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(54) Title: FUSED RING COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES

(57) Abstract: The invention relates to certain fused ring compounds, or pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, that are useful as immunosuppressive agents and for treating and preventing inflammatory conditions, allergic disorders, and immune disorders.

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FUSED RING COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES

FIELD OF THE INVENTION

This invention relates to biologically active chemical compounds, that may be used for immunosuppression or to treat or prevent inflammatory conditions and immune disorders.

BACKGROUND OF THE INVENTION

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

Interleukin 2 (IL-2) is a cytokine that is secreted by T cells in response to calcium ion influx into the cell. IL-2 modulates immunological effects on many cells of the immune system. For example, it is a potent T cell mitogen that is required for the T cell proliferation, promoting their progression from G1 to S phase of the cell cycle; it stimulates the growth of NK cells; and it acts as a growth factor to B cells and stimulates antibody synthesis.

IL-2, although useful in the immune response, can cause a variety of problems. IL-2 damages the blood-brain barrier and the endothelium of brain vessels. These effects may be the underlying causes of neuropsychiatric side effects observed under IL-2 therapy, e.g. fatigue, disorientation and depression. It also alters the electrophysiological behaviour of neurons.

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

T cells that are unable to produce IL-2 become inactive (anergic). This renders them potentially inert to any antigenic stimulation they might receive in the future. As a result, agents which inhibit IL-2 production can be used for 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/or autoimmune disorders or at least provides a useful choice to currently used drugs and/or methods. 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.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

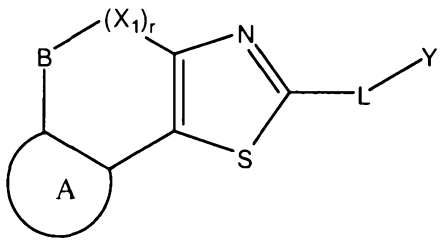
2007300450 24 Apr 2009

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

SUMMARY OF THE INVENTION

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

The invention relates to compounds of formula (X):



(X)

wherein:

Ring A is a 5 or 6 membered aryl or heteroaryl ring wherein the members of the ring are selected from the group consisting of -CZ-, -S-, -O- or –N-;

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

B is $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

each X_1 is independently $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, $-C(O)R_4$, or $-C(O)OR_4$;

R_1 and R_2, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an

optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_1 and R_2 taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4; and

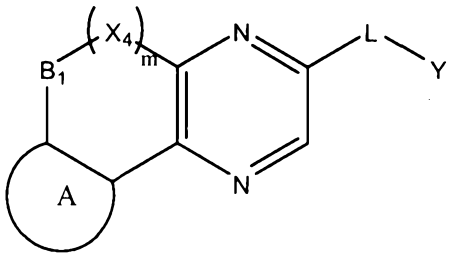
p is 0, 1, or 2;

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

In one aspect of compounds of formula (X), when r is 1, X_1 is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl.

In one aspect of compounds of formula (X), when X_1 is $-CH_2-$, r is 1, B is $-CH_2-$ and ring A is an unsubstituted phenyl group, L is not –NH- or –CH=CH-.

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



(XI)

wherein:

X_4 is $-C(R^a)_2-$;

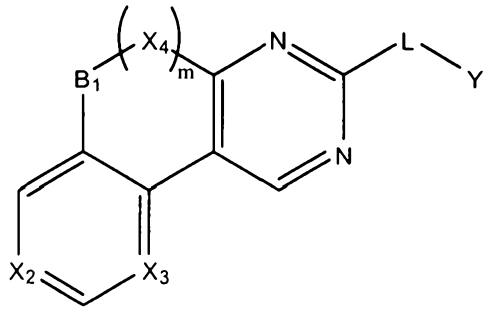
B_1 is $-C(R^a)_2-$, -C(O)-; or –O-;

m is 1 or 2; and

Ring A, L and Y are defined as for formula (X);

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

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



(XII)

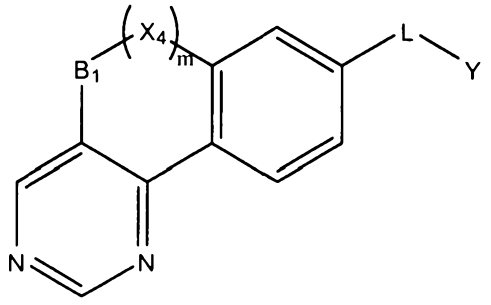
wherein:

X_2 and X_3 are independently selected from the group consisting of -CR^a- or –N-; and

Ring A, L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

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



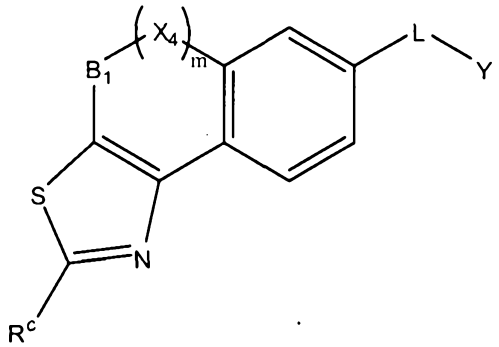
(XIII)

wherein:

L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

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



(XIV)

wherein:

R^c is –H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

In one embodiment of compounds of formula (XIV), when X_5 is $-C(NH_2)-$ and m is 1, then Y is not an unsubstituted phenyl.

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

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

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

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

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

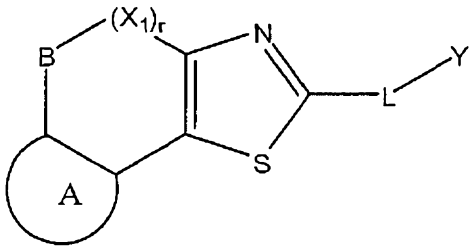
The invention further encompasses methods for inhibiting immune cell activation, including inhibiting proliferation of T cells and/or B cells, *in vivo* or *in vitro* comprising administering to the cell an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate,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

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

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

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

In a first preferred aspect the invention provides a compound represented by formula (X):



(X)

wherein:

Ring A is a 5 or 6 membered aryl or heteroaryl ring wherein the members of the ring are selected from the group consisting of -CZ-, -S-, -O- or –N-;

Y is an aryl optionally substituted with one to two substituents independently selected from lower alkyl and halo; or an optionally substituted heteroaryl;

B is $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

each X_1 is independently $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, -C(O)R_4, or -C(O)OR_4;

R_1 and R_2, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl,

or an optionally substituted heteraralkyl; or R_1 and R_2 taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4;

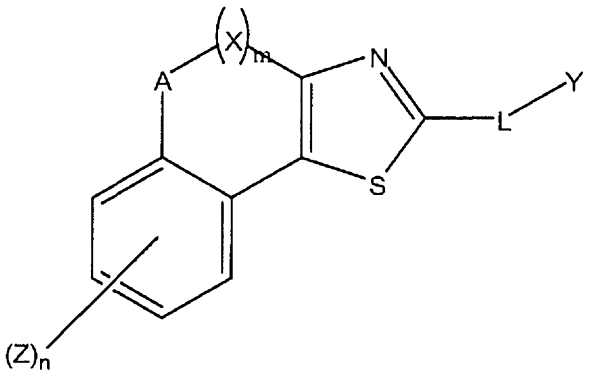
p is 0, 1, or 2; and

provided that when r is 1, X_1 is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when X_1 is $-CH_2-$, r is 1, B is $-CH_2-$ and ring A is an unsubstituted phenyl group, L is not –NH- or –CH=CH-;

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

In a second preferred aspect the invention provides a compound represented by formula (II):



(II)

wherein:

Y is an aryl optionally substituted with one to two substituents independently selected from lower alkyl and halo; or an optionally substituted heteroaryl;

A is $-C(R^a)_2-$ or –O-;

each X is independently $-C(R^a)_2-$ or -C(O)-;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$,

$-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

m is 1 or 2;

n is 0, 1, 2, 3 or 4;

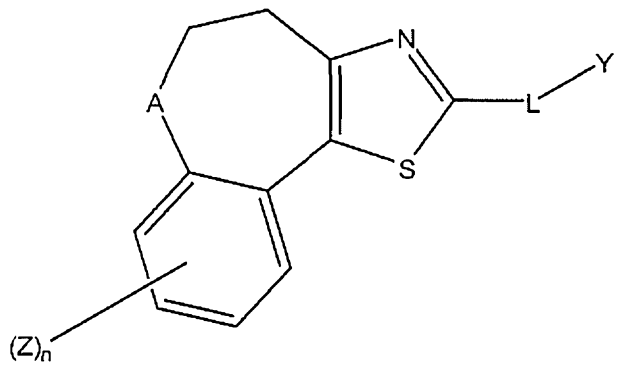
p is 0, 1, or 2; and

provided that when m is 1, X is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when m is 1 and n is 0, L is not –NH-;

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

In a third preferred aspect the invention provides a compound represented by formula (III):



(III)

wherein:

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

A is $-C(R^a)_2-$ or –O-;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

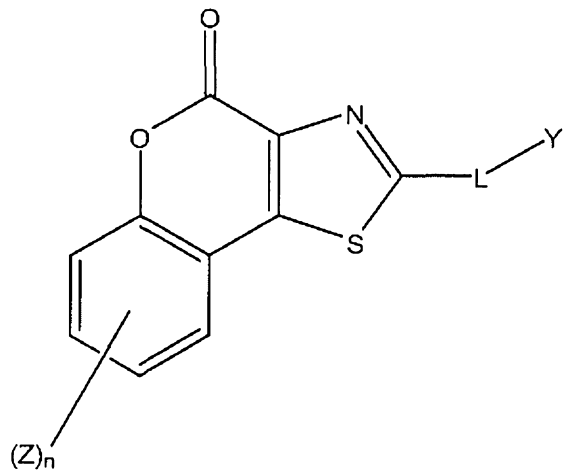
R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

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

p is 0, 1, or 2;

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

In a fourth preferred aspect the invention provides a compound represented by formula (VII):



(VII)

wherein:

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

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

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

p is 0, 1, or 2;

provided that when L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when n is 0, L is not –NH-;

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

In a fifth preferred aspect the invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of the first, second, third or fourth preferred aspects.

In a sixth preferred aspect the invention provides a method of inhibiting immune cell activation comprising administering to the cell a compound according to any one of the first, second, third or fourth preferred aspects.

In a seventh preferred aspect the invention provides a method of inhibiting cytokine production in a cell, comprising administering to a cell a compound according to any one of the first, second, third or fourth preferred aspects.

In a eighth preferred aspect the invention provides 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 according to any one of the first, second, third or fourth preferred aspects.

In a ninth preferred aspect the invention provides a method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to the cell a compound according to any one of any one of the first, second, third or fourth preferred aspects.

In a tenth preferred aspect the invention provides 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 according to any one of any one of the first, second, third or fourth preferred aspects, 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.

In a eleventh preferred aspect the invention provides 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 according to any one of any one of the first, second, third or fourth preferred aspects, 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.

In a twelfth preferred aspect the invention provides a method for suppressing the immune system of a subject in need thereof, comprising administering to the subject an effective amount of a compound according to any one of any one of the first, second, third or fourth preferred aspects.

In a thirteenth preferred aspect the invention provides 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 according to any one of any one of the first, second, third or fourth preferred aspects.

In a fourteenth preferred aspect the invention provides the use of a compound of any one of any one of the first, second, third or fourth preferred aspects in the manufacture of a medicament for any one of the following:

inhibiting immune cell activation,

inhibiting cytokine production in a cell,

modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation,

inhibiting T-cell and/or B-cell proliferation in response to an antigen,

treating or preventing an immune disorder 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,

treating or preventing an inflammatory condition 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,

suppressing the immune system,

treating or preventing an allergic disorder.

DETAILED DESCRIPTION OF THE INVENTION

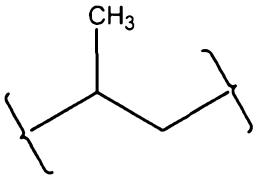
DEFINITIONS

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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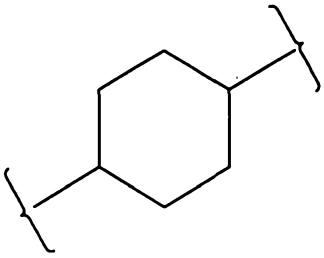

, etc., wherein the brackets indicate the points of attachment). Alkylene groups may be substituted or unsubstituted.

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

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

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

The term "alkyl sulfanyl," as used herein, refers to an alkyl group which is linked to another moiety though a divalent sulfur atom. Alkyl sulfanyl groups can be substituted or unsubstituted.

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

As used herein, the term "alkenyl" means a straight chain or branched, hydrocarbon radical typically having from 2 to 10 carbon atoms and having at least one carbon-carbon double bond. Representative straight chain and branched alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, 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 $-OCHF_2$.

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

As used herein, the term "linker" means a diradical having from 1-3 atoms in contiguous linear connectivity (*i.e.*, as defined above and excluding atoms present in any side chains and branches), that covalently connects the isothiazole portion of a compound of this invention to the Y group of the compound, as illustrated in formula (I). The atoms of the linker in contiguous linear connectivity may be connected by saturated or unsaturated covalent bonds. Linkers include, but are not limited to, alkylidene, alkenylidene, alkynylidene and cycloalkylidene (such as lower alkylidene, cycloalkylidene, alkylycloalkylidene and alkyl-substituted alkylidene) linkers wherein one or more (*e.g.*, between 1 and 3, (*e.g.*, 1 or 2)) carbon atoms may be optionally replaced with O, S, or N and wherein two or more (*e.g.*, 2-3 (*e.g.*, 2 or 3)) adjacent atoms may be optionally linked together to form a carbocyclic or heterocyclic moiety within the linker (which may be monocyclic, polycyclic and/or fused, and which may be saturated, unsaturated, or aromatic). Examples of specific linkers useful in the compounds of the invention include (without limitation) diradicals of alkyl, alkenyl, alynyl, alkoxy, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, alkylcycloalkyl, and alkyl-substituted alkylcycloalkyl (wherein one or more carbon atoms in any of these linkers may be optionally replaced with O, S, or N).

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

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

As used herein, the term "lower" refers to a group having up to four carbon atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, and a "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms,

respectively. A lower alkoxy or a lower alkyl sulfanyl refers to an alkoxy or a alkyl sulfanyl having from 1 to 4 carbon atoms. Lower substituents are typically preferred.

Where a particular substituent, such as an alkyl substituent, occurs multiple times in a given structure or moeity, 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, $-C(O)R_{15}$, $-NR_{13}R_{14}$, $-SR_{15}$, $-C(O)OR_{15}$, $-OC(O)R_{15}$, $-NR_{15}C(O)NR_{13}R_{14}$, $-OC(O)NR_{13}R_{14}$, $-NR_{15}C(O)OR_{16}$, $-S(O)_pR_{15}$, 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, $=N\text{-}R_{15}$.

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 protecting groups for hydroxy include benzyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the entire teachings of which are incorporated herein by reference.

As used herein, the term "compound(s) of this invention" and similar terms refers to a compound of any one of formulas (I) through (XIV), 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 (XIV), 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 (XIV), 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 (XIV) 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 (XIV) 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 (XIV) 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 (XIV) 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).

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 autoimmune disorders, a beneficial clinical outcome includes reduction in the extent or severity of the symptoms associated with the disease or disorder and/or an increase in the longevity and/or quality of life of the subject compared with the absence of the treatment. The precise amount of compound administered to a subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex,

body weight and tolerance to drugs. It will also depend on the degree, severity and type of inflammatory disorder or autoimmune disorder or the degree of immunosuppression sought. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective amounts of the disclosed compounds typically range between about 1 mg/m^2 per day and about 10 $grams/m^2$ per day, and preferably between 10 mg/m^2 per day and about 1 $gram/m^2$.

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 (XIV) 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.

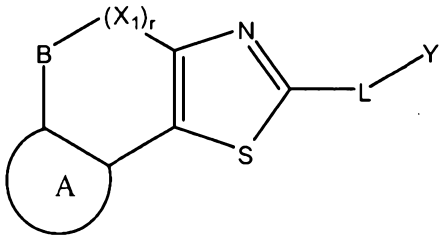
Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

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 (X):



(X)

wherein:

Ring A is a 5 or 6 membered aryl or heteroaryl ring wherein the members of the ring are selected from the group consisting of -CZ-, -S-, -O- or –N-;

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

B is $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $–N(R^b)-$;

each X_1 is independently $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $–N(R^b)-$;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, $-C(O)R_4$, or $-C(O)OR_4$;

R_1 and R_2, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an

optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_1 and R_2 taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4; and

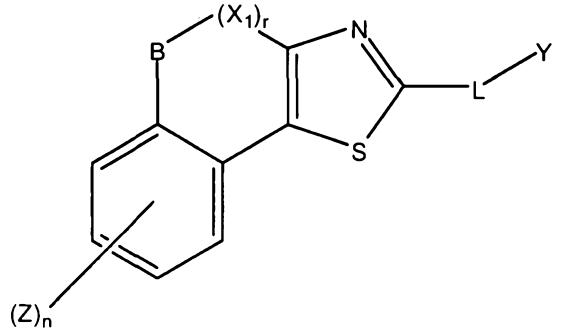
p is 0, 1, or 2;

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

In one aspect of compounds of formula (X), when r is 1, X_1 is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl.

In one aspect of compounds of formula (X), when X_1 is $-CH_2-$, r is 1, B is $-CH_2-$ and ring A is an unsubstituted phenyl group, L is not –NH- or –CH=CH-.

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



(I)

wherein:

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

B is $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

each X_1 is independently $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, $-C(O)R_4$, or $-C(O)OR_4$;

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

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4;

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

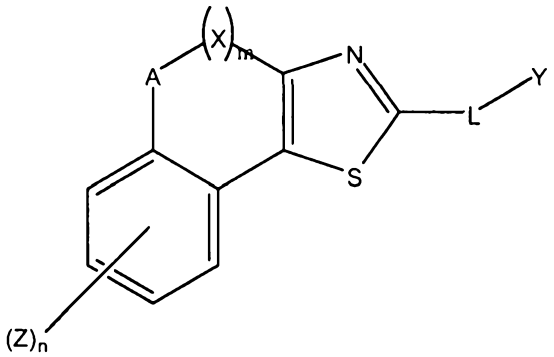
p is 0, 1, or 2;

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

In one aspect of compounds of formula (I), when r is 1, X_1 is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl.

In one aspect of compounds of formula (I), when r is 1 and n is 0, L is not –NH-.

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



(II)

wherein:

A is $-C(R^a)_2-$ or –O-;

each X is independently $-C(R^a)_2-$ or -C(O)-;

m is 1 or 2; and

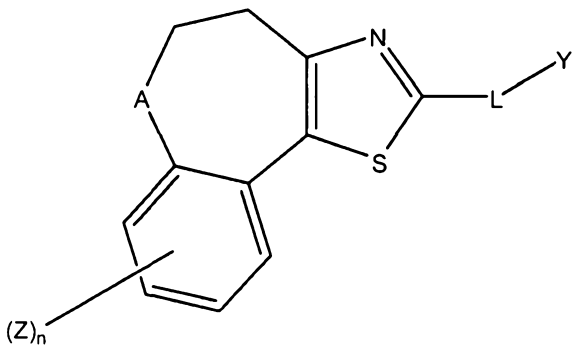
Z, L, and Y are defined as for formula (I);

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

In one aspect of compounds of formula (II), when m is 1, X is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl.

In another aspect of compounds of formula (II), when m is 1 and n is 0, L is not –NH-.

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

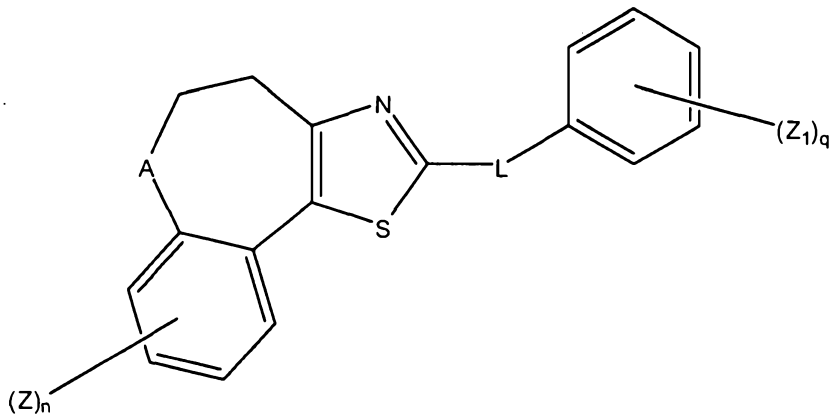


(III)

wherein Z, Y, L and n are defined as for formula (I) and A is defined as for formula (II);

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

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

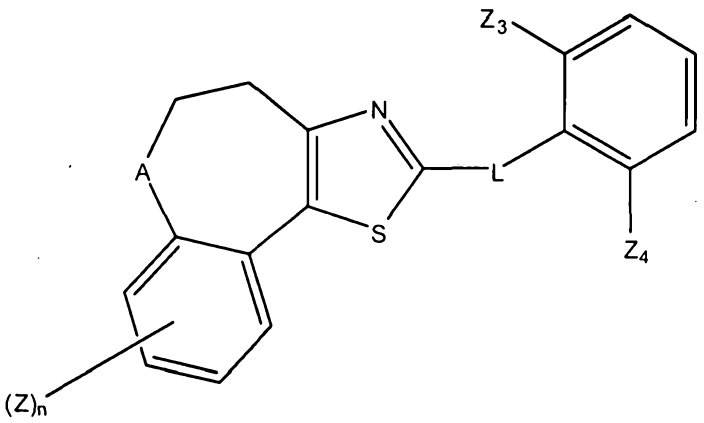


(IV)

wherein Z_1 is a substituent; q is 0, 1, 2, 3, 4, or 5; Z , n, and L are defined as for formula (I); and A is defined as for formula (II);

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

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

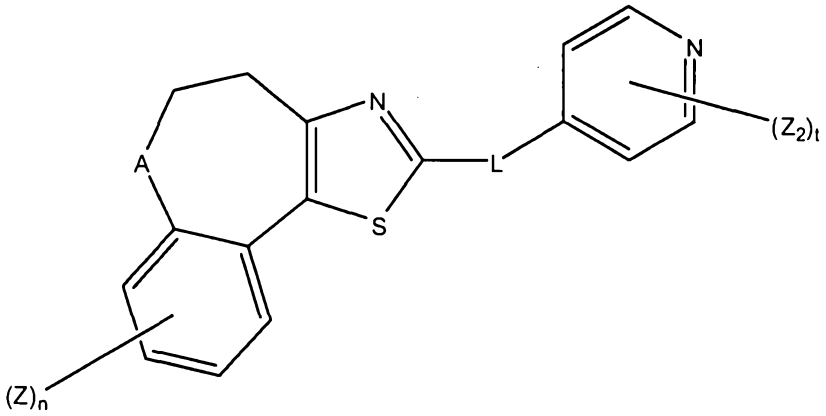


(V)

wherein Z_3 and Z_4 are each independently substituents; Z, n, and L are defined as for formula (I); and A is defined as for formula (II);

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

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

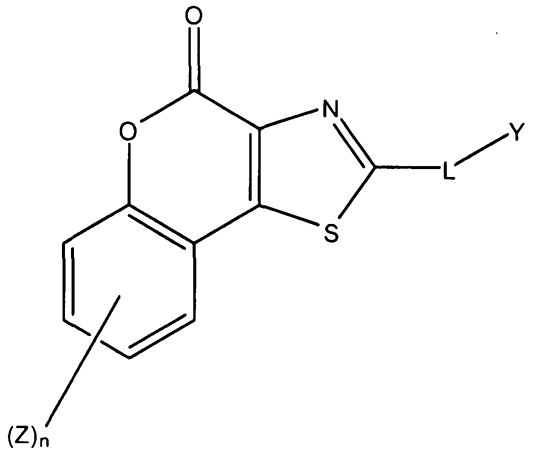


(VI)

wherein Z_2 is a substituent; t is 0, 1, 2 , 3 or 4; Z, n, and L are defined as for formula (I); and A is defined as for formula (II);

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

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



(VII)

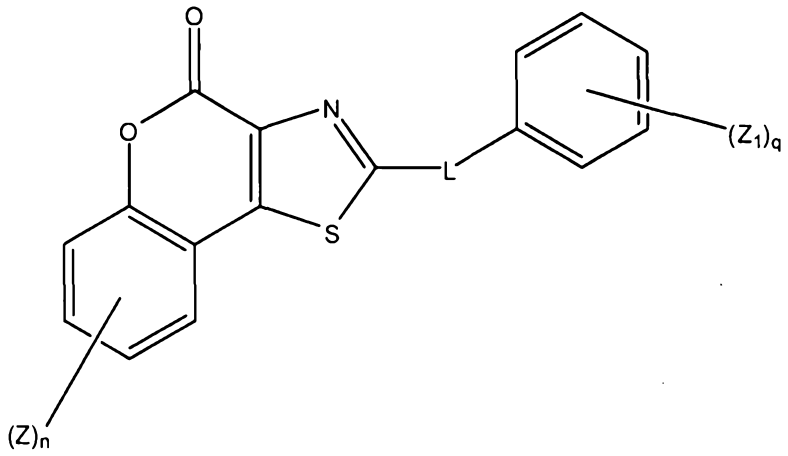
wherein Z, n, L, and Y are defined as for formula (I);

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

In one aspect of compounds of formula (VII), when L is –NHC(O)-, Y is not phenyl or methylphenyl.

In one aspect of compounds of formula (VII), when n is 0, L is not –NH-.

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



(VIII)

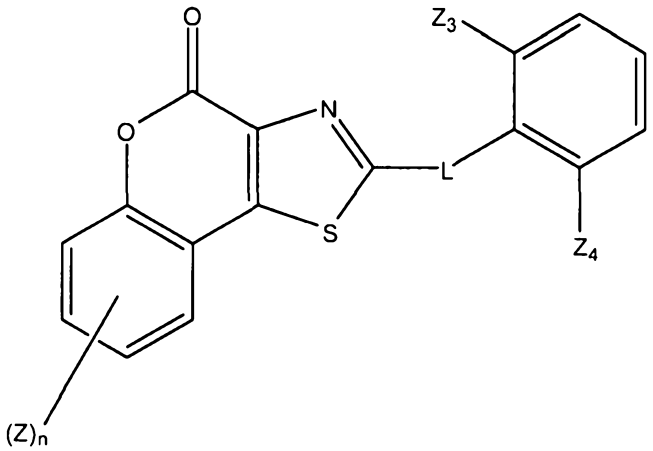
wherein Z_1 is a substituent; q is 0, 1, 2, 3, 4, or 5; and Z, n and L are defined as for formula (I).

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

In one aspect of compounds of formula (VIII), when L is –NHC(O)-, Y is not phenyl or methylphenyl.

In one aspect of compounds of formula (VIII), when n is 0, L is not –NH-.

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



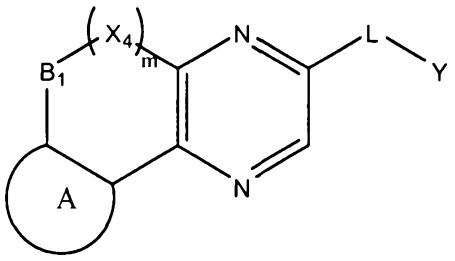
(IX)

wherein Z_3 and Z_4 are each independently substituents; and Z, n, and L are defined as for formula (I);

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

In one aspect of compounds of formula (IX), when n is 0, L is not –NH-.

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



(XI)

wherein:

X_4 is $-C(R^a)_2-$;

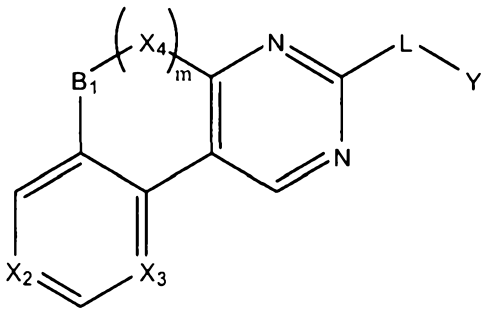
B_1 is $-C(R^a)_2-$, -C(O)-; or –O-;

m is 1 or 2; and

Ring A, L and Y are defined as for formula (X);

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

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



(XII)

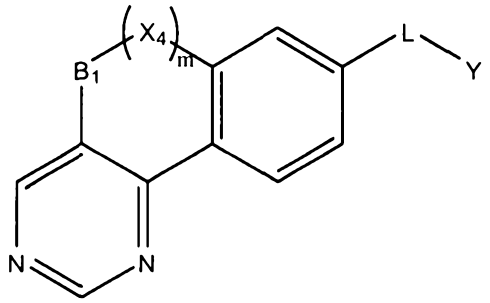
wherein:

X_2 and X_3 are independently selected from the group consisting of $-CR^a-$ or –N-; and

Ring A, L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

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



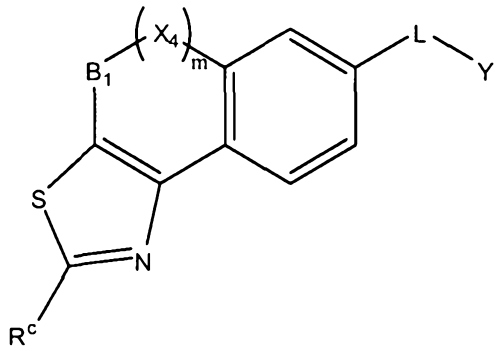
(XIII)

wherein:

L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

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



(XIV)

wherein:

R^c is –H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$; and

L and Y are defined as for formula (X) and B_1, X_4, and m are defined as for formula (XI);

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

In one embodiment of compounds of formula (XIV), when X_5 is $-C(NH_2)-$ and m is 1, then Y is not an unsubstituted phenyl.

In one embodiment, in compounds represented by formula (I)-(XIV), L is $-NRCH_2-$, $-CH_2NR-$, $-C(O)-$, $-NR-C(O)-$, $-C(O)-NR-$, $-OC(O)-$, $-C(O)O-$, $-C(S)-$, $-NR-C(S)-$, $-C(S)-NR-$, $-NRC(NR_9)-$ or $-C(NR_9)NR-$;

R, for each occurrence, is independently –H, alkyl, $-C(O)-R_7$, or $-C(O)OR_7$;

R_9, for each occurrence, is independently –H, halo, an alkyl, $-OR_7$, $-NR_{11}R_{12}$, $-C(O)R_7$, $-C(O)OR_7$, or $-C(O)R_{11}R_{12}$;

R_7, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

R_{11} and R_{12}, 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_{11} and R_{12} taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl.

In one aspect, in compounds represented by formula (I)-(XIV), L is $-NRCH_2-$, $-CH_2NR-$, $-NR-C(O)-$, or $-C(O)-NR-$. In another aspect, R is –H. In a further aspect, L is $-NH-C(O)-$ or $-C(O)-NH-$. In another aspect, L is $-NH-C(O)-$. In another aspect, L is $-C(O)-NH-$.

In one embodiment, in compounds represented by formula (I)-(XIV), L is $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRS(O)_2NR-$, $-NRC(O)NR-$, $-NRC(NR)NR-$, $-NRC(S)NR-$, $-NRCH_2NR-$, $-NRN=CR_6-$, $-C(NR)-$, or $-CR_6=NNR-$;

R, for each occurrence, is independently –H, alkyl, $-C(O)-R_7$, or $-C(O)OR_7$;

R_6, for each occurrence, is –H or alkyl; and

R_7, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.

In one aspect, in compounds represented by formula (I)-(XIV), R is –H; and R_6 is –H. In another aspect, L is $-NHS(O)_2-$, $-NHC(O)NH-$, $-NHC(S)NH-$, or $-NHN=CH-$. In one aspect, L is $-NHC(O)NH-$.

In one aspect, in compounds represented by formula (I)-(XIV), L is $-C(=NR_{20})NR-$. R_{20} is –H, alkyl, $-C(O)-R_7$, $-OR_7$, or $-C(O)OR_7$. In one aspect, R is –H.

In one embodiment, in compounds represented by formula (I)-(X), Z is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted imidazolyl, an optionally substituted pyridinyl, an optionally substituted pyrazolyl, an optionally substituted pyrrolyl, an optionally substituted thiophenyl, an optionally substituted furanyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. In one aspect, Z is an an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted pyridinyl, or an optionally substituted tetrazolyl. In another aspect, Z is thiazol-2-yl, pyridin-2-yl, tetrazol-5-yl, oxadiazol-3-yl, or oxazol-5-yl. In one aspect, Z is thiazol-2-yl. In one aspect, Z is pyridin-2-yl. In one aspect, Z is tetrazol-5-yl. In one aspect, Z is oxadiazol-3-yl. In one aspect, Z is oxazol-5-yl.

In one embodiment, in compounds represented by formula (I)-(X), Z is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, $-NO_2$, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, $-OR_4$, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$. In one aspect, Z is halo, cyano, $-NO_2$, $-OR_4$, $-C(O)OR_4$, or an optionally substituted alkyl. In another aspect, Z is –Br, -Cl, -F, $-OCH_3$, $-C(O)OCH_3$, or CF_3. In one aspect, Z is –OH, $-OCH_3$, or $-C(O)OCH_3$. In another aspect, Z is cyano or $-NO_2$.

In one embodiment, in compounds represented by formula (I)-(IX), n is 1 or 0. In one aspect, n is 1. In another aspect n is 0.

In one embodiment, in compounds represented by formula (I)-(IX), n is 3.

In one embodiment, in compounds represented by formula (I), (II), (III), (VII), (X), (XI), (XII), (XIII), or (XIV), Y is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substitute pyrazolyl, an optionally substituted pyridinyl, an optionally substituted pyridazinyl, an optionally substituted thiadiazolyl, an optionally substituted pyrimidinyl, or an optionally substituted thiophenyl. In one aspect, Y is

unsubstituted. In another aspect, Y is an optionally substituted phenyl or an optionally substituted pyridinyl. In a further aspect, Y is substituted with one to two substituents. In another aspect, the one to two substituents on Y are each independently a lower alkyl or a halo. In one aspect, Y is difluorophenyl. In a further aspect, Y is an optionally substituted thiadiazolyl. In another aspect, Y is an optionally substituted thiophenyl. In one aspect, Y is an optionally substituted pyridazinyl. In another aspect, Y is an optionally substituted pyrimidinyl. In another aspect, Y is thiadiazolyl substituted with one methyl group. In another aspect, Y is thiophenyl substituted with one methyl group. In another aspect, Y is pyridazinyl substituted with one methyl group.

In one embodiment, in compounds represented by formula (I) or (X), r is 3.

In one embodiment, in compounds represented by formula (I) or (X), r is 4.

In one embodiment, in compounds represented by formula (I) or (X), r is 2.

In one embodiment, in compounds represented by formula (I) or (X), B is $-C(R^a)_2-$ or –O- and each X_1 is $-C(R^a)_2-$.

In one embodiment, in compounds represented by formula (I) or (X), r is 3; B is $-C(R^a)_2-$ or –O-; and each X_1 is $-C(R^a)_2-$.

In one embodiment, in compounds represented by formula (II)-(VI), A is –O-.

In one embodiment, in compounds represented by formula (II)-(VI), A is $-CH_2-$.

In one embodiment, in compounds represented by formula (II), X is $-C(R^a)_2-$ and m is 1.

In one embodiment, in compounds represented by formula (II), X is $-C(R^a)_2-$ and m is 2.

In one embodiment, in compounds represented by formula (II), X is -C(O)-and m is 1.

In one embodiment, in compounds represented by formula (II), X is -C(O)-and m is 2.

In one embodiment, in compounds represented by formula (II), (XI), (XII), or (XIII), m is 1.

In one embodiment, in compounds represented by formula (II), (XI), (XII), or (XIII), m is 2.

In one embodiment, in compounds represented by formula (IV) or formula (VIII), Z_1 is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, $-NO_2$, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, $-OR_4$, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$. In one aspect, Z_1 is halo.

In one embodiment, in compounds represented by formula (IV) or formula (VIII), q is 2.

In one embodiment, in compounds represented by formula (IV) or formula (VIII), q is 3.

In one embodiment, in compounds represented by formula (IV) or formula (VIII), q is 1.

In one embodiment, in compounds represented by formula (V) or formula (IX), Z_3 and Z_4 are each independently an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, $-OR_4$, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$. In one aspect, Z_3 and Z_4 are the same. In another aspect, Z_3 and Z_4 are each –F.

In one embodiment, in compounds represented by formula (V) or formula (IX), Z is –Br, -Cl, -F, $-OCH_3$, $-C(O)OCH_3$, or CF_3; Z_3 and Z_4 are each –F; and L is –NH-C(O)- or -C(O)-NH-.

In one embodiment, in compounds represented by formula (V), Z is –Br, -Cl, -F, $-OCH_3$, $-C(O)OCH_3$, or CF_3; Z_3 and Z_4 are each –F; A is $-CH_2-$; and L is –NH-C(O)- or -C(O)-NH-.

In one embodiment, in compounds represented by formula (V), Z is –Br, -Cl, -F, $-OCH_3$, $-C(O)OCH_3$, or CF_3; Z_3 and Z_4 are each –F; A is $-CH_2-$; n is 1; and L is –NH-C(O)- or -C(O)-NH-.

In one embodiment, in compounds represented by formula (VI), Z_2 is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, $-OR_4$, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$. In one aspect, Z_2 is halo or optionally substituted lower alkyl. In another aspect, Z_2 is –F or $-CH_3$. In one aspect, Z_2 is $-CH_3$, $-NH_2$, $-OCH_3$, Cl, or F.

In one embodiment, in compounds represented by formula (VI), t is 1.

In one embodiment, in compounds represented by formula (VI), Z_2 is –F or $-CH_3$ and t is 1.

In one embodiment, in compounds represented by formula (X) or (XI), Ring A is a 5-membered heteroaromatic ring containing one heteroatom. In one aspect, that one heteroatom is –S-.

In one embodiment, in compounds represented by formula (X) or (XI), Ring A is a 6-membered aromatic ring, containing no heteroatoms.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), B_1 is $-C(R^a)_2-$ or –O-. In one aspect, B_1 is $-C(R^a)_2-$. In one aspect, B_1 is $-CH_2-$.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), X_4 is $-CH_2-$. In one aspect, m is 2.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), m is 1.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), m is 2.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), B_1 is $-C(R^a)_2-$ or –O- and each X_4 is $-CH_2-$.

In one embodiment, in compounds represented by formula (XI) or (XII), (XIII), or (XIV), B_1 is $-C(R^a)_2-$ and each X_4 is $-CH_2-$.

In one embodiment, in compounds represented by formula (XII), at least one of X_2 and X_3 is –N-. In one aspect, X_2 and X_3 are both –N-.

In one embodiment, in compounds represented by formula (XII), X_2 and X_3 are both –CH-.

In one embodiment, in compounds represented by formula (XIV), R_c is an optionally substituted aryl or an optionally substituted heteroaryl. In one aspect, R_c is an optionally substituted heteroaryl. In one aspect, R_c is an optionally substituted pyridyl.

In one embodiment, in compounds represented by formula (XIV), R_c is is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted imidazolyl, an optionally substituted pyridinyl, an optionally substituted pyrazolyl, an optionally substituted pyrrolyl, an optionally substituted thiophenyl, an optionally substituted furanyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, or an optionally substituted tetrazolyl. In one aspect, R_c is an an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted pyridinyl, or an optionally substituted tetrazolyl. In another aspect, R_c is thiazol-2-yl, pyridin-2-yl, tetrazol-5-yl, oxadiazol-3-yl, or oxazol-5-yl. In one aspect, R_c is thiazol-2-yl. In one aspect, R_c is pyridin-2-yl. In one aspect, R_c is tetrazol-5-yl. In one aspect, R_c is oxadiazol-3-yl. In one aspect, R_c is oxazol-5-yl.

In one embodiment, in compounds represented by formula (XIV), R_c is halo, cyano, $-NO_2$, $-OR_4$, $-C(O)OR_4$, or an optionally substituted alkyl. In another aspect, R_c is –Br, -Cl, -F, $-OCH_3$, $-C(O)OCH_3$, or CF_3. In one aspect, R_c is –OH, $-OCH_3$, or $-C(O)OCH_3$. In another aspect, R_c is cyano or $-NO_2$.

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

In another embodiment, compounds of any one of formula (I) through (XIV), 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 (XIV), or Table 1, or a pharmaceutically acceptable salt,

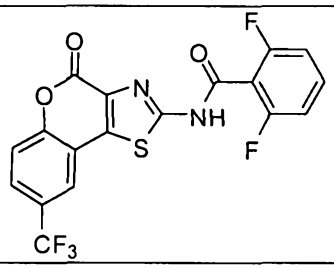
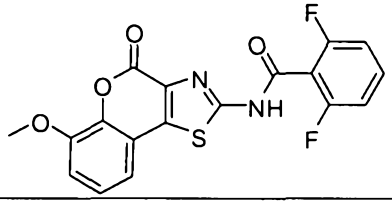
solvate, clathrate, or prodrug thereof, can inhibit the production of IL-2, IL-4, IL-5, IL-13, GM-CSF, IFN-γ, TNF-α and combinations thereof. In one embodiment, a compound of any one of formulas (I) through (XIV), or Table 1, inhibits cytokine production in a mammal (*e.g.*, a human).

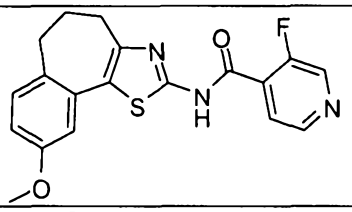
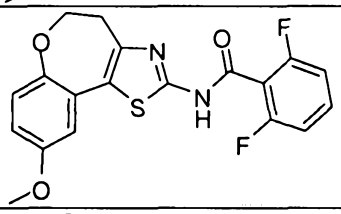
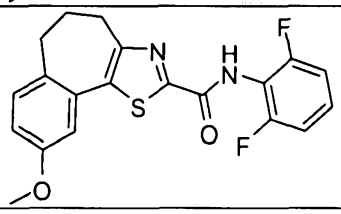
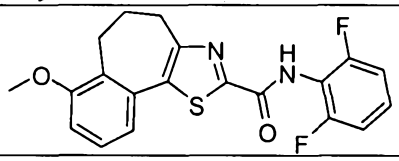
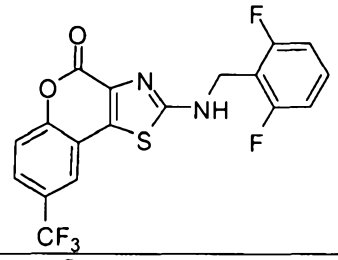
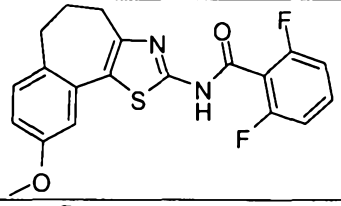
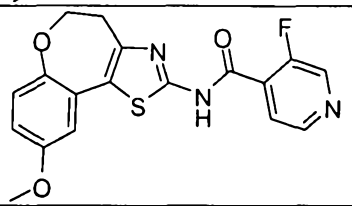
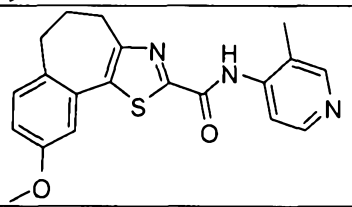
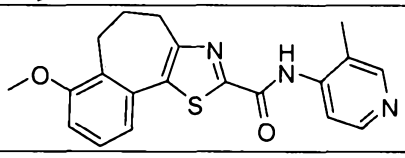
In another embodiment, compounds of any one of formulas (I) through (XIV), or Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels. In one embodiment, a compound of any one of formulas (I) through (XIV) or Table 1 can inhibit the influx of calcium ions into an immune cell (*e.g.*, T cells and/or B cells) by inhibiting the action of CRAC ion channels. In general, a decrease in I_{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 (XIV) or Table 1 modulates an ion channel in a mammal (*e.g.*, a human).

