77-7.36 (m, 10 H), 7.04-6.96 (m, 2 H), 2.33 (s, 3 H); ESMS cacld ($C_{25}H_{18}F_2N_2O$): 400.1; found: 401.1

(M+H).

Compound 25: 4-Methyl-[1,2,3]thiadazole-5- carboxylic acid [2'-methoxy-5'-(oxazol-5-yl)-biphenyl-4-yl]- amide

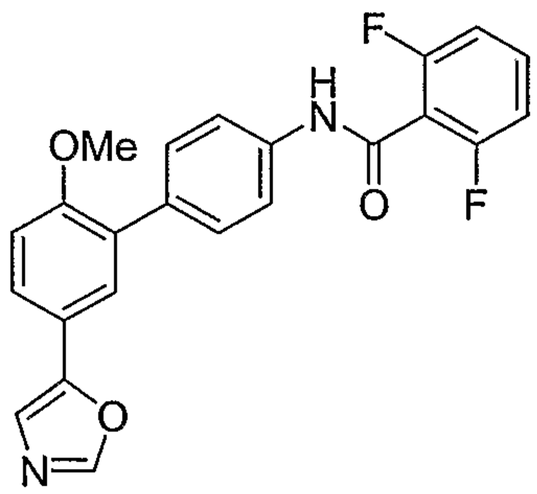
Scheme XI



The mixed solution of 3-bromo-4-methoxybenzaldehyde (200 mg, 0.93 mmol) in methanol (4 mL) was added tosylmethyl isocyanide (200 mg, 1.02 mmol) and K_2CO_3 (260 mg, 1.88 mmol). The reaction was stirred at room temperature for 5 min before heated to 80 °C in the sealed tube. After 30 min, the solution was cooled to room temperature and concentrated. Column chromatography afforded 5-(3-bromo-4-methoxyphenyl)oxazole (**o**) (190 mg, 80%). Following the procedures analogous to the Suzuki and amide coupling reactions described for Compound 20, Compound 25 was prepared.

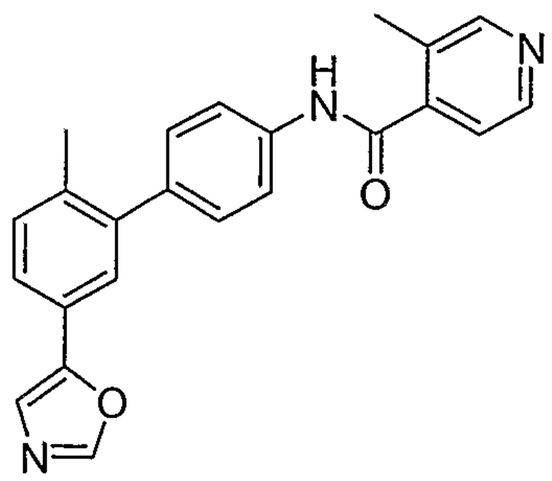
^{1}H NMR (300 MHz, CD_3OD) δ 8.22 (s, 1 H), 7.74-7.65 (m, 4 H), 7.57-7.54 (m, 2 H), 7.43 (s, 1 H), 7.20-7.16 (m, 1 H), 3.87 (s, 3 H), 2.89 (s, 3 H); ESMS cacld ($C_{20}H_{16}N_4O_3S$): 392.1; found: 393.1 (M+H).

Compound 27: 2,6-Difluoro-N-[2'-methyl-5'- (oxazol-5-yl)-biphenyl-4-yl]- benzamide



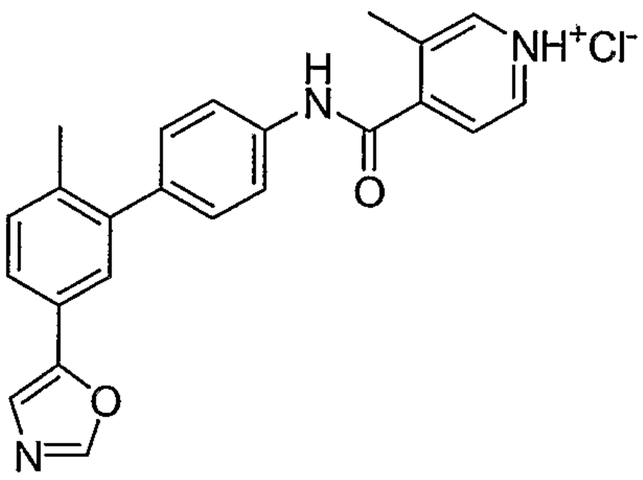
^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (s, 1 H), 7.73-7.40 (m, 8 H), 7.16-7.09 (m, 3 H), 3.84 (s, 3 H); ESMS cacld ($C_{23}H_{16}F_2N_2O_3$): 406.1; found: 407.0 (M+H).

Compound 26: 3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57-8.54 (m, 2 H), 7.89 (s, 1 H), 7.81 (s, 1 H), 7.73-7.70 (m, 2 H), 7.57-7.51 (m, 2 H), 7.40-7.31 (m, 5 H), 2.52 (s, 3 H), 2.31 (s, 3 H); ESMS cacld ($C_{23}H_{19}N_3O_2$): 369.1; found: 370.2 (M+H).

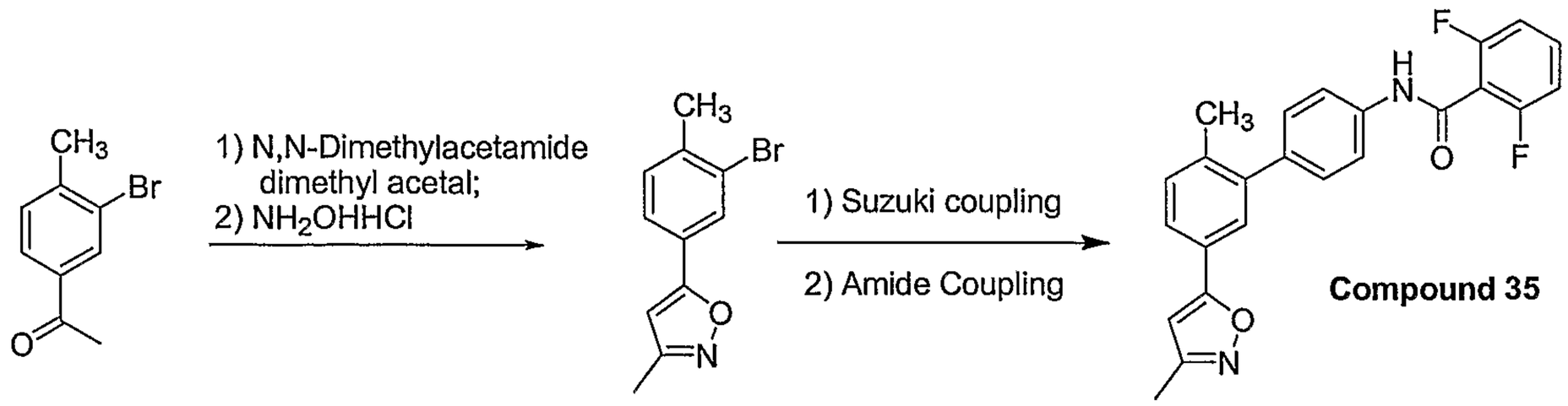
Compound 29: 3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide, hydrochloride salt



^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.97 (s, 1 H), 8.86 (s, 1 H), 8.82 (d, J = 5.4 Hz, 1 H), 8.42 (s, 1 H), 7.96 (d, J = 5.4 Hz, 1 H), 7.82 (d, J = 8.7 Hz, 2 H), 7.69 (s, 1 H), 7.63-7.54 (m, 2 H), 7.43-7.38 (m, 2 H), 4.10 (brs, 1 H), 3.31 (s, 3 H), 2.47 (s, 3 H); ESMS cacld ($C_{23}H_{19}N_3O_2$): 369.1; found: 370.1 (M+H).

Compound 35: 2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-isoxazole-5-yl)-biphenyl-4-yl]-benzamide

Scheme XII



Compound 35

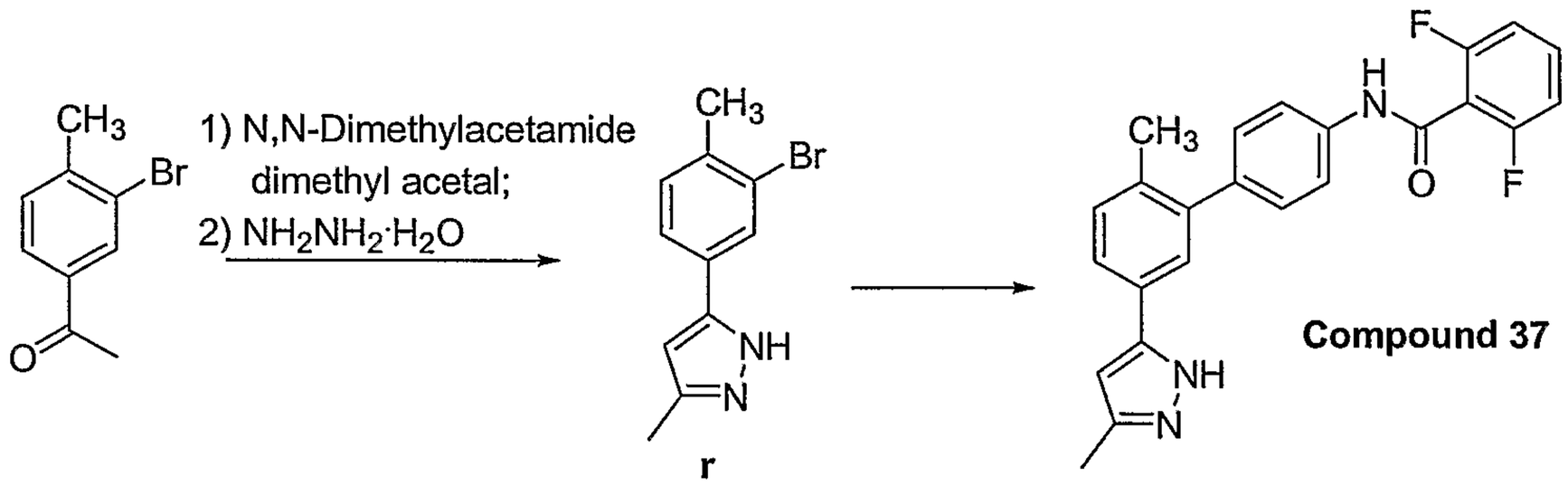
q

A solution of 3'-bromo-4'-methylacetophenone (1 g, 4.69 g) in *N,N*-dimethylacetamide dimethyl acetal (2.5 mL) was refluxed at 100 °C for 12 hr. The solvent was removed and the residue and hydroxylamine hydrochloride (490 mg, 7.1 mmol) was dissolved in ethanol (10 mL). The solution was refluxed at 90 °C for 2 hr before it was concentrated. Column chromatography afforded compound **q** in 65% overall yield. Compound 35 was obtained following a Suzuki coupling and amide coupling procedures analogous to that described for compound 20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.61 (m, 5 H), 7.49-7.36 (m, 4 H), 7.04-6.96 (m, 2 H), 6.32 (s, 1 H), 2.37 (s, 3 H), 2.34 (s, 3 H); ESMS cacld ($C_{24}H_{18}F_2N_2O_2$): 404.1; found: 405.1 (M+H).

Compound 37: 2,6-Difluoro-N-[2'-methyl-5'- (3-methyl-1*H*-pyrazol-5-yl)-biphenyl-4-yl]-benzamide

Scheme XIII



Compound 37

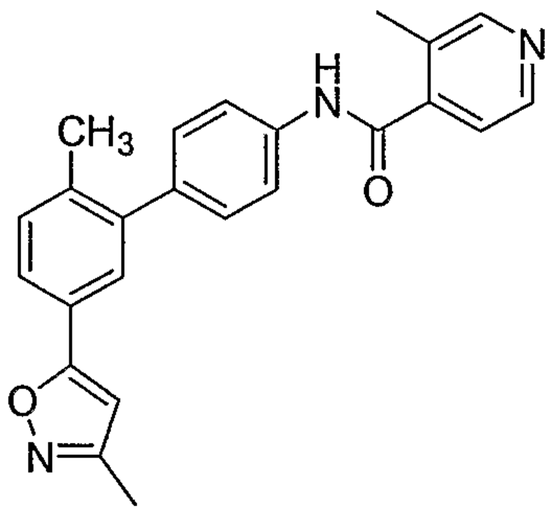
r

A solution of 3'-bromo-4'-methylacetophenone (1 g, 4.69 g) in *N,N*-dimethylacetamide dimethyl acetal (2.5 mL) was refluxed at 100 °C for 12 hr. The solvent was removed and the residue and hydrazine monohydrate (355 mg, 7.1 mmol) was dissolved in ethanol (10 mL). The solution was refluxed at 90 °C for 1 hr

before it was concentrated. Column chromatography afforded compound **r** in 75% overall yield. Compound 37 was obtained by a Suzuki coupling reaction analogous to that described for Compound 20.

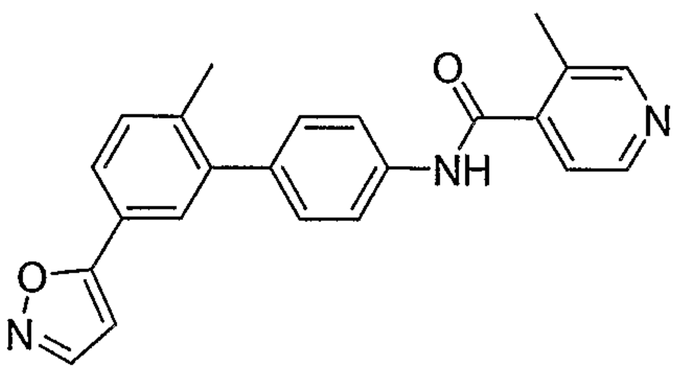
^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.91 (s, 1 H), 7.79-7.21 (m, 11 H), 6.41 (s, 1 H), 2.22 (s, 6 H); ESMS cacld ($C_{24}H_{19}F_2N_3O$): 403.1; found: 404.1 (M+H).

Compound 36: 3-Methyl-N-[5'-(3-methyl- isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



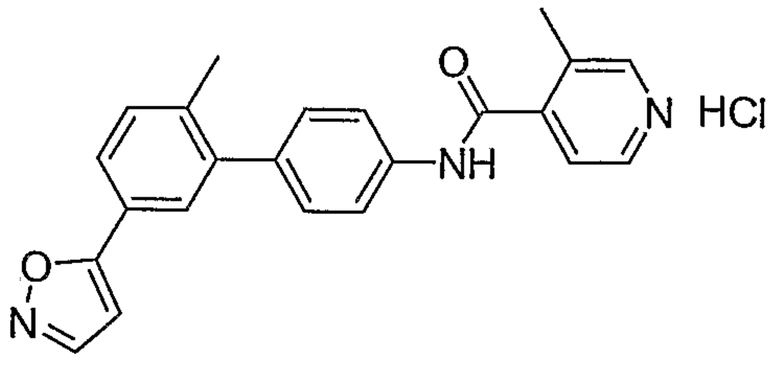
^{1}H NMR (300 MHz, CD_3OD) δ 8.54-8.51 (m, 2 H), 7.81-7.28 (m, 8 H), 6.62 (s, 1 H), 2.48 (s, 3 H), 2.32 (s, 6 H); ESMS cacld ($C_{24}H_{21}N_3O_2$): 383.1; found: 484.2 (M+H).

Compound 32: 3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



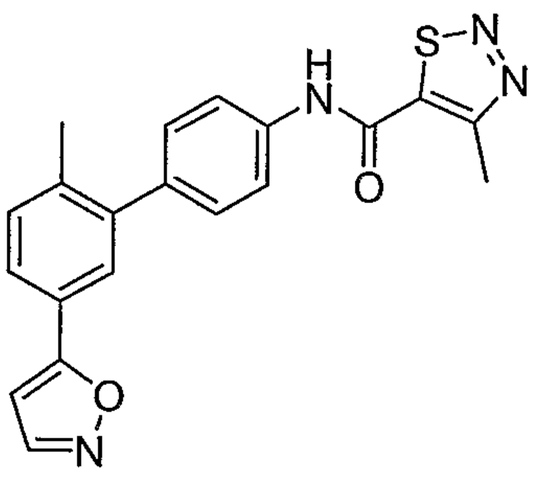
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59-8.56 (m, 2 H), 8.27 (d, J = 1.8 Hz, 1 H), 7.73-7.65 (m, 5 H), 7.40-7.37 (m, 4 H), 6.49 (d, J = 1.8 Hz, 1 H), 2.52 (s, 3 H), 2.34 (s, 3 H); ESMS cacld ($C_{23}H_{19}N_3O_2$): 369.1; found: 370.2 (M+H).

Compound 34: 3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide, HCl salt



^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.84 (s, 1 H), 8.78 (s, 1 H), 8.75 (d, J = 5.1 Hz, 1 H), 8.64-8.63 (m, 1 H), 7.83-7.69 (m, 5 H), 7.48-7.41 (m, 3 H), 7.04 (d, J = 1.5 Hz, 1 H), 3.72 (brs, 1 H), 2.45 (s, 3 H), 2.30 (s, 3 H);); ESMS cacld ($C_{23}H_{19}N_3O_2$): 369.1; found: 370.1 (M+H).

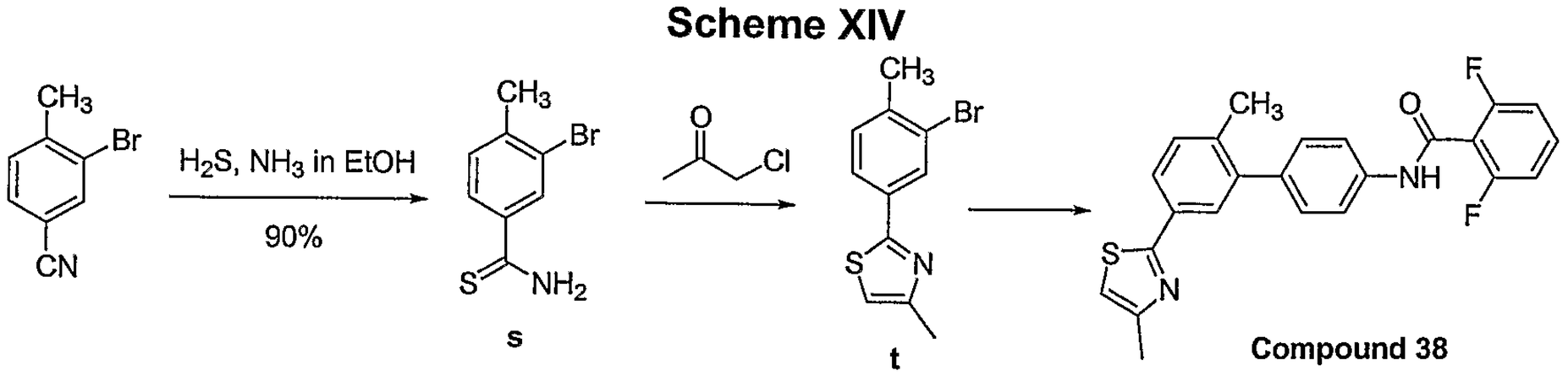
Compound 33: 4-Methyl-[1,2,3]thiadazole-5- carboxylic acid [2'-methyl-5'-(isoxazol-5-yl)-biphenyl-4-yl]- amide



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.24 (d, J = 1.8 Hz, 1 H), 7.71-7.63 (m, 4 H), 7.38-7.34 (m, 3 H), 6.50 (d, J = 2.1 Hz, 1 H), 2.95 (s, 3 H), 2.31 (s, 3 H); ESMS cacld ($C_{20}H_{16}N_4O_2S$): 376.1; found: 377.1 (M+H).

