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

(57) Abrégé/Abstract:

The invention relates to certain fused ring compounds, or pharmaceutically acceptable salts thereof, that are useful as immunosuppressive agents and for treating and preventing inflammatory conditions, allergic disorders, and immune disorders.

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

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

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COMPOUNDS FOR INFLAMMATION AND IMMUNE-RELATED USES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application Nos. 61/010,523, filed January 7, 2008; 61/070,721, filed March 25, 2008; and 61/072,696, filed April 1, 2008. The contents of each of these applications are incorporated herein by reference in their entireties.

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, $\text{TNF-}\alpha$ and $\text{TNF-}\beta$ secretion, as well as stimulating the synthesis of IFN- γ in peripheral leukocytes.

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

Over production of proinflammatory cytokines other than IL-2 has also been implicated in many autoimmune diseases. For example, Interleukin 5 (IL-5), a cytokine that increases the production of eosinophils, is increased in asthma. Overproduction of IL-5 is associated with accumulation of eosinophils in the asthmatic bronchial mucosa, a 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 asthma and inflammatory bowel disease would benefit from the development of new drugs that inhibit IL-4 and IL-13 production.

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

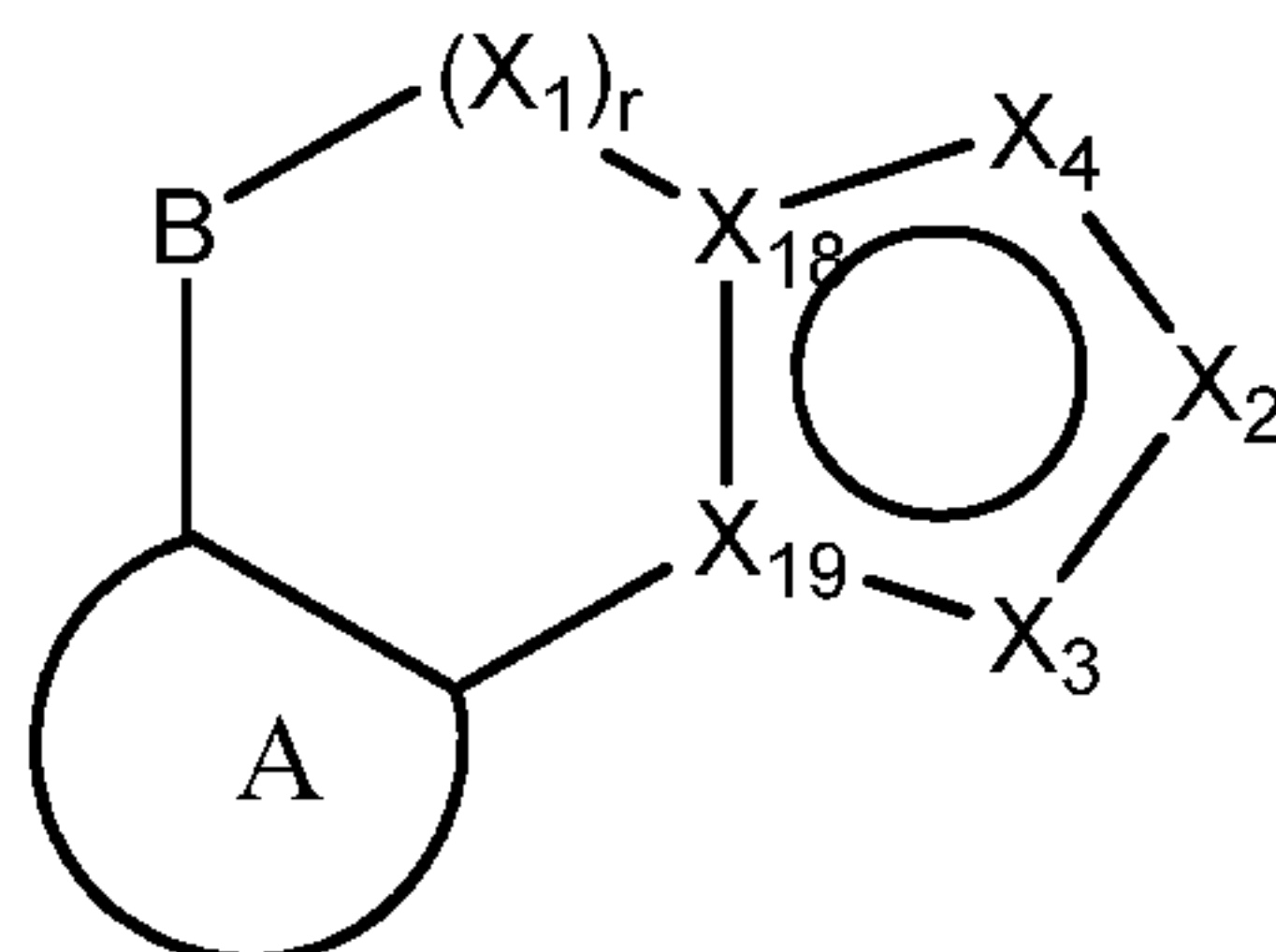
There is therefore a continuing need for new drugs which overcome one or more of the shortcomings of drugs currently used for immunosuppression or in the treatment or prevention of inflammatory disorders, allergic disorders and autoimmune disorders. Desirable properties of new drugs include efficacy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

SUMMARY OF THE INVENTION

This invention meets the above-mentioned needs by providing certain 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 IFN γ . 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 (IA):



(IA)

wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl ring wherein the ring atoms are selected from the group consisting of C, S, O, and N;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

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

one of X_2 , X_3 or X_4 is $-\text{C}(\text{L}-\text{Y})-$ or $-\text{C}(\text{R}^a)(\text{L}-\text{Y})-$ and the others are independently $-\text{O}-$, $-\text{S}-$, $-\text{N}-$, $-\text{N}(\text{R}^b)-$, $-\text{C}(\text{R}^a)_2-$, or $-\text{C}(\text{R}^a)-$;

each of X_{18} or X_{19} is independently $-\text{N}-$, $-\text{C}-$, or $-\text{C}(\text{R}^a)-$;

L is a linker;

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

each R^b is independently $-\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, $-\text{C}(\text{O})\text{R}_4$, or $-\text{C}(\text{O})\text{OR}_4$;

R_1 and R_2 , for each occurrence are, independently, H, an optionally substituted alkyl, an

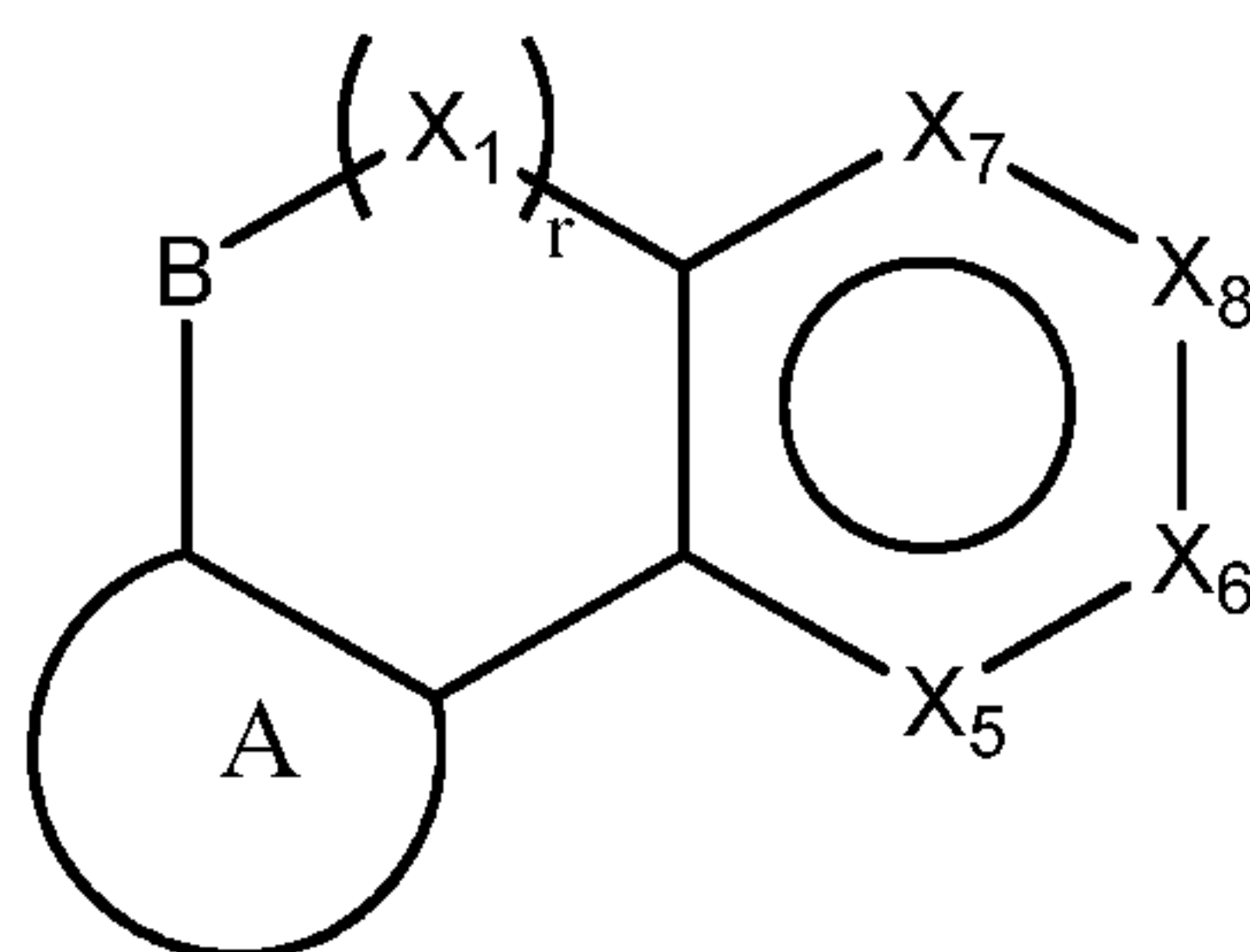
optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally 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 thereof.

In one embodiment of compounds of formula (IA), the compound is not 4H-thieno[3,2-d][1]benzazine-2-carboxamide, 6-[4-[[[1,1'-biphenyl]]-2-ylcarbonyl)amino]benzoyl]-N-cyclopropyl-5,6-dihydro- or 4H-benzo[6,7]cyclohepta[1,2-d]thiazole-2-carboxamide, 5,6-dihydro-N-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl].

The invention also relates to compounds of formula (VI):

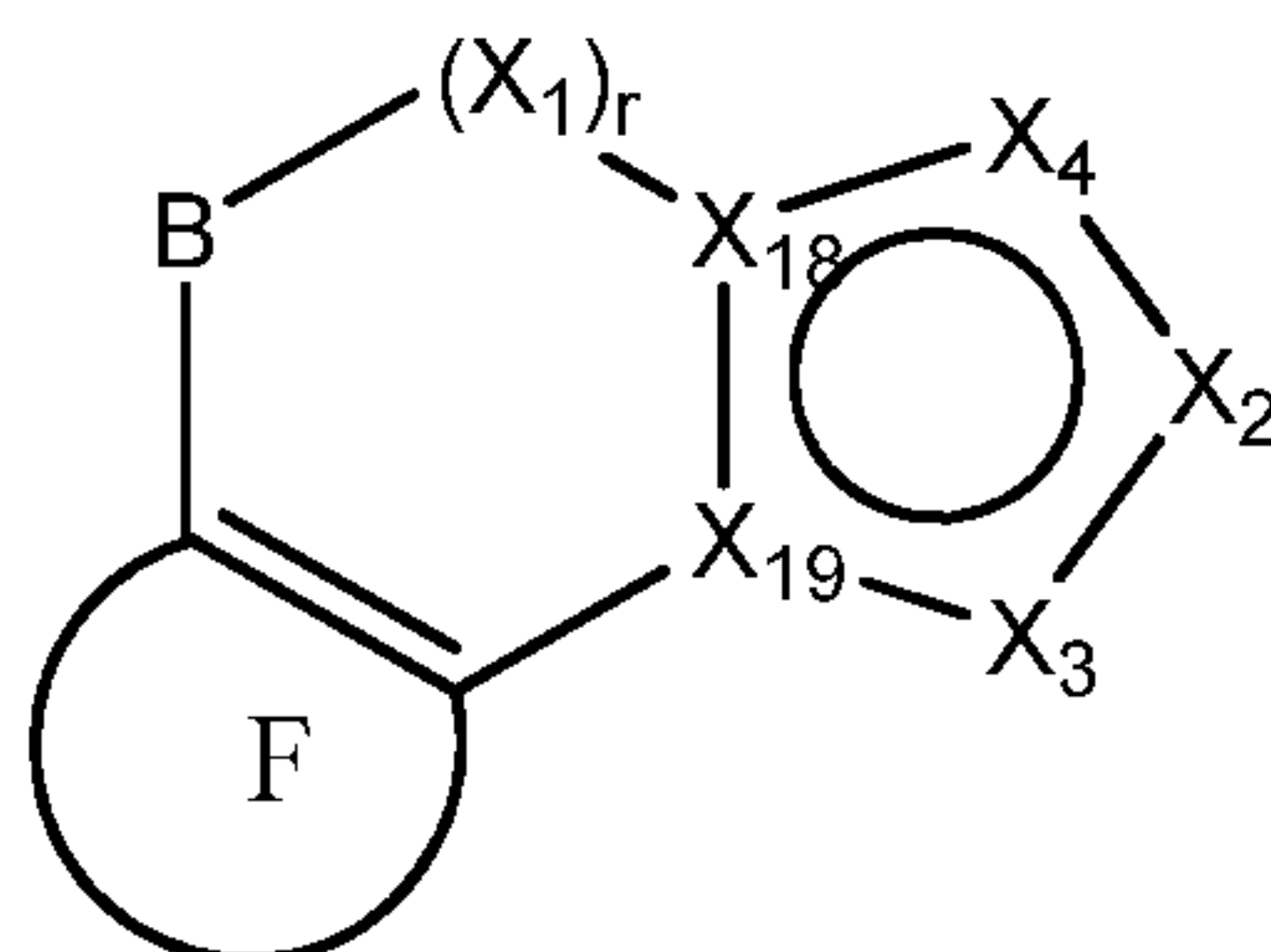


(VI)

or a pharmaceutically acceptable salt thereof, wherein:

one of X_5 , X_6 , X_7 , and X_8 is $-C(L-Y)-$ and the others are independently $-N-$ or $-CR^a-$; and Ring A, B, X_1 , and r are defined as for formula (I).

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



(X)

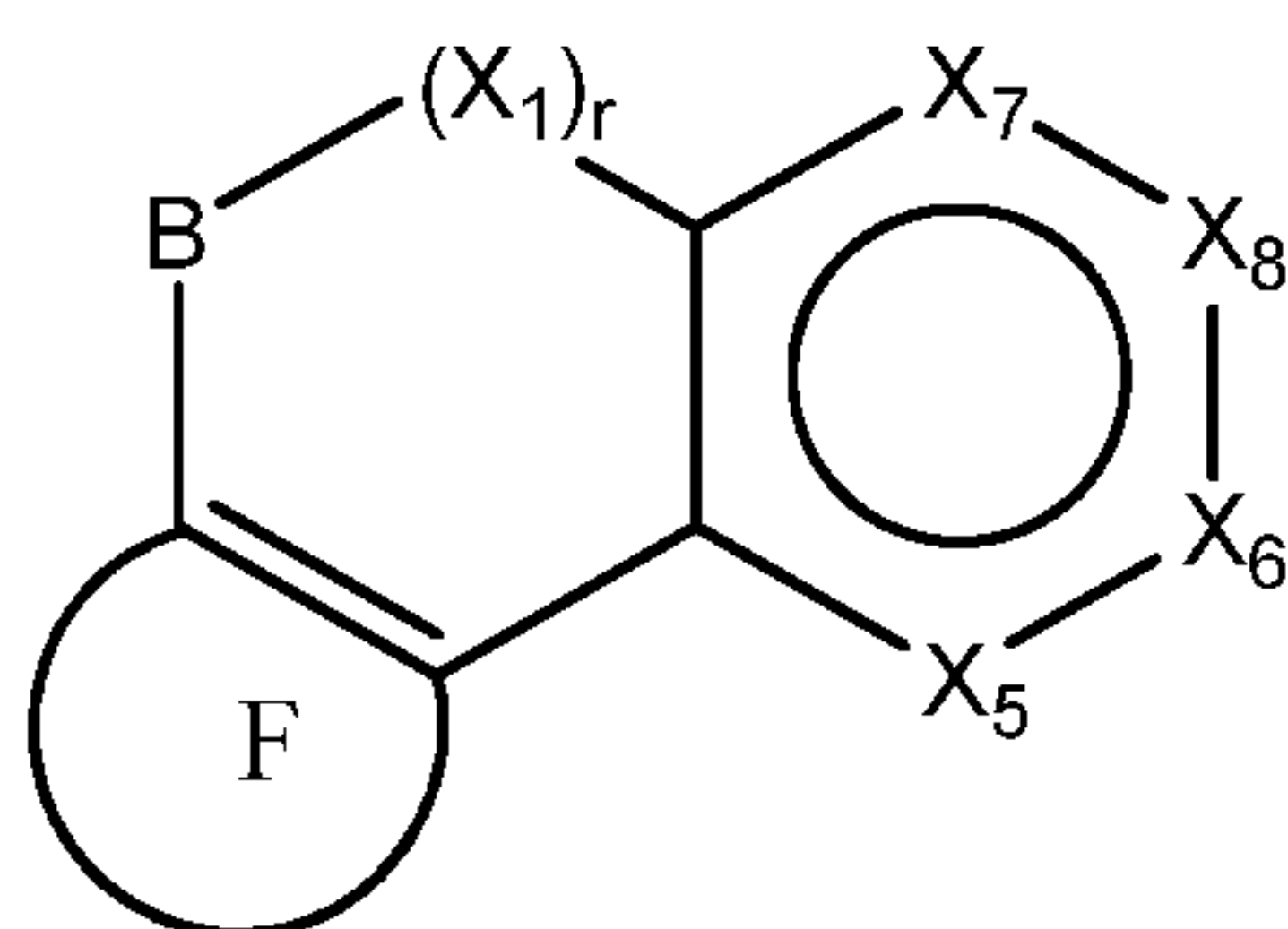
or a pharmaceutically acceptable salt thereof, wherein:

Ring F is an optionally substituted 5 or 6-membered non-aromatic ring containing atoms selected from the group consisting of C, S, O, and N;

B, X_1 , r, X_2 , X_3 , X_4 , X_{18} , and X_{19} are defined as for formula (I).

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



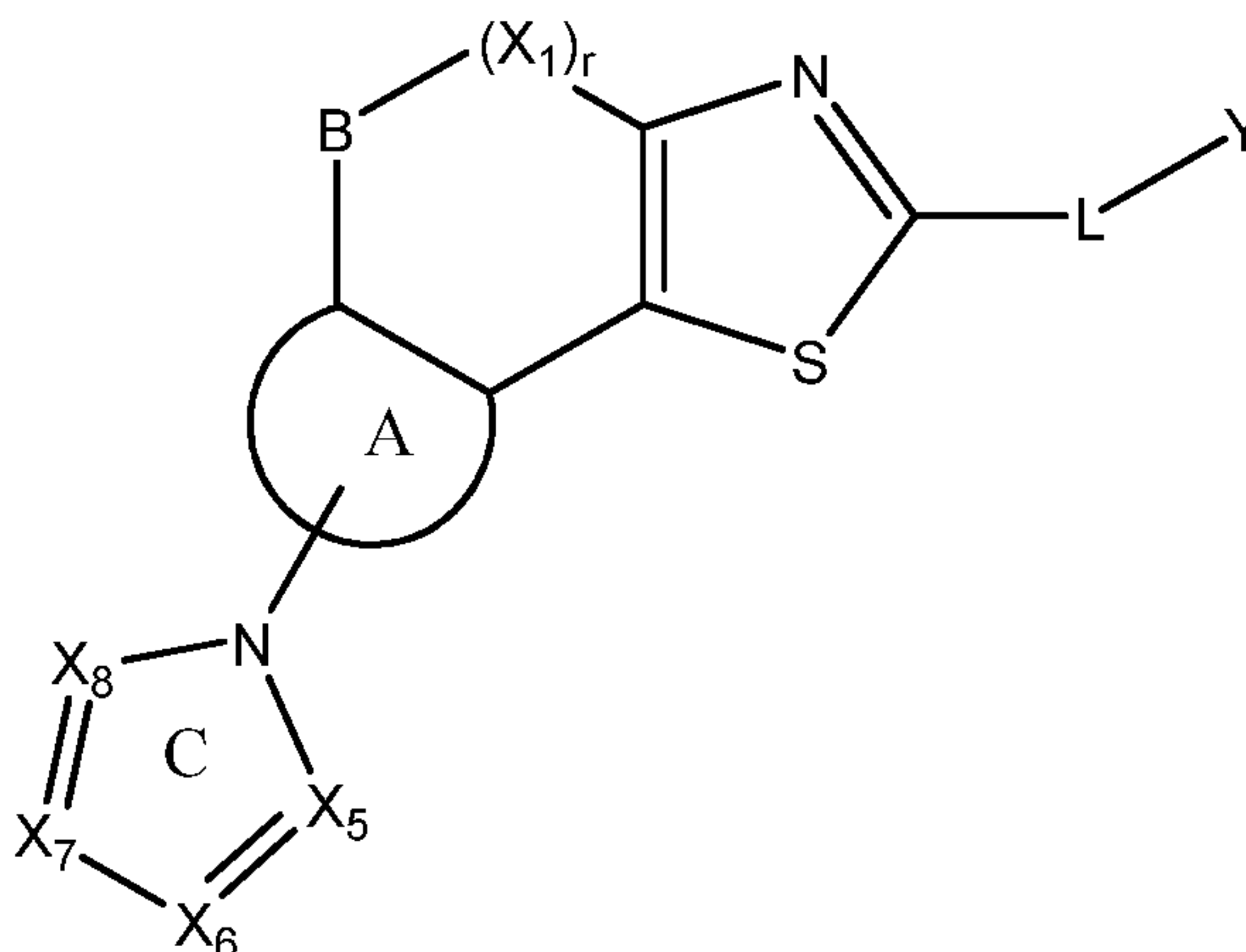
(XVII)

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or a pharmaceutically acceptable salt thereof, wherein:

Ring F is defined as for formula (X), B, X_1 , r, X_5 , X_6 , X_7 , and X_8 are defined as for formula (VI).

The invention relates to compounds of formula (XXII):



(XXII)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl wherein the ring atoms are selected from the group consisting of C, S, O, or N, and wherein Ring A contains at least one C atom that is bonded to Ring C;

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 $-N(R^b)$ -;

each of X_5 , X_6 , X_7 , and X_8 is independently $-N$ - or $-C(R^c)$ -;

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)NR₁R₂, –NR₄C(O)R₅, halo, –OR₄, cyano, nitro, haloalkoxy, –C(O)R₄, –NR₁R₂, –SR₄, –C(O)OR₄, –OC(O)R₄, –NR₄C(O)NR₁R₂, –OC(O)NR₁R₂, –NR₄C(O)OR₅, –S(O)_pR₄, or –S(O)_pNR₁R₂;

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)NR₁R₂, –C(O)R₄, or –C(O)OR₄;

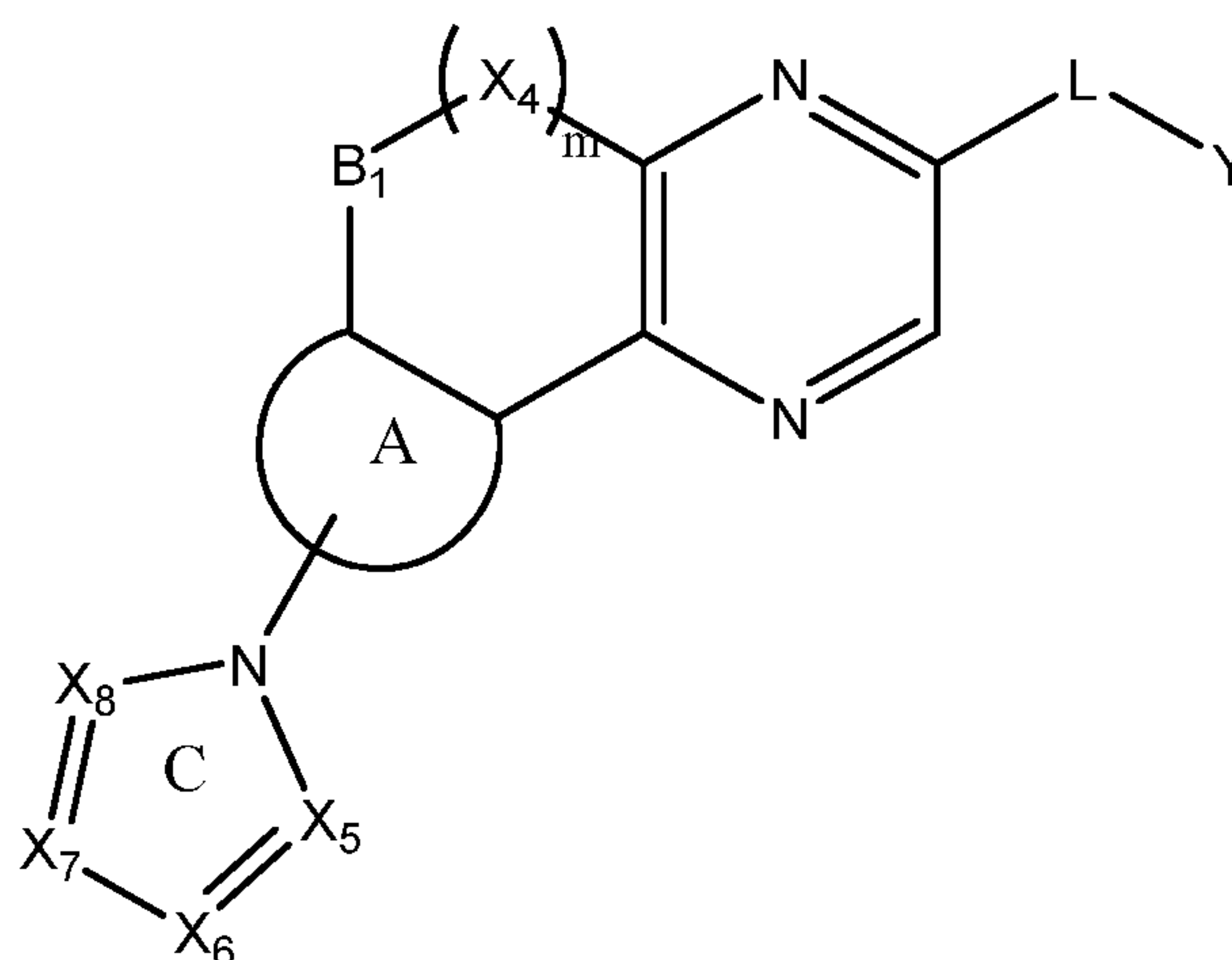
each R^c is independently –H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, nitro, or cyano;

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

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

r is 1, 2, 3, or 4; and p is 0, 1, or 2.

The invention also relates to compounds of formula (XXVI):



(XXVI)

or a pharmaceutically acceptable salt thereof, wherein:

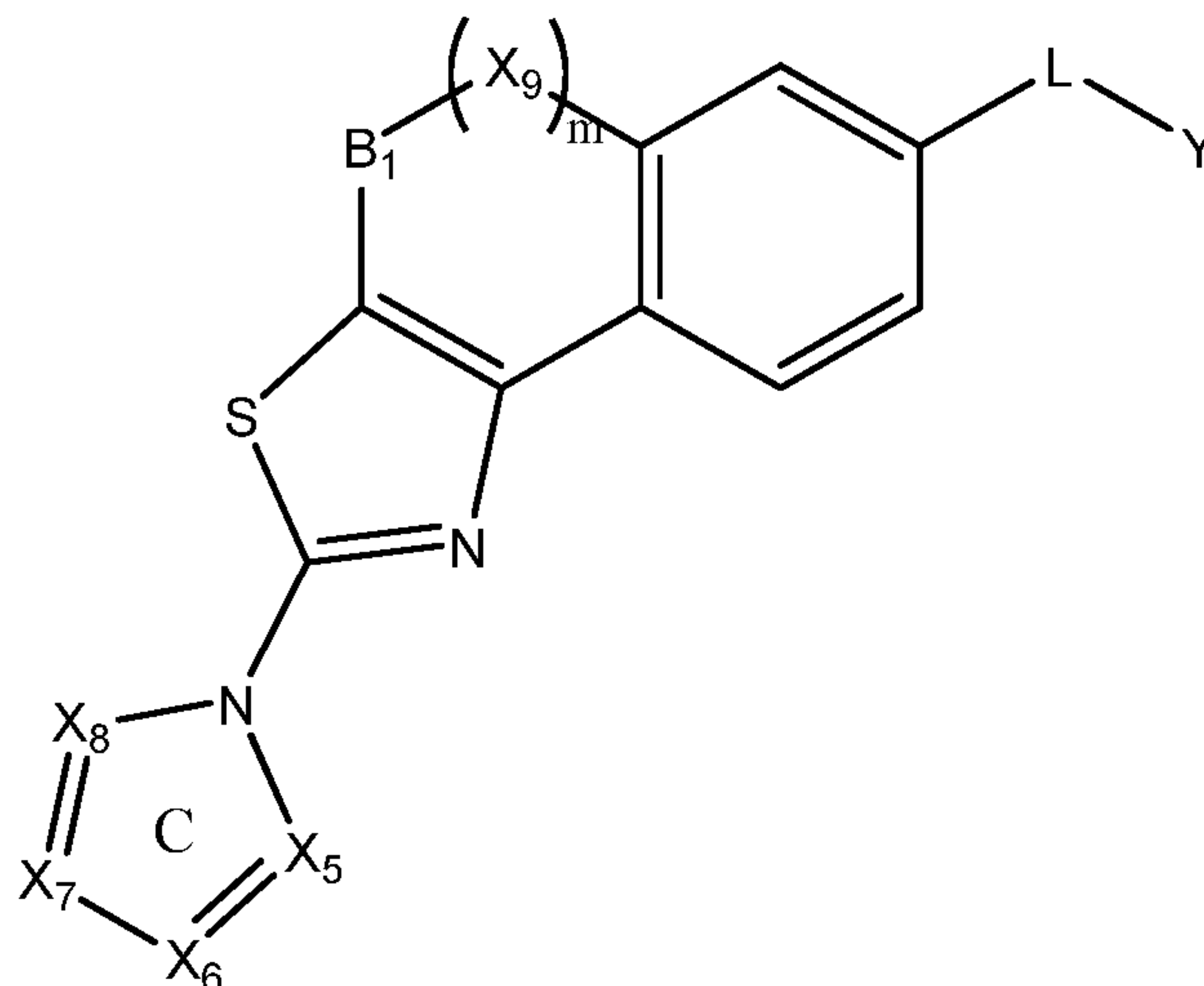
X_4 is $-C(R^a)_2-$;

B_1 is $-C(R^a)_2-$, $-C(O)-$; or $-O-$;

m is 1 or 2; and

X_5 , X_6 , X_7 , X_8 , Ring A, L and Y are defined as for formula (XXII).

The invention also relates to compounds of formula (XXIX):



(XXIX)

or a pharmaceutically acceptable salt thereof, wherein:

B_1 , X_4 , and m are defined as for formula (V) and X_5 , X_6 , X_7 , X_8 , Ring A, L and Y are defined as for formula (XXII).

A compound of the invention 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 can inhibit the production of certain cytokines that regulate immune cell activation. For example, a compound of the invention 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 can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels.

5 A compound of the invention is particularly useful for immunosuppression or for treating or preventing inflammatory conditions, allergic disorders, and immune disorders.

10 The invention also encompasses pharmaceutical compositions comprising a compound of the invention 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.

15 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 pharmaceutical composition comprising a compound of the invention. These methods may also comprise administering to the subject an additional agent separately or in a combination composition with the compound of the invention.

20 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 pharmaceutical composition comprising a compound of the invention. 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 thereof.

25 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 pharmaceutical composition comprising a compound of the invention.

30 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 pharmaceutical composition comprising a compound of the invention.

35 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 pharmaceutical composition comprising a compound of the invention.

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.

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DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

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

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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.

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

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The term alkylene refers to an alkyl group that has two points of attachment to two moieties (e.g., $\{-\text{CH}_2-\}$, $\{-\text{CH}_2\text{CH}_2-\}$,



, etc., wherein the brackets

5 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.

10 The term “alkoxy,” as used herein, refers to an alkyl group which is linked to another moiety through 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.

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

20 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.

25 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

30 unsubstituted.

As used herein, the term “alkynyl” means a straight chain or branched, hydrocarbon radical typically having from 2 to 10 carbon atoms and having at least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-methyl-1-butylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonyl, 2-nonyl, 8-nonyl, 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, adamantyl, decahydronaphthyl, octahydronaphthalene, bicyclo[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 an unsaturated non-aromatic ring. A 3-membered heterocycle can contain up to 3 heteroatoms, and a 4- to 14-membered heterocycle can contain from 1 to about 8 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include 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, indoliziny, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, pyridinyl, thiadiazolyl, pyrazinyl, quinolyl, isoquinolyl, indazolyl, benzoxazolyl, benzofuryl, benzothiazolyl, indoliziny, imidazopyridinyl, isothiazolyl, tetrazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinoxalinyl, 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 -CF₃, -CHF₂, -CCl₃, -CH₂CH₂Br, -CH₂CH(CH₂CH₂Br)CH₃, -CHICH₃, and the like.

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

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

As used herein, the term "linker" means a diradical having from 1-3 atoms in contiguous linear connectivity (*i.e.*, as defined above and excluding atoms present in any side chains and branches), that

covalently connects the fused portion of a compound of this invention to the Y group of the compound, for example, as illustrated in formula (II). 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, alkyloalkylidene 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 moiety, the identity of the substituent is independent in each case and may be the same as or different from other occurrences of that substituent in the structure or moiety. Furthermore, individual substituents in the specific embodiments and exemplary compounds of this invention are preferred in combination with other such substituents in the compounds of this invention, even if such individual substituents are not expressly noted as being preferred or not expressly shown in combination with other substituents.

The compounds of the invention are defined herein by their chemical structures and/or chemical names.

Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

Suitable substituents for an alkyl, alkoxy, alkyl sulfanyl, alkylamino, dialkylamino, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, 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 $=O$, $=S$, $=N-R_{15}$.

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.

5 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
10 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
15 as, without limitation, carboxy, hydroxy, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one or more protecting groups. Suitable protecting groups for carboxy moieties include benzyl, tert-butyl, and the like. Suitable protecting groups for amino and amido groups include acetyl, tert-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for hydroxy include benzyl and the like.
20 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 "a compound of the invention" and similar terms refer to a compound of any
25 one of formulas (IA), (I) through (XXX), a compound included in Tables 1 through 3, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, polymorph 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
30 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 (IA), (I) through (XXX), or Tables 1-3, that comprise biohydrolyzable moieties such as
35 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 (IA), (I) through (XXX), or of Table 1, Table 2, or Table 3 that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed), the entire teachings of which are incorporated herein by reference.

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

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from an acid and a basic group of one of the compounds of any one of formulas (IA), (I) through (XXX), or Tables 1-3. 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 (IA), (I) through (XXX) or Table 1, Table 2, or Table 3 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 (IA), (I) through (XXX) or Table 1, Table 2, or Table 3 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.