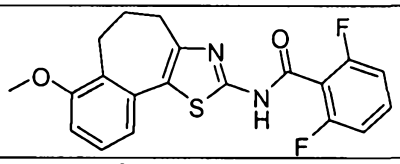
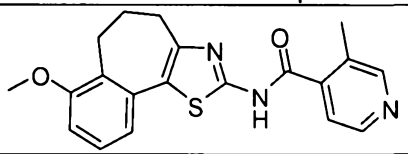
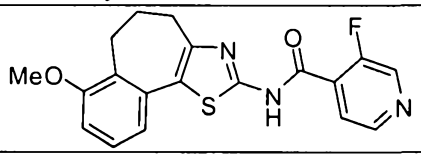
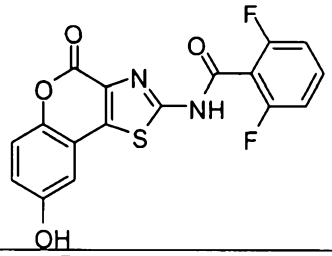
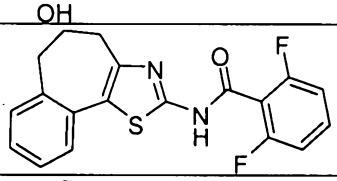
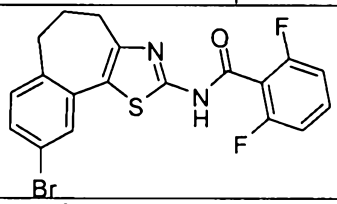
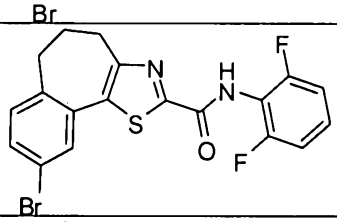
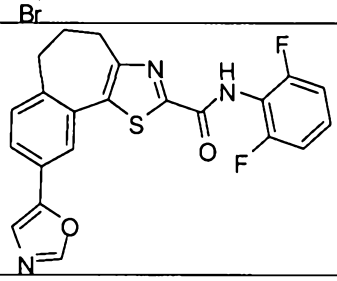
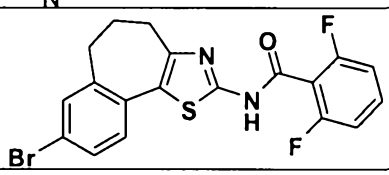
EXEMPLARY COMPOUNDS OF THE INVENTION

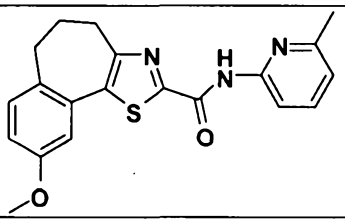
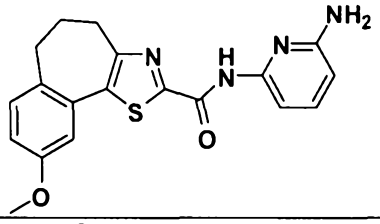
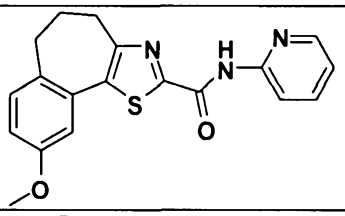
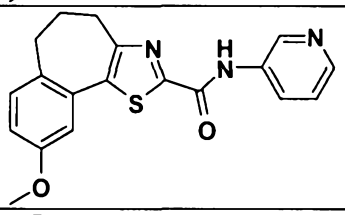
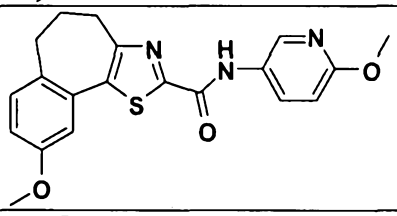
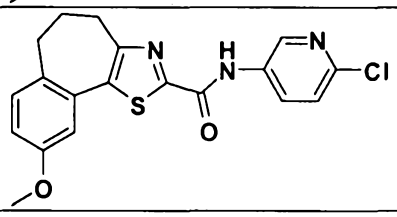
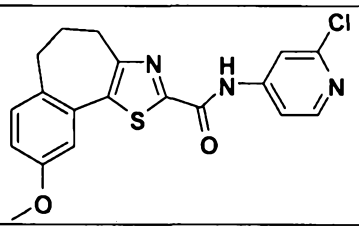
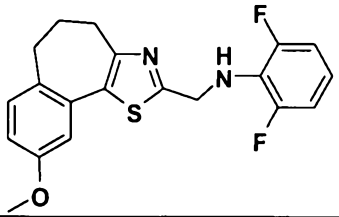
Exemplary compounds of the invention are depicted in Table 1 below.

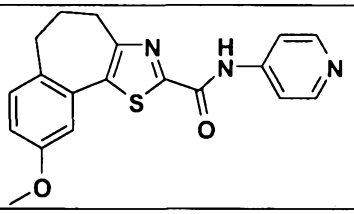
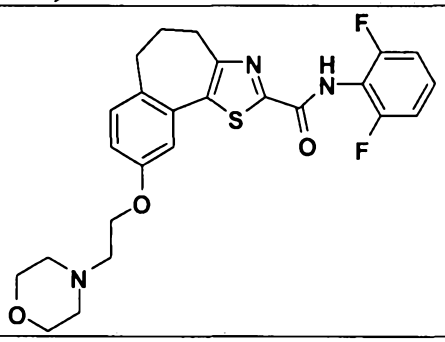
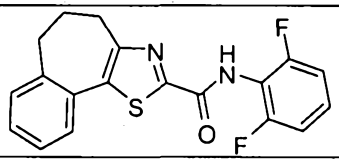
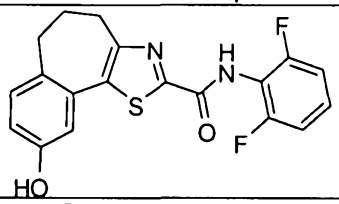
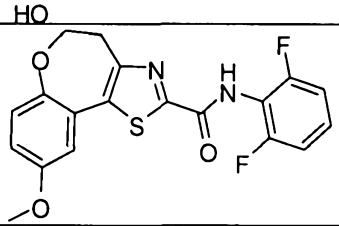
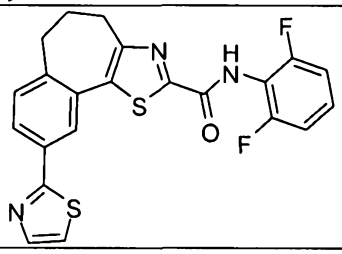
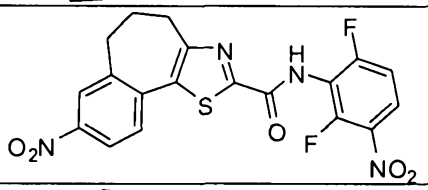
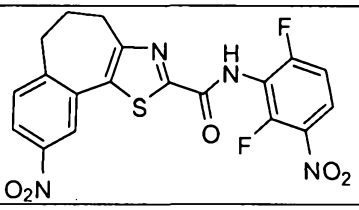
Table 1

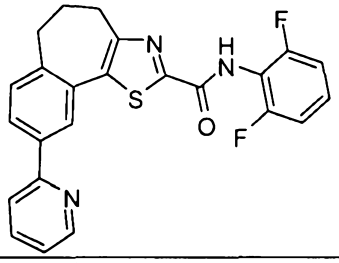
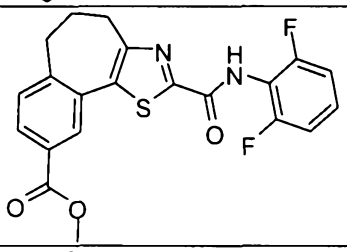
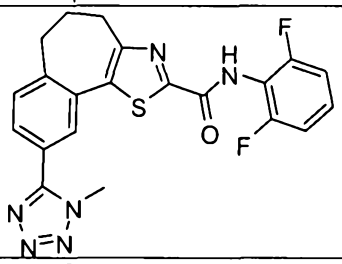
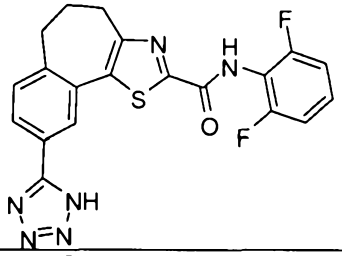
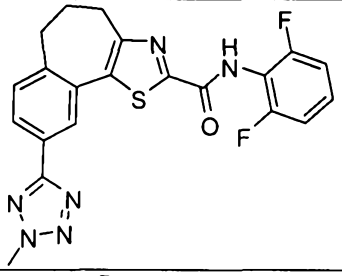
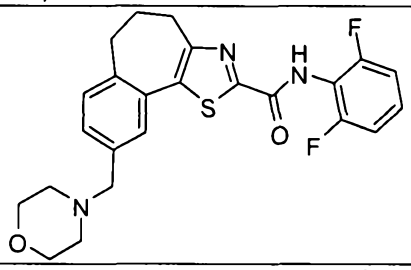
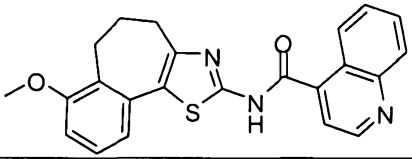
Compound No.	Structure
1	
2	

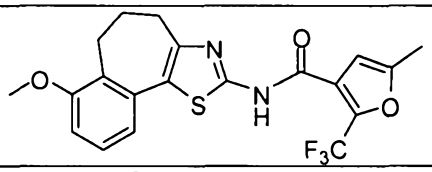
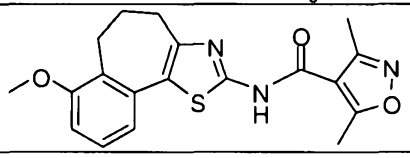
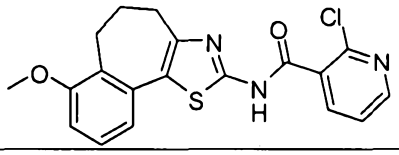
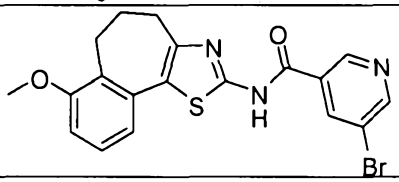
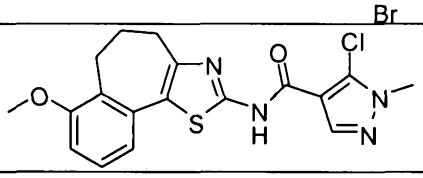
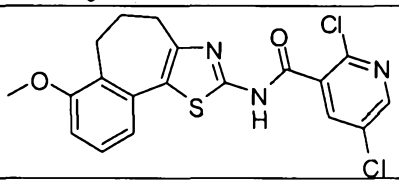
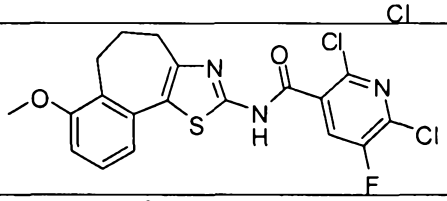
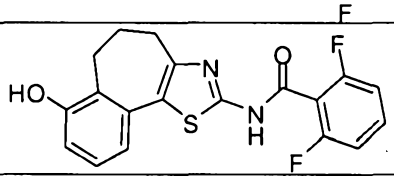
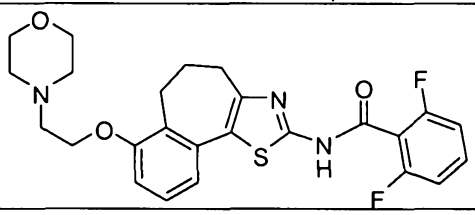
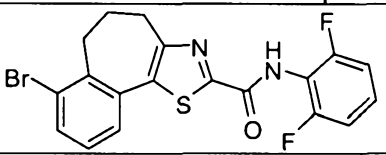
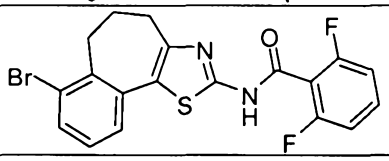
3	
4	
5	
6	
7	
8	
9	
10	
11	

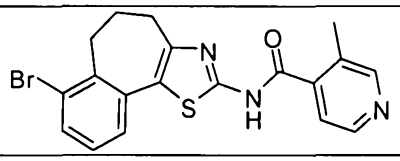
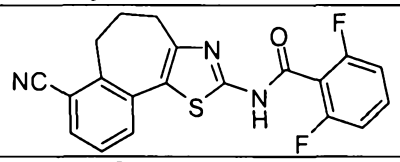
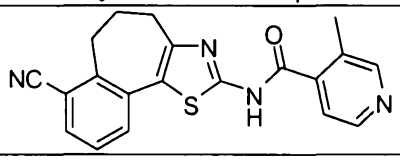
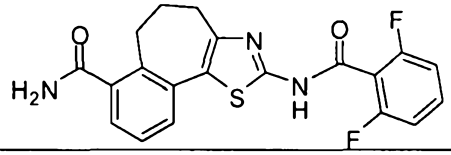
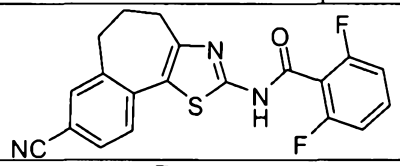
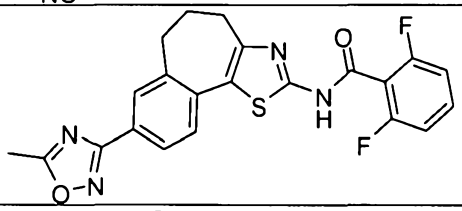
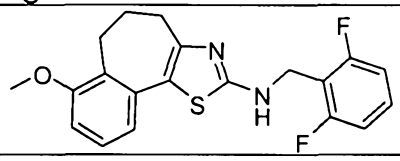
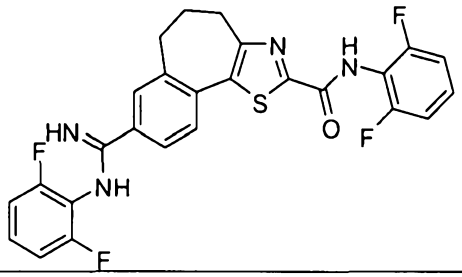
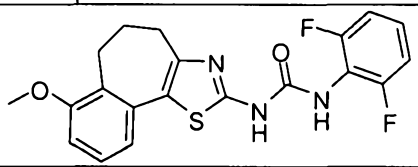
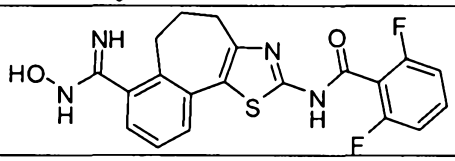
12	
13	
14	
15	
16	
17	
18	
19	
20	

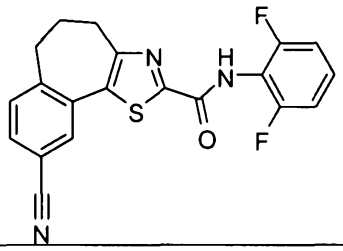
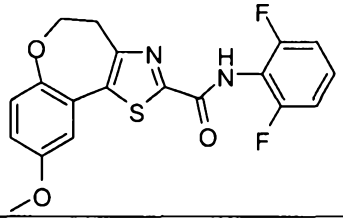
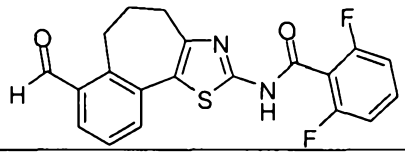
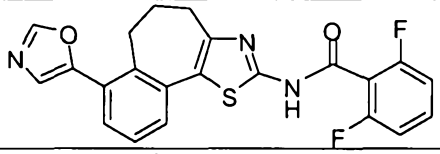
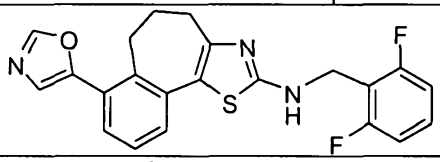
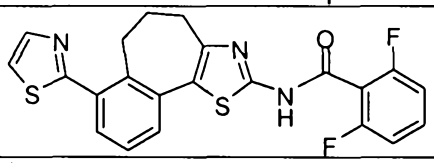
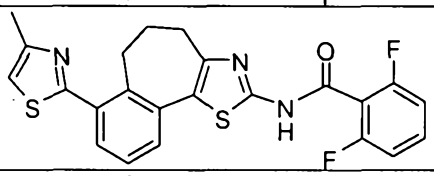
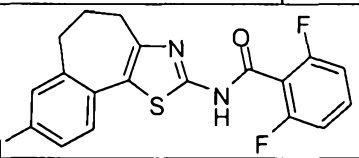
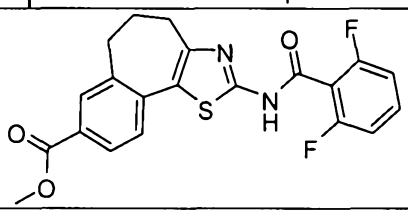
21	
22	
23	
24	
25	
26	
27	
28	

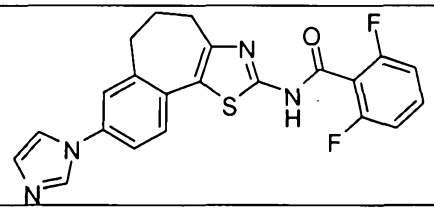
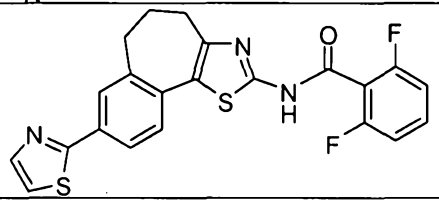
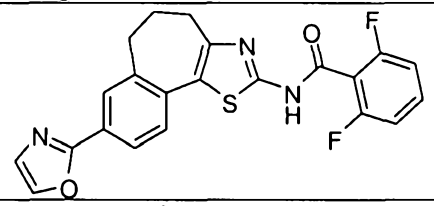
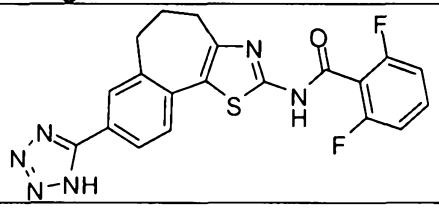
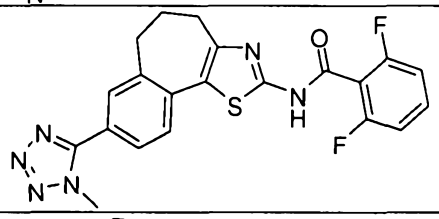
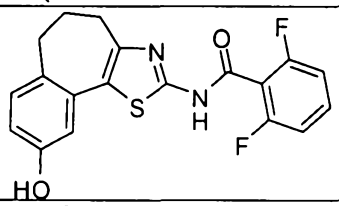
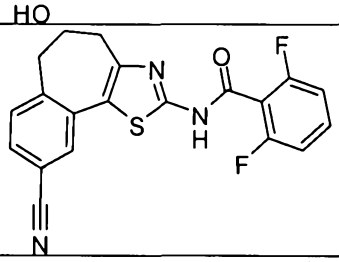
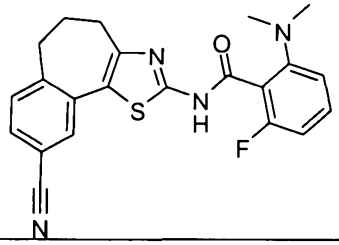
29	
30	
31	
32	
33	
34	
35	
36	

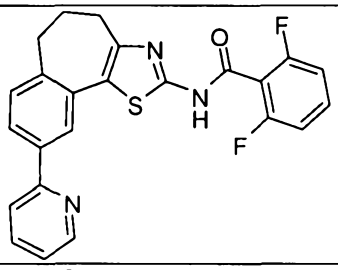
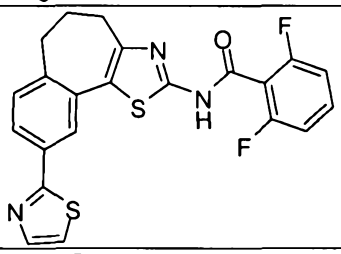
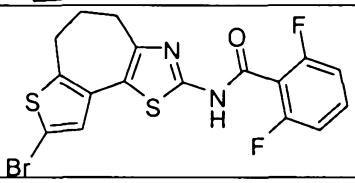
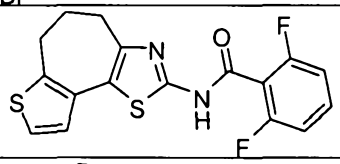
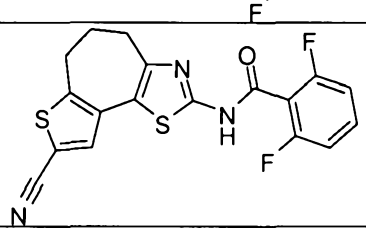
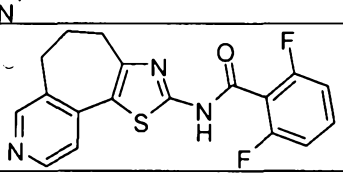
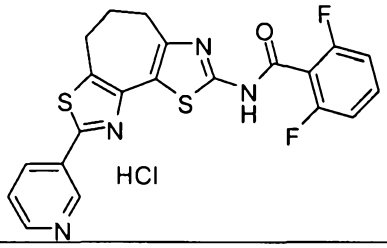
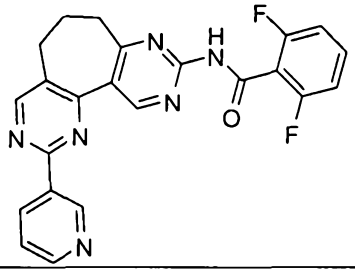
37	
38	
39	
40	
41	
42	
43	

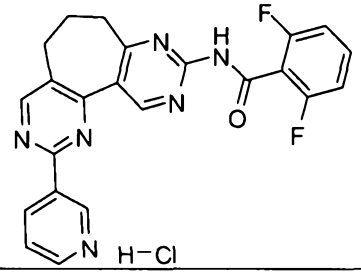
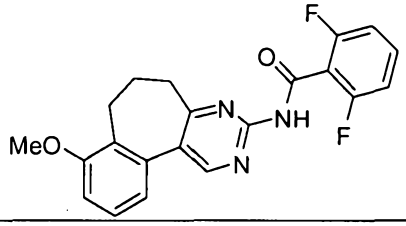
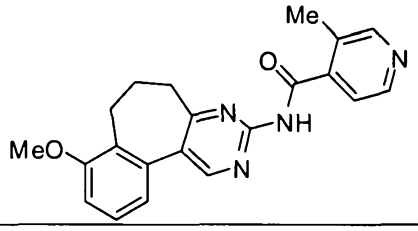
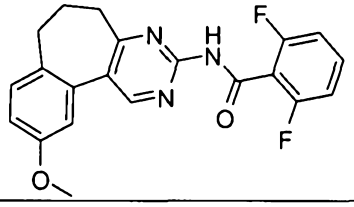
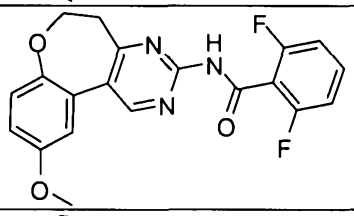
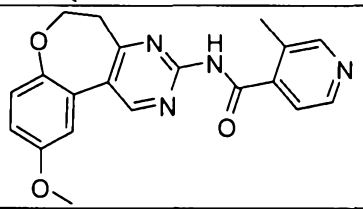
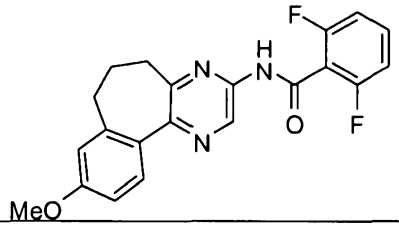
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	

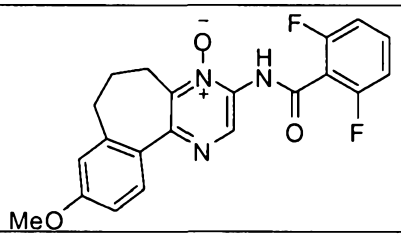
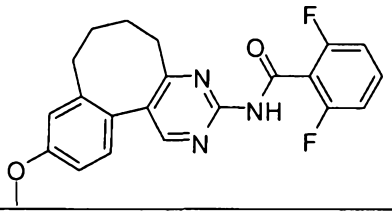
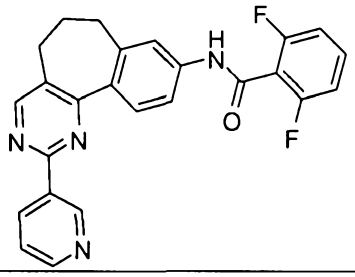
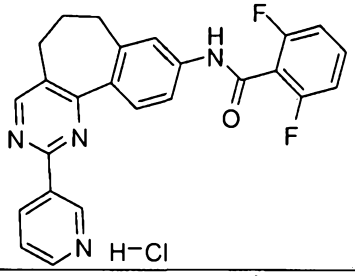
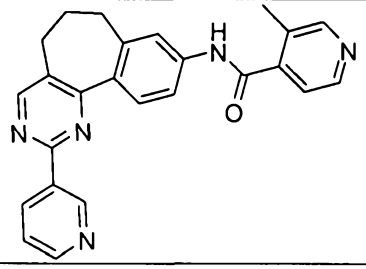
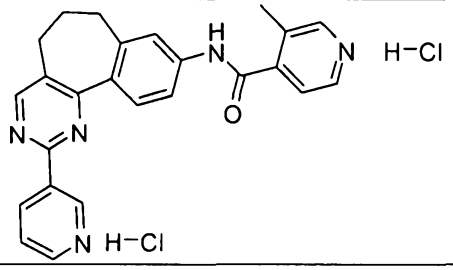
55	
56	
57	
58	
59	
60	
61	
62	
63	
64	

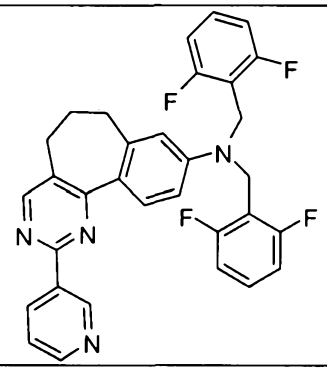
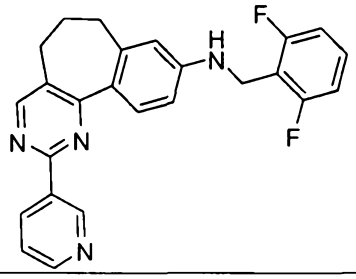
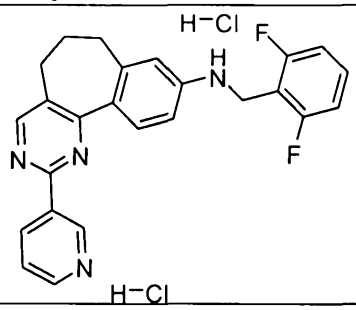
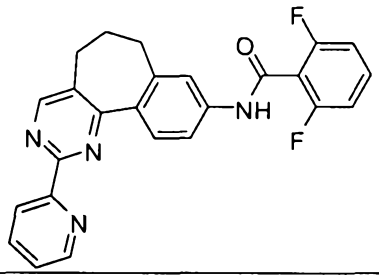
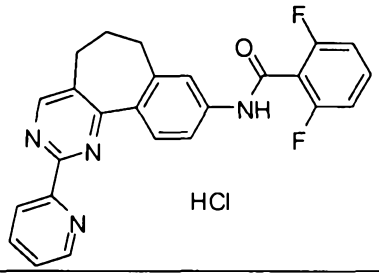
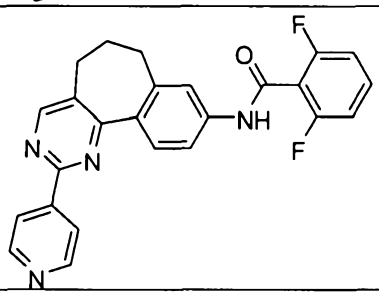
65	
66	
67	
68	
69	
70	
71	
72	
73	

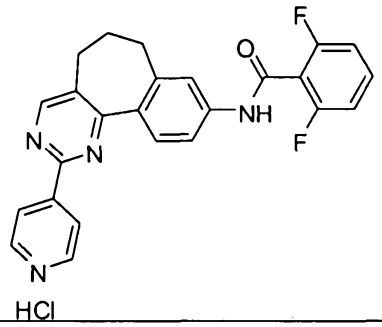
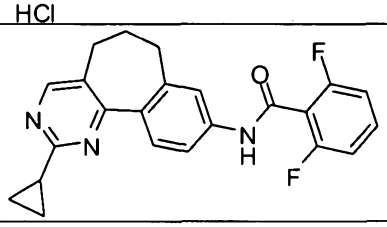
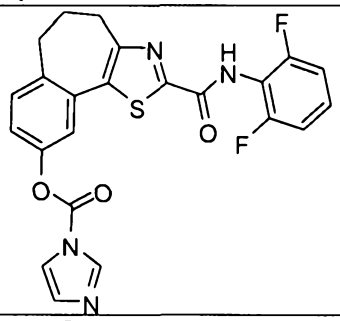
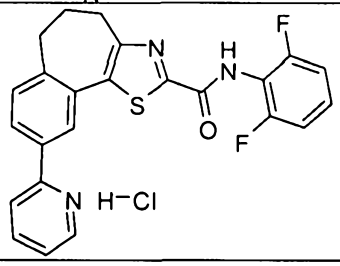
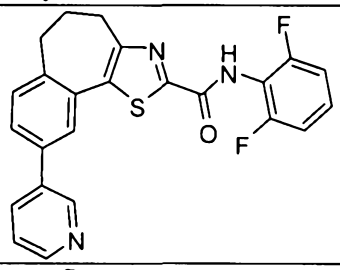
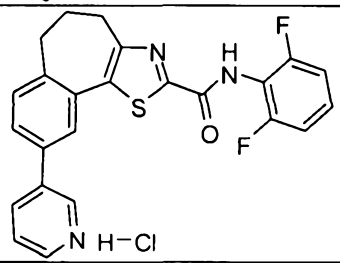
74	
75	
76	
77	
78	
79	
80	
81	

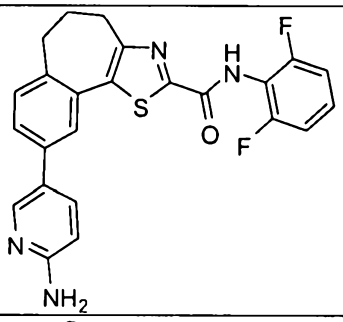
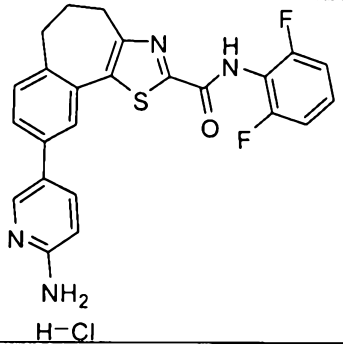
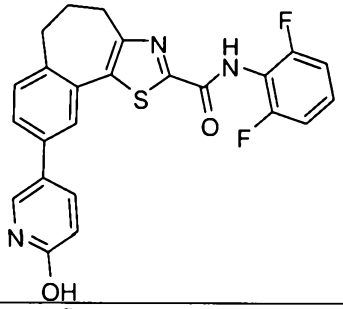
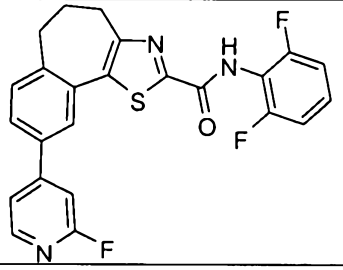
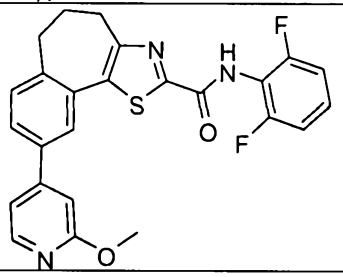
82	
83	
84	
85	
86	
87	
88	
89	

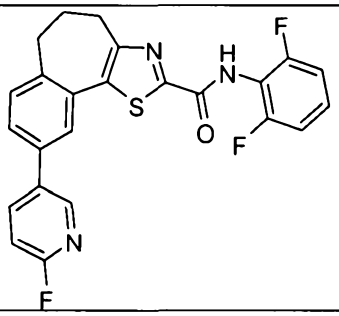
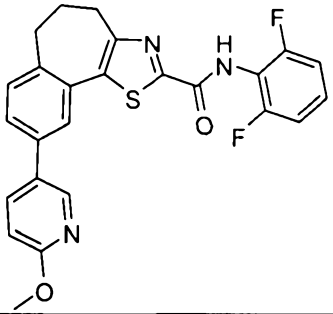
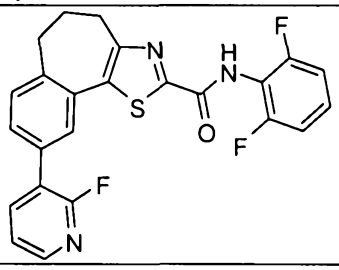
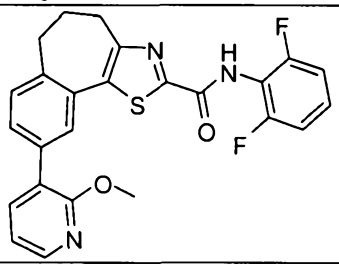
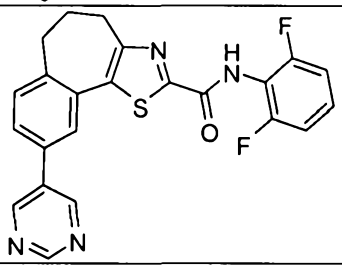
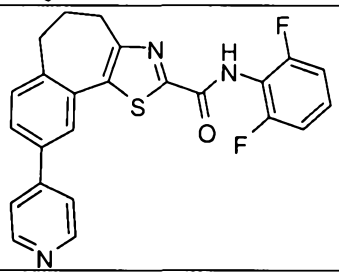
90	
91	
92	
93	
94	
95	
96	

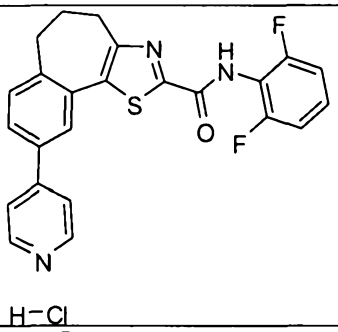
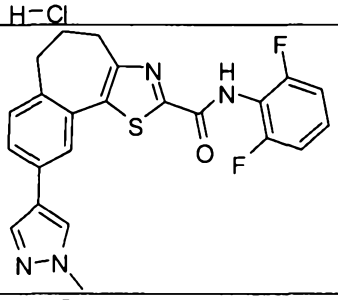
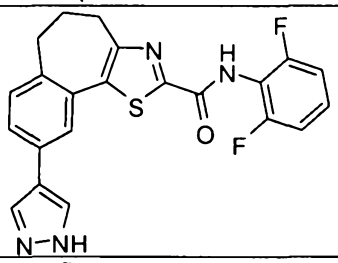
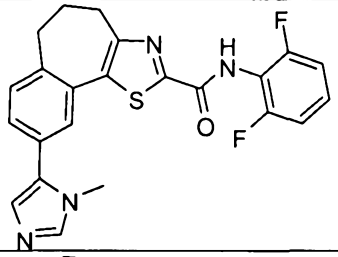
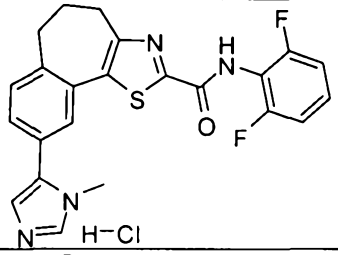
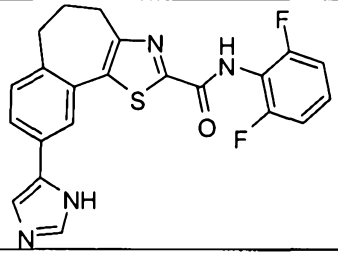
97	
98	
99	
100	
101	
102	

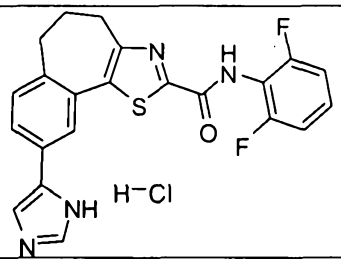
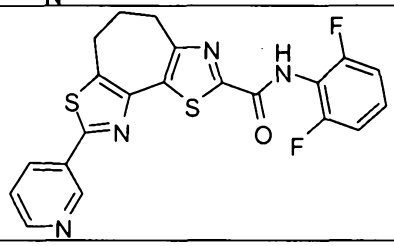
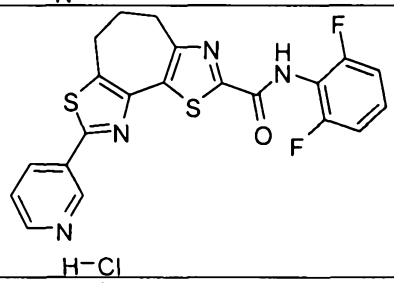
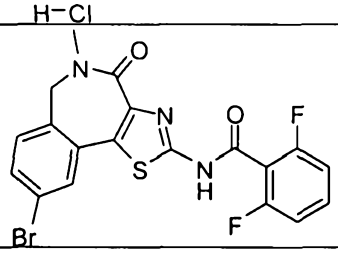
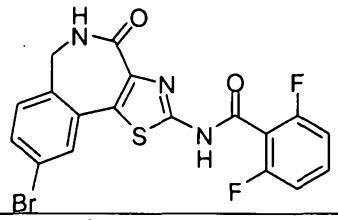
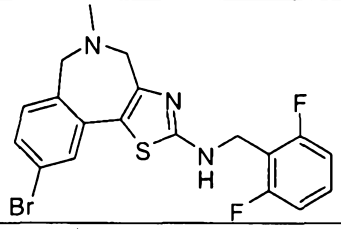
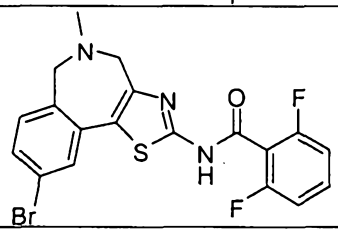
103	
104	
105	
106	
107	
108	

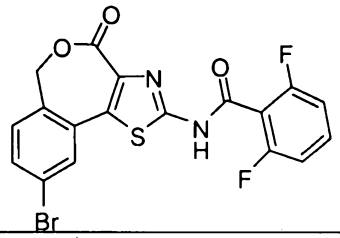
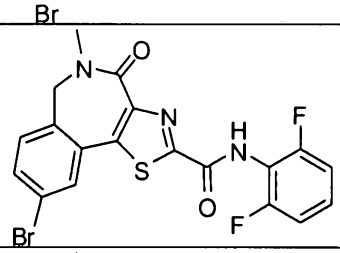
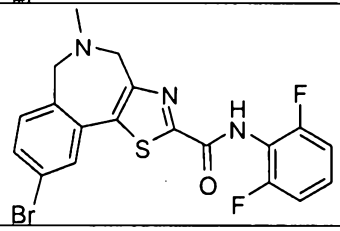
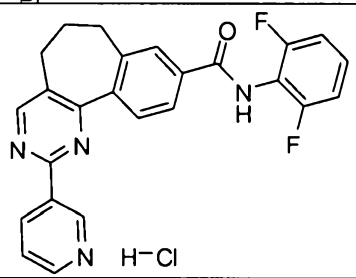
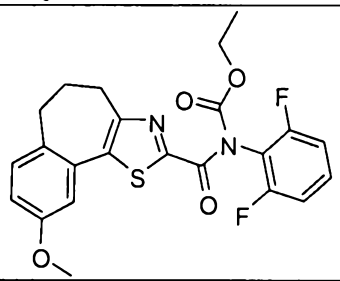
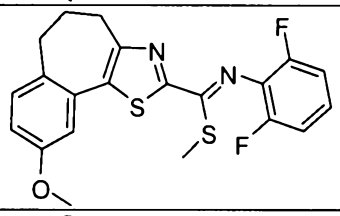
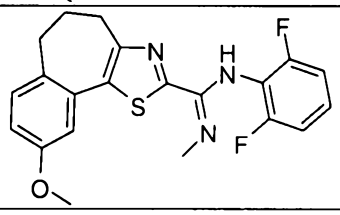
109	
110	
111	
112	
113	
114	