Compound 38: 2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide

Scheme XIV



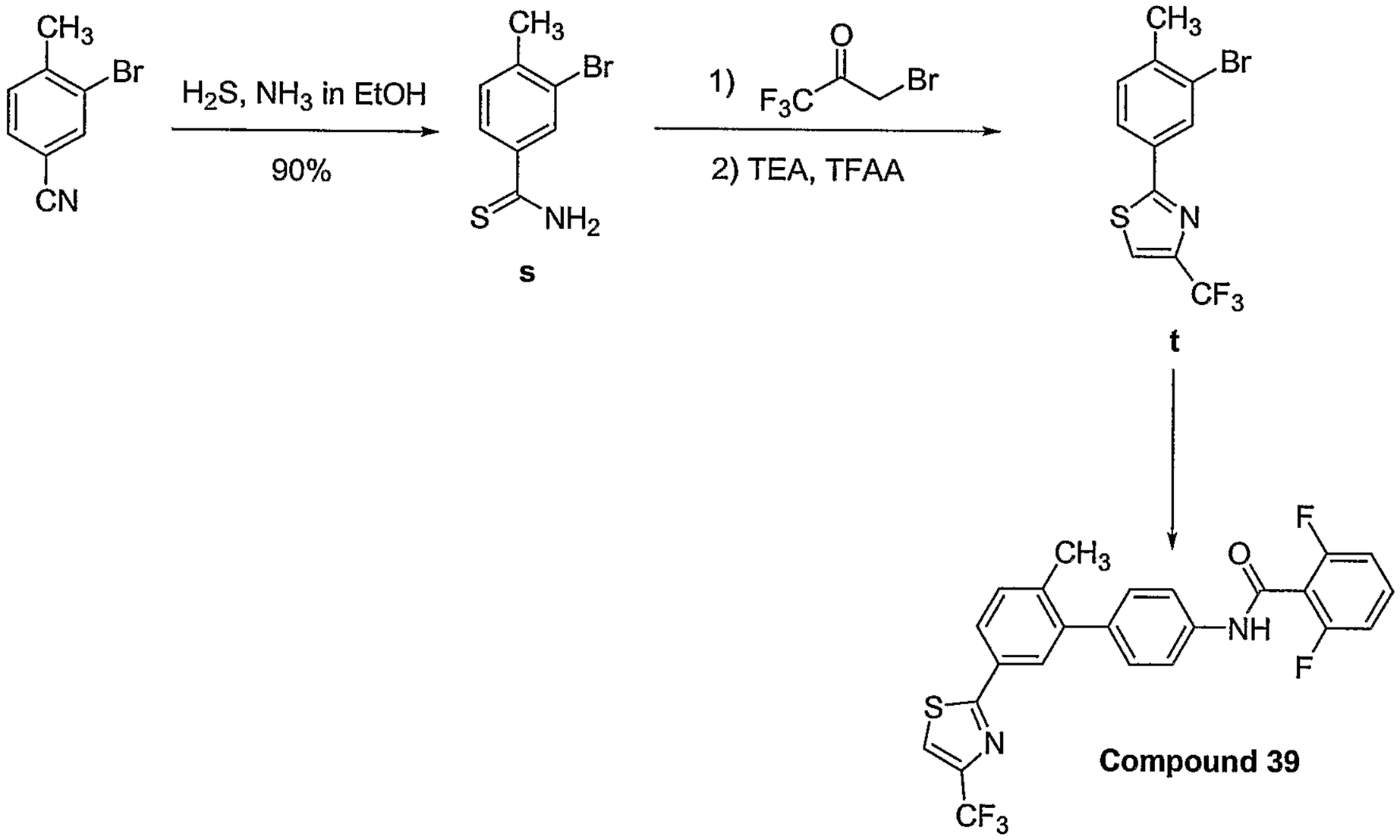
A solution of 3-bromo-4-methyl-benzonitrile (500 mg, 2.55 mmol) in ammonia solution (2 M in ethanol, 10 mL) was bubbled with H_2S gas slowly for 1 hr. The

solution was stirred for 3 hr at room temperature before the nitrogen was bubbled through the solution to remove H_2S. The solution was concentrated to give the crude **s** (450 mg) which was used directly in the next reaction.

The solution of **s** (100 mg, 0.43 mmol) and 1-chloropropan-2-one (200 μL, 2.5 mmol) in ethanol (2 mL) was refluxed at 85 °C for 10 hr. The solvent was removed and column chromatography afforded **t** (60 mg, 52%). Compound 38 was obtained by a Suzuki coupling reaction analogous to that described for Compound 20.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.80-7.68 (m, 4 H), 7.40-7.29 (m, 4 H), 7.03-6.96 (m, 2 H), 6.82 (s, 1 H), 2.48 (s, 3 H), 2.31 (s, 3 H); ESMS cacld ($C_{24}H_{18}F_2N_2OS$): 420.1; found: 421.1 (M+H).

Compound 39: 2,6-Difluoro-N-[2'-methyl-5'- (4-trifluoromethyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide

Scheme XV

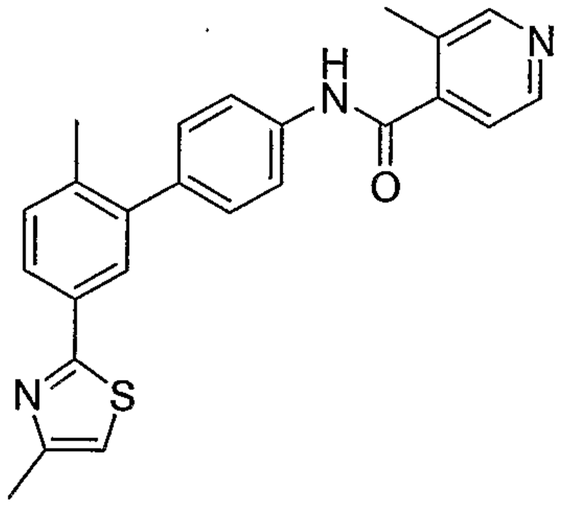


A solution of **s** (100 mg, 0.43 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (270 μL, 2.57 mmol) in ethanol (4 mL) was refluxed at 85 °C for 4 hr. The solvent was removed and the residue was dissolved in dichloromethane (4 mL) with TEA (120 μL,

0.86 mmol) and TFAA (120 μL, 0.86 mmol). The reaction was stirred at room temperature for 30 min before the solution was concentrated. Column chromatography afforded **t** (100 mg, 68%). Compound 39 was obtained by a Suzuki coupling reaction analogous to that described for Compound 20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.64 (m, 6 H), 7.48-7.38 (m, 4 H), 7.07-7.02 (m, 2 H), 2.33 (s, 3 H); ESMS cacld ($C_{24}H_{15}F_5N_2OS$): 474.1; found: 475.0 (M+H).

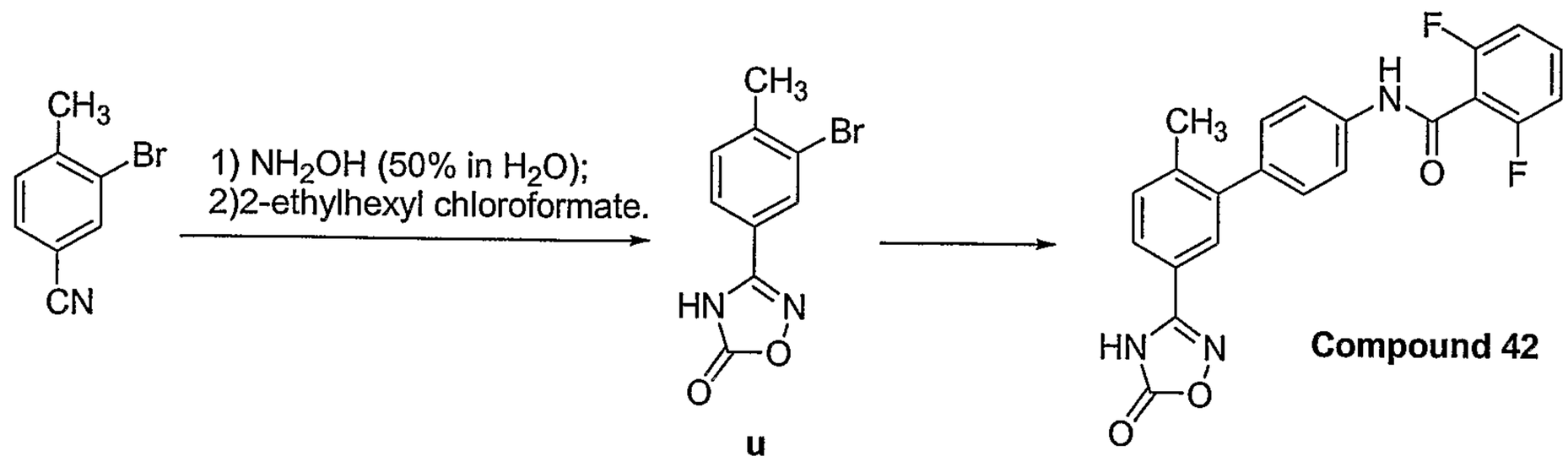
Compound 40: 3-Methyl-N-[5'-(4-methyl-thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



^{1}H NMR (300 MHz, CD_3OD) δ 8.54-8.51 (m, 2 H), 7.81-7.76 (m, 2 H), 7.68-7.52 (m, 5 H), 7.41-7.38 (m, 2 H), 7.11 (s, 1 H), 2.47 (s, 3 H), 2.45 (s, 3 H), 2.34 (s, 3 H); ESMS cacld ($C_{24}H_{21}N_3OS$): 399.1; found: 400.1 (M+H).

Compound 42: 2,6-Difluoro-N-[2'-methyl-5'- (5-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)-biphenyl-4-yl]-benzamide

Scheme XVI



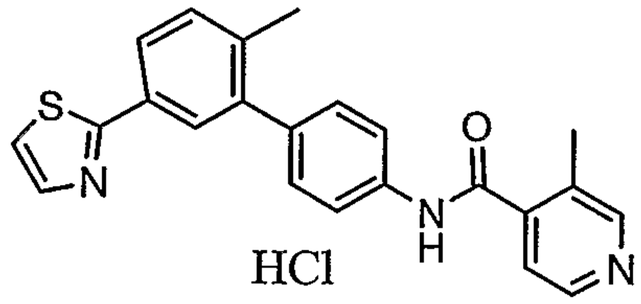
A mixed solution of 3-bromo-4-methylbenzonitrile (500 mg, 2.6 mmol) and NH_2OH (50% in H_2O, 0.4 mL, 6.5 mmol) in EtOH (3 mL) was refluxed in a sealed tube at 85

°C for 5 hr. The solvent was removed and the residue was dissolved in THF (4 mL). To the solution was added pyridine (0.31 mL, 3.8 mmol) and 2-ethylhexy chloroformate (0.75 mL, 3.8 mmol) at 0 °C and stirred at this temperature for 1 hr. The organic phase was washed with H_2O and brine and concentrated to give a residue that was dissolved in xylene (5 mL). The solution was refluxed at 110 °C for 12 hr, concentrated, and partitioned between water and ethyl acetate. The organic phase was separated, washed with water and brine, and dried. Concentration followed by column chromatography afforded **u** (350 mg).

Following a Suzuki coupling procedure analogous to that described for Compound 20, Compound 42 was obtained as solid.

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.92 (s, 1 H), 7.82-7.19 (m, 11 H), 2.24 (s, 3 H); ESMS cacld ($C_{22}H_{15}F_2N_3O_3$): 407.1; found: 408.1 (M+H).

Compound 9: 3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotinamide, hydrochloride salt

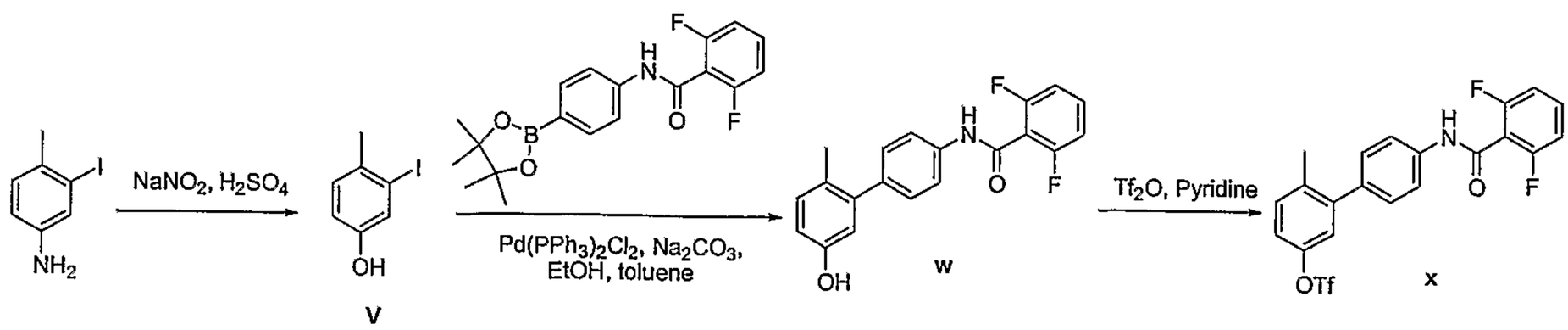


To a stirred suspension of Compound 42 (3g) in methanol (60 mL) was added HCl (2 eq) in methanol (40mL). Ether (200 mL) was then added to the resultant solution at room temperature. After 2 hrs, precipitates were collected and dried to give the title compound as a solid (3.1g).

^{1}H-NMR ($DMSOd_6$) δ (ppm), 11.12 (s, 1H), 8.99-7.37(m, 12H), 7.51-7.38(m, 3H), 2.51 (s, 3H), 2.27 (s, 3H). ESMS clcd for $C_{23}H_{20}ClN_3OS$: 421.10; Found: 386.1 $(M\text{-}HCl+H)^+$.

General Method for the Synthesis of Compounds 41, 43, 47, and 52:

Scheme XVII



To a solution of 3-iodo-4-methylaniline (1 g, 4.29 mmol) in H_2O (25 mL) was added H_2SO_4 (0.5 M, 25 mL). The solution was heated to 80 °C until all solid dissolved. Then the reaction was cooled to 0 °C and $NaNO_2$ (444 mg, 6.39 mmol) was added in small portions. After 2 hr at this temperature, urea (126 mg, 2.1 mmol) was added at 0 °C. The solution was allowed to warm up to room temperature and H_2SO_4 (0.5 M, 25 mL) was added. The reaction was refluxed for 30 min and cooled down to room temperature. The solution was extracted with EtOAc and Et_2O and the combined organic phases were dried over Na_2SO_4, concentrated, and chromatographied to give the pure product **v** (800 mg, 80%).

2,6-Difluoro-N-(5'-hydroxy-2'-methylbiphenyl-4-yl)benzamide), **w**, was prepared from **v** and 2,6-Difluoro-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-benzamide following Suzuki coupling procedure described above for Compound 20. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.68-7.62 (m, 2 H), 7.42-7.28 (m, 3 H), 7.11-6.85 (m, 3 H), 6.78-6.72 (m, 2 H), 2.18 (s, 3 H); ESMS cacld ($C_{20}H_{15}F_2NO_2$): 339.1; found: 340.1 (M+H).

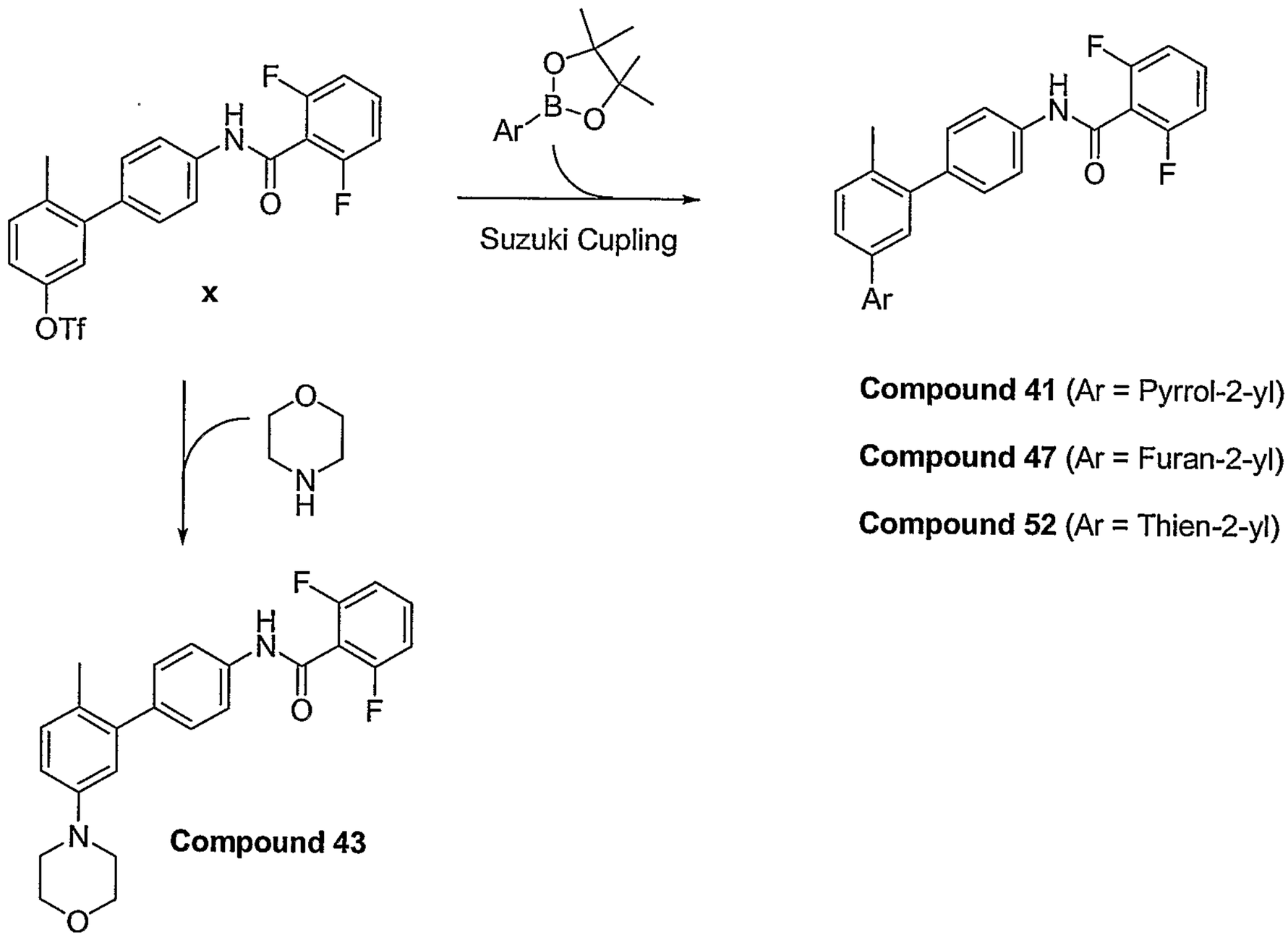
To a solution of **w** (1 g, 2.94 mmol) and pyridine (355 μL, 4.39 mmol) in dichloromethane (DCM) (15 mL) was added trifluoromethanesulfonic anhydride (545 μL, 3.24 mmol) in drop wise at 0 °C. After 10 min at this temperature, the solvent was removed and column chromatography afforded (4'-(2,6-difluorobenzamido)-6-methylbiphenyl-3-yl trifluoromethanesulfonate, **x**, (1.17 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.66 (m, 3 H), 7.49-7.31 (m, 4 H), 7.20-7.11 (m, 2 H), 7.08-6.99 (m, 2 H), 2.28 (s, 3 H); ESMS cacld ($C_{21}H_{14}F_5NO_4S$): 471.1; found: 472.0 (M+H).

Compound 41, Compound 47 and Compound 52 were synthesized from x using a

Suzuki coupling analogous to that described for Compound 20. Compound 43 was prepared by neucleophilic substitution of the aromatic triflate by morpholino:

Scheme XVIII



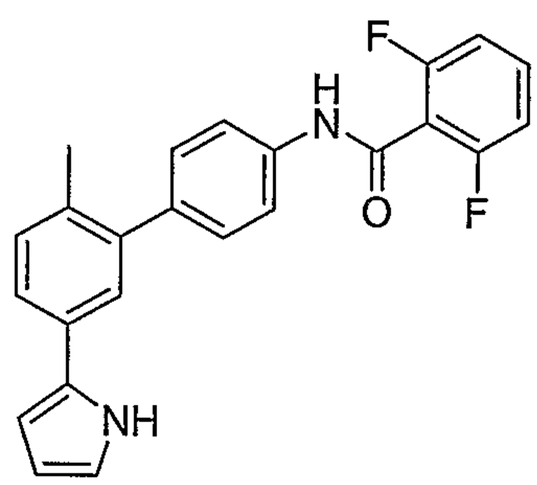
Compound 41 (Ar = Pyrrol-2-yl)

Compound 47 (Ar = Furan-2-yl)

Compound 52 (Ar = Thien-2-yl)

Compound 43

Compound 41: 2,6-Difluoro-N-[2'-methyl-5'- (1*H*-pyrrol-2-yl)-biphenyl-4-yl]-benzamide

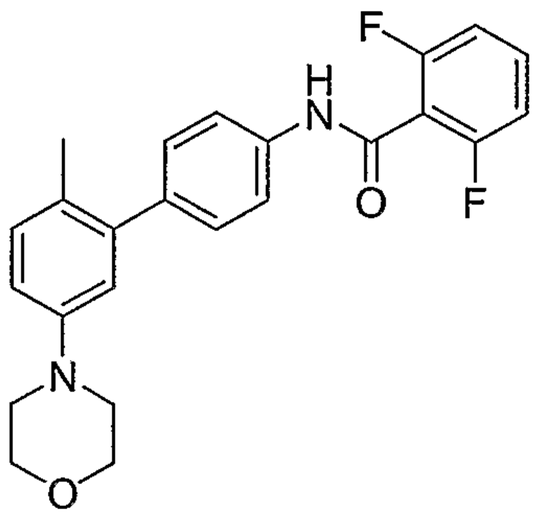


Compound 41 was prepared from **w** following a Suzuki coupling reaction analogous to that described for Compound 20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1 H), 7.93 (s, 1 H), 7.67-7.64 (m, 2 H), 7.41-7.22

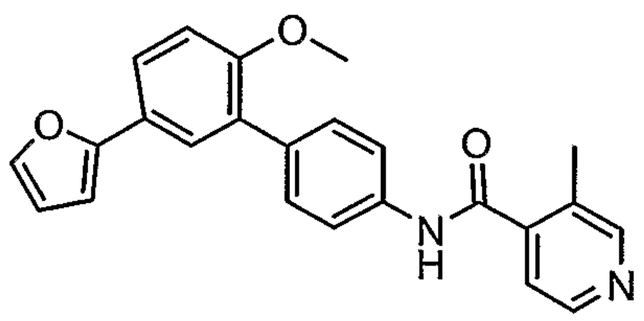
(m, 5 H), 7.02-6.96 (m, 2 H), 6.82-6.80 (m, 1 H), 6.51-6.49 (m, 1 H), 6.30-6.28 (m, 1 H), 2.25 (s, 3 H); ESMS cacld ($C_{24}H_{18}F_2N_2O$): 388.1; found: 389.1 (M+H).