When a disclosed compound is named or depicted by structure, it is to be understood that solvates (e.g., hydrates) of the compound or its pharmaceutically acceptable salts are also included. "Solvates" refer to crystalline forms wherein solvent molecules are incorporated into the crystal lattice during crystallization. Solvate may include water or nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and EtOAc. Solvates, wherein water is the solvent molecule incorporated into the crystal lattice, are typically referred to as "hydrates". Hydrates include a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

When a disclosed compound is named or depicted by structure, it is to be understood that the compound, including solvates thereof, may exist in crystalline forms, non-crystalline forms or a mixture thereof. The compounds or solvates may also exhibit polymorphism (i.e. the capacity to occur in different crystalline forms). These different crystalline forms are typically known as "polymorphs." It is to be understood that when named or depicted by structure, the disclosed compounds and solvates (e.g., hydrates) also include all polymorphs thereof. As used herein, the term "polymorph" means solid crystalline forms of a compound of the present invention or complex thereof. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for

example, the shape or size distribution of particles of it. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

When a disclosed compound is named or depicted by structure, it is to be understood that clathrates (“inclusion compounds”) of the compound or its pharmaceutically acceptable salts, solvates or polymorphs are also included. 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.

5 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,
10 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
15 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,
20 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
25 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.

30 “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.

35 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/m² per day and about 10 grams/m² per day, and preferably between 10 mg/m² per day and about 1 gram/m².

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.

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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.

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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 (IA), (I) through (XXX) or Table 1, Table 2, or Table 3.

15

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.

20

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.

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30

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.

35

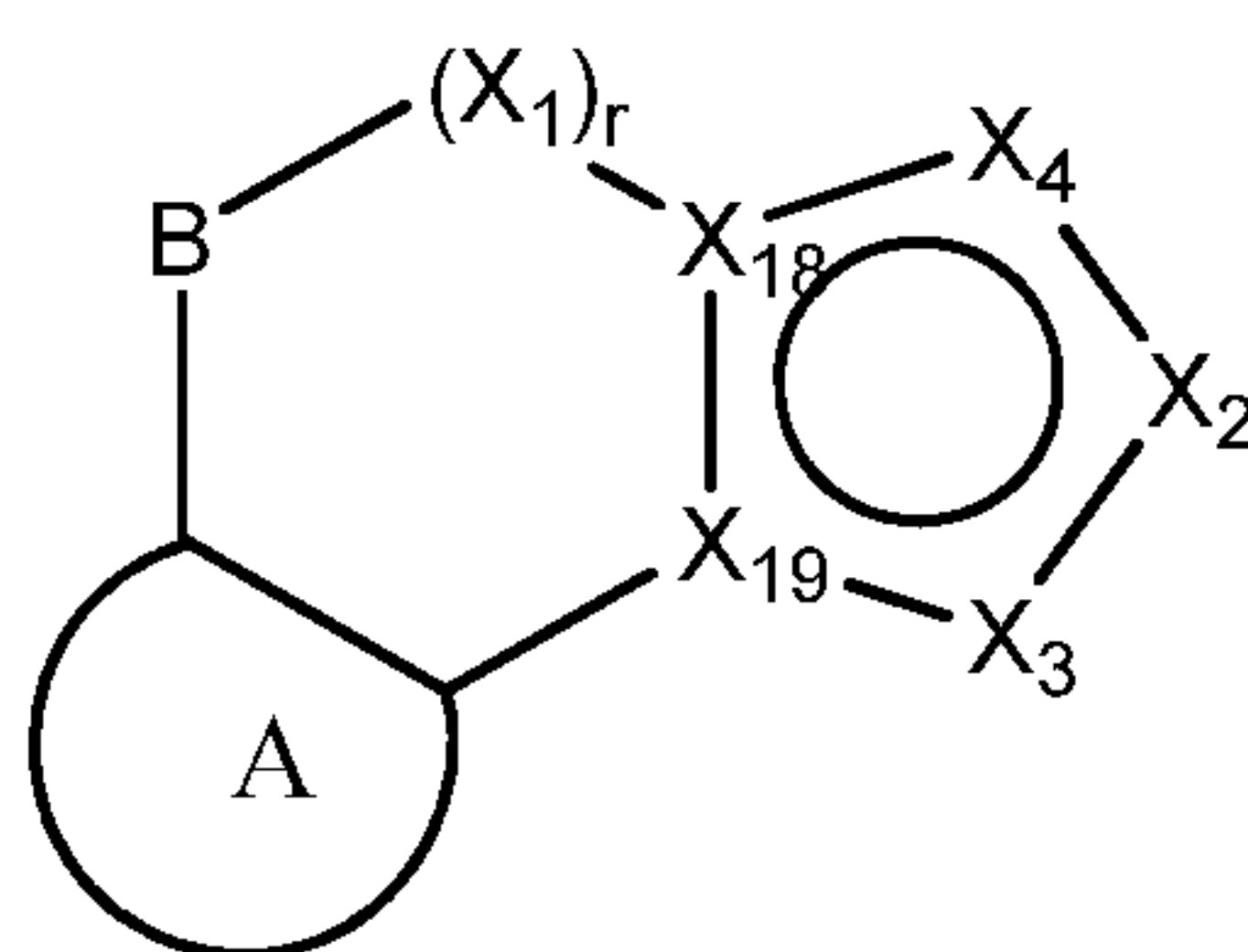
The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

SPECIFIC EMBODIMENTS

5

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 (IA):



10

(IA)

wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl ring wherein the ring atoms are selected from the group consisting of C, S, O, and N;

15

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

B is -C(R^a)₂-, -C(O)-; -O-, -S-, or -N(R^b)-;

20

each X₁ is independently -C(R^a)₂-, -C(O)-; -O-, -S-, or -N(R^b)-;

one of X₂, X₃ or X₄ is -C(L-Y)- or -C(R^a)(L-Y)- and the others are independently -O-, -S-, -N-, -N(R^b)-, -C(R^a)₂-, or -C(R^a)-;

each of X₁₈ or X₁₉ is independently -N-, -C-, or -C(R^a)-;

L is a linker;

25

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)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)_pR₄, or -S(O)_pNR₁R₂;

30

each R^b is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl,

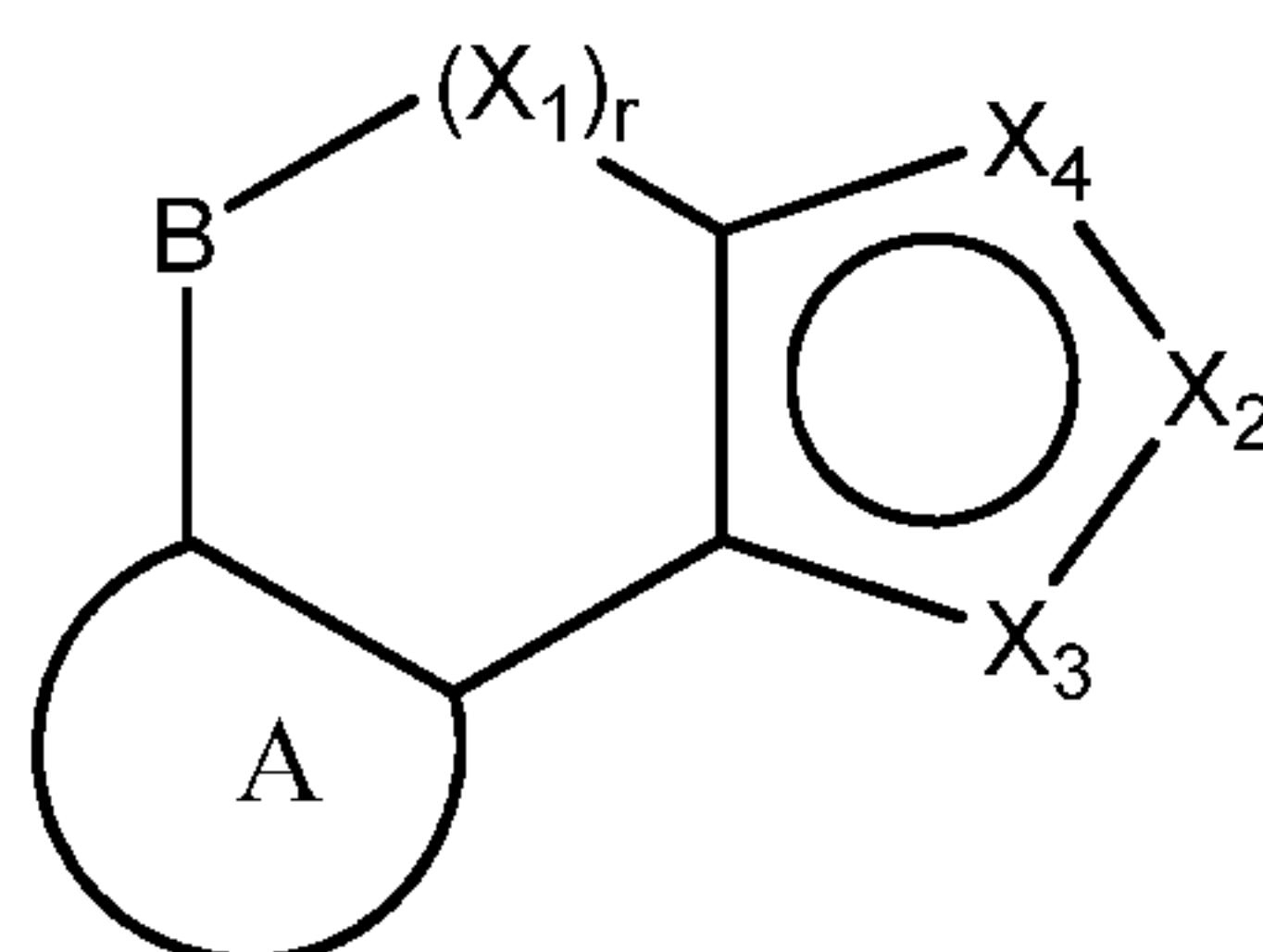
an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, $-\text{C}(\text{O})\text{R}_4$, or $-\text{C}(\text{O})\text{OR}_4$;

5 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;

10 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;

15 r is 1, 2, 3, or 4; and p is 0, 1, or 2; or a pharmaceutically acceptable salt thereof.

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



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl ring wherein the ring atoms are selected from the group consisting of C, S, O, and N;

25 Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

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

30 one of X_2 , X_3 or X_4 is $-\text{C}(\text{L}-\text{Y})-$ or $-\text{C}(\text{R}^a)(\text{L}-\text{Y})-$ and the others are independently $-\text{O}-$, $-\text{S}-$, $-\text{N}-$, $-\text{N}(\text{R}^b)-$, $-\text{C}(\text{R}^a)_2-$, or $-\text{C}(\text{R}^a)-$;

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
 5 haloalkyl, –C(O)NR₁R₂, –NR₄C(O)R₅, halo, –OR₄, cyano, nitro, haloalkoxy, –C(O)R₄, –NR₁R₂, –SR₄, –C(O)OR₄, –OC(O)R₄, –NR₄C(O)NR₁R₂, –OC(O)NR₁R₂, –NR₄C(O)OR₅, –S(O)_pR₄, or –S(O)_pNR₁R₂;

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
 10 haloalkyl, halo, –C(O)NR₁R₂, –C(O)R₄, or –C(O)OR₄;

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

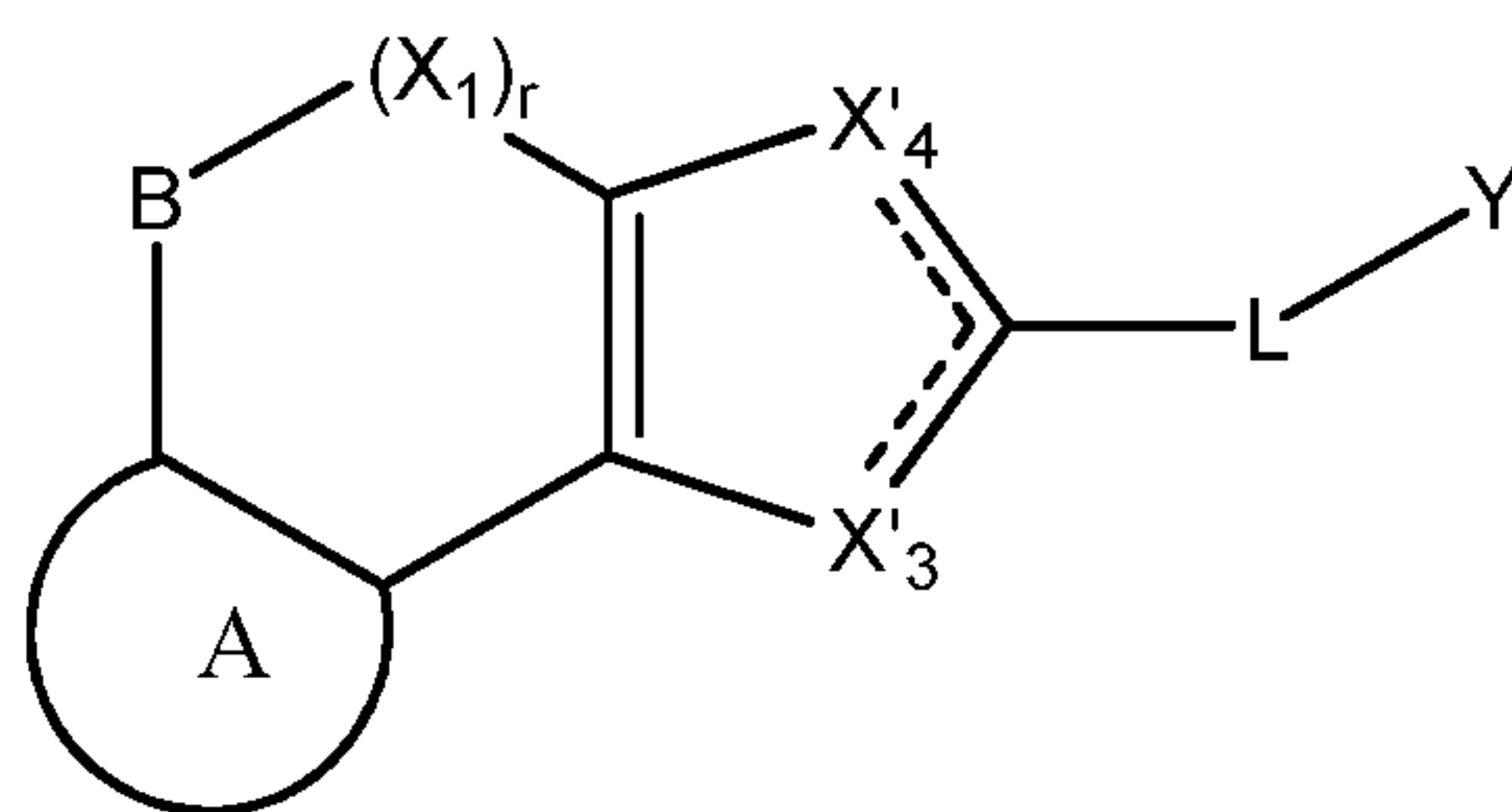
R₄ and R₅, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl,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

r is 1, 2, 3, or 4; and p is 0, 1, or 2.

In one embodiment of compounds of formula (IA) or (I), one or more of the following provisos apply:

- 1) when X₁ is CH₂, r is 2, X₄ is –S–, X₂ is –C(L–Y)–, X₃ is –N–, –B is –CH₂– or –NC(O)R₄–, and L is –NH–C(O)– or –NHC(O)NH–, then Ring A is not an optionally substituted phenyl;
- 2) when X₁ is CH₂, r is 2, X₄ is –N–, X₂ is –C(L–Y)–, X₃ is –S–, L is –NH–C(O)– and Y is methyl, then Ring A is not a pyrazole;
- 3) when Y is an optionally substituted aryl or an optionally substituted heteroaryl, X₂ is –C(L–Y)–, and X₃ is –S–, then X₄ is not –N–.

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



(II)

or a pharmaceutically acceptable salt thereof, wherein:

each of X'₃ and X'₄ is independently -O-, -S-, -N-, -N(R^b)-, -C(R^a)₂-, or -C(R^a)- provided that when Y is an optionally substituted aryl or an optionally substituted heteroaryl and X₃ is -S-, then X₄ is not -N-; and

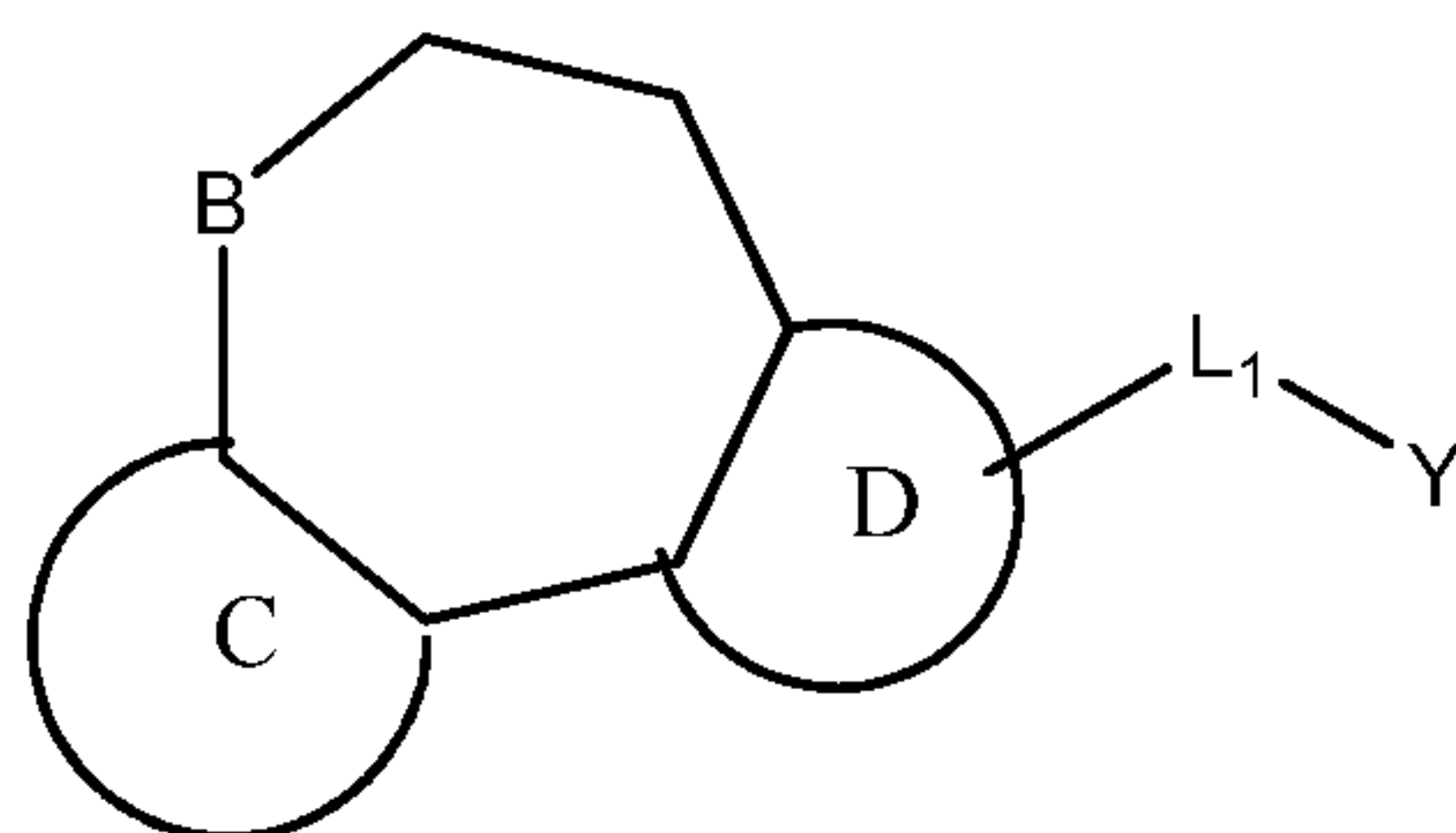
Ring A , B , X_1 , r , L and Y are defined as for formula (I).

In one embodiment of compounds of formulae (IA), (I) or (II), the compound is not 4H-thieno[3,2-d][1]benzazepine-2-carboxamide, 6-[4-[(1,1'-biphenyl)]-2-ylcarbonyl)amino]benzoyl]-N-cyclopropyl-5,6-dihydro- or 4H-benzo[6,7]cyclohepta[1,2-d]thiazole-2-carboxamide, 5,6-dihydro-N-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl].

In one embodiment of compounds of formula (II), one or more of the following provisos apply:

- 1) when X_1 is CH_2 , r is 2, X'_4 is $-\text{S}-$, X'_3 is $-\text{N}-$, $-\text{B}$ is $-\text{CH}_2-$ or $-\text{NC}(\text{O})\text{R}_4-$, and L is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{NHC}(\text{O})\text{NH}-$, then Ring A is not an optionally substituted phenyl;
- 2) when X_1 is CH_2 , r is 2, X'_4 is $-\text{N}-$, X'_3 is $-\text{S}-$, L is $-\text{NH}-\text{C}(\text{O})-$ and Y is methyl, then Ring A is not a pyrazole.

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



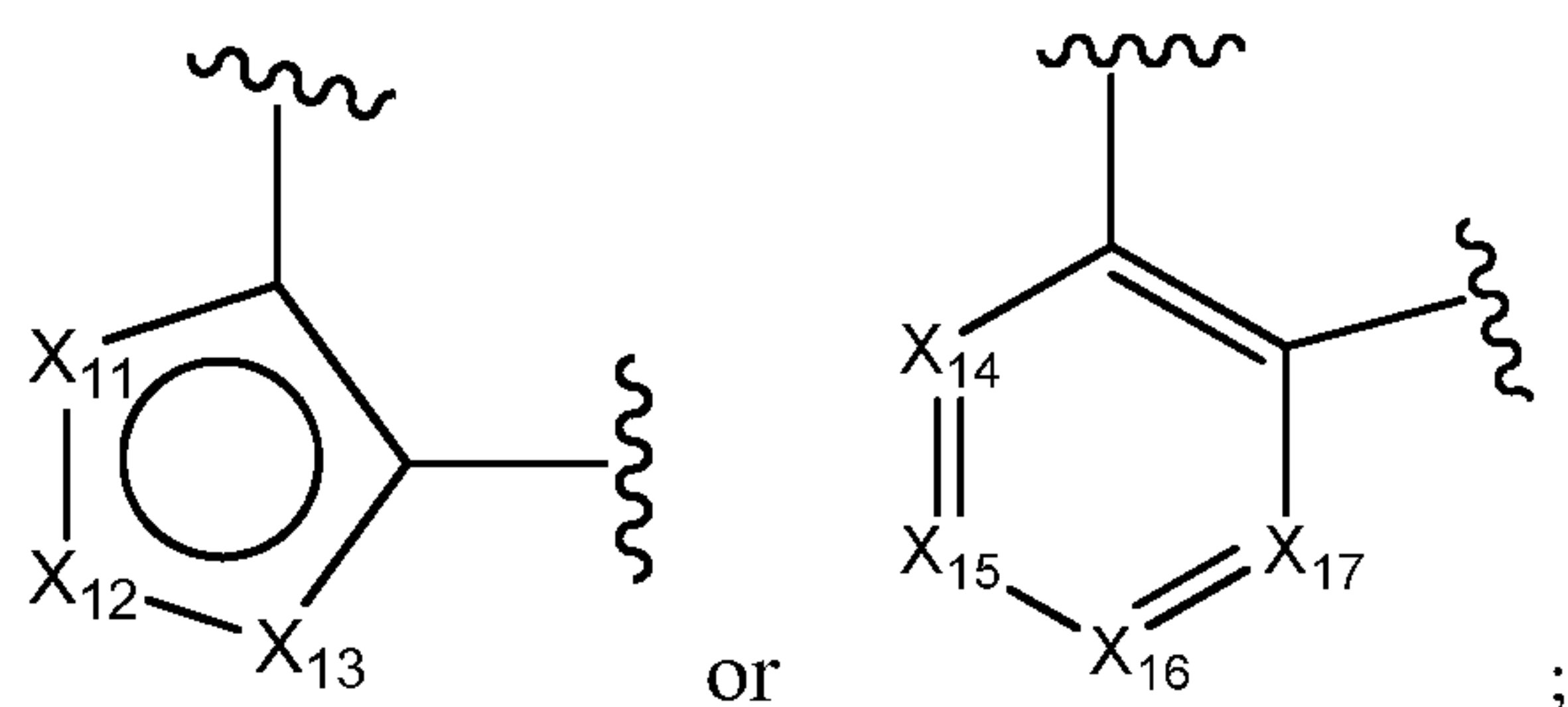
(III)

or a pharmaceutically acceptable salt thereof, wherein:

B and Y are as described for Formula (I);

L₁ is -NHCH₂-, -CH₂NH-, -NH-C(O)-, -C(O)-NH-, or -NHC(O)NH-;

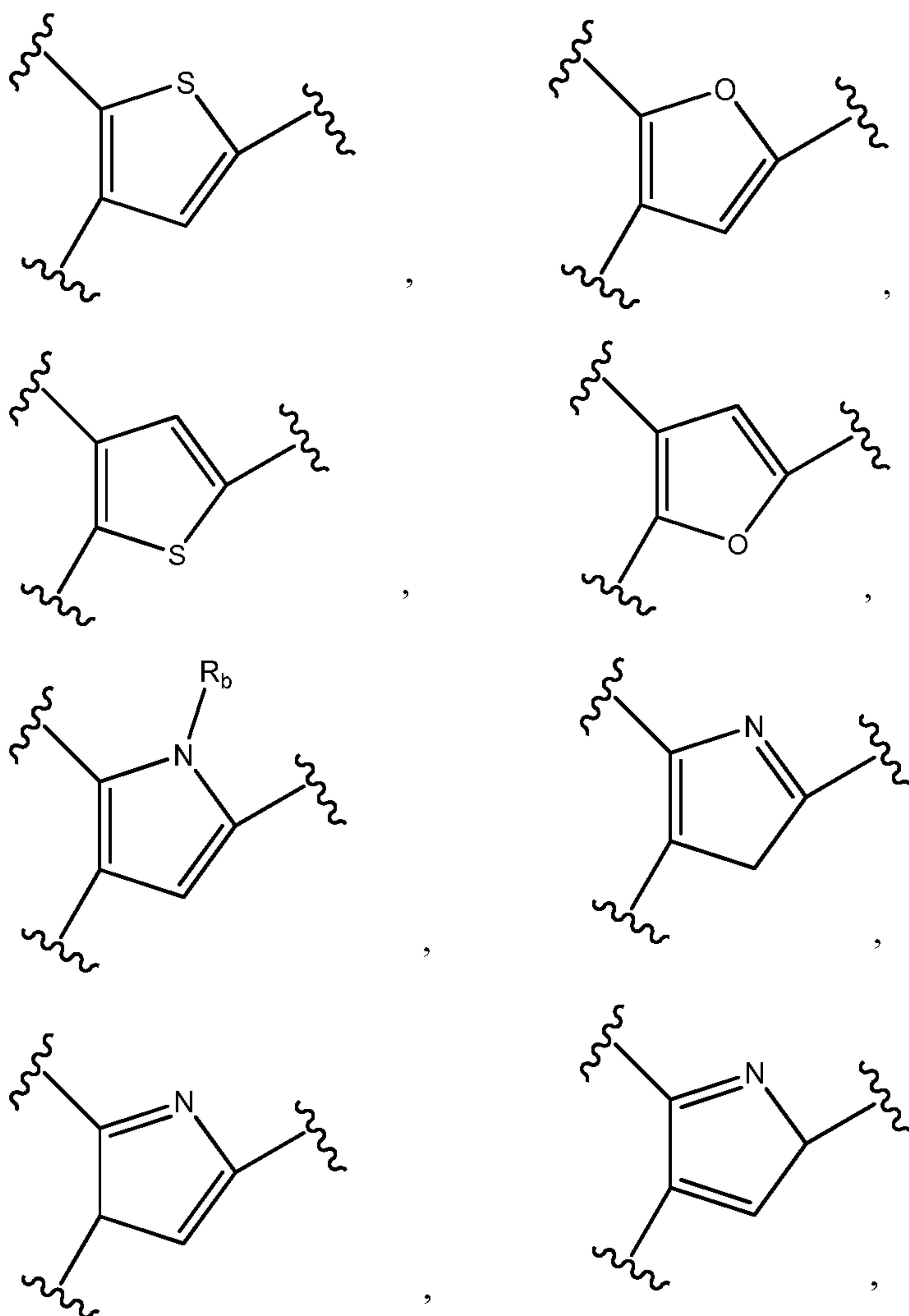
Ring C is selected from



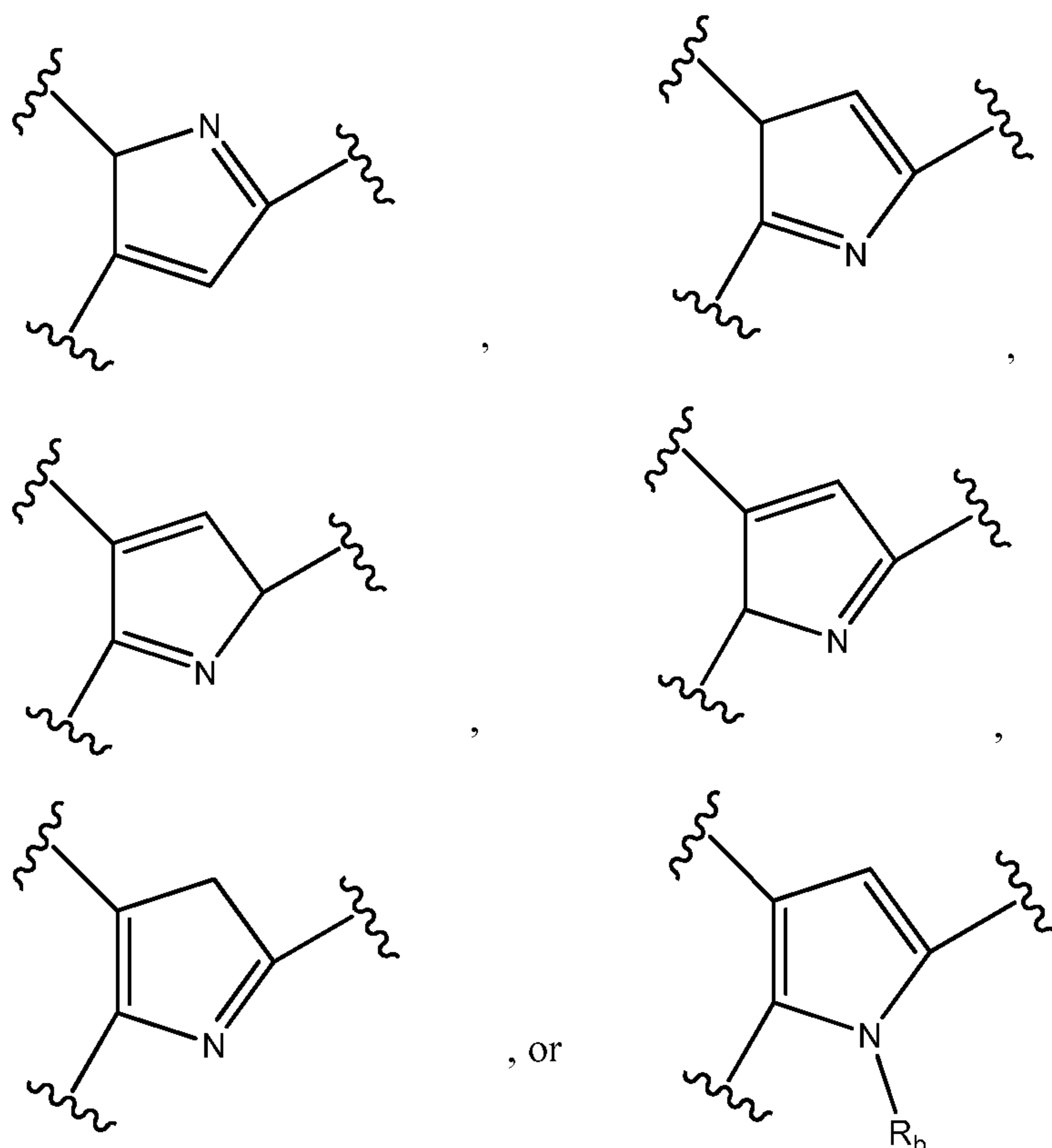
each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R^a)-$, $-C(R^a)_2-$, $-S-$, $-O-$, $-N-$, or $-N(R^b)-$;

5 each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R^a)-$ and $-N-$;

Ring D is selected from:

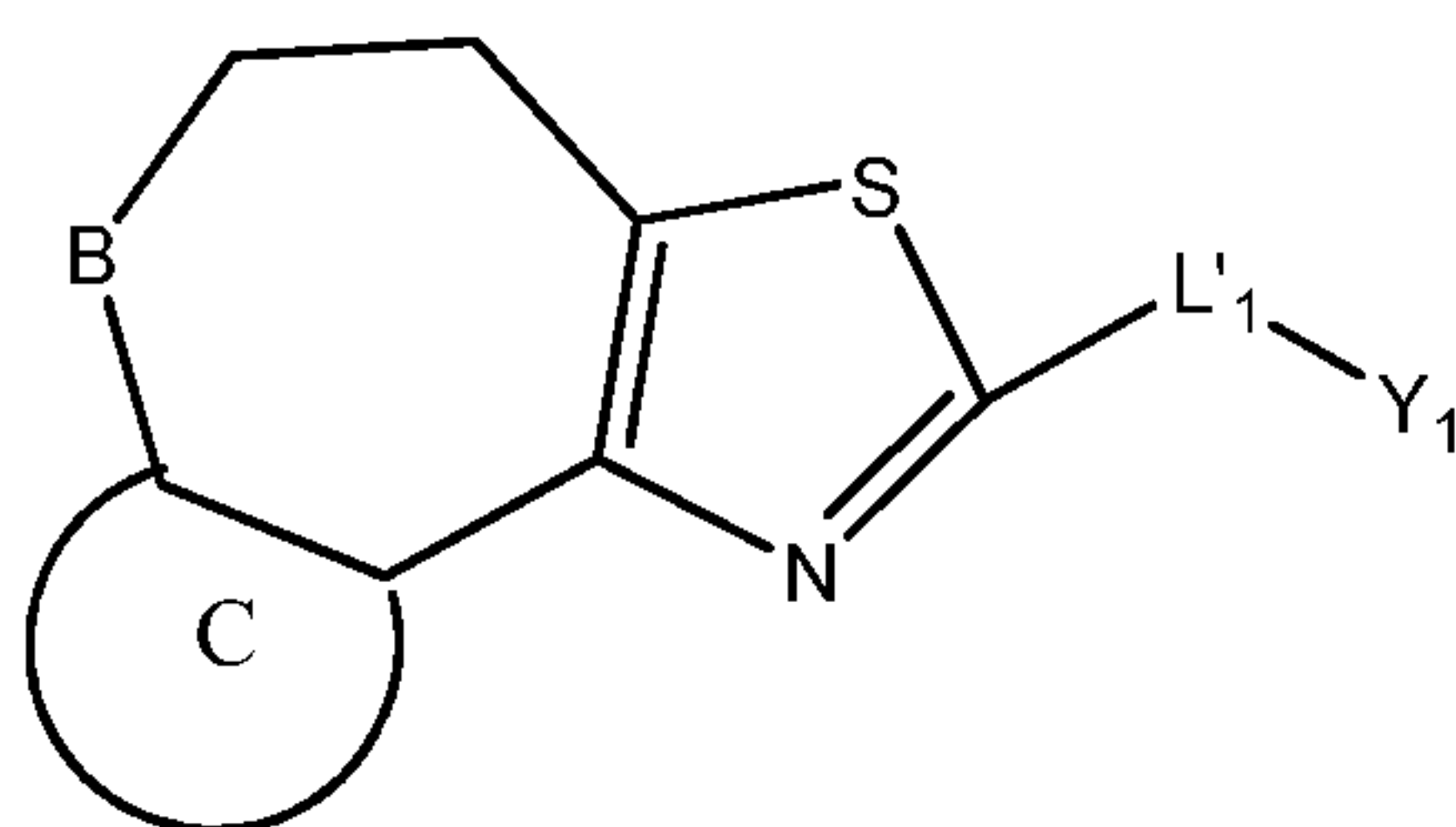


10



5 In one embodiment of compounds of formula (III), the compound is not 4H-thieno[3,2-d][1]benzapyne-2-carboxamide, 6-[4-[[[1,1'-biphenyl]]-2-ylcarbonyl)amino]benzoyl]-N-cyclopropyl-5,6-dihydro.