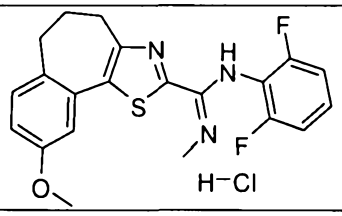
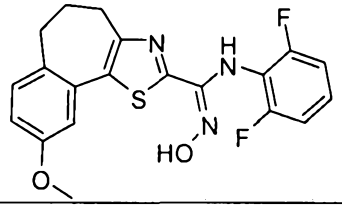
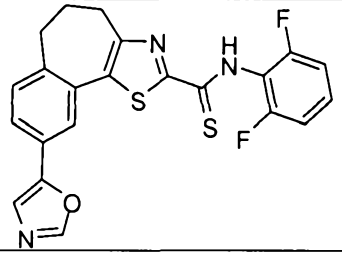
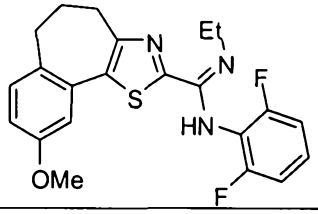
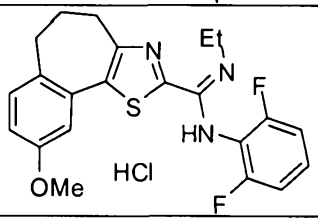
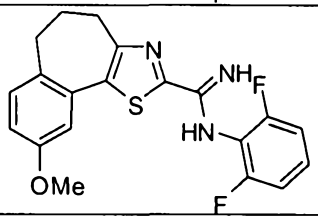
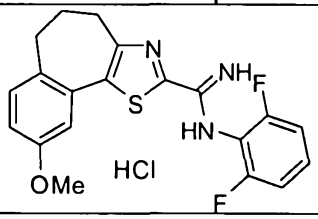
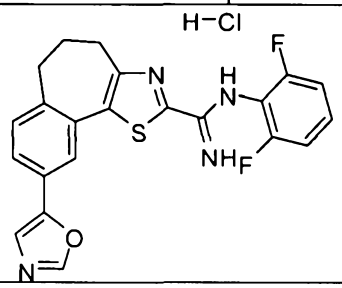
115	
116	
117	
118	
119	

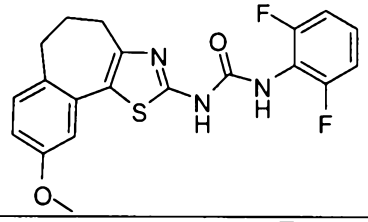
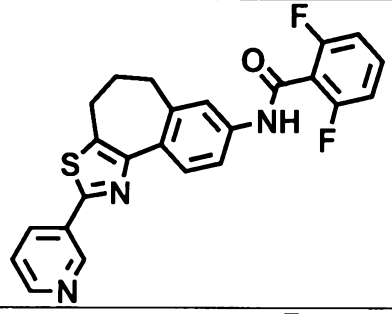
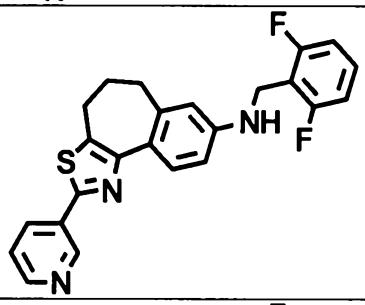
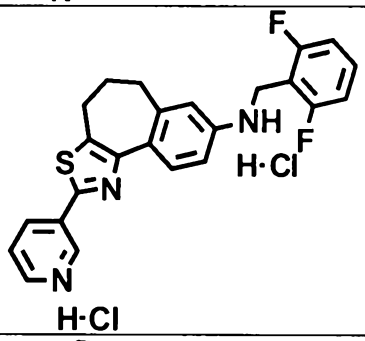
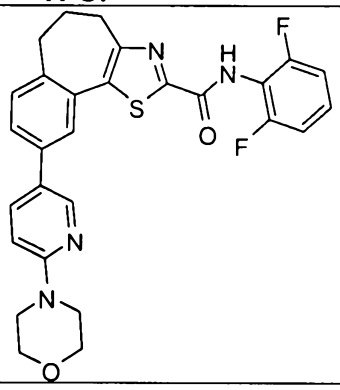
120	
121	
122	
123	
124	
125	

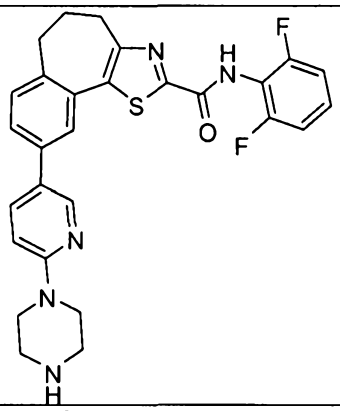
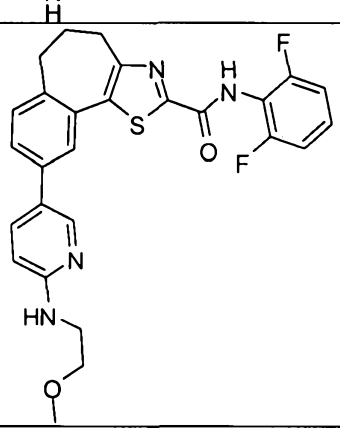
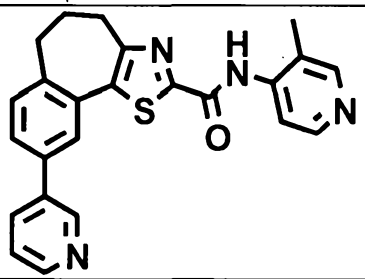
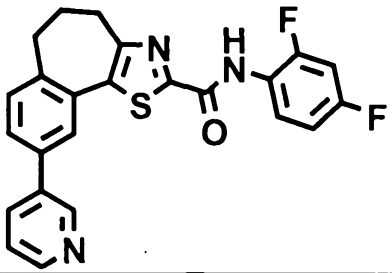
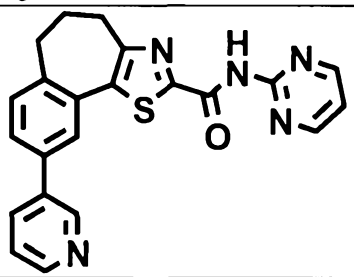
126	
127	
128	
129	
130	
131	

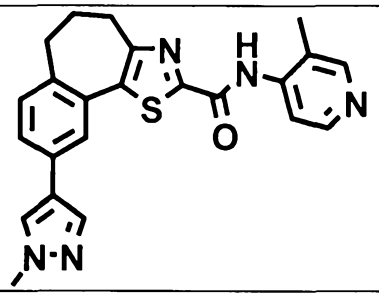
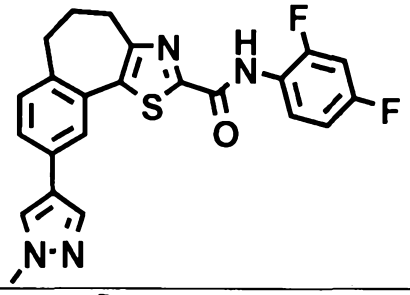
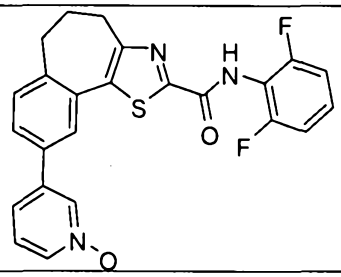
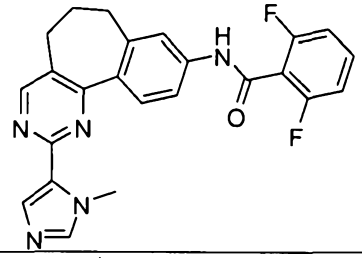
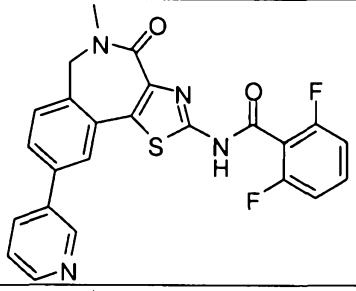
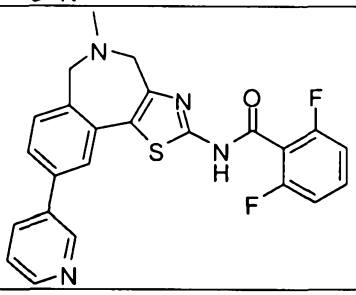
132	
133	
134	
135	
136	
137	
138	

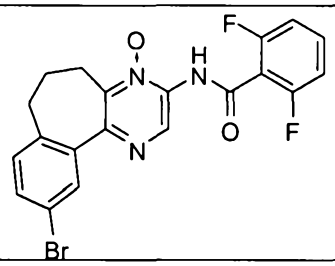
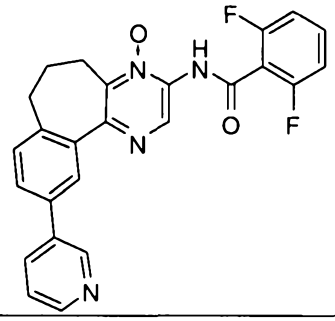
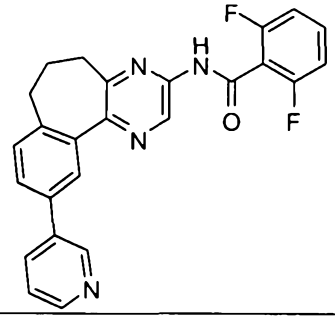
139	
140	
141	
142	
143	
144	
145	

146	
147	
148	
149	
150	
151	
152	
153	

154	
155	
156	
157	
158	

159	
160	
161	
162	
163	

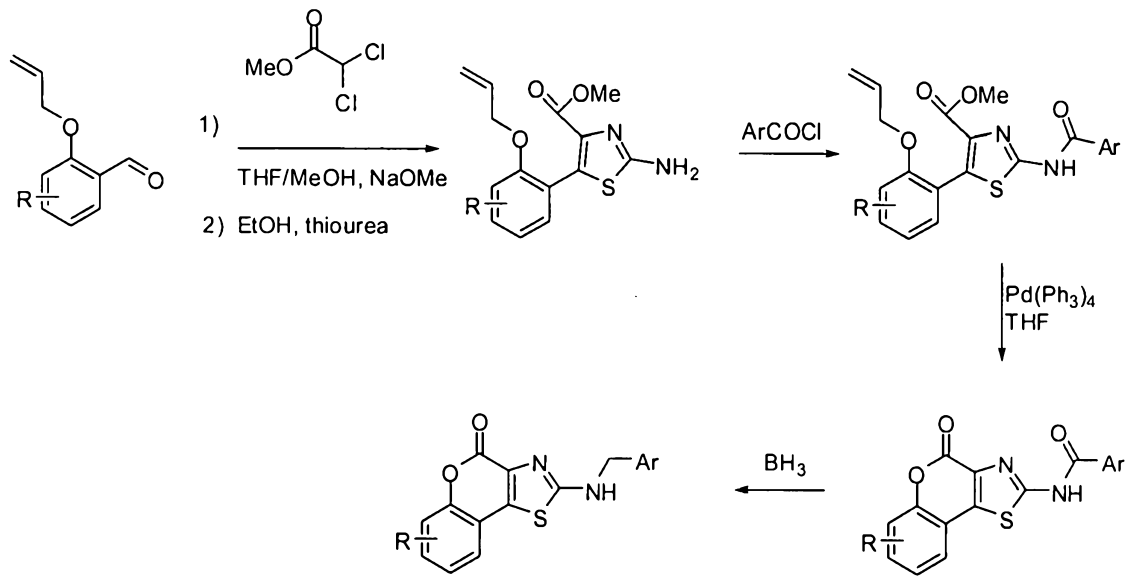
164	
165	
166	
167	
168	
169	

170	
171	
172	

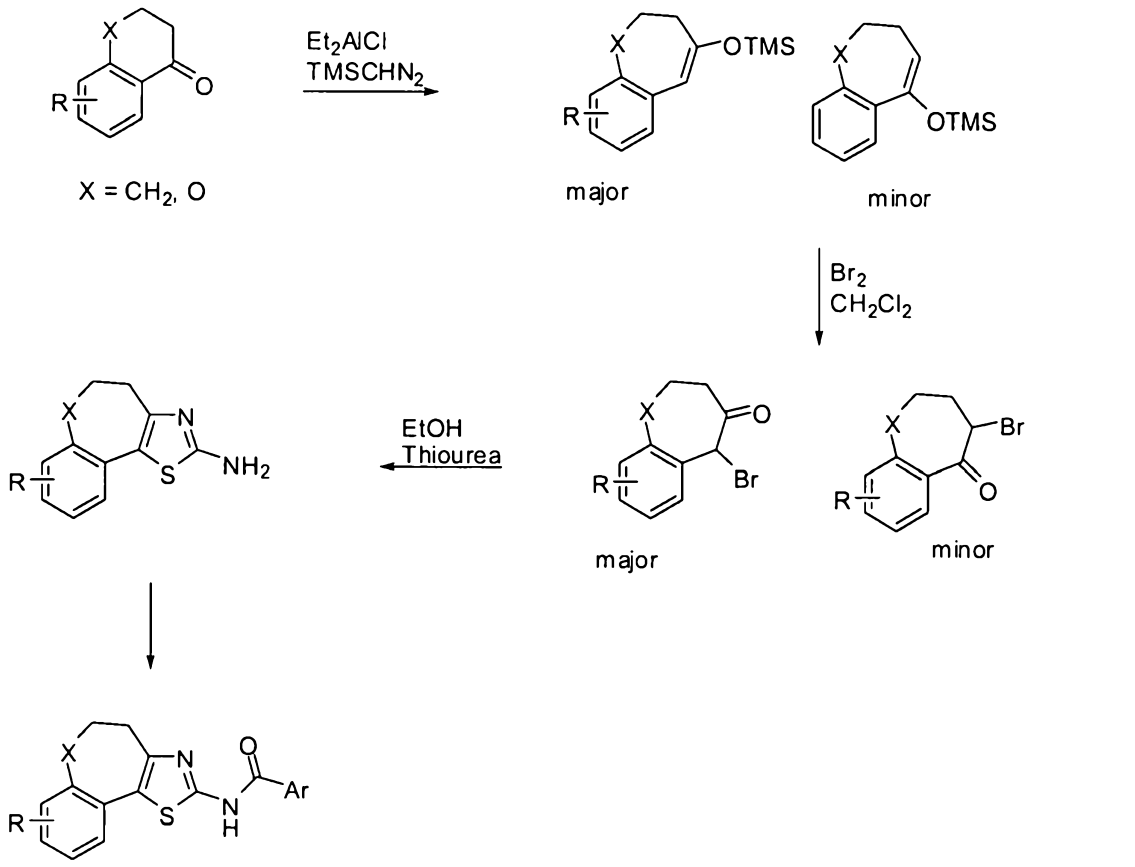
METHODS FOR MAKING COMPOUNDS OF THE INVENTION

Compounds of the invention can be obtained via standard, well-known synthetic methodology, see e.g., March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992. In particular, compounds of the invention can be obtained by the following reaction schemes.

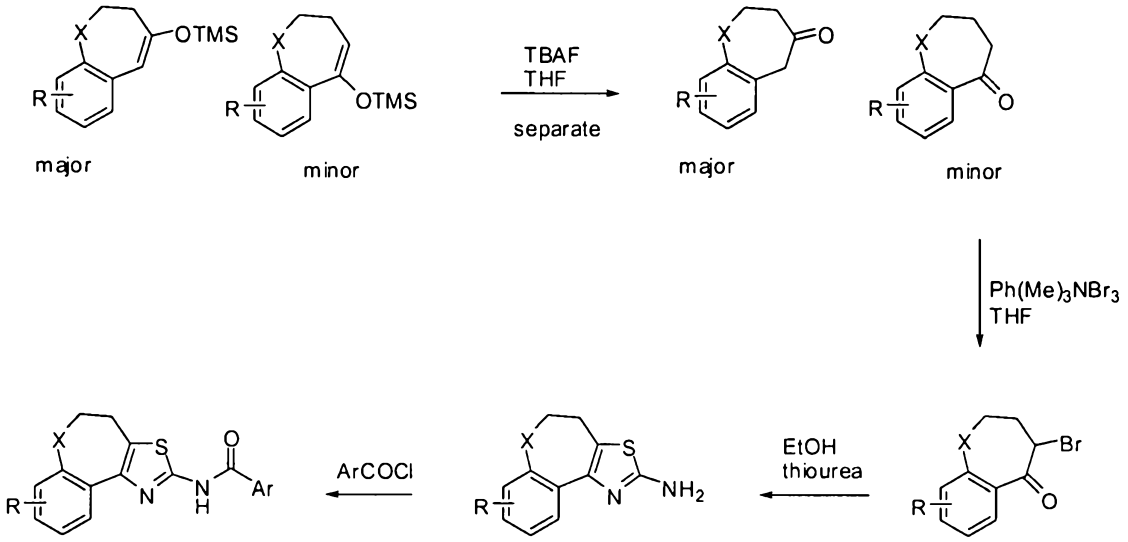
Scheme 1:



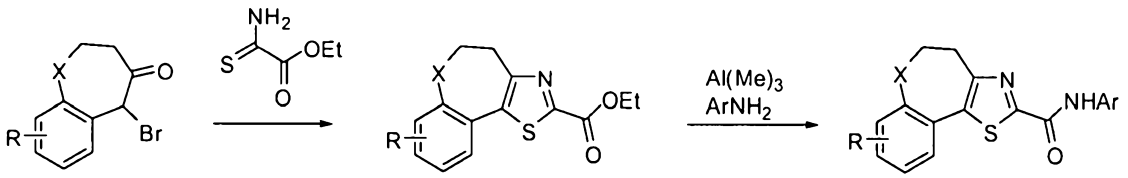
Scheme 2:



Scheme 3:



Scheme 4:



MECHANISM OF ACTION

Activation of T-lymphocytes in response to an antigen is dependent on calcium ion oscillations. Calcium ion oscillations in T-lymphocytes are triggered through stimulation of the T-cell antigen receptor, and involve calcium ion influx through the stored-operated Ca^{2+}-release-activated Ca^{2+} (CRAC) channel. Although the molecular structure of the CRAC ion channel has not been identified, a detailed electrophysiological profile of the channel exist. Thus, inhibition of CRAC ion channels can be measured by measuring inhibition of the I_{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 (XIV) 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 (XIV) 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 (XIV), or Table 1, or pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof can be assayed *in vitro* or *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, known animal models of inflammatory conditions, immune disorders, or allergic disorders can be used to demonstrate the safety and efficacy of compounds of this invention.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

Pharmaceutical compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form can be used for immunosuppression or to treat or prevent inflammatory conditions, immune disorders, and allergic disorders. Preferred pharmaceutical compositions and dosage forms comprise a compound of any one of formulas (I) through (XIV), 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 (XIV), 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 (XIV), 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.

5

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 formula (I) through (XIV), 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 (XIV), 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.

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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 antihistamine. 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 antagonists (such as aminopterin and methotrexate), antibiotics (such as rapamycin, actinomycin D, mitomycin C, puramycin, and chloramphenicol), human IgG, antilymphocyte globulin (ALG), and antibodies (such as anti-CD3 (OKT3), anti-CD4 (OKT4), anti-CD5, anti-CD7,

anti-IL-2 receptor, anti-alpha/beta TCR, anti-ICAM-1, anti-CD20 (Rituxan), anti-IL-12 and antibodies to immunotoxins).

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

OTHER EMBODIMENTS

The compounds of this invention may be used as research tools (for example, as a positive control for evaluating other potential CRAC inhibitors, or IL-2, IL-4, IL-5, IL-13, GM-CSF, TNF-α, and/or INF-α 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

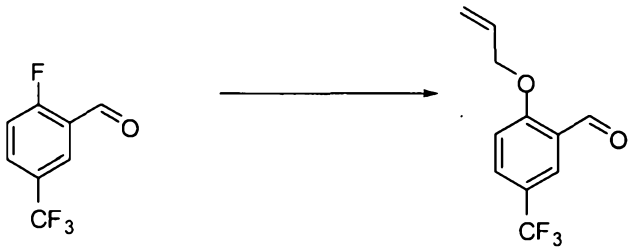
Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on

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:

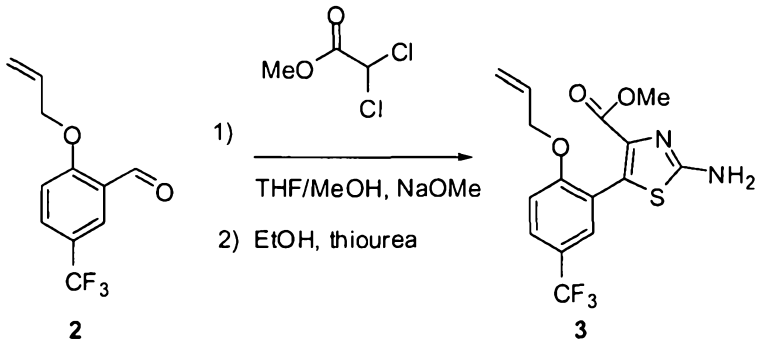


1 2

Into a solution of **1** (3.00g, 15.6 mmol) in allyl alcohol was added K_2CO_3 (2.80g, 20.0 mmol). The mixture was heated to 60° C for 5 hours, cooled to room temperature, taken up in ethyl acetate, washed with water, then with brine and dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with a solution of ethyl acetate: hexane, 1:19) to give **2** (2.15g, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.12 (d, J = 1.5 Hz, 1H), 7.76 (dd, J = 1.5, 8 Hz,

1H), 7.07 (d, J = 8 Hz, 1H), 6.18-5.84 (m, 1H), 5.36-5.16 (m, 2H), 4.75 (d, J = 6 Hz, 2H).

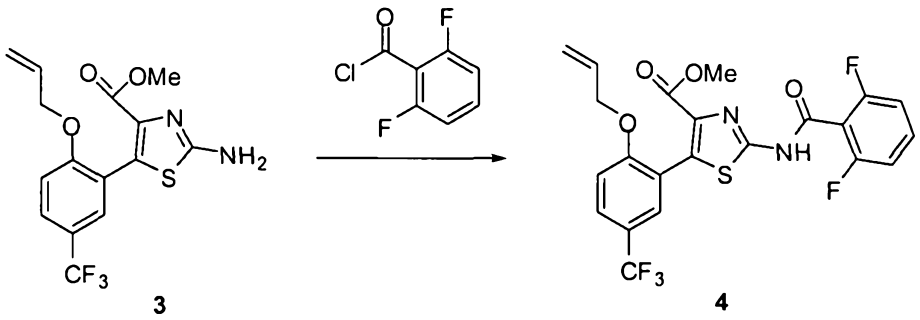


2 3

Into a mixture of 25% NaOMe in MeOH (2.30 mL, 10.0 mmol) and THF (40 mL) at -78°C was added dropwised a solution of **2** (2.15g, 9.34 mmol) and methyl dichloroacetate (1.43 g, 10.0 mmol) in THF (10 mL). The mixture was stirred at -78 °C for 3 hours, then at room temperature overnight. The reaction mixture was quenched with the addition of ice, extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), filtered and concentrated to give **3** (2.05g, 61% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8 Hz, 1H), 7.57 (s, 1H), 6.96 (d, J = 8 Hz, 1H), 5.92 (tdd, J = 5.4, 10.5, 17 Hz, 1H), 5.31 (d, J = 17 Hz, 1H), 5.23 (d, J = 10.5 Hz, 1H), 4.58 (d, J = 5.4, 2H), 3.70 (s, 3H).

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



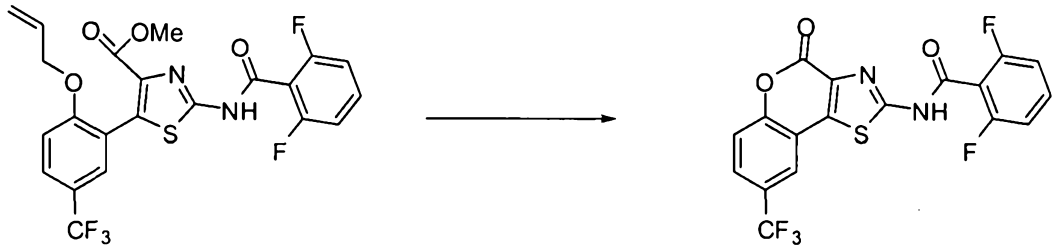
3 4

Into a solution of **3** (2.00g, 5.60 mmol), triethylamine (1.01g, 10.0 mmol), and catalytic amount of DMAP (20.0 mg, 0.16 mmol) in methylene chloride (20.0 mL) at room temperature was added 2,6-difluorobenzoylchloride. The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in MeOH (20.0 mL). K_2CO_3 (1.38g, 10.0 mmol) was added. The mixture was stirred at room temperature for 1 hour, diluted with methylene chloride, washed with water, dried (Na_2SO_4), filtered and concentrated. The

residue was purified on silica (eluted with methylene chloride) to give **4** (2.21g, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (bs, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56-7.46 (m, 1H), 7.07-7.01 (m, 3H), 5.94 (tdd, J = 5.4, 10, 17 Hz, 1H), 5.32 (d, J = 17 Hz, 1H), 5.26 (d, J = 10 Hz, 1H), 4.61 (d, J = 5.4, 2H), 3.71 (s, 3H).

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

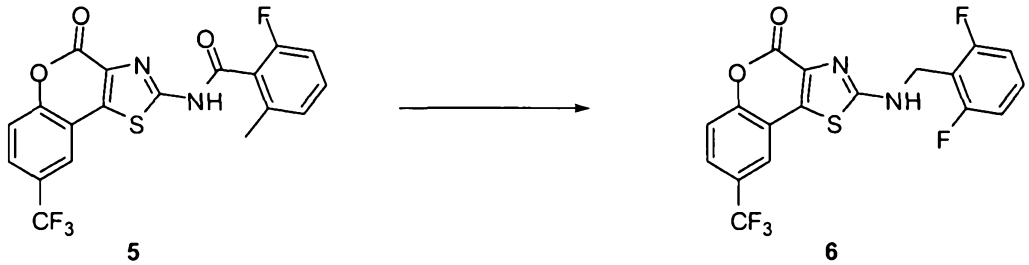


Into a solution of **4** (100 mg, 0.20 mmol) and pyrrolidine (36 mg, 0.5 mmol) in THF (2.0 mL) at room temperature was added palladium-tetrakis(triphenylphosphine) (20 mg, 0.02mmol). The mixture was degassed by vacuum/nitrogen-fill method (3x) then heated to 65 °C for 2 hours, cooled to room temperature, concentrated under reduced pressure. Into the residue, trifluoroacetic acid (1.0 mL) was added. The mixture was heated to 65 °C for 2 hours, cooled to room temperature, concentrated under reduced pressure. The residue was taken up in methylene chloride. The resulting solution was washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride) to give **5** (Compound 1)(67 mg, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.78 (dd, J = 1.9, 8.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.60-7.50 (m, 1H), 7.12-7.06 (m, 2H).

MS (ESI) [M+H$^+$]: 427

Compound 7:

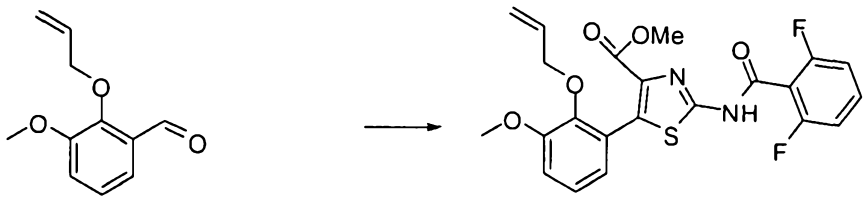


5 6 (Compound 7)

Into a solution of **5** (50.0 mg, 0.12 mmol) in THF at room temperature was added 1M borane-methyl sulfide complex in THF (0.5 mL, 0.5 mmol). The mixture was stirred at 60 °C overnight, cooled to room temperature, quenched with ice, extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride then with ethyl acetate) to give **6** (Compound 7)(11.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.34-7.26 (m, 1H), 7.15-6.93 (m, 2H), 6.20 (bs, 1H), 4.76 (d, J = 5.7 Hz, 2H).
MS (ESI) [M+H$^+$]: 413

Compound 2:



7 8

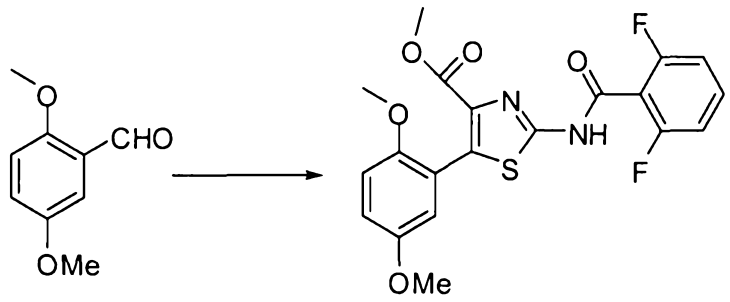
8 was prepared from aldehyde **7** as described for the preparation of **4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (bs, 1H), 7.54-7.44 (m, 1H), 7.13-6.91 (series of m, 5H), 5.84 (tdd, J = 6.0, 9.0, 17.1 Hz, 1H), 5.15 (d, J = 17.1 Hz, 1H), 5.18 (d, J = 9.0 Hz, 1H), 4.40 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.68 (s, 3H) .
MS (ESI) [M+H$^+$]: 461

9 (Compound 2) was prepared from **8** as described for the preparation of **5**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-6.90 (series of m, 6H), 4.95(s, 3H).
MS (ESI) [M+H$^+$]: 389

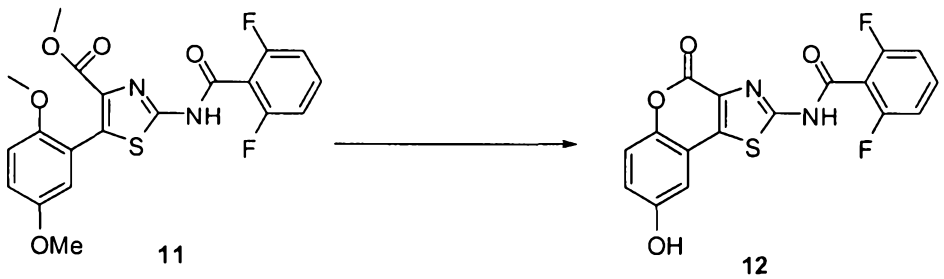
Compound 15:



10 **11**

11 was prepared from 2,5-dimethoxybenzaldehyde as described for the preparation of **4**.

^{1}H NMR (300 MHz, CDCl3+CD_3OD) δ 7.75-7.65 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.05 (br, 2H), 6.99 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H).
MS (ESI) [M+H$^+$]: 435.



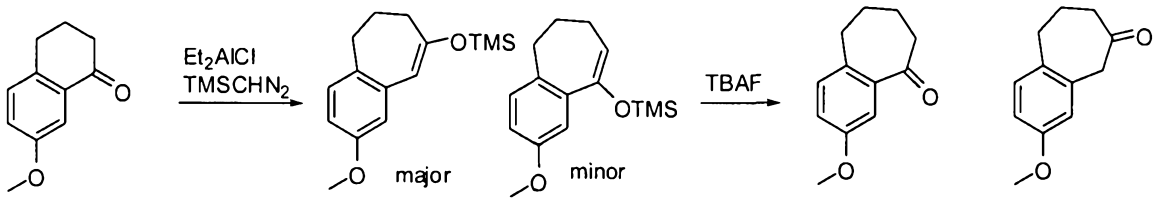
11 **12 (Compound 15)**

12 (Compound 15)

Into a solution of **11** (434 mg, 1 mmol) in CH_2Cl_2 (15.0 mL) at –78°C under N_2 was added dropwised BBr_3 (1M solution in CH_2Cl_2, 2.0 mmol). The solution was stirred at –78°C for 1 hour, warmed to room temperature for overnight. The reaction mixture was quenched with ice water, acidified with 1N HCl and extracted with methylene chloride (2X). The solution was treated with 0.1 mL of TFA and stirred at room temperature for 30 minutes. The solution was evaporated under reduced pressure. The residue was recrystallized in MeOH to give **12** (Compound 15)(230 mg, 61%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (brs, 1H, NH), 7.75-7.65 (m, 1H), 7.38 (d, J = 9.1 Hz, 1H), 7.33 (t, J = 8.2 Hz, 2H), 7.14 (d, J = 2.2 Hz, 1H), 7.03 (dd, J = 9.1, 2.2 Hz, 1H). MS (ESI) [M+H$^+$]: 375.

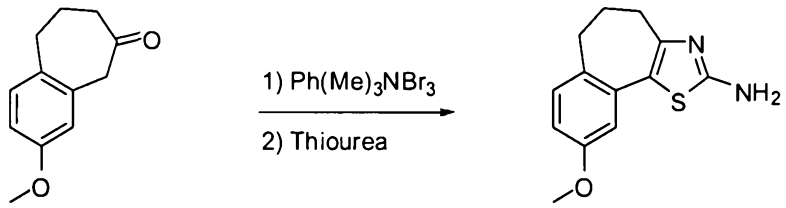
Compound 8:



Into a solution of **13** (1.76g, 10.0 mmol) in methylene chloride (20.0 mL) at 0 °C was added dropwised a solution of 1 M diethylaluminum chloride in hexane (15.0 mL, 15.0 mmol), followed by a solution of 2M (trimethylsilyl)diazomethane in diethyl ether (7.50 mL, 15.0 mmol). The mixture was stirred at 0 °C for 10 minutes, quenched by addition of ice, acidified with 1N HCl, extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was filtered through a short plug of silica (eluted with a solution of ethyl acetate: hexane, 1:9) to give a crude 9:1 mixture of **14**:**15** respectively (2.91g). The mixture was taken up in THF (40 mL), cooled to 0 °C. Into the mixture, a solution of 1M TBAF in THF was added (12.0 mL, 12.0 mmol). The resulting solution was stirred at 0 °C for 10 minutes, quenched with ice, extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with a solution of ethyl acetate: hexane, 1:9) to give **16** (168 mg) followed by **17** (1.12g).

16: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 2.5 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 2H), 2.90-2.84 (m, 2H), 2.58-2.52 (m, 2H), 2.00-1.91 (m, 2H).

17: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 1H), 6.74-6.66 (m, 2H), 6.73 (dd, J = 2.7, 8.4 Hz, 1H), 3.83 (s, 3H), 2.83-2.75 (m, 4H), 2.13-2.04 (m, 2H).

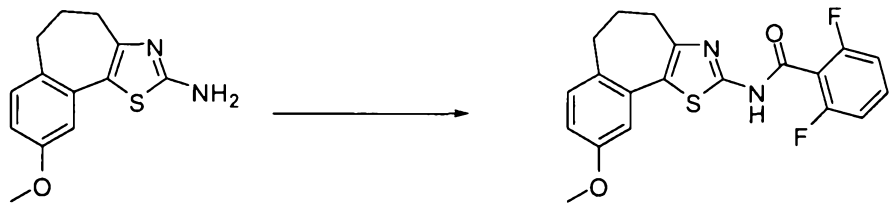


17 18

Into a solution of **17** (1.12g, 5.86mmol) in THF (20 mL) at 0 °C was added phenyltrimethylammonium tribromide (2.20g, 5.86 mmol). The mixture was stirred at 0 °C for 1 hour, quenched by ice addition, extracted with methylene chloride (2X). The combined extracted was dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with methylene chloride) to give **18** (780mg).

18 can also be prepared by direct bromination of the mixture of the enol silyl ether **14** and **15**, followed by cyclization with thiourea.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.7 Hz, 1H), 6.60 (dd, J = 2.7, 8.4 Hz, 1H), 3.75 (s, 3H), 2.87-2.62 (m, 4H), 2.02-1.90 (m, 2H).
MS (ESI) [M+H$^+$]: 247



18 19 (Compound 8)

19 (Compound 8) was prepared from **18** as described for the preparation of **4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.39 (m, 1H), 7.06-6.94 (m, 4H), 6.73 (dd, J = 2.4, 8.4 Hz, 1H), 3.83 (s, 3H), 2.65-2.47 (m, 4H), 1.95-1.82 (m, 2H).
MS (ESI) [M+H$^+$]: 387

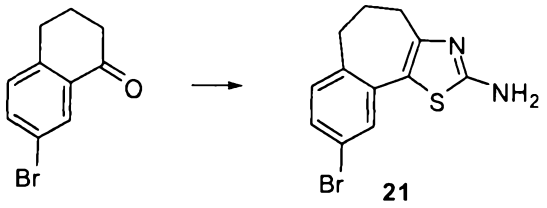
Compound 3:

20 (Compound 3) was prepared from **18** as described for the preparation of **4** using the

corresponding acid chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 2.7 Hz, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.05 (dd, J = 5.4, 6.0 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.74 (dd, J = 2.7, 8.4 Hz, 1H), 3.82 (s, 3H), 3.00 (dd, J = 6.6, 7.2 Hz, 2H), 2.78-2.74 (m, 2H), 2.20-2.10 (m, 2H).
MS (ESI) [M+H$^+$]: 370

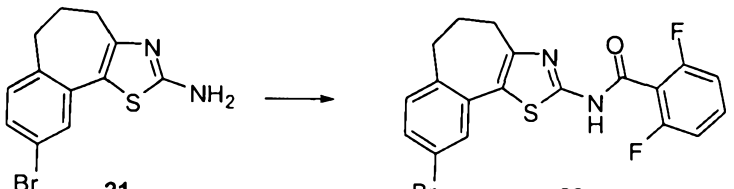
Compound 17:



21

21 was prepared from 7-bromo-1-tetralone as described for the preparation of **18**.

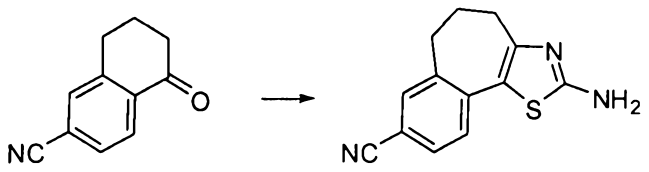
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 1.9 Hz, 1H), 7.19 (dd, J = 8.0, 1.9 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 2.90 (t, J = 6.9 Hz, 2H), 2.83-2.74 (m, 2H), 2.02-1.94 (m, 2H).
MS (ESI) [M+H$^+$]: 297, 295.



22 (Compound 17) was prepared from **21** as described for the preparation of **4.**

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (brs, 1H, NH), 7.68 (d, J = 1.9 Hz, 1H), 7.53-7.43 (m, 1H), 7.28 (dd, J = 8.0, 1.9 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 2H), 2.77-2.69 (m, 2H), 2.07-1.94 (m, 2H).
MS (ESI) [M+H$^+$]: 437, 435.

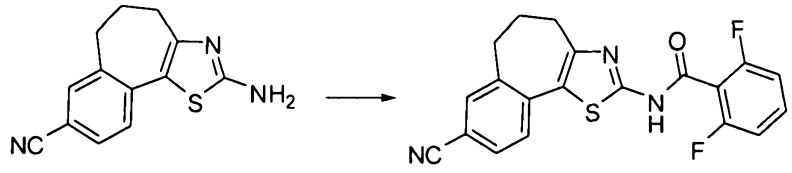
Compound 59:



23

23 was prepared from 6-nitrile-1-tetralone as described for the preparation of **18**.

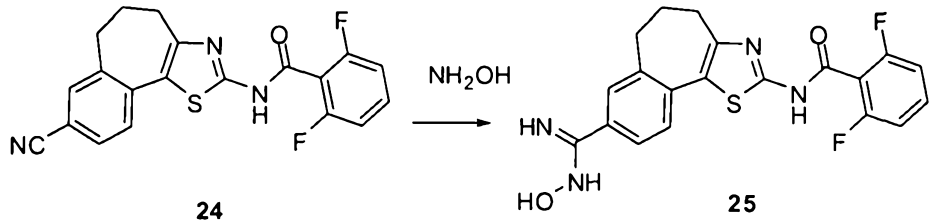
^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.58 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H) 3.04 (t, J = 7.0 Hz, 2H), 2.96-2.92 (m, 2H), 2.13-2.05 (m, 2H).
MS (ESI) [M+H$^+$]: 242.



23 24 (Compound 59)

24 (Compound 59) was prepared from **23** as described for the preparation of **4**.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 1H), 7.54-7.45 (m, 3H), 7.01 (t, J = 8.2 Hz, 2H), 2.78-2.74 (m, 2H), 2.66 (t, J = 7.2 Hz, 2H), 1.99-1.91 (m, 2H).
MS (ESI) [M+H$^+$]: 382.

Compound 60:

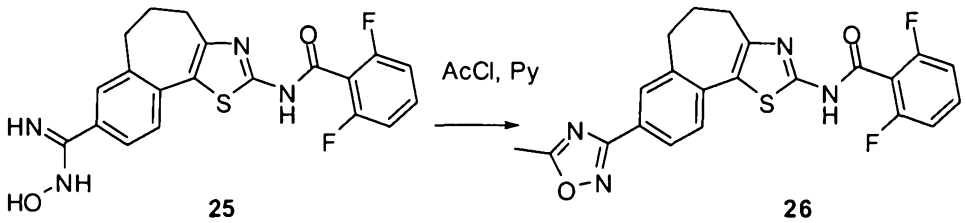


24 25

Into a solution of **24** (38.1 mg, 0.1 mmol) in 5 mL of MeOH was added hydroxyamine hydrochloride (21 mg, 0.3 mmol) and $NaHCO_3$ (50 mg, 0.6 mmol). The mixture was heated to reflux for 5 hours. After the reaction was cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was taken up with 20 mL of Et_2O. The solution was washed with a solution of saturated NH_4Cl, dried (Na_2SO_4), filtered and

concentrated. The residue was purified by flash chromatography on silica gel (eluted with ethyl acetate-hexane mixtures) to give **25** (36 mg) as a white solid.

MS (ESI) [M+H$^+$]: 415.



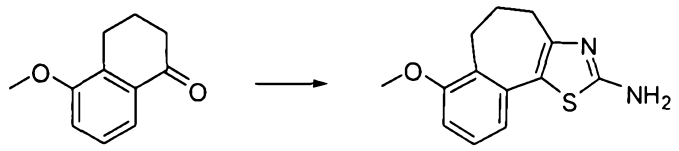
25 **26 (Compound 60)**

Into a solution of **25** (21 mg, 0.05 mmol) in 1 mL of AcCl was added 0.1 mL of pyridine. The mixture was heated at 100°C for 3 hours under N_2. The reaction was concentrated under reduced pressure. The residue was taken up with 10 mL of Et_2O, the solution was washed with a saturated solution of $NaHCO_3$ then with a saturated solution of NH_4Cl. The organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluted with ethyl acetate-hexane mixtures) to give **26** (Compound 60)(12 mg, 55%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (br s, 1H, NH), 7.91 (dd, J = 8.2, 1.8 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.54-7.45 (m, 1H), 7.04 (t, J = 8.2 Hz, 2H), 2.92-2.81 (m, 4H), 2.68 (s, 3H), 2.09-2.01 (m, 2H).

MS (ESI) [M+H$^+$]: 439.

Compound 12:

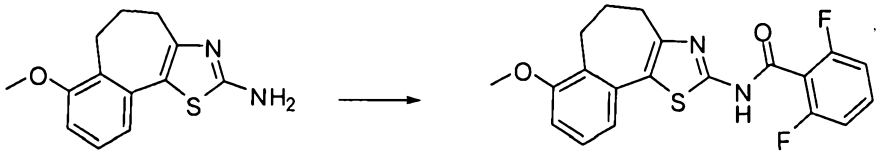


27

27 was prepared from 5-methoxy-1-tetralone as described for the preparation of **18**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 2H, NH_2), 7.20 (t, J = 8,0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.00-2.92 (m, 4H), 2.04-1.96 (m, 2H).