Compound 43: 2,6-Difluoro-N-[2'-methyl-5'-(morpholino-4-yl)-biphenyl-4-yl]-benzamide



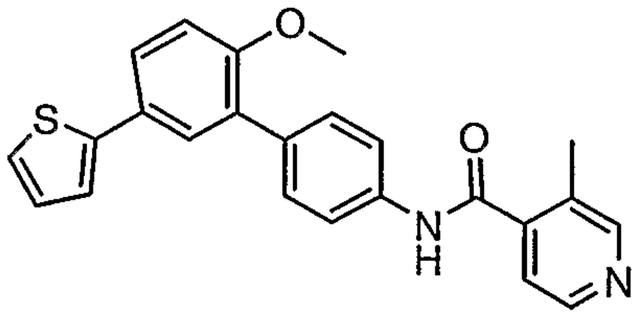
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 7.70-7.65 (m, 2 H), 7.43-7.15 (m, 4 H), 7.02-6.95 (m, 2 H), 6.85-6.78 (m, 2 H), 3.85 (t, *J* = 5.1 Hz, 4 H), 3.13 (t, *J* = 5.1 Hz, 4 H), 2.19 (s, 3 H); ESMS cacld ($C_{24}H_{22}F_2N_2O_2$): 408.2; found: 409.3 (M+H).

Compound 47: 3-Methyl-N-[2'-methoxy-5'-(furan-2-yl)-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR (CD_3Cl) δ (ppm), 8.52(s, 1H), 8.49(d, , *J* =4.2, 1H), 7.95-7.28(m, 11H), 3.79 (s, 3H), 2.46 (s, 3H). ESMS clcd for $C_{24}H_{20}N_2O_3$: 384.15; Found: 385.2. $(M+H)^+$.

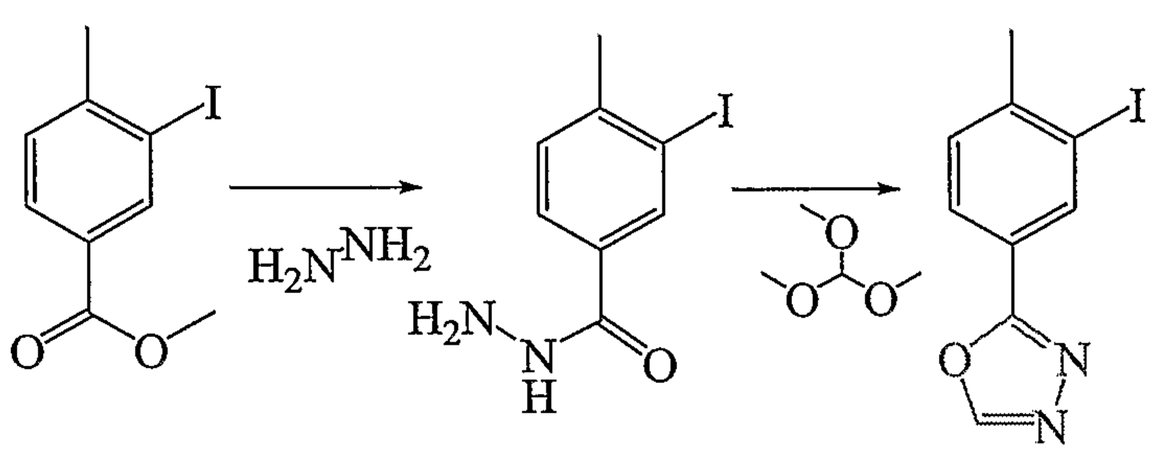
Compound 52: 3-Methyl-N-[5'-(thien-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR (CD_3Cl) δ (ppm), 8.53(s, 1H), 8.49(d, , *J* =4.1, 1H), 7.75-7.35(m, 11H), 3.79 (s, 3H), 2.47 (s, 3H). ESMS clcd for $C_{24}H_{20}N_2O_2S$: 400.12; Found: 401.1. $(M+H)^+$.

General Method for the Synthesis of Compounds 46, 68, 69, 70, and 71:

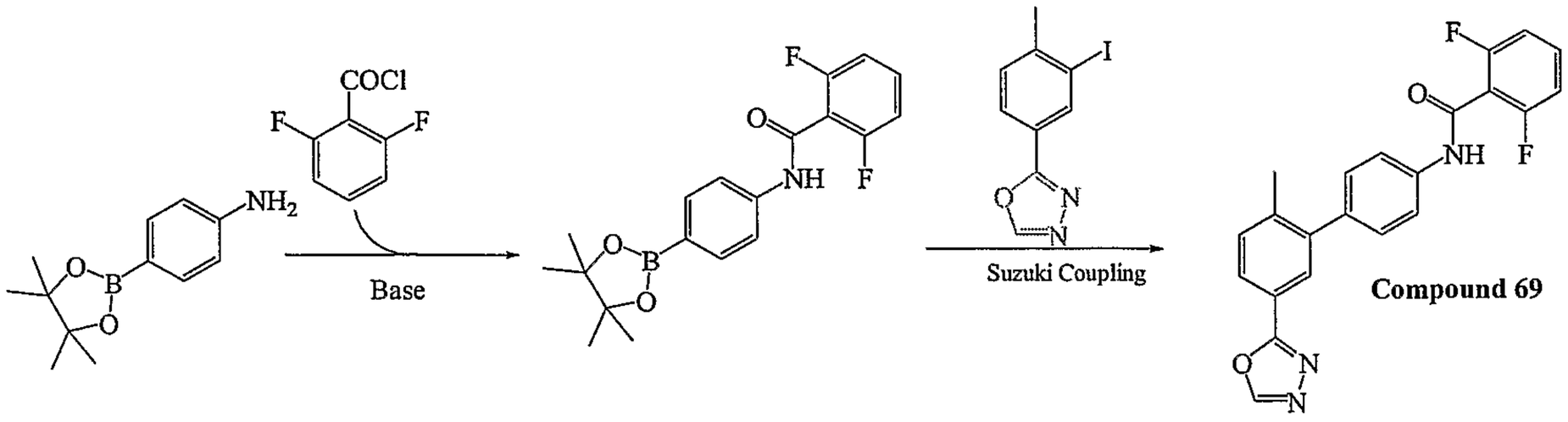
Scheme XIX



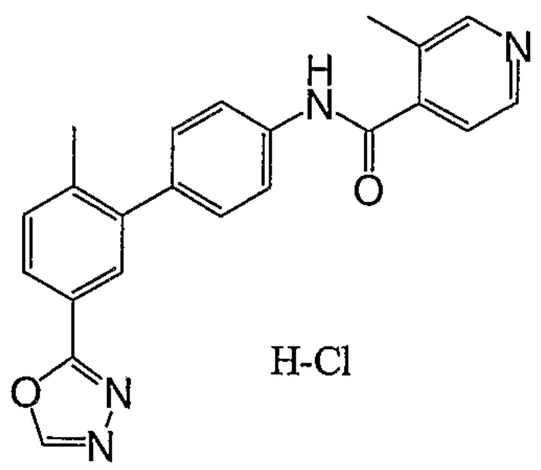
Ref: JMC, 2001, 44 (8), 1268-85

3-Iodo-4-methyl benzoic acid methyl ester was treated with hydrazine to form 3-Iodo-4-methyl benzoic acid hydrazide. 2-(3-Iodo-4-methyl-phenyl)-[1,3,4]oxadiazole was prepared from 3-iodo-4-methyl benzoic acid hydrazide according to a method analogous to that described in *J. of Medicinal Chemistry* (2001), *44*(8):1268-85, the entire teachings of which are incorporated herein by reference. Compounds 46, 68, 69, 70, and 71 were prepared via an amide coupling reaction analogous to that described in step A of the synthesis of Compound 1, followed by a Suzuki coupling reaction analogous to that described in step B of the synthesis of Compound 1. The amide coupling reaction and Suzuki coupling reaction are shown for Compound 69 in Scheme XX below:

Scheme XX



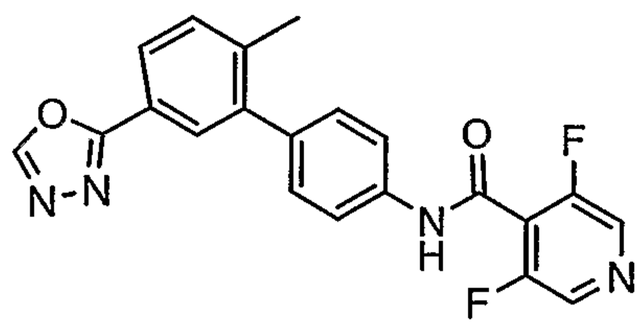
Compound 46: 3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide, HCl salt



H-Cl

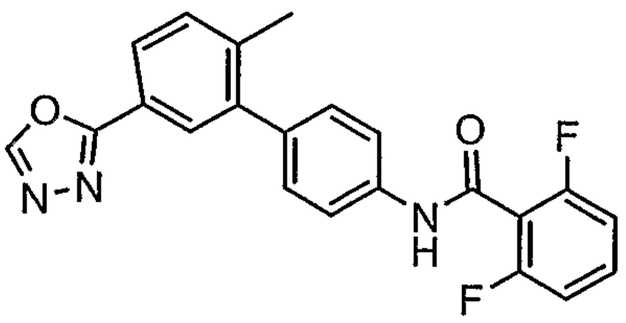
^{1}H-NMR (CD_3OD) δ (ppm), 9.02 (s, 1H), 8.89 (s, 1H), 8.61(d, *J* =5.2, 1H), 8.18(d, *J* =5.2, 1H), 7.91(m, 2H), 7.82 (d, *J* =7.6, 2H), 7.53 (d, *J* =6.4, 1H), 7.42 (d, *J* =7.6, 2H), 2.63 (s, 3H), 2.38 (s, 3H). ESMS clcd for $C_{22}H_{19}ClN_4O_2$: 406.12; Found: 371.1 $(M\text{-}HCl+H)^+$.

Compound 68: 3,5-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR ($CDCl_3$) δ, 8.52(s, 2H), 8.43(s, 1H), 7.99-7.92 (m, 2H), 7.83(s, 1H), 7.71(d, *J* =7.5, 2H), 7.43(m, 1H), 7.38(d, *J* =7.5, 2H), 2.38(s, 3H). ESMS clcd for $C_{21}H_{14}F_2N_4O_2$: 392.11; Found: 393.1. $(M+H)^+$.

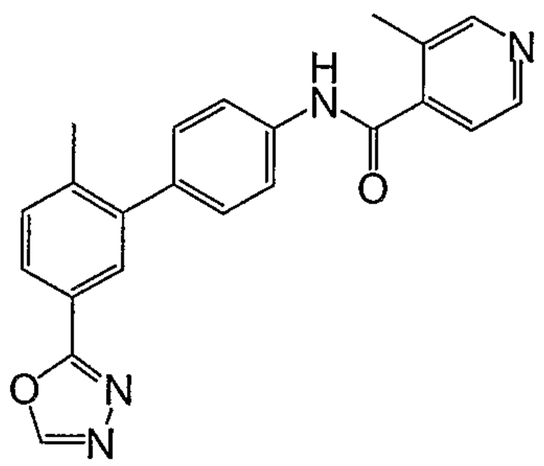
Compound 69: 2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-benzamide



^{1}H-NMR ($CDCl_3$) δ (ppm), 8.42(s, 1H), 8.02-7.34(m, 8H), 7.11(m, 2H), 2.36 (s, 3H). ESMS clcd for $C_{22}H_{15}F_2N_3O_2$: 391.11; Found: 392.1 $(M+H)^+$.

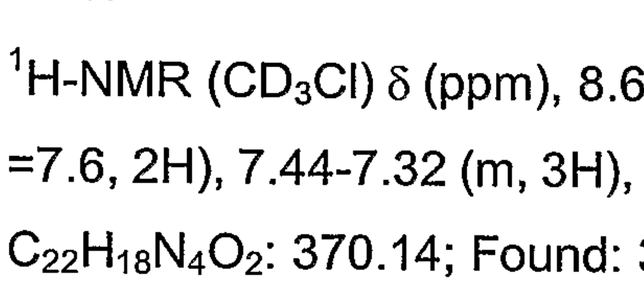
Compound 70: 3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)- biphenyl-4-yl]-

isonicotinamide



^{1}H-NMR (CD_3Cl) δ (ppm), 8.60-8.52 (m, 2H), 8.42 (s, 1H), 7.99(m, 3H), 7.71(d, *J* =7.6, 2H), 7.44-7.32 (m, 3H), 7.91(m, 2H), 2.52 (s, 3H), 2.36 (s, 3H). ESMS clcd for $C_{22}H_{18}N_4O_2$: 370.14; Found: 371.1 $(M+H)^+$.

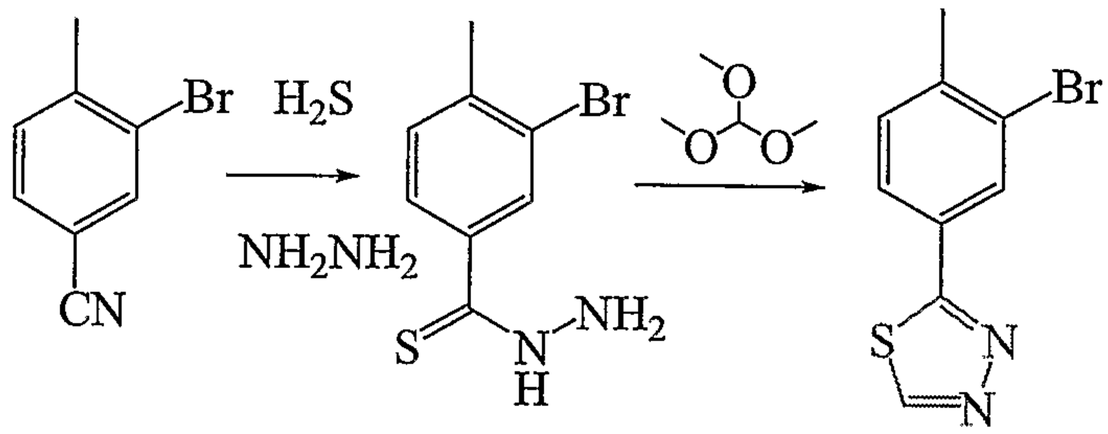
Compound 71: 3-Fluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR ($CDCl_3$) δ, 8.72-7.84(m, 7H), 7.73(d, *J* =7.5, 2H), 7.42 (m, 1H), 7.38(d, *J* =7.5, 2H), 2.38(s, 3H). ESMS clcd for $C_{21}H_{15}FN_4O_2$: 374.12; Found: 375.1. $(M+H)^+$.

General Method for the Synthesis of Compounds 53, 59, 60, and 61:

Scheme XXI

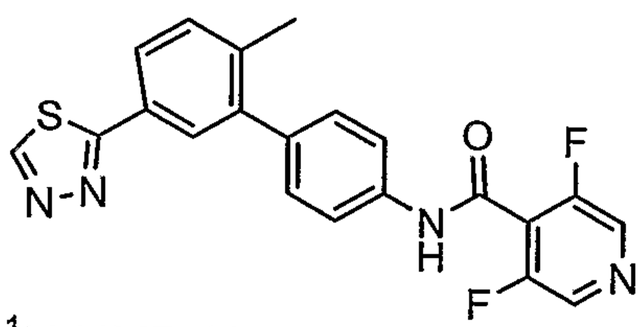


Ref: JACS 1955, 77, 1148

A solution of 2-bromo-4-cyano-toluene and hydrazine was treated with hydrogen sulfide to form 2-3-bromo-4-methyl-thiobenzoic acid hydrazide. 2-(3-Bromo-4-

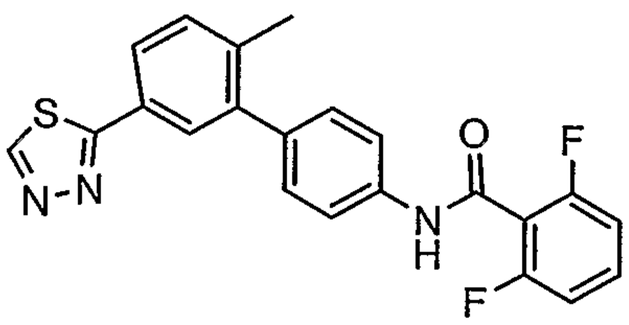
methyl-phenyl)-[1,3,4]thiadiazole was prepared from 2-3-bromo-4-methyl-thiobenzoic acid hydrazide according to a method analogous to that described in *J. of the American Chemical Society* (1955), *77*:1148, the entire teachings of which are incorporated herein by reference. Compounds 53, 59, 60, and 61 were prepared via an amide coupling reaction analogous to that described in step A of the synthesis of Compound 1, followed by a Suzuki coupling reaction (see step B of the synthesis of Compound 1) analogous to that as shown for Compound 69 in Scheme XX above.

Compound 53: 3,5-Difluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



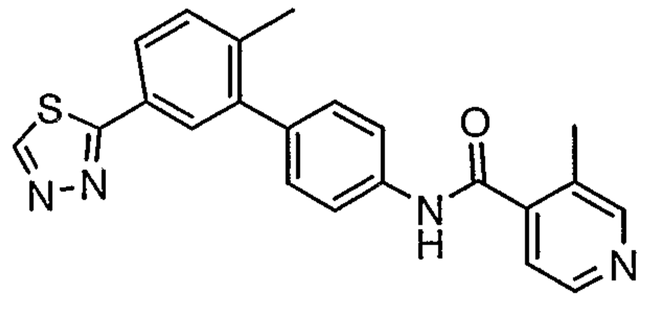
^{1}H-NMR ($CDCl_3$l) δ, 9.12(s, 1H), 8.53(s, 2H), 7.93-7.79(m, 3H), 7.65(d, *J* =7.5, 2H), 7.38(d, *J* =7.5, 2H), 2.37(s, 3H). ESMS clcd for $C_{21}H_{14}F_2N_4OS$: 408.09; Found: 409.1. $(M+H)^+$.

Compound 59: 2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide



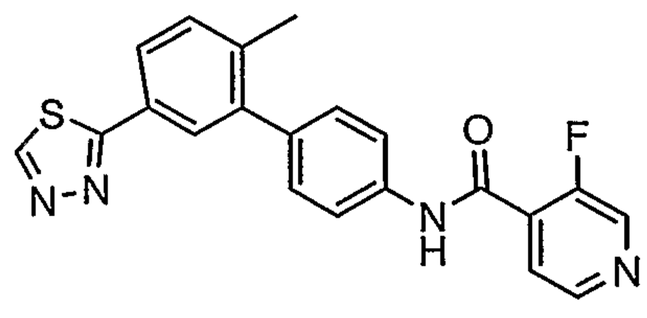
^{1}H-NMR (CD_3Cl) δ (ppm), 9.14 (s, 1H), 7.96-7.15 (m, 8H), 7.04(m, 2H), 2.37 (s, 3H). ESMS clcd for $C_{22}H_{15}ClF_2N_3OS$: 407.09; Found: 408.1. $(M+H)^+$.

Compound 60: 3-Methyl-N-[5'-([1,3,4]thiadiazol-2-yl)- 2'-methyl-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR (CD_3Cl) δ (ppm), 9.05(s, 1H), 8.49(m, 2H), 8.24(s, 1H), 7.94-7.32 (m, 8H), 2.48(s, 3H), 2.39 (s, 3H). ESMS clcd for $C_{22}H_{18}N_4OS$: 386.12; Found: 387.1. $(M+H)^+$.