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



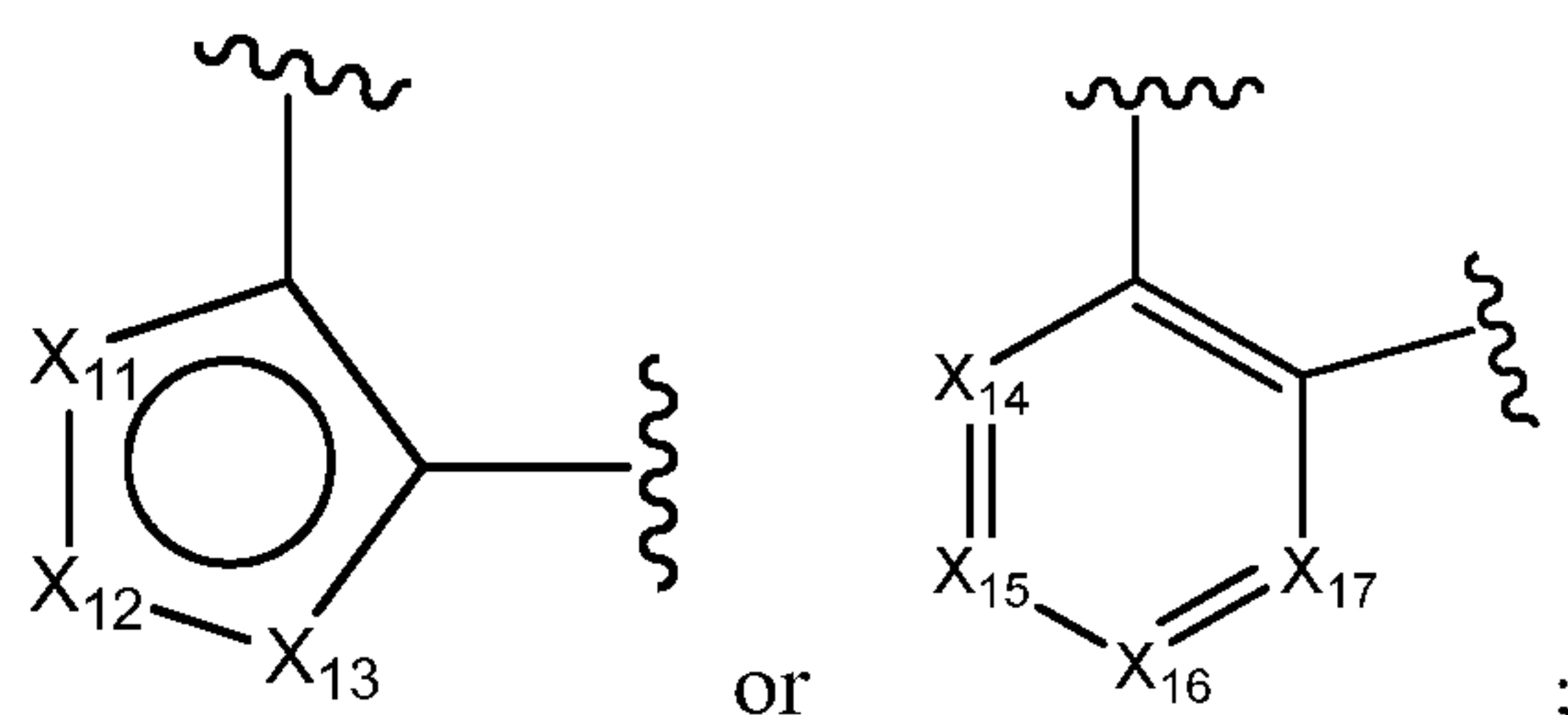
(IV)

or a pharmaceutically acceptable salt thereof, wherein:

L'_1 is $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y_1 is a 5 or 6 membered aromatic ring optionally substituted with C1-C4 alkyl, halo, or C1-C4 alkoxy, an optionally substituted 5 or 6 membered heteroaromatic ring, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl;

Ring C is selected from



each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R^a)-$, $-C(R^a)_2-$, $-S-$, $-O-$, $-N-$, or $-N(R^b)-$; and

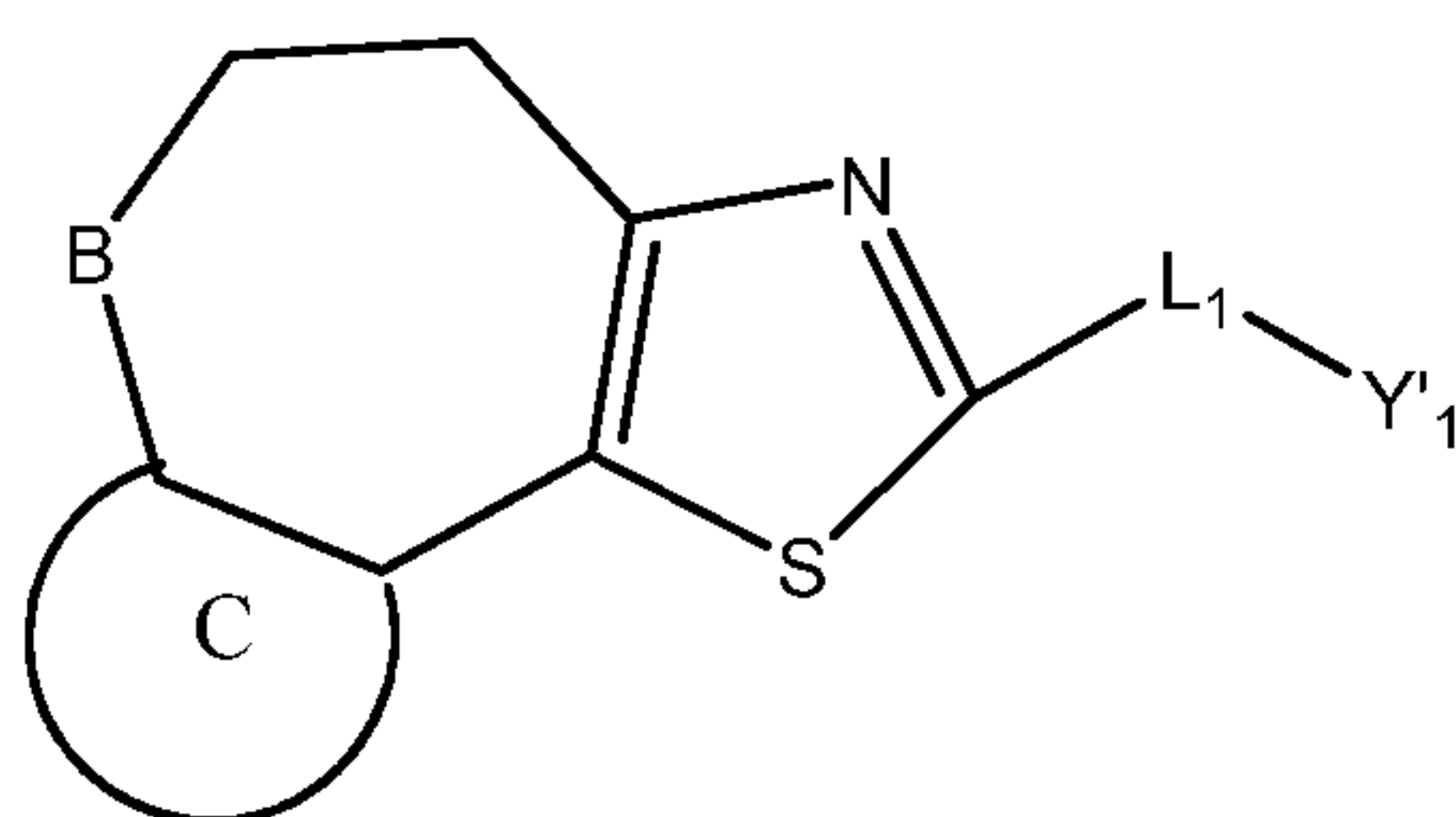
5 each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R^a)-$ and $-N-$.

In one embodiment of compounds of formula (IV), when B is $-CH_2-$ or $-NC(O)R_4-$, and L'_1 is $-NH-C(O)-$ or $-NHC(O)NH-$, then X_{14} , X_{15} , X_{16} , and X_{17} are not all $-C(R^a)-$.

In one embodiment of compounds of formula (IV), the compound is not 4H-benzo[6,7]cyclohepta[1,2-d]thiazole-2-carboxamide, or

10 5,6-dihydro-N-[2-(1-phenylmethyl-4-piperdiny)ethyl].

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



(V)

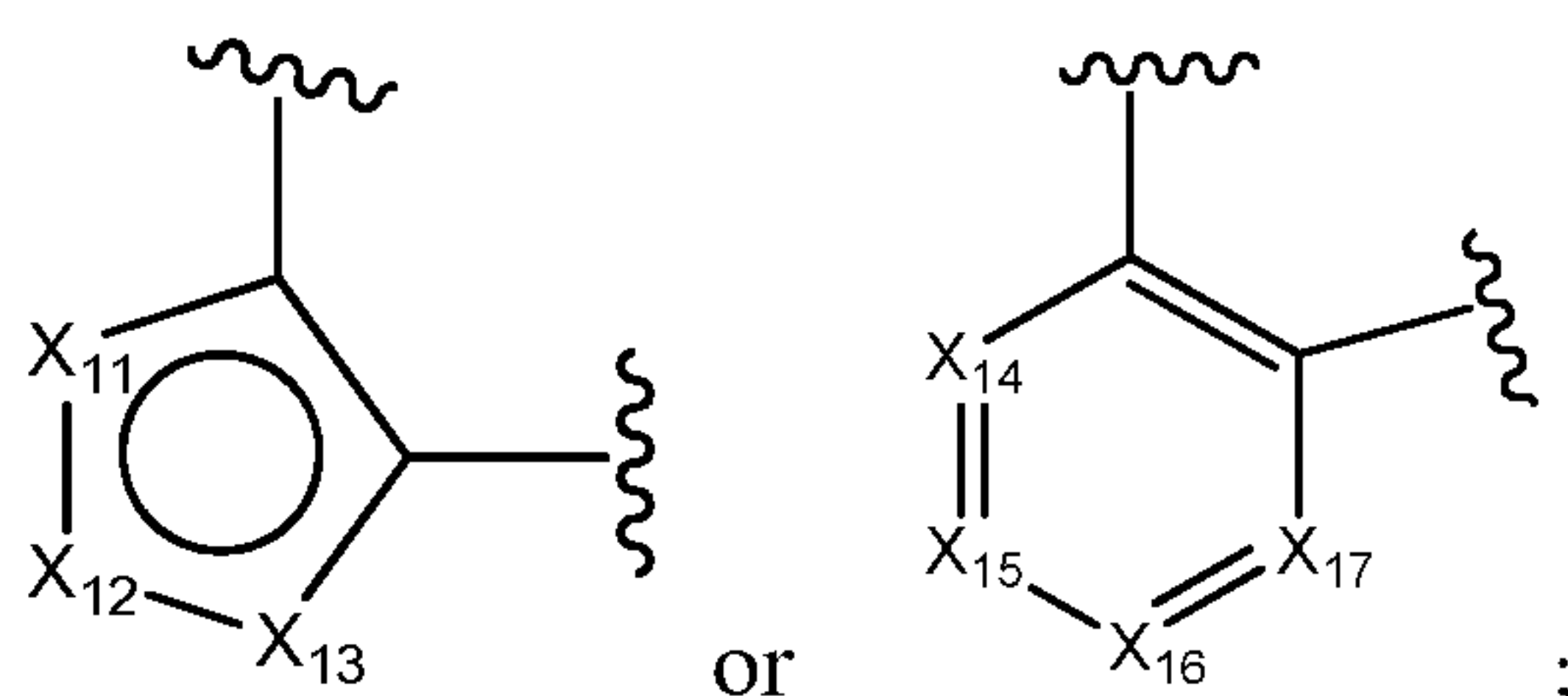
15 or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

Y'_1 is an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, or an optionally substituted cycloalkenyl;

Ring C is selected from

20



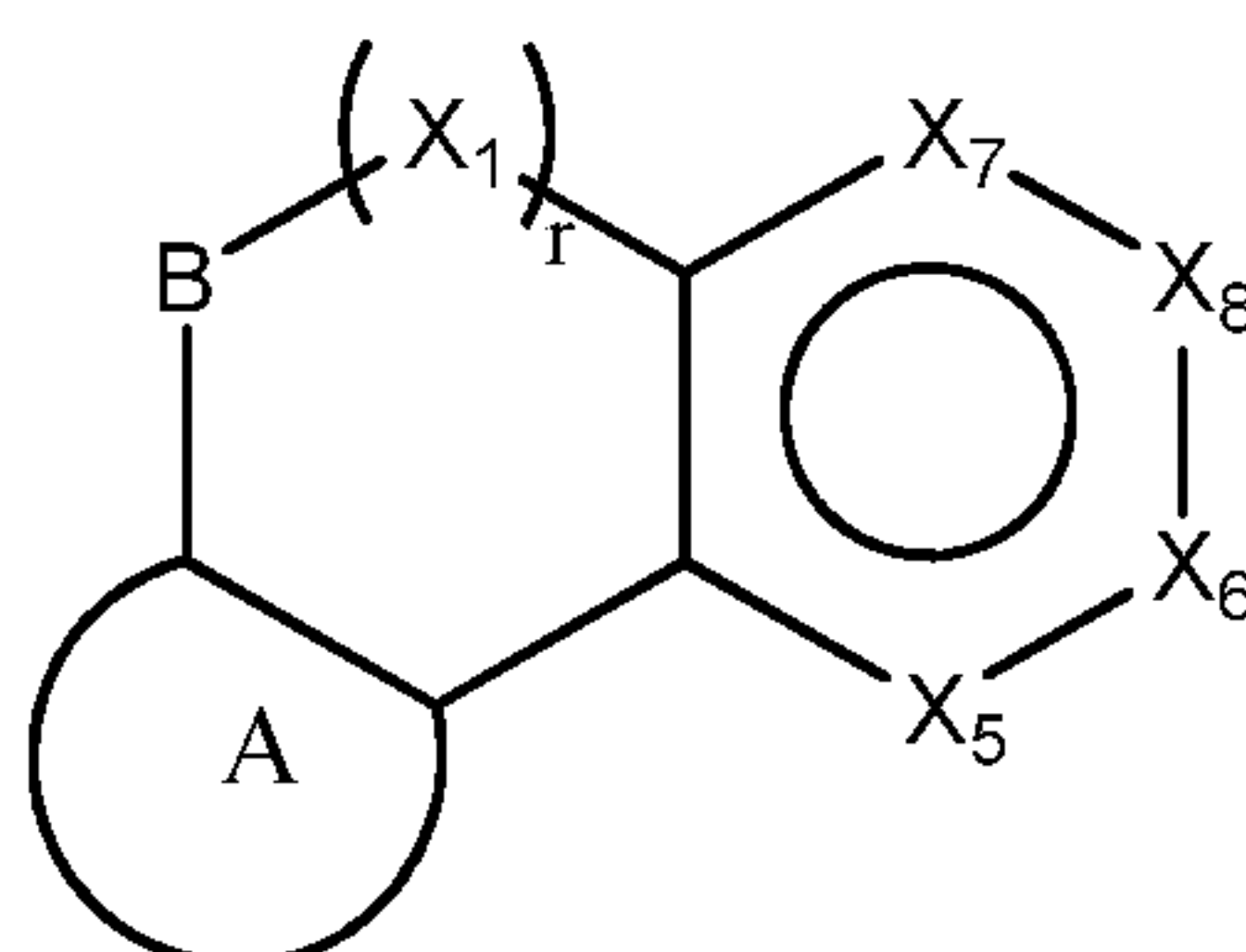
each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R^a)-$, $-C(R^a)_2-$, $-S-$, $-O-$, $-N-$, or $-N(R^b)-$; and

each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R^a)-$ and $-N-$; and the rest of the variables are as described in formula (I).

In one embodiment of compounds of formula (V), when L_1 is $-NH-C(O)-$ and Y is methyl, then Ring C is not a pyrazole.

5

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



(VI)

10

or a pharmaceutically acceptable salt thereof, wherein:

one of X_5 , X_6 , X_7 , and X_8 is $-C(L-Y)-$ and the others are independently $-N-$ or $-CR^a-$; and Ring A, B, X_1 , and r are defined as for formula (I).

In one embodiment of compounds of formula (VI), one or more of the following provisos apply:

15

1) when X_1 is CH_2 , r is 2, X_5 and X_6 are N and X_7 is $-CR^a-$, X_8 is $-C(L-Y)-$, Y is an optionally substituted alkyl, and L is $-NH-CH_2-$, then Ring A is not an optionally substituted phenyl or a thiophene.

2) when Y is an optionally substituted aryl or an optionally substituted heteroaryl, X_5 and X_7 are not both $-N-$,

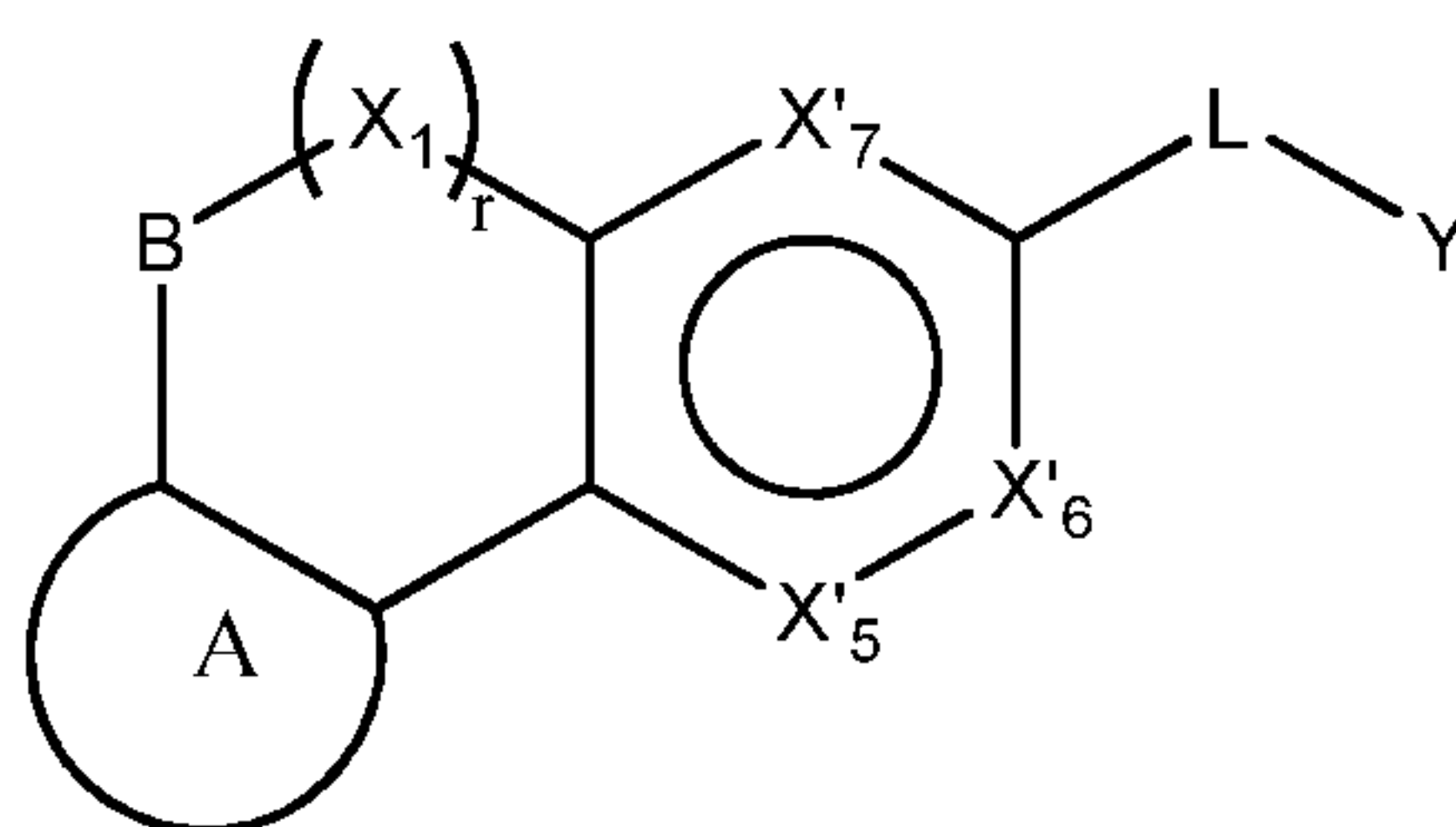
20

3) when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is an optionally substituted phenyl or a 6-membered N -containing heteroaryl, one of X_6 or X_7 is not $-N-$.

4) when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is a N -containing heteroaryl, then at least one of X_5 , X_6 , and X_7 must be $-N-$.

25

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



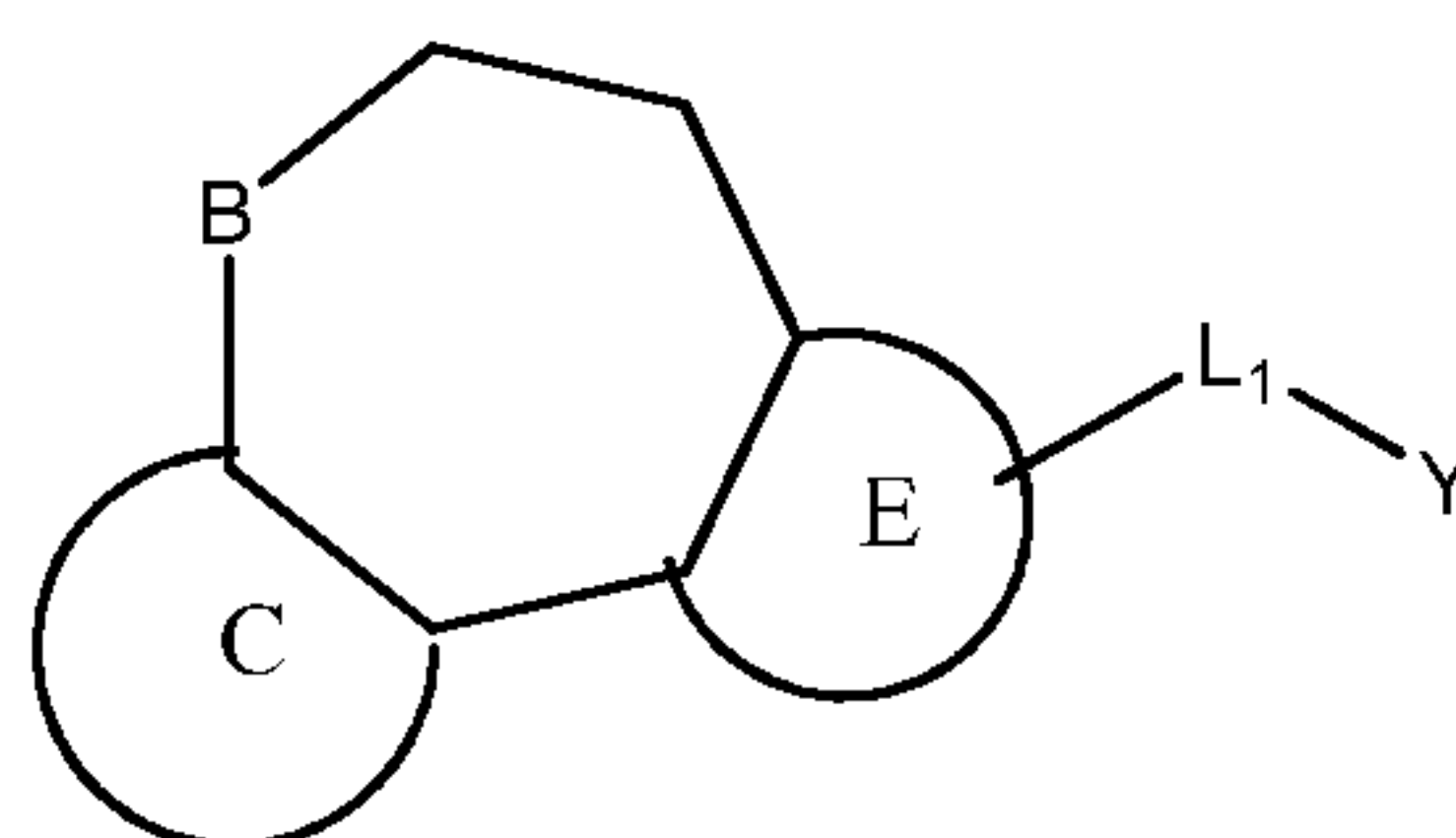
(VII)

or a pharmaceutically acceptable salt thereof, wherein:

each of X'_5 , X'_6 , and X'_7 is independently -N-, or $-CR^a$ -, provided that when Y is an optionally substituted aryl or an optionally substituted heteroaryl, X'_5 and X'_7 are not both -N-, when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is an optionally substituted phenyl or a 6-membered N-containing heteroaryl, one of X'_6 or X'_7 is not -N-, and when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is a N-containing heteroaryl, then at least one of X'_5 , X'_6 , and X'_7 must be -N-; and Ring A, B, X_1 , r, L and Y are defined as for formula (VI).

In one embodiment of compounds of formula (VII), when X_1 is CH_2 , r is 2, X'_5 and X'_6 are N and X'_7 is $-CR^a$ -, Y is an optionally substituted alkyl, and L is $-NH-CH_2$ -, then Ring A is not an optionally substituted phenyl or a thiophene.

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

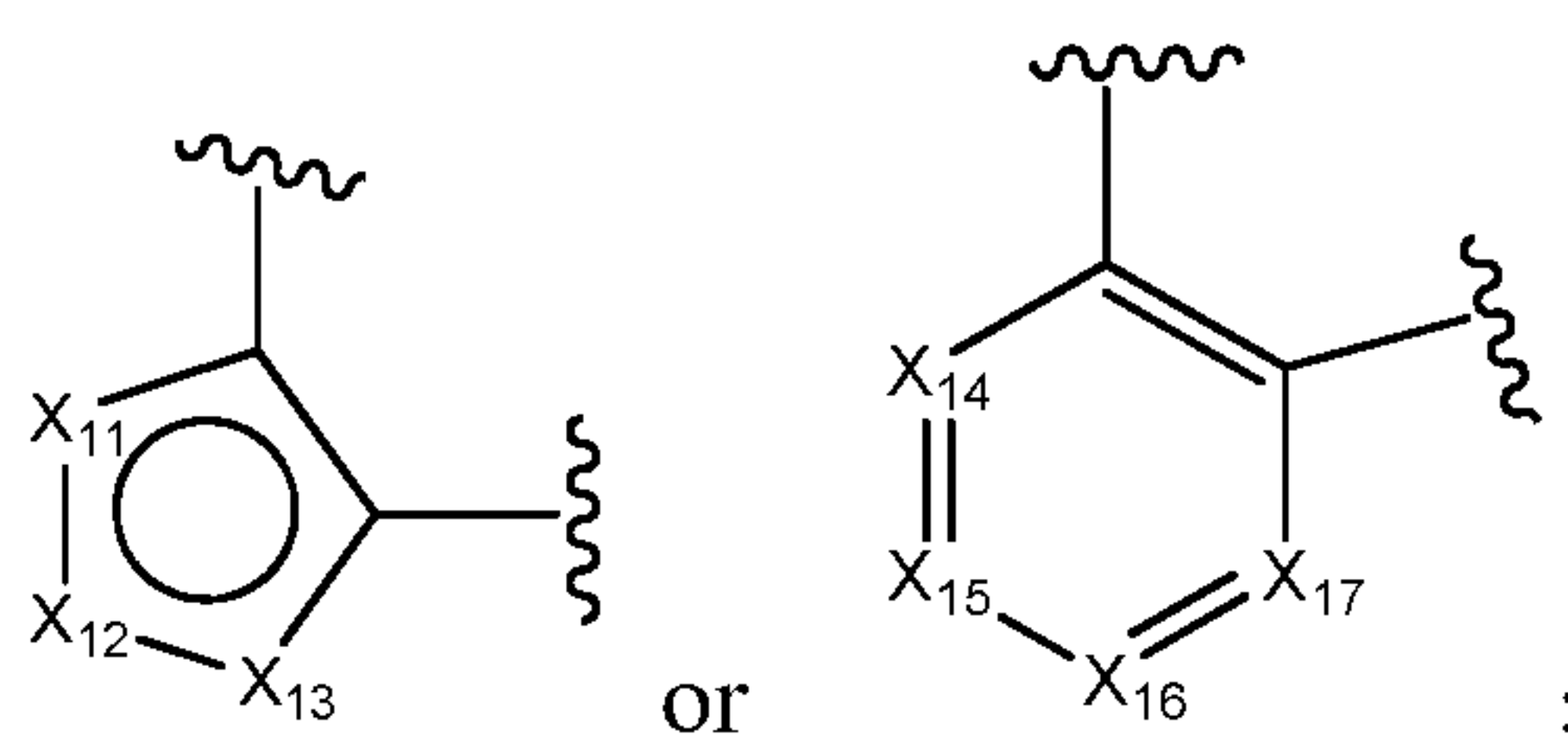


(VIII)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2$ -, $-CH_2NH$ -, $-NH-C(O)$ -, $-C(O)-NH$ -, or $-NHC(O)NH$ -;

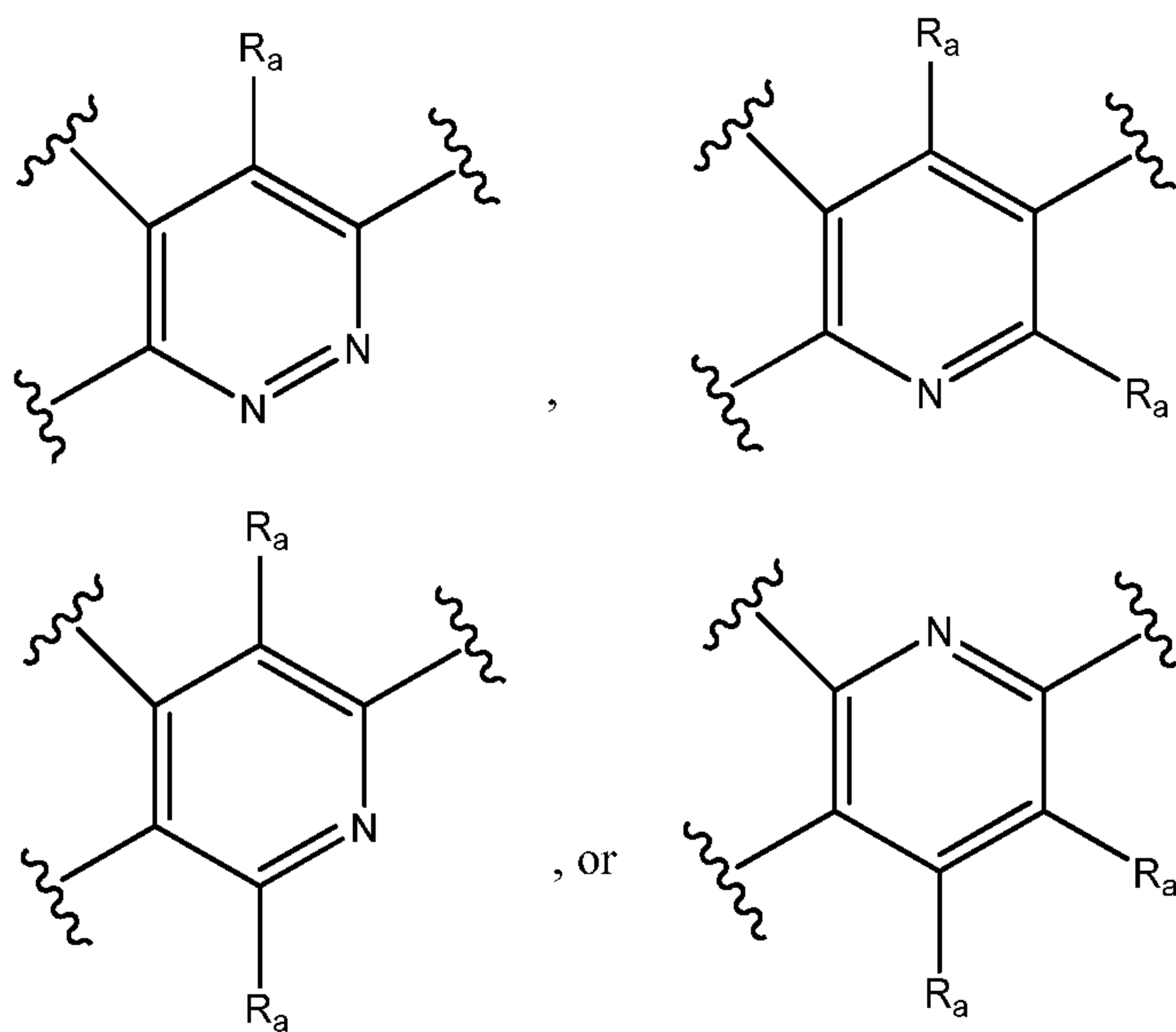
Ring C is selected from



each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R^a)$ -, $-C(R^a)_2$ -, -S-, -O-, -N-, or $-N(R^b)$ -;

each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R^a)$ - and -N-;

Ring E is selected from:

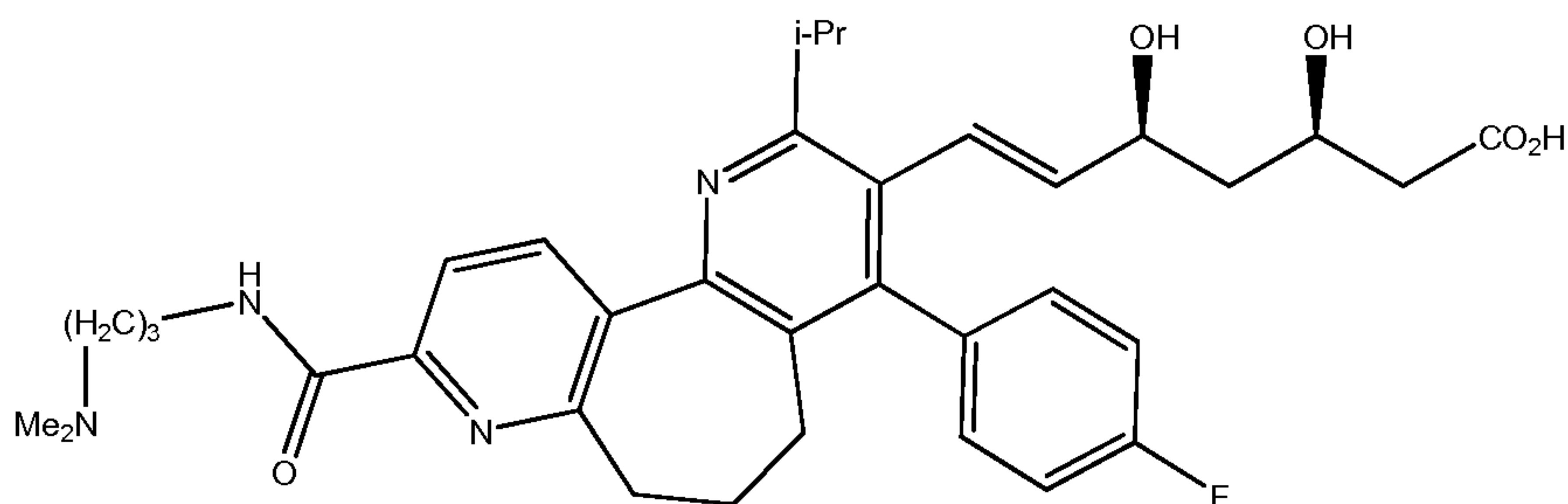


; and the rest of the variables are as

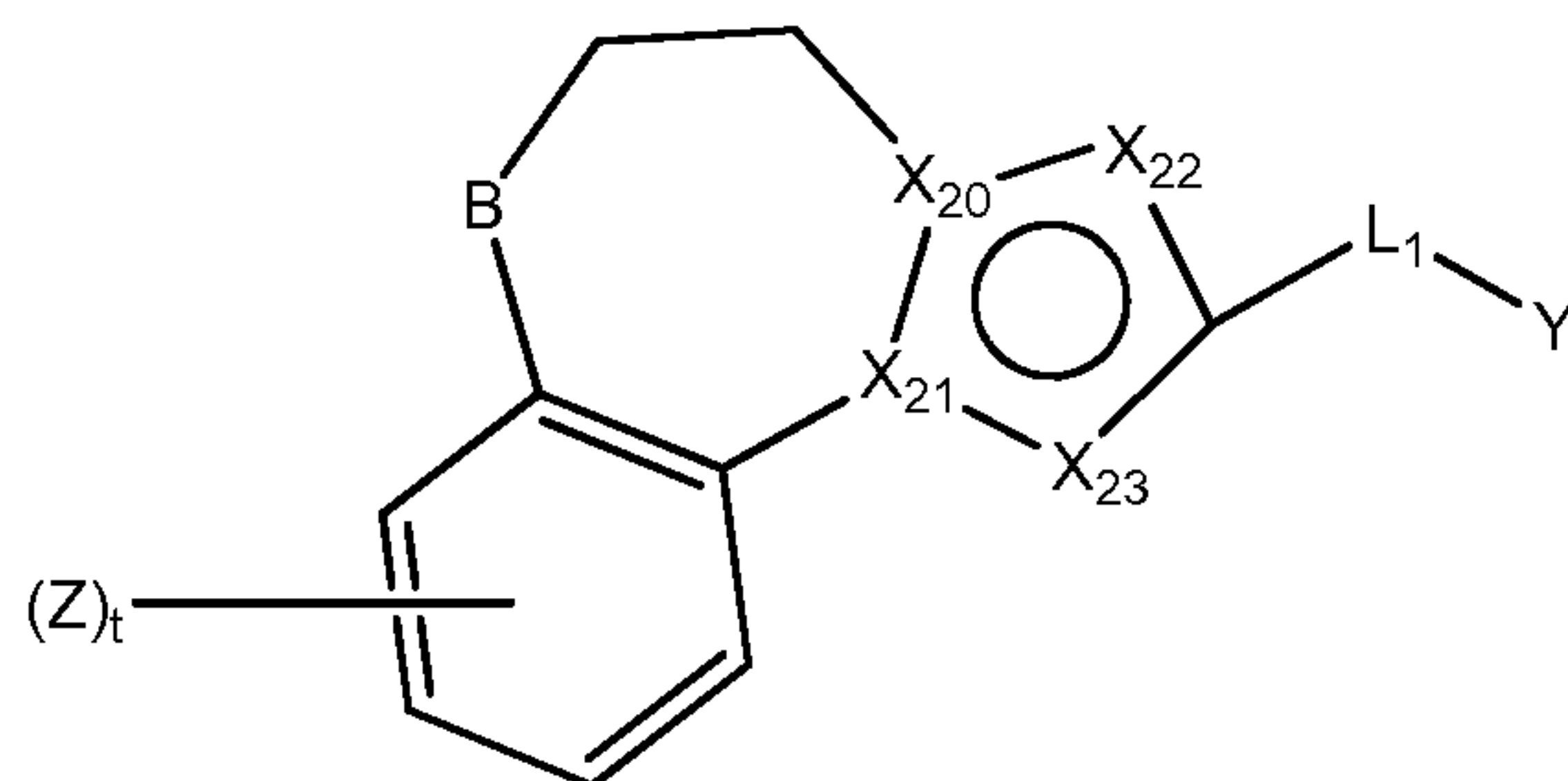
described for formula (IV).