MS (ESI) [M+H$^+$]: 247.



27 28 (Compound 12)

28 (Compound 12) was prepared from **27** as described for the preparation of **4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.40 (m, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.00 (t, d = 8.2 Hz, 2H), 6.82 (d, J = 7.7 Hz, 1H), 3.85 (s, 3H), 2.81-2.77 (m, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.02-1.94 (m, 2H).
MS (ESI) [M+H$^+$]: 387.

29 to **38** were prepared similarly from **27** as described for the preparation of **4** using the corresponding acid chloride.

Compound 13:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.54 (d, J = 5.0 Hz, 1H), 7.36 (d, J = 5.0 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 3.85 (s, 3H), 2.80-2.76 (m, 2H), 2.52 (s, 3H), 2.49 (t, J = 7.3 Hz, 2H), 2.03-1.94 (m, 2H).
MS (ESI) [M+H$^+$]: 366.

Compound 14:

^{1}H NMR (300 MHz, $CDCl_3$) δ .8.62 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 4.9 Hz, 1H), 7.93 (dd, J = 6.1, 5.2 Hz, 1H), 7.12 (dd, J = 7.9, 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 3.77 (s, 3 H), 2.85 (t, J = 7.1 Hz, 2H), 2.80-2.76 (m, 2H), 2.04-1.94 (m, 2H). MS (ESI) [M+H$^+$]: 370.

Compound 43:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 4.2 Hz, 1H), 9.40 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.81 (dt, J = 1.1, 8.6 Hz, 1H), 7.65 (dt, J = 1.1, 8.6 Hz, 1H), 7.23 (d, J = 4.2 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.79-2.75 (m, 2H), 2.51 (t, J = 7.2 Hz, 2H), 1.94-1.86 (m, 1H). MS (ESI) [M+H$^+$]: 402.

Compound 46:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (dd, J = 4.7, 1.9 Hz, 1H), 8.21 (dd, J = 6.7, 1.9 Hz, 1H), 7.42 (dd, J = 6.7, 4.7 Hz, 1H), 7.20 (dd, J = 8.0, 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.83 (dd, J = 8.0, 1.1 Hz, 1H), 3.86 (s, 3H), 2.84-2.80 (m, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.10-2.00 (m, 2H). MS (ESI) [M+H$^+$]: 386.

Compound 49:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 8.0, 7.9 Hz, 1H), 7.13 (dd, J = 8.0, 1.1 Hz, 1H), 6.83 (dd, J = 7.9, 1.1 Hz, 1H), 3.86 (s, 3H), 2.85-2.81 (m, 2H), 2.73 (t, J = 7.1 Hz, 2H), 2.09-2.00 (m, 2H). MS (ESI) [M+H$^+$]: 420.

Compound 47:

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.44 (dd, J = 2.2, 1.9 Hz, 1H), 7.22 (dd, J = 8.0, 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.91-2.86 (m, 4H), 2.12-2.02 (m, 2H). MS (ESI) [M+H$^+$]: 432, 430.

Compound 50:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.2 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.1 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 2.86-2.84 (m, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.10-2.02 (m, 2H).
MS (ESI) [M+H$^+$]: 438.

Compound 48:

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.19 (dd, J = 8.0, 7.7 Hz, 1H), 7.11 (dd, J = 7.7, 1.1 Hz, 1H), 6.82 (dd, J = 8.0, 1.1 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 2.92 (t, J = 7.3 Hz, 1H), 2.89-2.84 (m, 2H), 2.13-2.05 (m, 2H).
MS (ESI) [M+H$^+$]: 389.

Compound 45:

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.95 (br s, 1H, NH), 7.20 (dd, J = 8.0, 7.7 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.87-2.80 (m, 4H), 2.69 (s, 3H), 2.53 (s, 3H), 2.12-2.04 (m, 2H).
MS (ESI) [M+H$^+$]: 370.

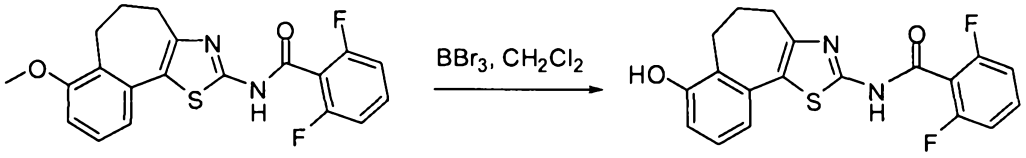
Compound 44:

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (br s, 1H, NH), 7.22 (dd, J = 8.0, 7.7 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.42 (s, 1H), 3.85 (s, 3H), 2.91-2.83 (m, 4H), 2.40 (s, 3H),

2.14-2.06 (m, 2H).

MS (ESI) [M+H$^+$]: 423.

Compound 51:

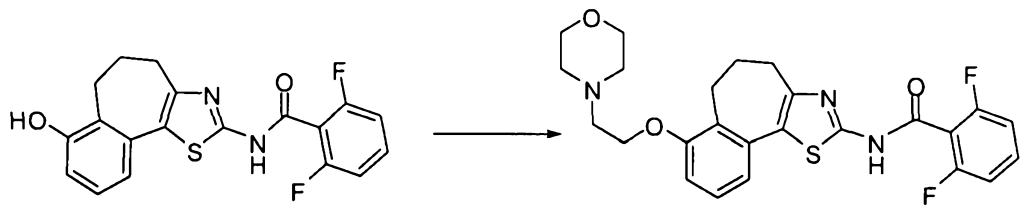


28 **39 (Compound 51)**

To a solution of **28** (386 mg, 1 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added a solution of 1 M BBr_3 in CH_2Cl_2 (2.0 mL, 2.0 mmol). The mixture was kept at -78°C for 30 minutes then to 0° C for 1.5 hours. The mixture was quenched by addition of a saturated solution of $NaHCO_3$, diluted with ethyl acetate. The organic layer was washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by a flash chromatography on silica gel (eluted with ethyl acetate-hexane mixtures) to give **39** (Compound 51)(353 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.40 (m, 1H), 7.08-6.84 (m, 4H), 6.75 (dd, J = 6.4, 2.8 Hz, 1H), 2.76-2.72 (m, 2H), 2.57 (t, J = 6.9 Hz, 2H), 2.00-1.92 (m, 2H). MS (ESI) [M+H$^+$]: 373.

Compound 52:



39 **40 (Compound 52)**

40

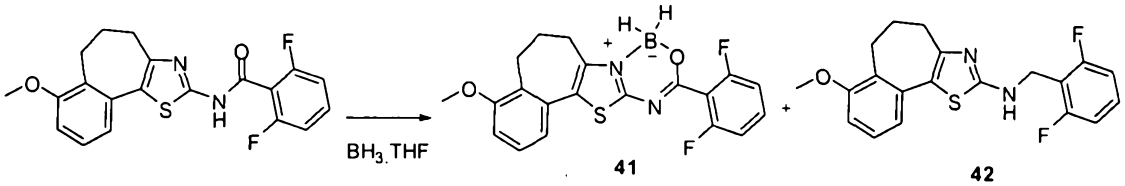
Into a solution of **39** (18.2 mg, 0.05 mmol) in THF (3.0 mL) at room temperature was added 4-(2-chloroethyl)morpholine hydrochloride (18.6 mg, 0.1 mmol) and K_2CO_3 (20 mg, 0.14 mmol), the solution was stirred at reflux for 3 hours, cooled to room temperature, diluted with 10 mL of Et_2O and washed with water. The organic phase was dried (Na_2SO_4), filtered and evaporated. The residue was purified on silica (eluted with ethyl acetate-hexane mixtures) to

give **40** (Compound 52)(15.0 mg, 62%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.42 (m, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 8.2 Hz, 2H), 6.70 (d, J = 7.2 Hz, 1H), 4.21 (t, J = 6.6 Hz, 2H), 3.58 (br, 4H), 2.97 (t, J = 7.2 Hz, 2H), 2.86-2.82 (m, 2H), 2.65 (t, J = 6.6 Hz, 2H), 2.31 (br, 4H), 2.20-2.12 (m, 2H).

MS (ESI) [M+H$^+$]: 486.

Compound 61:



28 **41** **42 (Compound 61)**

Into a solution of **28** (38.6 mg, 0.10 mmol) in THF at room temperature was added a solution of 1M borane-THF complex in THF (0.5 mL, 0.5 mmol). The mixture was stirred at reflux for 2 hours. The reaction was cooled to room temperature, quenched with ice, extracted with methylene chloride. The extracted was washed with water, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica (eluted with ethyl acetate-hexane mixtures) to give **41** (32.0 mg) as a white solid, followed by **42** (Compound 61)(3.8 mg).

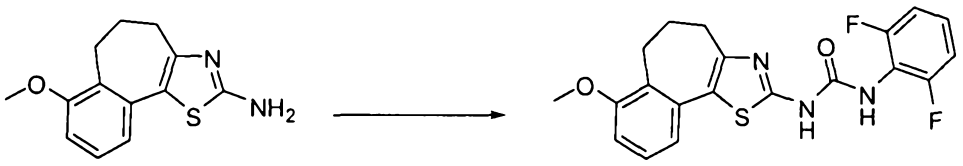
41: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.35 (m, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 7.7 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.93-2.86 (m, 4H), 2.16-2.07 (m, 2H).

MS (ESI) [M+H$^+$]: 399.

42: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.96-6.88 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 5.37 (br s, 1H, NH), 4.57 (s, 2H), 3.82 (s, 3H), 2.89-2.84 (m, 4H), 2.05-1.96 (m, 2H).

MS (ESI) [M+H$^+$]: 373.

Compound 63:



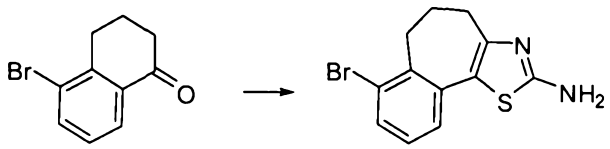
27 43 (Compound 63)

A solution of **27** (50 mg, 0.2 mmol) and 2,6-difluorophenyl isocyanate (32 mg, 0.2 mmol) in 3 mL of toluene was heated to 60°C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica (eluted with ethyl acetate-hexane mixtures) to give **43** (Compound 63)(61 mg, 76%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.14 (m, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 2H), 6.79 (d, J = 8.0 Hz, 1H), 2.93 (t, J = 7.1 Hz, 2H), 2.89-2.86 (m, 2H), 2.13-2.05 (m, 2H).

MS (ESI) [M+H$^+$]: 402.

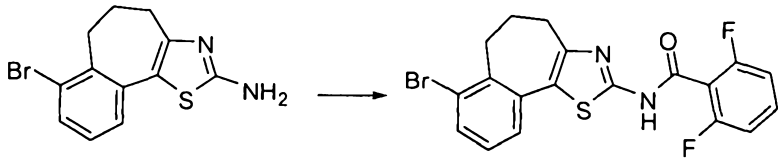
Compound 54:



45

45 was prepared from 5-bromo-1-tetralone similarly as described for the preparation of **18**.

MS (ESI) [M+H$^+$]: 295, 297.



45 **46 (Compound 54)**

46 (Compound 54) was prepared from **45** as described for the preparation of **4.**

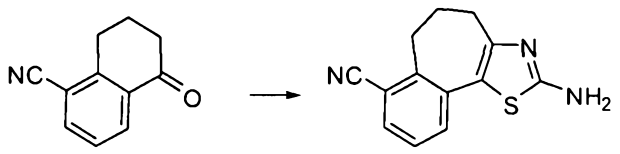
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (br s, 1H, NH), 7.50-7.39 (m, 3H), 7.10 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 8.2 Hz, 2H), 2.88-2.84 (m, 2H), 2.36 (dd, J = 7.3 Hz, 2H), 1.99-1.90 (m, 2H).
MS (ESI) [M+H$^+$]: 437, 435.

Compound 55:

(Compound 55) was prepared as described for the preparation of **4** using the corresponding acid chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.55 (d, J = 5.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.09 (t, J = 8.0 Hz, 1H), 2.97-2.93 (m, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.53 (s, 3H), 2.05-1.97 (m, 2H).
MS (ESI) [M+H$^+$]: 416, 414.

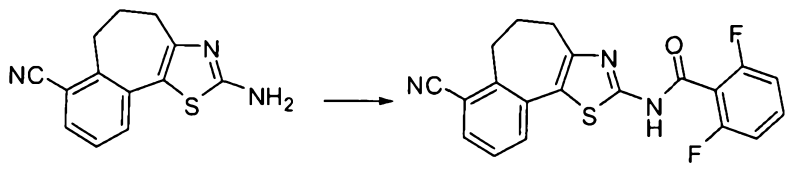
Compound 56:



48

48 was prepared from 5-nitrile-1-tetralone as described for the preparation of **18**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.26 (t, J = 8.0 Hz, 1H), 3.12-3.28 (m, 2H), 2.93 (t, J = 7.2 Hz, 2H), 2.08-2.00 (m, 2H).
MS (ESI) [M+H$^+$]: 242.



48 **49**
(Compound 56)

49 (Compound 56) was prepared from **48** as described for the preparation of **4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.3 (br s, 1H, NH), 7.72 (dd, J = 7.7, 1.1 Hz, 1H), 7.56-7.48 (m, 2H), 7.35 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 8.5 Hz, 2H), 3.02-3.06 (m, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.15-2.06 (m, 2H).

MS (ESI) [M+H$^+$]: 382.

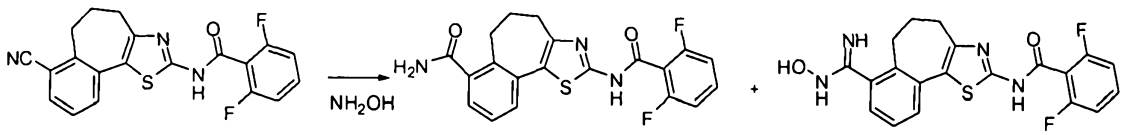
Compound 57:

(Compound 57) was prepared from **48** similarly as described for the preparation of **4** using the corresponding acid chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.6 (br s, 1H, NH), 8.59 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 5.2 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 3.05-3.01 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.54 (s, 3H), 2.10-2.00 (m, 2H).

MS (ESI) [M+H$^+$]: 361.

Compounds 58 and 64:



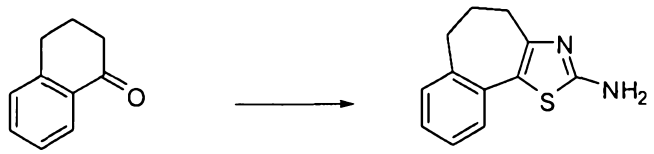
Into a solution of **49** (38.1 mg, 0.1 mmol) in 5 mL of MeOH was added hydroxyamine hydrochloride (21 mg, 0.3 mmol) and $NaHCO_3$ (50 mg, 0.6 mmol). The mixture was heated to reflux for 5 hours. After the reaction was cooled to room temperature, the reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was taken up with 20 mL of Et_2O, the solution was washed with NH_4Cl, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluted with ethyl acetate-hexane mixtures) to give **51** (Compound 58)(8.0 mg) as a white solid followed by benamidoxime **52** (Compound 64)(25 mg) as a white solid.

51: ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.73 (br s, NH), 7.59-7.47 (m, 3H), 7.36-7.27 (m, 2H), 7.07 (t, J = 8.2 Hz, 2H), 2.94-2.85 (m, 4H), 2.30-2.21 (m, 2H).

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

52: MS (ESI) [M+H$^+$]: 415.

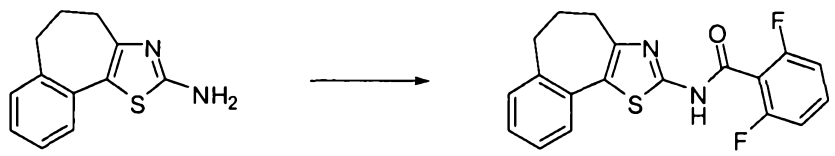
Compound 16:



53

53 was prepared from 1-tetralone as described for the preparation of **18**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.10 (m, 4H), 2.95-2.80 (m, 4H), 2.05-1.98 (m, 2H).
MS (ESI) [M+H$^+$]: 217

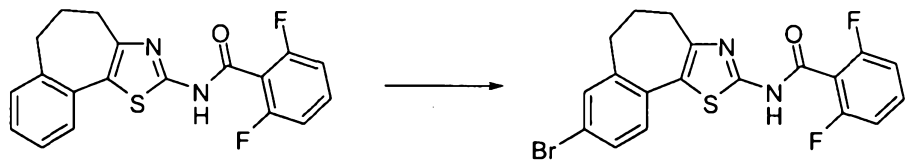


53 **54 (Compound 16)**

54 (Compound 16) was prepared from **53** as described for the preparation of **4**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.46 (m, 2H), 7.29-7.20 (m, 3H), 7.06 (t, J = 8.0 Hz, 2H), 3.03-2.98 (t, J = 7.2, 2H), 2.86-2.82 (m, 2H), 2.18-2.10 (m, 2H).
MS (ESI) [M+H$^+$]: 357.

Compound 20:



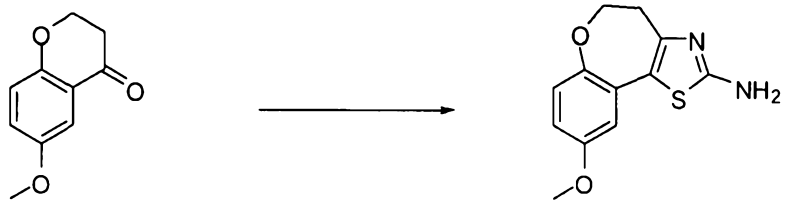
54 **55 (Compound 20)**

Into a solution of **54** (500 mg, 1.40 mmol) in methylene chloride (6.0 mL) at room temperature was added dropwise a solution of bromine (320 mg, 2.00 mmol) in methylene chloride (1.0 mL).

The mixture was stirred at room temperature overnight, taken up in additional methylene chloride, washed with an aqueous solution of 10% $NaHSO_3$, then with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **55** (Compound 20)(584 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.37 (m, 4H), 7.06-7.00 (m, 2H), 2.85-2.70 (m, 4H), 2.10-2.00 (m, 2H).
MS (ESI) [M+H$^+$]: 437

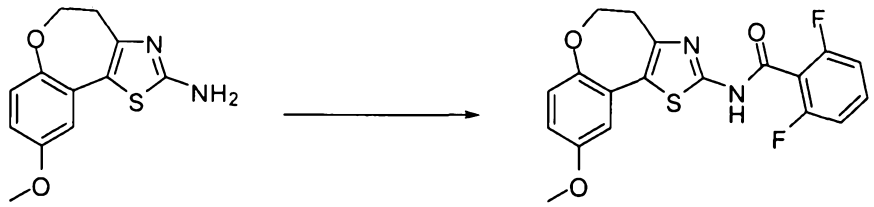
Compound 4:



56

56 was prepared from 6-methoxychroman-4-one as described for the preparation of **18**.

^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 3.0, 8.7 Hz, 1H), 4.21(dd, J = 5.5, 5.5 Hz, 2H), 3.76 (s, 3H), 3.14 (dd, J = 5.5, 5.5 Hz, 2H).
MS (ESI) [M+H$^+$]: 249



56 **57 (Compound 4)**

57 (Compound 4) was prepared from **56** as described for the preparation of **4**.

^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.45 (m, 1H), 7.06-6.99 (m, 4H), 6.94 (d, J = 8.7 Hz, 1H), 6.72 (dd, J = 2.4, 8.7 Hz, 1H), 4.20-4.15 (m, 2H), 3.82 (s, 3H), 3.05-2.95 (m, 2H).
MS (ESI) [M+H$^+$]: 389.

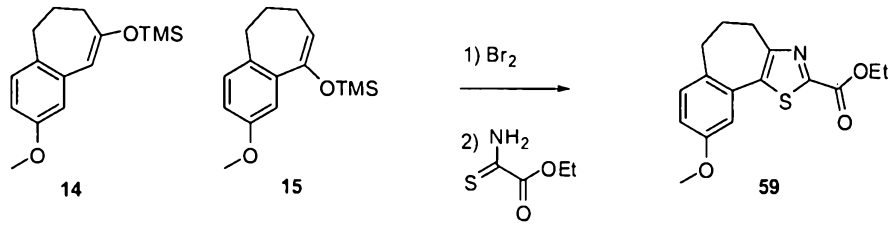
Compound 9:

(Compound 9) was prepared from **56** as described for the preparation of **4** using the

corresponding acid chloride.

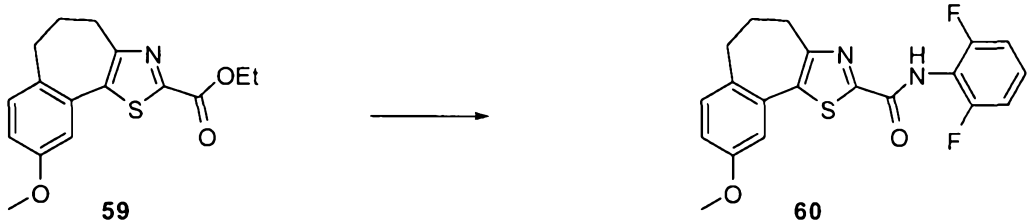
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73(d, J = 2.7 Hz, 1H), 8.70 (dd, J = 1.5, 4.8 Hz, 1H), 8.08 (dd, J = 4.8, 6.3 Hz, 1H), 7.07 (d, J = 3.0 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.73 (dd, J = 3.0, 8.7 Hz, 1H), 4.32 (dd, J = 5.4, 5.4 Hz, 2H), 3.83 (s, 3H), 3.33 (dd, J = 5.4, 5.4 Hz, 2H).
MS (ESI) [M+H$^+$]: 372.

Compound 5:



Into a 9:1 crude mixture of **14** and **15** respectively (995 mg, 3.80 mmol) in methylene chloride (50 mL) at 0 °C was added dropwise solution of bromine (800 mg, 5.0 mmol) in methylene chloride (10.0 mL). The bromine addition was stopped whence brownish color of the reaction mixture ceased to disappear. The mixture was concentrated under reduced pressure. The residue was taken up in ethanol (20.0 ml). Ethyl thiooxamate (670 mg, 5.0 mmol) was added. The mixture was stiired at room temperature overnight. An aqueous solution of saturated $NaHCO_3$ was added. The resulting mixture was extracted with methylene chloride (2X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with a solution of ethyl acetate: hexane, 1:9) to give **59** (520 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8 Hz, 1H), 7.00 (d, J = 2 Hz, 1H), 6.83 (dd, J = 2, 8 Hz, 1H), 4.45 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 3.04 (dd, J = 7.2, 7.4 Hz, 2H), 2.65-2.60 (m, 2H), 2.26-2.18 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H).
MS (ESI) [M+H$^+$]: 304



Into a solution of **59** (100 mg, 0.33 mmol) and 2,6-difluoro aniline (65.0 mg, 0.50 mmol) in anhydrous toluene (3.0 mL) at room temperature was added a solution 2M trimethylaluminum in toluene (0.5 mL, 1.0 mmol). The resulting solution was heated to 80 °C for 2 hours, cooled to room temperature, poured over ice, acidified with 2N HCl, extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with a solution of ethyl acetate: hexane, 1:9) to give **60** (Compound 5)(65mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.31-7.22 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.05-6.99 (m, 3H), 6.84 (dd, *J* = 2.5, 8.2 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, *J* = 7.2, 7.2 Hz, 2H), 2.75-2.71 (m, 2H), 2.27-2.18 (m, 2H).
MS (ESI) [M+H$^+$]: 387.

Compound 21:

(Compound 21) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H), 7.65 (dd, *J* = 8, 8 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 6.82 (dd, *J* = 2.5, 8 Hz, 1H), 3.83 (s, 3H), 3.05 (dd, *J* = 7.1, 7.2 Hz, 2H), 2.74-2.70 (m, 2H), 2.51 (s, 3H), 2.24-2.15 (m, 2H).
MS (ESI) [M+H$^+$]: 366.

Compound 22:

(Compound 22) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.83 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 4.37 (bs, 2H), 3.83 (s, 3H), 3.05 (dd, *J* = 7.1, 7.1 Hz, 2H), 2.74-2.70 (m, 2H), 2.24-2.15 (m, 2H).
MS (ESI) [M+H$^+$]: 367

Compound 23:

(Compound 23) was prepared from **59** similarly as described for the preparation of **60** using the

corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.38-8.33 (m, 2H), 7.80-7.74 (m, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.12-7.08 (m, 1H), 7.04 (d, J = 2.7 Hz, 1H), 6.84 (dd, J = 2.7, 8.2 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, J = 7.2, 7.4 Hz, 2H), 2.75-2.71 (m, 2H), 2.25-2.16 (m, 2H).
MS (ESI) [M+H$^+$]: 352

Compound 24:

(Compound 24) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.79 (d, J = 2.5 Hz, 1H), 8.41 (dd, J = 1.5, 5.0 Hz, 1H), 8.35 (dd, J = 1.5, 8.4 Hz, 1H), 7.35 (dd, J = 5.0, 8.4 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 2.5, 8.3 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, J = 7.1, 7.4 Hz, 2H), 2.74-2.70 (m, 2H), 2.26-2.18 (m, 2H).
MS (ESI) [M+H$^+$]: 352.

Compound 25:

(Compound 25) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.40 (d, J = 2.7 Hz, 1H), 8.11 (dd, J = 2.7, 8.9 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 2.5, 8.9 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.05 (dd, J = 7.1, 7.4 Hz, 2H), 2.74-2.70 (m, 2H), 2.26-2.17 (m, 2H).
MS (ESI) [M+H$^+$]: 382

Compound 26:

(Compound 26) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.89 (dd, J = 2.6, 8.1 Hz, 1H), 8.17 (dd, J = 1.6, 4.7 Hz, 1H), 7.33 (dd, J = 4.7, 8.1 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 6.85 (dd, J = 1.6, 8.5 Hz, 1H), 3.84 (s, 3H), 3.09 (dd, J = 7.1, 7.2 Hz, 2H), 2.75-2.70 (m, 2H), 2.28-2.19 (m, 2H).

MS (ESI) [M+H$^+$]: 386.

Compound 10:

(Compound 10) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 5.4 Hz, 1H), 8.36 (s, 1H), 8.31 (d, J = 5.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 2.7 Hz, 1H), 6.83 (dd, J = 2.7, 8.4 Hz, 1H), 3.84 (s, 3H), 3.08 (dd, J = 7, 7 Hz, 2H), 2.74-2.59 (m, 2H), 2.37 (s, 3H), 2.26-2.17 (m, 2H).

MS (ESI) [M+H$^+$]: 366

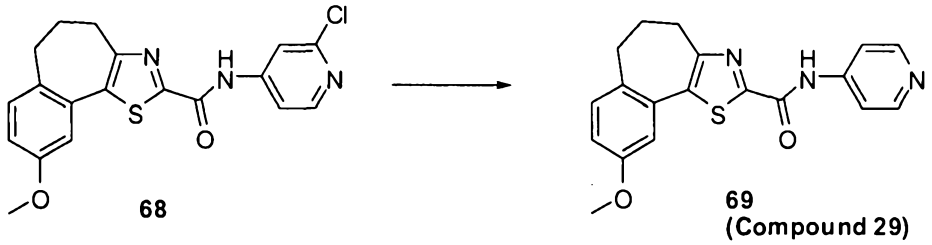
Compound 27:

(Compound 27) was prepared from **59** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.34 (d, J = 5.5 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 2.0, 5.7 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 2.7 Hz, 1H), 6.85 (dd, J = 2.7, 8.2 Hz, 1H), 3.84 (s, 3H), 3.05 (dd, J = 7.2, 7.4 Hz, 2H), 2.74-2.70 (m, 2H), 2.27-2.18 (m, 2H).

MS (ESI) [M+H$^+$]: 386

Compound 29:

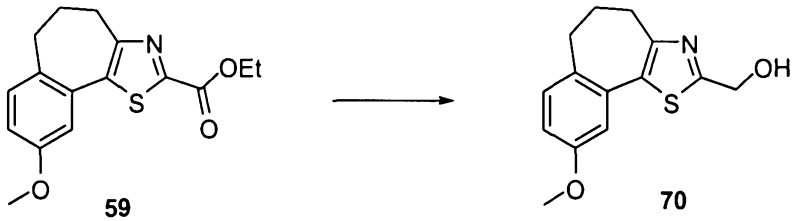


Into a solution of **68** (20.0 mg, 0.05 mmol) in ethanol (2.0 mL) was added 10% Pd/C (10.0 mg). The mixture was stirred under 3 atmosphere of hydrogen for 2 days. The mixture was filtered through a short plug of silica to give **69** (Compound 29) (12.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.63-8.51 (m, 2H), 7.71-7.60 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 2.5, 8.5 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, J = 7.2, 7.4 Hz, 2H), 2.74-2.70 (m, 2H), 2.27-2.18 (m, 2H).

MS (ESI) [M+H$^+$]: 352

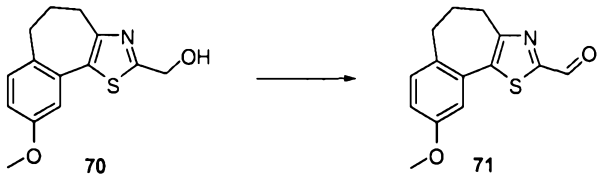
Compound 28:



59 70

Into a solution of **59** (300 mg, 1.0 mmol) in THF (5.0 mL) at 0 °C was added dropwise a solution of 1M aluminum hydride in THF (2.0 mL, 2.0 mmol). The mixture was stirred at room temperature for 1 hour, cooled to 0 °C. Into the mixture ice was added followed by 2N NaOH. The mixture was extracted with methylene chloride (2X). The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to give **70** (248 mg).

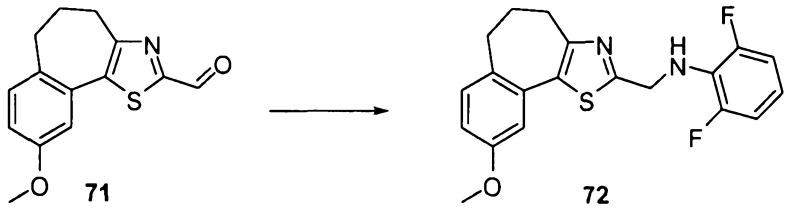
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 2.7 Hz, 1H), 6.76 (dd, J = 2.7, 8.5 Hz, 1H), 4.92 (bd, J = 5.5 Hz, 2H), 3.82 (s, 3H), 3.06 (dd, J = 7.2, 7.2 Hz, 2H), 2.75-2.71 (m, 2H), 2.17-2.10 (m, 2H).
MS (ESI) [M+H$^+$]: 262



70 71

Into a solution of **70** (248 mg, 0.95 mmol) in methylene chloride (10.0 mL) at room temperature was added pyridinium dichromate (564 mg, 1.50 mmol). The mixture was stirred at room temperature overnight, filtered through a short plug of silica gel to give **71** (205 mg).

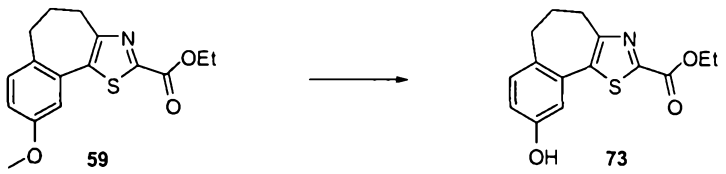
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 2.5, 8.2 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, J = 7.2, 7.5 Hz, 2H), 2.72-2.68 (m, 2H), 2.29-2.20 (m, 2H).
MS (ESI) [M+H$^+$]: 260



Into a solution of **71** (20.0 mg, 0.077 mmol) and 2,6-difluoroaniline (13.0 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at room temperature was added TFA (2 drops). The mixture was stirred at room temperature for 1 hour. Into the mixture $Na(OAc)_3BH$ (42.0 mg, 0.20 mmol). The resulting solution was stirred at room temperature overnight, taken up in CH_2Cl_2, washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica to give **72** (compound 28). ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.87-6.69 (series of m, 4H), 4.75 (d, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.06 (dd, J = 6.9, 7.1 Hz, 2H), 2.74-2.70 (m, 2H), 2.16-2.07 (m, 2H).

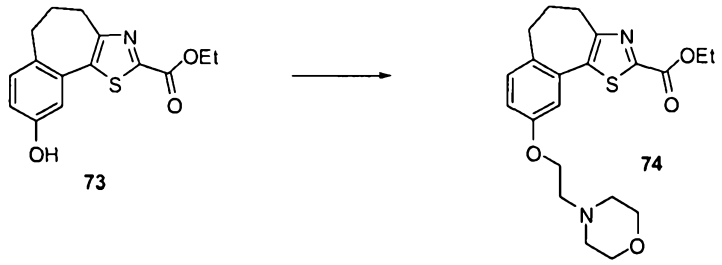
MS (ESI) [$M+H^+$]: 373

Compound 30:



Into a solution of **59** (300 mg, 1.0 mmol) in methylene chloride (5.00 mL) at - 78 °C was added a solution of 1M BBr_3 (2.0 mL, 2.0 mmol). The mixture was gradually warmed to room temperature over 2 hours, poured over ice, extracted with methylene chloride (2X). The extracts were washed with water and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **73** (210 mg).

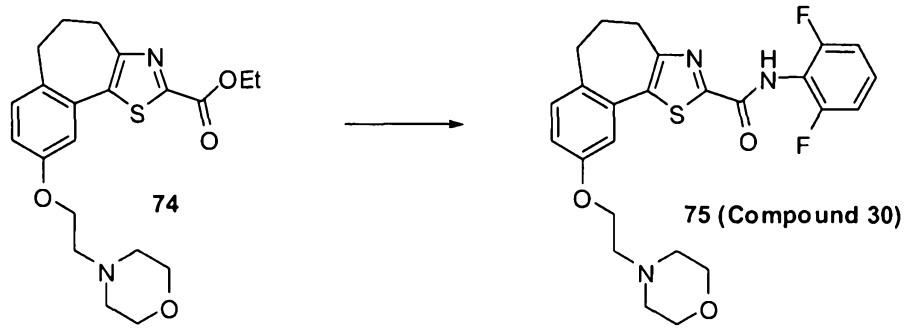
MS (ESI) [$M+H^+$]: 290



Into a solution of **73** (58.0 mg, 0.20 mmol), 4-(2-chloroethyl)morpholine hydrochloride (56 mg, 0.30 mmol) and NaI (3 mg, 0.02 mmol) in DMF (4.0 mL) at room temperature was added K_2CO_3 (83.0 mg, 0.60 mmol). The mixture was stirred at 60 °C overnight, cooled to room temperature, diluted with ethyl acetate, washed with water (3X) then with brine and dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **74** (65 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8 Hz, 1H), 7.02 (d, J = 2 Hz, 1H), 6.83 (dd, J = 2, 8 Hz, 1H), 4.48 (q, J = 7 Hz, 2H), 4.12 (t, J = 5.7 Hz, 2H), 3.77-3.73 (m, 4H), 3.07 (dd, J = 7, 7 Hz, 2H).

MS (ESI) [M+H$^+$]: 403



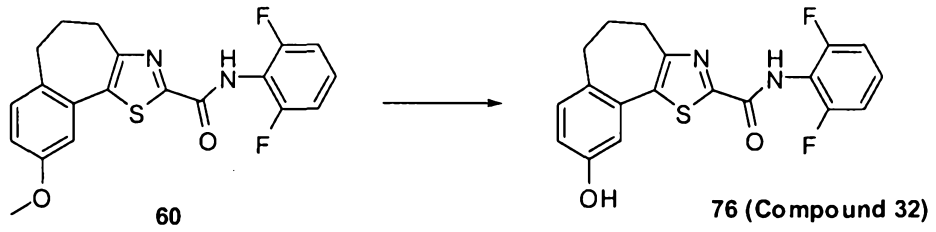
Into a solution of the crude **74** (65 mg) and 2,6-difluoroaniline (52.0 mg, 0.40 mmol) in toluene (2.0 mL) at room temperature was added a solution of 2M trimethylaluminum in hexane (0.2 mL, 0.40 mmol). The mixture was heated to 80 °C for 2 hours, cooled to room temperature, poured over ice, basified with 2N NaOH, extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **75** (Compound 30)(12 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (bs, 1H), 7.31-7.21 (m, 1H), 7.16 (d, J = 8 Hz, 1H), 7.04 (d, J = 2.7 Hz, 1H), 7.01 (d, J = 8 Hz, 1H), 6.84 (dd, J = 2.7, 8 Hz, 1H), 4.13 (t, J = 5.7 Hz, 2H), 3.76-3.73 (m, 4H), 3.06 (dd, J = 7.1, 7.2 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H), 2.74-2.70 (m, 2H),

2.60-2.57 (m, 2H), 2.26-2.17 (m, 2H).

MS (ESI) [M+H$^+$]: 486

Compound 32:

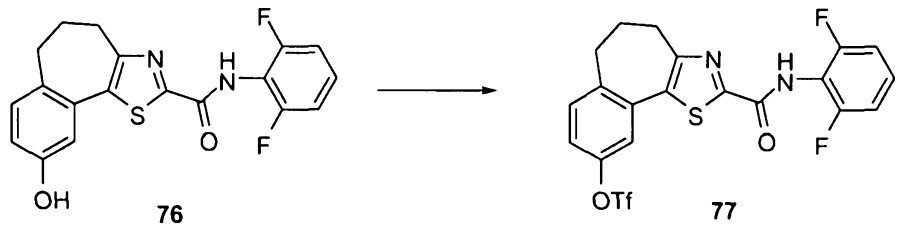


Into a solution of **60** (450 mg, 1.16 mmol) in methylene chloride (5.00 mL) at - 78 °C was added a solution of 1M BBr_3 (2.0 mL, 2.0 mmol). The mixture was gradually warmed to room temperature over 2 hours, poured over ice, extracted with methylene chloride (2X). The extracts were washed with water and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **76** (Compound 32)(398 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (bs, 1H), 7.33-7.24 (m, 1H), 7.13-7.00 (m, 4H), 6.77 (dd, *J* = 2, 8 Hz, 1H), 3.05 (dd, *J* = 7, 7 Hz, 2H), 2.73-2.68 (m, 2H), 2.26-2.18 (m, 2H).

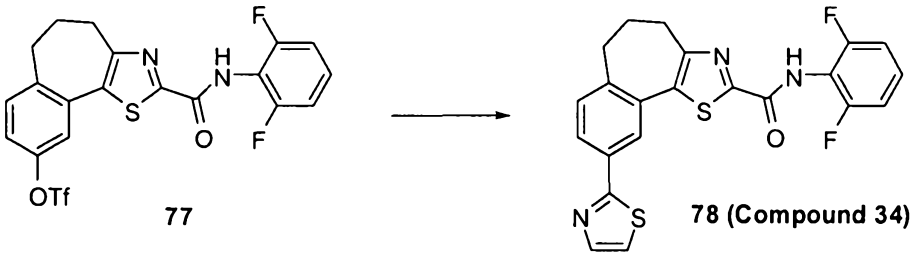
MS (ESI) [M+H$^+$]: 373

Compound 34:



Into a solution of **76** (398 mg, 1.07 mmol) and pyridine (277 mg, 3.50 mmol) in methylene chloride (5.0 mL) at 0 °C was added triflic anhydride (1.00g, 3.50 mmol). The mixture was stirred at room temperature for 4 hours, diluted with methylene chloride, washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **77** (541mg), which was used without purification.

MS (ESI) [M+H$^+$]: 505



Into a solution of **77** (50.0 mg, 0.10 mmol) in THF (2.0 mL) at room temperature was added tetrakis(triphenylphosphine)palladium (23.0 mg, 0.02 mmol) followed by a solution of 0.5M 2-thiazolzinc bromide in THF (0.6 mL, 0.3 mmol). The mixture was degassed by vacumm/N_2-fill method (3X). The degassed solution was heated to 60 °C overnight, cooled to room temperature, quenched with ice, extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **78** (Compound 34)(31.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 8.10 (d, *J* = 1.7 Hz, 1H), 7.88 (d, *J* = 3.3 Hz, 1H), 7.86 (dd, *J* = 1.7, 8.2 Hz, 1H), 7.36-7.22 (m, 3H), 7.05-6.99 (m, 2H), 3.10 (dd, *J* = 7.2, 7.5 Hz, 2H), 2.85-2.81 (m, 2H), 2.31-2.23 (m, 2H).

MS (ESI) [M+H$^+$]: 440

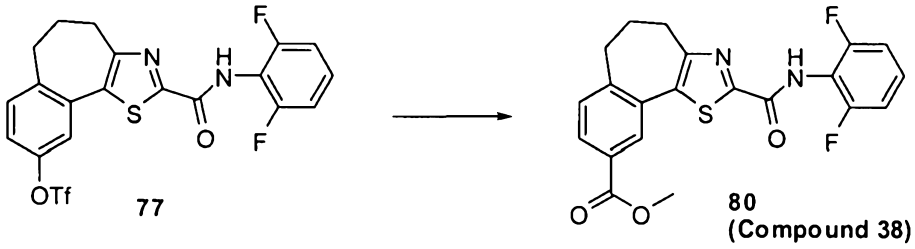
Compound 37:

(Compound 37) was prepared from **77** similarly as described for the preparation of **78** using a solution of 0.5M 2-pyridylzinc bromide in THF.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.61 (m, 2H), 8.15 (bs, 1H), 7.94-7.73 (m, 3H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.30-7.22 (m, 1H), 7.05-7.00 (m, 2H), 3.11 (dd, *J* = 6.9, 7.2 Hz, 2H), 2.87-2.83 (m, 2H), 2.31-2.24 (m, 2H).