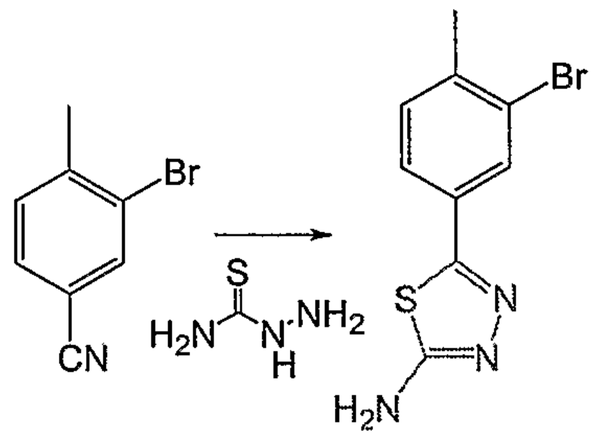
Compound 61: 3-Fluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



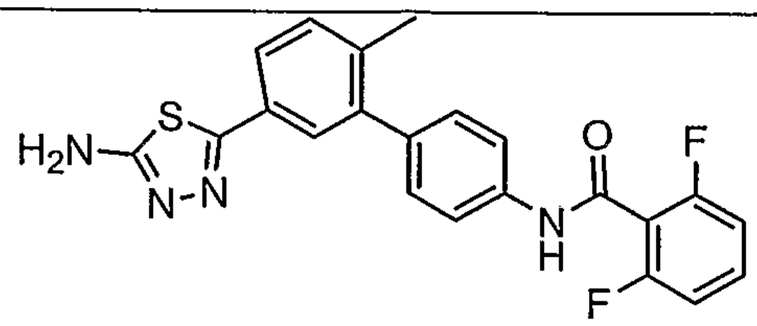
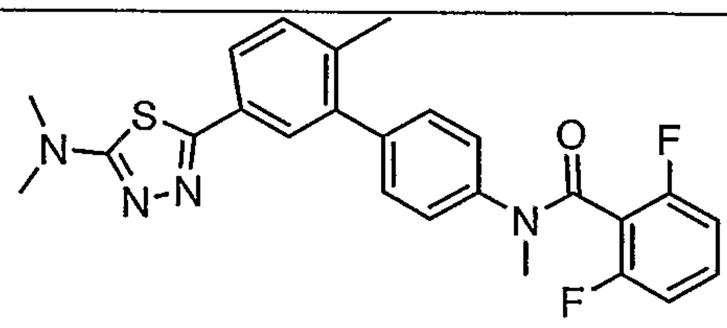
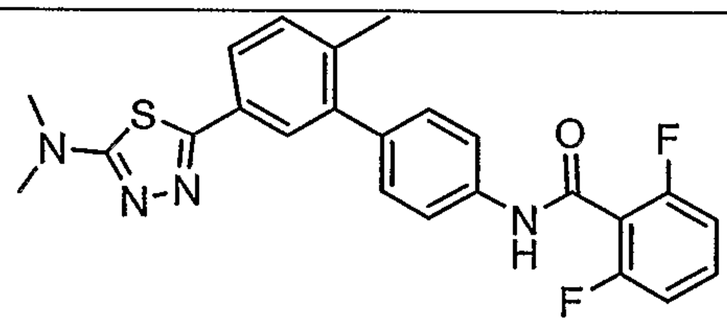
^{1}H-NMR ($CDCl_3$) δ (ppm), 9.81(s, 1H), 8.72-7.86(m, 6H), 7.74(d, J =7.5, 2H), 7.41(d, J =7.5, 2H), 2.37 (s, 3H). ESMS clcd for $C_{21}H_{15}FN_4OS$: 390.10; Found: 391.1 $(M+H)^+$.

General Method for the Synthesis of Compounds 62, 63, and 64:

Scheme XXII

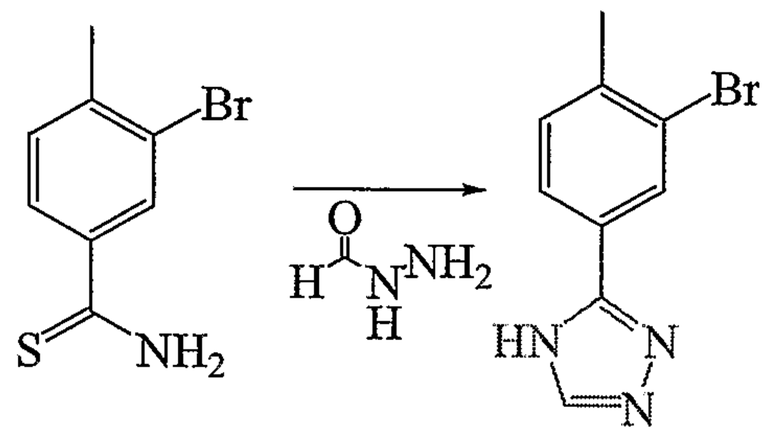


2-(3-Bromo-4-methyl-phenyl)-5-amino [1,3,4]thiadiazole was prepared according to a method analogous to that described in Suzuki, *et al.*, *Chem. Pharm. Bull.* (1992), *40*:357-363, the entire teachings of which are incorporated herein by reference. Compounds 62, 63, and 64 were prepared via an amide coupling reaction analogous to that described in step A of the synthesis of Compound 1, followed by a Suzuki coupling reaction (see step B of the synthesis of Compound 1) analogous to that as shown for Compound 69 in Scheme XX above.

#	Chemical Name	Structure	ESMS
62	2,6-Difluoro-N-[2'-methyl-5'-(5-amino-[1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide		422.10
63	2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl- 4-yl}-N-methyl-benzamide		464.15
64	2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]-biphenyl- 4-yl}-benzamide		450.13

General Method for the Synthesis of Compounds 66 and 67:

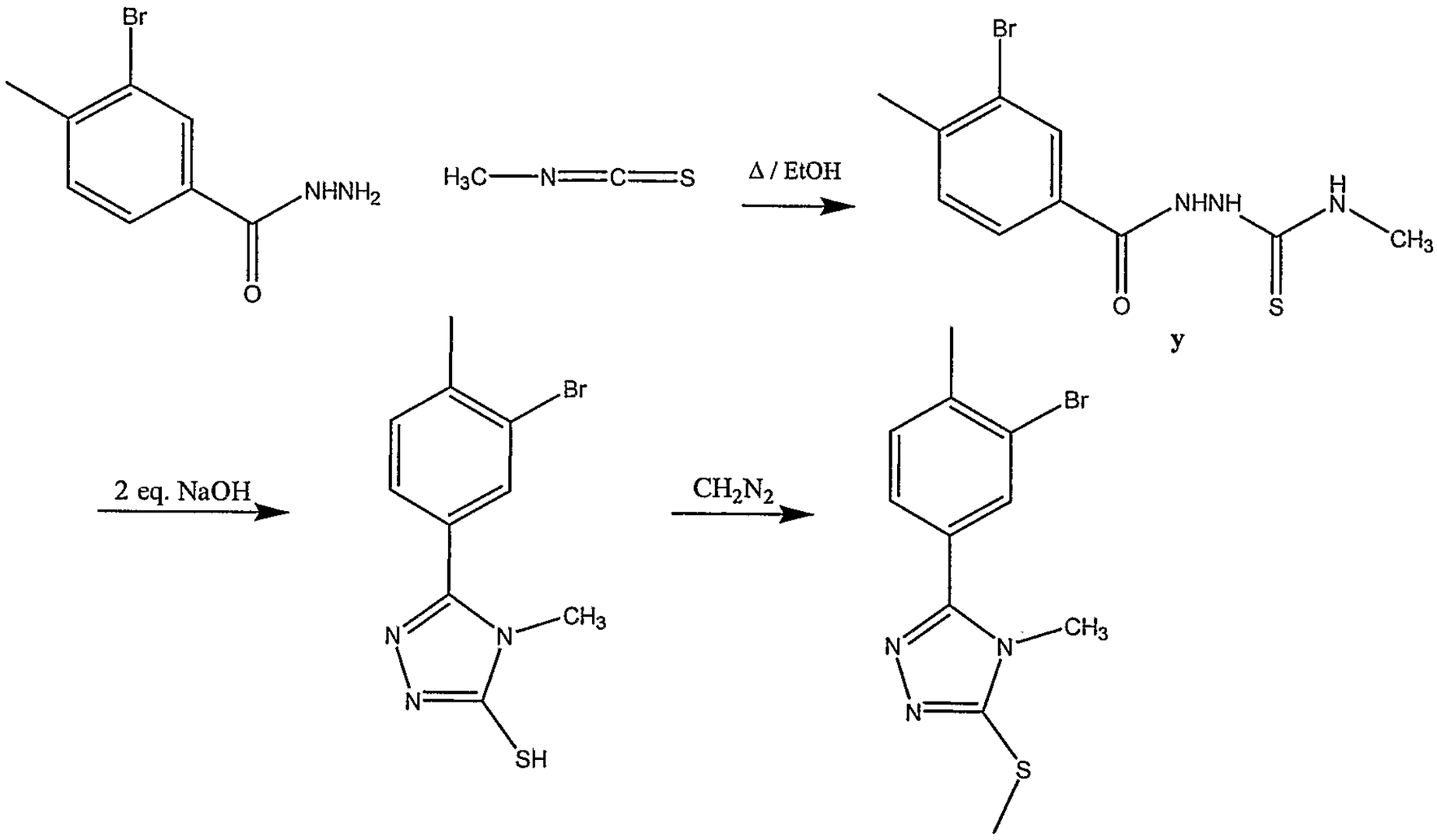
Scheme XXIII



3-(3-Bromo-4-methyl-phenyl)-[1,2,4]triazole was prepared according to a method analogous to that described in *Organic Letters* (2004), *6*(7):1111-1114; *J. of Chemistry* (2002), *67*(10):3266-3271; European Patent Application No. 636625, or *J. Heterocylic Chem.* (1988), *25*(4):1151-1154, the entire teachings of each of thes references are incorporated herein by reference. Compounds 66 and 67 were prepared via an amide coupling reaction analogous to that described in step A of the synthesis of Compound 1, followed by a Suzuki coupling reaction (see step B of the synthesis of Compound 1) analogous to that as shown for Compound 69 in Scheme XX above.

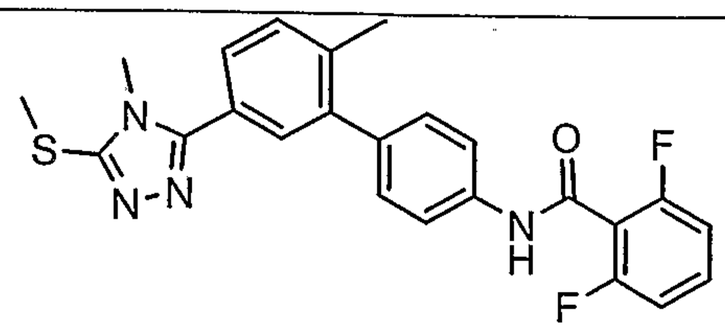
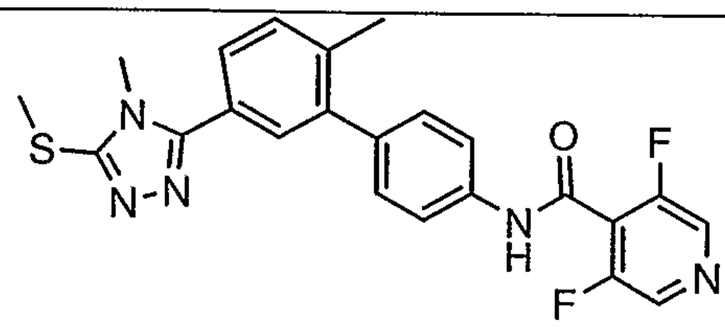
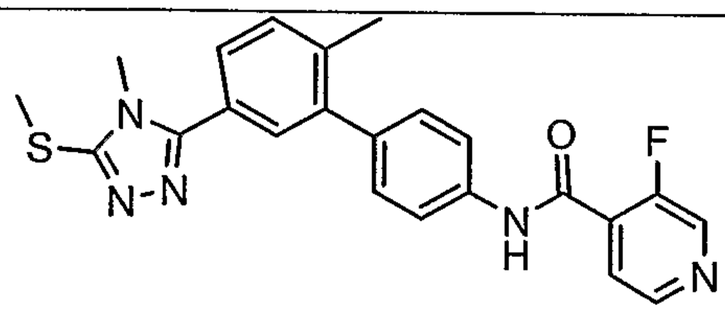
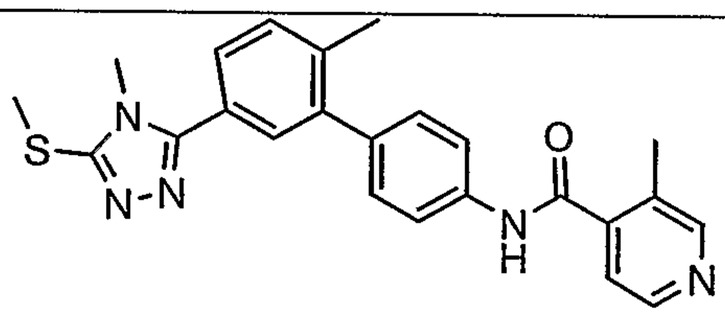
General Method for the Synthesis of Compounds 72, 73, 74, and 75:

Scheme XIV



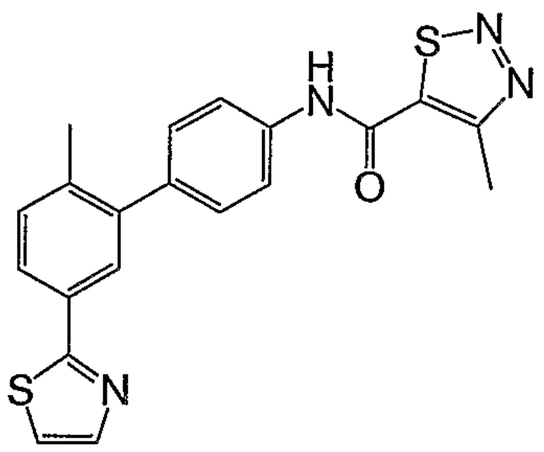
3-Bromo-4-methyl-benzoic acid hydrazide was prepared by treating 3-bromo-4-methyl-benzoic acid methyl ester with hydrazine and heat. 3-Bromo-4-methyl-benzoic acid hydrazide was then prepared by heating it wth isothiocyanate in ethanol to form intermediate **y**. Intermediate **y** was cyclized to form 5-(3-bromo-4-methyl-phenyl)-4-methyl-4H-[1,2,4]triazole-3-thiol by heating it in an aqueous solution containing 2 molar equivalents of NaOH. The mercapto group was then methylated by treating 5-(3-bromo-4-methyl-phenyl)-4-methyl-4H-[1,2,4]triazole-3-thiol with CH_2N_2 to form 5-(3-bromo-4-methyl-phenyl)-4-methyl-5-methylsulfanyl-4H-[1,2,4]triazole. Compounds 72, 73, 74, and 75 were prepared via an amide coupling reaction analogous to that described in step A of the synthesis of Compound 1, followed by a Suzuki coupling reaction (see step B of the synthesis of Compound 1) analogous to that as shown for Compound 69 in Scheme XX above.

#	Chemical Name	Structure	ESMS

72	2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide		450.13
75	3,5-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide		451.13
73	3-Fluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide		433.14
74	3-Methyl-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide		429.16

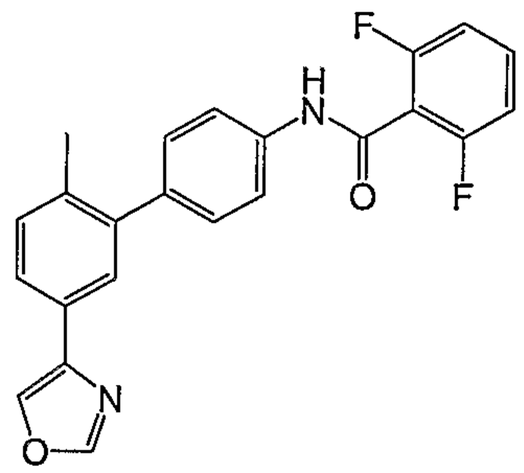
The following examples were prepared using procedures analogous to those described above:

Compound 76: 4-Methyl-[1,2,3]thiadazole-5- carboxylic acid [2'-methyl-5'-(thiazol-2-yl)-biphenyl-4-yl]- amide



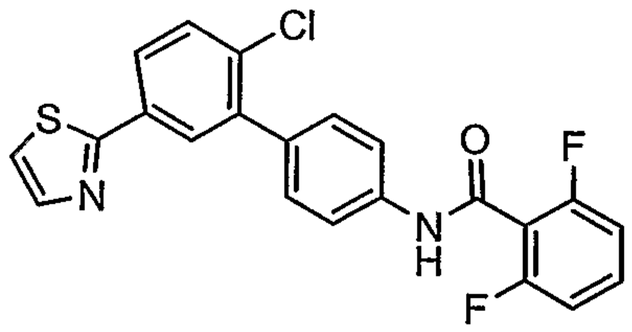
^{1}H-NMR (CD_3OD) δ (ppm), 7.88-7.72 (m, 5H), 7.59(d, J =4.8, 1H), 7.51-7.38(m, 3H), 2.84 (s, 3H), 2.31 (s, 3H). ESMS clcd for $C_{20}H_{16}N_4OS_2$: 392.08; Found: 393.1 $(M+H)^+$.

Compound 77: 2,6-Difluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-benzamide



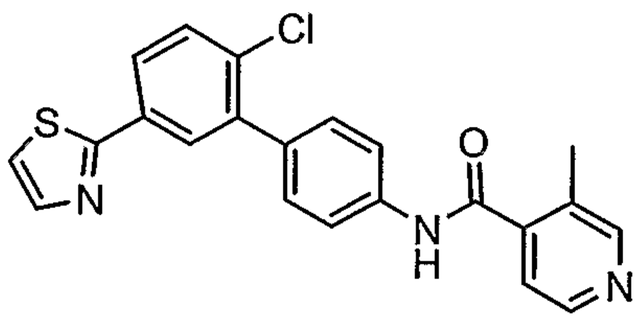
^{1}H-NMR (CD_3OD) δ (ppm), 7.88-7.72 (m, 5H), 7.59(d, *J* =4.8, 1H), 7.51-7.38(m, 3H), 2.84 (s, 3H), 2.31 (s, 3H). ESMS clcd for $C_{23}H_{16}F_2N_2O_2$: 390.12; Found: 391.1 $(M+H)^+$.

Compound 56: 2,6-Difluoro-N-[2'-chloro-5'-(thiazol-2-yl)-biphenyl-4-yl]-benzamide



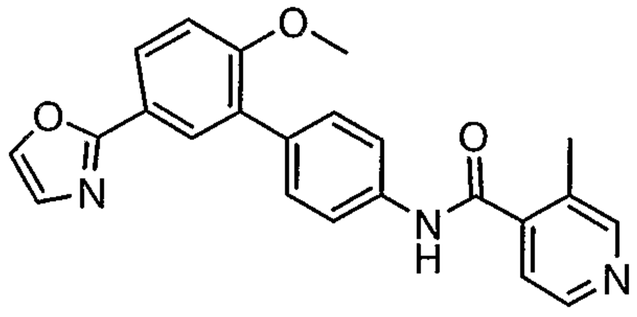
^{1}H-NMR (CD_3Cl) δ (ppm), 7.99-7.32(m, 10H), 7.11(m, 2H). ESMS clcd for $C_{22}H_{13}ClF_2N_2OS$: 426.04; Found: 427.1. $(M+H)^+$.

Compound 55: 3-Methyl-N-[5'-(thiazol-2-yl)-2'- chloro-biphenyl-4-yl]-isonicotinamide



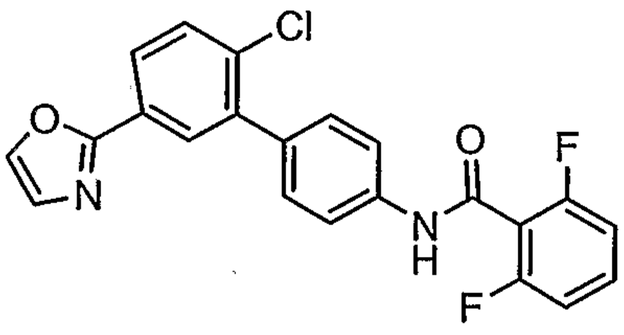
^{1}H-NMR (CD_3Cl) δ (ppm), 8.51(s, 1H), 8.48(d, , *J* =4.2, 1H), 8.41(s, 1H), 7.95-7.36(m, 10H), 2.51 (s, 3H). ESMS clcd for $C_{22}H_{16}ClN_3OS$: 405.07; Found: 406.1. $(M+H)^+$.

Compound 50: 3-Methyl-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide



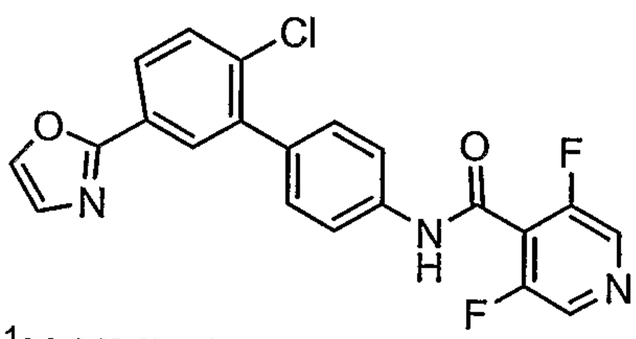
^{1}H-NMR (CD_3Cl) δ (ppm), 8.56(s, 1H),8.02(s, 1H), 7.75- 7.03(m, 10H), 3.86 (s, 3H), 2.53 (s, 3H). ESMS clcd for $C_{23}H_{19}N_3O_3$: 385.14; Found: 386.2. $(M+H)^+$.