5 In one embodiment of compounds of formula (VIII), when Ring E is pyridazine, Y is an optionally substituted alkyl, and L'_1 is $-NH-CH_2-$, then Ring C is not a phenyl, an optionally substituted phenyl or a thiophene; and

In one embodiment of compounds of formula (VI), (VII) or (VIII), the compound is not



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



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

Z is a substituent:

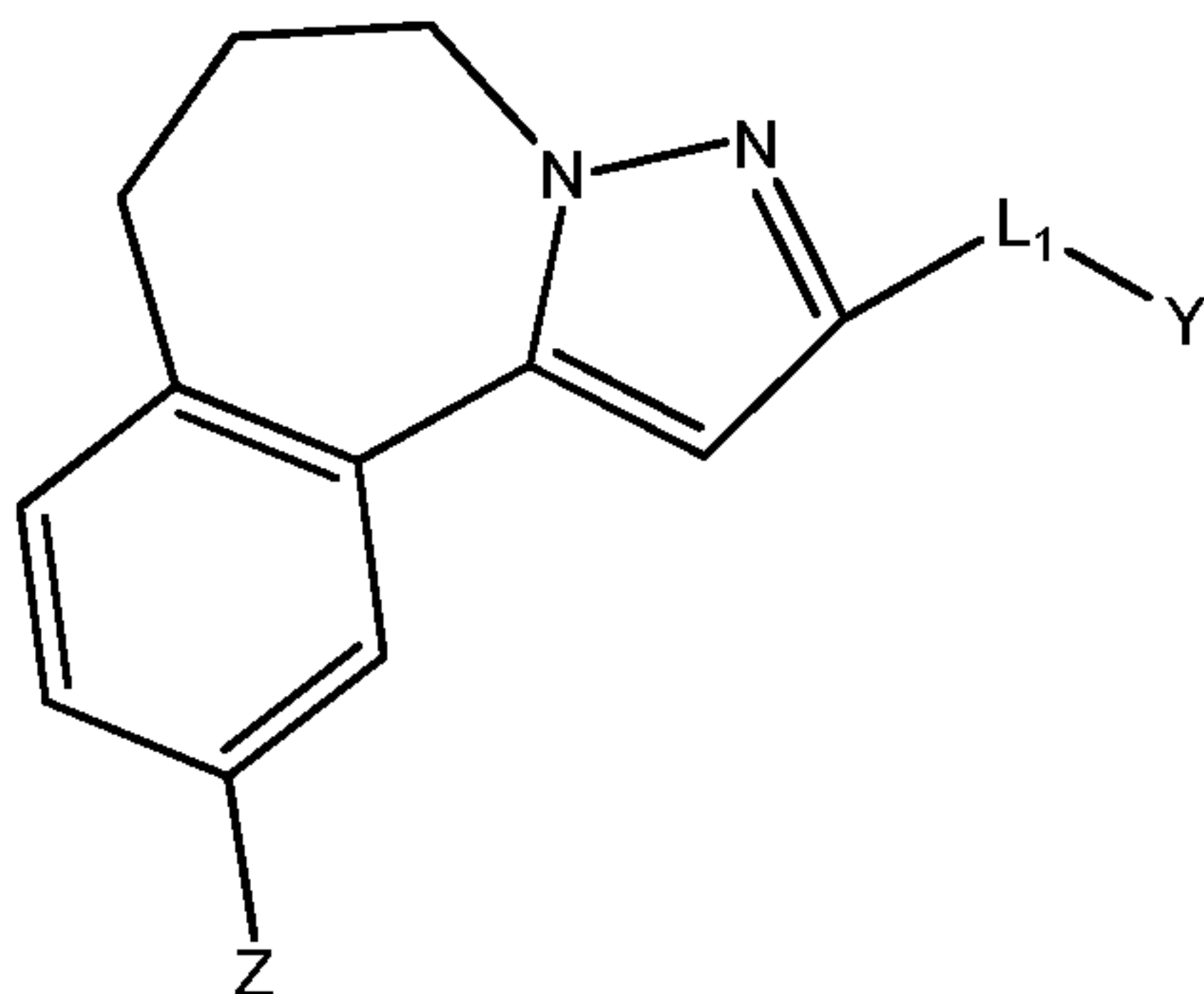
t is 0, 1, 2, 3, or 4;

X_{20} and X_{21} are independently $-N-$, $-CR^a-$, or $-C-$, provided that one of X_{20} or X_{21} is $-CR^a-$, or $-C-$;

X_{22} and X_{23} are independently $-N-$, $-CR^a-$, or $-C(R^a)_2-$;

and B, L_1 and Y are defined in formula (I).

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

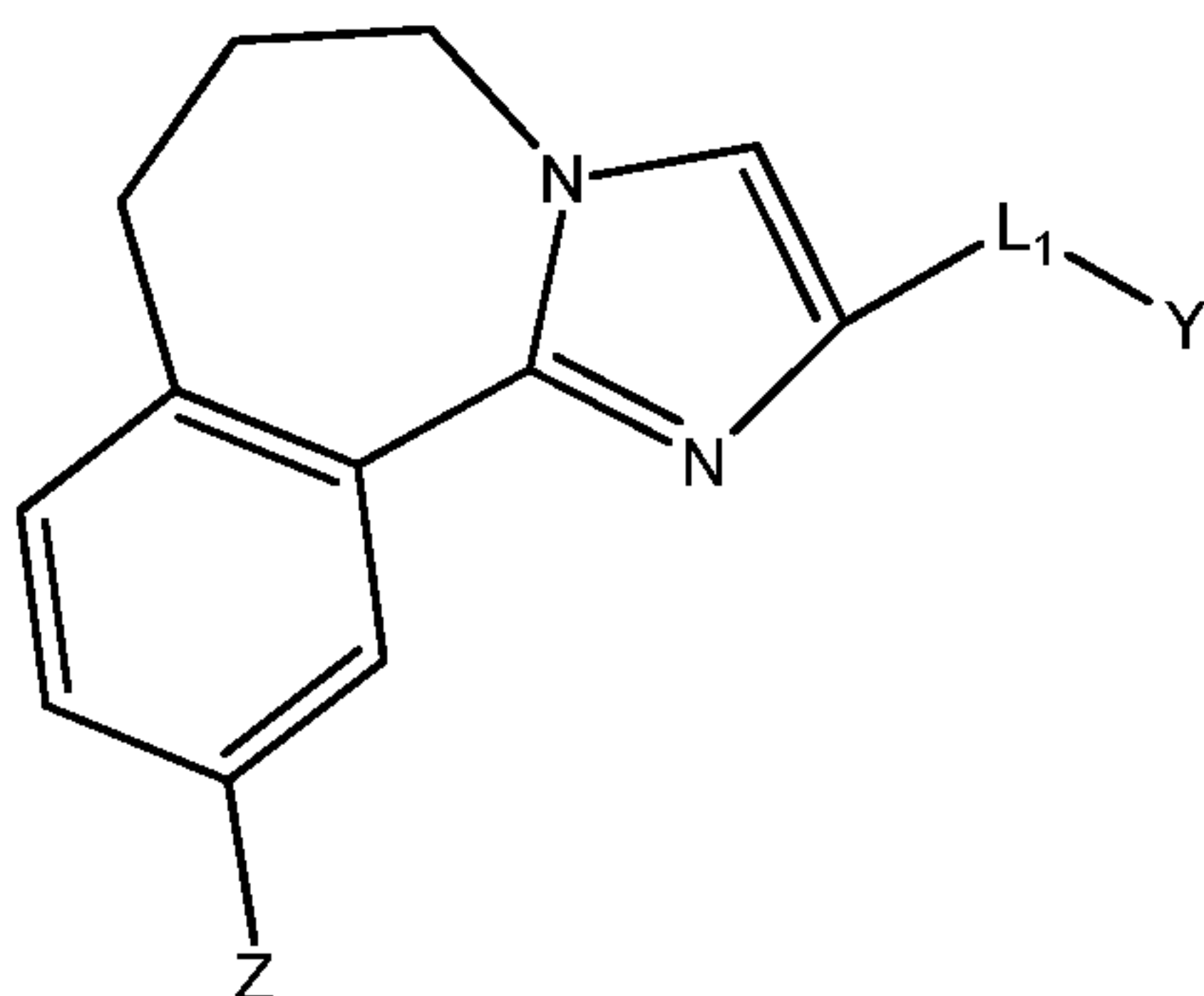


(IXa)

or a pharmaceutically acceptable salt thereof, wherein Z, L_1 and Y are defined as for formula (IX).

10

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

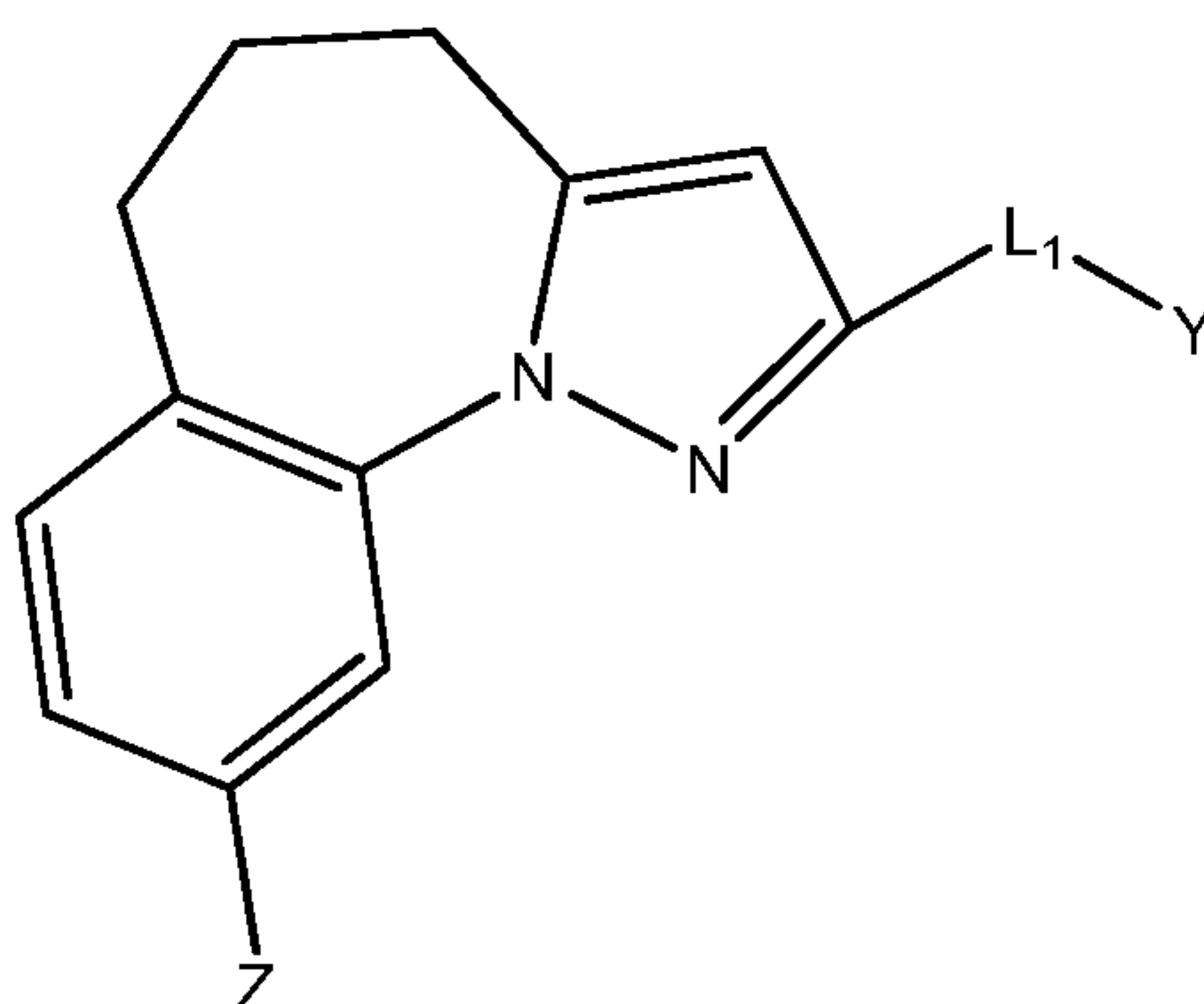


(IXb)

or a pharmaceutically acceptable salt thereof, wherein Z, L_1 and Y are defined for formula (IX).

15

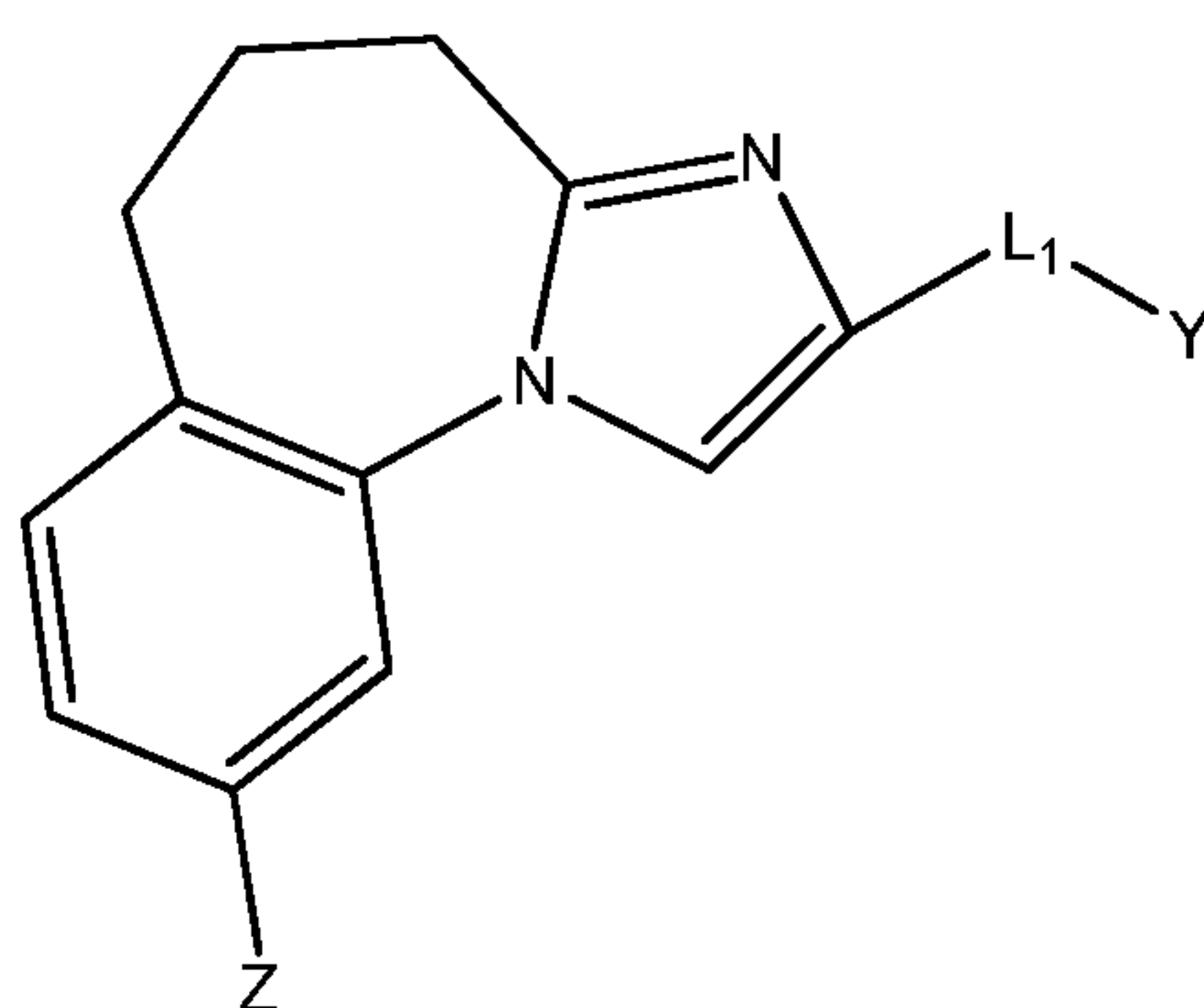
Another embodiment of the invention relates to compounds of formula (IXc):



(IXc)

or a pharmaceutically acceptable salt thereof, wherein Z, L_1 and Y are defined for formula (IX).

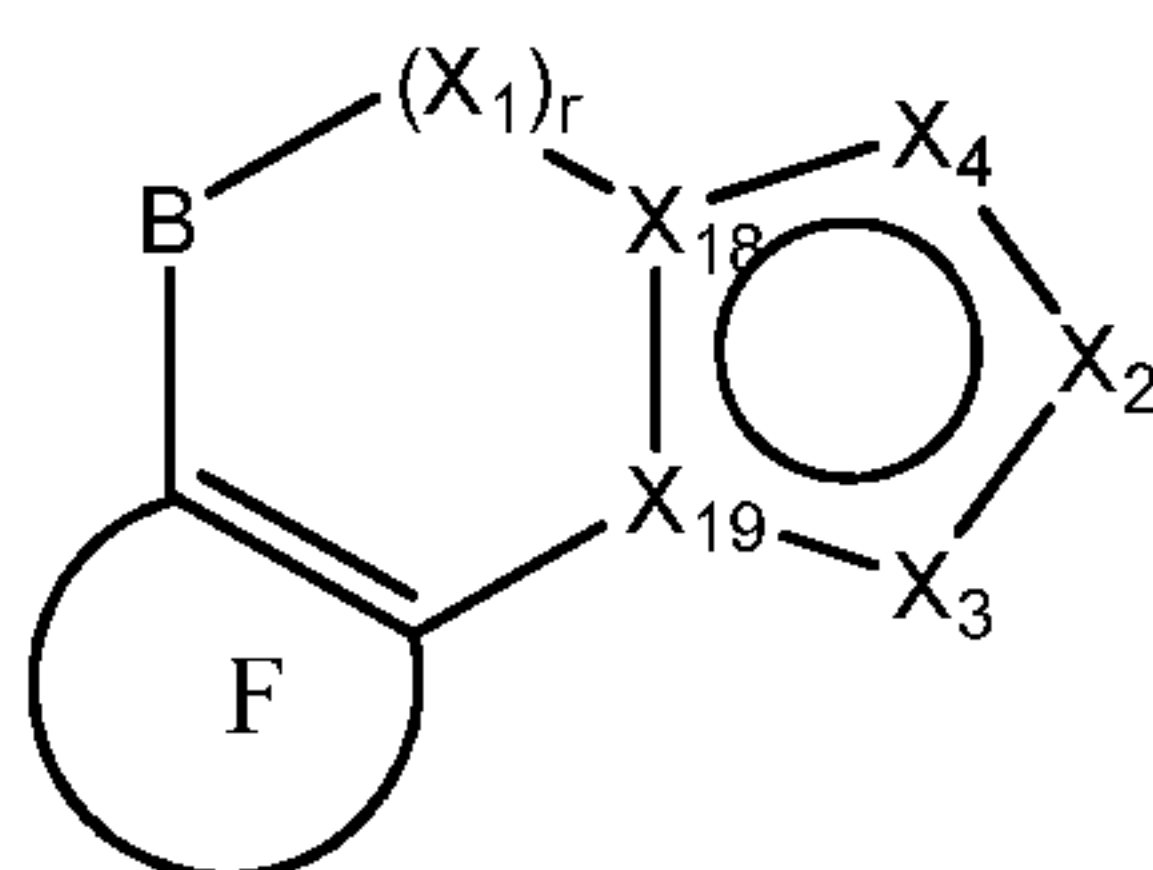
Another embodiment of the invention relates to compounds of formula (IXd):



(IXd)

or a pharmaceutically acceptable salt thereof, wherein Z, L₁ and Y are defined for formula (IX).

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



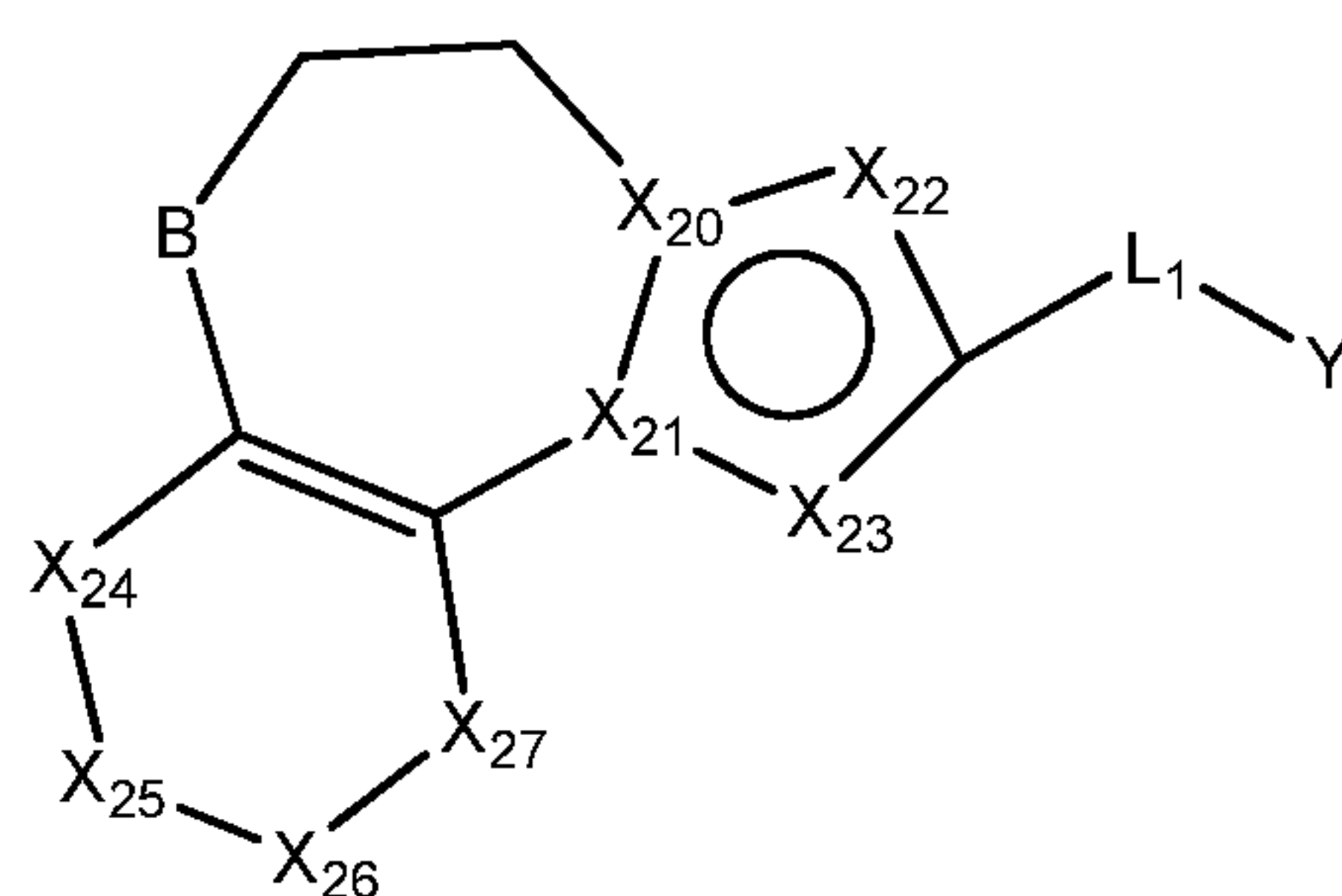
(X)

or a pharmaceutically acceptable salt thereof, wherein:

Ring F is an optionally substituted 5 or 6-membered non-aromatic ring containing atoms
10 selected from the group consisting of C, S, O, and N; and

B, X₁, r, X₂, X₃, X₄, X₁₈, and X₁₉ are defined as for formula (I).

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



(XI)

or a pharmaceutically acceptable salt thereof, wherein:

X₂₀ and X₂₁ are independently -N-, -CR^a-, or -C-, provided that one of X₂₀ or X₂₁ is -CR^a-, or
15 -C-;

X₂₂ and X₂₃ are independently -N-, -CR^a-, or -C(R^a)₂-;

X₂₄, X₂₅, X₂₆ and X₂₇ are each independently -O-, -S-, -N(R^b)-, -C(R^a)₂-;

and B, L₁ and Y are defined in formula (I).

5



A diagram of a 2D lattice site. It features a central nitrogen atom (N) bonded to two X_{28} atoms. The X_{28} atoms are further bonded to other atoms, represented by wavy lines, indicating a continuation of the lattice structure.

(b)

10

and B , L_1 and Y are defined for formula (XI).

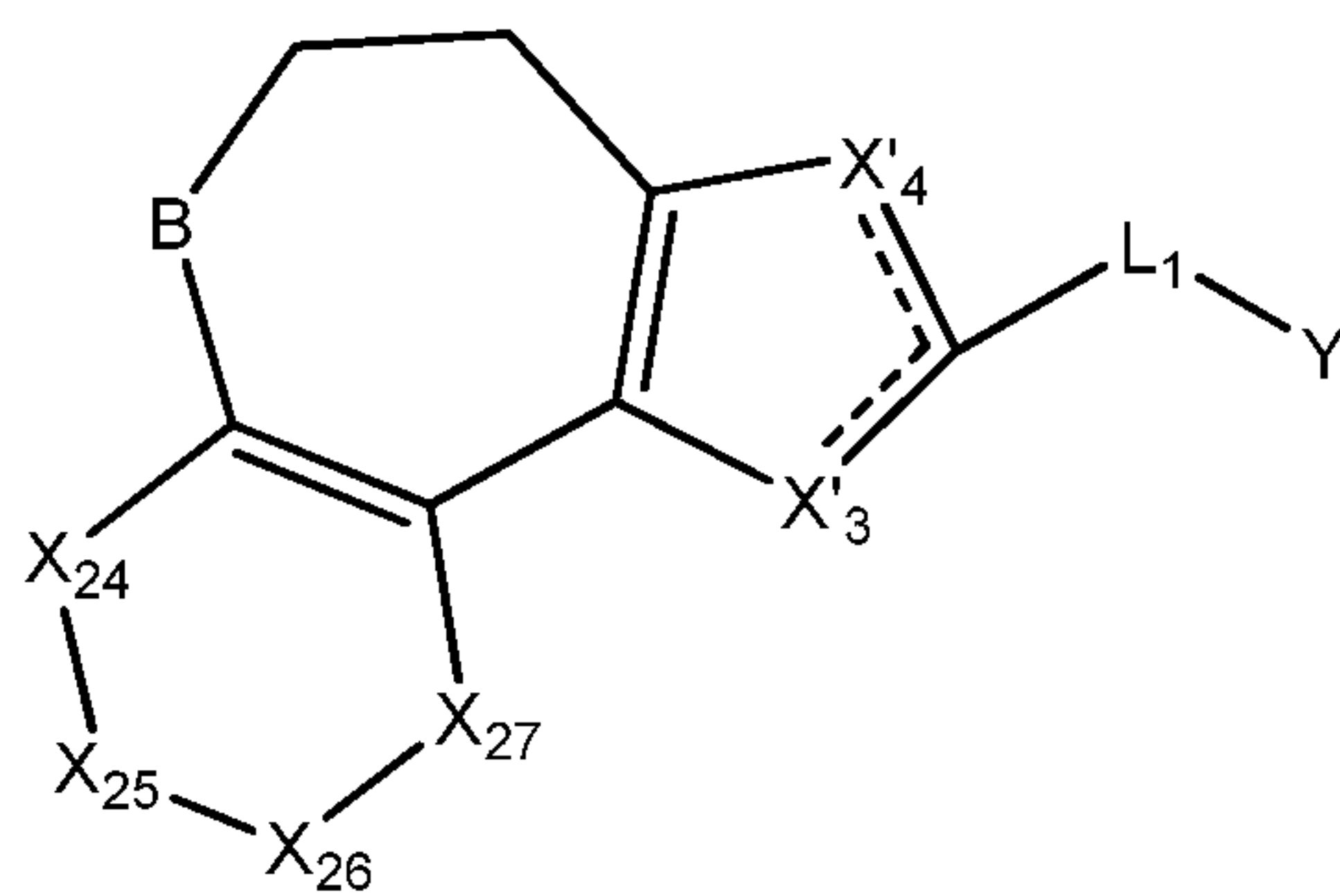
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- 35 -

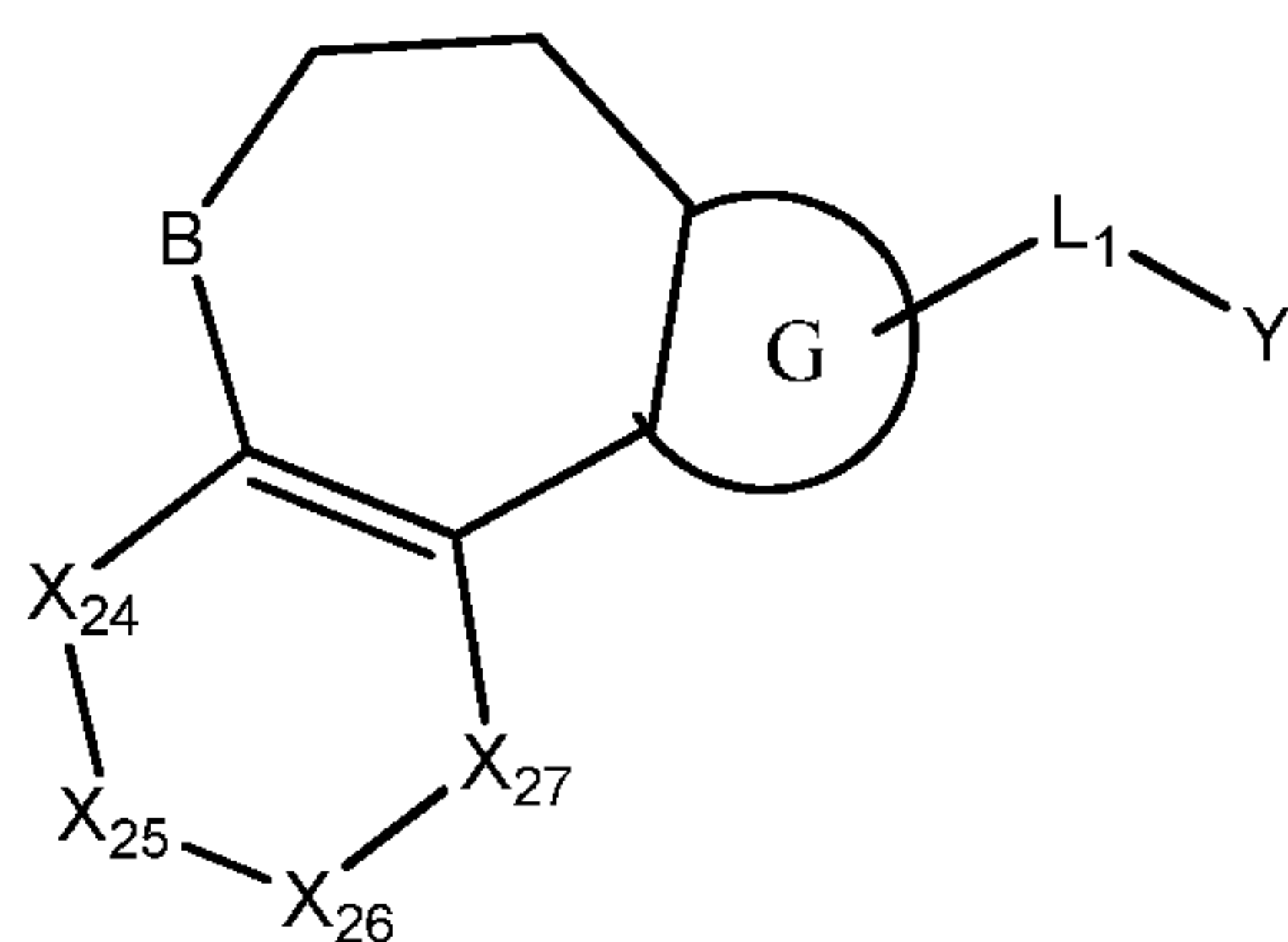
Another embodiment of the invention relates to compounds of formula (XIV):



(XIV)

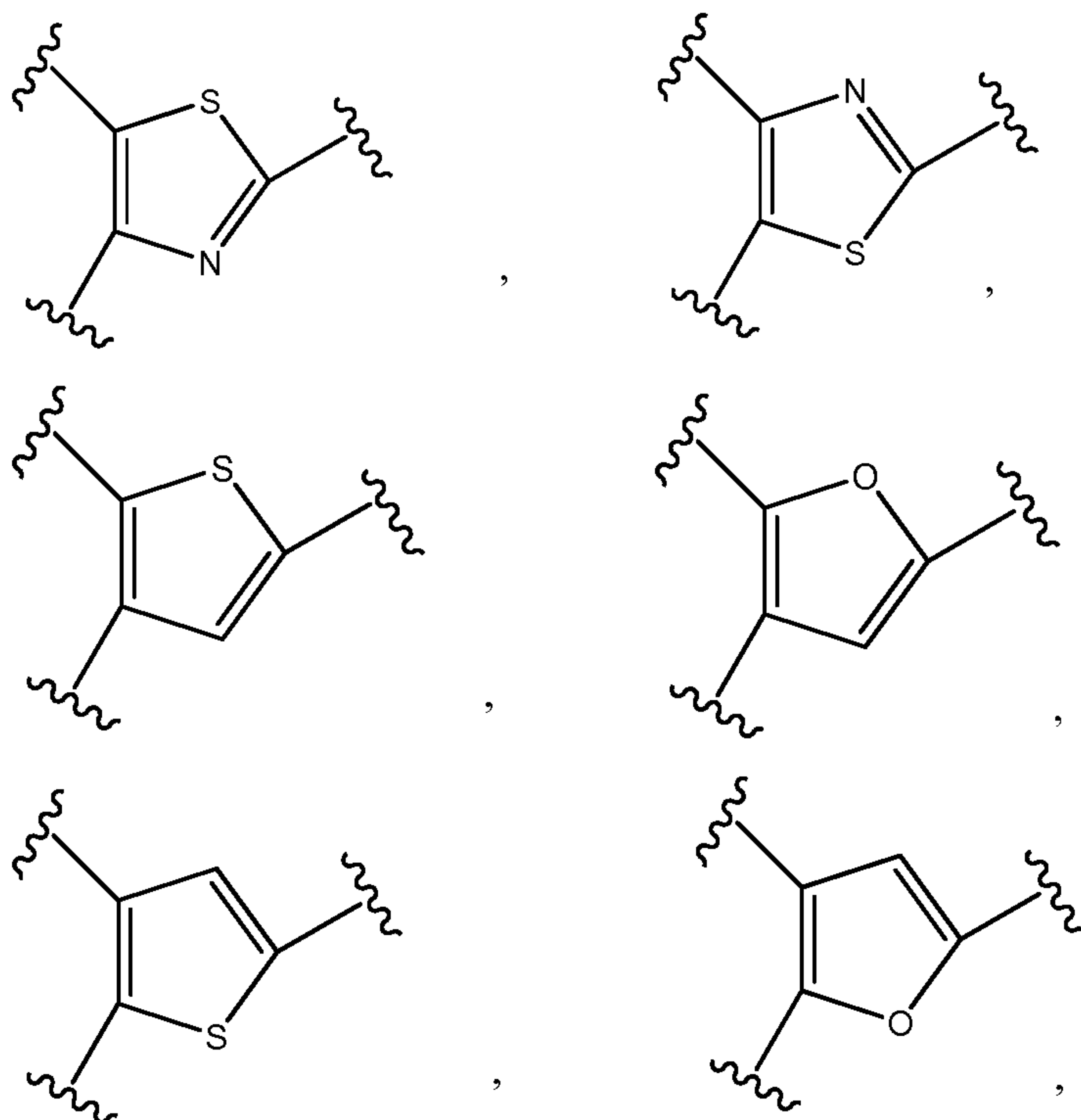
5 or a pharmaceutically acceptable salt thereof, wherein: X'_3 , X'_4 , X_{24} , X_{25} , X_{26} and X_{27} , B, L_1 and Y are defined for formula (XI).