MS (ESI) [M+H$^+$]: 434

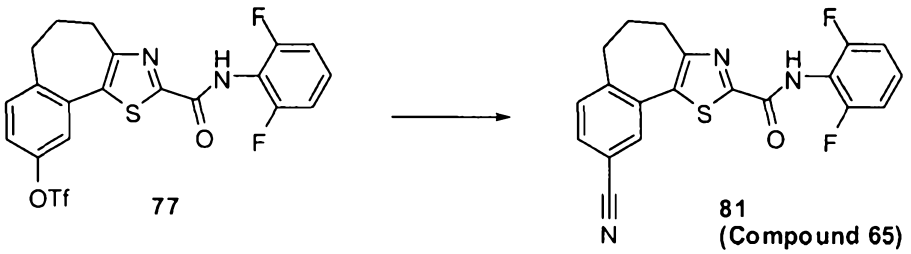
Compound 38:



Into a solution of **77** (50.0 mg, 0.10 mmol) in MeOH (2.0 mL) at room temperature was added $Pd(OAc)_2$ (11.0 mg, 0.05 mmol), 1,3-bis(diphenylphosphino)propane (21.0 mg, 0.05 mmol) and triethylamine (50.0 mg, 0.5 mmol). A slow stream of CO gas was bubbling through the solution, which was heated to 50 °C for 2 days. The mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified on silica to give **80** (Compound 38)(30.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (bs, 1H), 8.17 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 1.5, 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.30-7.23 (m, 1H), 7.05-7.00 (m, 2H), 3.94 (s, 3H), 3.10 (dd, J = 6.9, 7.2 Hz, 2H), 2.87-2.83 (m, 2H), 2.30-2.22 (m, 2H).
MS (ESI) [M+H$^+$]: 415

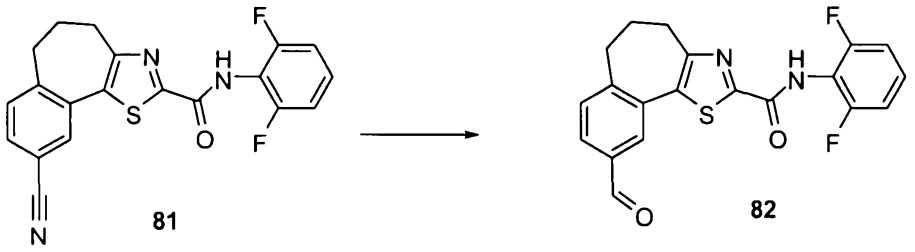
Compound 65:



Into a solution of **77** (200 mg, 0.4 mmol) in DMF (4.0 mL) at room temperature were added Zinc cyanide (117 mg, 1.00 mmol) and tetrakis(triphenylphosphine)palladium (92.0 mg, 0.08 mmol). The mixture was degassed by vacumm/N_2-fill method (3X). The degassed solution was heated to 110 °C overnight, cooled to room temperature, diluted with methylene chloride, washed with water (3X). The organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **81** (Compound 65)(132 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (bs, 1H), 7.78 (d, J = 1.7 Hz, 1H), 7.52 (dd, J = 1.7, 7.7 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.33-7.23 (m, 1H), 7.05-7.00 (m, 2H), 3.11 (dd, J = 7.1, 7.5 Hz, 2H), 2.87-2.83 (m, 2H), 2.32-2.23 (m, 2H).
MS (ESI) [M+H$^+$]: 382

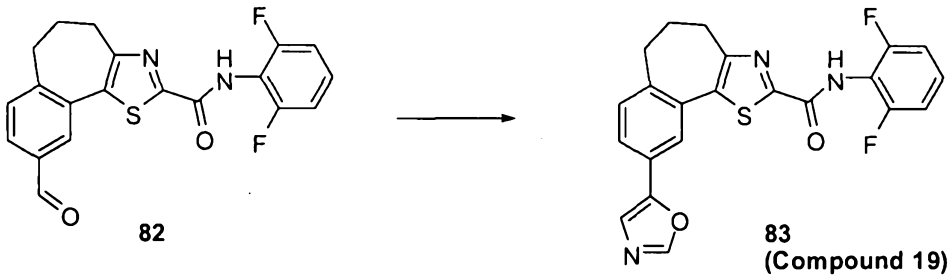
Compound 19:



81 82

Into a solution of **81** (58 mg, 0.15 mmol) in THF (2.0 mL) at 0 °C was added dropwise a solution of 1M di-isobutylaluminum hydride in THF (0.5 mL, 0.5 mmol). The mixture was stirred at room temperature for 1 hour, cooled to 0 °C, poured over an ice-cooled solution of 1N HCl. The mixture was extracted with methylene chloride (2X). The combined extract was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **82** (42 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.61 (bs, 1H), 7.99 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 1.7, 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.32-7.23 (m, 1H), 7.06-6.99 (m, 2H), 3.12 (dd, J = 7.2, 7.2 Hz, 2H), 2.90-2.83 (m, 2H), 2.32-2.23 (m, 2H).
MS (ESI) [M+H$^+$]: 385

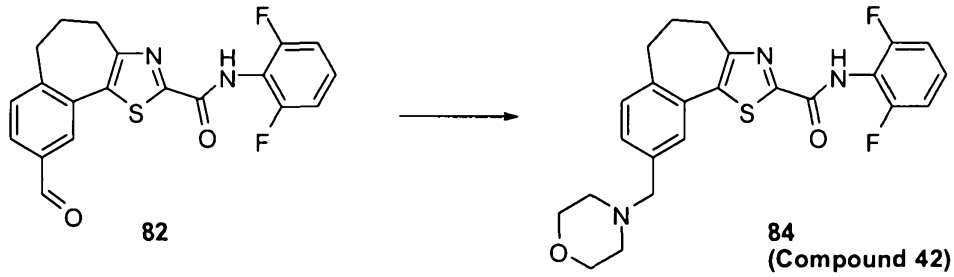


82 83 (Compound 19)

Into a solution of **82** (15 mg, 0.04 mmol) and *p*-toluenesulfonylmethyl isocyanide (20 mg, 0.1 mmol) in MeOH (1.0 mL) at room temperature was added potassium carbonate (14 mg, 0.1 mmol). The mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, diluted with methylene chloride, washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **83** (Compound 19)(12 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (bs, 1H), 7.94 (s, 1H), 7.79 (d, J = 1.7 Hz, 1H), 7.56 (dd, J = 1.7, 8.0 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.30-7.23 (m, 1H), 7.06-7.00 (m, 2H), 3.11 (dd, J = 7.4, 8.3 Hz, 2H), 2.85-2.81 (m, 2H), 2.31-2.23 (m, 2H).
MS (ESI) [M+H$^+$]: 424

Compound 42:

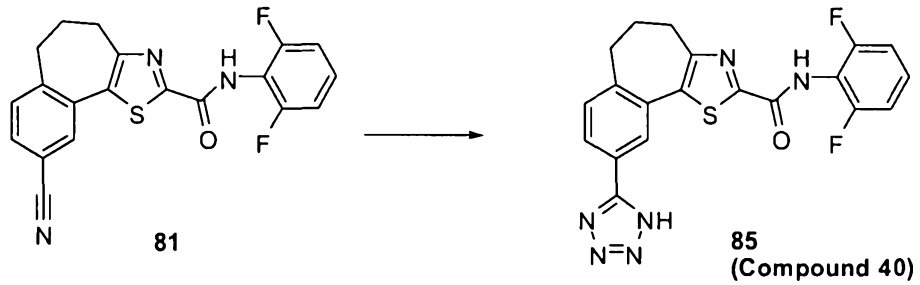


Into a solution of **82** (15 mg, 0.04 mmol) and morpholine (9.0 mg, 0.1 mmol) in methylene chloride at room temperature was added $Na(OAc)_3BH$ (21 mg, 0.1 mmol). The mixture was stirred at room temperature overnight, diluted with methylene chloride, washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **84** (Compound 42)(9 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.48 (s, 1H), 7.34-7.19 (m, 3H), 7.06-6.98 (m, 2H), 3.86-3.70 (m, 4H), 3.51 (s, 2H), 3.08 (dd, J = 7.0, 7.2 Hz, 2H), 2.80-2.76 (m, 2H), 2.48-2.45 (m, 4H), 2.27-2.19 (m, 2H).

MS (ESI) $[M+H^+]$: 456

Compound 40:

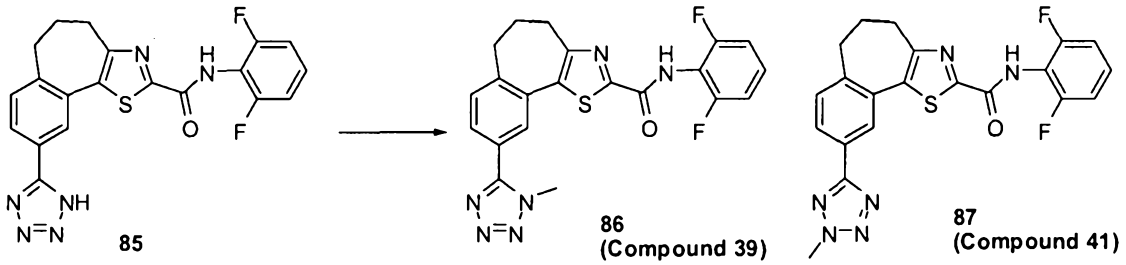


A solution of **81** (48 mg, 0.13 mmol), sodium azide (25 mg, 0.38 mmol) and ammonium chloride (21 mg, 0.38 mmol) in DMF (2.0 mL) was heated at 110 °C overnight. The mixture was cooled to room temperature, diluted with methylene chloride, washed with water (3X), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **85** (Compound 40)(35mg).

^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (bs, 1H), 8.19 (d, J = 1.8 Hz, 1H), 8.13 (dd, J = 1.8, 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.16-7.07 (m, 1H), 6.81-6.76 (m, 2H), 3.12 (dd, J = 7.2, 7.5 Hz, 2H), 2.90-2.85 (m, 2H), 2.35-2.26 (m, 2H).

MS (ESI) [M+H$^+$]: 425

Compounds 39 and 41:

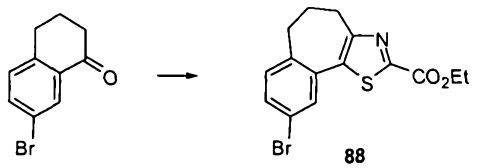


Into a solution of **85** (35 mg) in methylene chloride (2 mL) was added a solution of 2M trimethylsilyldiazomethane in ether (0.5 mL, 1.0 mmol). The mixture was concentrated under reduced pressure. The residue was purified on silica to give **86** (Compound 39)(32 mg) followed by **87** (Compound 41)(3 mg).

86: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (bs, 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 1.5, 7.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.33-7.23 (m, 1H), 7.05-6.98 (m, 2H), 4.41 (s, 3H), 3.11 (dd, J = 7.2, 7.2 Hz, 2H), 2.87-2.83 (m, 2H), 2.32-2.23 (m, 2H).
MS (ESI) [M+H$^+$]: 439

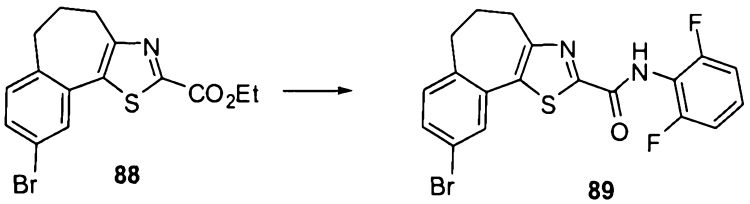
87: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.67 (dd, J = 1.5, 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.33-7.23 (m, 1H), 7.06-6.98 (m, 2H), 4.23 (s, 3H), 3.14 (dd, J = 7.2, 7.2 Hz, 2H), 2.90-2.86 (m, 2H), 2.35-2.27 (m, 2H).
MS (ESI) [M+H$^+$]: 439

Compound 18:



88 was prepared from 5-bromo-1-tetralone similarly as described for the preparation of **59.**

MS (ESI) [M+H$^+$]: 354, 352.

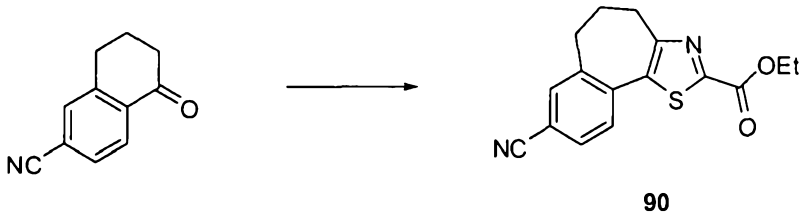


89 (Compound 18) was prepared from **88** similarly as described for the preparation of **60**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 1H, NH), 7.64 (d, J = 2.1 Hz, 1H), 7.40 (dd, J = 8.0, 2.1 Hz, 1H), 7.32-7.22 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 2.77-2.73 (m, 2H), 2.28-2.21 (m, 2H).

MS (ESI) [M+H$^+$]: 437, 435.

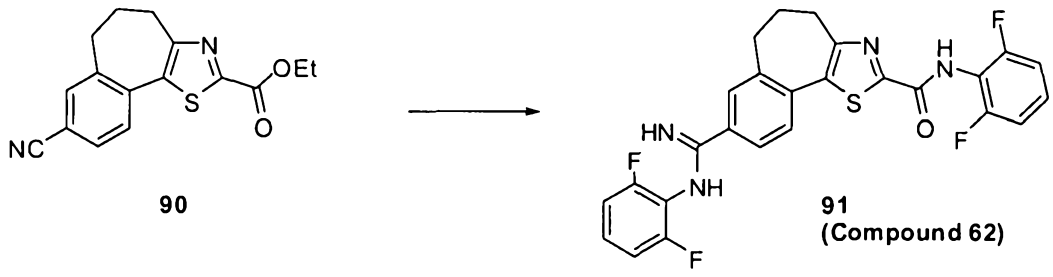
Compound 62:



90

90 was prepared from 6-nitrile-1-tetralone similarly as described for the preparation of **59.**

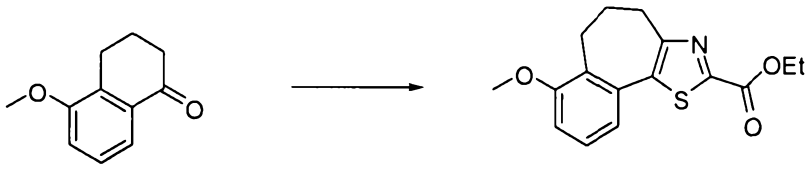
MS (ESI) [M+H$^+$]: 299.



Into a solution of **90** (50 mg, 0.17 mmol) in toluene (2.0 mL) at room temperature was added a solution of 2M trimethylalluminum in toluene (0.5 mL, 1.0 mmol). The mixture was heated to 60°C overnight, cooled to room temperature, poured over ice, basified with 2N NaOH, extracted with methylene chloride (2X). The combined extracts was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **91** (Compound 62)(15 mg).

MS (ESI) [M+H$^+$]: 511.

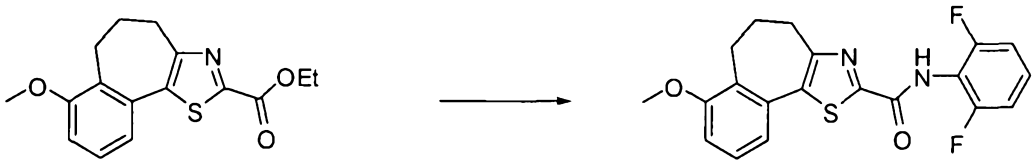
Compound 6:



92

92 was prepared from 5-methoxy-1-tetralone as described for the preparation of **59**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, J = 8, 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 6.89 (d, J = 8 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.00 (dd, J = 7.2, 7.5 Hz, 2H), 2.78-2.74 (m, 2H), 2.26-2.21 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H).
MS (ESI) [M+H$^+$]: 304



92

93
(Compound 6)

93 (Compound 6) was prepared from **92** similarly as described for the preparation of **60**.

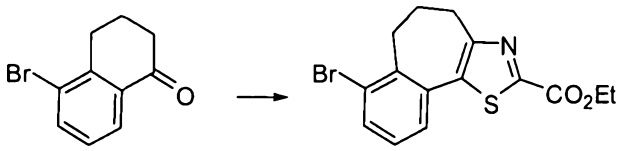
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.28-7.02 (series of m, 5H), 6.91 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 2.98 (dd, J = 7.2, 7.5 Hz, 2H), 2.84-2.79 (m, 2H), 2.30-2.21 (m, 2H).
MS (ESI) [M+H$^+$]: 387

Compound 11:

(Compound 11) was prepared from **92** similarly as described for the preparation of **60** using the corresponding amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.43 (s, 1H), 8.33 (d, J = 5.5 Hz, 1H), 7.26 (dd, J = 8, 8 Hz, 1H),7.09 (d, J = 8 Hz, 1H), 6.91 (dd, J = 8, 8 Hz, 1H), 3.88 (s, 3H), 2.97 (dd, J = 7.2, 7.5 Hz, 2H), 2.83-2.79 (m, 2H), 2.41 (s, 3H), 2.35-2.20 (m, 2H).
MS (ESI) [M+H$^+$]: 366

Compound 53:

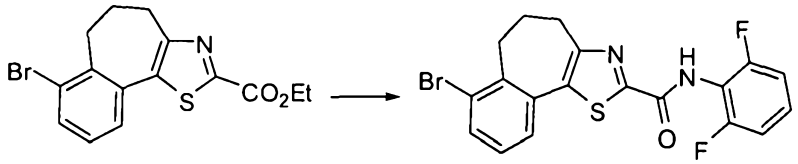


95

95 was prepared from 5-bromo-1-tetralone as described for the preparation of **59**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.12 (dd, J = 8.0, 7.7 Hz, 1H), 4.98 (q, J = 7.2 Hz, 2H), 2.95-2.85 (m, 4H), 2.34-2.25 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H).

MS (ESI) [M+H$^+$]: 354, 352.



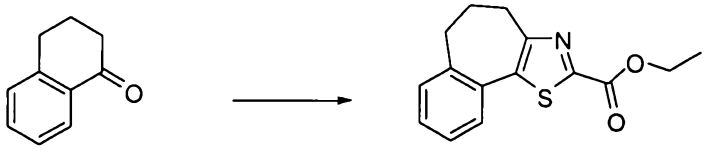
95 **96 (Compound 53)**

96 (Compound 53) was prepared from **95** as described for the preparation of **60**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (br s, 1H, NH), 7.61-7.47 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.03 (t, J = 8.2 Hz, 2H), 2.98-2.90 (m, 4H), 2.39-2.30 (m, 2H).

MS (ESI) [M+H$^+$]: 437, 435.

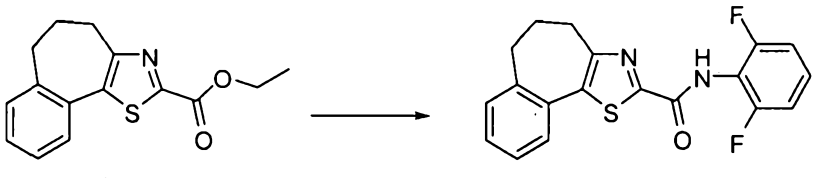
Compound 31:



97

97 was prepared from 1-tetralone as described for the preparation of **59**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.47 (m, 1H), 7.31-7.26 (m, 3H), 4.50 (q, J = 7 Hz, 2H), 3.11 (dd, J = 7.2, 7.5 Hz, 2H), 2.78-2.74 (m, 2H), 2.26-2.22 (m, 2H), 1.45 (t, J = 7 Hz, 3H).
MS (ESI) [M+H$^+$]: 274

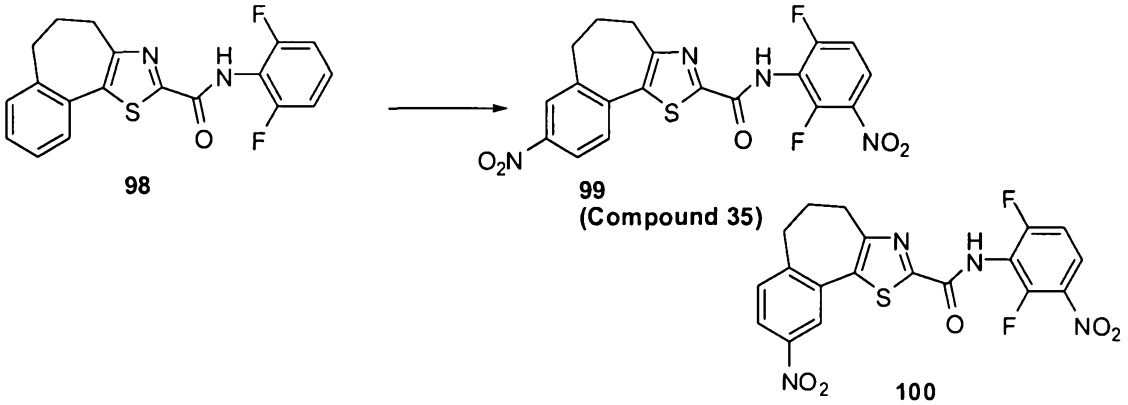


97 **98 (Compound 31)**

98 (Compound 31) was prepared from **97** as described for the preparation of **60**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.53-7.49 (m, 1H), 7.29-7.22 (m, 4H), 7.05-6.99 (m, 2H), 3.09 (dd, J = 7.1, 7.1Hz, 2H), 2.82-2.71 (m, 2H), 2.30-2.21 (m, 2H).
MS (ESI) [M+H$^+$]: 357

Compounds 35 and 36:



98 **99 (Compound 35)** **100 (Compound 36)**

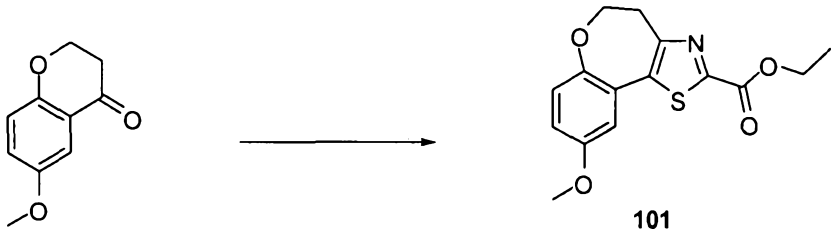
Into a solution of **98** (50 mg) in concentrated sulfuric acid (1.0 mL) at 0 °C was added dropwise a solution of concentrated nitric acid (0.1 mL). The mixture was stirred at 0 °C for 30 minutes, poured over ice, extracted with methylene chloride (2X). The combined extracts was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica to give **99** (Compound 35)(14 mg) and **100** (Compound 36)(13 mg).

99: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.14 (m, 3H), 7.68 (d, J = 10 Hz, 1H), 7.24-7.18 (m, 1H), 3.18 (dd, J = 7.2, 7.4 Hz, 2H), 2.96-2.92 (m, 2H), 2.37-2.27 (m, 2H).
MS (ESI) [M+H$^+$]: 447

100: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 2.1 Hz, 3H), 8.15-8.07 (m, 2H), 7.44 (d, J = 11 Hz, 1H), 7.20-7.14 (m, 1H), 3.11 (dd, J = 7.2, 7.5 Hz, 2H), 2.90-2.86 (m, 2H), 2.33-2.26 (m, 2H).

MS (ESI) [M+H$^+$]: 447

Compound 66:

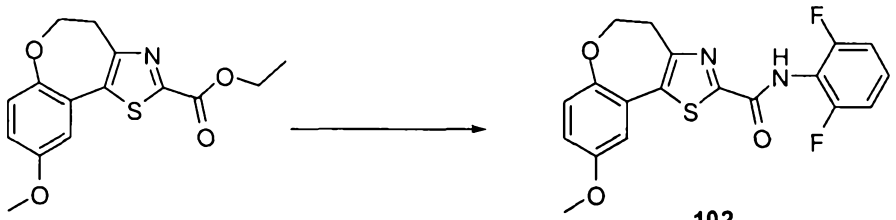


101

101 was prepared from 6-methoxychroman-4-one as described for the preparation of **59**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 3.0 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 3.0, 8.8 Hz, 1H), 4.50 (q, J = 7.0 Hz, 2H) 4.33 (dd, J = 5.1, 5.7 Hz, 2H), 3.82 (s, 3H), 3.52 (dd, J = 5.1, 5.7 Hz, 2H), 1.45 (t, J = 7.0 Hz, 3H).

MS (ESI) [M+H$^+$]: 306



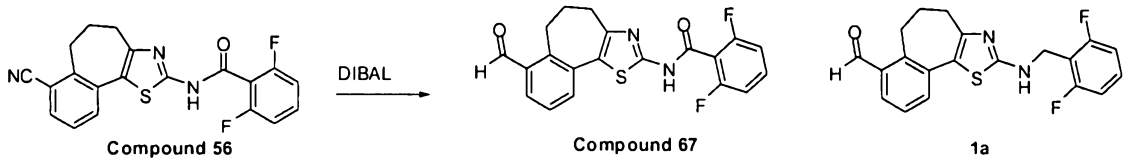
101 **102 (Compound 66)**

102 (Compound 66) was prepared from **101** as described for the preparation of **60**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.32-7.22 (m, 1H), 7.10 (d, J = 2.7 Hz, 1H), 7.06-6.99 (m, 3H), 6.81 (dd, J = 2.7, 8 Hz, 1H), 4.35 (dd, J = 5.2, 5.5 Hz, 2H), 3.82 (s, 3H), 3.47 (dd, J = 5.1, 5.7 Hz, 2H).

MS (ESI) [M+H$^+$]: 389

Compound 67:



Compound 56 Compound 67 1a

Into the solution of Compound 56 (762 mg, 2 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added dropwise a 1M solution of DIBAl-H in THF (6.0 mL, 6.0 mmol). The mixture was stirred at room temperature for 1 hour, cooled to 0 °C, poured over an ice-cooled solution of 1N HCl. The mixture was extracted with methylene chloride. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **1a** (110 mg, 15% yield) followed by Compound **67** (443 mg, 56% yield).

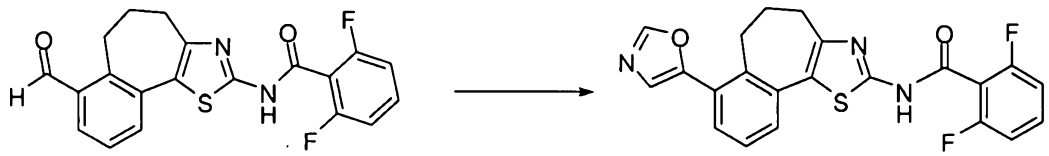
1a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.67 (dd, J = 1.1, 7.7 Hz, 1H), 7.53 (dd, J = 1.4, 7.7 Hz, 1H), 7.37-7.27 (m, 2H), 6.95 (t, J = 8.0 Hz, 2H), 4.59 (s, 2H), 3.11-3.07 (m, 2H), 2.82-2.75 (m, 2H), 2.22-2.10 (m, 2H).

MS (ESI) [M+H$^+$]: 371.

Compound 67: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (br s, 1H, NH), 10.33 (s, 1H), 7.75 (dd, J = 1.1, 7.7 Hz, 1H), 7.68 (dd, J = 1.4, 7.7 Hz, 1H), 7.50-7.41 (m, 2H), 6.99 (t, J = 8.2 Hz, 2H), 3.11-3.07 (m, 2H), 2.53-2.47 (m, 2H), 2.15-2.07 (m, 2H).

MS (ESI) [M+H$^+$]: 385

Compound 68:



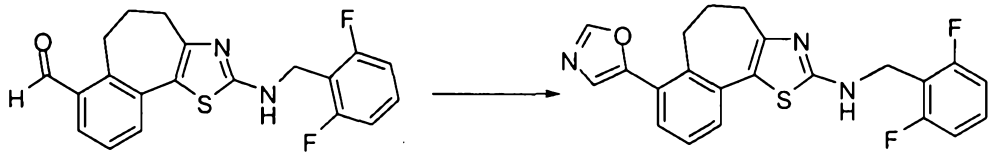
Compound 67 Compound 68

Into the solution of Compound **67** (30 mg, 0.08 mmol) and *p*-toluenesulfonylmethyl isocyanide (20 mg, 0.1 mmol) in 2 mL of MeOH at room temperature was added K_2CO_3 (28 mg, 0.2 mmol). The mixture was reflux for 1 hour. The mixture was cooled to room temperature, concentrated and redissolved in methylene chloride. The solution was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give Compound **68** (23 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (s, 1H), 7.55-7.32 (series of m, 4H), 7.23 (s, 1H), 7.04 (t, J = 8.2 Hz, 2H), 2.78-2.70 (m, 4H), 2.28-2.20 (m, 2H).

MS (ESI) [M+H$^+$]: 424

Compound 69:

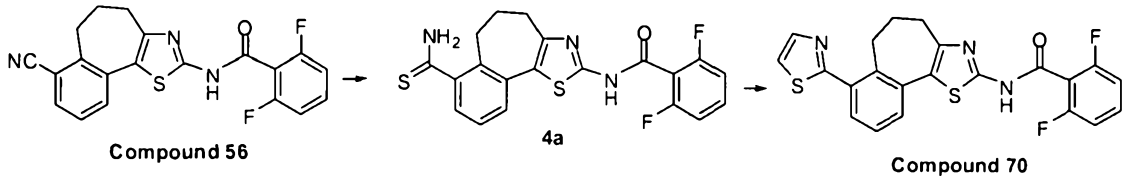


1a Compound 69

Compound **69** was prepared from **1a** similarly as described for the preparation of compound **68**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.37-7.23 (series of m, 4H), 7.19 (s, 1H), 6.94 (t, *J* = 7.5 Hz, 2H), 4.59 (s, 2H), 2.84-2.78 (m, 4H), 2.26-2.16 (m, 2H).

MS (ESI) [M+H$^+$]: 410

Compound 70:



Compound 56 4a Compound 70

The solution of **Compound 56** (38 mg, 0.1 mmol) and $(NH_4)_2S$ (0.1 mmol, 40 wt.% in H_2O) in MeOH (1 mL) was irradiated in a microwave synthesizer at 110 °C for 2 hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and H_2O. The aqueous layer was further extracted with EtOAc and the organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give crude thioamide **4a** (32 mg, 77% yield), which was used for next step without further purification.

MS (ESI) [M+H$^+$]: 416

The solution of **4a** (10 mg) and chloroacetaldehyde (45% aqueous solution, 0.1 mL) in 2 mL of CH_3CN was heated to 65°C in a sealed tube for 2 hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was further extracted with CH_2Cl_2 and the organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated under

reduced pressure. The residue was purified by column chromatography on silica gel to give compound **70** (3.0 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 3.3 Hz, 1H), 7.60-7.31 (series of m, 5H), 7.06 (t, J = 8.5 Hz, 2H), 2.90-2.83 (m, 4H), 2.36-2.25 (m, 2H).

MS (ESI) [M+H$^+$]: 440

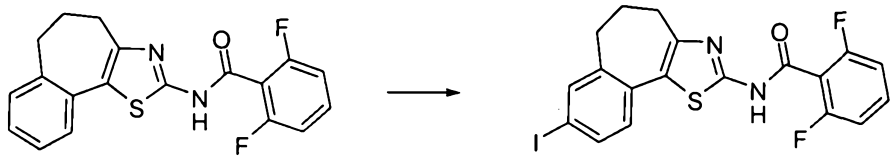
Compound 71:

Compound **71** was prepared from **4a** and 2-chloroacetone similarly as described for the preparation of compound **70)**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (br s, 1H, NH), 7.56-7.40 (series of m, 4H), 7.00 (t, J = 8.2 Hz, 2H), 6.98 (s, 1H), 2.84-2.76 (m, 2H), 2.64-2.54 (m, 2H), 2.54 (s, 3H), 2.22-2.12 (m, 2H).

MS (ESI) [M+H$^+$]: 454

Compound 72:



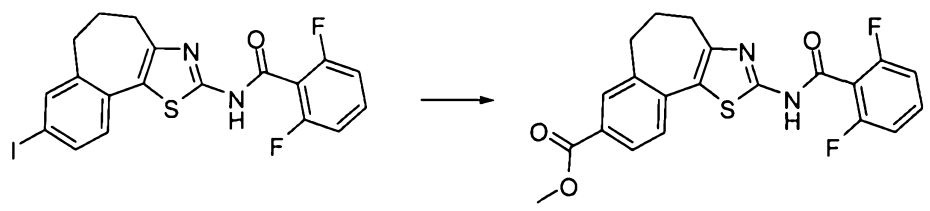
Compound 16 **Compund 72**

Into a solution of Compound **16** (1.00g, 2.80mmol) in concentrated H_2SO_4 (10.0 mL) at 0°C was added NIS (0.65 g, 2.80 mmol) slowly over 1hour. The mixture was stirred at room temperature for 2 hours. The reaction was quenched by addition of ice. The mixture was extracted with CH_2Cl_2. The extract was washed with water and a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with 1:9 EtOAc:hexanes, then with 3:7 EtOAc:hexanes) to give compound **72** (670 mg, 50% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.40 (m, 3H), 7.06-6.95 (m, 3H), 2.80-2.65 (m, 4H), 2.03-1.93 (m, 2H).

MS (ESI) [M+H$^+$]: 483

Compound 73:

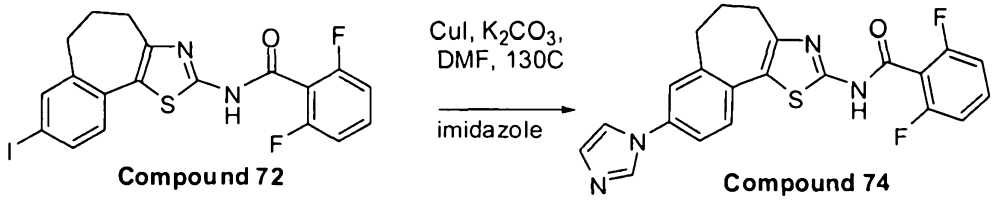


Compound 72 **Compound 73**

Into a solution of Compound **72** (50.0 mg, 0.10 mmol) and DIEA (26.0 mg, 0.20 mmol) in MeOH (2.0 mL) were added $Pd(OAc)_2$ (5.0 mg, 0.02 mmol) and PPh_3 (11 mg, 0.04 mmol). The reaction mixture was purged continuously with a slow bubbling stream of carbon monoxide. After 5 hours at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified on silica gel (eluted with 1:9 EtOAc:hexanes, then with CH_2Cl_2) to give Compound **73** (31mg).

MS (ESI) $[M+H^+]$: 415

Compound 74:

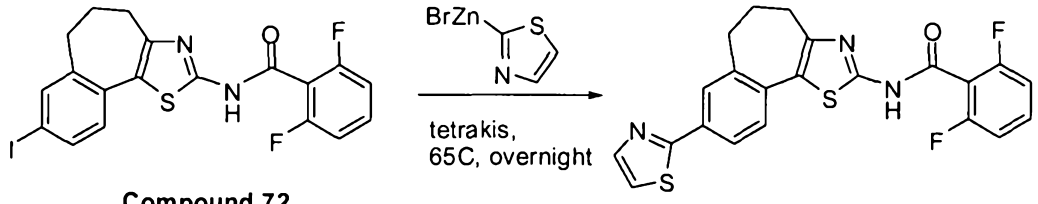


Compound 72 **Compound 74**

Into the solution of compound **72** (48 mg, 0.1 mmol) in DMF (3 mL) was added copper(I) iodide (19 mg, 0.1 mmol), imidazole (20 mg, 0.3 mmol) and K_2CO_3 (42 mg, 0.3 mmol). The mixture was heated in a sealed tube under nitrogen at 130 °C for 1 hour. The mixture was cooled and poured into water, and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **74** (12 mg, 28% yield)

MS (ESI) $[M+H^+]$: 423

Compound 75:



Compound 72 **Compound 75**

Into the solution of Compound **72** (48 mg, 0.10 mmol) in 2 mL of THF at room temperature was added tetrakis(triphenylphosphine)palladium (23.0 mg, 0.02 mmol) followed by a solution of 0.5M 2-thiazolzinc bromide in THF (0.5 mL, 0.25 mmol). The mixture was degassed by vacumm/N_2-fill method (3X). The degassed solution was heated to 65 °C overnight, cooled to

room temperature, quenched with ice water, extracted with methylene chloride. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **75** (16 mg, 36%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (br s, 1H, NH), 7.81 (s, 1H), 7.87-7.31 (series of m, 5H), 7.01 (t, J = 8.5 Hz, 2H), 2.86-2.71 (m, 4H), 2.06-1.97 (m, 2H).

MS (ESI) [M+H$^+$]: 440

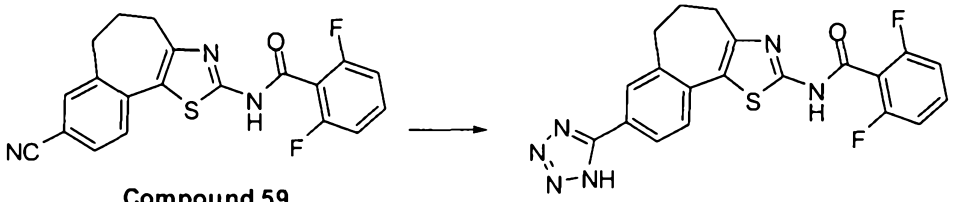
Compound 76:

Compound **76** was prepared from compound **72** and oxazol-2-ylzinc(II) chloride similarly as described for the preparation of compound **75**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (br s, 1H, NH), 7.91-7.86 (m, 2H), 7.72 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.51-7.42 (m, 1H), 7.28-7.25 (m, 1H), 7.01 (t, J = 8.5 Hz, 2H), 2.85-2.74 (m, 4H), 2.04-1.98 (m, 2H).

MS (ESI) [M+H$^+$]: 424

Compound 77:



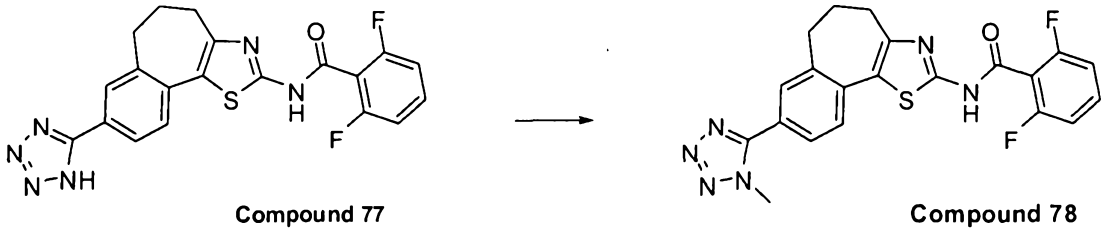
Compound 59 **Compound 77**

A solution of Compound **59** (50 mg, 0.13 mmol), azidotrimethylsilane (0.1 mL, 0.76 mmol), and ammonium chloride (21 mg, 0.39 mmol) in DMF (2.0mL) was heated to 90°C for 3 days. The mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with 1N HCl, with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with CH_2Cl_2) to give the desired compound **77** (25mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 8.2, 1.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.52-7.42 (m, 1H), 7.02 (dd, J = 8, 8 Hz, 2H), 3.04-3.00 (m, 2H), 2.91-2.85 (m, 2H), 2.16-2.08 (m, 2H).

MS (ESI) [M+H$^+$]: 425

Compound 78:



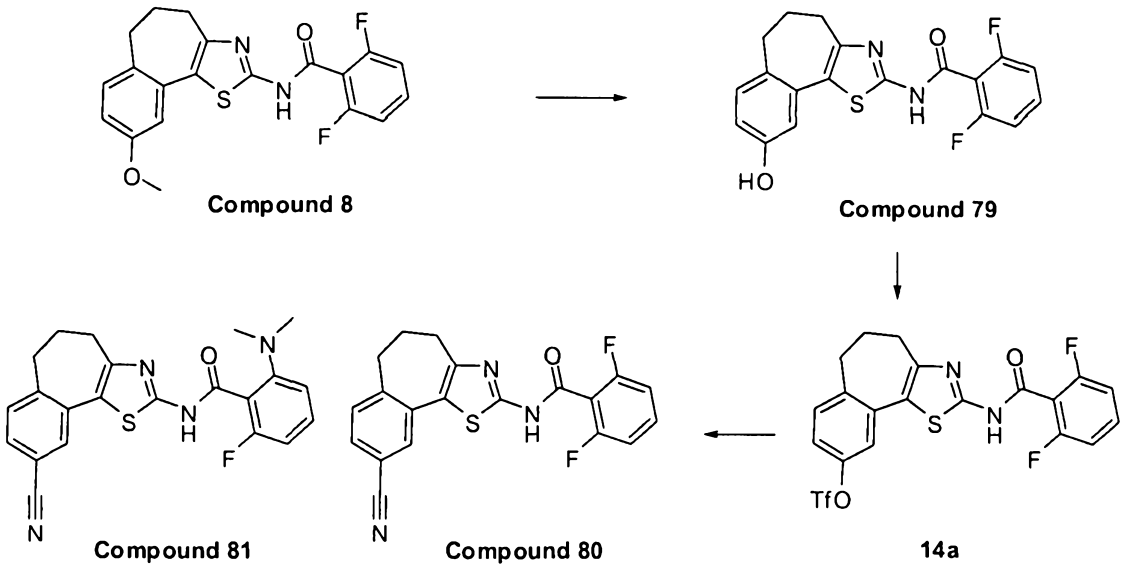
Compound 77 Compound 78

Into a solution of compound **77** (10 mg, 0.024 mmol) in CH_2Cl_2 (1.0 mL) at 0°C was added dropwise a solution of 2M $TMSCHN_2$ in ether (5 drops) in CH_2Cl_2 (1.0 mL). The reaction was continuously monitored for completion by TLC (eluted with CH_2Cl_2). The solvent was removed under reduced pressure. The residue was purified by eluting through a short plug of silica (eluted with CH_2Cl_2) to give the product Compound **78** (9 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.55-7.45 (m, 1H), 7.06 (dd, J = 8.5, 8.3 Hz, 2H), 4.41 (s, 3H), 2.96-2.89 (m, 4H), 2.16-2.08 (m, 2H).

MS (ESI) [$M+H^+$]: 439

Compounds 79, 80 and 81:



Compound 8 Compound 79

Compound 81 Compound 80 14a

Into a solution of Compound **8** (200 mg, 0.52 mmol) in CH_2Cl_2 (4.0 mL) at 0°C was added a solution of 1M BBr_3 (2.0 mL, 1.0 mmol). The mixture was stirred at 0°C for 30 minutes, then at room temperature for 2 hours. The reaction was quenched by addition of ice. The resulting aqueous solution was extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), filtered and concentrated. The residue can be purified on silica gel (eluted first with CH_2Cl_2 then with EtOAc) to give compound **79**).

^1H NMR (300 MHz, $CDCl_3$) δ 7.57-7.47 (m, 1H), 7.26 (s, 1H), 7.09-6.99 (m, 2H), 6.92 (d, J =

2.5Hz, 1H), 6.71 (dd, J = 8.2, 2.5Hz, 1H) 3.10-3.05 (m, 2H), 2.75-2.72 (m, 2H), 2.15-2.05 (m, 2H).