Compound 31: 2,6-Difluoro-N-[2'-chloro-5'-(oxazol-2-yl)-biphenyl-4-yl]-benzamide



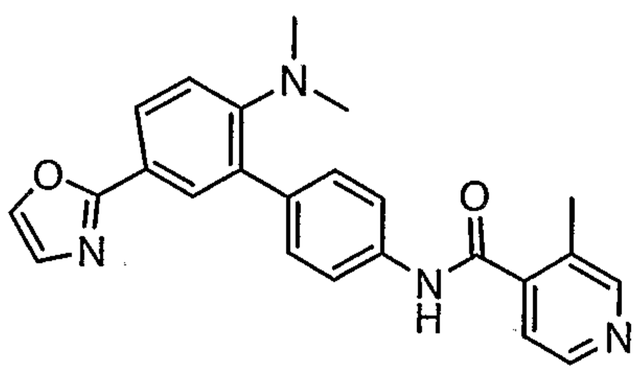
^{1}H-NMR (CD_3Cl) δ (ppm), 7.98-7.32 (m, 10H), 7.03(m, 2H). ESMS clcd for $C_{22}H_{13}ClF_2N_2O_2$: 410.06; Found: 411.1. $(M+H)^+$.

Compound 45: 3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide



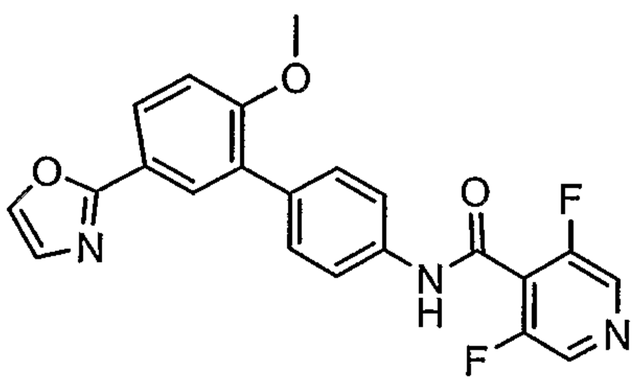
^{1}H-NMR ($CDCl_3$) δ, 8.53(s, 2H), 8.11-7.28(m, 9H). ESMS clcd for $C_{21}H_{12}ClF_2N_3O_2$: 411.06; Found: 412.1. $(M+H)^+$.

Compound 48: 3-Methyl-N-[5'-(oxazol-2-yl)-2'-(N,N-dimethylamino)-biphenyl-4-yl]-isonicotinamide



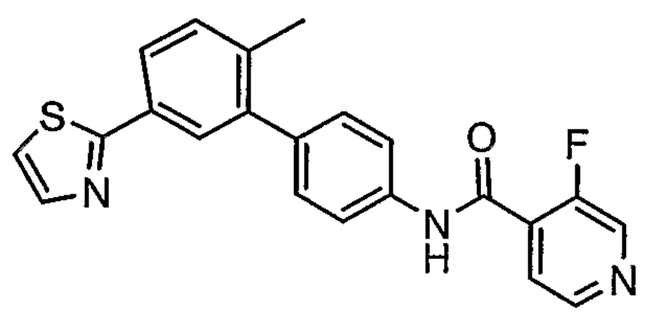
^{1}H-NMR ($CDCl_3$) δ, 7.75-7.40(m, 12H), 8.53(s, 2H), 7.93-7.79(m, 3H), 2.43(s, 3H), 1.36(s, 6H). ESMS clcd for $C_{24}H_{22}N_4O_2$: 398.17; Found: 399.1. $(M+H)^+$.

Compound 51: 3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide



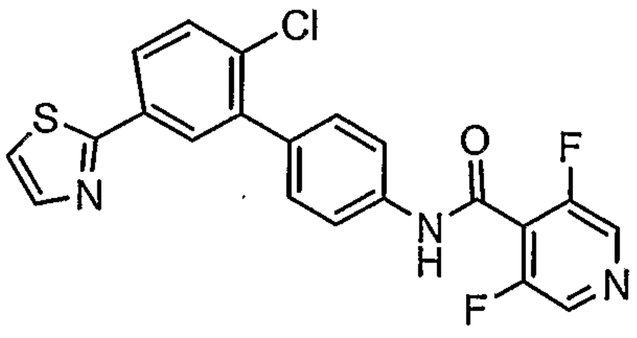
^{1}H-NMR ($CDCl_3$) δ (ppm), 8.40 (s, 2H), 7.81-7.30(m, 9H), 3.84 (s, 3H). ESMS clcd for $C_{21}H_{14}F_2N_4OS$: 407.11; Found: 408.1. $(M+H)^+$.

Compound 54: 3-Fluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



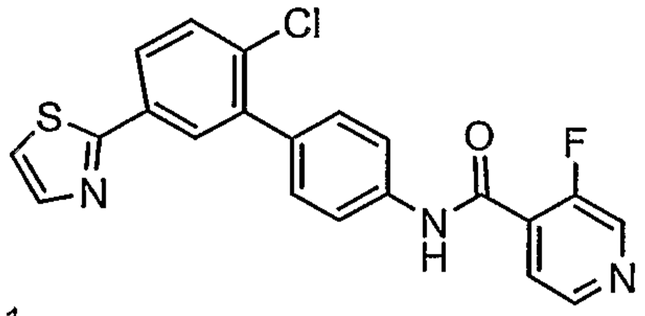
^{1}H-NMR ($CDCl_3$) δ, 9.12(s, 1H), 8.53(s, 2H), 7.93-7.79(m, 3H), 7.65(d, J =7.5, 2H), 7.38(d, J =7.5, 2H), 2.37(s, 3H). ESMS clcd for $C_{22}H_{16}FN_3OS$: 389.10; Found: 390.1. $(M+H)^+$.

Compound 57: 3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide



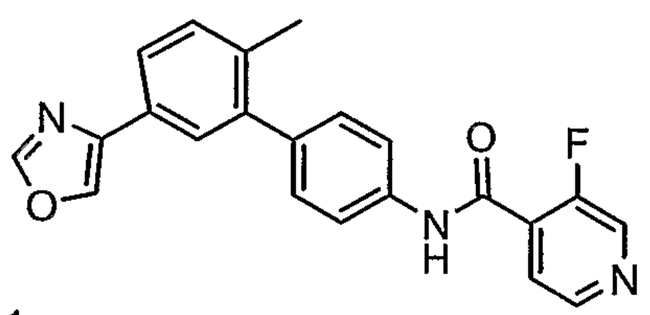
^{1}H-NMR ($CDCl_3$) δ , 8.45(s, 2H), 7.95-7.41(m, 9H). ESMS clcd for $C_{21}H_{12}ClF_2N_3O_2$: 427.04; Found: 428.1. $(M+H)^+$.

Compound 58: 3-Fluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide



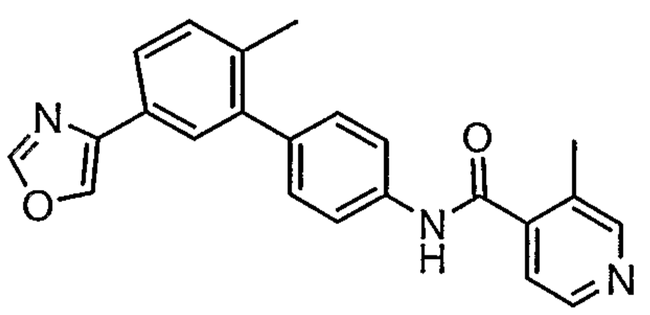
^{1}H-NMR (CD_3OD) δ , 8.62(s, 1H), 8.53(d, *J* =4.1, 1H), 7.99-7.42 (m, 10H). ESMS clcd for $C_{21}H_{13}ClFN_3$ OS: 408.09; Found: 409.1. $(M+H)^+$.

Compound 78: 3-Fluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide



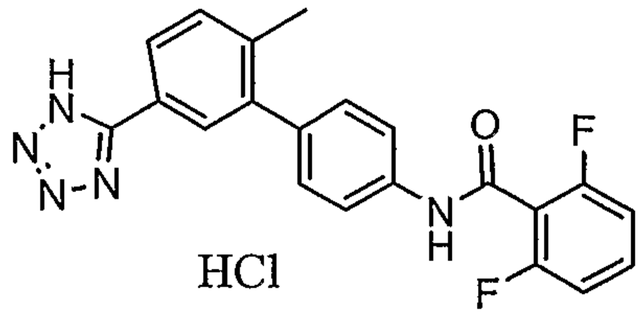
^{1}H-NMR ($CDCl_3$) δ, 8.73-7.27(m, 12H), 2.38(s, 3H). ESMS clcd for $C_{22}H_{16}FN_3O_2$: 373.12; Found: 374.1. $(M+H)^+$.

Compound 79: 3-Methyl-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR ($CDCl_3$) δ, 8.63(s, 1H), 7.92(s, 1H), 7.85-7.28(m,10H), 2.53(s, 3H), 2.36(s, 3H). ESMS clcd for $C_{23}H_{19}N_3O_2$: 369.15; Found: 370.1. $(M+H)^+$.

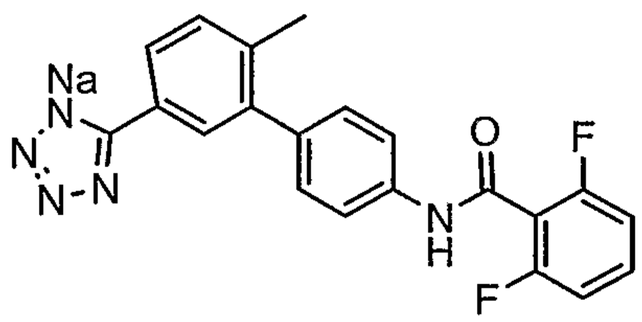
Compound 81: 2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide, hydrochloride salt



HCl

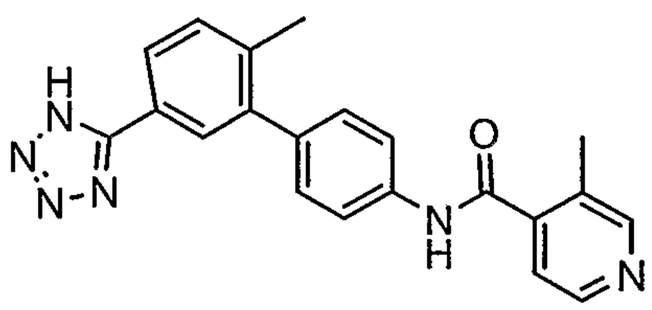
^{1}H-NMR ($CDCl_3$) δ, 7.95-7.24(m,8H), 7.11-7.01(m,2H), 2.38(s, 3H). ESMS clcd for $C_{21}H_{16}ClF_2N_5O$: 427.10; Found: 392.1. $(M-HCl+H)^+$.

Compound 65: 2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide, sodium salt



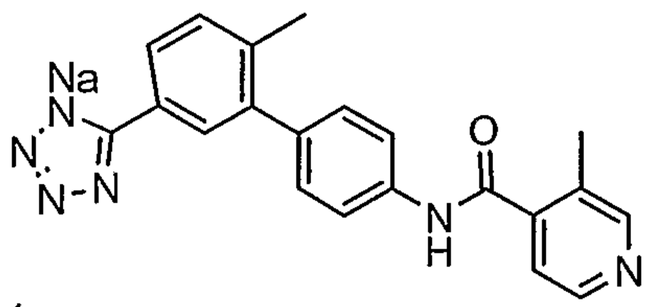
^{1}H-NMR ($CDCl_3$) δ, 7.95-7.24(m,8H), 7.11-7.01(m,2H), 2.38(s, 3H). ESMS clcd for $C_{21}H_{14}F_2N_5NaO$: 413.11; Found: 392.1. $(M-Na+H)^+$.

Compound 44: 3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide



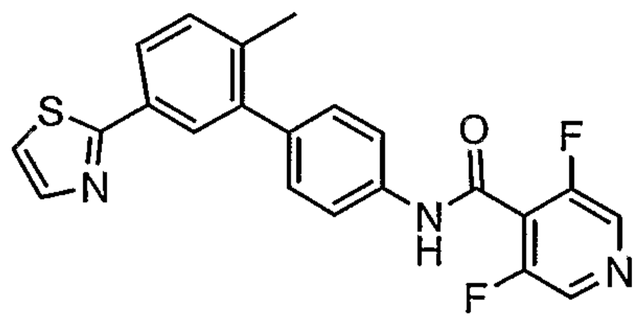
^{1}H-NMR ($CDCl_3$) δ, 8.58-7.31(m,10H), 2.52(s, 3H), 2.37(s, 3H). ESMS clcd for $C_{21}H_{18}N_6O$: 370.15; Found: 371.1. $(M+H)^+$.

Compound 80: 3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide, sodium salt



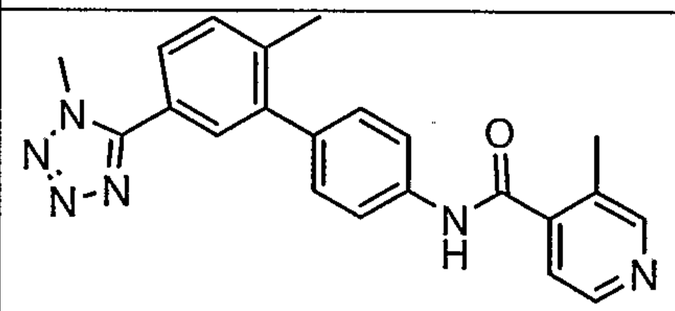
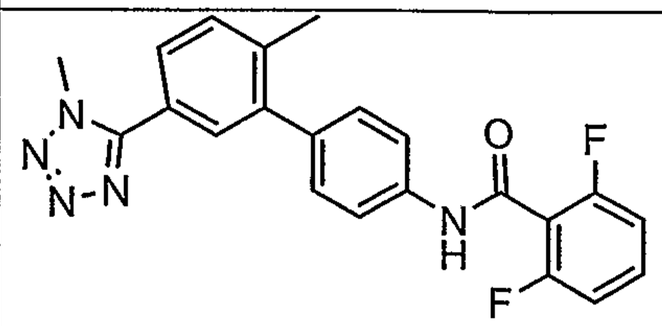
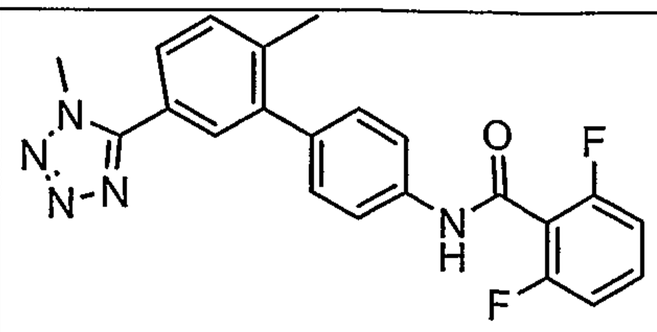
^{1}H-NMR (CD_3OD) δ, 9.06-7.31(m,10H), 2.63(s, 3H), 2.32(s, 3H). ESMS clcd for $C_{21}H_{17}N_6NaO$: 392.14; Found: 371.1. $(M-Na+H)^+$.

Compound 28: 3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide



^{1}H-NMR ($CDCl_3$) δ, 8.45(s, 2H), 7.93-7.31(m, 9H), 2.43(s, 3H). ESMS clcd for $C_{22}H_{15}F_2N_3OS$: 407.09; Found: 408.1. $(M+H)^+$.

Other examples are listed in the following table:

#	Chemical Name	Structure	ESMS
49	3-Methyl-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide		384.17
82	2,6-Difluoro-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide		405.14
83	2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide		405.14

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 CO_2. 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_{50} value was calculated as the concentration at which 50% of maximum IL-2 production after stimulation was inhibited versus a non-stimulation control.

Compound #	IC_{50}
1	2-4 nM
2	9 nM
3	1.6 nM
4	2 nM
5	1 nM
6	9 nM
7	8 nM
8	13 nM
9	7 nM
10	3 nM
11	3 nM
12	5 nM
13	6 nM
14	10 nM
15	2 nM
16	14
17	7 nM

18	9 nM
19	19 nM
20	8 nM
21	6 nM
22	1 nM
23	5 nM
24	15 nM
25	3 nM
26	5 nM
27	4 nM
28	7 nM
29	9 nM
30	3 nM
31	6 nM
32	4 nM
33	4 nM
34	11 nM
35	2 nM
36	4 nM
37	11 nM
38	3 nM
39	13 nM
40	11 nM
41	18 nM
42	>1000 nM
43	26 nM
44	>1000 nM
45	50 nM
47	59 nM
48	320 nM
49	12 nM

50	23 nM
51	11 nM
52	35 nM
53	6 nM
54	12 nM
55	6 nM
56	2 nM
57	3 nM
58	2 nM
59	3 nM
60	13 nM
61	6 nM
62	19 nM
63	>1000 nM
64	53 nM
65	>1000 nM
66	8 nM
67	27 nM
68	3 nM
69	5 nM
70	13 nM
71	6 nM
72	>1000 nM
73	>1000 nM
74	>1000 nM
75	>1000 nM
76	7 nM
77	10 nM
78	9 nM
79	10
80	>1000

81	138
82	8
83	317

Inhibition of other cytokines, such as IL-4, IL-5, IL-13, GM-CSF, TNF-α, and INF-γ, 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_{CRAC} CURRENT IN RBL CELLS, JURKAT CELLS, AND PRIMARY T CELLS

In general, a whole cell patch clamp method was used to examine the effects of a compound of the invention on a channel that mediates I_{crac}. In such experiments, a baseline measurement was established for a patched cell. Then a compound to be tested was perfused (or puffed) to cells in the external solution and the effect of the compound on I_{crac} was measured. A compound that modulates I_{crac} (e.g., inhibits) is a compound that is useful in the invention for modulating CRAC ion channel activity.

1) <u>RBL cells</u>

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; IP3 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_2PO_4 0.4mM; $Na_2HPO_4 \cdot H_2O$ 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

I_{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 I_{CRAC} currents were stabilized, the cells were perfused with a test compound in the extracellular solution. At the end of an experiment, the remaining I_{CRAC} currents were then challenged with a control compound (SKF96365, 10 μM) to ensure that the current could still be inhibited.

Data analysis

The I_{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 I_{CRAC} current inhibition for each concentration was calculated using peak amplitude in the beginning of the experiment from the same cell. The IC_{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 I_{CRAC} current in RBL cells. As can be seen from the data in the table, representative compounds of the invention inhibit I_{CRAC} current at concentration of 30 nM or less.

Compound Number	IC_{50}
1	20 nM
3	30 nM
4	90 nM
5	80 nM
7	70 nM
8	330 nM
9	150 nM
10	40 nM
11	60 nM
12	20 nM
14	80 nM
15	70 nM
16	80 nM
17	40 nM
26	160 nM
32	60 nM
36	130 nM
58	40 nM
70	390 mM

SKF96365	4 μM

2) Jurkat cells

Cells

Jurkat T cells were 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 contained 10 mM CaNaR, 11.5 mM glucose and a test compound at various concentrations.

Intracellular Pipette Solution

The standard intracellular pipette solution contained: 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 was 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 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). Sylgard®-coated 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 ms duration spanning the voltage range of –100 to +100 mV were 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 were corrected for a liquid junction potential of 10 mV between external and internal solutions. Currents were filtered at 2.3 kHz and digitized at 100 µs intervals. Capacitive currents and series resistance were 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) were digitally filtered at 2 kHz, pooled and used for leak-subtraction of all subsequent current records. The low-resolution temporal development of inward currents was extracted from the leak-corrected individual ramp current records by measuring the current amplitude at -80 mV or a voltage of choice.

Compound 1 was determined to be a strong inhibitor of I_{CRAC} in human Jurkat T cells.

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 PBM cells. In addition,

compounds of the invention are not expected to inhibit the anti-inflammatory cytokine, IL-10.

EXAMPLE 5: COMPOUNDS OF THE INVENTION ARE POTENT INHIBITORS OF DEGRANULATION IN RBL CELLS

Procedure:

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

On the following day, the cells were washed once with PRS (2.6 mM glucose and 0.1% BSA) and 160μL of PRS was added to each well. A test compound was 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) was added. Maximum degranulation occurred between 15 to 40 minutes after addition of anti-IgE.

Results:

The table below shows the concentration of compounds of the invention which inhibits 50 % of degranulation in RBL cells. As can be seen from the data in the table below, representative compounds of the invention inhibit degranulation at concentration of 4.5 μM or less. SKF96365 was used as a positive control.

	IC_{50}
Compound 1	2.52 μM
Compound 2	4.85 μM
Compound 3	4.5 μM
Compound 4	1.45 μM
Compound 5	1.1 μM

Compound 6	5.01 μM
Compound 8	0.52 μM
Compound 9	1.41 μM
Compound 12	0.48 μM
SKF96365	>20 μM

EXAMPLE 6: COMPOUNDS OF THE INVENTION ARE POTENT INHIBITORS OF CHEMOTAXIS IN T CELLS

T-cell isolation:

Twenty ml aliquots of heparinized whole blood (2 pig, 1 human) were subjected to density gradient centrifugation on Ficoll Hypaque. The buffy coat layers representing peripheral blood mononuclear cells (PBMCs) containing lymphocytes and monocytes were 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, were resuspended in complete RPMI media and placed in loosely packed activated nylon wool columns that had been equilibrated with warm media. After 1 hr at 37°C, the non-adherent T cell populations were eluted by washing of the columns with additional media. The T cell preparations were centrifuged, resuspended in 5 ml of incomplete RPMI, and counted using a hemocytometer.