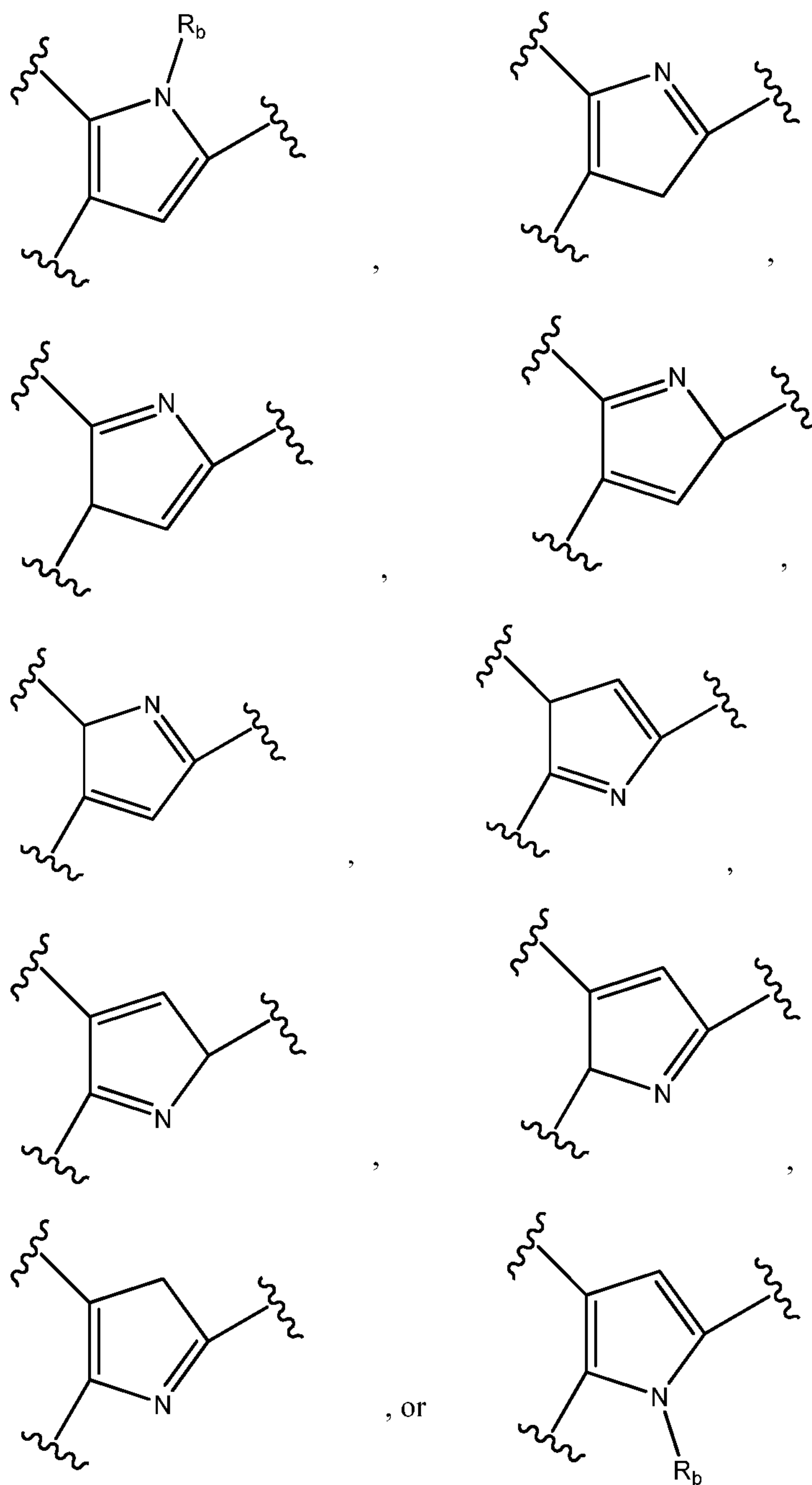
Another embodiment of the invention relates to compounds of formula (XV):



(XV)

10 or a pharmaceutically acceptable salt thereof, wherein: Ring G is selected from:

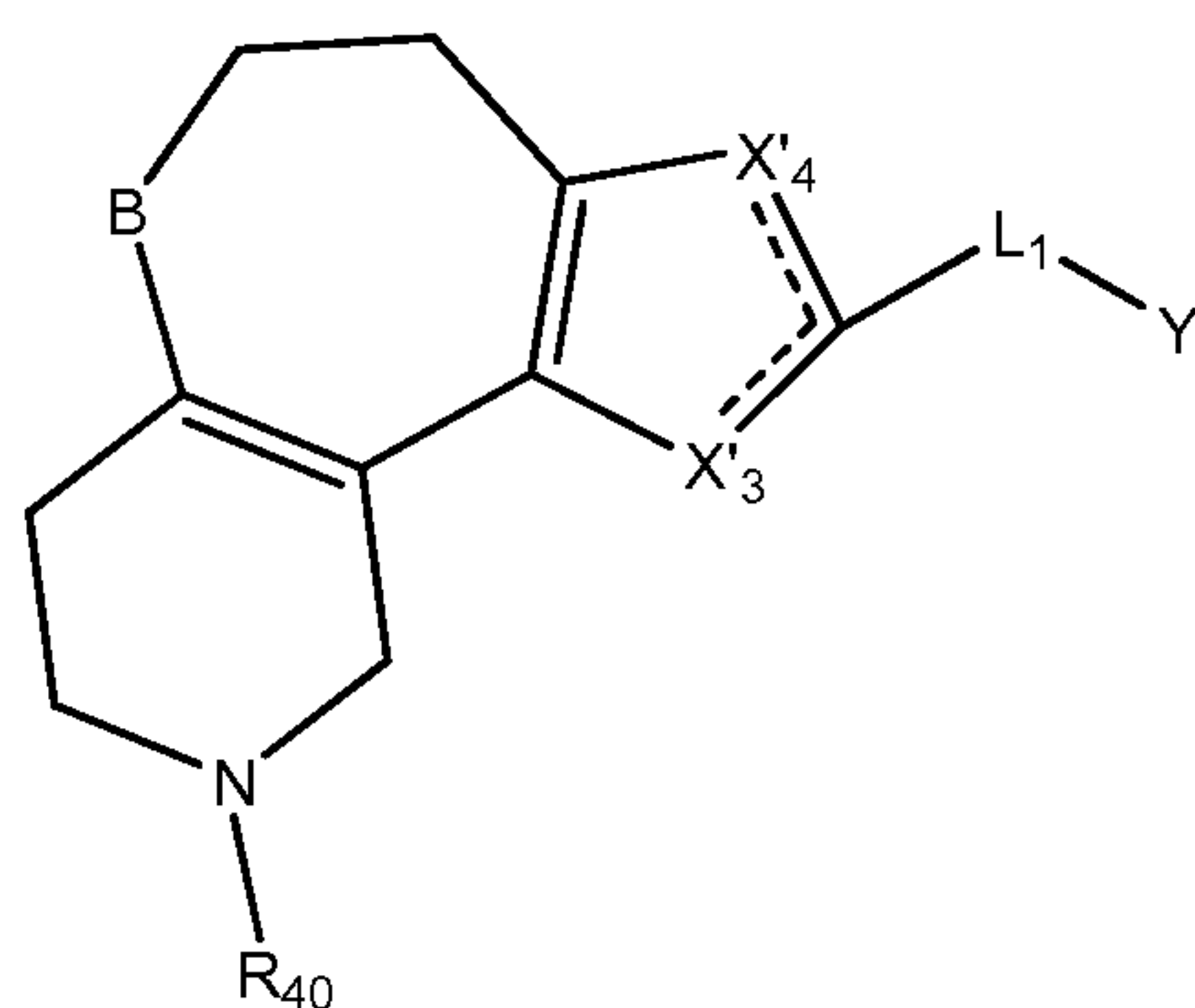




5

and X'_3 , X'_4 , X_{24} , X_{25} , X_{26} and X_{27} , B, L_1 and Y are defined for formula (XI).

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

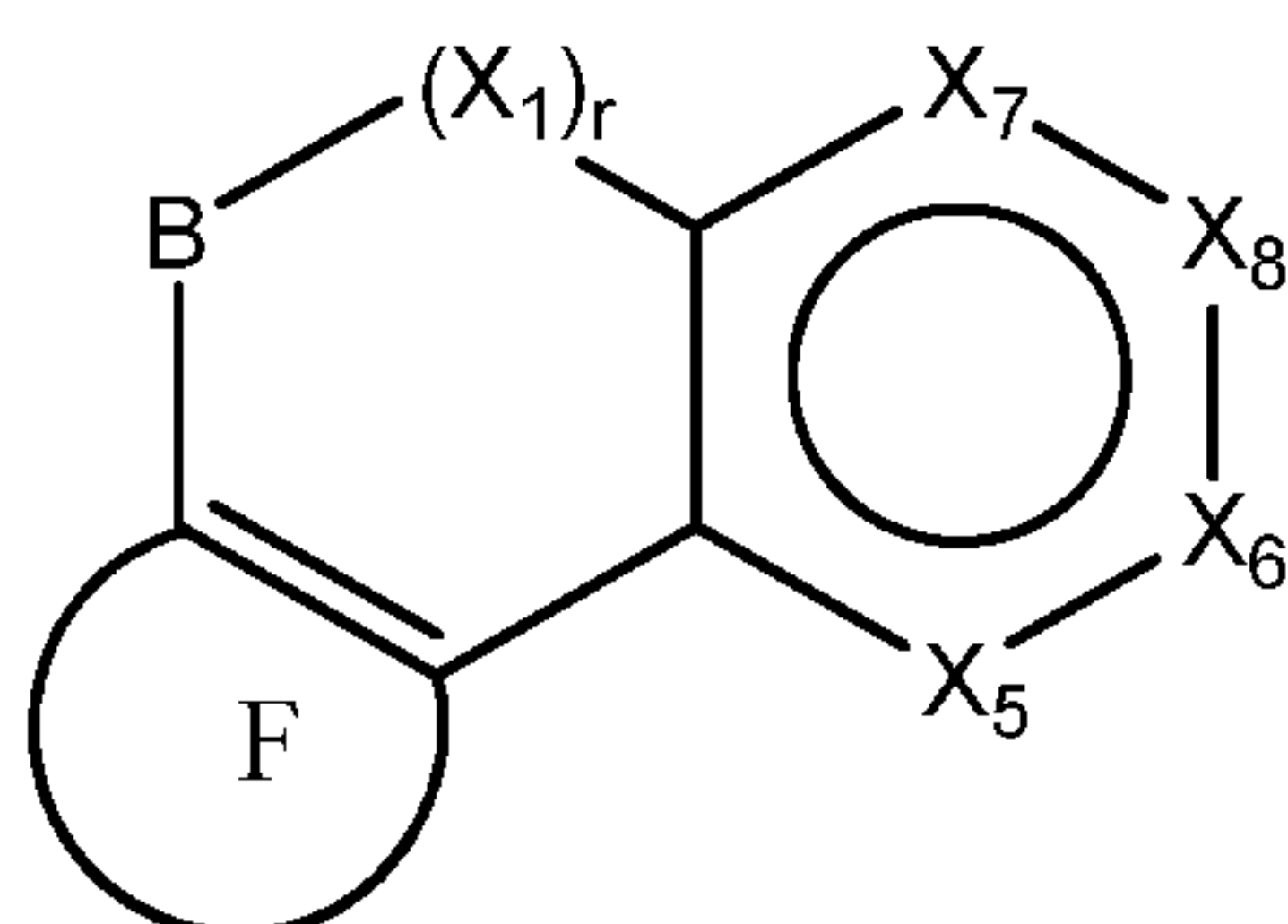


(XVI)

or a pharmaceutically acceptable salt thereof, wherein: R_{40} , B, L_1 and Y are defined for formula (XIII).

5

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

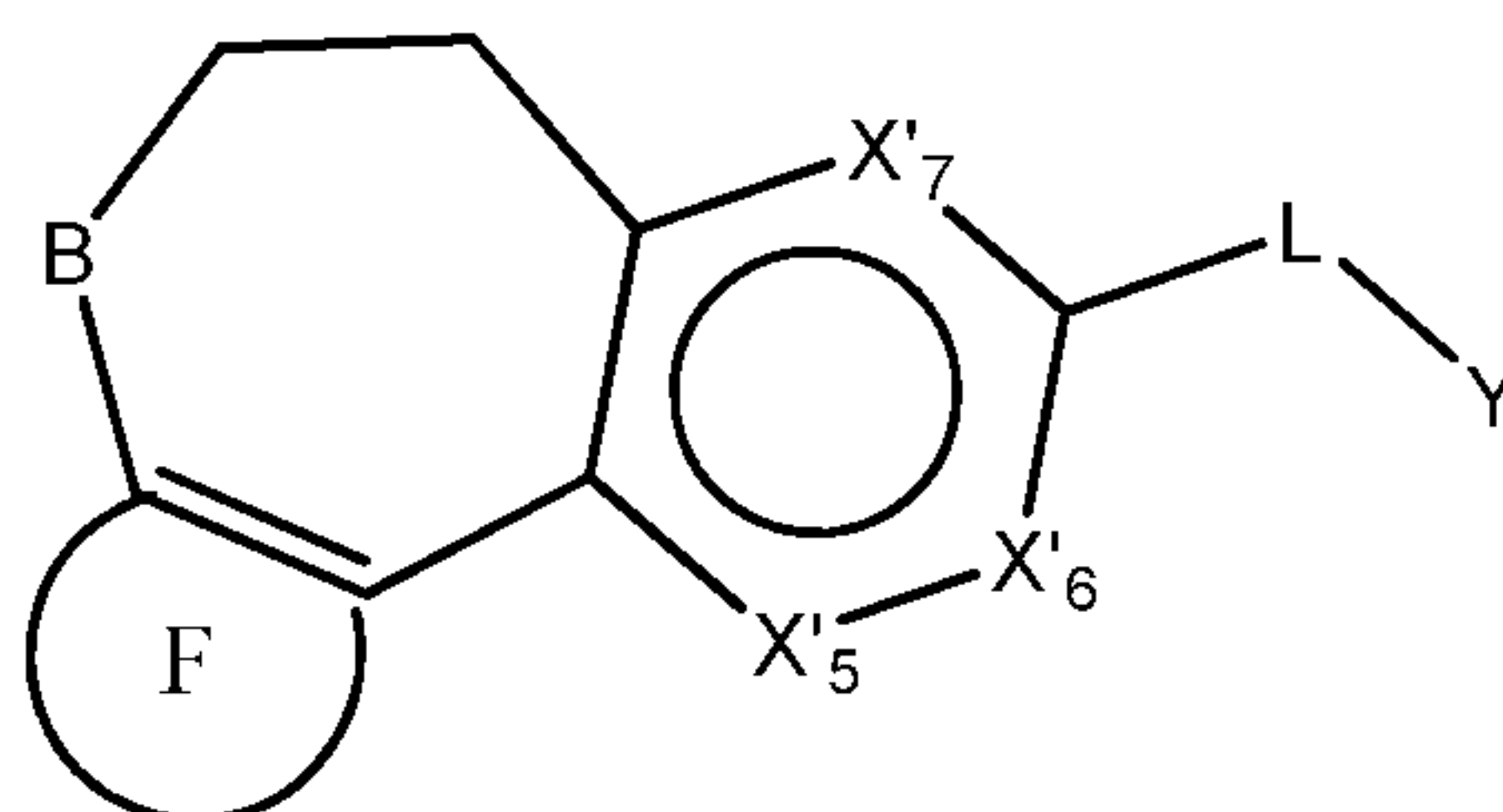


(XVII)

or a pharmaceutically acceptable salt thereof, wherein:

Ring F is defined as for formula (X), B, X_{1r} , X_5 , X_6 , X_7 , and X_8 are defined as for formula (VI).

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

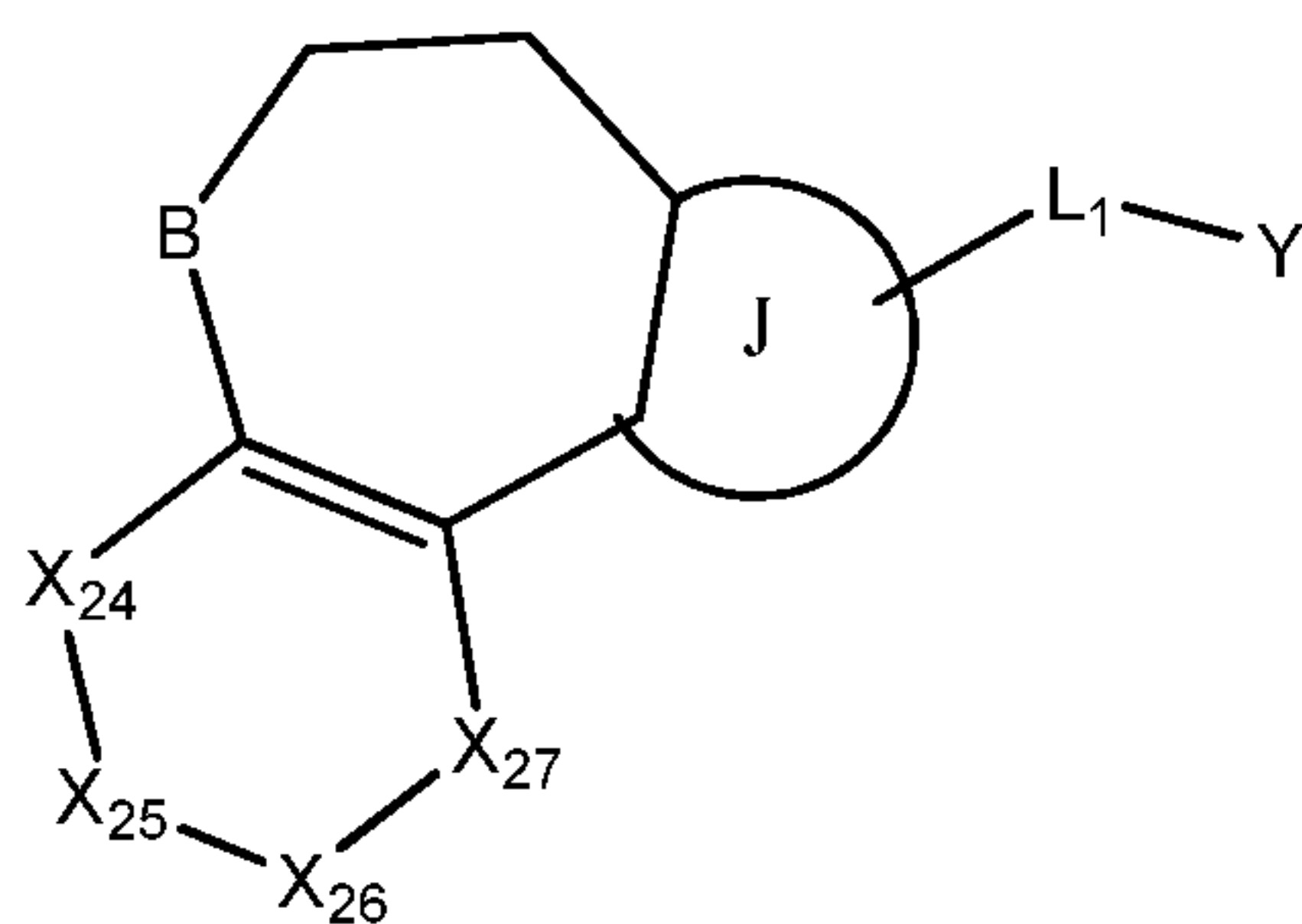


(XVIII)

or a pharmaceutically acceptable salt thereof, wherein:

each of X'_5 , X'_6 , and X'_7 is independently -N-, or -CR^a-; and B, L and Y are defined as for formula (VI), and Ring F is defined as for formula (X).

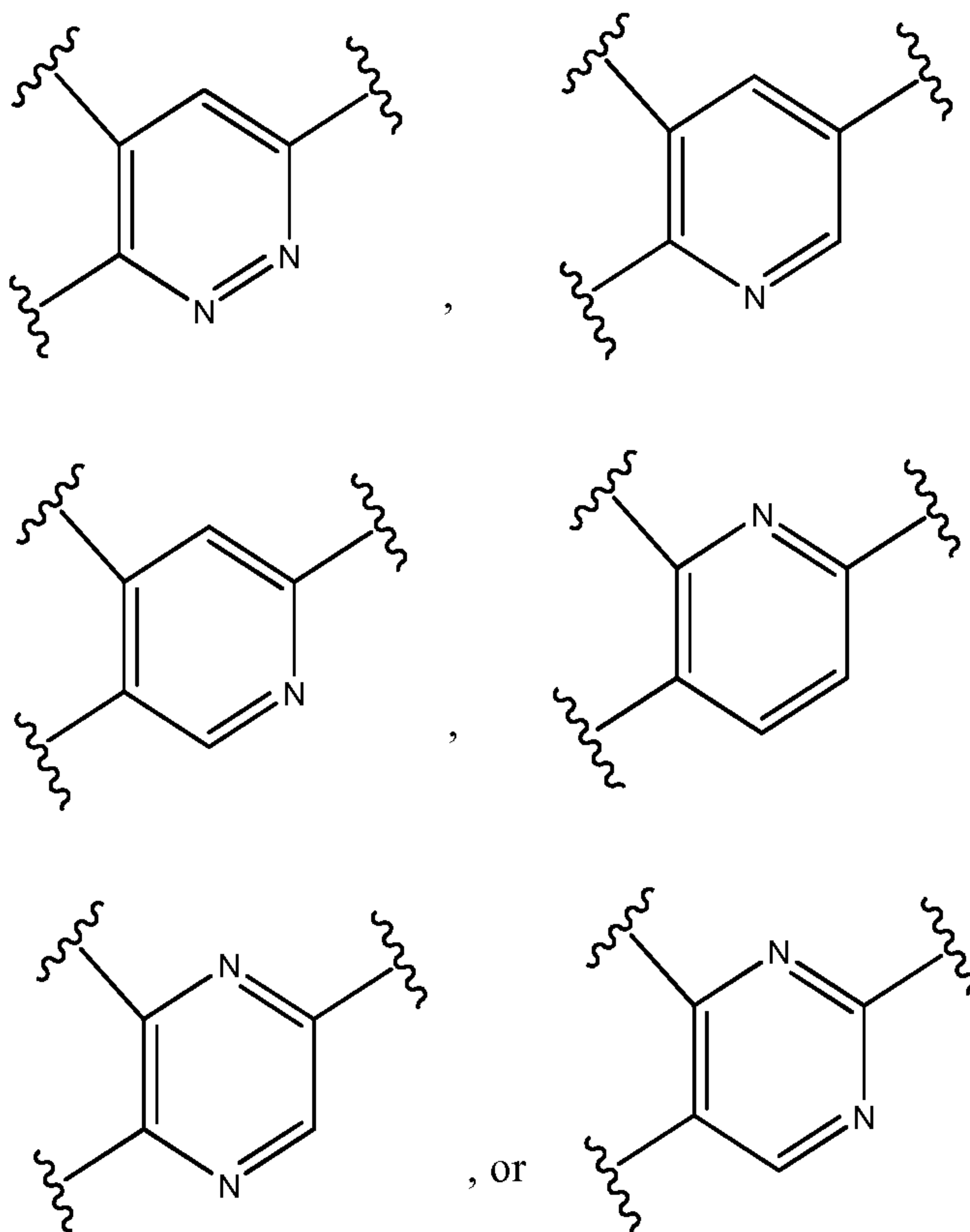
Another embodiment of the invention relates to compounds of formula (XIX):



(XIX)

or a pharmaceutically acceptable salt thereof, wherein:

Ring J is:

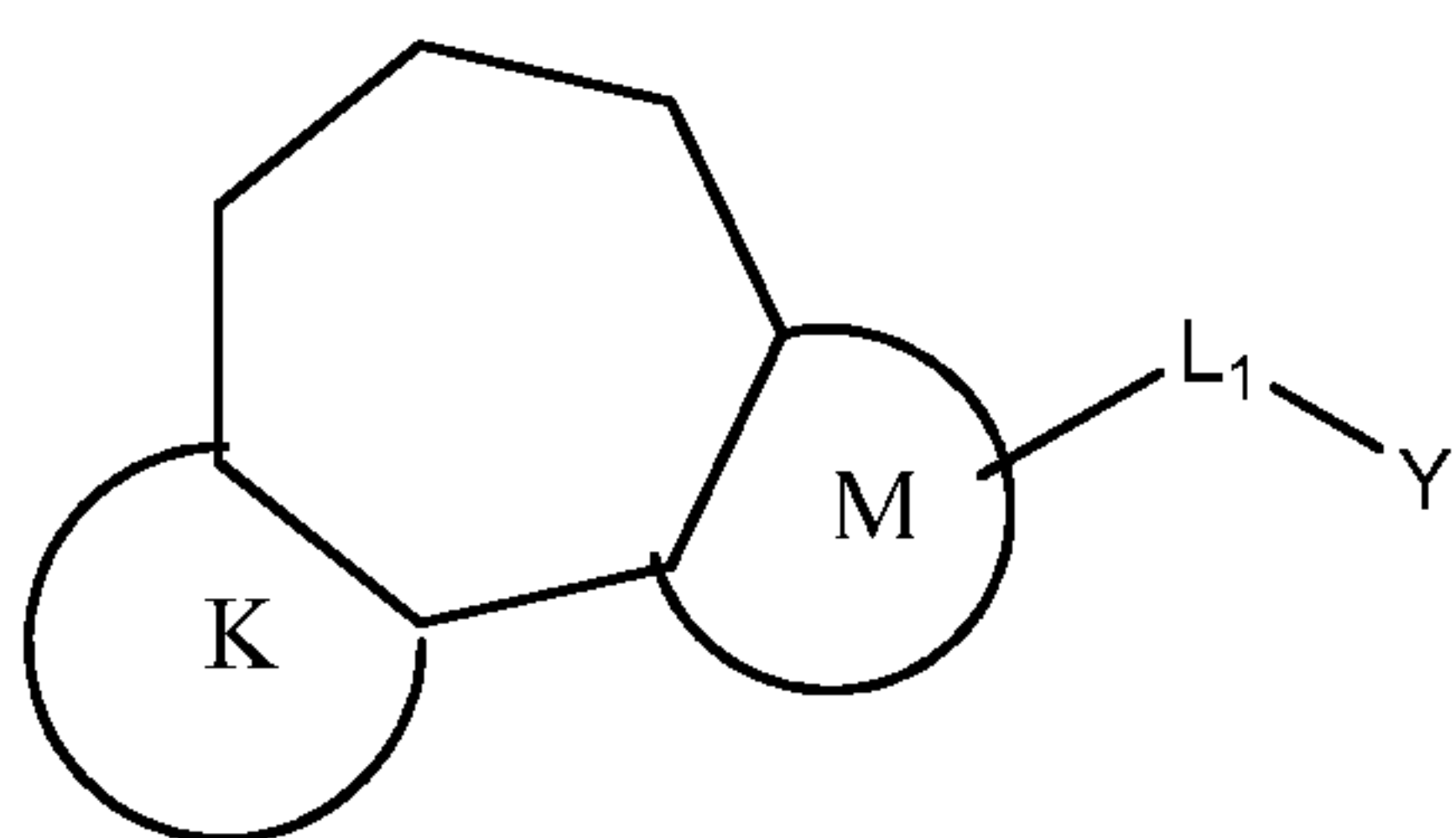


5

X_{24} , X_{25} , X_{26} and X_{27} are defined as for formula (XI);

B, L and Y are defined as for formula (VI), and Ring F is defined as for formula (X).