MS (ESI) [M+H$^+$]: 373

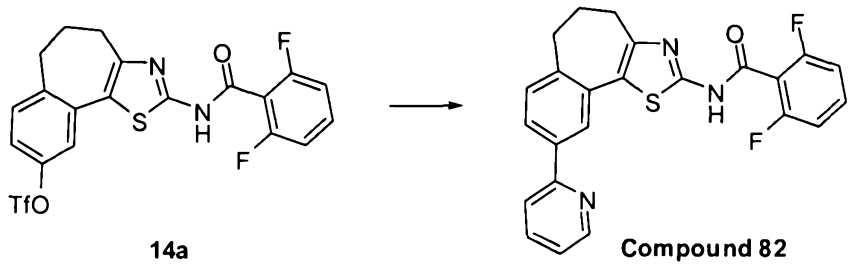
The crude mixture of compound **79,** obtained above, was taken up in pyridine (158 mg, 2.0 mmol) and CH_2Cl_2 (2.0 mL). The mixture was cooled to 0°C. Into the cooled reaction mixture a solution of trifluoromethanesulfonic acid anhydride (282 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added. The mixture was stirred at room temperature for 3 hours, diluted with CH_2Cl_2, washed with 1N HCl then with water, dried (Na_2SO_4), filtered and concentrated. The residue was filtered through a short plug of silica gel (eluted with CH_2Cl_2) to give the crude triflate product **14a**. The crude **14a** was taken up in DMF (1.0 mL). $Zn(CN)_2$ (60.0 mg, 0.51 mmol) and $Pd(PPh_3)_4$ (22.0 mg, 0.02 mmol) were added. The mixture was degassed by vacuum/N_2-filled method (4X). The reaction mixture was sealed and heated to 100°C for 1 day, cooled to room temperature, diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with CH_2Cl_2) to give compound **80** (35 mg) and compound **81** (9 mg).

Compound 80: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.56-7.43 (m, 1H), 7.45 (dd, J = 7.7, 1.4 Hz, 1H), 7.27 (d, J = 7.7Hz, 1H), 7.04-6.99 (m, 2H), 2.83-2.65 (m, 4H), 2.05-1.93 (m, 2H).

MS (ESI) [M+H$^+$]: 382

Compound 81: MS (ESI) [M+H$^+$]: 407

Compound 82:



14a **Compound 82**

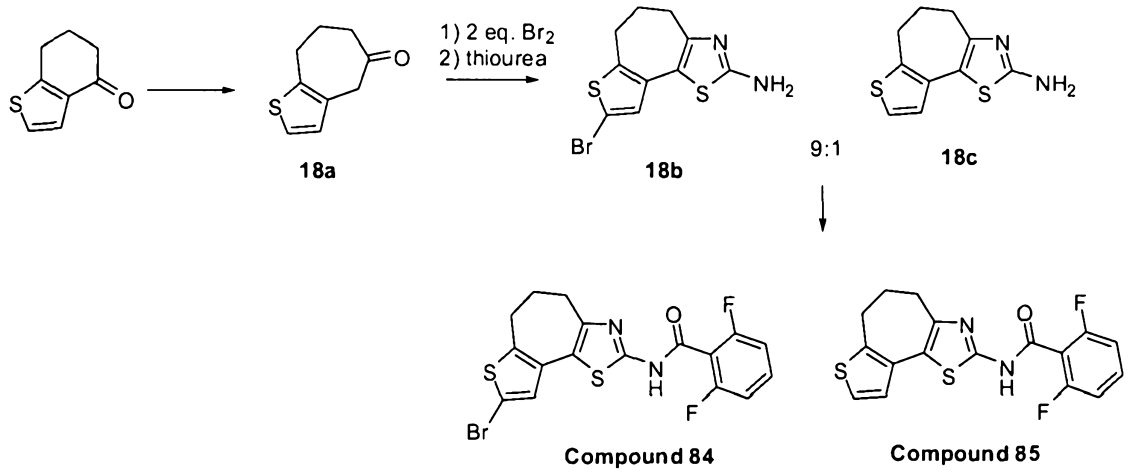
A reaction mixture of **14a** (50.0 mg, 0.10 mmol), 0.5M 2-pyridylzinc bromide in THF (1.0 mL, 0.50 mmol), and $Pd(Ph_3)_4$ (23.0 mg, 0.02 mmol) in THF (0.5 mL) was degassed by vacuum/N_2-filled method (4X). The mixture was heated to 65°C overnight, cooled to room temperature, concentrated under reduced pressure. The residue was purified on silica gel (eluted

with a solution of 1:9 EtOAc:hexanes, then with CH_2Cl_2) to give compound **82** (36mg).
MS (ESI) [M+H$^+$]: 434

Compound 83:

Compound **83** was prepared from **14a** as described for the preparation of Compound **82** using a solution of 0.5M 2-thiazolzinc bromide in THF.
MS (ESI) [M+H$^+$]: 440

Compounds 84 and 85:



Into a solution of 6,7-dihydrobenzo[b]thiophen-4(5H)-one (0.76 g, 0.50 mmol) in CH_2Cl_2 (20.0 mL) at 0°C were added a solution of 1M Et_2AlCl in hexanes (5.0 mL, 5.0 mmol). The mixture was stirred at 0°C for 10 minutes then at room temperature for 20 minutes. The reaction mixture was quenched by ice addition and acidified by addition of a solution of 3N HCl. The resulting mixture was extracted with CH_2Cl_2 (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to give crude **18a**. The crude product was taken up in CH_2Cl_2 (30.0 mL). The mixture was cooled to 0°C. A solution of Br_2 (1.60 g, 10.0 mmol) in CH_2Cl_2 (10.0 mL) was added. The mixture was stirred at 0°C for 30 minutes, quenched by addition of a solution of 10%$NaHSO_3$. The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was filtered through a short plug of silica gel (eluted with a solution of 1:9 EtOAc:hexanes then with CH_2Cl_2) to give crude 9:1 mixture of **18b** and **18c** respectively (255 mg).

18b: MS (ESI) [M+H$^+$]: 301

18c: MS (ESI) [M+H$^+$]: 223

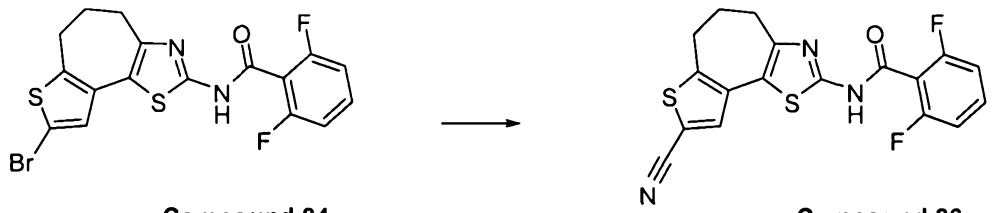
Into a solution of a 9:1 mixture of **18b** and **18c** (155 mg, 0.49 mmol) in CH_2Cl_2 (2.0 mL) at room

temperature were added DMAP (10 mg, 0.082 mmol), Et_3N (101mg, 1.0mmol), and 2,6-difluorobenzoylchloride (176 mg, 1.00 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was taken up in MeOH (2.0 mL). K_2CO_3 (138 mg, 1.00 mmol) was added. The mixture was stirred at room temperature for 1 hour, diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica (eluted with a solution of 1:9 EtOAc:hexanes then with a solution of 3:7 EtOAc:hexanes) to give enriched fractions of compound **84** and **85**. Pure Compound **84** (75 mg), and Compound **85** (8 mg) were obtained by recrystalization from ether.

Compound 84: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.40 (m, 1H), 7.05 (s, 1H), 7.02-6.90 (m, 2H), 2.90-2.80 (m, 2H), 2.78-2.60 (m, 2H), 1.95-1.80 (m, 2H).
MS (ESI) [M+H$^+$]: 443

Compound 85: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.33 (m, 1H), 7.38 (d, J = 5.2 Hz), 6.98 (d, J = 5.2 Hz), 6.92 (dd, J = 8.2, 8.2 Hz, 2H), 3.10-3.05 (m, 4H), 2.16-2.09 (m, 2H).
MS (ESI) [M+H$^+$]: 363

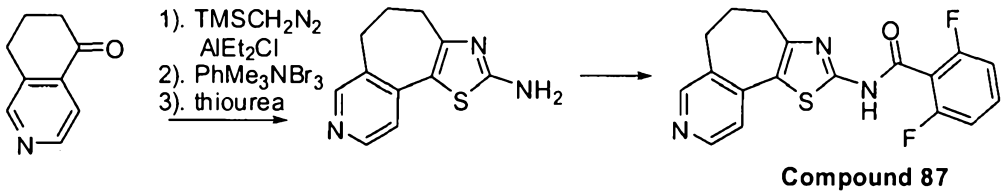
Compound 86:



Compound 84 **Compound 86**

A mixture of Compound **84** (70 mg, 0.16 mmol), $Zn(CN)_2$ (59 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol) in DMF (1.0 mL) was degassed by vacuum/nitrogen-fill method (3X). The resulting mixture was sealed and heated to 100°C for 1 day, cooled to room temperature, diluted with CH_2Cl_2, washed with water (3X), dried (Na_2SO_4), filtered, and concentrated. The residue was purified on silica gel (eluted with a solution of 1:9 EtOAc:hexanes, then with a solution of 3:7 EtOAc:hexanes) to give compound **86** (21 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.57-7.47 (m, 1H), 7.08-7.05 (m, 2H), 3.09-2.95 (m, 4H), 2.15-2.05 (m, 2H).
MS (ESI) [M+H$^+$]: 388

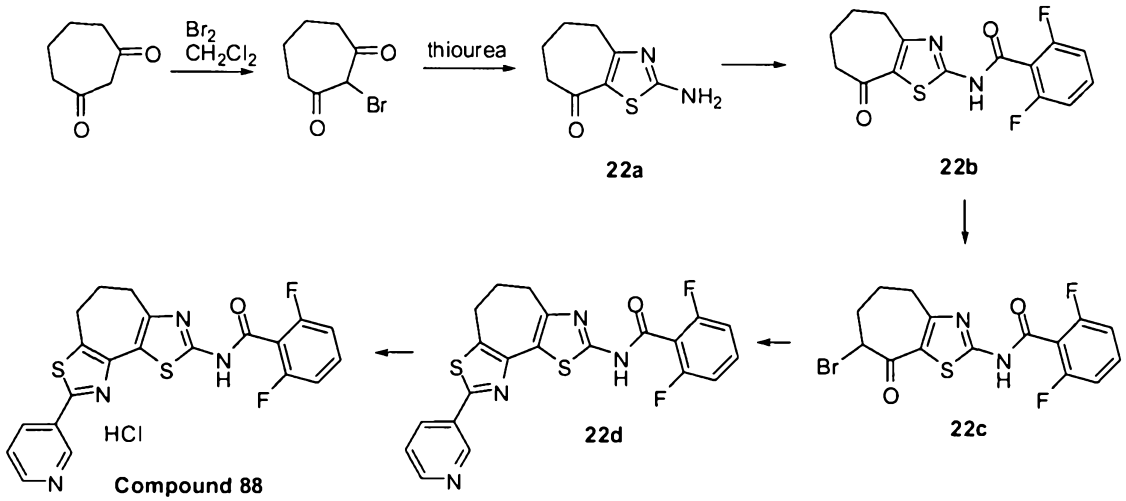
Compound 87:



Compound **87** was prepared from 7,8-dihydroisoquinolin-5(6H)-one similarly as described for the preparation of compound **12**.

MS (ESI) [M+H$^+$]: 358

Compound 88:



Into the solution of 1,3-cycloheptanedione (252 mg, 2.0 mmol) in 5 mL of CH_2Cl_2 was added a solution of Br_2 (320 mg, 2.0 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature for 15 minutes. The white solid was collected, washed with CH_2Cl_2, and dried to give 2-bromo-1,3-cycloheptanedione (330 mg), which was used for next step with no further purification.

Into the solution of 2-bromo-1,3-cycloheptanedione (205 mg, 1 mmol) in 5 mL of MeOH was added thiourea (152 mg, 2 mmol) and K_2CO_3 (276 mg, 2 mmol). The mixture was stirred at 70°C for 1 hour, cooled down to room temperature. The solution was concentrated, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated to give the crude thiazole **22a** as a yellow solid.

MS (ESI) [M+H$^+$]: 183

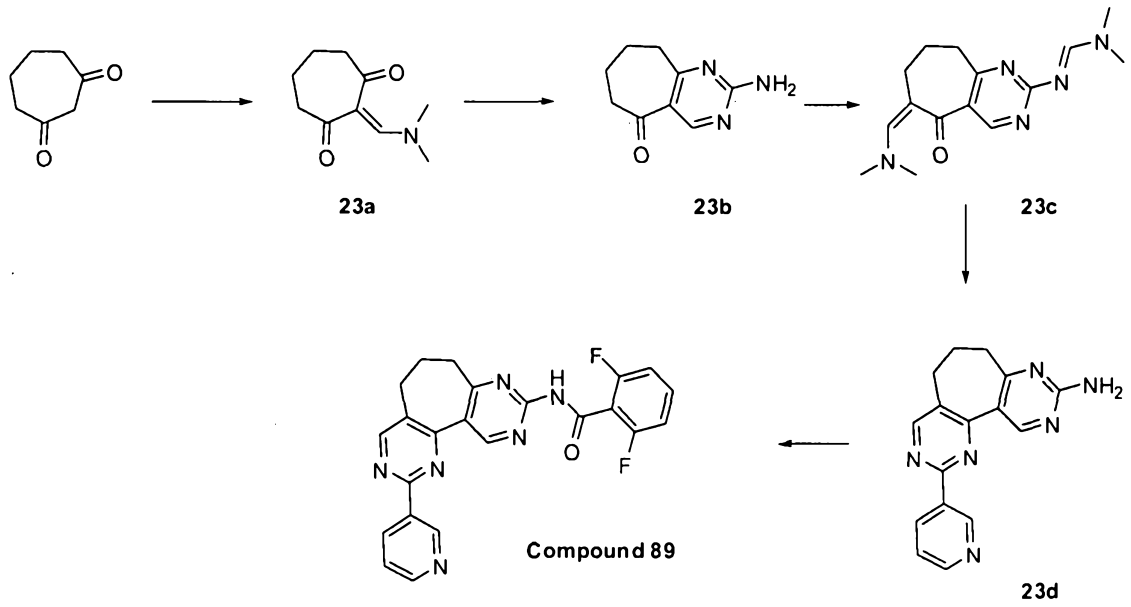
The crude thiazole **22a** was suspended in 5 mL of CH_2Cl_2. To the mixture was added triethylamine (202 mg, 2 mmol), 2,6-difluorobenzoylchloride (176 mg, 1.0 mmol) and catalytic amount of DMAP. The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **22b** (113 mg) as a white solid.
MS (ESI) $[M+H^+]$: 323

Into the solution of **22b** (32 mg, 0.1 mmol) in THF (2 mL) at 0 °C was added phenyltrimethylammonium tribromide (38 mg, 0.1 mmol). The mixture was stirred at 0 °C for 1 hour, quenched by ice addition, extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), filtered and concentrated to give crude **22c** (20 mg) as a solid.
MS (ESI) $[M+H^+]$: 403, 401.

Into the solution of crude **22c** (20 mg, 0.05 mmol) in 3 mL of MeOH was added 3-pyridinecarbothioamide (10 mg, 0.07 mmol) and K_2CO_3 (14 mg, 0.1 mmol). The mixture was stirred at 80 °C in a sealed tube for 2 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and H_2O. The aqueous layer was washed with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated, The residue was purified by column chromatography on silica gel to give **22d** (16 mg) as a yellow solid.

A solution of **22d** (5 mg) in 0.5 mL of CH_2Cl_2 was treated with 0.1 mL of 2 M HCl in Et_2O. The precipitate formed was collected and dried to give **Compound 88** (5 mg) as a white solid
MS (ESI) $[M-Cl^-]$: 441

Compound 89:



Into a reaction flask with 1,3-cyclohexadione (1.00 g, 7.94 mmol) was added N,N-dimethylformamide dimethyl acetal (7.0 mL, 53.0 mmol). The mixture was stirred at room temperature for 1 hour. The excess reagent was removed under reduced pressure to give crude **23a**. The residue was taken up in 2-methoxyethanol (5.0 mL). Guanidine hydrochloride (0.96 g, 10.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) were added. The mixture was heated to 80°C overnight, cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (2X). The combined extracted were dried (Na_2SO_4), filtered and concentrated to give **23b** (1.24 g).

MS (ESI) [M+H$^+$]: 178

Into a reaction flask with **23b** (400 mg, 2.25 mmol) was added N,N-dimethylformamide dimethyl acetal (3.00 mL, 22.7 mmol). The mixture was stirred at 90°C overnight, cooled to room temperature, concentrated under reduced pressure to give crude **23c** (690 mg).

MS (ESI) [M+H$^+$]: 288

Into a solution of **23c** (200 mg, 0.70 mmol) in 2-methoxyethanol (2.0 mL), 3-amidinopyridine hydrochloride (158 mg, 1.00 mmol) and K_2CO_3 (138 mg, 1.00 mmol) were added. The mixture was heated to 90°C overnight, cooled to room temperature, acidified with a solution of 2N HCl (4.00 mL). The mixture was stirred at room temperature for 1 hour, neutralized with an aqueous solution of saturated $NaHCO_3$, extracted with CH_2Cl_2 (2X). The combined extracted were washed with water, dried (Na_2SO_4), filtered and concentrated to give crude **23d** (70% pure, 190 mg).

MS (ESI) [M+H$^+$]: 291

Compound **89** was prepared from **23d** and 2,6-difluorobenzoyl chloride as described for the

preparation of **Compound 8**.

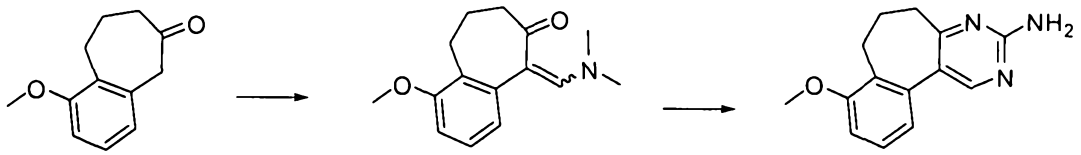
MS (ESI) [M+H$^+$]: 431

Compound 90:

Compound **90** was prepared from compound **89** as described for the preparation of compound **88**

MS (ESI) [M-Cl$^-$]: 431

Compound 91:



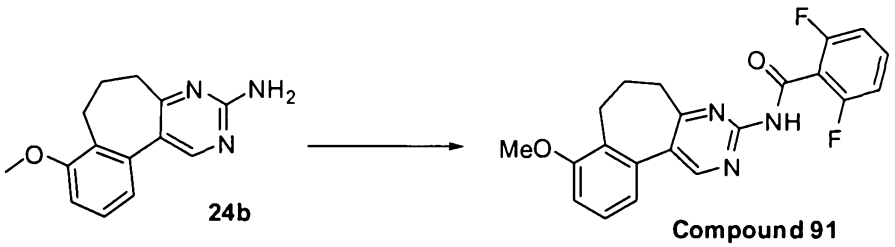
24a **24b**

The solution of 5,7,8,9-tetrahydro-1-methoxy-6*H*-benzocyclohepten-6-one (1.9 g, 10 mmol) in 3 mL of dimethylformamide dimethylacetal was heated in a sealed tube at 90°C for 6 hours. After cooling to room temperature, the reaction was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **24a** (2.30 g, 94% yield) as a pale yellow oil.

MS (ESI) [M+H$^+$]: 246

Into the solution of NaOMe (270 mg, 5 mmol) in 50 mL of anhydrous MeOH was added guanidine hydrochloride (480 mg, 5 mmol). The mixture was stirred at room temperature for 0.5 hour. Into the reaction mixture a solution of **24a** (1.23 g, 5 mmol) in 10 mL of MeOH was added. The resulting mixture was heated to reflux for 8 hours under nitrogen atmosphere. The solution was then cooled to room temperature, concentrated under reduced pressure. The residue was partitioned between Et_2O and H_2O. The aqueous phase was extracted with ether. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **24b** (0.93 g, 77% yield) as a white solid.

MS (ESI) [M+H$^+$]: 242



Into the solution of **24b** (48 mg, 0.2 mmol), triethylamine (41 mg, 0.4 mmol), and a catalytic amount of DMAP in 5 mL of methylene chloride at room temperature was added 2,6-difluorobenzoylchloride (44 mg, 0.25 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was taken up in 5 mL of MeOH. The solution was treated with K_2CO_3 (100 mg). The mixture was stirred at room temperature for 1 hour, concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O, the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give Compound **91** (32 mg, 40% yield) as a white solid.

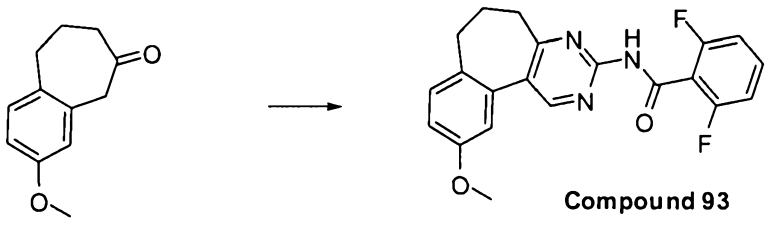
MS (ESI) [M+H$^+$]: 382

Compound 92:

Compound **92** was prepared from **24b** and 3-methylisonicotinoyl chloride similarly as described for the preparation of compound **91**.

MS (ESI) [M+H$^+$]: 361

Compound 93:



Compound **93** was prepared from 3-methoxy-8,9-dihydro-5H-benzo[7]annulen-6(7H)-one similarly as described for the preparation of compound **91.**

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 1H), 7.46-7.37 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.3, 8.0 Hz, 2H), 6.91-6.86 (m, 2H), 2.63-2.52 (m, 2H), 2.50-2.47 (m, 2H), 2.30-2.10 (m, 2H).

MS (ESI) [M+H$^+$]: 382

Compound 94:

Compound **94** was prepared from 7-methoxy-2,3-dihydrobenzo[b]oxepin-4(5H)-one similarly as described for the preparation of compound **91.**

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (bs, 1H), 8.54 (s, 1H), 7.47-7.37 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.02-6.87 (series of m, 4H), 4.59-4.55 (m, 2H), 2.91-2.87 (m, 2H).

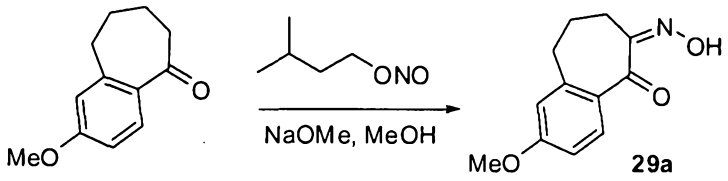
MS (ESI) [M+H$^+$]: 384

Compound 95:

Compound **95** was prepared similarly as described for the preparation of compound **94** using 3-methylisonicotinoyl chloride.

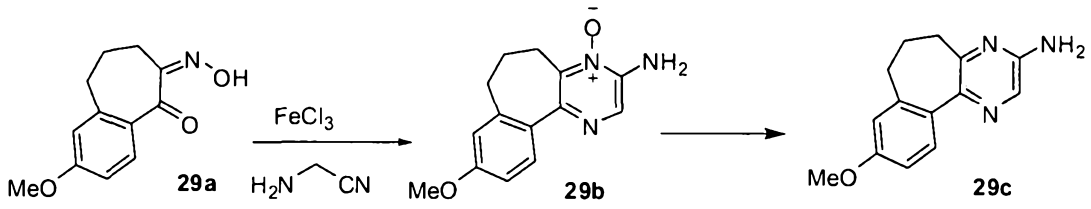
MS (ESI) [M+H$^+$]: 363

Compound 96:



Into the solution of NaOMe (810 mg, 15 mmol) in 50 mL of MeOH was added 7-methoxybenzosuberone (1.90 g, 10 mmol) and isopentyl nitrite (1.48 mL, 11 mmol). The mixture was stirred at room temperature for 48 hours. The reaction mixture was concentrated under reduced pressure. The residue was taken up in methylene chloride, washed with H_2O. The aqueous layer was neutralized with 1N aqueous HCl and extracted with methylene chloride. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was recrystallized from CH_2Cl_2/hexanes to give **29a** (1.6 g, 73%) as a white solid.

MS (ESI) [M+H$^+$]: 220



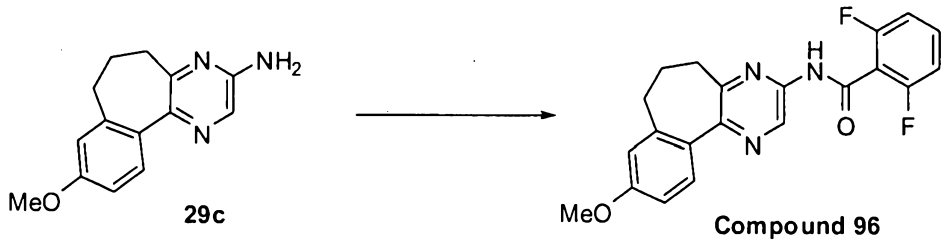
Into the solution of aminoacetonitrile sulfate (720 mg, 5 mmol) in 5 mL of MeOH at room temperature were added 12 N aqueous NaOH (10 mmol), **29a** (550 mg, 2.5 mmol) and ferric

chloride (407 mg, 2.5 mmol). The resulting mixture was stirred at 50°C for 2 hours then at reflux for 4 hours. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give **29b** (420 mg, 65% yield) as a white solid.

MS (ESI) [M+H$^+$]: 258

Into the solution of **29b** (257 mg, 1 mmol) in 10 mL of MeOH was added Pd/C (10%w/w, 150 mg). The mixture was stirred under a pressure of hydrogen (3 atm) at 50°C for 48 hours. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc. The solution was washed with water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel to give **29c** (150 mg, 63%) as a white solid.

MS (ESI) [M+H$^+$]: 242



Compound **96** was prepared from **29c** similarly as described for the preparation of compound **91.**

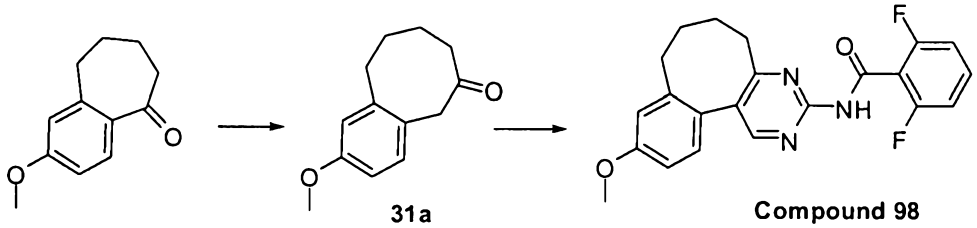
MS (ESI) [M+H$^+$]: 382

Compound 97:

Compound **97** was prepared from **29b** similarly as described for the preparation of compound **96.**

MS (ESI) [M+H$^+$]: 398

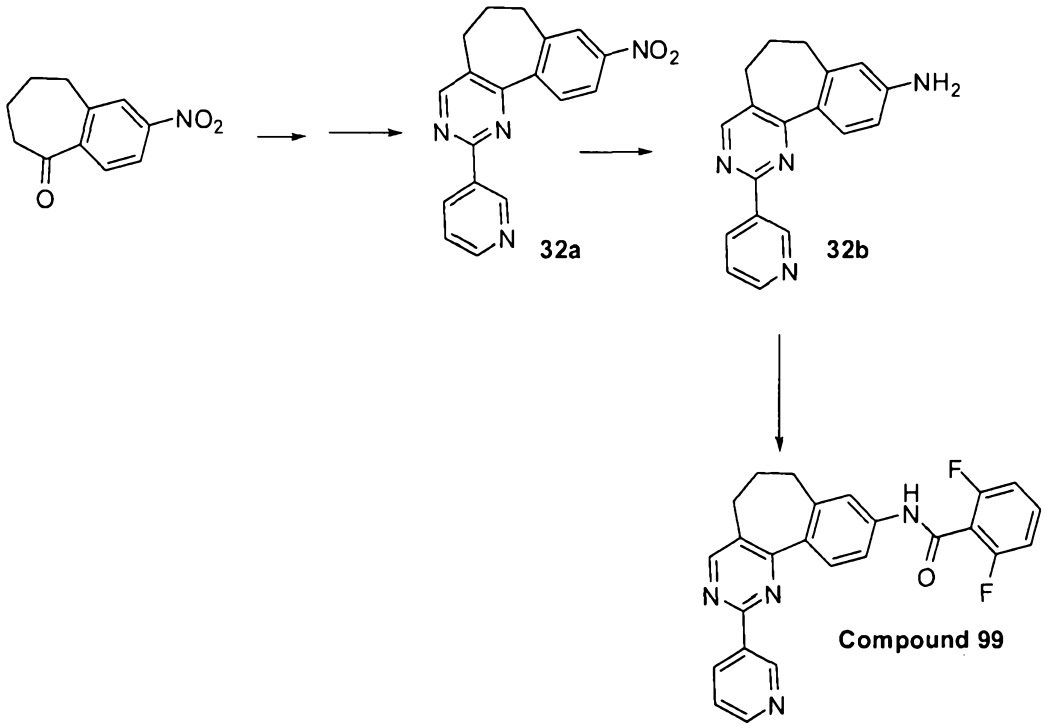
Compound 98:



Compound **98** was prepared from **31a** as described for the preparation of compound **91**. **31a** was prepared from 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one by ring-expansion method described in the preparation of Compound **8**.

MS (ESI) [M+H$^+$]: 396

Compound 99:



32a was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one as described for the preparation of **24b**.

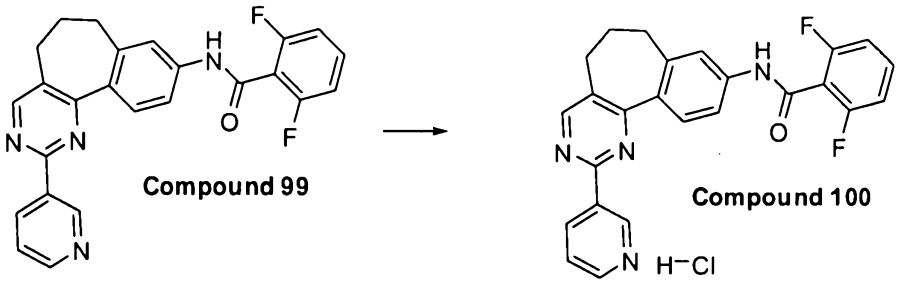
Into a solution of **32a** (400 mg) in ethanol (10.0 mL) at room temperature were added a solution of 2N HCl (1.0 mL) and 10% Pd/C (100 mg). The mixture was stirred under hydrogen gas (1atm) for 3 hours. The mixture was neutralized with a solution of saturated $NaHCO_3$, extracted with CH_2Cl_2 (2X). The combined extracts were dried (Na_2SO_4), filtered and concentrated to give **32b** (317 mg).

MS (ESI) [M+H$^+$]: 289

Compound **99** was prepared from **32b** as described for the preparation of compound **91.**

MS (ESI) [M+H$^+$]: 429

Compound 100:



Into a solution of compound **99** (7 mg) in methylene chloride (1.0 mL) at room temperature was added a solution of 4M HCl in 1,4-dioxane (0.1 mL). The solvent and excess reagent were removed under reduced pressure. The residue was washed with ether and dried to give compound **100** (7 mg).

MS (ESI) [M-Cl$^-$]: 429

Compound 101:

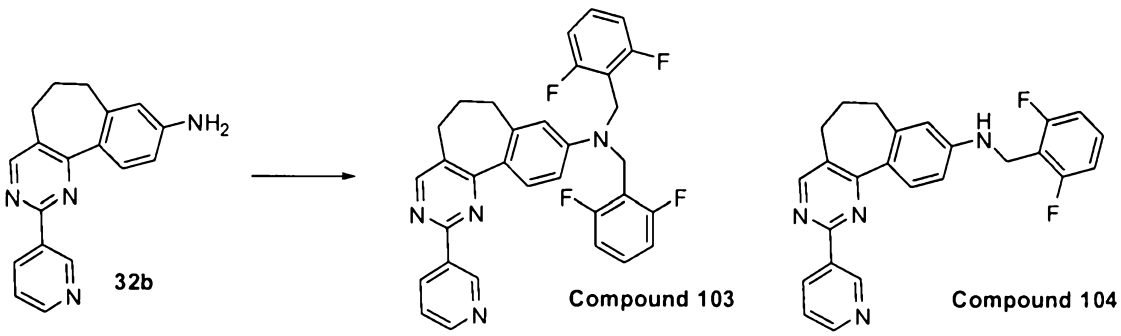
Compound **101** was prepared from **32b** as described for the preparation of compound **92.**

MS (ESI) [M+H$^+$]: 408

Compound 102:

Compound **102** was prepared from compound **101** as described for the preparation of Compound **100**. MS (ESI) [M-HCl-Cl$^-$]: 408

Compounds 103 and 104



Into a solution of the amine **32b** (30 mg, 0.1 mmol) and 2,6-difluorobenzaldehyde (14 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1 drop). The mixture was stirred at room temperature for 30 minutes. $Na(OAc)_3BH$ (42 mg, 0.2 mmol) was added. The mixture was stirred at room temperature overnight, diluted with CH_2Cl_2, washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with 1:9, EtOAc:hexanes) to give compound **103** (15 mg) and compound **104** (9 mg).

Compound 103: MS (ESI) [M+H$^+$]: 541.

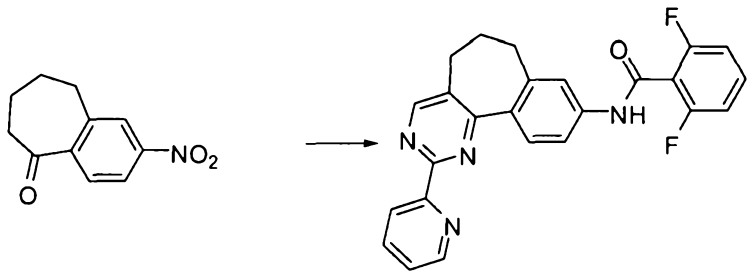
Compound 104: MS (ESI) [M+H$^+$]: 415.

Compound 105:

Compound **105** was prepared from compound **104** as described for the preparation of Compound **100.**

MS (ESI) [M-HCl-Cl$^-$]: 415.

Compound 106:

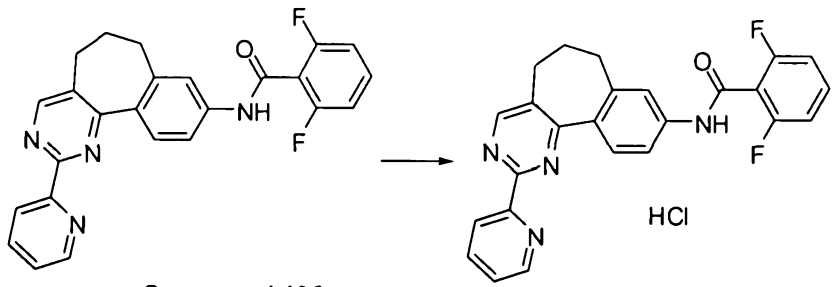


Compound 106

Compound **106** was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one and 2-amidinopyridine hydrochloride similarly as described for the preparation of compound **99:**

MS (ESI) [M+H$^+$]: 429

Compound 107:

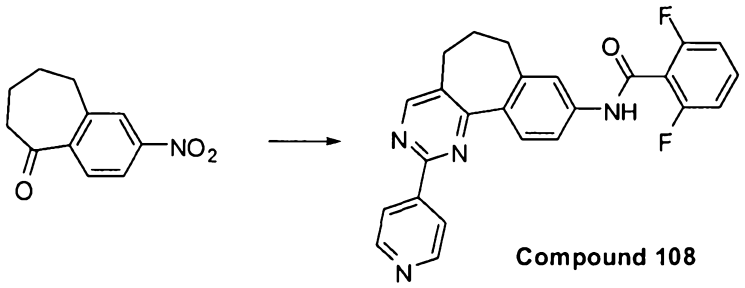


Compound 106 **Compound 107**

A solution of Compound **106** (10 mg) in 0.5 mL of CH_2Cl_2 was treated with 0.1 mL of 2 M HCl in Et_2O. The precipitate formed was collected and dried to give Compound **107** (10 mg) as a white solid.

MS (ESI) [M-Cl$^-$]: 429

Compound 108:

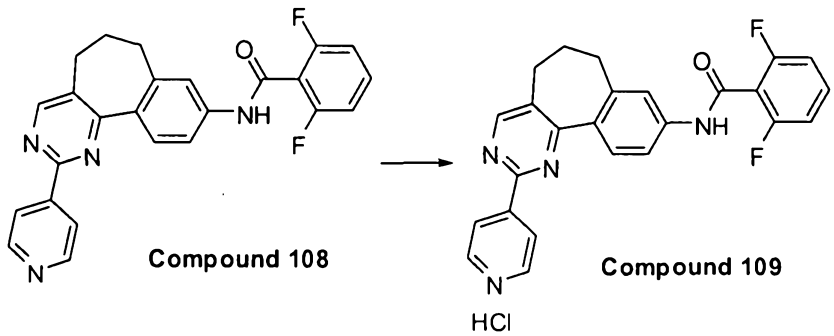


Compound 108

Compound **108** was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one and 4-amidinopyridine hydrochloride similarly as described for the preparation of compound **99:**

MS (ESI) [M+H$^+$]: 429

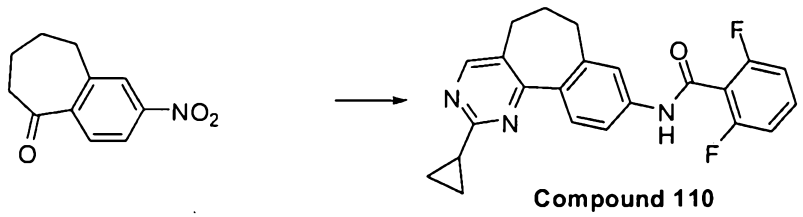
Compound 109:



A solution of compound **108** (5 mg) in 0.5 mL of CH_2Cl_2 was treated with 0.1 mL of 2 M solution of HCl in Et_2O. The precipitate formed was collected and dried to give compound **109** (5 mg) as a white solid.

MS (ESI) [M-Cl$^-$]: 429

Compound 110:

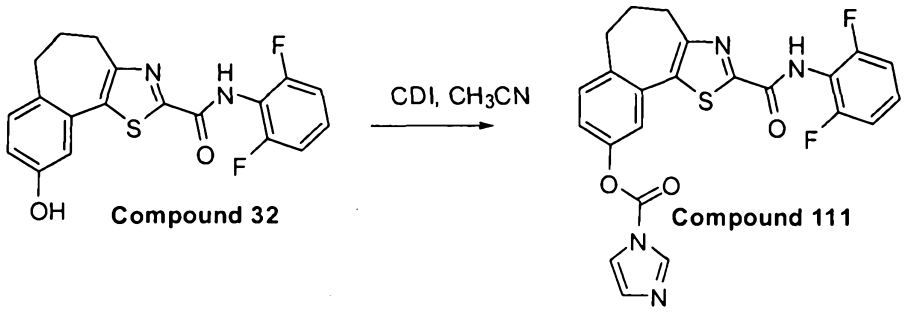


Compound 110

Compound **110** was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one and cyclopropycarbamidine hydrochloride similarly as described for the preparation of compound **99:**

MS (ESI) [M+H$^+$]: 392

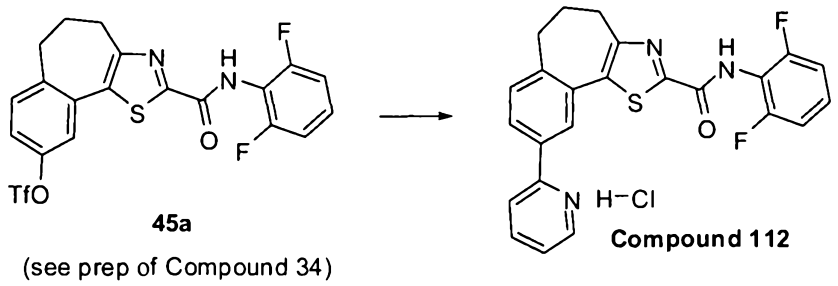
Compound 111:



Into the solution of Compound **32** (100 mg, 0.27 mmol) in 4 mL of CH_3CN was added 1,1-carbonylbis-1*H*-imidazole (150 mg, 0.93 mmol). The mixture was heated to reflux for 30 minutes. The reaction was cooled to room temperature, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **111** (88 mg, 70% yield) as a white solid.

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

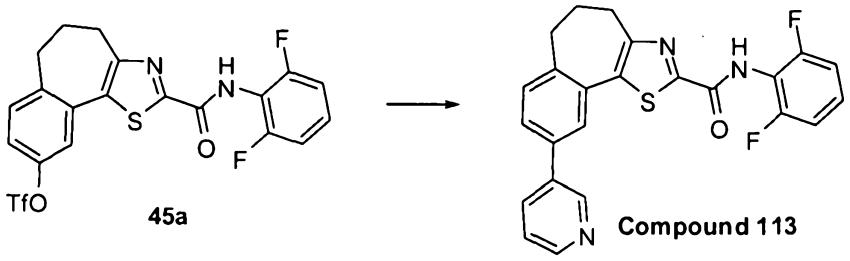
Compound 112:



Compound **112** was prepared from the triflate **45a** similarly as described for the preparation of compound **82** followed by salt formation as described for the preparation of compound **107.**

MS (ESI) [$M-Cl^-$]: 434

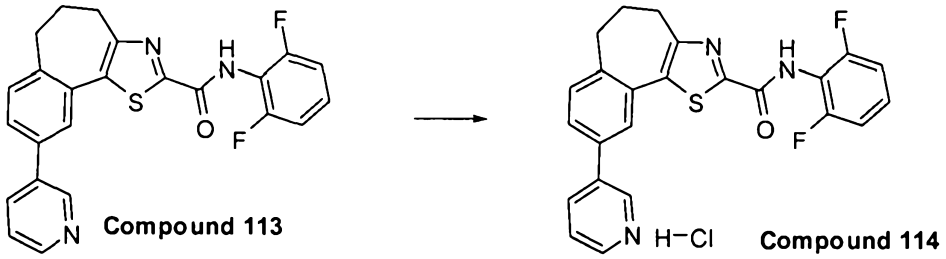
Compound 113:



A mixture of **45a** (400 mg, 0.79 mmol), pyridin-3-ylboronic acid (185 mg, 1.50 mmol), potassium acetate (196 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (100 mg, 0.1 mmol) in 10:1 solution of ethanol:water (5.5 mL) was purged with nitrogen for 10 minutes. The mixture was sealed and heated to 85°C overnight, cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (2X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with CH_2Cl_2 then with a solution of 4:1 CH_2Cl_2:EtOAc) to give compound **113** (230 mg).

MS (ESI) [M+H$^+$]: 434

Compound 114:



Into a solution of compound **113** (230 mg, 0.53 mmol) in CH_2Cl_2 (10.0 mL) at room temperature was added a solution of 2M HCl in ether (2.0 mL, 2.0 mmol). The mixture was stirred at room temperature for 10 minutes. Solvent and excess reagent was removed under reduced pressure. The solid was washed with ether to give compound **114** (198 mg).

^{1}H NMR (300 MHz, CD_3OD) δ 10.65 (s, 1H), 9.45 (s, 1H), 8.85-8.65 (m, 2H), 8.00 (s, 1H), 7.96-7.18 (series of m, 6H), 3.17-3.11 (m, 2H), 2.89-2.80 (m, 2H), 2.25-2.15 (m, 2H).