Cell migration assay:

Aliquots of each T cell preparation were labeled with Calcien 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 $CaCl_2$ and 0.8 mM $MgCl_2$, pH 7.4 (HHBSS). An equal volume of HHBSS containing 0, 20 nM, 200 nM or 2000 nM of compound 1 or 20 nM EDTA was then added and the cells incubated for 30 min at 37°C. Fifty μl aliquots of the cell suspensions (60,000 cells) were placed on the membrane (pore size 5 μm) of a Neuroprobe ChemoTx 96 well chemotaxis unit that had been affixed

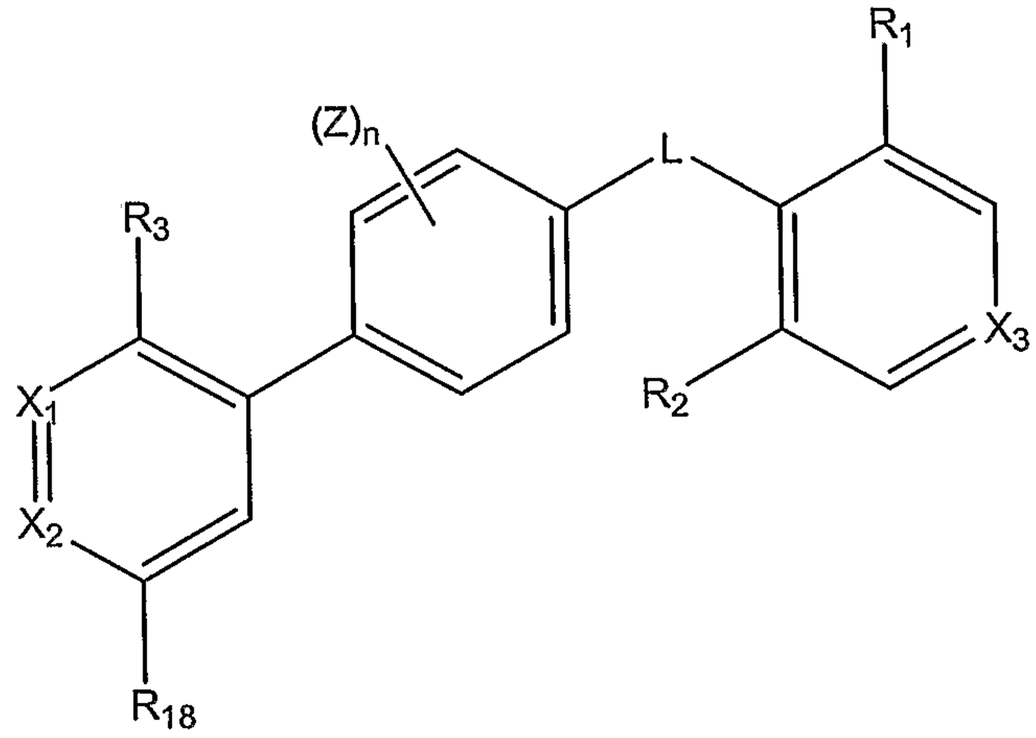
over wells containing 10 ng/ml MIP-1α in HHBSS. The T cells were allowed to migrate for 2 hr at 37°C, after which the apical surface of the membrane was wiped clean of cells. The chemotaxis units were then placed in a CytoFlour 4000 (PerSeptive BioSystems) and the fluorescence of each well measured (excitation and emission wavelengths of 450 and 530 nm, respectively). The number of migrating cells in each well was 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.

Results: Compound 1 is inhibitory to the chemotactic response of porcine T cells to 10 ng/ml MIP-1α (IC_{50} values of ~5 nM) and in human T cells to 100 ng/ml MIP-1α (see Figure 1). The data represent the averages of triplicates. EDTA was used as a control compound in this assay (data not shown).

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.

WE CLAIM:

1. A compound represented by formula (I):



(I)

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

L is a linker selected from the group consisting of a covalent bond, –NRCH$_2$-, -CH$_2$NR-, –C(O)-, –NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, –NR-C(S)-, -C(S)-NR-;

X_1 and X_3 are each, independently, CH or N;

X_2 is CH, CR_{10} or N;

each Z is independently selected from the group consisting of a lower alkyl, a lower haloalkyl, a halo, a lower alkoxy, a lower alkyl sufanyl, cyano, nitro, or lower haloalkoxy;

R, for each occurrence is independently selected from -H, an alkyl, -C(O)R_5, or -C(O)OR_5;

R_1 and R_2 are each, independently, a halo, a haloalkyl, a lower alkyl, a lower alkoxy, or a haloalkoxy;

R_3 is an alkyl, a haloalkyl, a halo, a haloalkoxy, -OR_5, -SR_5, or -NR_6R_7;

R_{18} is a halo, cyano, nitro, -C(O)R_5, -C(O)OR_5, -C(O)SR_5, -C(O)NR_6R_7, -C(S)R_5, -C(S)OR_5, -C(S)SR_5, -C(S)NR_6R_7, -C(NR_8)R_5, -C(NR_8)OR_5, -C(NR_8)SR_5, -C(NR_8)NR_6R_7, -S(O)$_p$$R_5$, -S(O)$_pNR_5$, -S(O)$_pOR_5$, -P(O)(O$R_5$)$_2$, -OP(O)(O$R_5$)$_2$, -P(O)($R_5$)$_2$, a five or six membered optionally

substituted heterocycloalkyl, a five or six membered optionally substituted heterocyclyl, or a five or six membered optionally substituted heteroaryl;

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;

R_6 and R_7, 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_6 and R_7 taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_8, for each occurrence, is independently –H, a halo, an alkyl, $-OR_5$, $-NR_6R_7$, $-C(O)R_5$, $-C(O)OR_5$, or $-C(O)NR_6R_7$;

R_{10} is a lower alkyl, a lower alkoxy, a halo, a lower haloalkyl, a lower haloalkoxy, a cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, or $-P(O)(R_5)_2$;n is zero or an integer from 1 to 4; and

p, for each occurrence, is independently 1 or 2.

2. The compound of Claim 1, wherein L is –NR-C(O)-.

3. The compound of Claim 2, wherein R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally

substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl.

4. The compound of Claim 3, wherein R_{18} is unsubstituted or substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

5. The compound of Claim 1, wherein the compound is selected from the group consisting of:

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-3-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(pyridine-4-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-isoxazole-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(3-methyl-1*H*-pyrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1*H*-pyrrol-2-yl)-biphenyl-4-yl]- benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(5-oxo-4,5-dihydro-[1,2,4]- oxadiazol-3-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(morpholino-4-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(5-amino-[1,3,4]thiadiazol-2-yl)-biphenyl-4-yl]- benzamide;

2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]- biphenyl- 4-yl}-N-methyl-benzamide;

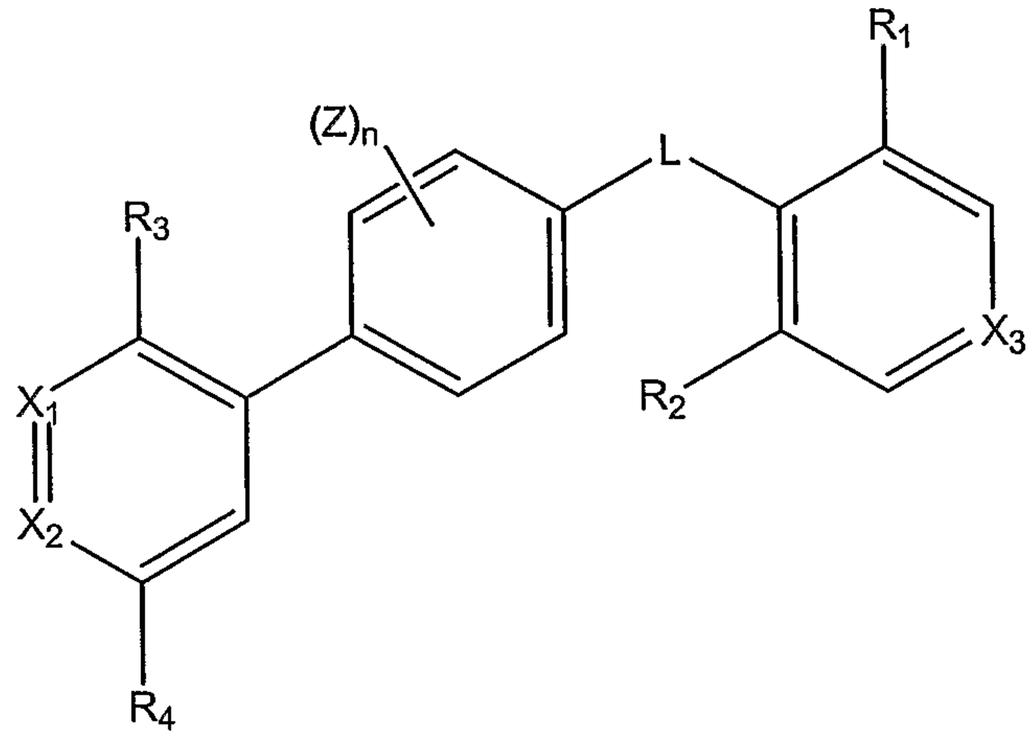
2,6-Difluoro-N-{2'-methyl-5'-[5-(N,N-dimethylamino)-[1,3,4]thiadiazol-2-yl]- biphenyl- 4-yl}-benzamide;

and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

6. The compound of Claim 2, wherein R_{18} is an ester, amide or carboxylic acid bioisostere.

7. The compound of Claim 5, wherein R_{18} is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

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



(II)

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

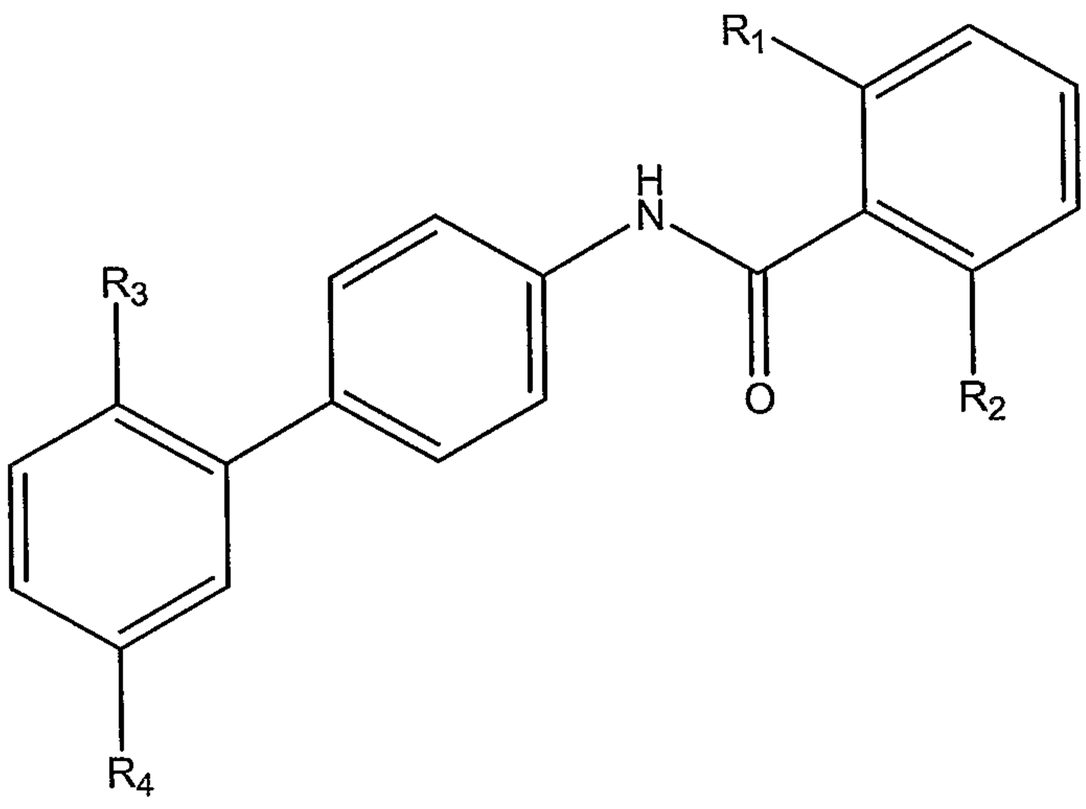
R_4 is a halo, cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, $-P(O)(R_5)_2$, or an ester, amide or carboxylic acid bioisostere.

9. The compound of Claim 8, wherein n is 0.

10. The compound of Claim 8, wherein Z, for each occurrence, is independently, a lower alkyl, a lower alkoxy, a lower haloalkoxy, a halo, cyano, or haloalkyl and n is 1 or 2.

11. The compound of Claim 8, wherein L is –NHC(O)-.

12. The compound of Claim 11, wherein the compound is represented by formula (III):



(III)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

13. The compound of Claim 12, wherein R_1 and R_2 are each, independently, a halo.

14. The compound of Claim 13, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

15. The compound of Claim 14, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

16. The compound of Claim 15, wherein R_4 is a 5-membered heteroaryl.

17. The compound of Claim 16, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

18. The compound of Claim 14, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

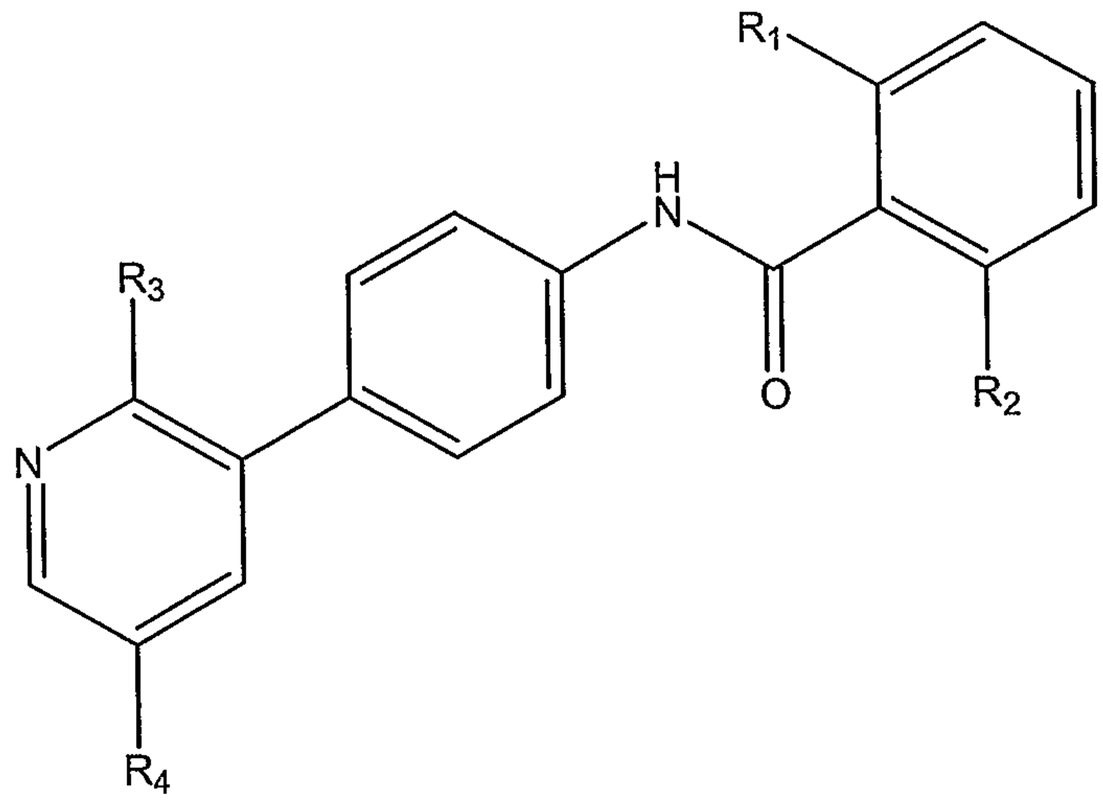
R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

19. The compound of Claim 14, wherein R_1 and R_2 are each a fluoro group.

20. The compound of Claim 11, wherein the compound is represented by structural formula (IV):



(IV)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

21. The compound of Claim 20, wherein R_1 and R_2 are each, independently, a halo.

22. The compound of Claim 21, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

23. The compound of Claim 22, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

24. The compound of Claim 23, wherein R_4 is a 5-membered heteroaryl.

25. The compound of Claim 24, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

26. The compound of Claim 22, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

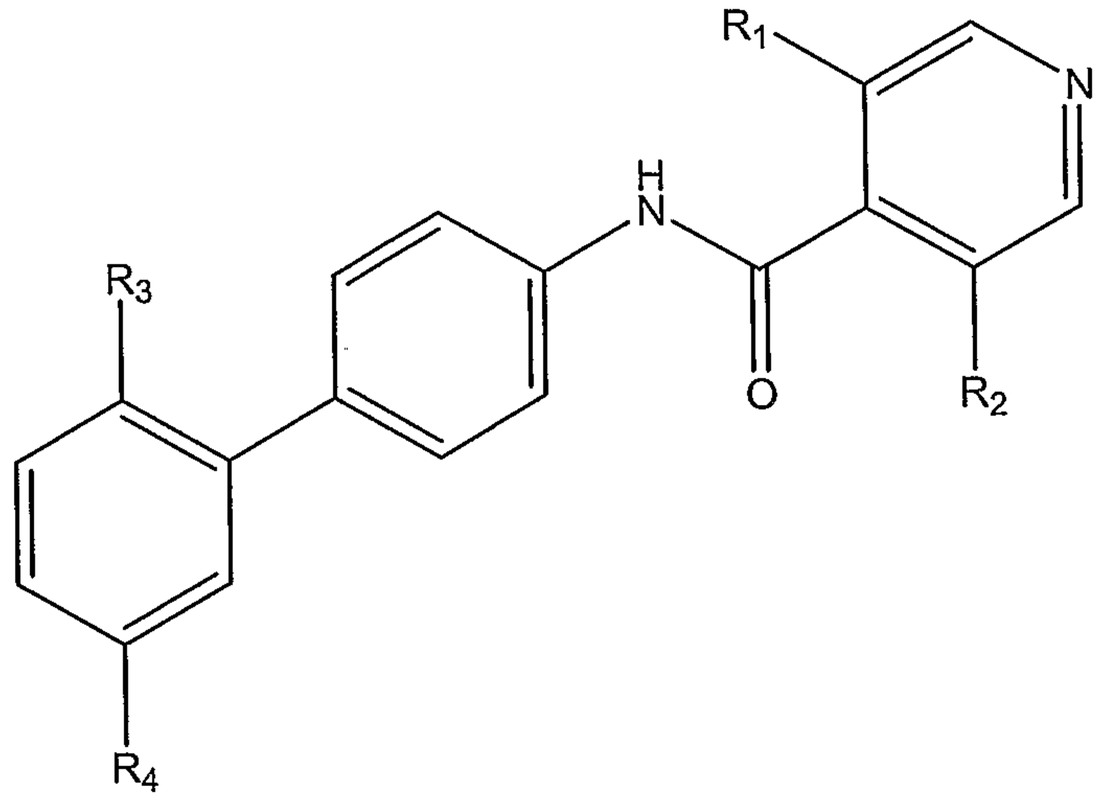
R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

27. The compound of Claim 22, wherein R_1 and R_2 are each a fluoro group.

28. The compound of Claim 11, wherein the compound is represented by structural formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