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



(XX)

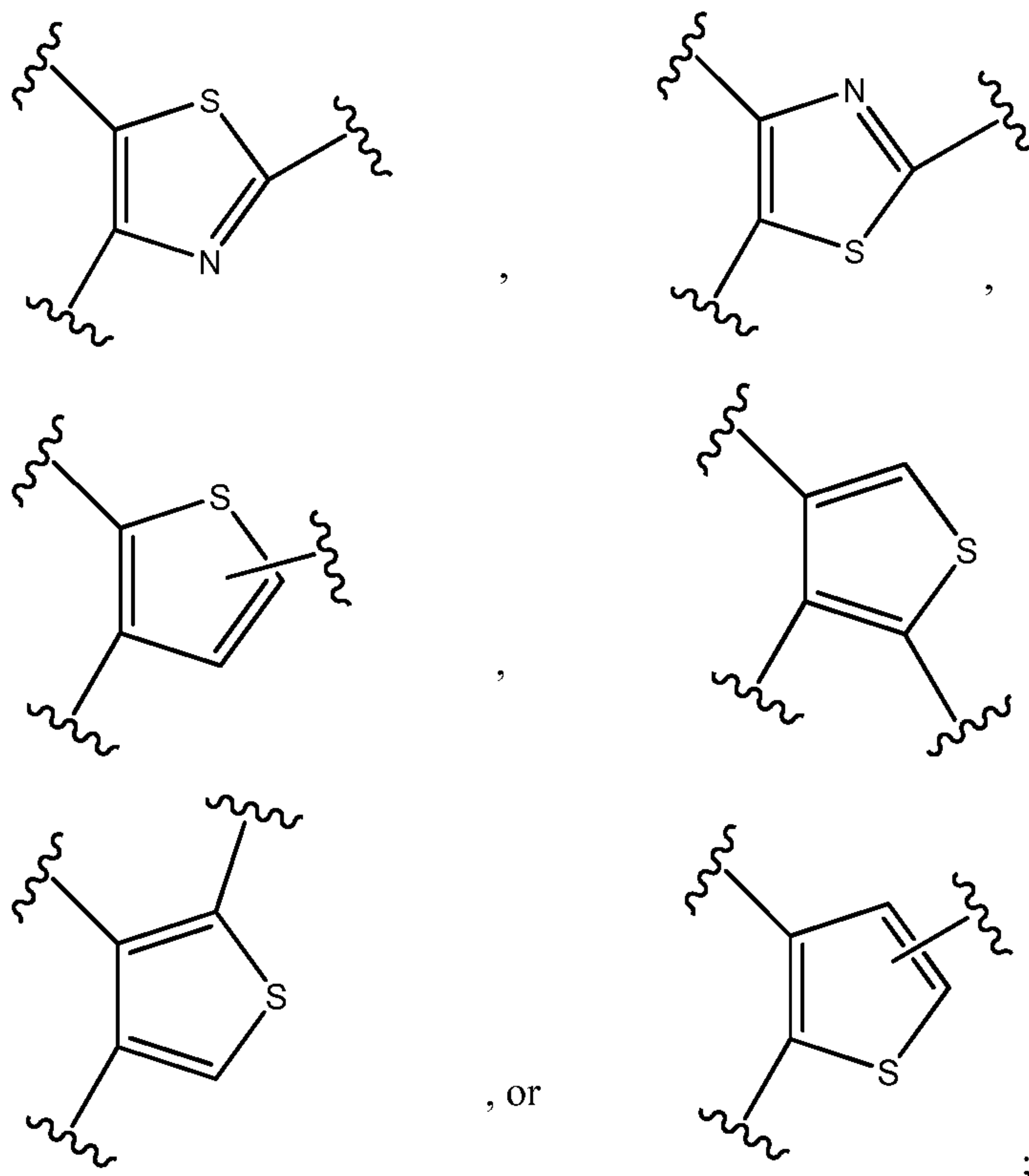
10

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

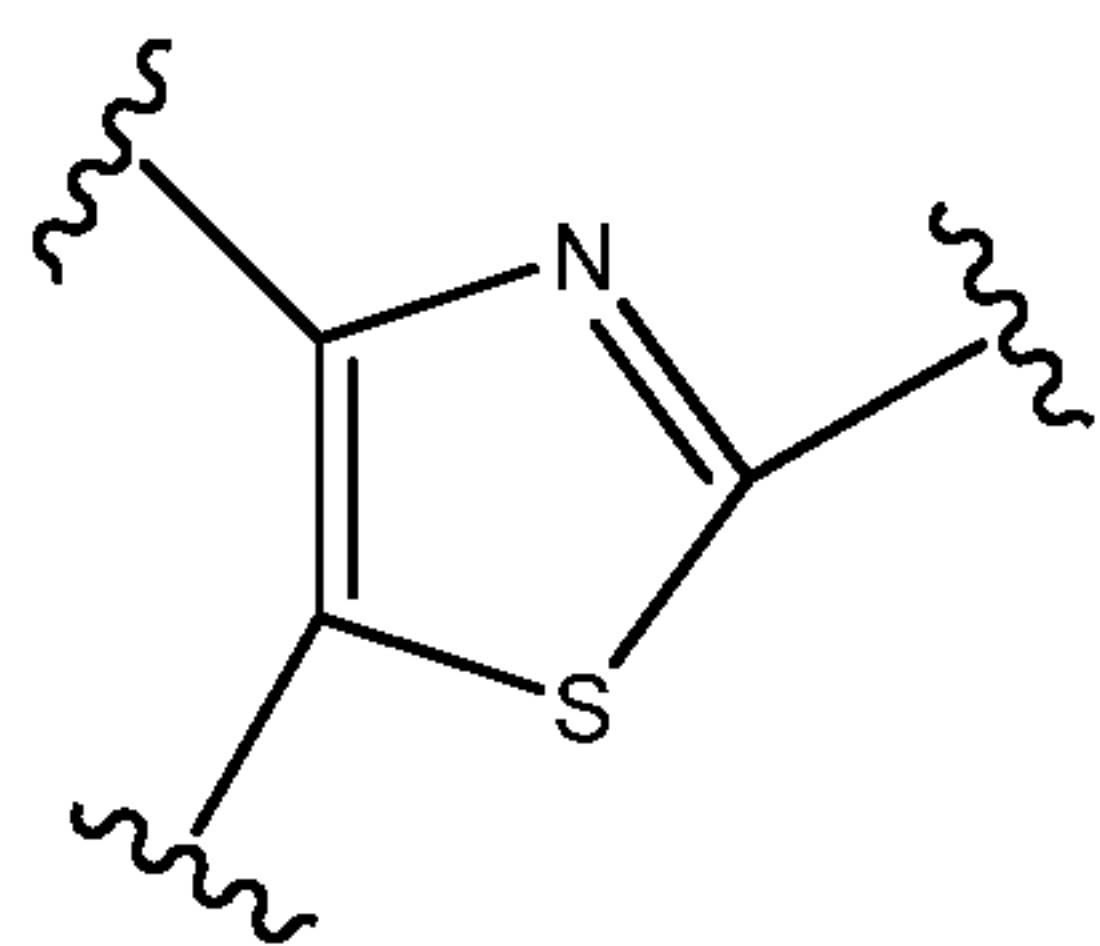
Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl;

Ring M is selected from:

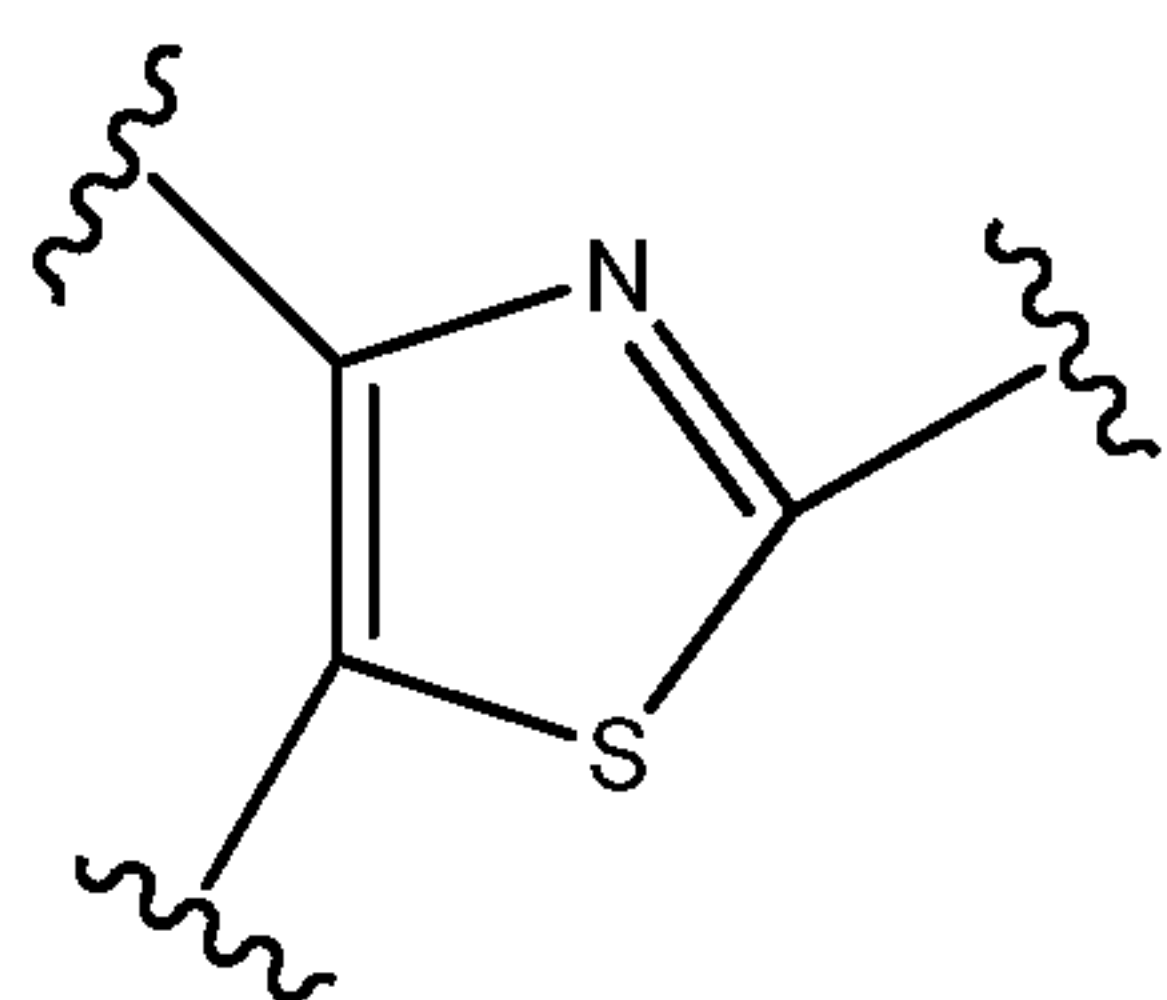


Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

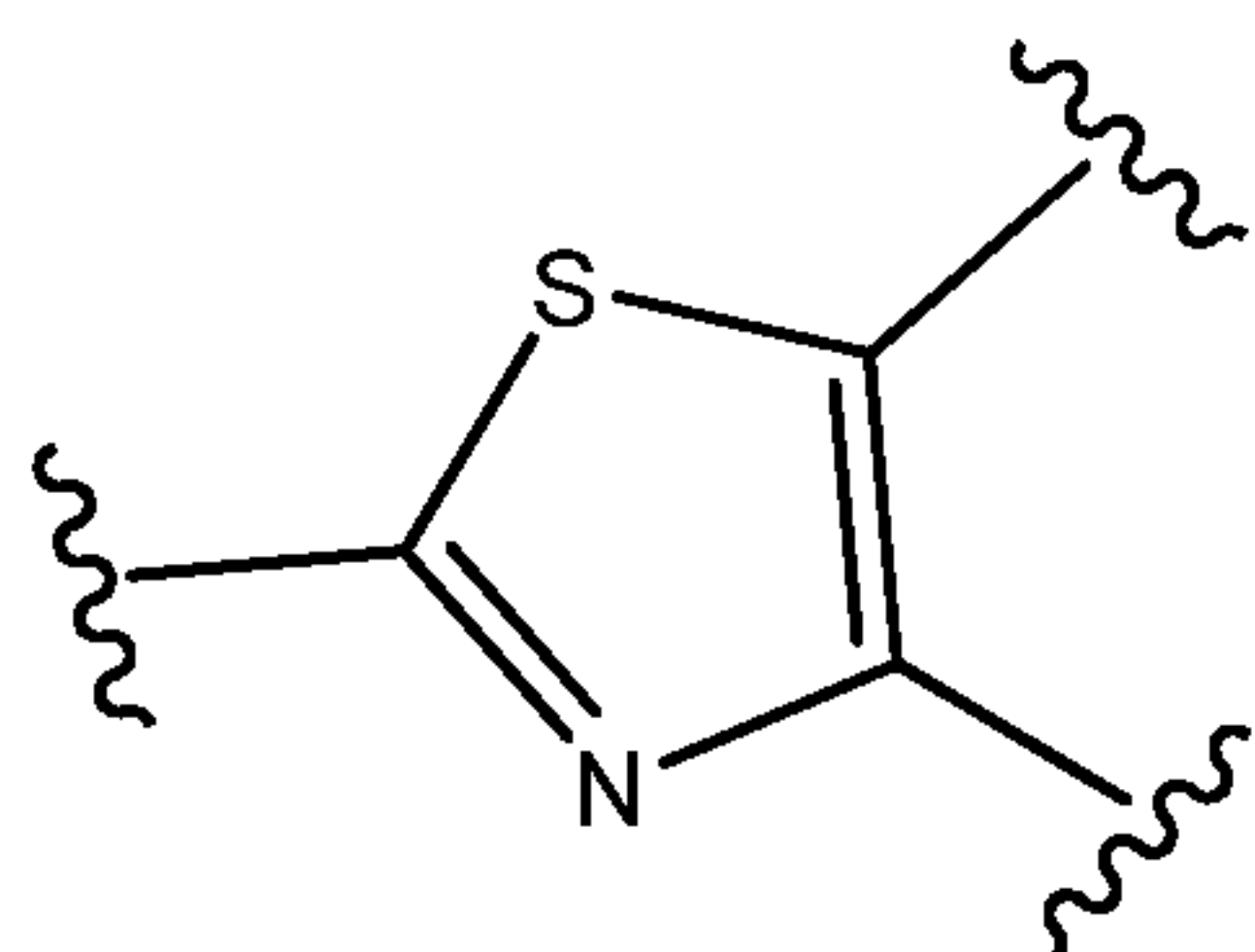
In one embodiment of compounds of formula (XX), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl, then Ring M is not



In another embodiment of compounds of formula (XX), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl and Ring M is

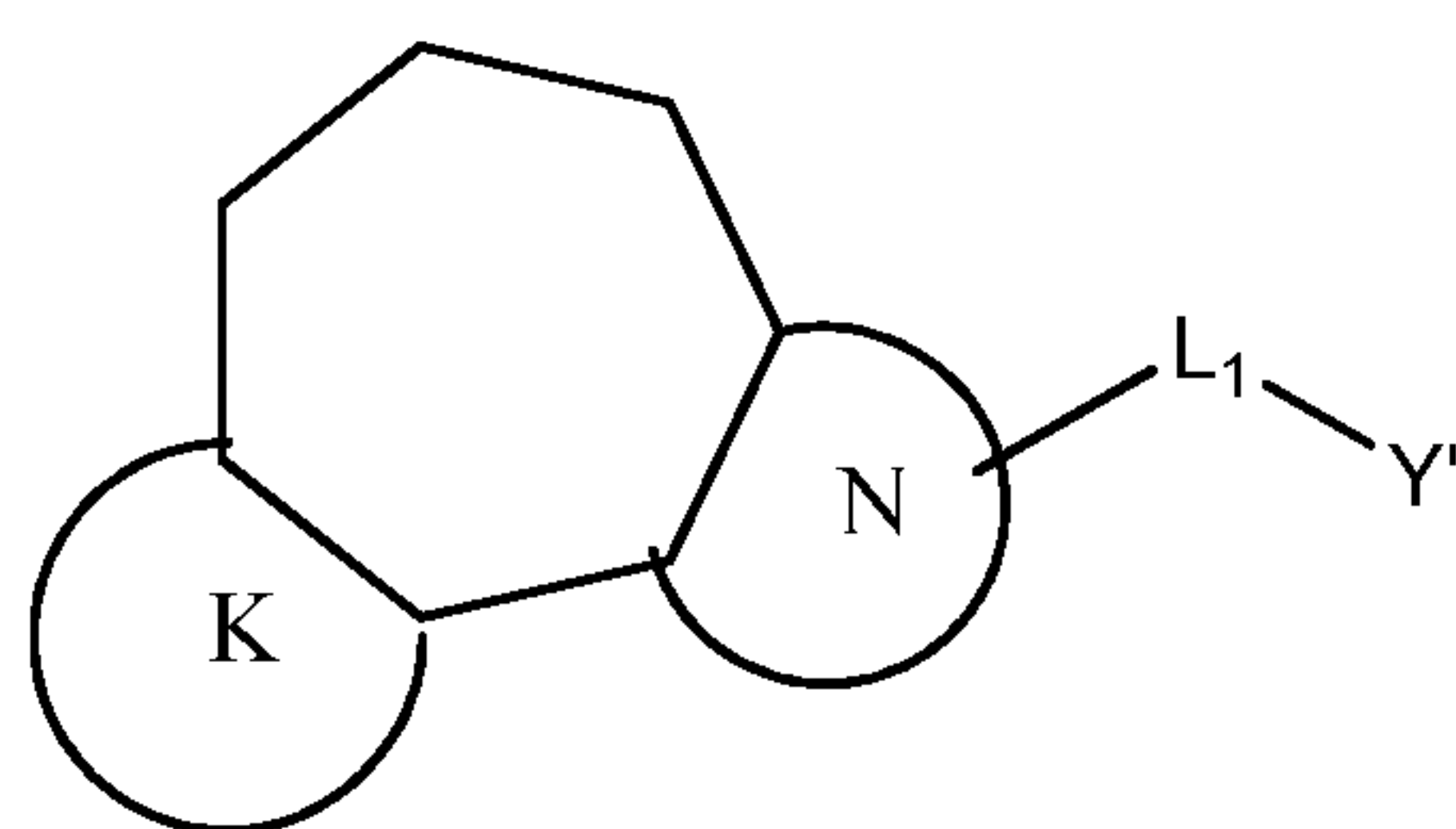


then Ring K is not phenyl or



5

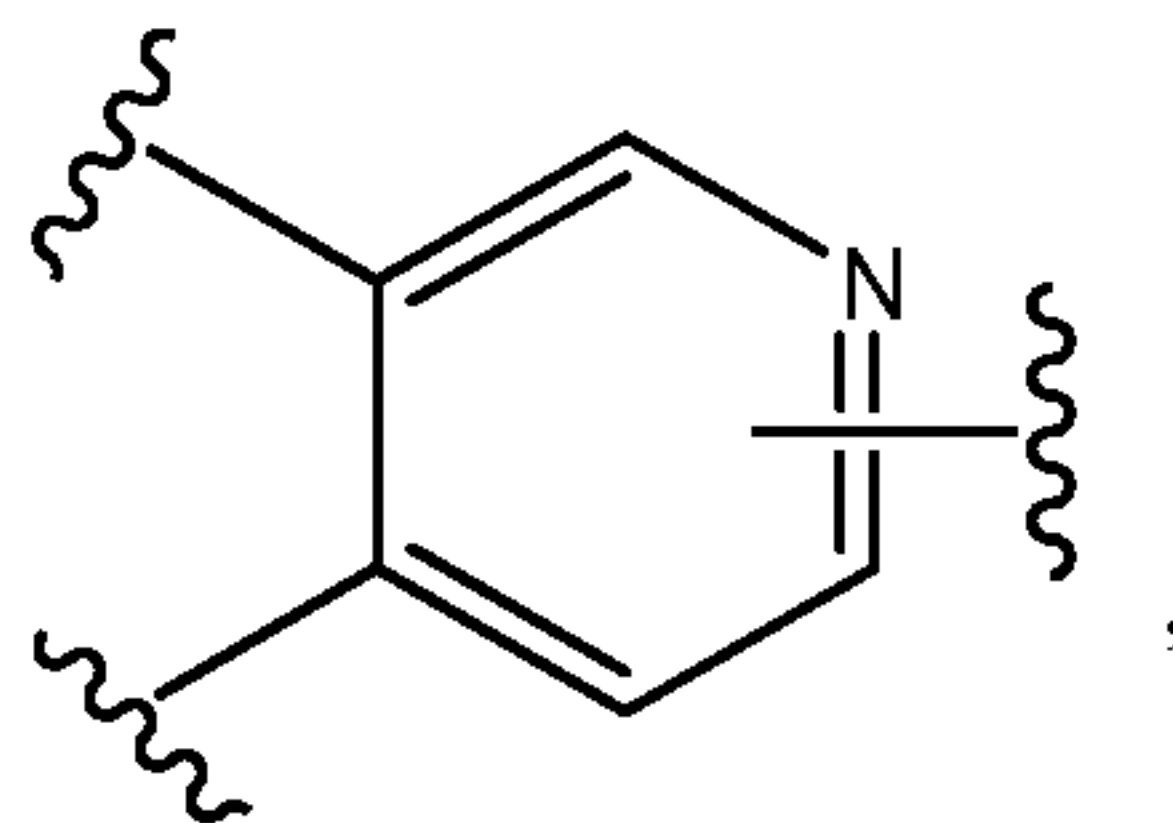
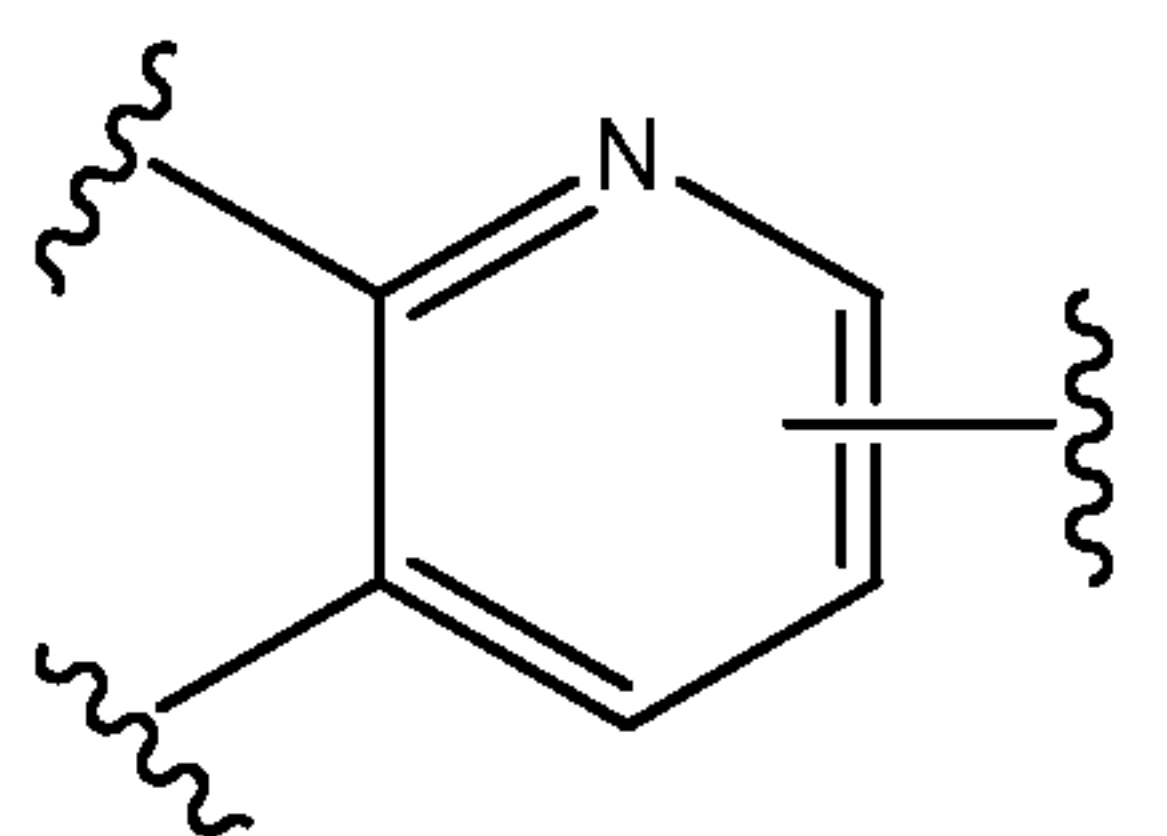
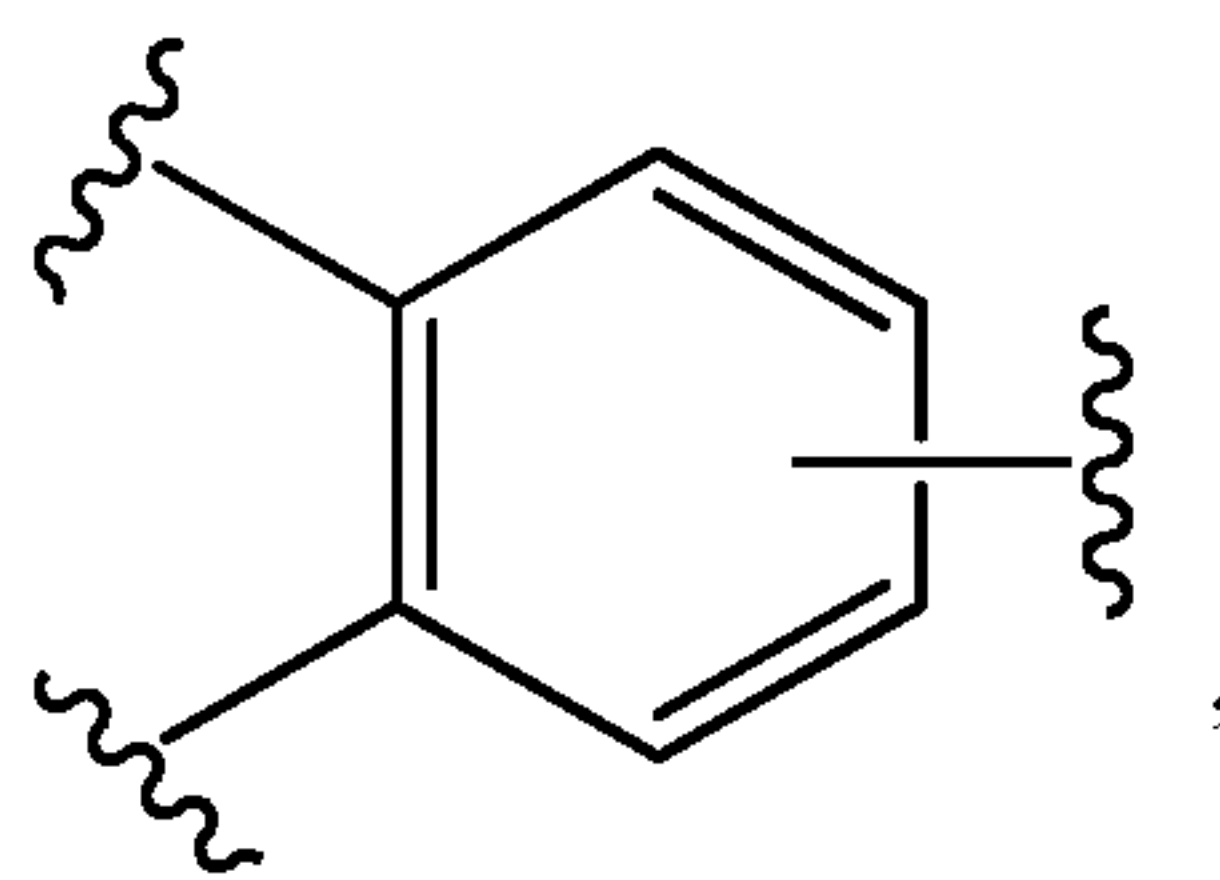
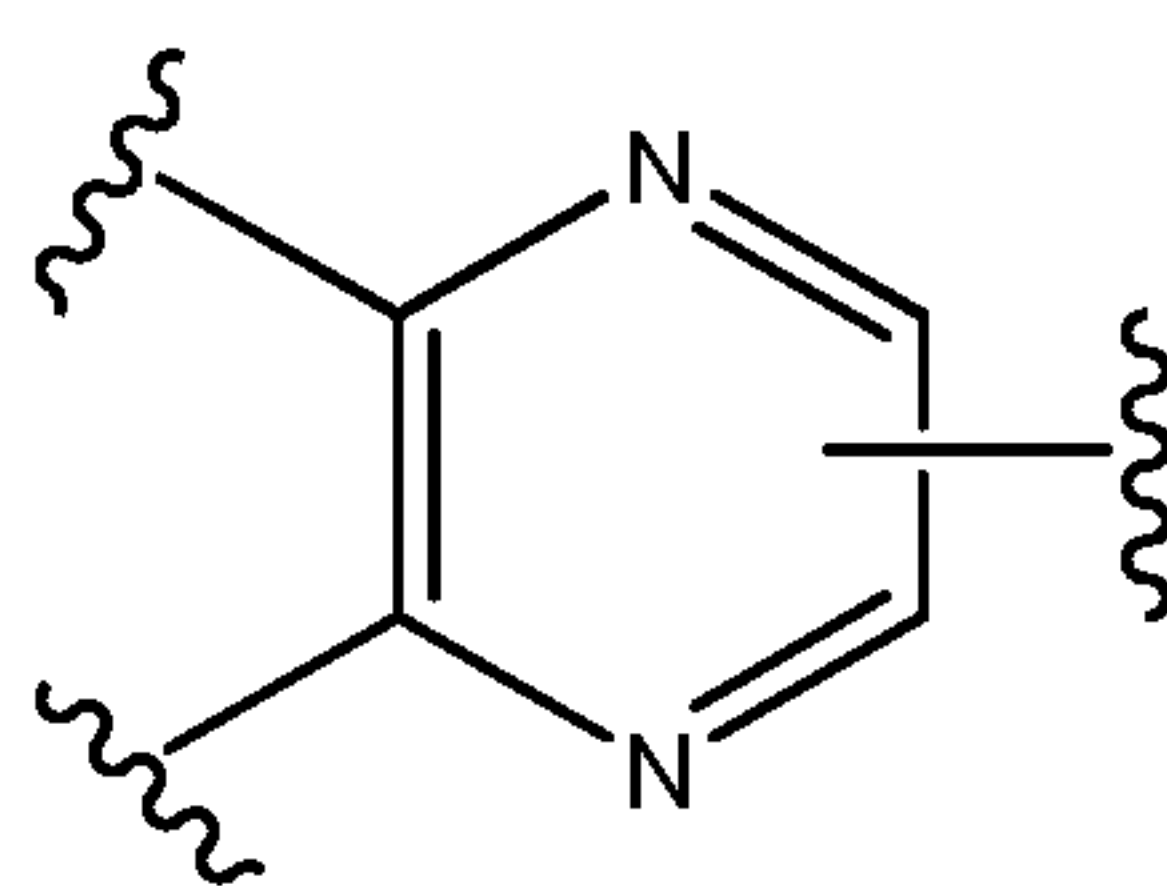
Another embodiment of the invention relates to compounds of formula (XXI):



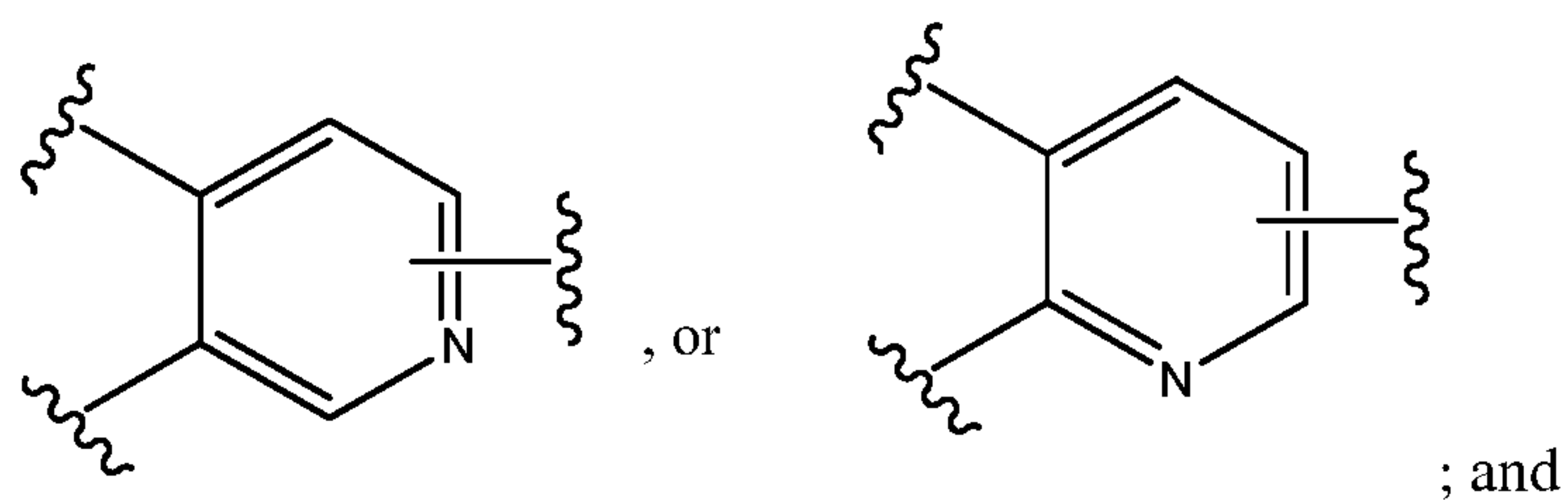
(XXI)

or a pharmaceutically acceptable salt thereof, wherein:

Ring N is:

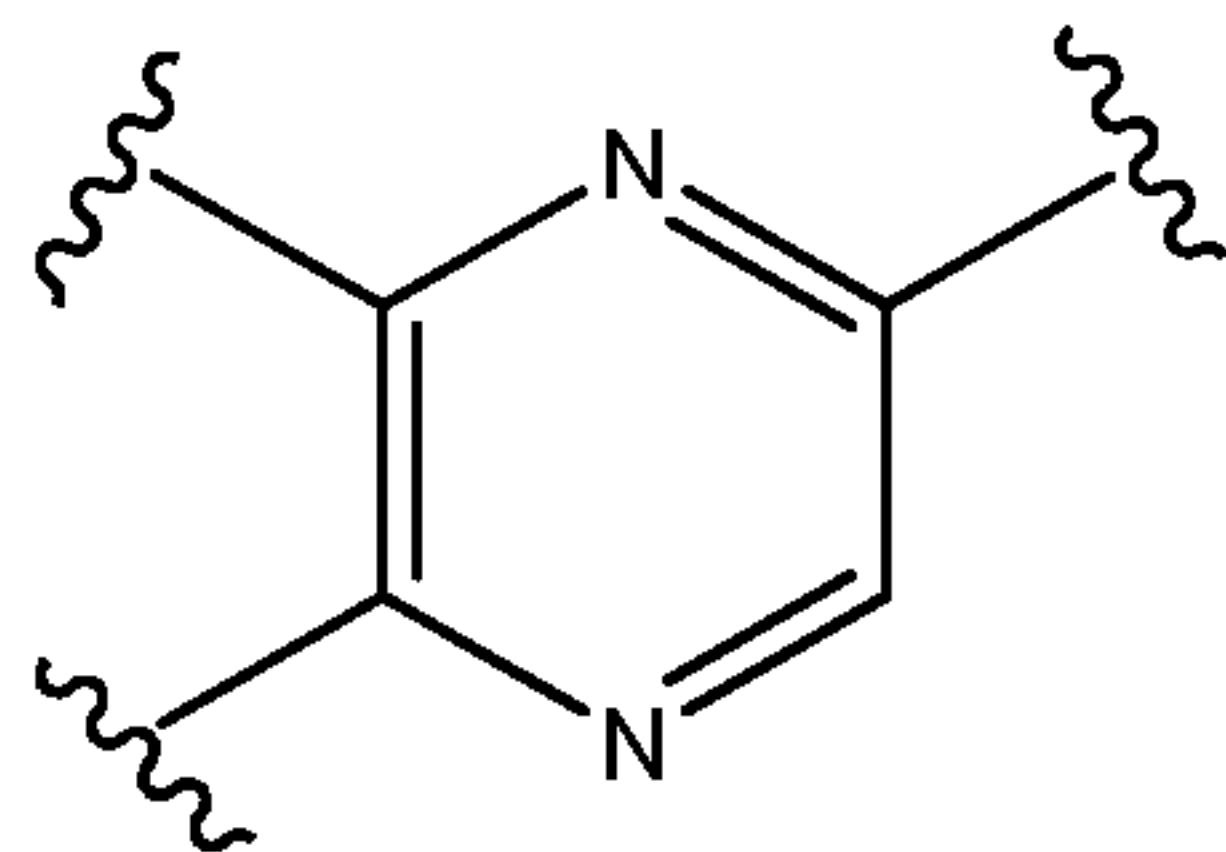


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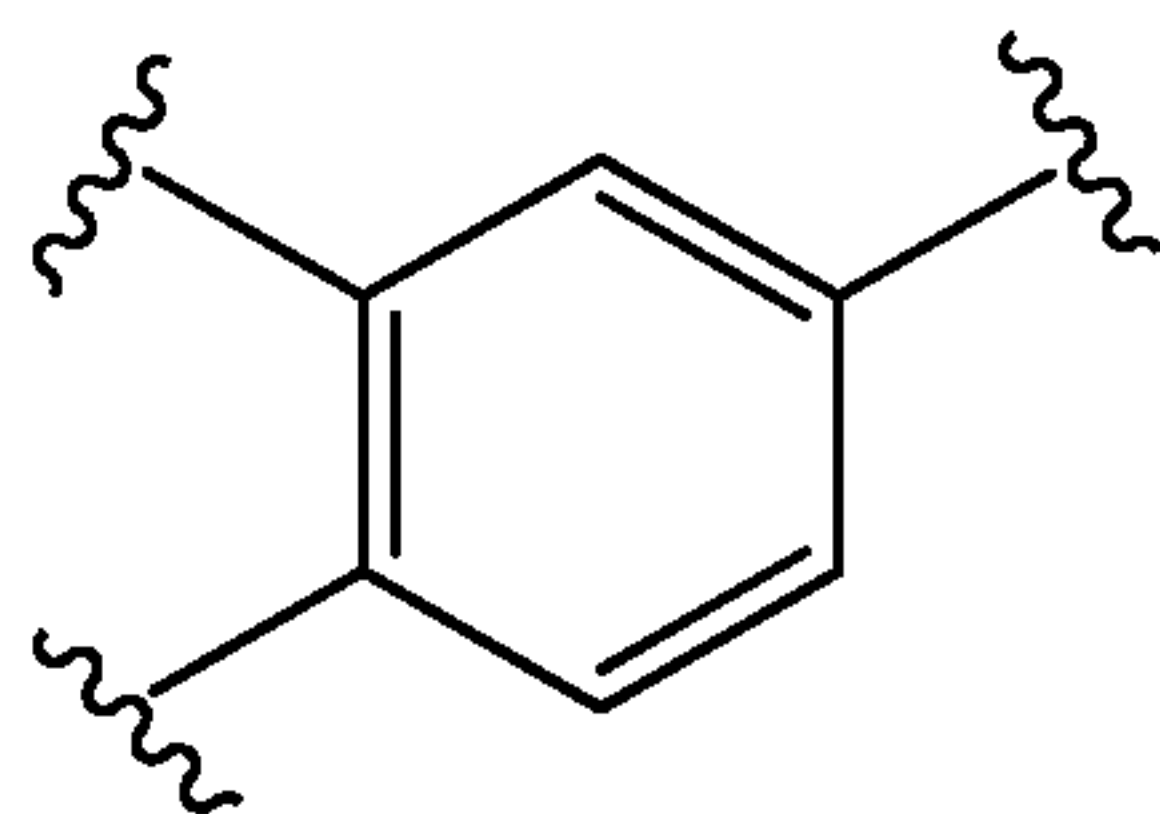
Ring K, L₁ and Y' are defined as for formula (XX).