MS (ESI) [M-Cl$^-$]: 434

Compound 115:

Compound **115** was prepared as described for the preparation of compound **113** using 2-aminopyridine-5-boronic acid pinacol ester.

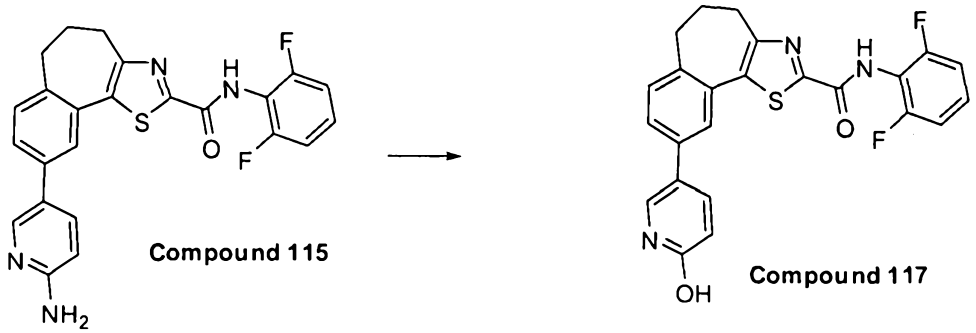
MS (ESI) [M+H$^+$]: 449

Compound 116:

Compound **116** was prepared from compound **115** as described for the preparation of compound **114.**

MS (ESI) [M-Cl$^-$]: 449

Compound 117:



Into a solution of compound **115** (10.0 mg, 0.022 mmol) in acetic acid (1.0 mL) at 0°C was added $NaNO_2$ (10.0 mg, 0.14 mmol). The mixture was stirred at 0°C for 1 hour then at room temperature overnight, concentrated under reduced pressure. The residue was taken up in a solution of methanol (0.5 mL) and pyridine (0.5 mL). The mixture was heated to 50°C for 1 hour, cooled to room temperature, concentrated under reduced pressure. The residue was taken up in water, acidified with acetic acid, extracted with CH_2Cl_2 (3X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on a short plug of silica gel (eluted with CH_2Cl_2 then with EtOAc) to give compound **117** (8 mg).

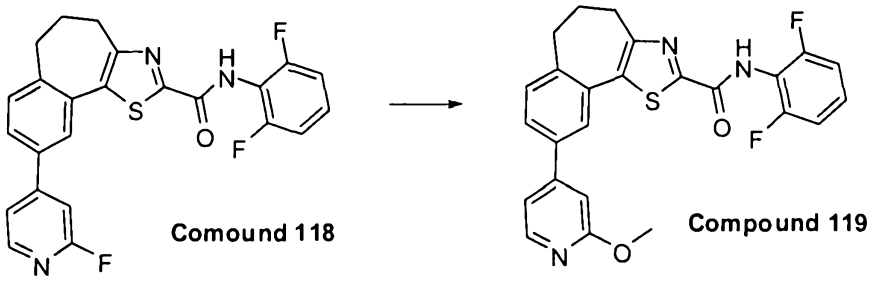
MS (ESI) [M+H$^+$]: 450

Compound 118:

Compound **118** was prepared as described for the preparation of compound **113** using 2-fluoropyridine-4-boronic acid.

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

Compound 119:



Into a solution of compound **118** (10.0 mg, 0.022 mmol) in methanol (1.0 mL) at room temperature was added a solution of 25% NaOMe in methanol (0.2 mL, 0.88 mmol). The mixture was heated to 50°C for 1 day, cooled to room temperature, diluted with water, acidified with acetic acid, extracted with CH_2Cl_2 (2X). The combined extracts were washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give compound **119** (8 mg).

MS (ESI) [M+H$^+$]: 464

Compound 120:

Compound **120** was prepared as described for the preparation of compound **113** using 6-fluoropyridine-3-boronic acid.

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

Compound 121:

Compound **121** was prepared from compound **120** similarly as described for the preparation of compound **119**.

MS (ESI) [M+H$^+$]: 464

Compound 122:

Compound **122** was prepared as described for the preparation of compound **113** using 2-fluoropyridine-3-boronic acid.

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

Compound 123:

Compound **123** was prepared from compound **122** similarly as described for the preparation of compound **119**.

MS (ESI) [M+H$^+$]: 464

Compound 124:

Compound **124** was prepared as described for the preparation of compound **113** using pyrimidine-5-boronic acid.

MS (ESI) [M+H$^+$]: 435

Compound 125

Compound **125** was prepared as described for the preparation of compound **113** using pyridine-4-boronic acid.

MS (ESI) [M+H$^+$]: 434

Compound 126:

Compound **126** was prepared from compound **125** as described for the preparation of compound **113.**

MS (ESI) [M-Cl$^-$]: 434

Compound 127:

Compound **127** was prepared as described for the preparation of compound **113** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

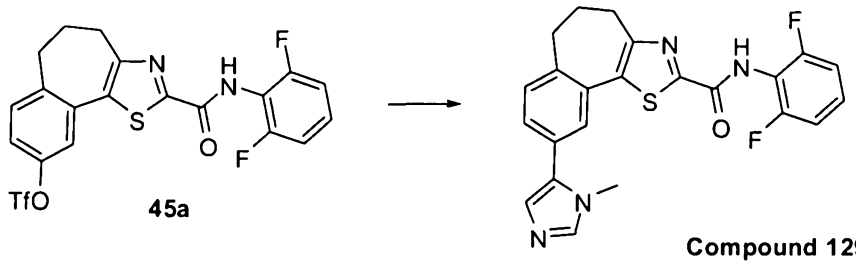
MS (ESI) [M+H$^+$]: 437

Compound 128:

Compound **128** was prepared as described for the preparation of compound **113** using tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate. Deprotection occurred *in situ* to provide compound **128**.

MS (ESI) [M+H$^+$]: 423

Compound 129:



Compound 129

Into a solution of **45a** (600 mg, 1.19 mmol) and 1-methyl-5-(tributylstannyl)-1H-imidazole (888 mg, 2.38 mmol) in DMF (5.0mL) was added $Pd(PPh_3)_4$ (300 mg, 0.26 mmol). The mixture was degassed by vacuum/nitrogen-filled method. The resulting mixture was sealed and heated to 100°C overnight, cooled to room temperature, diluted with ethyl acetate, washed with water (3X)

then with brine and dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with 1:9 MeOH:CH_2Cl_2 to give compound **129** (245 mg).

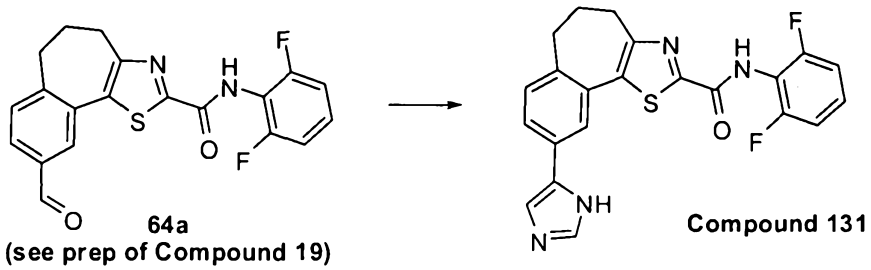
MS (ESI) [$M+H^+$]: 437

Compound 130:

Compound **130** was prepared from compound **129** similarly as described for the preparation of compound **114.**

MS (ESI) [$M-Cl^-$]: 437

Compound 131:



64a
(see prep of Compound 19)

Compound 131

Into a slurry of **64a** (50 mg, 0.13 mmol), toluenesulfonylamide (34 mg, 0.2 mmol) and silica (200 mg) in toleuene (4.0 mL) was heated to 80°C for 4 hours. The mixture was cooled to room temperature, filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was taken up in MeOH (1.0 mL) and 1,2-dimethoxyethane (2.0 mL). *p*-Toluenesulfonylmethyl isocyanide (78 mg, 0.40 mmol) and K_2CO_3 (138 mg, 1.00 mmol) were added. The mixture was heated to 80°C for 1 day, cooled to room temperature, diluted with CH_2Cl_2, washed with water (2X), dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give Compound **131** (18 mg).

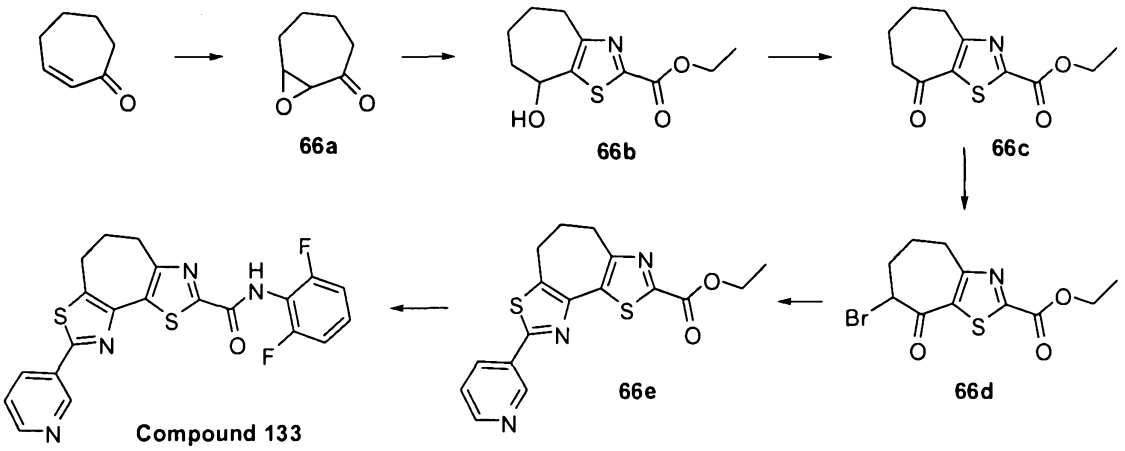
MS (ESI) [$M+H^+$]: 423

Compound 132:

Compound **132** was prepared from compound **131** similarly as described for the preparation of compound **114.**

MS (ESI) [$M-Cl^-$]: 423

Compound 133:



Into a solution of 2,3-cycloheptenone (1.00 g, 0.90 mmol) in THF (10.0 mL) at 0°C were added 2M NaOH (5.0 mL, 10.0 mmol) followed by a solution of 30% aqueous H_2O_2 (0.5 mL, 4.3 mmol). The mixture was stirred at room temperature for 1 hour, diluted with water, ectracted with CH_2Cl_2 (4X). The combined extracts were dried (Na_2SO_4), filtered and concentrated to give the crude epoxide **66a**. The crude epoxide **66a** obtained was taken up in ethanol (10.0 mL). Into the mixture ethyl thiooxamate (1.33 g, 10.0 mmol) was added. The mixture was heated to 80°C for 5 days, cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (3X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give **66b** (950 mg, 44% for 2 steps).

MS (ESI) [M+H$^+$]: 242

Into a solution of **66b** (950 mg, 3.93 mmol) in CH_2Cl_2 (10.0mL) at 0°C was added Dess-Martin reagent (2.12 g, 5.00 mmol). The mixture was stirred at 0°C for 30 minutes then at room temperature for 2 hours. The reaction mixture was quenched by addition of a solution of 10% $NaHSO_3$. After 10 minutes at room temperature, the reaction mixture was neutralized with a solution of saturated $NaHCO_3$, extracted with CH_2Cl_2 (3X). The combined extracts were washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **66c** (895 mg, 95%).

MS (ESI) [M+H$^+$]: 240

Into a solution of **66c** (239 mg, 1.00 mmol) in THF at 0°C was added trimethylphenylammonium tribromide (376 mg, 1.0 mmol). The mixture was stirred at 0°C for 10 minutes then at room temperature for 2 hours. The mixture was diluted with water, extracted with CH_2Cl_2. The extract was washed with a solution of 10% $NaHSO_3$, then with water and dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **66d** (325 mg), which was used without further purification.

Into the crude **66d** (325 mg, 1 mmol) in ethanol (5.0 mL) was added pyridine-3-carbothioamide (138 mg, 1.00 mmol). The mixture was stirred at room temperature for 1 day, diluted with a solution of saturated $NaHCO_3$, extracted with CH_2Cl_2 (2X). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by recrystalization form ether to give **66e** (185 mg).

MS (ESI) $[M+H^+]$: 358

Into a solution of **66e** (22 mg, 0.06 mmol) in toluene (1.0 mL) were added 2,6-difluoroaniline (26 mg, 0.2 mmol) and a solution of 2M trimethylaluminum in hexane (0.1 mL, 0.2 mmol). The mixture was heated to 85°C for 2 hours, cooled to room temperature, quenched with addition of ice. The mixture was extracted with methylene chloride. The extract was washed with a solution of 1N NaOH, then with water and dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica to give compound **133** (16 mg).

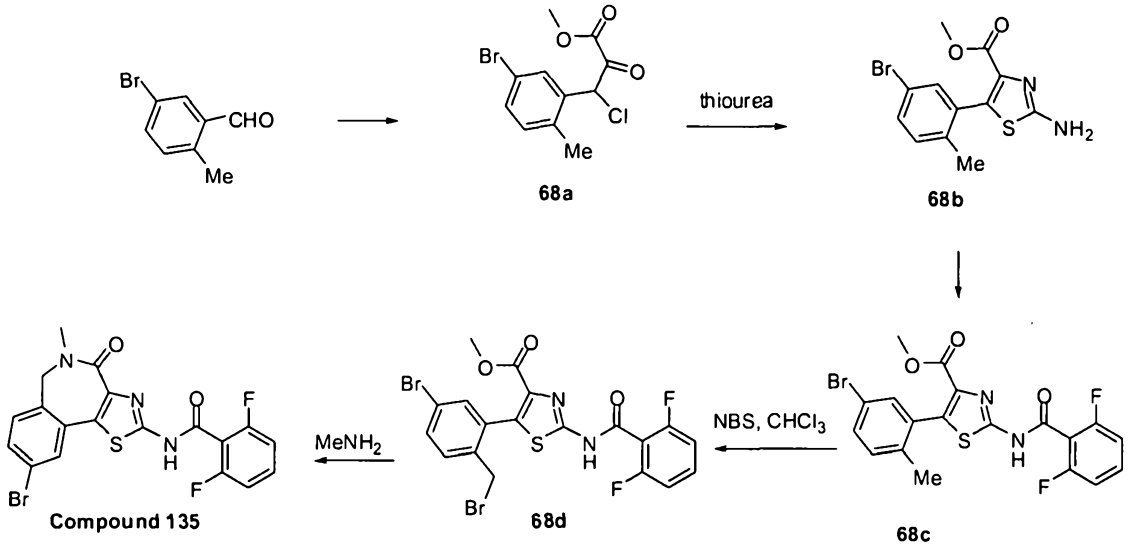
MS (ESI) $[M+H^+]$: 441

Compound 134:

Compound **134** was prepared from compound **133** similarly as described for the preparation of compound **114.**

MS (ESI) $[M-Cl^-]$: 441

Compound 135:



25% NaOMe in MeOH (2.30 mL, 10.0 mmol) was dissolved in 40 mL of THF. The solution was cooled to -78° C and treated dropwise with a solution of 5-bromo-2-methylbenzaldehyde (2.0 g, 10 mmol) in 5 mL of THF and methyl 2,2-dichloroacetate (1.43 g, 10.0 mmol). The mixture was stirred at -78 ° C for 3 hours, then at room temperature overnight. The reaction was quenched with H_2O and the mixture was extracted with methylene chloride. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel to give **68a** (3.0 g).

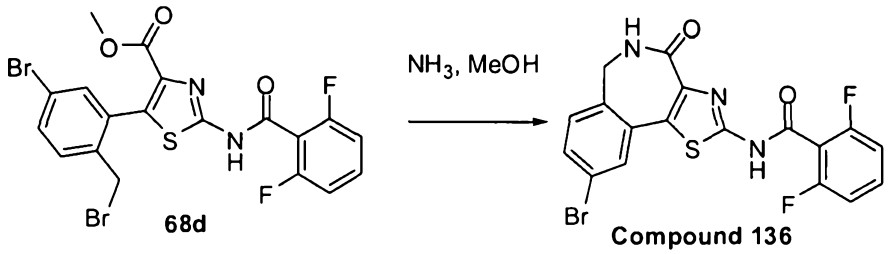
Into the solution of **68a** (1.5 g, 4.9 mmol) in 20 mL of MeOH was added thiourea (0.76 g, 10.0 mmol) at room temperature. The mixture was stirred 80 °C for 1 hour, cooled to room temperature, concentrated. The residue was partitioned between EtOAc and H_2O, the aqueous phase was basified with $NaHCO_3$, extracted with EtOAc. The combined organic phases were washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel to give **68b** (2.0 g, 61% yield) as a solid.
MS (ESI) [M+H$^+$]: 329, 327.

Into the solution of **68b** (654 mg, 2.0 mmol), triethylamine (404 mg, 4.0 mmol), and catalytic amount of DMAP in 10 mL of CH_2Cl_2 at room temperature was added 2,6-difluorobenzoylchloride (492 mg, 2.8 mmol). The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with methylene chloride) to give **68c** (660 mg, 71% yield).
MS (ESI) [M+H$^+$]: 469, 467

Into the solution of **68c** (234 mg, 0.5 mmol) in 5 mL of anhydrous $CHCl_3$ was added NBS (90 mg, 0.5 mmol) and benzoyl peroxide (24 mg, 0.1 mmol). The reaction mixture was reflux under nitrogen atmosphere for 3 hours, cooled to room temperature, and diluted with CH_2Cl_2. The mixture was washed with aqueous $NaHCO_3$ and H_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **68d** (223 mg) as a solid.
MS (ESI) [M+H$^+$]: 549, 547, 545.

Into the solution of **68d** (55 mg, 0.1 mmol) in 2 mL of MeOH was added 2 M solution of $MeNH_2$ in MeOH (0.2 mL). The resulting solution was stirred at room temperature overnight. The reaction was concentrated and the residue was purified by column chromatography on silica gel to give compound **135** (38 mg) as a white solid.
MS (ESI) [M+H$^+$]: 466, 464.

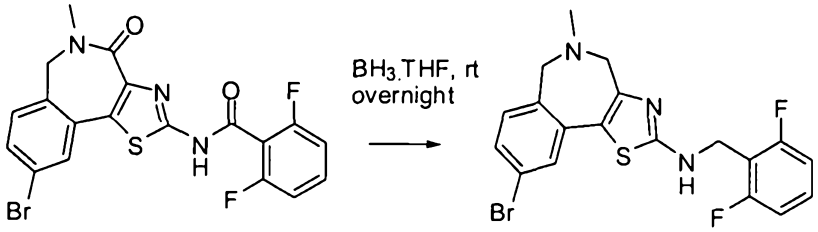
Compound 136:



Into the solution of **68d** (55 mg, 0.1 mmol) in 2 mL of MeOH was added 2 M solution of ammonia in MeOH (0.5 mL). The resulting solution was stirred at room temperature overnight. The reaction was concentrated and the residue was purified by column chromatography on silica gel to give compound **136** (33 mg) as a white solid.

MS (ESI) [M+H$^+$]: 452, 450

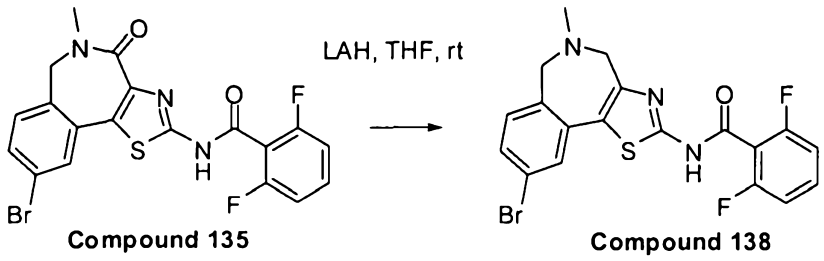
Compound 137:



Into solution of compound **135** (23.5 mg, 0.05 mmol) in 2 mL of THF at room temperature was added a 1.0 M solution of BH_3-THF in THF (1.0 mL). The mixture was stirred at room temperature overnight, quenched with water and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel to give compound **137** (10 mg) as a yellow solid.

MS (ESI) [M+H$^+$]: 436, 434

Compound 138:

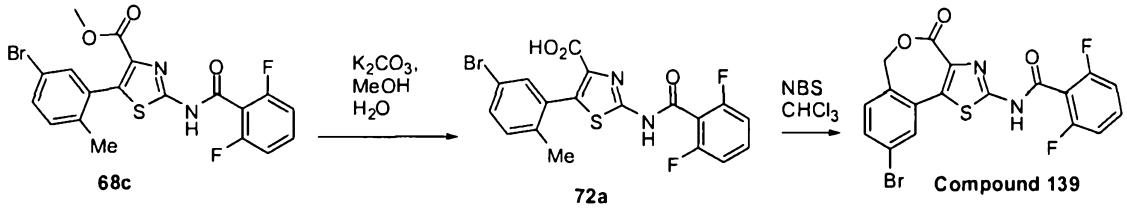


Compound 135 Compound 138

Into solution of compound **135** (23.5 mg, 0.05 mmol) in 2 mL of THF at room temperature was added a 1.0 M solution of Lithium aluminum hydride in THF (0.2 mmol, 0.2 mL). The mixture was stirred at room temperature for 1 hour, cooled to 0 °C and quenched with water followed by 2 M aqueous NaOH. The mixture was extracted with EtOAc, the extracts were washed with water, dried (Na_2SO_4), concentrated. The residue was purified by column chromatography on silica gel to give compound **138** (8.8 mg) as a yellow solid.

MS (ESI) [M+H$^+$]: 452, 450

Example 139:



68c 72a Compound 139

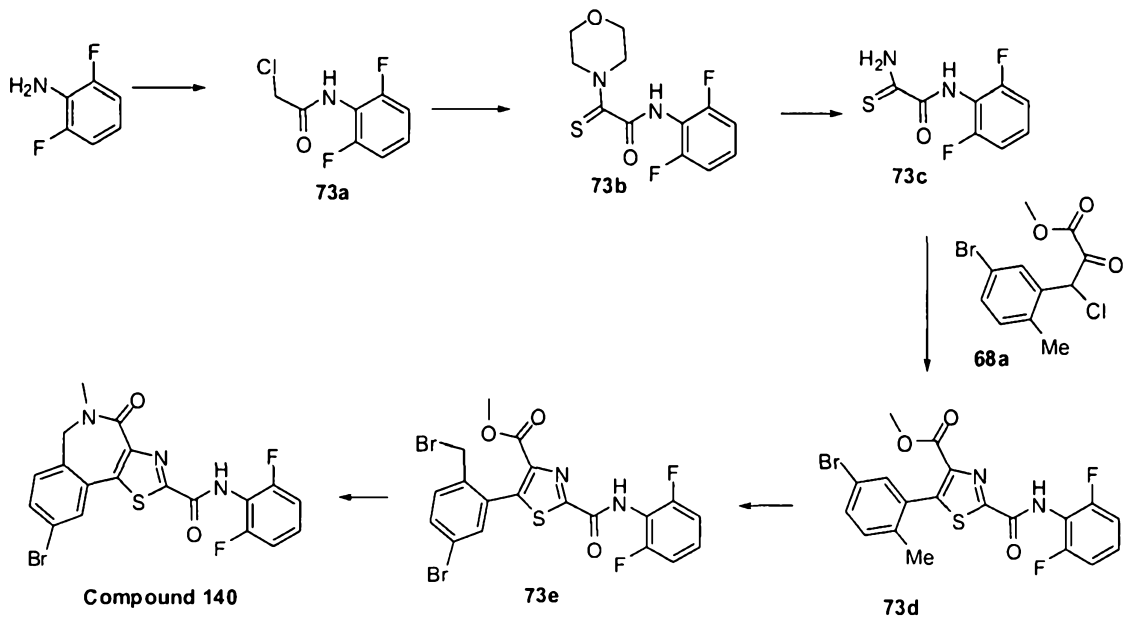
Into the solution of **68c** (234 mg, 0.5 mmol) in 2 mL of MeOH/H_2O (1:1) was added K_2CO_3 (100 mg). The solution was heated to reflux for 2 hours and cooled down to room temperature. The reaction was neutralized with 2 M aqueous HCl and extracted with Et_2O. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to give crude acid **72a** which was used for the next step with no further purification.

MS (ESI) [M+H$^+$]: 455, 453

The crude **72a** was dissolved in 5 mL of $CHCl_3$. The solution was treated with NBS (90 mg, 0.5 mmol) and benzoyl peroxide (24 mg, 0.1 mmol). The reaction mixture was reflux under nitrogen atmosphere overnight, cooled to room temperature, and diluted with CH_2Cl_2. The solution was washed with aqueous $NaHCO_3$ and H_2O. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **139** (133 mg) as a solid.

MS (ESI) [M+H$^+$]: 453, 451

Compound 140:



Into a mixture of 1 M aqueous NaOH (98 mL) and 2,6-difluoroaniline (12.9 g, 0.1 mol) in 100 mL of Et_2O was added dropwise a solution of 2-chloroacetyl chloride (13.3 g, 117 mmol) in 100 mL of Et_2O over 20 minutes at room temperature. The mixture was stirred for 30 minutes at room temperature and the reaction was cooled to 0°C. The white precipitate was collected by filtration to give the first portion of product **73a** (12 g). The organic layer of the filtrate was separated and washed with saturated $NaHCO_3$ and brine, dried and concentrated. The residue was recrystallized from EtOAc to give the second portion of **73a** (7.5 g) as a white solid.
MS (ESI) $[M+H^+]$: 206

Into the solution of **73a** (2.05 g, 10 mmol) in 10 mL of DMF was added morpholine (0.84 g, 11 mmol) and sulfur (1.4 g). The mixture was stirred at room temperature overnight. The reaction mixture was poured into 100 mL of ice water and the white solid formed was collected, dried and recrystallized from EtOH to give **73b** (2.2 g, 77% yield) as a pale yellow solid.
MS (ESI) $[M+H^+]$: 287

Into the solution of **73b** (1.2 g, 4.2 mmol) in 5 mL of pyridine was slowly past through anhydrous ammonia gas. The reaction was stirred at room temperature and monitored by TLC. When the starting material was totally consumed, ammonia was removed and the reaction was concentrated under reduced pressure to remove pyridine. The residue was purified by column chromatography on silica gel to give **73c** (580 mg, 64% yield) as a yellow solid.

The solution of **68a** (305 mg, 1 mmol) and **73c** (216 mg, 1mmol) in 10 mL of EtOH was heated to reflux overnight. After cooling to room temperature, the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give **73d** (288 mg, 62% yield) as a pale yellow solid.

MS (ESI) $[M+H^+]$: 469, 467

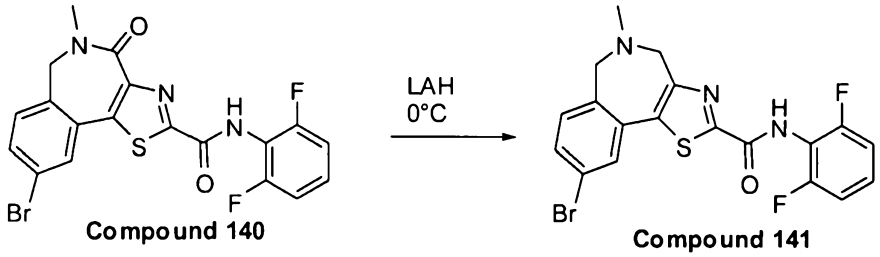
Into the solution of **73d** (234 mg, 0.5 mmol) in 5 mL of anhydrous $CHCl_3$ was added NBS (90 mg, 0.5 mmol) and benzoyl peroxide (24 mg, 0.1 mmol). The reaction mixture was reflux under nitrogen atmosphere for 16 hours, cooled to room temperature, and diluted with CH_2Cl_2. The mixture was washed with aqueous $NaHCO_3$ and H_2O. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **73e** (200 mg, 73% yield) as a solid.

MS (ESI) $[M+H^+]$: 549, 547, 545

Into the solution of compound **73e** (22 mg, 0.04 mmol) in 2 mL of MeOH was added 2 M solution of $MeNH_2$ in MeOH (0.1 mL). The resulting solution was stirred at room temperature overnight. The reaction was concentrated and the residue was purified by column chromatography on silica gel to give compound **140** (14 mg) as a white solid.

MS (ESI) $[M+H^+]$: 466, 464

Compound 141:

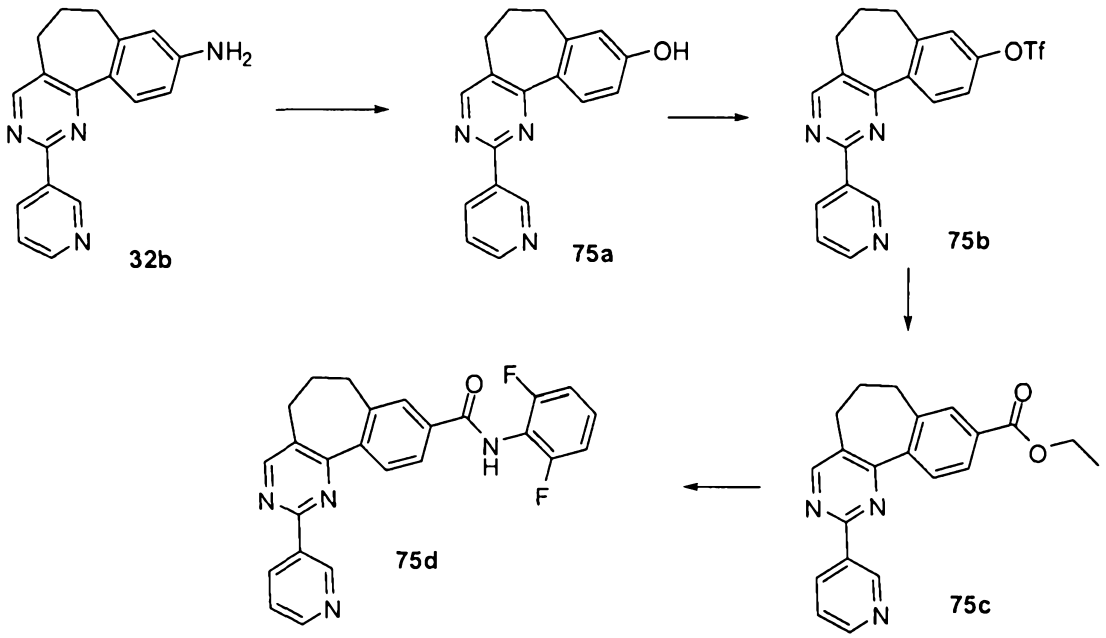


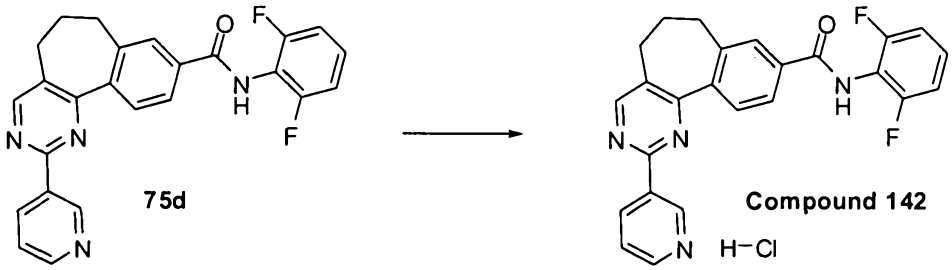
Compound 140 **Compound 141**

Into solution of compound **140** (10 mg) in 2 mL of THF at 0 °C was added a 1.0 M solution of Lithium aluminum hydride in THF (0.2 mmol, 0.2 mL). The mixture was stirred at 0°C for 1 hour, and quenched with ice water followed by 2 M NaOH. The mixture was extracted with EtOAc. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **141** (5.6 mg) as a yellow solid.

MS (ESI) $[M+H^+]$: 452, 450

Compound 142:





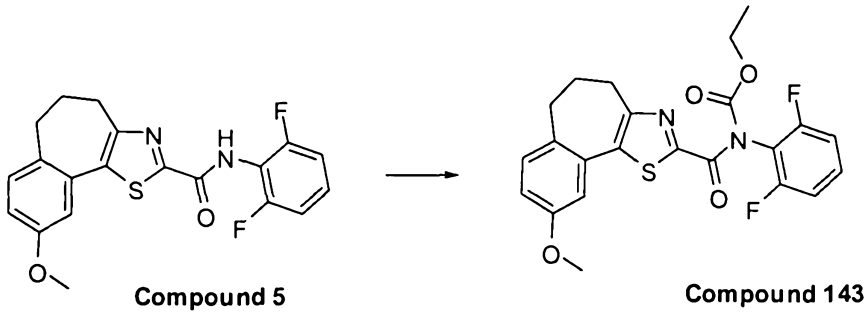
Into a solution of **32b** (317mg, 1.10 mmol) in acetic acid (5.0 mL) at 0°C was added sodium nitrite (175 mg, 2.50 mmol). The mixture was stirred at room temperature overnight. Another portion of sodium nitrite (175 mg, 2.50 mmol) was added. The mixture was heated to 80°C for 5 hours, cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (4X). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was taken up in methanol (2.0 mL). Into the mixture a solution of 2M NaOH (0. 2 mL) was added. The mixture was stirred at room temperature for 30 minutes, neutralized with acetic acid, extracted with CH_2Cl_2 (4X). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **75a**. The crude mixture and pyridine (350 mg, 4.4 mmol) were taken in CH_2Cl_2 (2.0 mL). The mixture was cooled to 0°C. A solution of

triflouromethanesulfonic acid anhydride (620 mg, 2.2 mmol) in CH_2Cl_2 (1.0 mL) was added slowly. The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **75b** (340 mg).
MS (ESI) [M+H$^+$]: 422.

Into a solution of crude **75b** (340 mg) in ethanol (5.0 mL) were added DIEA (0.50 mL), triphenylphosphine (80 mg, 0.30 mmol), and $Pd(OAc)_2$ (40 mg, 0.18 mmol). Into the mixture slow stream of bubbling carbon monoxide was introduced. The mixture was stirred at room temperature overnight, then concentrated under reduced pressure. The residue was purified on silica gel to give **75c** (60% pure, 210 mg).
MS (ESI) [M+H$^+$]: 346.

Compound **142** was prepared from **75d** similarly as described for the preparation of compound **114.**
MS (ESI) [M-Cl$^-$]: 429.

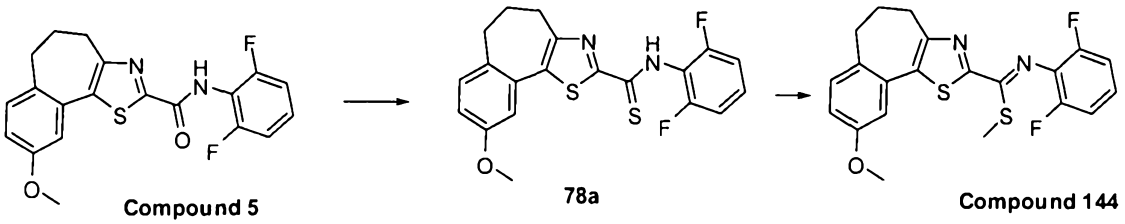
Compound 143:



Compound 5 **Compound 143**

Into a solution of Compound **5** (50 mg, 0.13 mmoL) in THF (2.0 mL) at 0°C was added NaH (60% pure, 40 mg, 1.0 mmol). The mixture was stirred at 0°C for 30 minutes. Into the mixture, ethyl chloroformate (70 mg, 0.65 mmol) in THF (1.0mL) was added. The mixture was stirred at 0°C for 30 minutes then poured over ice. The mixture was extracted with methylene chloride (2X). The combined extracts were dried (Na_2SO_4), filtered concentrated. The residue was purified on silica gel (eluted with 1:9 EtOAc:hexanes) to give compound **143** (45mg).
MS (ESI) [M+H$^+$]: 459

Compound 144:



Compound 5 78a Compound 144

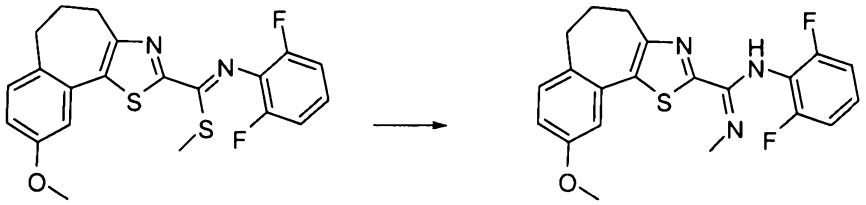
Into a solution of Compound **5** (300 mg, 0.78 mmol) in toluene (10.0 ml) at room temperature was added Lawesson's reagent (600 mg, 1.5 mmol). The mixture was stirred at 100°C overnight, cooled to room temperature. The solid was removed by filtration an discarded. The filtrate was concentrated. The residue was purified on silica gel (eluted with a solution of 1:9 EtOAc:hexanes) to give a semipure thioamide **78a** (415 mg).

MS (ESI) $[M+H^+]$: 403

Into a solution of the semipure **78a** (415 mg, 1 mmol) in DMF (2.0 mL) at 0°C was added NaH (60% pure, 120 mg, 3.0 mmol). The mixture was stirred at 0°C for 30 minutes. Methyl iodide (0.3 mL, 2.0 mmol) in DMF (1.0 mL) was added. After 10 minutes at 0°C, the reaction mixture was quenched by addition of ice. The resulting mixture was extracted with CH_2Cl_2 (2X). The combined extracts were washed with water (3X), dried (Na_2SO_4), filtered concentrated. The residue was purified on silica gel (eluted with 1:19 EtOAc:hexanes) to give **144** (305 mg).

MS (ESI) $[M+H^+]$: 417

Compound 145:



Compound 144 Compound 145

A mixture of Compound **144** (10 mg, 0.024 mmol) in a solution of 1M methylamine in methanol (1.0 mL) was sealed and heated to 65°C for 1 day. The mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified on silica gel (eluted initially with 1:9 EtOAc:hexanes then with EtOAc) to give compound **145** (7 mg).

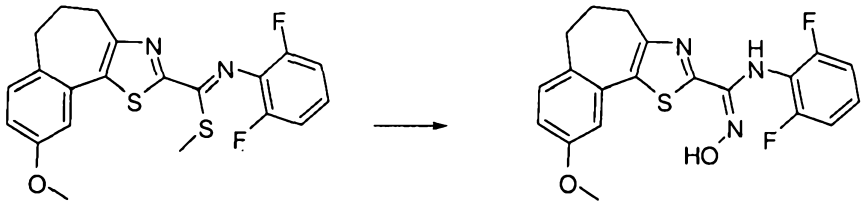
MS (ESI) $[M+H^+]$: 400

Compound 146:

Compound **146** was prepared from compound **145** similarly as described for the preparation of compound **114.**

MS (ESI) $[M-Cl^-]$: 400

Compound 147:

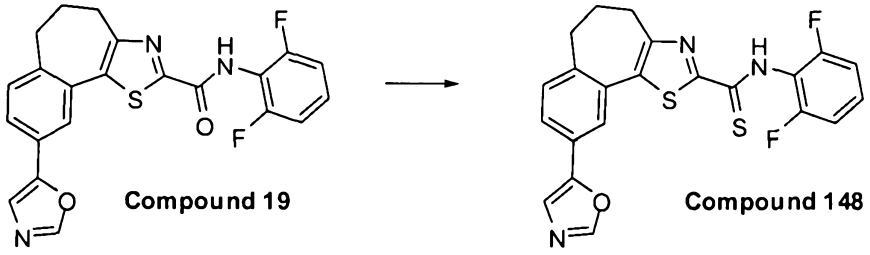


Compound 144 **Compound 147**

Into a solution of compound **144** (20 mg, 0.048 mmol) in pyridine (1.0 mL) at room temperature was added hydroxylamine hydrochloride (14 mg, 0.2 mmol). The mixture was heated to 80°C overnight, cooled to room temperature, diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with 1:9 MeOH:CH_2Cl_2) to give compound **147** (13 mg).

MS (ESI) [M+H$^+$]: 402

Compound 148:

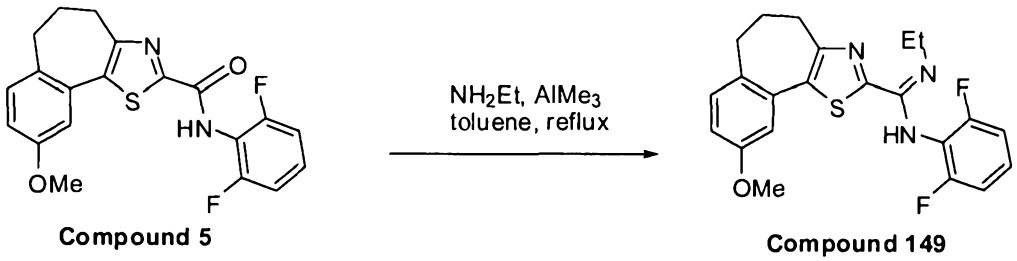


Compound 19 **Compound 148**

Into a solution of Compound **19** (50.0 mg, 0.12 mmol) in toluene (2.0 mL) at room temperature was added Lawesson's reagent (100 mg, 0.25 mmol). The mixture was heated to 100°C overnight, cooled to room temperature. The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified on silica gel (eluted with a solution of 1:19 EtOAc:hexanes) to give compound **148** (32 mg).

MS (ESI) [M+H$^+$]: 440

Compound 149:

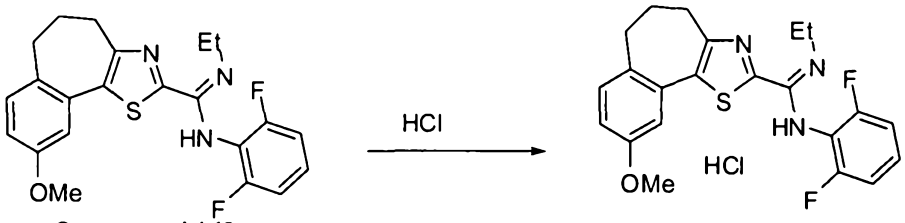


Compound 5 **Compound 149**

Into the solution of Compound **5** (50 mg, 0.13 mmol) and ethylamine hydrochloride (40 mg) in 5 mL of toluene at room temperature was added a 2 M solution of trimethylaluminum in hexanes (0.2 mL, 0.40 mmol). The mixture was heated to reflux for 3 hours and then cooled to room temperature. The reaction was poured over ice water and basified with 2N NaOH. The mixture was extracted with methylene chloride (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **149** (41 mg, 77% yield).