29. The compound of Claim 28, wherein R_1 and R_2 are each, independently, a halo.

30. The compound of Claim 29, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

31. The compound of Claim 30, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

32. The compound of Claim 31, wherein R_4 is a 5-membered heteroaryl.

33. The compound of Claim 32, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

34. The compound of Claim 30, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

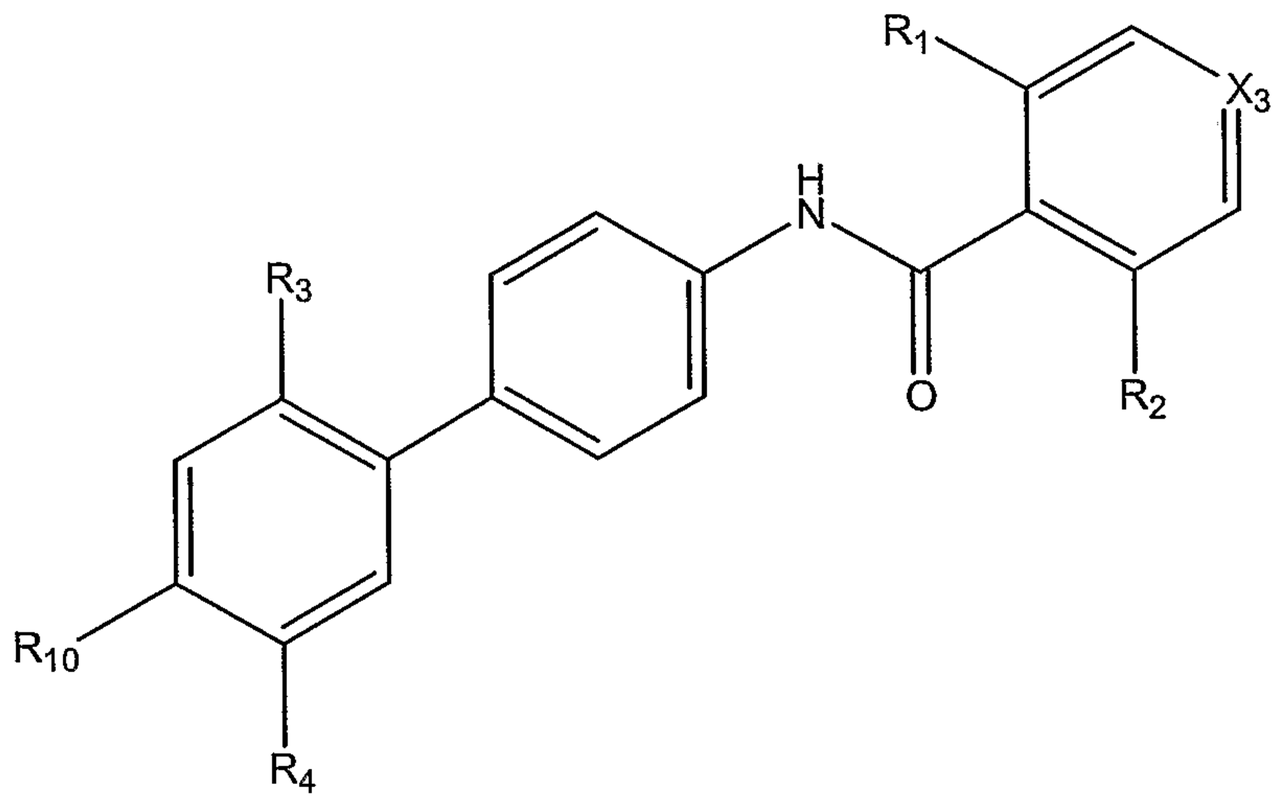
R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

35. The compound of Claim 30, wherein R_1 and R_2 are each a fluoro group.

36. The compound of Claim 11, wherein the compound is represented by structural formula (VI):



(VI)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

37. The compound of Claim 36, wherein R_1 and R_2 are each, independently, a halo.

38. The compound of Claim 37, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

39. The compound of Claim 38, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

40. The compound of Claim 39, wherein R_4 is a 5-membered heteroaryl.

41. The compound of Claim 40, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

42. The compound of Claim 38, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

43. The compound of Claim 38, wherein R_1 and R_2 are each a fluoro group.

44. The compound of Claim 8, wherein the compound is selected from the group consisting of:

4'-(2,6-Difluoro-benzoylamino)-6-methyl-biphenyl-3-carboxylic acid methyl ester;

6-Chloro-4'-(2,6-difluoro-benzoylamino)-biphenyl-3-(carboxylic acid 2-methoxyethyl ester);

2,6-Difluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-bezamide;

4'-[(3,5-Difluoro-pyridine-4-cabonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester;

N-[4-(5-Chloro-2-methoxy-pyridin-3-yl)-phenyl]-2,6-difluoro-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-(2'-methyl-5'- oxazol-2-yl-biphenyl-4-yl)- isonicotinamide;

2,6-Difluoro-N-(2'-methoxy-5'- oxazol-2-yl-biphenyl-4-yl)- benzamide;

2,6-Difluoro-N-[2'-methyl-5'- (oxazol-5-yl)-biphenyl-4-yl]- benzamide;

3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-chloro-5'-(oxazol-2-yl)-biphenyl-4-yl]- benzamide;

Date of Mailing: January 9)

2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(4-trifluoromethyl-thiazol-2-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3,5-Difluoro-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-chloro-5'- (thiazol-2-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

2,6-Difluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-benzamide;

3,5-Difluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide

2,6-Difluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-benzamide;

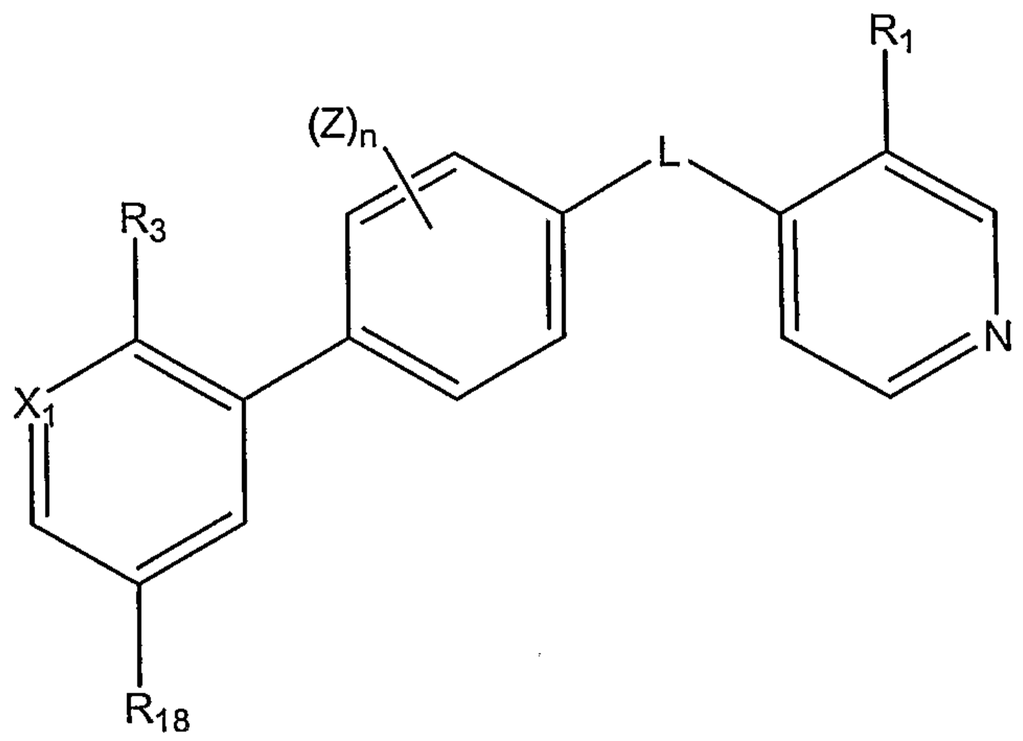
2,6-Difluoro-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

2,6-Difluoro-N-[2'-methyl-5'-(2-methyl-2*H*-tetrazol-5-yl)-biphenyl-4-yl]-benzamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

45. A compound represented by formula (VII):



(VII)

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

L is a linker selected from the group consisting of a covalent bond, –NRCH$_2$-, -CH$_2$NR-, –C(O)-, –NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, –NR-C(S)-, -C(S)-NR-;

X_1 is CH or N;

each Z is independently selected from the group consisting of a lower alkyl, a lower haloalkyl, a halo, a lower alkoxy, a lower alkyl sufanyl, cyano, nitro, or lower haloalkoxy;

R, for each occurrence is independently selected from -H, an alkyl, -C(O)R_5, or -C(O)OR_5;

R_1 is a halo, a haloalkyl, a lower alkyl, a lower alkoxy, or a haloalkoxy;

R_3 is an alkyl, a haloalkyl, a halo, a haloalkoxy, -OR_5, -SR_5, or -NR_6R_7;

R_{18} is a halo, cyano, nitro, -C(O)R_5, -C(O)OR_5, -C(O)SR_5, -C(O)NR_6R_7, -C(S)R_5, -C(S)OR_5, -C(S)SR_5, -C(S)NR_6R_7, -C(NR_8)R_5, -C(NR_8)OR_5, -C(NR_8)SR_5, -C(NR_8)NR_6R_7, -S(O)$_p$$R_5$, -S(O)$_pNR_5$, -S(O)$_pOR_5$, -P(O)(O$R_5$)$_2$, -OP(O)(O$R_5$)$_2$, -P(O)($R_5$)$_2$, a five or six membered optionally substituted heterocycloalkyl, a five or six membered optionally substituted heterocyclyl, or a five or six membered optionally substituted heteroaryl;

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;

R_6 and R_7, 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_6 and R_7 taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_8, for each occurrence, is independently –H, a halo, an alkyl, $-OR_5$, $-NR_6R_7$, $-C(O)R_5$, $-C(O)OR_5$, or $-C(O)NR_6R_7$;

n is zero or an integer from 1 to 4; and

p, for each occurrence, is independently 1 or 2.

46. The compound of Claim 45, wherein L is –NR-C(O)-.

47. The compound of Claim 46, wherein R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl.

48. The compound of Claim 47, wherein R_{18} is unsubstituted or substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

49. The compound of Claim 45, wherein the compound is selected from the group consisting of:

3-Methyl-N-[5'-(pyridin-3-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]- isonicotinamide;

3-Methyl-N-[5'-(3-methyl-isoxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methoxy-5'-(furan-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(thien-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

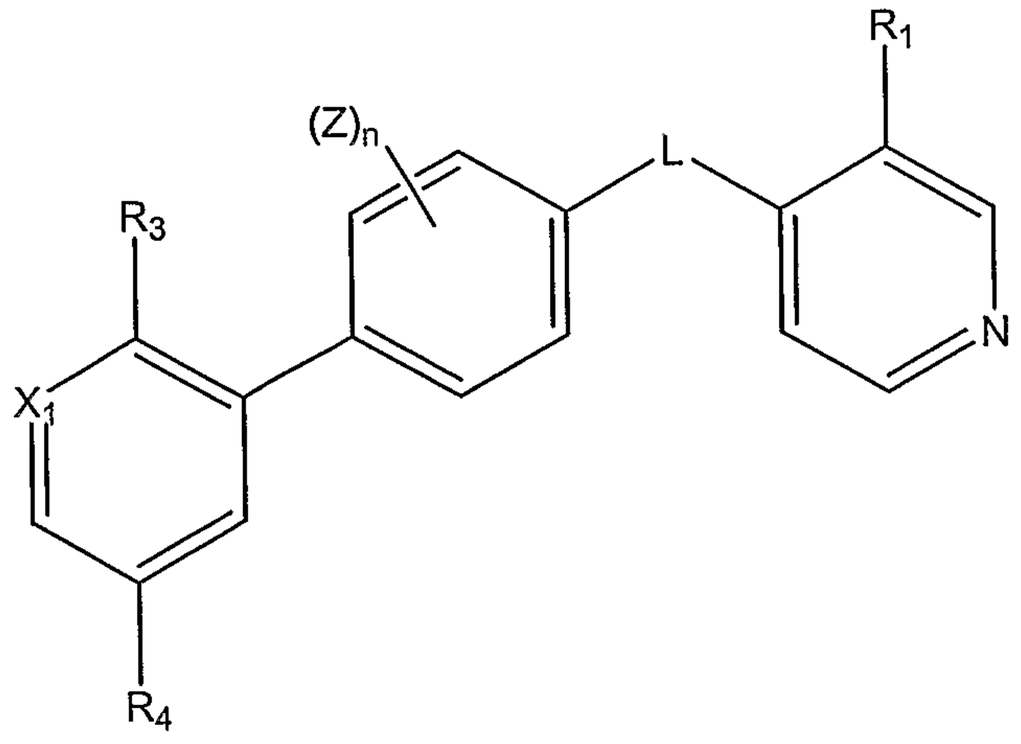
3-Fluoro-N-[5'-([1,3,4]thiadiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

50. The compound of Claim 46, wherein R_{18} is an ester, amide or carboxylic acid bioisostere.

51. The compound of Claim 50, wherein R_{18} is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

52. The compound of Claim 45, wherein the compound is represented by formula (VI):



(VI)

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

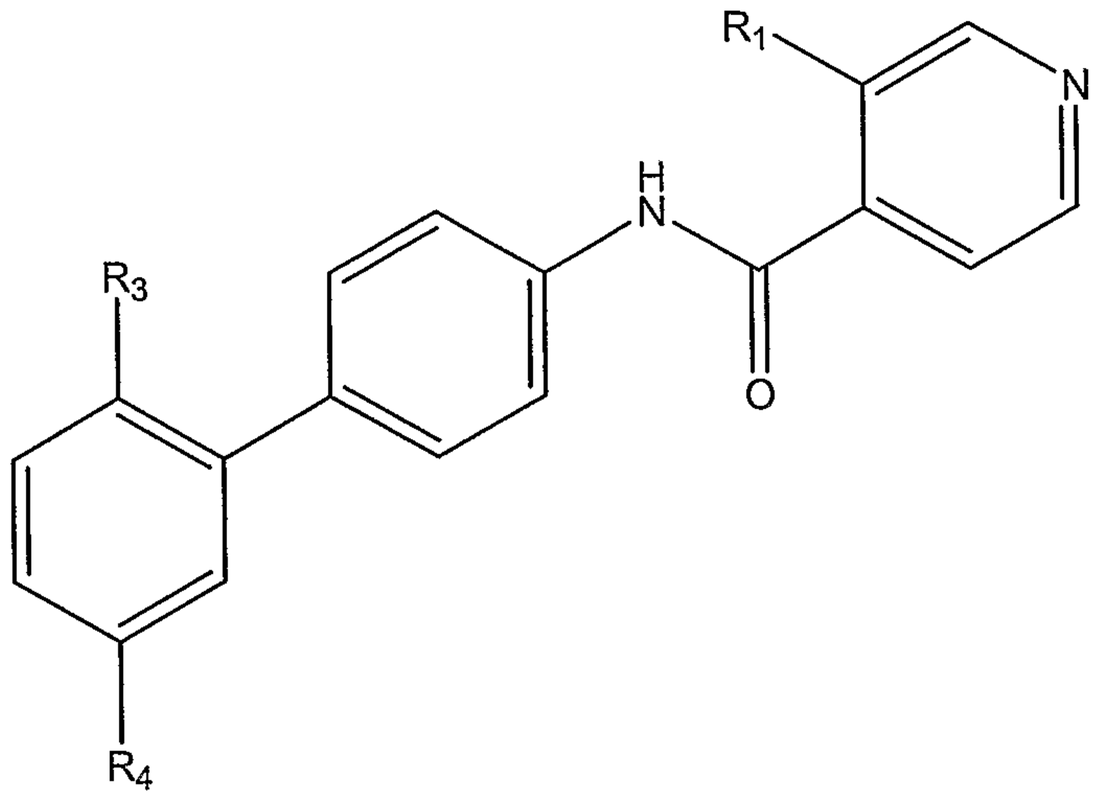
R_4 is a halo, cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, $-P(O)(R_5)_2$, or an ester, amide or carboxylic acid bioisostere.

53. The compound of Claim 52, wherein n is 0.

54. The compound of Claim 52, wherein Z, for each occurrence, is independently, a lower alkyl, a lower alkoxy, a lower haloalkoxy, a halo, cyano, or haloalkyl and n is 1 or 2.

55. The compound of Claim 52, wherein L is –NHC(O)-.

56. The compound of Claim 55, wherein the compound is represented by formula (IX):



(IX)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

57. The compound of Claim 56, wherein R_1 is a lower alkyl or a halo.

58. The compound of Claim 57, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

59. The compound of Claim 58, wherein R_3 is a lower alkyl.

60. The compound of Claim 58, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

61. The compound of Claim 60, wherein R_4 is a 5-membered heteroaryl.

62. The compound of Claim 61, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

63. The compound of Claim 58, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

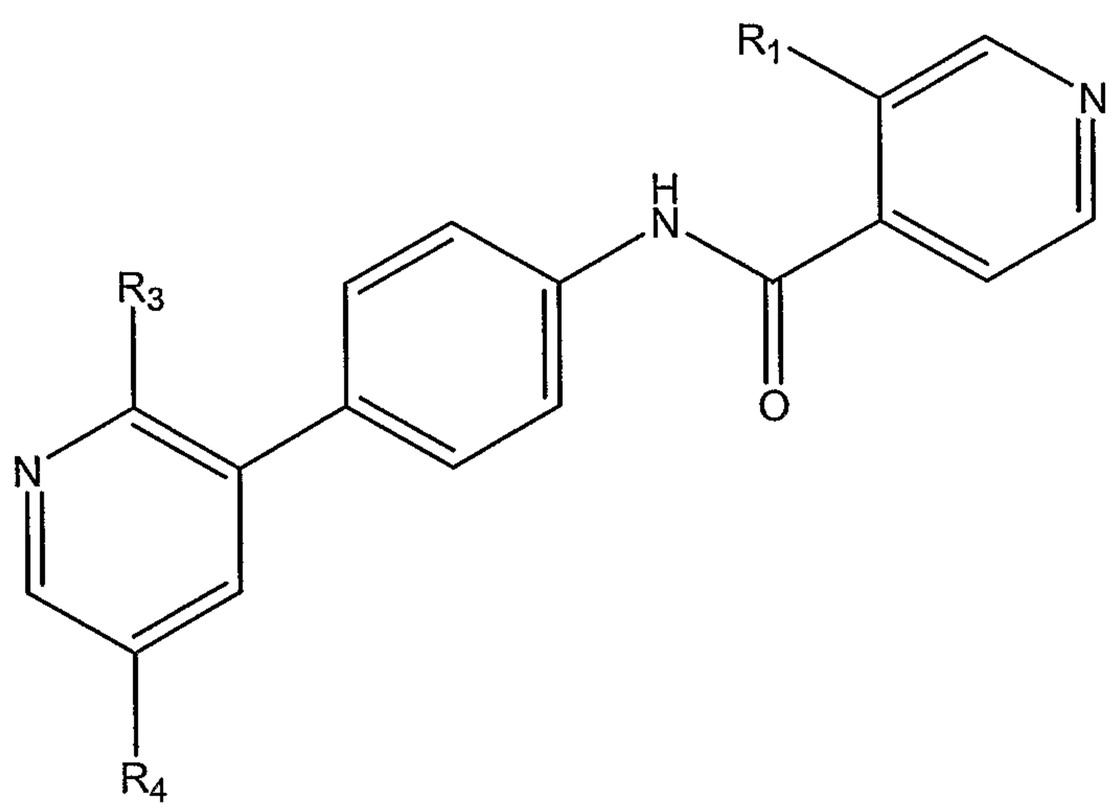
R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

64. The compound of Claim 58, wherein R_1 is fluoro or methyl.

65. The compound of Claim 55, wherein the compound is represented by formula (X):



(X)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

66. The compound of Claim 65, wherein R_1 is a lower alkyl or a halo.

67. The compound of Claim 66, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

68. The compound of Claim 67, wherein R_3 is a lower alkyl.

69. The compound of Claim 67, R_4 is a bioisostere of an ester, amide, or carboxylic acid.

70. The compound of Claim 69, wherein R_4 is a 5-membered heteroaryl.

71. The compound of Claim 70, wherein R_4 is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

72. The compound of Claim 67, wherein R_4 is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

73. The compound of Claim 67, wherein R_1 is fluoro or methyl.

74. The compound of Claim 38, selected from the group consisting of:

3-Methyl-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide;

3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotinamide;

3-Fluoro-N-(2'-methyl-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotinamide;

4'-[(3-Fluoro-pyridine-4- carbonyl)-amino]-6-methyl-biphenyl-3-carboxylic acid methyl ester;

3-Methyl-N-(2'-methyl-5'-thiazol-2-yl-biphenyl-4-yl)-isonicotin-amide;

3-Methyl-N-(2'-chloro-5'-oxazol-2-yl-biphenyl-4-yl)-isonicotin-amide;

3-Methyl-N-[4-(5-chloro-2-methoxy-pyridin-3-yl)-phenyl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-5-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(4-methyl-thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-2-yl)-2'-(N,N-dimethylamino)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1-methyl-1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(oxazol-2-yl)-2'-methoxy-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[5'-(thiazol-2-yl)-2'-methyl-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[5'-(thiazol-2-yl)-2'-chloro-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-([1,3,4]oxadiazol-2-yl)-biphenyl-4-yl]-isonicotinamide;

3-Fluoro-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(4-methyl-5-methylsulfanyl-4*H*-[1,2,4]triazol-3-yl)-biphenyl-4-yl]-isonicotinamide;

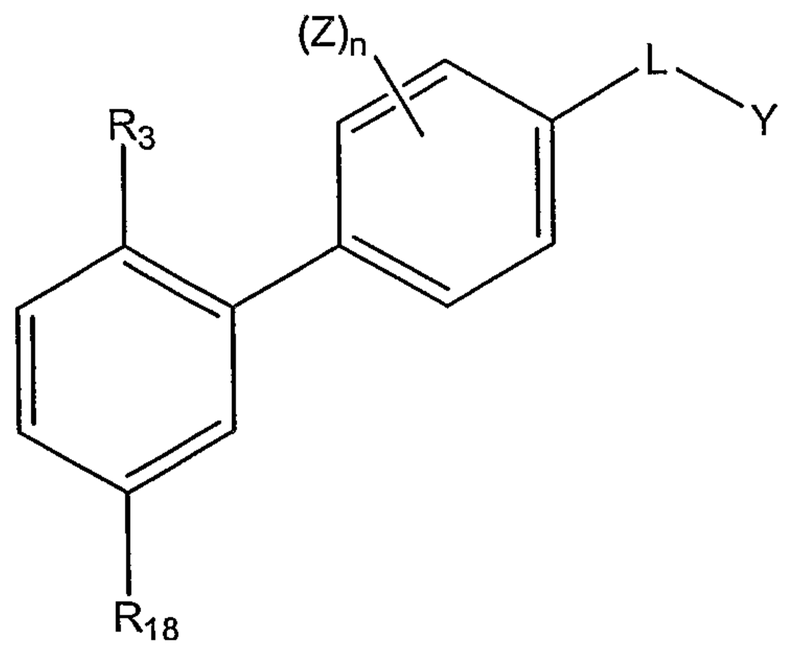
3-Fluoro-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(oxazol-4-yl)-biphenyl-4-yl]-isonicotinamide;