In one embodiment of compounds of formula (XXI), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl, then Ring N is not



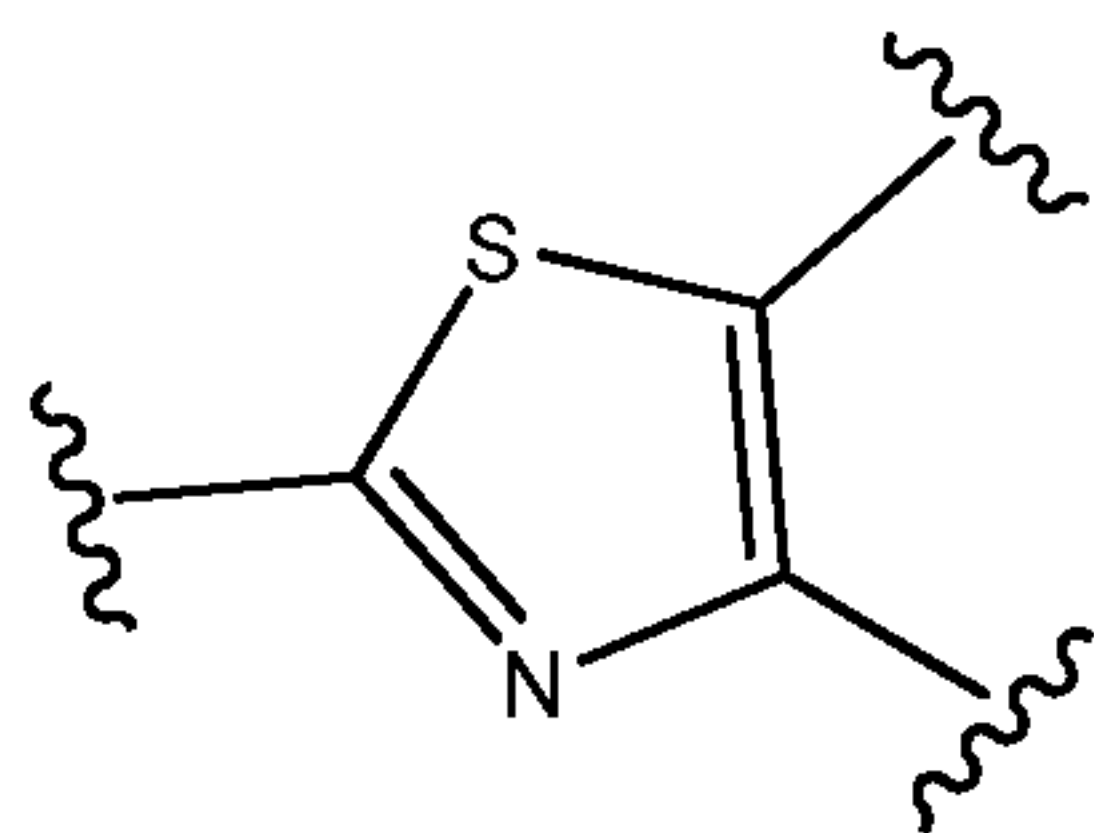
5

In one embodiment of compounds of formula (XXI), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl, Ring K is an optionally substituted thiazolyl, then Ring N is not:



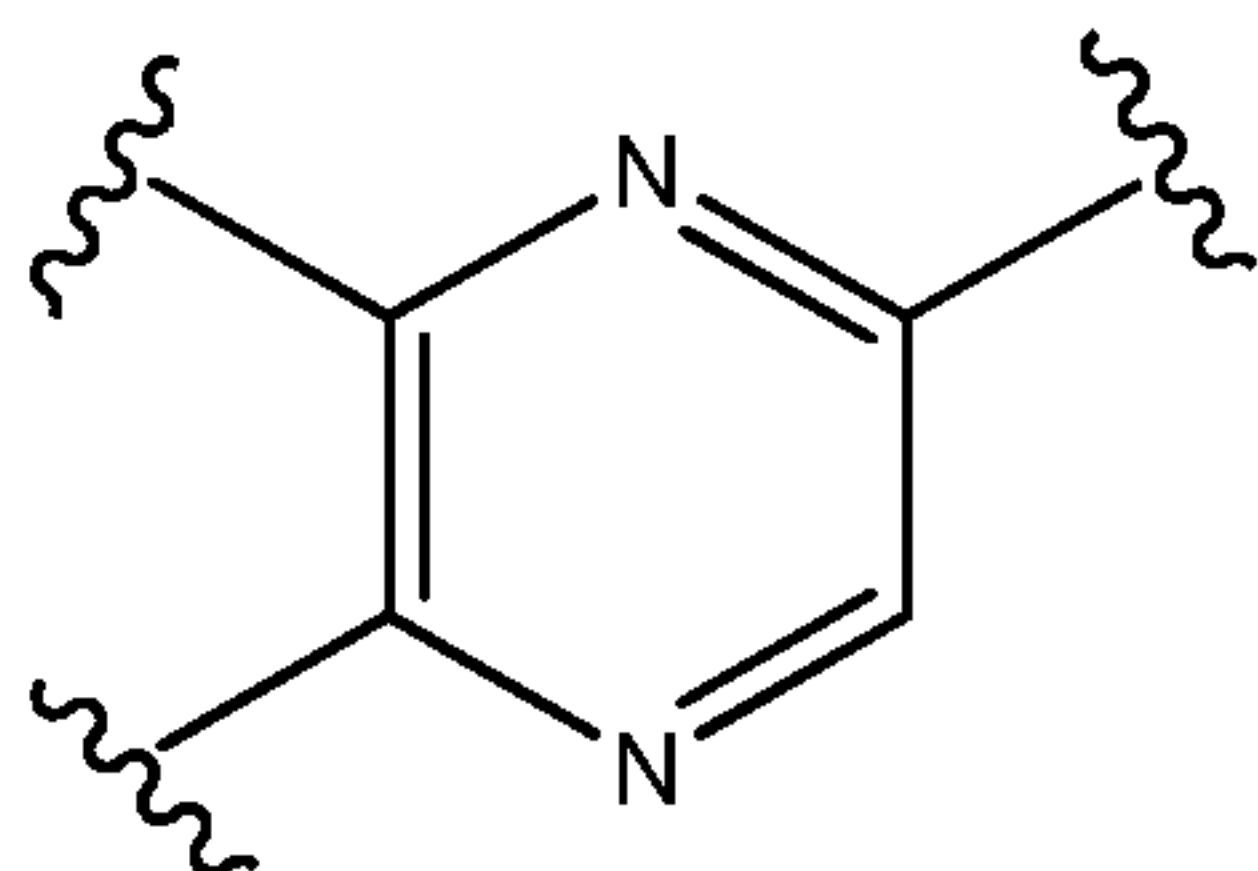
10

In another embodiment of compounds of formula (XXI), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl and Ring N is phenyl, then Ring K is not



15

In another embodiment of compounds of formula (XXI), when Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl and Ring N is



, then Ring K is not phenyl.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is $\text{-NRCH}_2\text{-}$, $\text{-CH}_2\text{NR-}$, -C(O)- , -NR-C(O)- , -C(O)-NR- , -OC(O)- , -C(O)O- , -C(S)- , -NR-C(S)- , -C(S)-NR- , $\text{-NRC(NR}_9\text{)-}$ or $\text{-C(NR}_9\text{)NR-}$;

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

R₉, for each occurrence, is independently -H , halo, an alkyl, -OR_7 , $\text{-NR}_{11}\text{R}_{12}$, -C(O)R_7 , -C(O)OR_7 , or $\text{-C(O)R}_{11}\text{R}_{12}$;

10 R₇, for each occurrence, is independently -H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

15 R₁₁ and R₁₂, 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 R₁₁ and R₁₂ taken together with the nitrogen to which they are attached are an optionally substituted heterocyclyl or optionally substituted heteroaryl.

20 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is $\text{-NRCH}_2\text{-}$, $\text{-CH}_2\text{NR-}$, -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- .

25 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is $\text{-NRCH}_2\text{-}$, $\text{-CH}_2\text{NR-}$, -NRC(O)NR- , -NR-C(O)- , or -C(O)-NR- . In one aspect, L is $\text{-NHCH}_2\text{-}$, $\text{-CH}_2\text{NH-}$, -NHC(O)NH- , -NH-C(O)- , or -C(O)-NH- . In one aspect, L is $\text{-NHCH}_2\text{-}$. In one aspect, L is $\text{-CH}_2\text{NH-}$. In one aspect, L is -NHC(O)NH- . In one aspect, L is -NH-C(O)- . In one aspect, L is -C(O)-NH- .

30 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is $\text{-NRS(O)}_2\text{-}$, $\text{-S(O)}_2\text{NR-}$, $\text{-NRS(O)}_2\text{NR-}$, -NRC(O)NR- , -NRC(NR)NR- , -NRC(S)NR- , $\text{-NRCH}_2\text{NR-}$, $\text{-NRN=CR}_6\text{-}$, -C(NR)- , or $\text{-CR}_6\text{=NNR-}$;

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

R₆, for each occurrence, is -H or alkyl; and

35 R₇, for each occurrence, is independently -H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally

substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl.

5 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), R is -H; and R₆ 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 embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is -C(=NR₂₀)NR-. R₂₀ is -H, alkyl, -C(O)-R₇, -OR₇, or -C(O)OR₇. In one aspect, R is -H. In one embodiment, in compounds
10 represented by formula (IA), (I), (II), (VI), (VII), (X), (XVII), or (XVIII), L is -NRCH₂-, -CH₂NR-, -NR-C(O)-, -C(O)-NR-, or -NRC(O)NR-. In one aspect, R is -H.

In one embodiment, in compounds represented by formula (III), (V), (VIII), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XIX), (XX), or (XXI), L₁ is -NH-C(O)- or -C(O)-NH-. In one aspect, L₁ is -NH-C(O)-. In another aspect, L₁ is -C(O)-NH-. In one embodiment, in compounds represented by
15 formula (III), (V), (VIII), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XIX), (XX), or (XXI), L₁ is -NHCH₂- or -CH₂NH-. In one aspect, L₁ is -NHCH₂-. In another aspect, L₁ is -CH₂NH-. In one embodiment, in compounds represented by formula (III), (V), (VIII), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XIX), (XX), or (XXI), L₁ is -NHC(O)NH-.

20 In one embodiment, in compounds represented by formula (IV), L'₁ is -NH-C(O)- or -C(O)-NH-. In one embodiment, in compounds represented by formula (IV), L'₁ is -CH₂NH-. In one embodiment, in compounds represented by formula (IV), L'₁ is -NHC(O)NH-.

25 In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (VI), (VII), or (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), Y is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, an optionally substituted pyridazinyl, an optionally substituted thiadiazolyl, an optionally substituted pyrimidinyl, or an optionally substituted
30 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 one aspect, Y is 2,6-difluorophenyl. In a further aspect, Y is an optionally substituted thiadiazolyl. In another aspect, Y is an optionally substituted thiophenyl. In one
35 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.

5 In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (VI), (VII), or (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), Y is optionally substituted alkyl or optionally substituted cycloalkyl. In one aspect, Y is optionally substituted C3-C5 alkyl or optionally substituted C3-C6 cycloalkyl.

10 In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (VI), (VII), or (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), Y is optionally substituted alkenyl or optionally substituted cycloalkenyl. In one aspect, Y is optionally substituted C3-C5 alkenyl or optionally substituted C3-C6 cycloalkenyl.

15 In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (VI), (VII), or (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), Y is optionally substituted heterocyclyl.

20 In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (VI), (VII), or (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), Y is an optionally substituted 5 or 6 membered aromatic or heteroaromatic ring, an optionally substituted C3-C5 akyl, or an optionally substituted 3 to 6 membered cycloalkyl. In one aspect, Y is an optionally substituted 5 or 6 membered aromatic or heteroaromatic ring. In one aspect, Y is an optionally substituted C3-C5 akyl. In one aspect, Y is an optionally substituted 3 to 6 membered cycloalkyl. In one aspect, Y is an optionally substituted C3-C5 akyl or an optionally substituted 3 to 6 membered cycloalkyl.

25 In one embodiment, in compounds represented by formula (IV) or (V), Y₁ is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, an optionally substituted pyridazinyl, an optionally substituted thiadiazolyl, or an optionally substituted thiophenyl. In one aspect, Y₁ is unsubstituted. In one aspect, Y₁ is an optionally substituted phenyl or an optionally substituted pyridinyl. In one aspect, Y₁ is substituted with one to two substituents. In one aspect, the one to two substituents are each independently C1-C4 alkyl or a halo. In one aspect, Y₁ is a difluorophenyl. In one aspect, Y₁ is an optionally substituted thiadiazolyl. In one aspect, Y₁ is an optionally substituted thiophenyl. In one aspect, Y₁ is an optionally substituted pyridazinyl. In one aspect, Y₁ is substituted with one methyl group. In one embodiment, in compounds represented by formula (IV) or (V), Y₁ is an optionally substituted C3-C5 alkyl or optionally substituted C3-C6 cycloalkyl.

30

35

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), or (XVII), r is 3. In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), or (XVII), r is 4. In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), or (XVII), r is 2.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), or (XVII), X_1 is $-C(R^a)_2-$ or $-C(O)-$. In one aspect, X_1 is $-C(R^a)_2-$. In one aspect, R^a is $-H$.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), (VII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), or (XIX), B is $-CH_2-$, $-O-$, $-N(R^b)-$, wherein R^b is lower alkyl. In one aspect, B is $-CH_2-$.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is substituted with a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Ring A is substituted with a 5-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Ring A is attached to the heteroaromatic substituent via a C-C bond. In one aspect, Ring A is attached to the heteroaromatic substituent via a C-N bond.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is substituted with a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Ring A is substituted with a 5-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens. In one aspect, Ring A is attached to the heteroaromatic substituent via a C-C bond. In one aspect, Ring A is attached to the heteroaromatic substituent via a C-N bond.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long.

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered

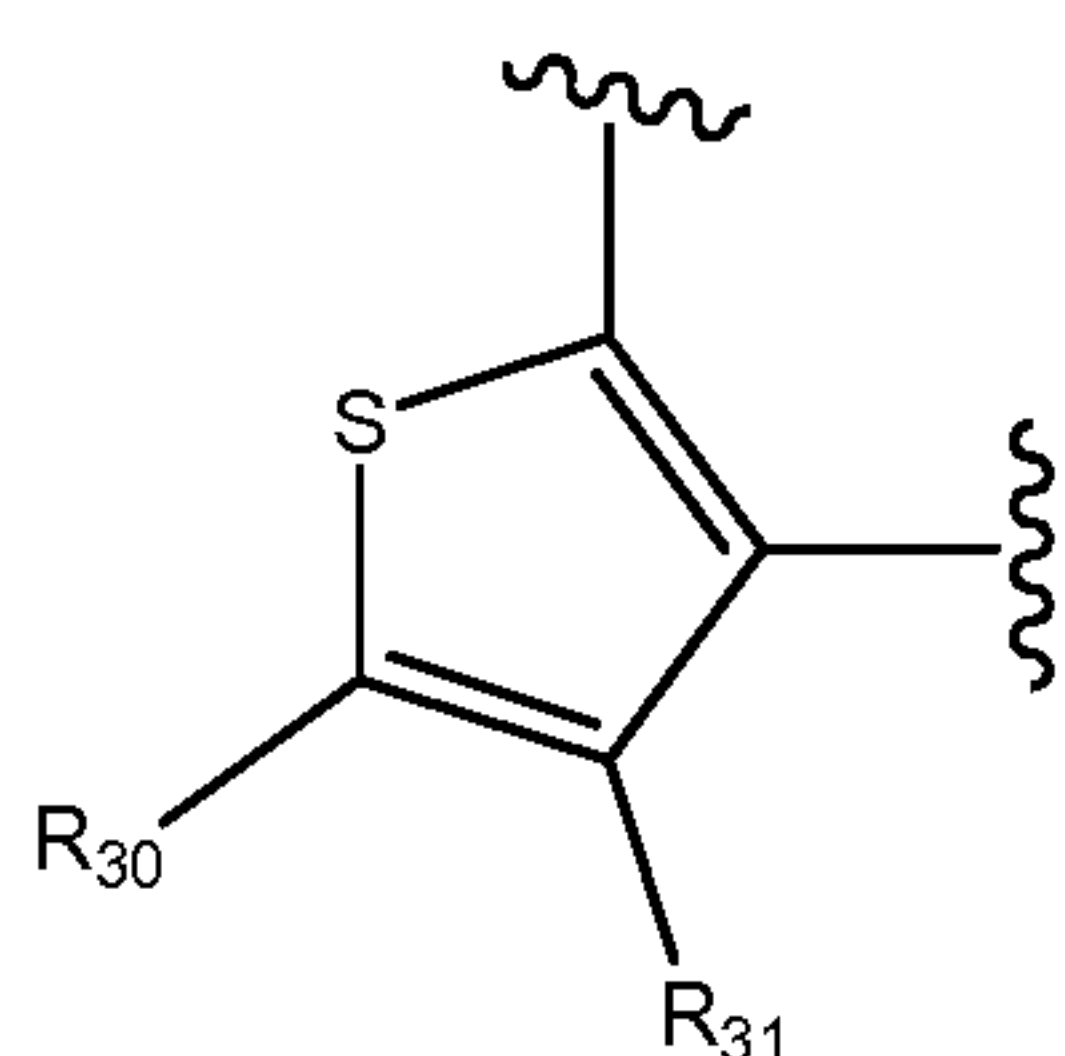
heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

5 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), where Ring A is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long, the 5 or 6-membered heteroaromatic ring is selected from the group consisting of pyridine, pyrazole, oxazole, thiazole, imidazole, or tetrazole. In one aspect, the 5-membered heteroaromatic ring has a substituent selected
10 from methyl or ethyl.

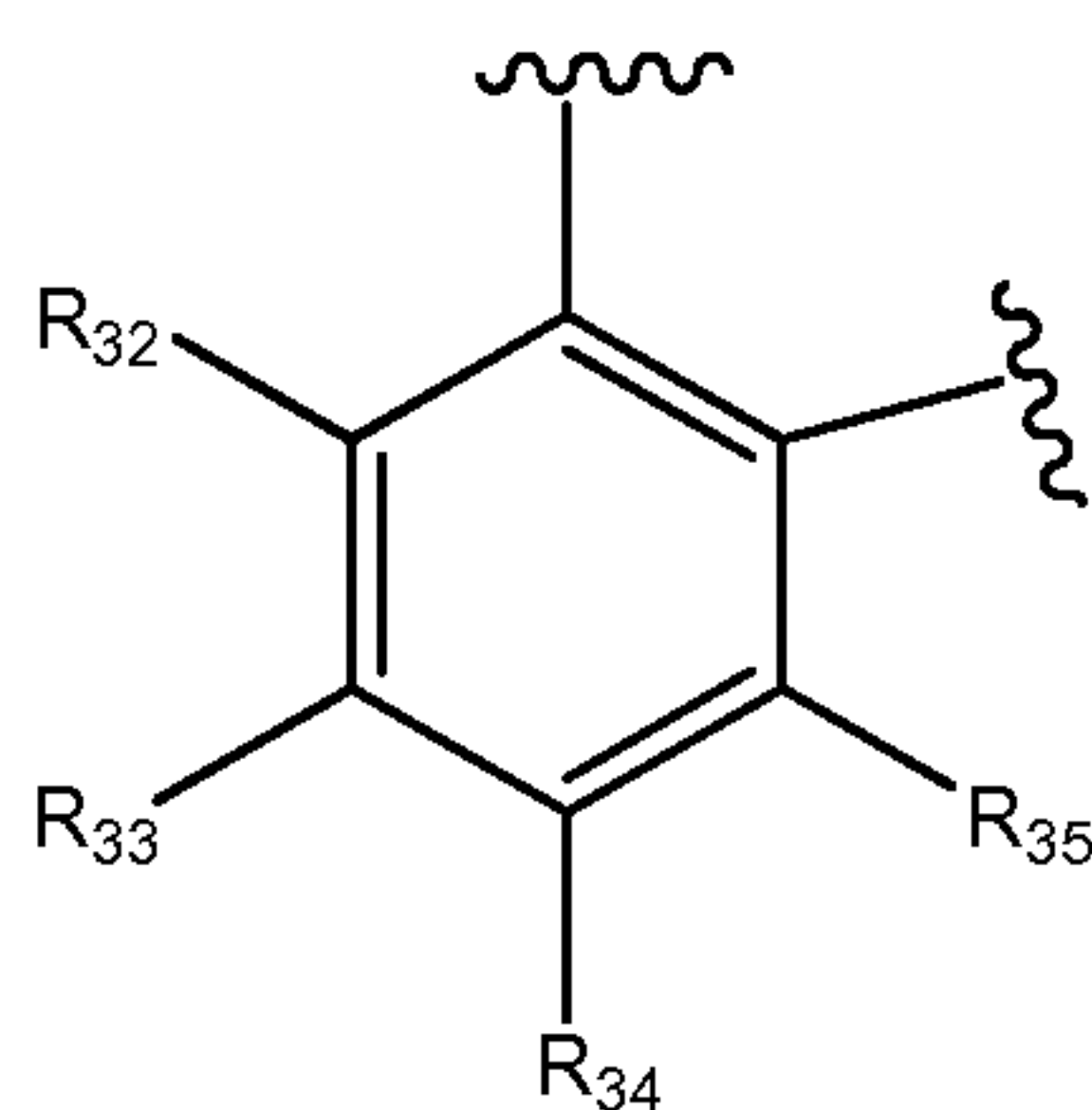
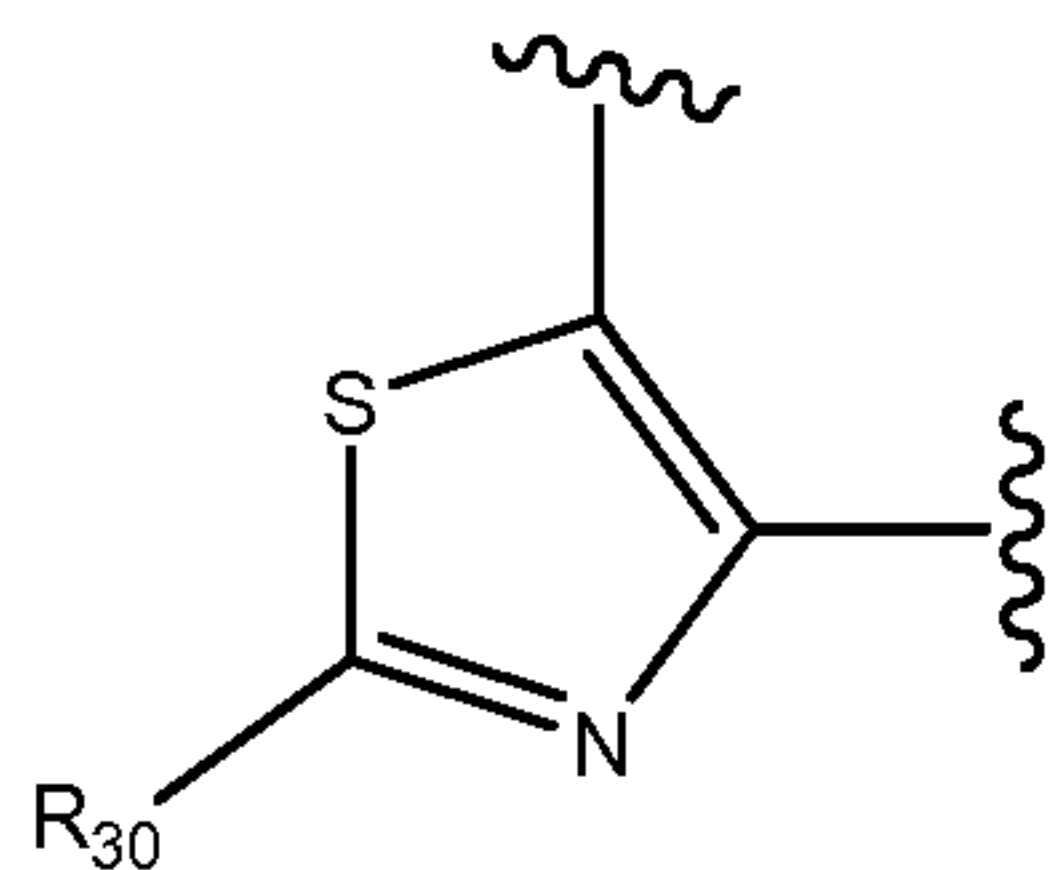
In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), where Ring A is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered
15 heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, the 5 or 6-membered heteroaromatic ring is selected from the group consisting of pyridine, pyrazole, oxazole, thiazole, imidazole, or tetrazole. In one aspect, the 5-membered heteroaromatic ring has a substituent selected from methyl or ethyl.

20 In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is selected from the group consisting of an optionally substituted phenyl, an optionally substituted pyrazinyl, an optionally substituted thiazolyl, an optionally substituted thienyl or an optionally substituted pyridyl. In one aspect, Ring A is an optionally substituted phenyl. In one aspect, Ring A is an optionally substituted pyrazinyl. In one aspect, Ring A is an optionally substituted thiazolyl. In one
25 aspect, Ring A is an optionally substituted thienyl. In one aspect, Ring A is an optionally substituted pyrazinyl.

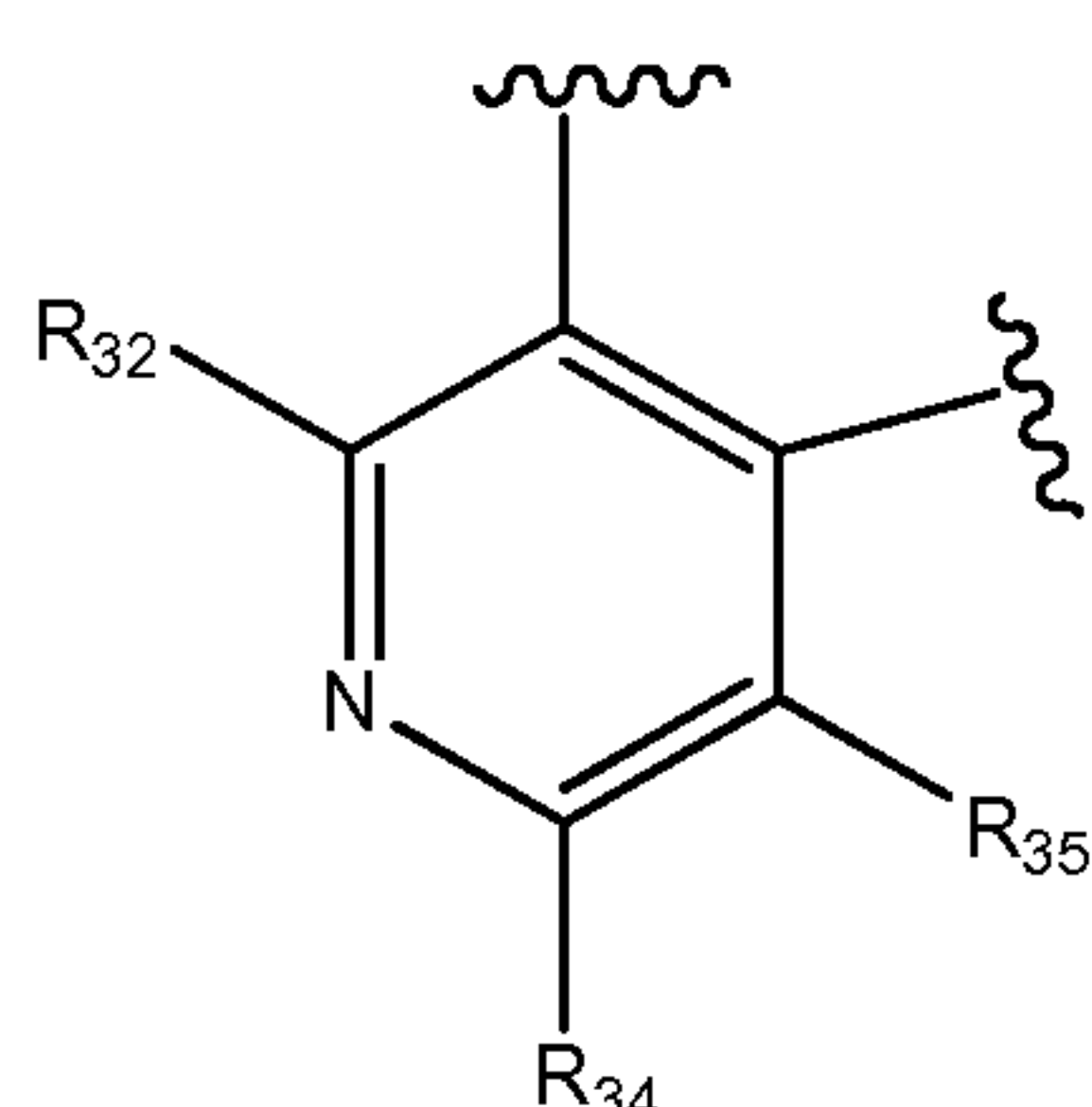
In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is



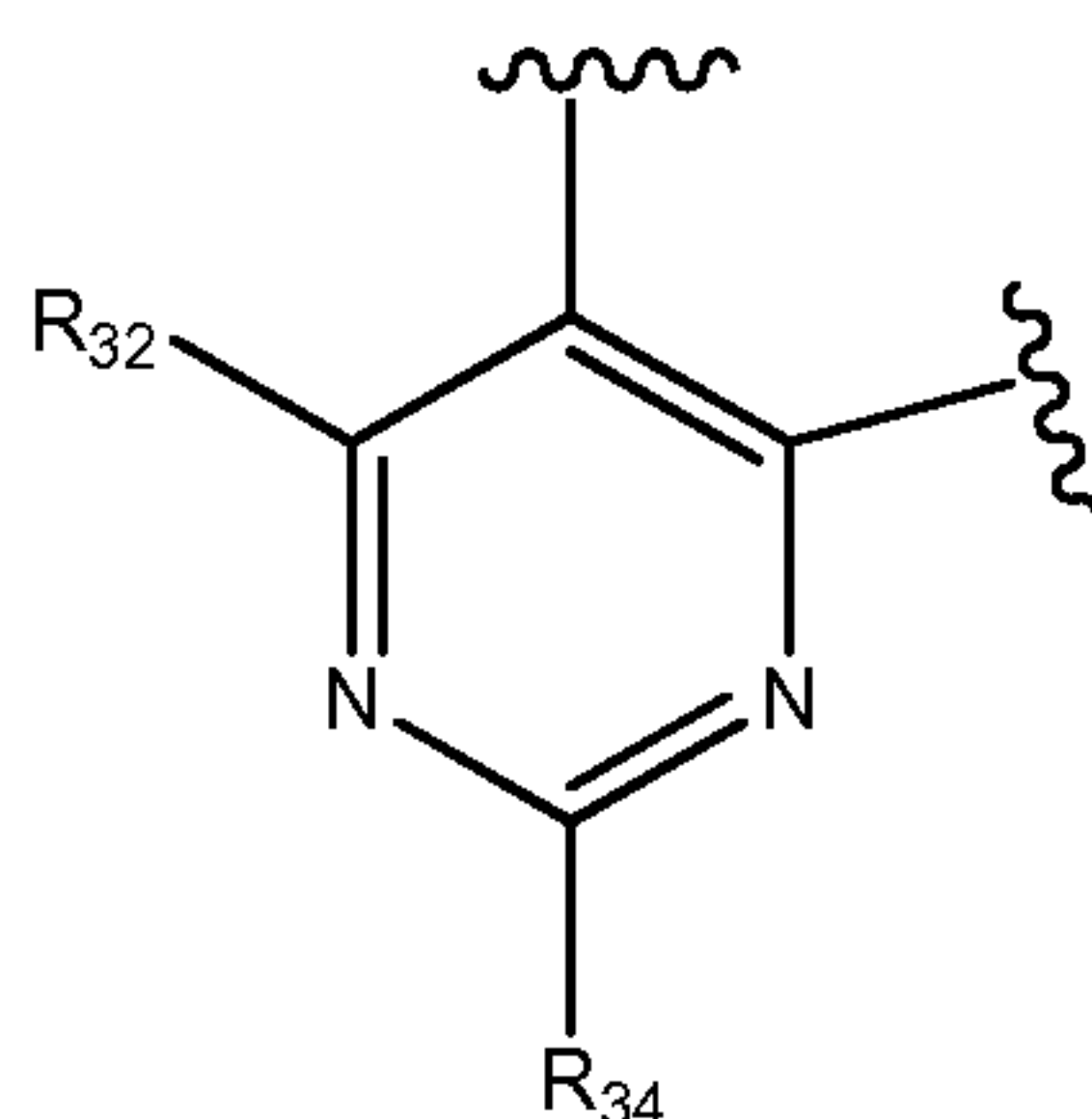
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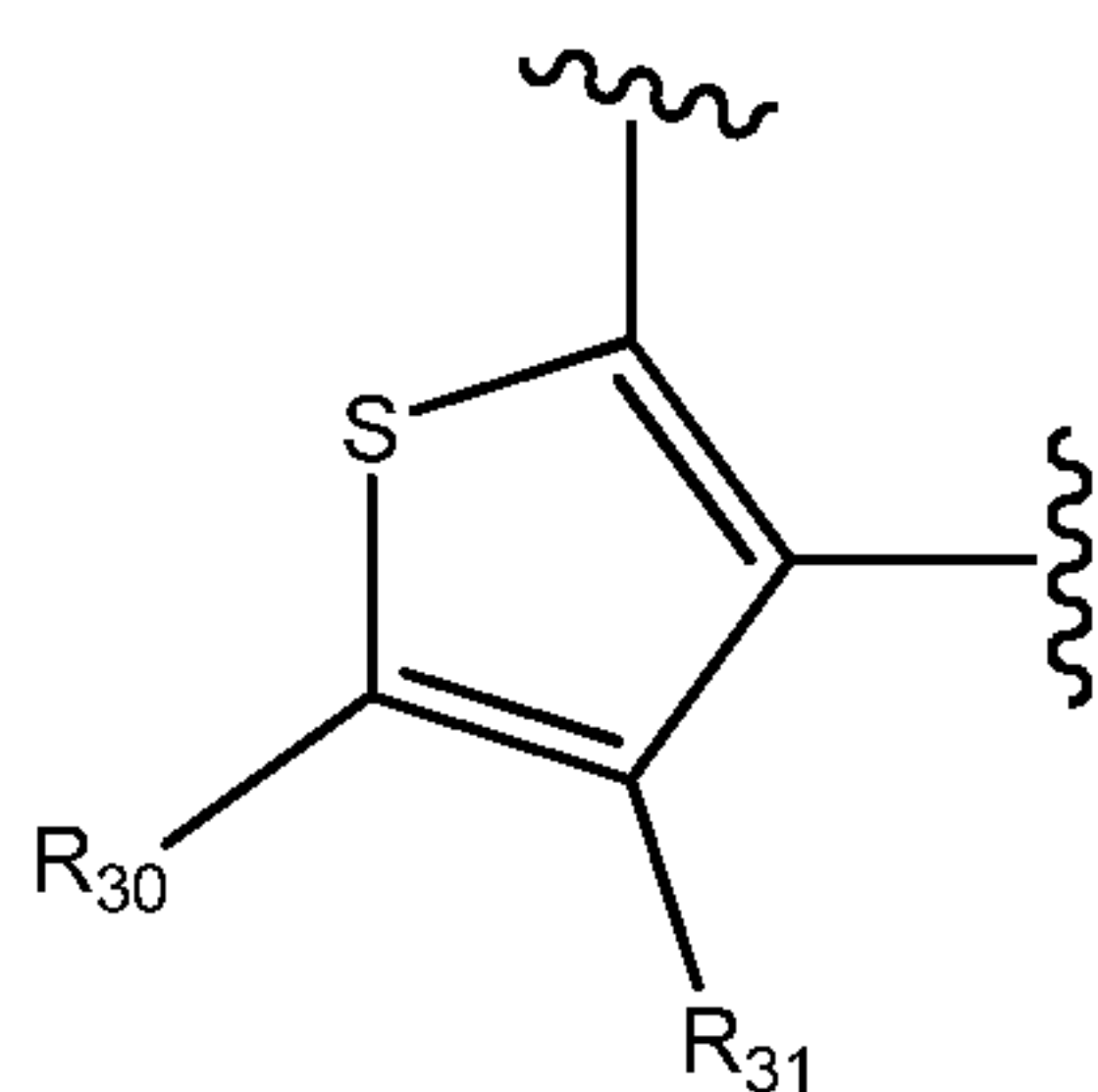