MS (ESI) [M+H$^+$]: 414

Compound 150:

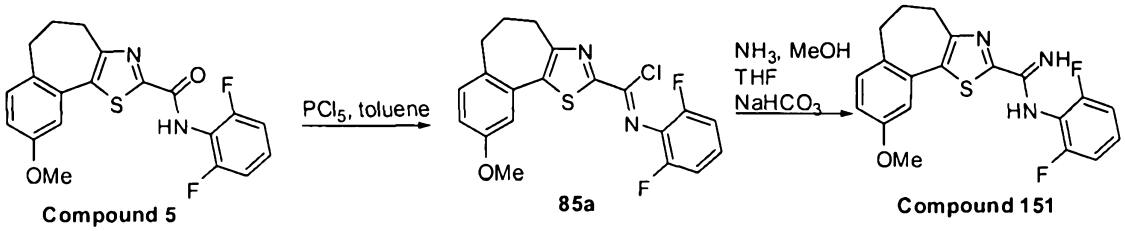


Compound 149 **Compound 150**

A solution of compound **149** (10 mg) in 0.5 mL of Et_2O was treated with 0.1 mL of 2 M HCl in Et_2O. The precipitate formed was collected and dried to give compound **150** (10 mg) as a white solid.

MS (ESI) [M-Cl$^-$]: 414

Compound 151:



Compound 5 **85a** **Compound 151**

The solution of Compound **5** (50 mg) and PCl_5 (100 mg) in 2 mL of toluene was stirred at room temperature overnight. The solution was concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc and the organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel to give **85a** (41 mg) as a white solid.

MS (ESI) [M+H$^+$]: 405

Into the solution of **85a** (20 mg) in 2 mL of THF was added $NaHCO_3$ (100 mg) and NH_3 (2.0 M solution in EtOH, 0.2 mL). The mixture was stirred at room temperature overnight. The solution was concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel to give compound **151** (17 mg) as a white solid.

MS (ESI) [M+H$^+$]: 386

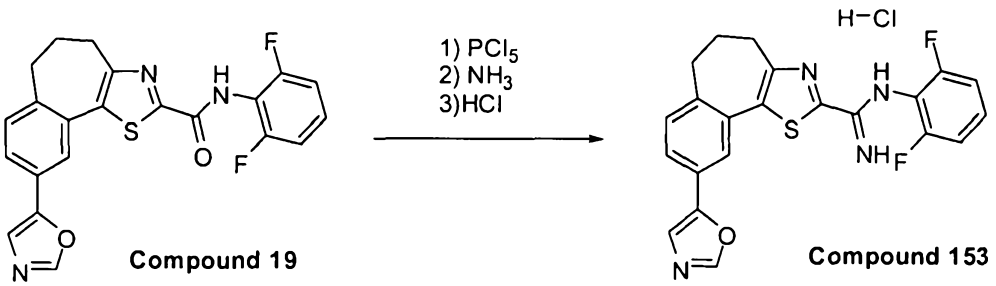
Compound 152:

Compound 151 **Compound 152**

A solution of compound **151** (5 mg) in 0.5 mL of CH_2Cl_2 was treated with 0.1 mL of 2 M HCl in Et_2O. The precipitate formed was collected and dried to give compound **152** as a white solid.

MS (ESI) [M-Cl$^-$]: 386

Compound 153:

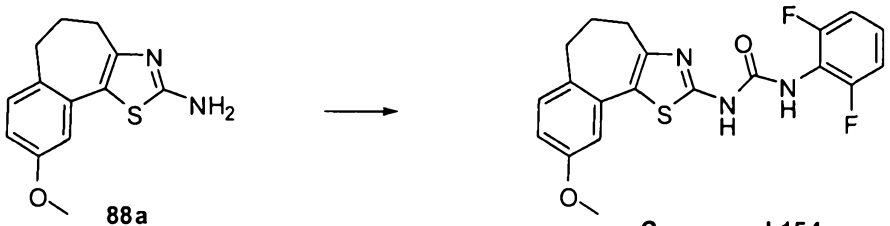


Compound 19 **Compound 153**

Compound **153** was prepared in 3 steps from Compound **19** similarly as described for the preparation of compound **152**.

MS (ESI) [M-Cl$^-$]: 423

Compound 154:

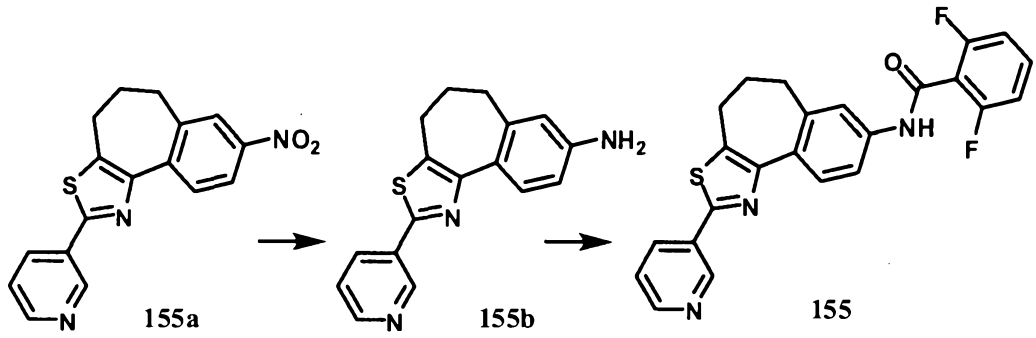


88a
(see prep of Compound 8)

Compound 154

Into a solution of compound **88a** (50 mg, 0.2 mmol) in methylene chloride (2.0 mL) at 0°C was added a solution of 1,3-difluoro-2-isocyanatobenzene (29 mg, 0.2 mmol) in methylene chloride (0.5 mL). The mixture was stirred at room temperature for 30 minutes, diluted with methylene chloride, washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give compound **154** (57 mg).
MS (ESI) [M-Cl$^-$]: 402.

Example 155:



155a 155b 155

Compound **155a** was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one as described for the preparation of compound **66e**. Nitro reduction to give **155b** followed by acylation as described for the preparation of compound **99** to give compound **155**.
MS (ESI) [M+H$^+$]: 434

Example 156:

Compound **156** was prepared from compound **155b** as described for the preparation of compound **104.**
MS (ESI) [M+H$^+$]: 420.

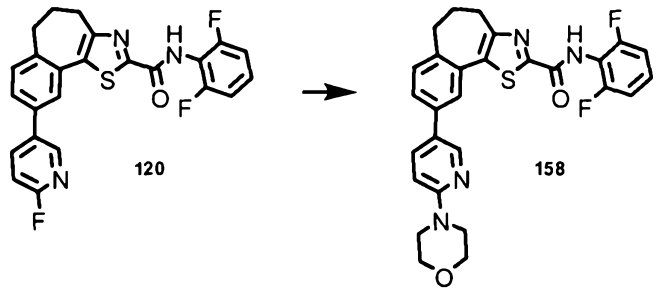
Example 157:

Compound **157** was prepared from compound **156** as described for the preparation of

Compound **152.**

MS (ESI) [M-H^+-2Cl^-]: 420.

Example 158:



A mixture of compound **120** (10.0mg, 0.022 mmol) in morpholine (0.1 mL) was heated to 120°C overnight, cooled to room temperature, taken up in methylene chloride, washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give compound **158.**

MS (ESI) [M+H^+]: 519.

Example 159:

Compound **159** was prepared from compound **120** and piperazine as described for the preparation of compound **158.**

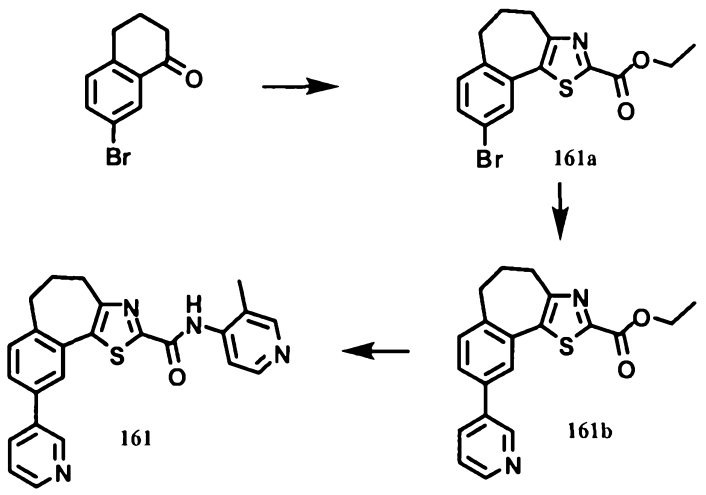
MS (ESI) [M+H^+]: 518.

Example 160:

Compound **160** was prepared from compound **120** and 2-methoxyethanamine as described for the preparation of compound **158.**

MS (ESI) [M+H^+]: 507.

Example 161:



Into a solution of 7-bromo-3,4-dihydronaphthalen-1(2H)-one (4.50g, 20.0mmol) in methylene chloride (200 mL) at 0°C was added a solution of 1M diethylaluminum chloride in hexane (22.0 mL, 22.0 mmol). Into the reaction mixture a solution of 2.0M trimethylsilyldiazomethane (11.0 mL, 22.0 mmol) was added slowly. The mixture was stirred at 0°C for 15 minutes then at room temperature for 10 minutes. Ice was added. The resulting mixture was acidified with a solution of 3N HCl, extracted with methylene chloride (2X). The combined extracts were washed with a solution of saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was taken in THF (100 mL). The mixture was cooled to 0°C. Into the reaction mixture, phenyltrimethylamonium tribromide (7.52g, 20.0 mmol) was added. The mixture was stirred at 0°C for 15 minutes then at room temperature for 1 hour. The reaction mixture was quenched by addition of a solution of 10% $NaHSO_3$, stirred at room temperature for 10 minutes, extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was taken in ethanol (20.0 mL). Into the mixture, ethyl thiooxamate (2.66g, 20.0 mmol) was added. The mixture was stirred at room temperature overnight, neutralized with a solution of saturated $NaHCO_3$, extracted with methylene chloride (2X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give **161a** (3.45g).

MS (ESI) [$M+H^+$]: 354, 352.

A slurry solution of **161a** (2.00g, 5.71mmol), pyridin-3-ylboronic acid (0.91g, 7.4mmol), potassium acetate (1.45g, 14.8mmol), and palladium tetrakistriphenylphosphine (628 mg, 0.57mmol) in 90% aqueous ethanol (20.0 mL) was purged with nitrogen for 20 minutes. The mixture was sealed and heated to 90°C overnight, cooled to room temperature, taken up in methylene chloride, washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel to give **161b** (1.45g).

MS (ESI) [$M+H^+$]: 351.

Compound **161** was prepared from **161b** and 3-methylpyridin-4-amine as described for the preparation of compound **5.**

MS (ESI) [M+H$^+$]: 413.

Example 162:

Compound **162** was prepared from **161b** and 2,4-difluoroaniline as described for the preparation of compound **5.**

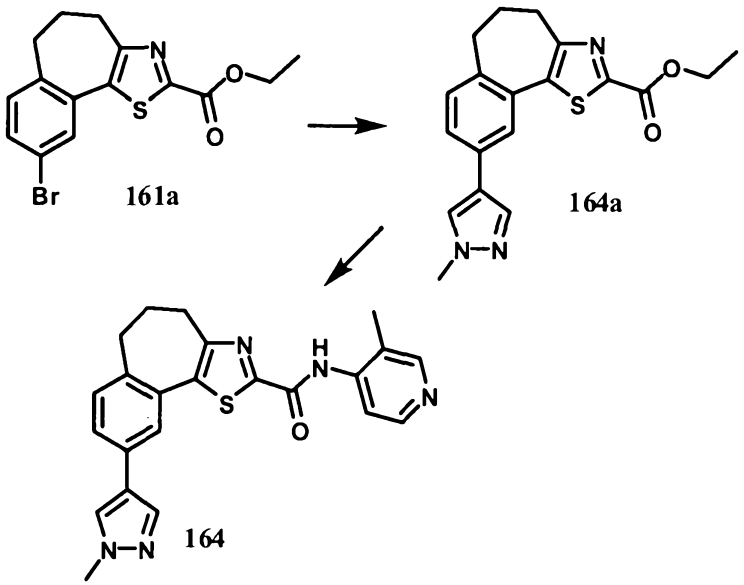
MS (ESI) [M+H$^+$]: 434.

Example 163:

Compound **163** was prepared from **161b** and 2-aminopyrimidine as described for the preparation of compound **5.**

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

Example 164:



Compound **164a** was prepared from **161a** and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as described for the preparation of **161b**.

MS (ESI) [M+H$^+$]: 354.

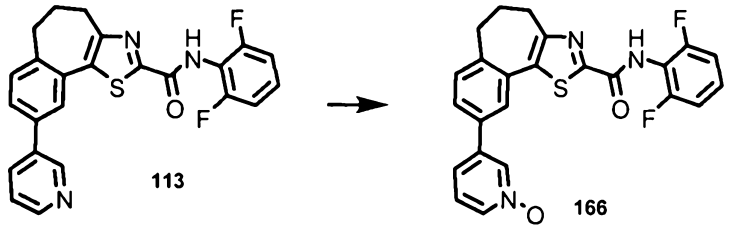
Compound **164** was prepared from **164a** and 3-methylpyridin-4-amine as described for the preparation of compound **5.**

Example 165:

Compound **165** was prepared from **164a** and 2,4-difluoroaniline as described for the preparation of compound **5.**

MS (ESI) [M+H$^+$]: 437.

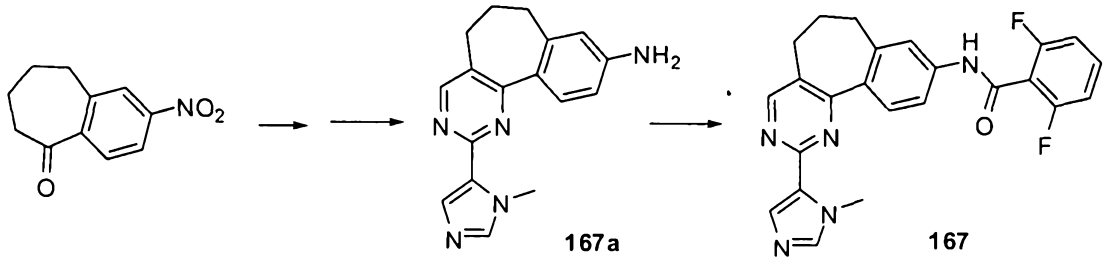
Example 166:



Into a solution of **113** (14.0 mg, 0.032mmol) in methylene chloride (1.0mL) at room temperature was added mCPBA (77% pure, 9.0mg, 0.04mmol). The mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure. The residue was purified on silica gel to provide **166** (12.0mg).

MS (ESI) [M+H$^+$]: 450.

Example 167:



Compound **101a** was prepared from 2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one and 1-methyl-1H-imidazole-5-carboximidamide as described for the preparation of **32b.**

MS(ESI) [MH$^+$]: 292

Compound **167** was prepared from **167a** as described for the preparation of compound **91.**

MS (ESI) [M+H$^+$]: 432

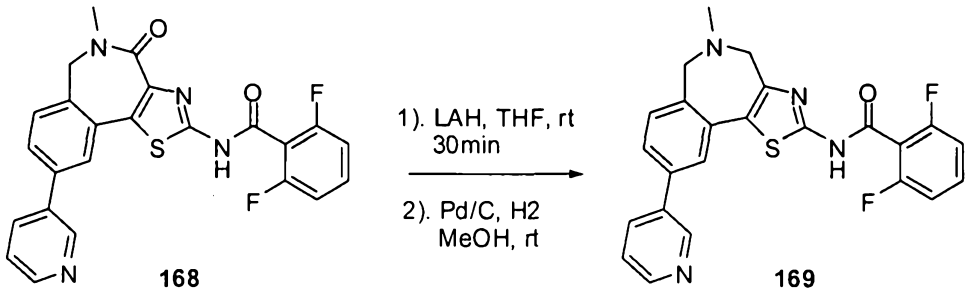
Example 168:

Compound **168** was prepared from compound **135** as described for the preparation of compound **113.**

MS (ESI) [M+H$^+$]: 463

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.96 (s, 1H), 8.73 (d, 1H), 8.20 (br d, 1H), 7.83 (s, 1H), 7.75 (dd, J = 2.0, 8.0 Hz, 1H), 7.69 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.31 (m, 1H), 7.03 (t, J = 8.0 Hz, 2H), 4.44 (br s, 2H), 3.30 (s, 3H).

Example 169:

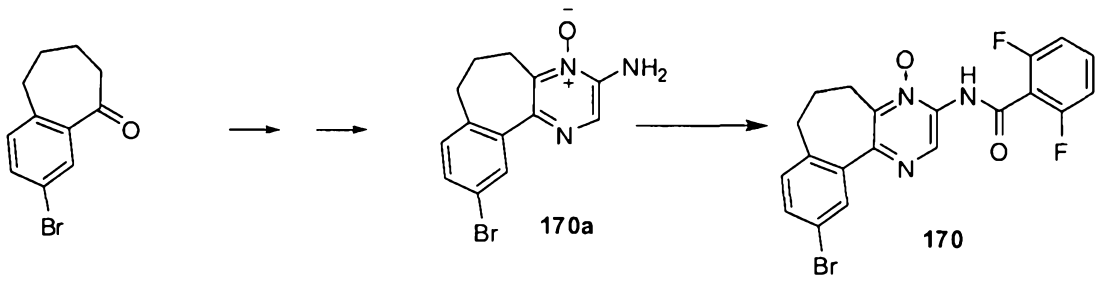


168 169

Into solution of compound **168** (10 mg) in 2 mL of THF at 0 °C was added a 1.0 M solution of Lithium aluminum hydride in THF (0.2 mmol, 0.2 mL). The mixture was stirred at rt for 1 hour, and quenched with ice water followed by 2 M NaOH. The mixture was extracted with EtOAc. The extracts were concentrated and redissolved in 2 mL of MeOH. To the solution was added 10 mg of Pd/C (10%w/w) and the mixture was stirred at rt under H_2 gas overnight. The catalyst was removed and the filtrate was concentrated and purified by column chromatography on silica gel to give compound **169** (2.3 mg) as a yellow solid.

MS (ESI) [M+H$^+$]: 449

Example 170:



170a **170**

Compound **170a** was prepared from 8-bromo-1-benzosuberone as described for the preparation of compound **29b.**

MS (ESI) [M+H$^+$]: 306, 308

Compound **170** was prepared from **170a** as described for the preparation of compound **91.**

MS (ESI) [M+H$^+$]: 446, 448

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (brs, 1H), 9.78 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.56-7.49 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 8.0 Hz, 2H), 3.07 (t, J = 7.1 Hz, 2H), 2.59 (t, J = 7.0 Hz, 2H), 2.41-2.34 (m, 2H).

Example 171:

Compound **171** was prepared from **170** as described for the preparation of compound **113.**

MS (ESI) [M+H$^+$]: 445

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (brs, 1H, NH), 9.81 (s, 1H), 8.92 (d, J = 2.4 Hz, 1H), 8.61 (dd, J = 4.9, 2.2 Hz, 1H), 8.01-7.96 (m, 2H), 7.70-7.38 (m, 4H), 7.08 (t, J = 8.0 Hz, 2H), 3.13 (dd, J = 7.3, 6.7 Hz, 2H), 2.69 (dd, J = 7.3, 6.7 Hz, 2H), 2.51-2.37 (m, 2H).

Example 172:

Compound **172** was prepared from **171** as described for the preparation of compound **29c.**

MS (ESI) [M+H$^+$]: 429

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.92 (s, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.40 (s, 1H), 7.97 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.51-7.34 (m, 4H), 7.06 (t, J = 8.0 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 2.67 (t, J = 7.0 Hz, 2H), 2.41 (m, 2H).

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.

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.

Compound #	IC_{50} (nM)

5, 12, 19, 34, 37, 38, 39, 78, 114, 122, 123, 127, 129, 130	≤ 30
8, 13, 18, 32, 51, 59, 60, 72, 73, 76, 87, 99, 100, 102, 108, 109, 112, 115, 116, 124, 125, 126, 133, 134, 148, 155	$30< IC_{50} \leq 100$
14, 33, 35, 70, 74, 75, 83, 91, 113, 117, 118, 119, 128, 142, 143, 149	$100< IC_{50} \leq 250$
6, 10, 16, 41, 69, 71, 79, 96, 101, 107, 110, 111, 120, 121, 132, 138, 153	$250< IC_{50} \leq 500$
36, 67, 81, 88, 89, 93, 97, 106, 131, 147, 152, 154	$500< IC_{50} \leq 1000$
1, 2, 3, 4, 7, 9, 11, 15, 17, 31, 40, 42, 77, 80, 82, 84, 85, 86, 90, 92, 94, 95, 98, 013, 104, 105, 135, 136, 137, 139, 140, 144, 145, 146, 151	>1000

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 is used to examine the effects of a compound of the invention on a channel that mediates I_{crac}. In such experiments, a baseline measurement is established for a patched cell. Then a compound to be tested is perfused (or puffed) to cells in the external solution and the effect of the compound on I_{crac} is 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) are grown in DMEM media supplemented with 10% fetal bovine serum in an atmosphere of 95% air/5% CO_2. Cells are seeded on glass coverslips 1-3 days before use.

Recording Conditions

Membrane currents of individual cells are recorded using the whole-cell configuration of the

patch clamp technique with an EPC10 (HEKA Electronik, Lambrecht, Germany). Electrodes (2-5 MΩ in resistance) are fashioned from borosilicate glass capillary tubes (Sutter Instruments, Novato, Ca). The recordings are done at room temperature.

Intracellular pipette solution

The intracellular pipette solution contains 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 is kept on ice and shielded from light before the experiment is preformed.

Extracellular solution

The extracellular solution contains 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 is diluted from a 10 mM stock in series using DMSO. The final DMSO concentration is always kept at 0.1 %.

Experimental procedure

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

Data analysis

The I_{CRAC} current level is 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 is calculated using peak amplitude in the beginning of the experiment from the same cell. The IC_{50} value and Hill coefficient for each compound is estimated by fitting all the individual data points to a single Hill equation.

2) <u>Jurkat cells</u>

Cells

Jurkat T cells are grown on glass coverslips, transferred to the recording chamber and kept in a standard modified Ringer's solution of the following composition: NaCl 145mM, KCl 2.8mM, CsCl 10mM, $CaCl_2$ 10mM, $MgCl_2$ 2mM, glucose 10mM, HEPES·NaOH 10mM, pH 7.2.

Extracellular Solution

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

Intracellular Pipette Solution

The standard intracellular pipette solution contains: Cs-glutamate 145 mM, NaCl 8 mM, $MgCl_2$ 1 mM, ATP 0.5 mM, GTP 0.3 mM, pH 7.2 adjusted with CsOH. The solution is supplemented with a mixture of 10 mM Cs-BAPTA and 4.3-5.3 mM $CaCl_2$ to buffer $[Ca^{2+}]i$ to resting levels of 100-150 nM.

Patch-clamp recordings

Patch-clamp experiments are performed in the tight-seal whole-cell configuration at 21-25 °C. High-resolution current recordings are acquired by a computer-based patch-clamp amplifier system (EPC-9, HEKA, Lambrecht, Germany). Sylgard®- coated patch pipettes have resistances between 2-4 MΩ after filling with the standard intracellular solution. Immediately following establishment of the whole-cell configuration, voltage ramps of 50 ms duration spanning the voltage range of −100 to +100 mV are delivered from a holding potential of 0 mV at a rate of 0.5 Hz over a period of 300 to 400 seconds. All voltages are corrected for a liquid junction potential of 10 mV between external and internal solutions. Currents are filtered at 2.3 kHz and digitized at 100 μs intervals. Capacitive currents and series resistance are determined and corrected before each voltage ramp using the automatic capacitance compensation of the EPC-9.

Data analysis

The very first ramps before activation of I_{CRAC} (usually 1 to 3) are digitally filtered at 2 kHz, pooled and used for leak-subtraction of all subsequent current records. The low-resolution temporal development of inward currents is extracted from the leak-corrected individual ramp current records by measuring the current amplitude at -80 mV or a voltage of choice.

3) <u>Primary T Cells</u>

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-α and TNF-γ in primary human PBM cells. In addition, compounds of the invention are not expected to inhibit the anti-inflammatory cytokine, IL-10.

EXAMPLE 5: INHIBITION OF DEGRANULATION IN RBL CELLS

Procedure:

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

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

Compounds of the invention are expected to inhibit degranulation.

EXAMPLE 6: INHIBITION OF CHEMOTAXIS IN T CELLS

T-cell isolation:

Twenty ml aliquots of heparinized whole blood (2 pig, 1 human) are subjected to density gradient centrifugation on Ficoll Hypaque. The buffy coat layers representing peripheral blood mononuclear cells (PBMCs) containing lymphocytes and monocytes are washed once, resuspended in 12 ml of incomplete RPMI 1640 and then placed in gelatin-coated T75 culture flasks for 1 hr at 37°C. The non-adherent cells, representing peripheral blood lymphocytes (PBLs) depleted of monocytes, are resuspended in complete RPMI media and placed in loosely packed activated nylon wool columns that have been equilibrated with warm media. After 1 hr at 37°C, the non-adherent T cell populations are eluted by washing of the columns with additional media. The T cell preparations are centrifuged, resuspended in 5 ml of incomplete RPMI, and counted using a hemocytometer.

Cell migration assay:

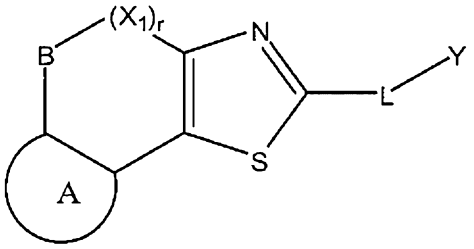
Aliquots of each T cell preparation are labeled with Calcien AM (TefLabs) and suspended at a concentration of 2.4 x10^6/ml in HEPES-buffered Hank's Balanced Salt Solution containing 1.83 mM $CaCl_2$ and 0.8 mM $MgCl_2$, pH 7.4 (HHBSS). An equal volume of HHBSS containing 0, 20 nM, 200 nM or 2000 nM of compound 1 or 20 nM EDTA is then added and the cells incubated for 30 min at 37 °C. Fifty µl aliquots of the cell suspensions (60,000 cells) are placed on the membrane (pore size 5 µm) of a Neuroprobe ChemoTx 96 well chemotaxis unit that have been affixed over wells containing 10 ng/ml MIP-1α in HHBSS. The T cells are allowed to migrate for 2 hr at 37 °C, after which the apical surface of the membrane is wiped clean of cells. The chemotaxis units are then placed in a CytoFlour 4000 (PerSeptive BioSystems) and the fluorescence of each well measured (excitation and emission wavelengths of 450 and 530 nm, respectively). The number of migrating cells in each well is determined from a standard curve generated from measuring the fluorescence of serial two-fold dilutions of the labeled cells placed in the lower wells of the chemotaxis unit prior to affixing the membrane.

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

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

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound represented by formula (X):



(X)

wherein:

Ring A is a 5 or 6 membered aryl or heteroaryl ring wherein the members of the ring are selected from the group consisting of -CZ-, -S-, -O- or –N-;

Y is an aryl optionally substituted with one to two substituents independently selected from lower alkyl and halo; or an optionally substituted heteroaryl;

B is $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

each X_1 is independently $-C(R^a)_2-$, -C(O)-; –O-, -S-, or $-N(R^b)-$;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, $-C(O)R_4$, or $-C(O)OR_4$;

R_1 and R_2, for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_1 and R_2

taken together with the nitrogen to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4;

p is 0, 1, or 2; and

provided that when r is 1, X_1 is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when X_1 is $–CH_2-$, r is 1, B is $–CH_2-$ and ring A is an unsubstituted phenyl group, L is not –NH- or –CH=CH-;

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

2. The compound of Claim 1, wherein:

L is $–NRCH_2-$, $-CH_2NR-$, –C(O)-, –NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, –NR-C(S)-, -C(S)-NR-, $-NRC(NR_9)-$, $–C(NR_9)NR-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRS(O)_2NR-$, -NRC(O)NR-, -NRC(NR)NR-, -NRC(S)NR-, $-NRCH_2NR-$, $-NRN=CR_6-$, -C(NR)-, or $-CR_6=NNR-$;

R, for each occurrence, is independently –H, alkyl, $-C(O)-R_7$, or $–C(O)OR_7$;

R_6, for each occurrence, is –H or alkyl;

R_7, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

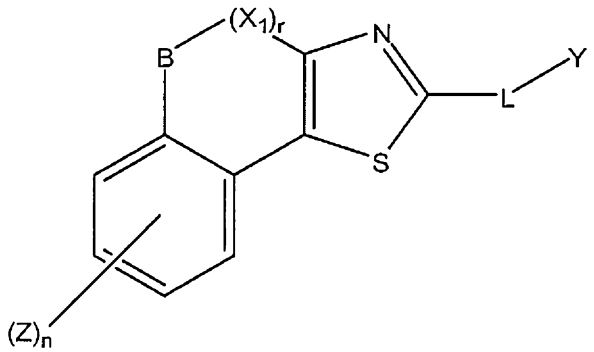
R_9, for each occurrence, is independently –H, halo, an alkyl, $-OR_7$, $-NR_{11}R_{12}$, $-C(O)R_7$, $-C(O)OR_7$, or $–C(O)R_{11}R_{12}$; and

R_{11} and R_{12}, 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_{11} and R_{12} taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl.

3. A compound according to Claim 1 or Claim 2, wherein Y is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substitute pyrazolyl, an optionally substituted pyridinyl, an optionally substituted pyridazinyl, an optionally substituted thiadiazolyl, or an optionally substituted thiophenyl; and wherein Z is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted thiazolyl, an optionally substituted imidazolyl, an optionally substituted pyridinyl, an optionally substituted pyrazolyl, an optionally substituted pyrrolyl, an optionally substituted thiophenyl, an optionally substituted furanyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted tetrazolyl, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, -NO_2, -$C(O)NR_1R_2$, -$NR_4C(O)R_5$, -OR_4, haloalkoxy, -$C(O)R_4$, -NR_1R_2, -SR_4, -$C(O)OR_4$, -$OC(O)R_4$, -$NR_4C(O)NR_1R_2$, -$OC(O)NR_1R_2$, -$NR_4C(O)OR_5$, -$S(O)_pR_4$, or -$S(O)_pNR_1R_2$.

4. A compound according to any of Claims 1 to 3, Ring A is a 5-membered heteroaromatic ring containing one heteroatom.

5. A compound according to Claim 1, wherein the compound is represented by formula (I):



(I)

wherein:

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

B is -$C(R^a)_2$-, -C(O)-; –O-, -S-, or –$N(R^b)$-;

each X_1 is independently -$C(R^a)_2$-, -C(O)-; –O-, -S-, or –$N(R^b)$-;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

each R^b 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, an optionally substituted heteraralkyl, a haloalkyl, halo, $-C(O)NR_1R_2$, $-C(O)R_4$, or $-C(O)OR_4$;

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

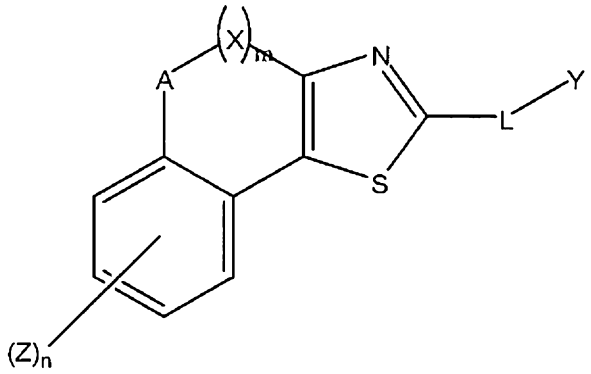
R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

r is 1, 2, 3, or 4;

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

p is 0, 1, or 2.

6. A compound represented by formula (II):



(II)

wherein:

Y is an aryl optionally substituted with one to two substituents independently selected from lower alkyl and halo; or an optionally substituted heteroaryl;

A is $-C(R^a)_2-$ or –O-;

each X is independently $-C(R^a)_2-$ or -C(O)-;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted

alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

m is 1 or 2;

n is 0, 1, 2, 3 or 4;

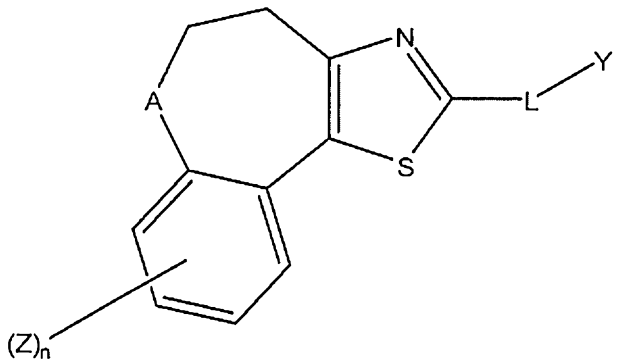
p is 0, 1, or 2; and

provided that when m is 1, X is C(O) and L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when m is 1 and n is 0, L is not –NH-;

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

7. A compound represented by formula (III):



(III)

wherein:

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

A is $-C(R^a)_2-$ or –O-;

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, -OC(

O)NR_1R_2, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

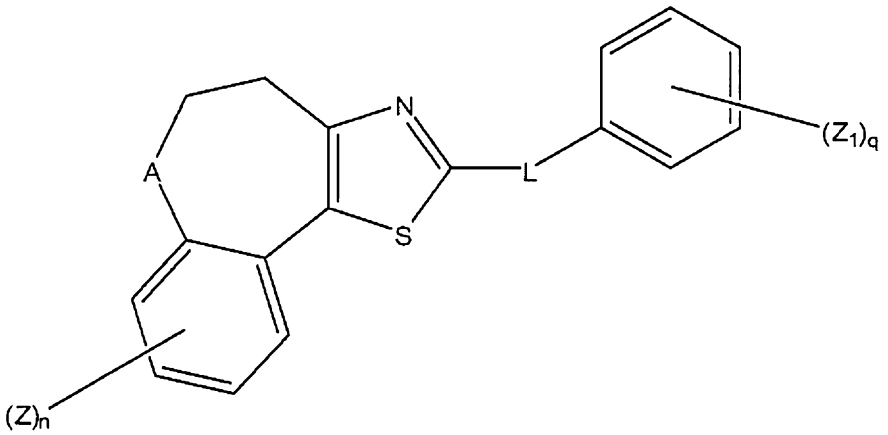
R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

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

p is 0, 1, or 2;

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

8. A compound according to Claim 7, wherein the compound is represented by formula (IV):



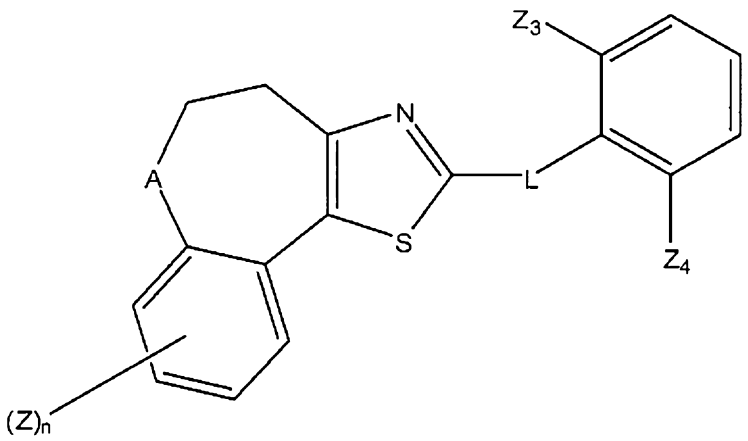
(IV)

wherein:

Z_1 is a substituent; and

q is 0, 1, 2, 3, 4, or 5.

9. A compound according to Claim 7, wherein the compound is represented by formula (V):

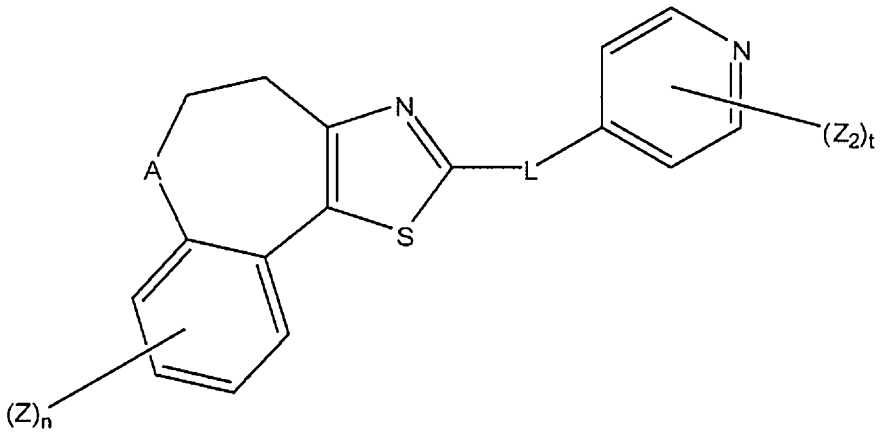


(V)

wherein:

Z_3 and Z_4 are each independently substituents.

10. The compound according to Claim 7, wherein the compound is represented by formula (VI):



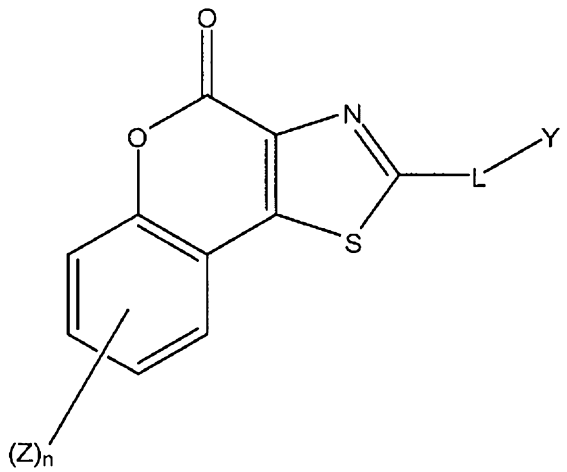
(VI)

wherein

Z_2 is a substituent; and

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

11. A compound represented by formula (VII):



(VII)

wherein:

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

Z is a substituent;

L is a linker;

each R^a 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, an optionally substituted heteraralkyl, a haloalkyl, $-C(O)NR_1R_2$, $-NR_4C(O)R_5$, halo, $-OR_4$, cyano, nitro, haloalkoxy, $-C(O)R_4$, $-NR_1R_2$, $-SR_4$, $-C(O)OR_4$, $-OC(O)R_4$, $-NR_4C(O)NR_1R_2$, $-OC(O)NR_1R_2$, $-NR_4C(O)OR_5$, $-S(O)_pR_4$, or $-S(O)_pNR_1R_2$;

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

R_4 and R_5, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted

heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

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

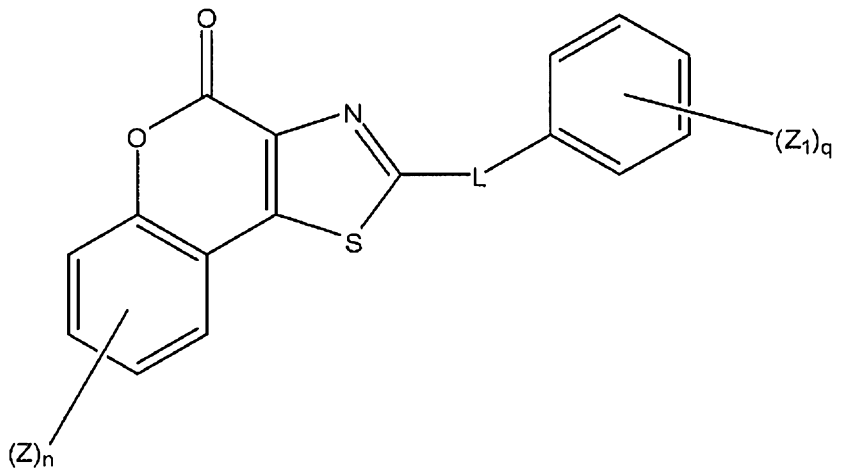
p is 0, 1, or 2;

provided that when L is –NHC(O)-, Y is not phenyl or methylphenyl;

provided that when n is 0, L is not –NH-;

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

12. A compound according to Claim 11, wherein the compound is represented by formula (VIII):



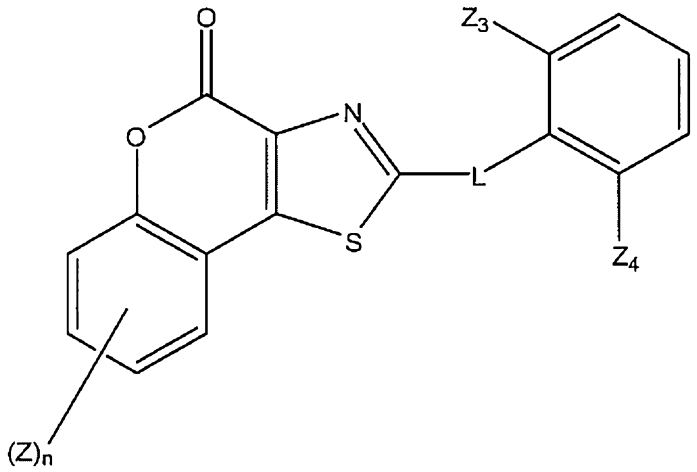
(VIII)

wherein:

Z_1 is a substituent; and

q is 0, 1, 2, 3, 4, or 5.

13. A compound according to Claim 11, wherein the compound is represented by formula (IX):



(IX)

wherein:

Z_3 and Z_4 are each independently substituents.

14. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of Claims 1 to 13.

15. A pharmaceutical composition according to Claim 14, further comprising one or more additional therapeutic agents selected from the group consisting of immunosuppressive agents, anti-inflammatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and suitable mixtures thereof.

16. A method of inhibiting immune cell activation comprising administering to the cell a compound according to any one of Claims 1 to 13.

17. A method of inhibiting cytokine production in a cell, comprising administering to a cell a compound according to any one of Claims 1 to 13.

18. A method according to Claim 17, wherein the cytokine is selected from the group consisting of IL-2, IL-4, IL-5, IL-13, GM-CSF, IFN-α, TNF-γ, and combinations thereof.

19. 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 according to any one of Claims 1 to 13.

20. The method according to Claim 19, wherein the ion channel is a Ca^{2+}-release-activated Ca^{2+} channel (CRAC).

21. A method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to the cell a compound according to any one of Claims 1 to 13.

22. 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 according to any one of Claims 1 to 13, 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.

23. 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 according to any one of Claims 1 to 13, 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.

24. A method for suppressing the immune system of a subject in need thereof, comprising administering to the subject an effective amount of a compound according to any one of Claims 1 to 13.

25. 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 according to any one of Claims 1 to 13.

26. A method according to Claim 25, 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.

27. The use of a compound of any one of Claims 1 to 13 in the manufacture of a medicament for any one of the following:

inhibiting immune cell activation,

inhibiting cytokine production in a cell,

modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation,

inhibiting T-cell and/or B-cell proliferation in response to an antigen,

treating or preventing an immune disorder 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,

treating or preventing an inflammatory condition 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,

suppressing the immune system,

treating or preventing an allergic disorder.