3-Methyl-N-[2'-methyl-5'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-isonicotinamide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

75. A compound represented by formula (XI):



(XI)

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

Y is an optionally substituted 5- or 6-membered heteroaryl;

L is a linker selected from the group consisting of a covalent bond, $-NRCH_2-$, $-CH_2NR-$, $-C(O)-$, $-NR-C(O)-$, $-C(O)-NR-$, $-OC(O)-$, $-C(O)O-$, $-C(S)-$, $-NR-C(S)-$, $-C(S)-NR-$;

each Z is independently selected from the group consisting of a lower alkyl, a lower haloalkyl, a halo, a lower alkoxy, a lower alkyl sufanyl, cyano, nitro, or lower haloalkoxy;

R, for each occurrence is independently selected from -H, an alkyl, $-C(O)R_5$, or $-C(O)OR_5$;

R_3 is an alkyl, a haloalkyl, a halo, a haloalkoxy, $-OR_5$, $-SR_5$, or $-NR_6R_7$;

R_{18} is a halo, cyano, nitro, $-C(O)R_5$, $-C(O)OR_5$, $-C(O)SR_5$, $-C(O)NR_6R_7$, $-C(S)R_5$, $-C(S)OR_5$, $-C(S)SR_5$, $-C(S)NR_6R_7$, $-C(NR_8)R_5$, $-C(NR_8)OR_5$, $-C(NR_8)SR_5$, $-C(NR_8)NR_6R_7$, $-S(O)_pR_5$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_5)_2$, $-OP(O)(OR_5)_2$, $-P(O)(R_5)_2$, a five or six membered optionally substituted heterocycloalkyl, a five or six membered optionally substituted heterocyclyl, or a five or six membered optionally substituted heteroaryl;

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;

R_6 and R_7, 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_6 and R_7 taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_8, for each occurrence, is independently –H, a halo, an alkyl, $-OR_5$, $-NR_6R_7$, $-C(O)R_5$, $-C(O)OR_5$, or $-C(O)NR_6R_7$;

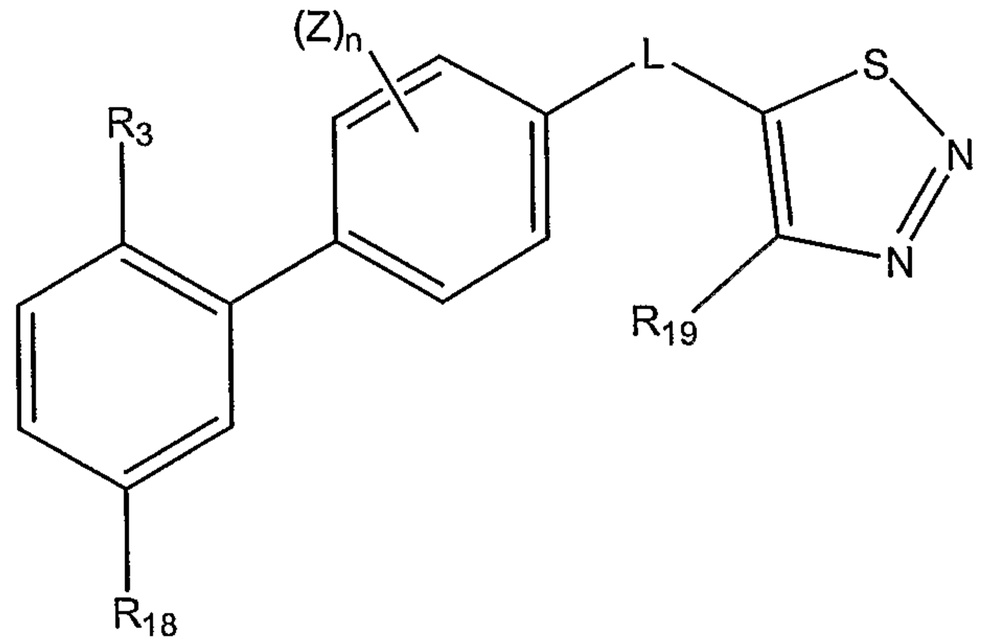
n is zero or an integer from 1 to 4; and

p, for each occurrence, is independently 1 or 2.

76. The compound of Claim 75, wherein Y is an optionally substituted 5-membered heteroaryl.

77. The compound of Claim 76, wherein Y is selected from the group consisting of an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl.

78. The compound of Claim 77, wherein the compound is represented by formula (XII):



(XII)

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

R_{19} is H, a halo, an optionally substituted alkyl, an optionally substituted alkoxy, or an optionally substituted alkyl sulfanyl.

79. The compound of Claim 78, wherein R_{19} is a halo or a lower alkyl.

80. The compound of Claim 78, wherein n is 0.

81. The compound of Claim 78, wherein L is –NHC(O)-.

82. The compound of Claim 81, wherein R_3 is a lower alkyl, a lower alkoxy, a lower alkyl sulfanyl, a lower alkylamino, a lower dialkylamino, or a halo.

83. The compound of Claim 81, wherein R_{18} is an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrrolyl, an optionally substituted morpholinyl, an optionally substituted furanyl, an optionally substituted thienyl, an optionally substituted thiadiazolyl, an optionally substituted triazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl.

84. The compound of Claim 83, wherein R_{18} is unsubstituted or substituted with one or more substituents selected from the group consisting of a lower alkyl, halo, a lower haloalkyl, an amino, a lower dialkyl amino, a lower alkyl amino, a lower alkoxy, and a lower alkyl sulfanyl.

85. The compound of Claim 81, wherein R_{18} is a bioisostere of an ester, amide, or carboxylic acid.

86. The compound of Claim 85, wherein R_{18} is a 5-membered heteroaryl.

87. The compound of Claim 86, wherein R_{18} is an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted 1H-tetrazolyl, an optionally substituted 1H-imidazolyl, an optionally substituted [1,2,4]oxadiazolyl, or an optionally substituted 4H-[1,2,4]triazolyl.

88. The compound of Claim 81, wherein R_{18} is a halo, $-C(O)R_9$, $-S(O)_pR_{11}$, $-S(O)_pNR_5$, $-S(O)_pOR_5$, $-P(O)(OR_{12})_2$, or $-P(O)(R_{11})_2$, wherein:

R_9 is a lower alkoxy, lower alkyl sulfanyl, or an alkoxyalkoxy;

R_{11}, for each occurrence, is independently, a lower alkyl; and

R_{12}, for each occurrence, is independently, H or a lower alkyl.

89. The compound of Claim 78, wherein the compound is selected from the group consisting of:

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-3-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(pyridin-2-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid [2'-methoxy-5'-(oxazol-5-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(isoxazol-5-yl)-biphenyl-4-yl]-amide;

4-Methyl-[1,2,3]thiadazole-5-carboxylic acid [2'-methyl-5'-(thiazol-2-yl)-biphenyl-4-yl]-amide;

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

90. A method of inhibiting immune cell activation comprising administering to the cell a compound of Claim 1, 45 or 75.

91. The method of Claim 90, wherein immune cell activation is inhibited in a subject by administering the compound to the subject.

92. The method of Claim 91, wherein the subject is human.

93. A method of inhibiting cytokine production in a cell, comprising administering to the cell a compound of Claim 1, 45 or 75.

94. The method of Claim 93, wherein cytokine production is inhibited in a subject by administering the compound to the subject.

95. The method of Claim 94, wherein the subject is human.

96. The method of Claim 94, 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.

97. The method of Claim 96, wherein the cytokine is IL-2.

98. 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 Claim 1, 45 or 75.

99. The method of Claim 98, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.

100. The method of Claim 99, wherein the subject is human.

101. The method of Claim 99, wherein the ion channel is a Ca^{2+}-release-activated Ca^{2+} channel (CRAC).

102. A method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to the cell a compound of Claim 1, 45, or 75.

103. The method of Claim 102, wherein T-cell and/or B-cell proliferation is inhibited in a subject by administering the compound to the subject.

104. The method of Claim 103, wherein the subject is human.

105. A method for treating or preventing an immune disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Claim 1, 45 or 75.

106. The method of Claim 105, wherein the subject is human.

107. The method of Claim 105, 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.

108. 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 Claim 1, 45 or 75.

109. The method of Claim 108, wherein the subject is human.

110. The method according to claim 108, 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; sclerodermatitis, psoriasis, eczema; chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration, 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 erythematodes; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer.

111. 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 Claim 1, 45 or 75.

112. The method of Claim 111, wherein the subject is human.

113. 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 Claim 1, 45, or 75.

114. The method of Claim 113, wherein the subject is human.

115. The method of Claim 113, 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.

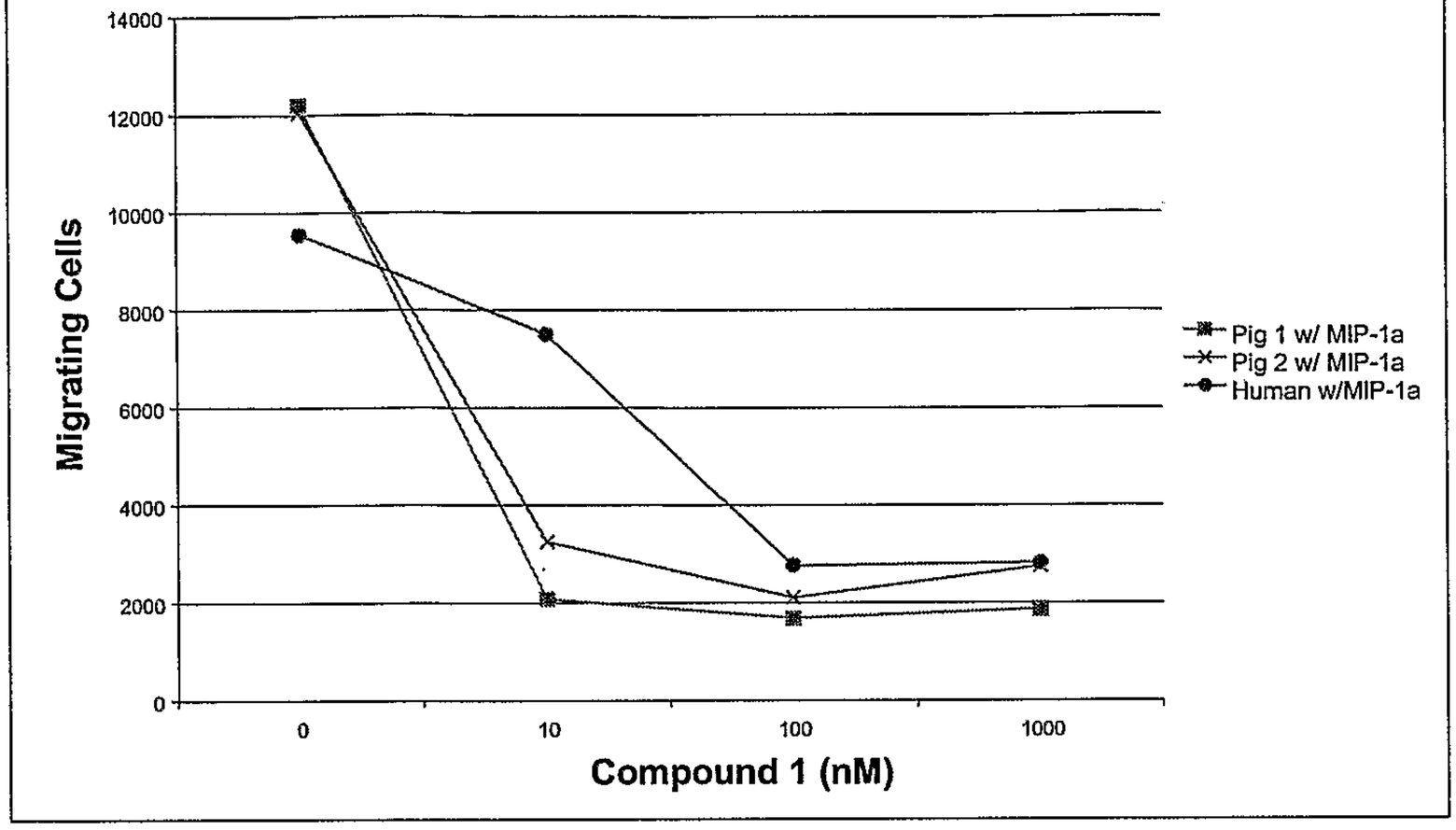
116. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of Claim 1, 45, or 75.

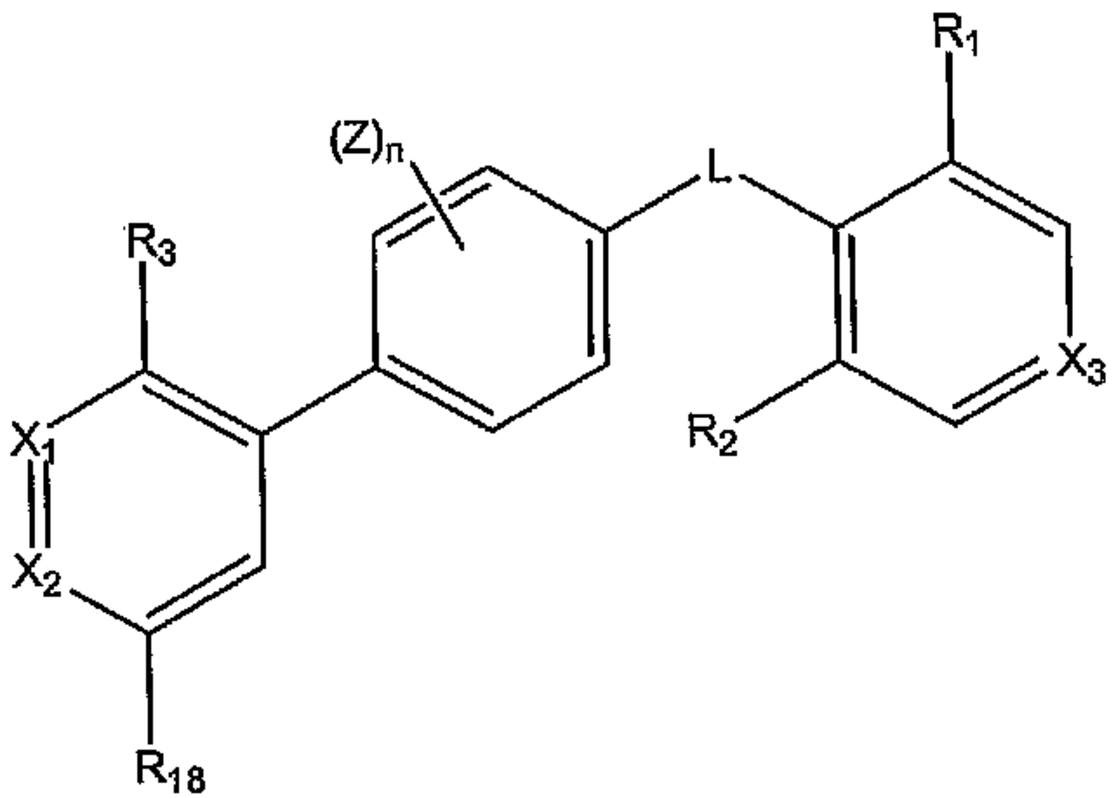
117. The pharmaceutical composition of Claim 116, further comprising one or more additional therapeutic agents.

118. The pharmaceutical composition according to Claim 117, wherein the additional therapeutic agent is selected from the group consisting of immunosuppressive agents, anti-inflammatory agents and suitable mixtures thereof.

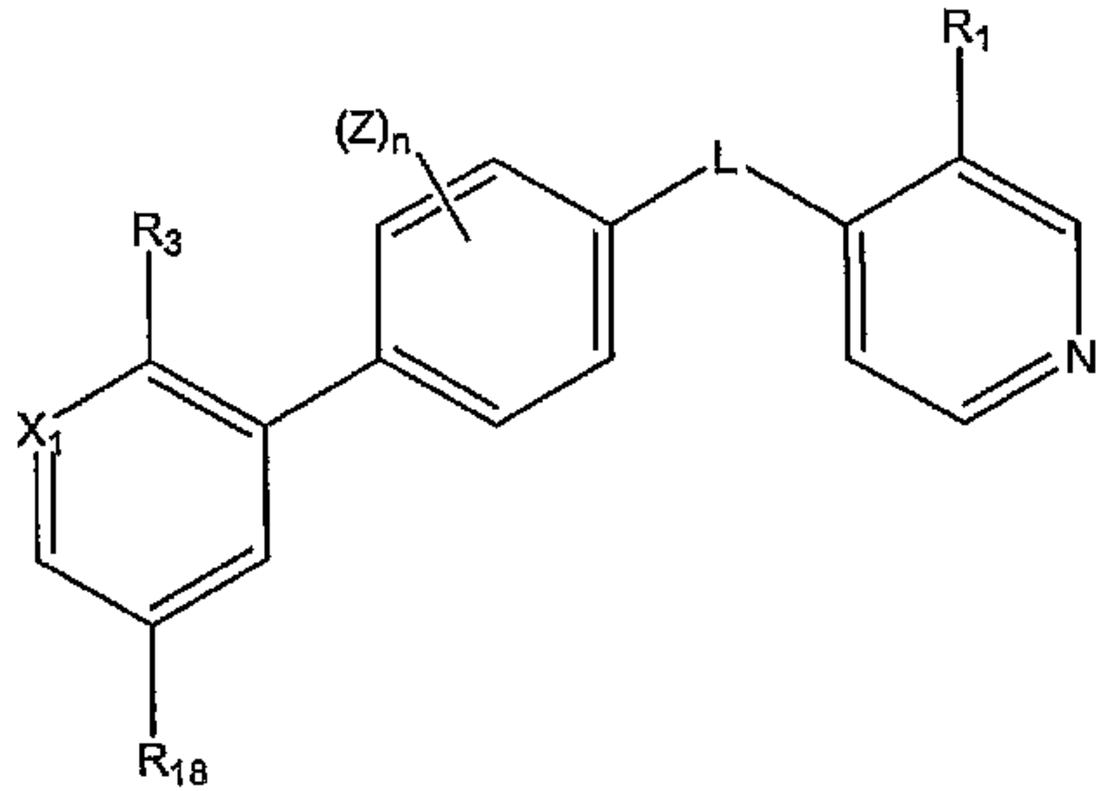
119. The pharmaceutical composition of Claim 118, wherein the additionaltherapeutic agent is selected from the group consisting of steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and suitable mixtures thereof.

Figure 1

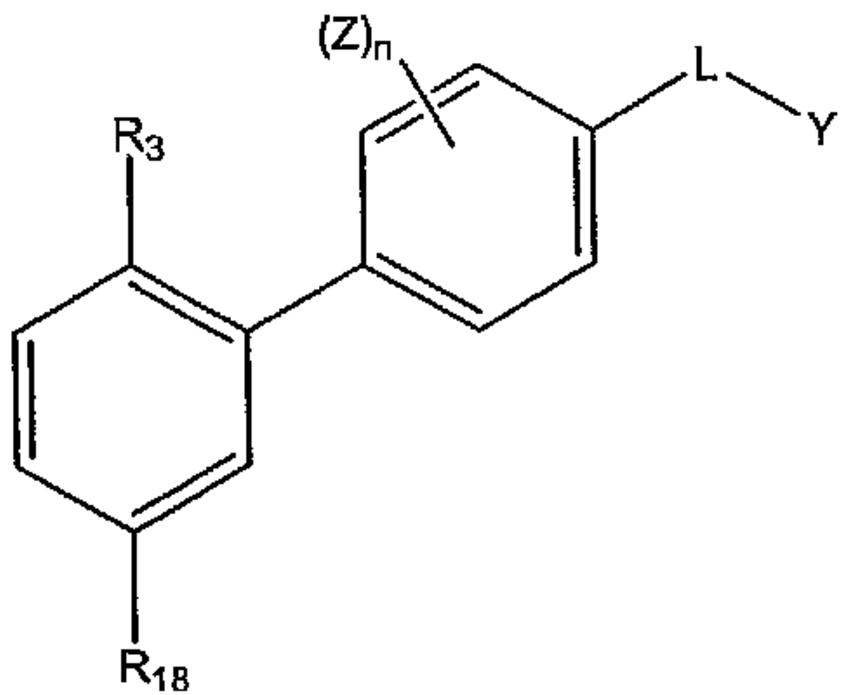

14000
12000
10000
8000
6000
4000
2000
0
Migrating Cells
0
10
100
1000
Compound 1 (nM)
Pig 1 w/ MIP-1a
Pig 2 w/ MIP-1a
Human w/MIP-1a



(I)



(VII)



(XI)