, or

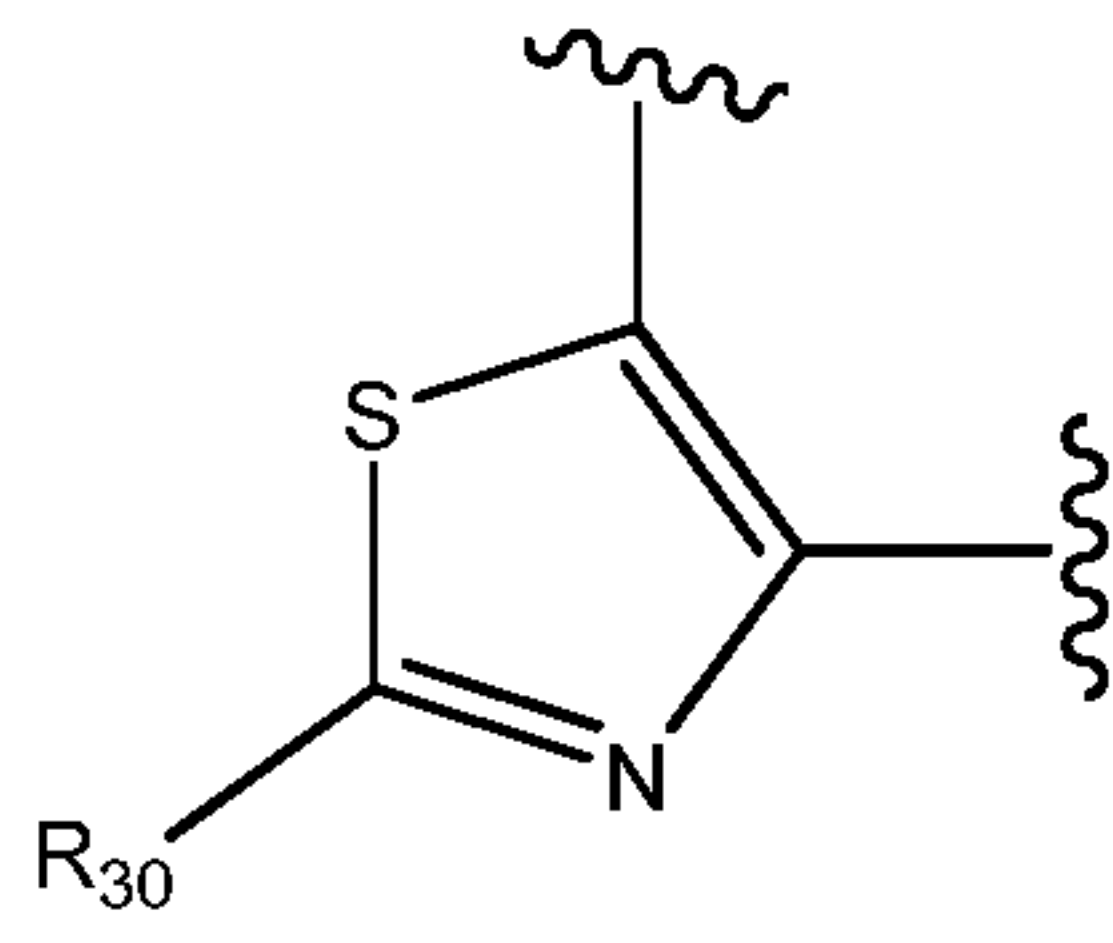


wherein each of R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, and R₃₅ is independently selected from -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, -C(O)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)_pR₄, or -S(O)_pNR₁R₂.

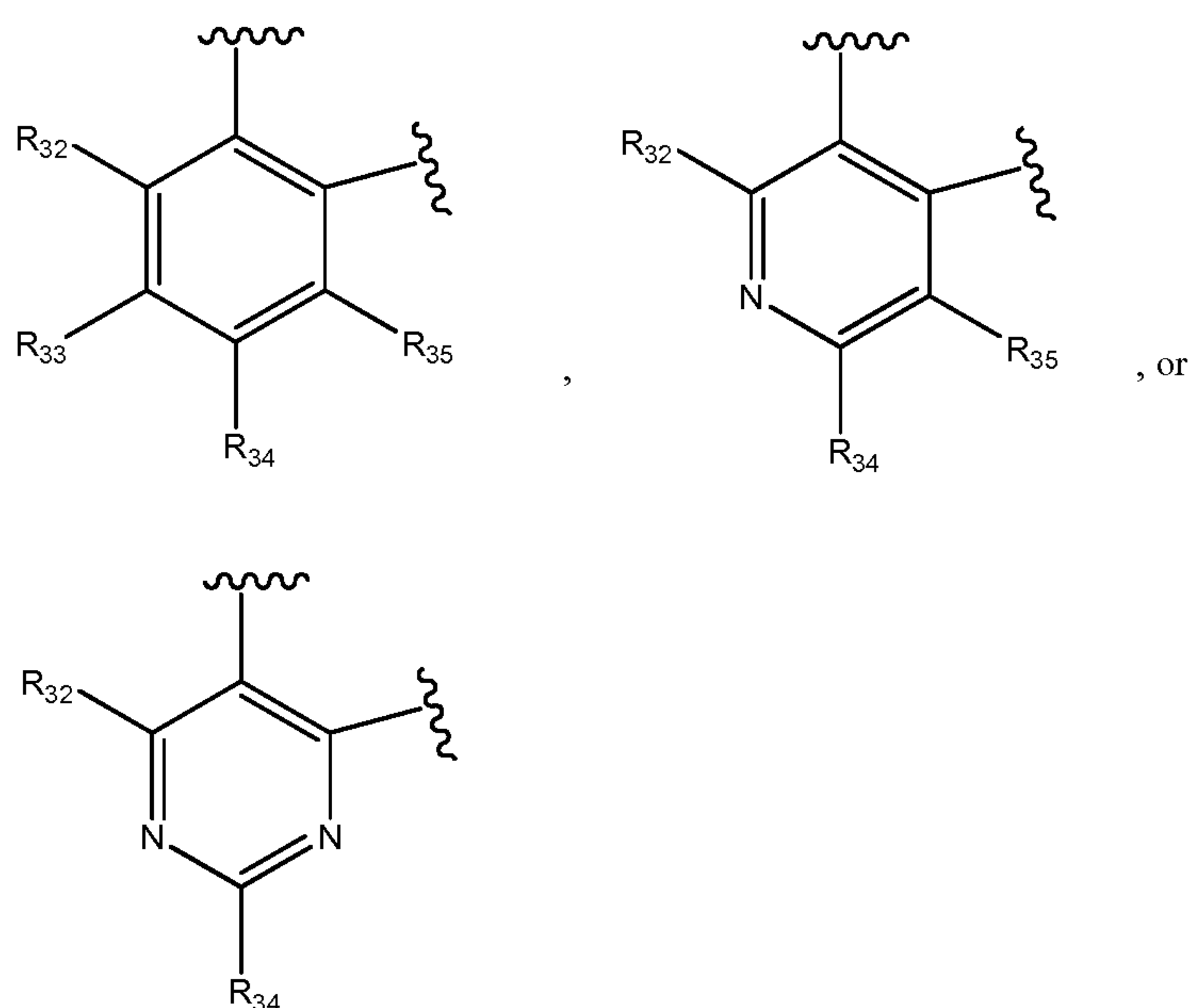
10 In one aspect, Ring A is



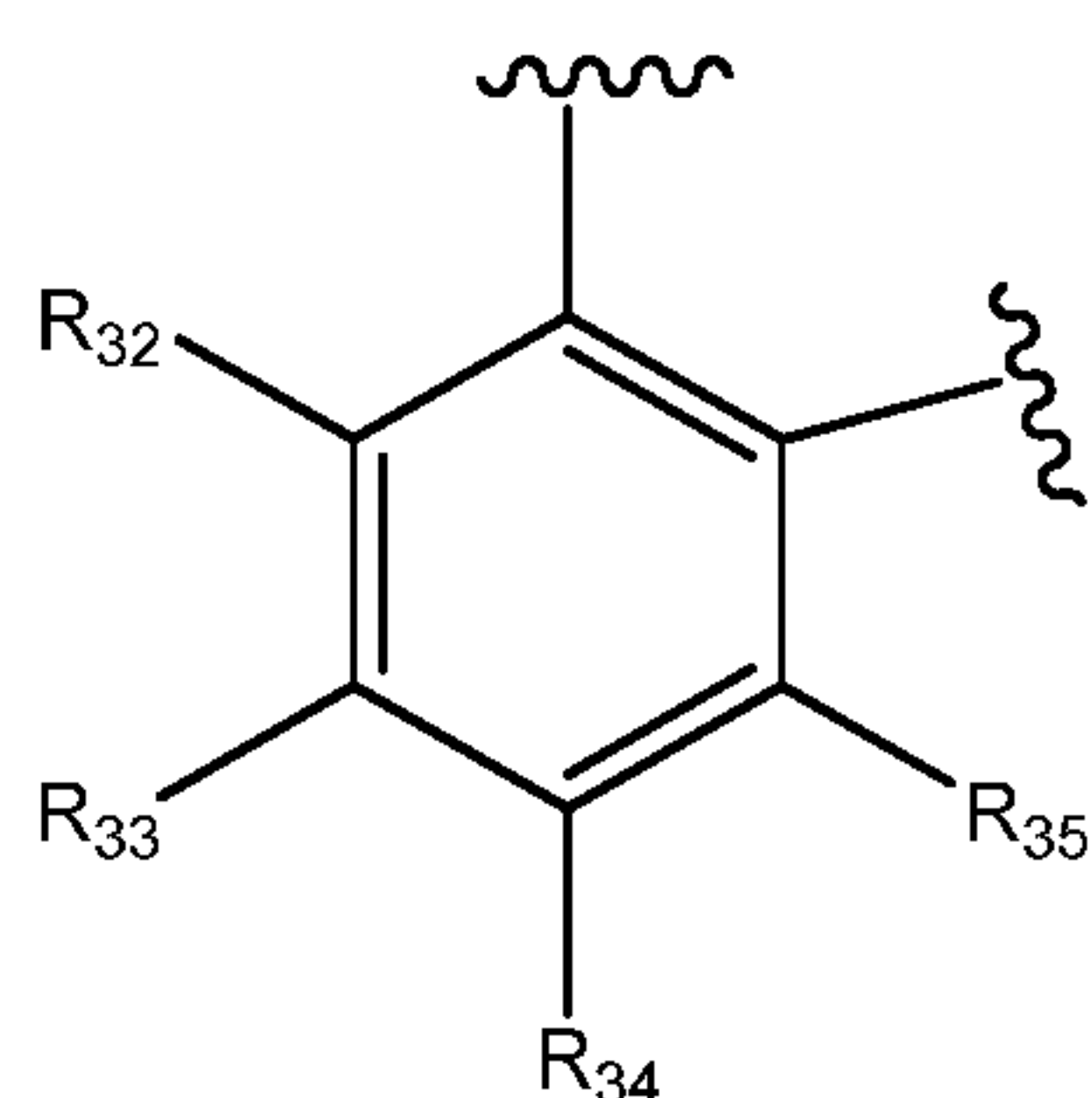
or



In another aspect, Ring A is

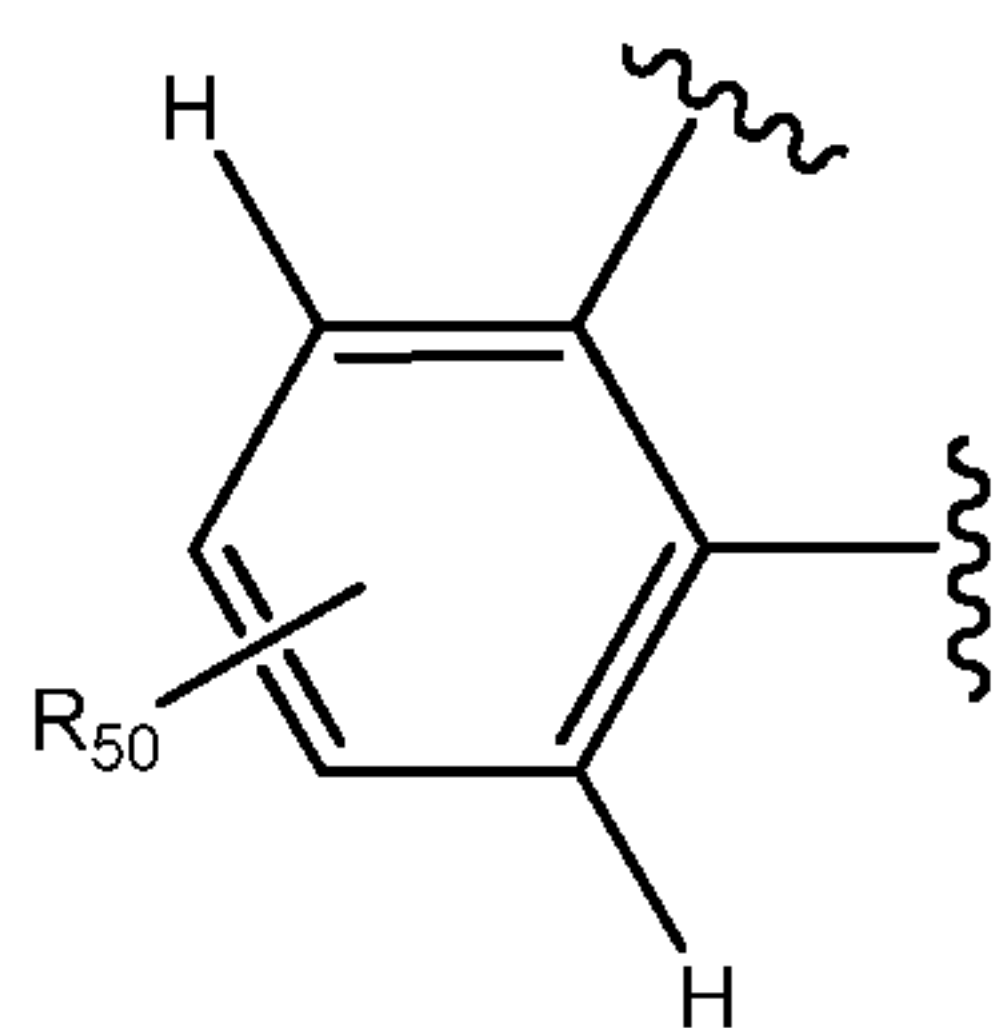


In another aspect, Ring A is



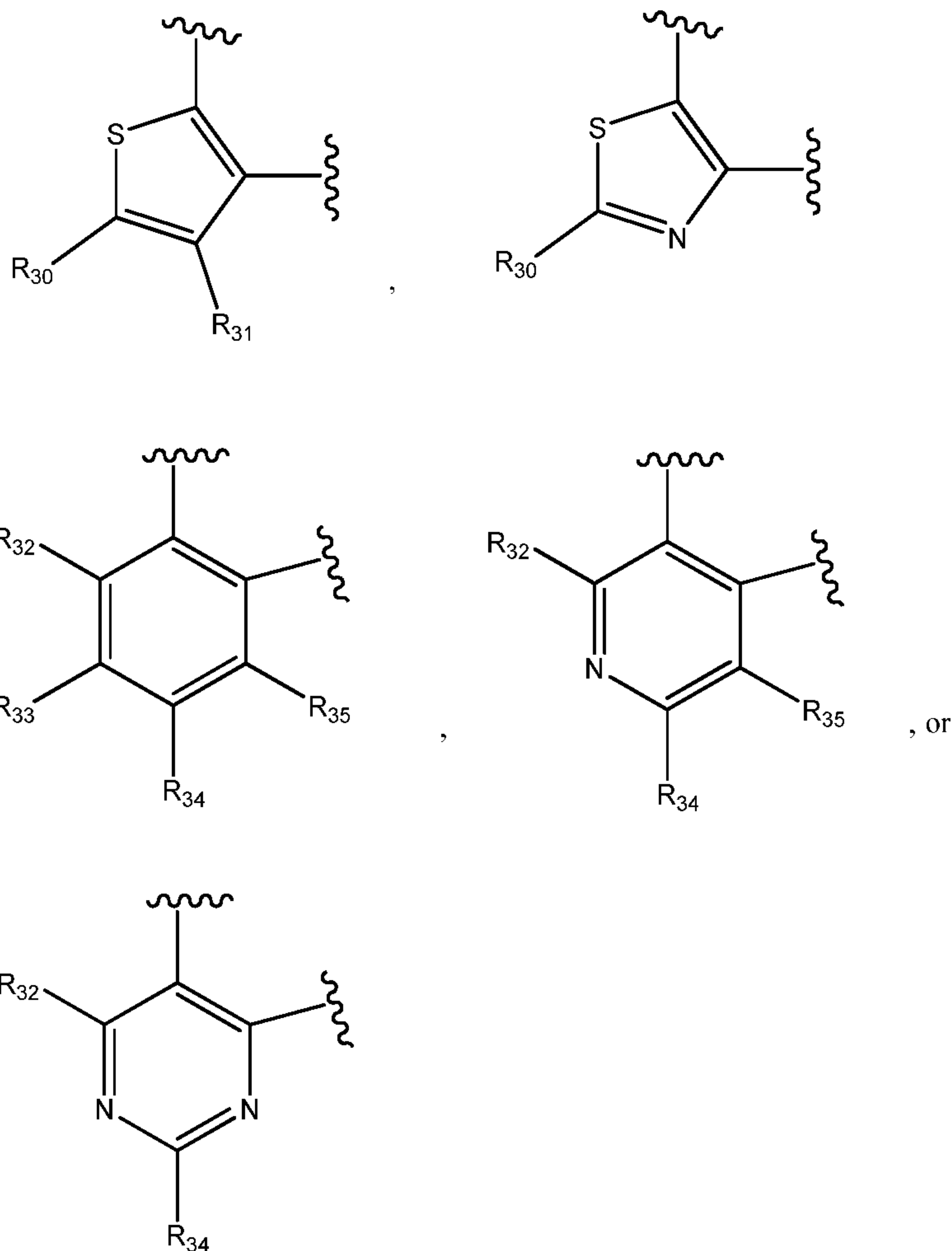
- 5 In another aspect, R_{32} , R_{33} , and R_{35} are all $-H$. In one aspect, R_{34} is selected from the group consisting of halo, cyano, haloalkyl, $-C(O)OR_4$, $-NR_1R_2$, $-OR_4$, $-C(O)NR_1R_2$, or an optionally substituted 5 or 6-membered heteroaryl, wherein R_1 , R_2 and R_4 are lower alkyl. In a further aspect, R_{34} is selected from the group consisting of Br, Cl, cyano, CF_3 , $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-N(CH_3)_2$, $-OCH_3$, $-C(O)NH_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.
- 10

In one embodiment, in compounds represented by formula (IA), (I), (II), (VI), or (VII), Ring A is:



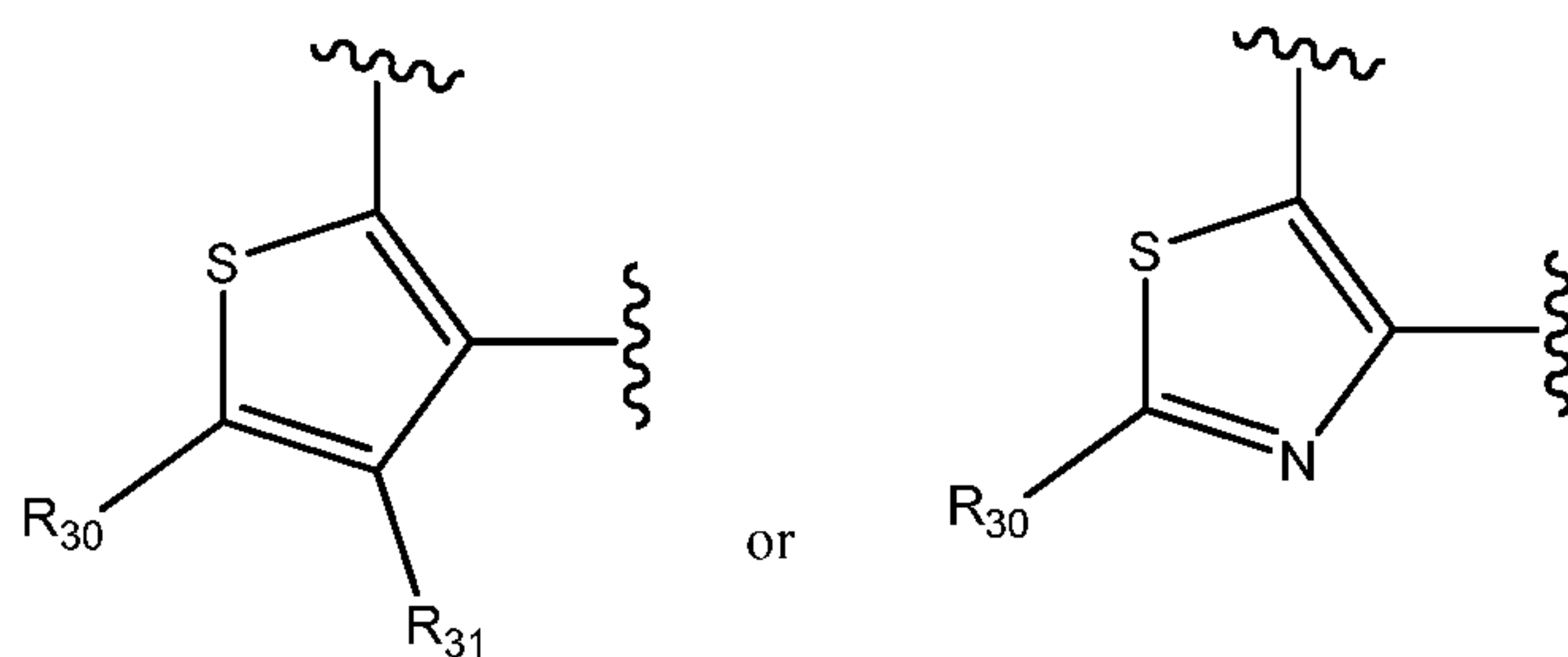
wherein R_{50} is a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long.

In one embodiment, in compounds represented by formula (III), (IV), (V), or (VIII), Ring C is

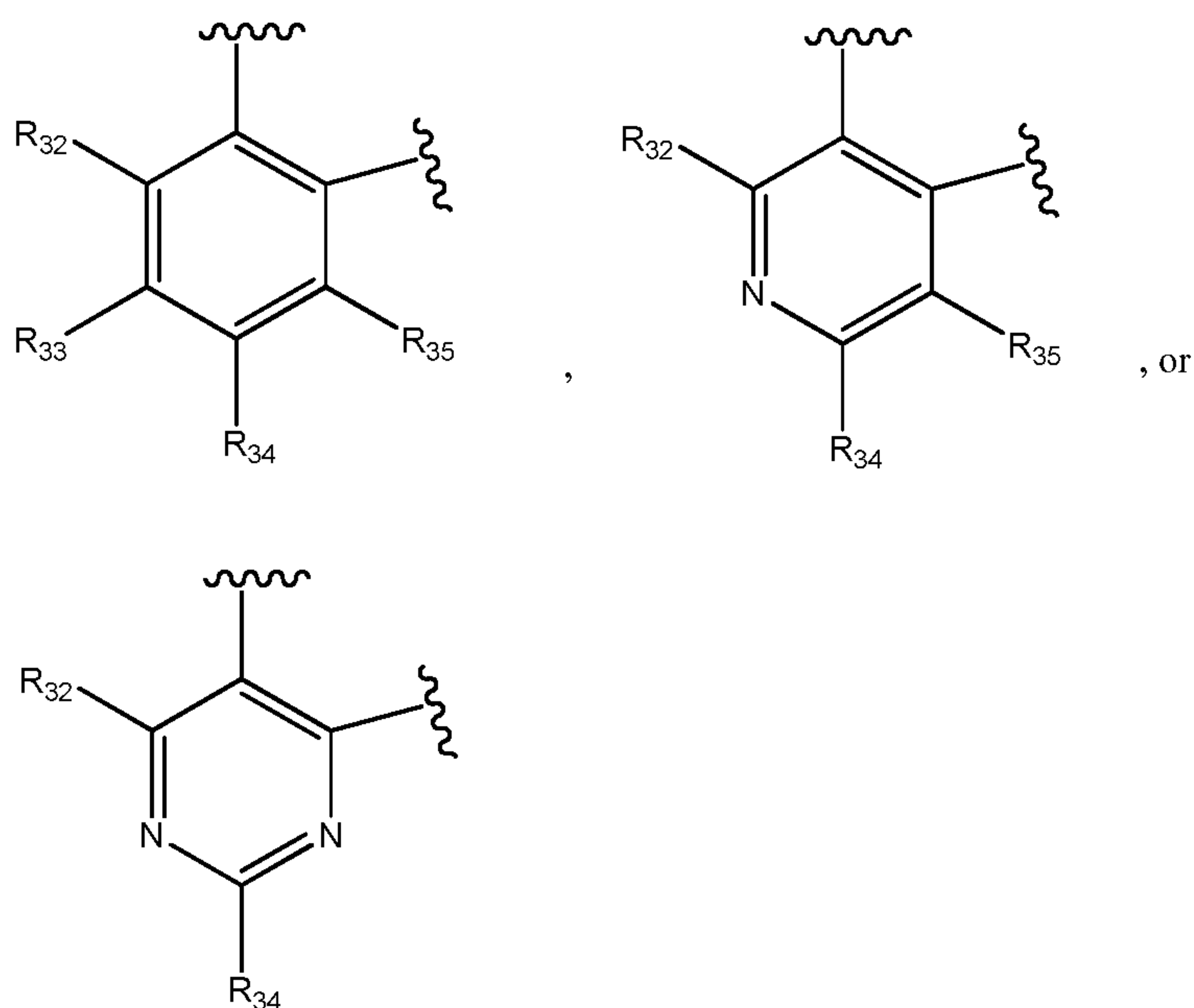


wherein each of R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , and R_{35} is independently selected from -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally 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 $-S(O)_pNR_1R_2$.

In one aspect, Ring C is

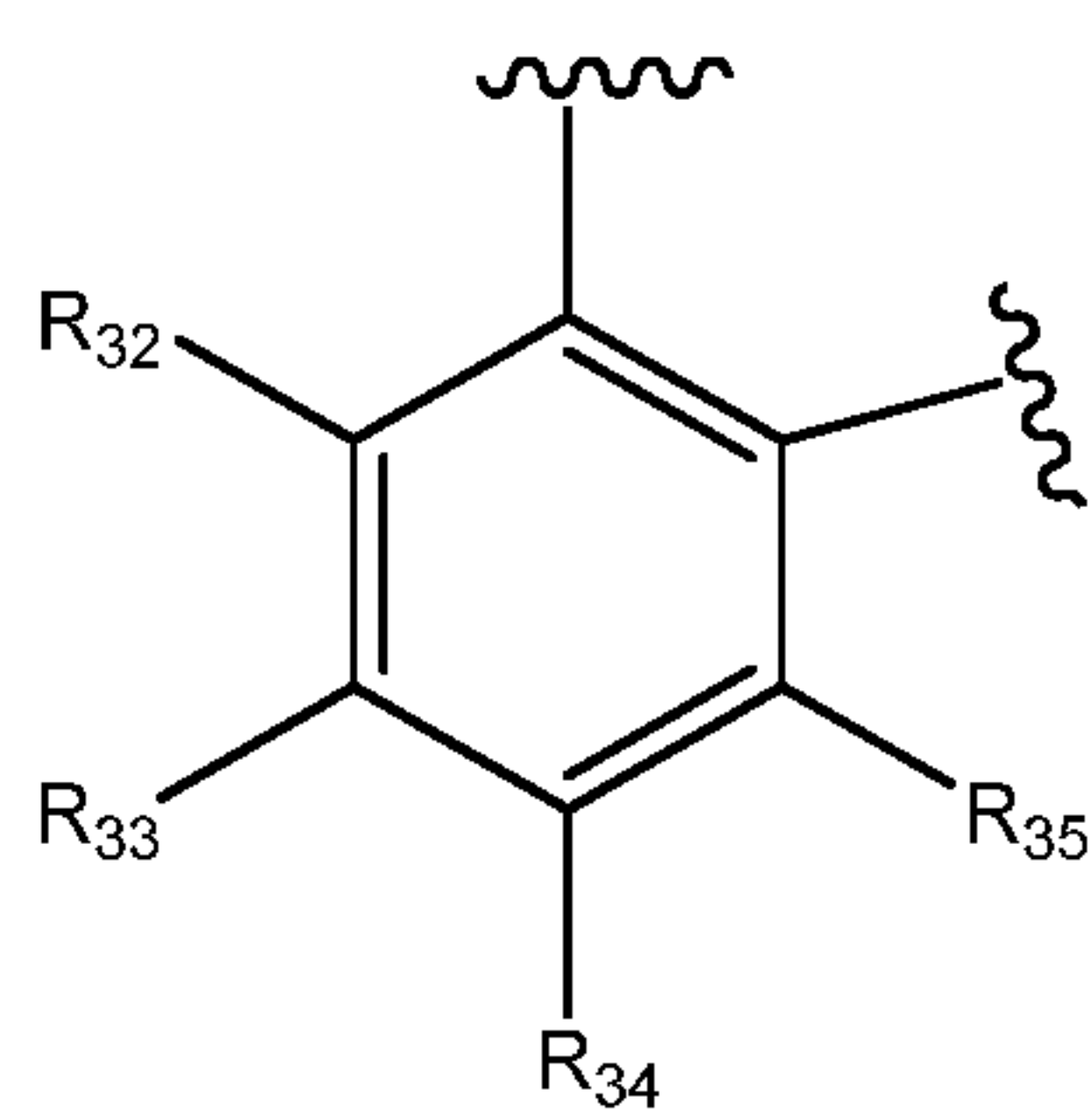


In another aspect, Ring C is



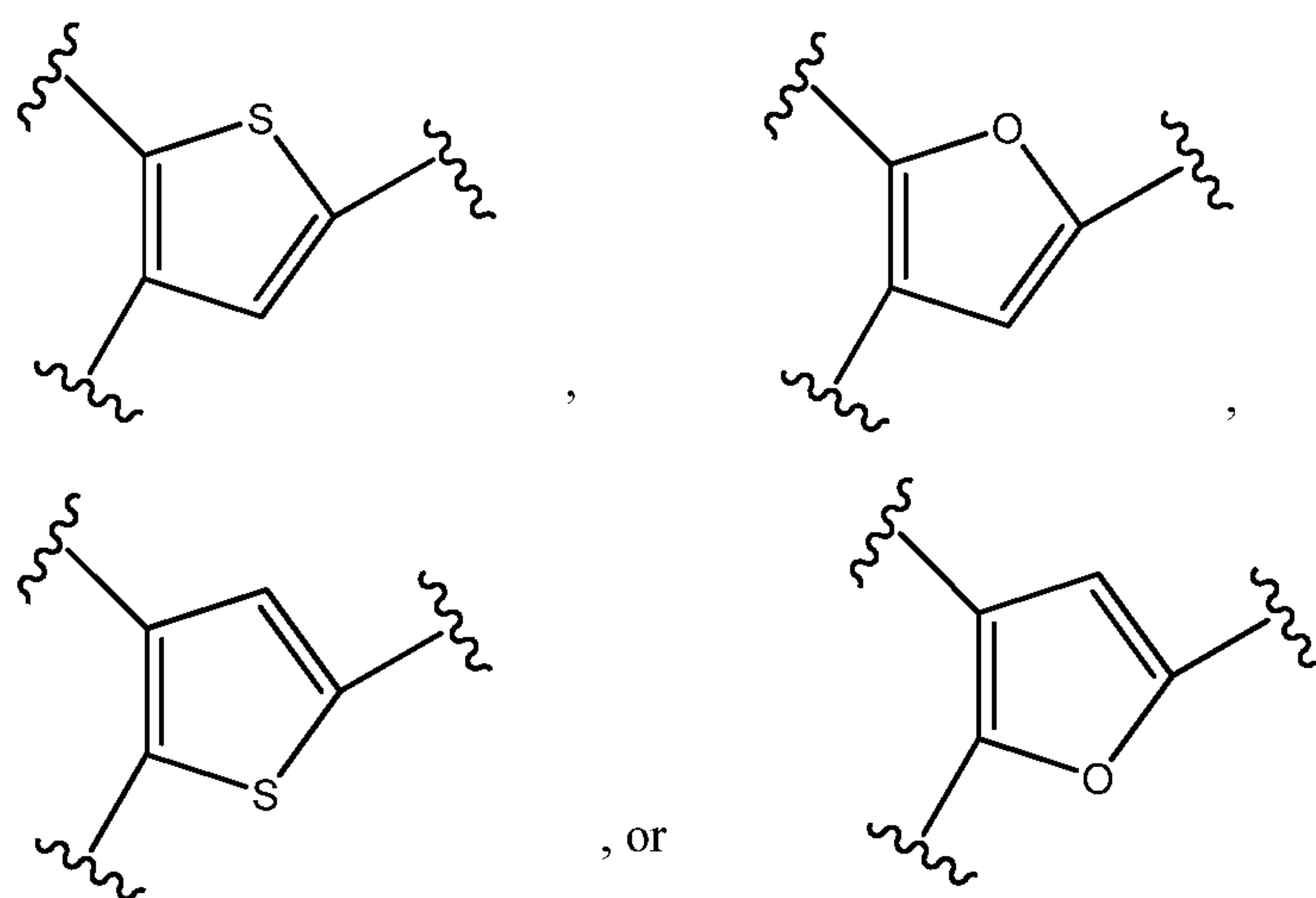
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In another aspect, Ring C is

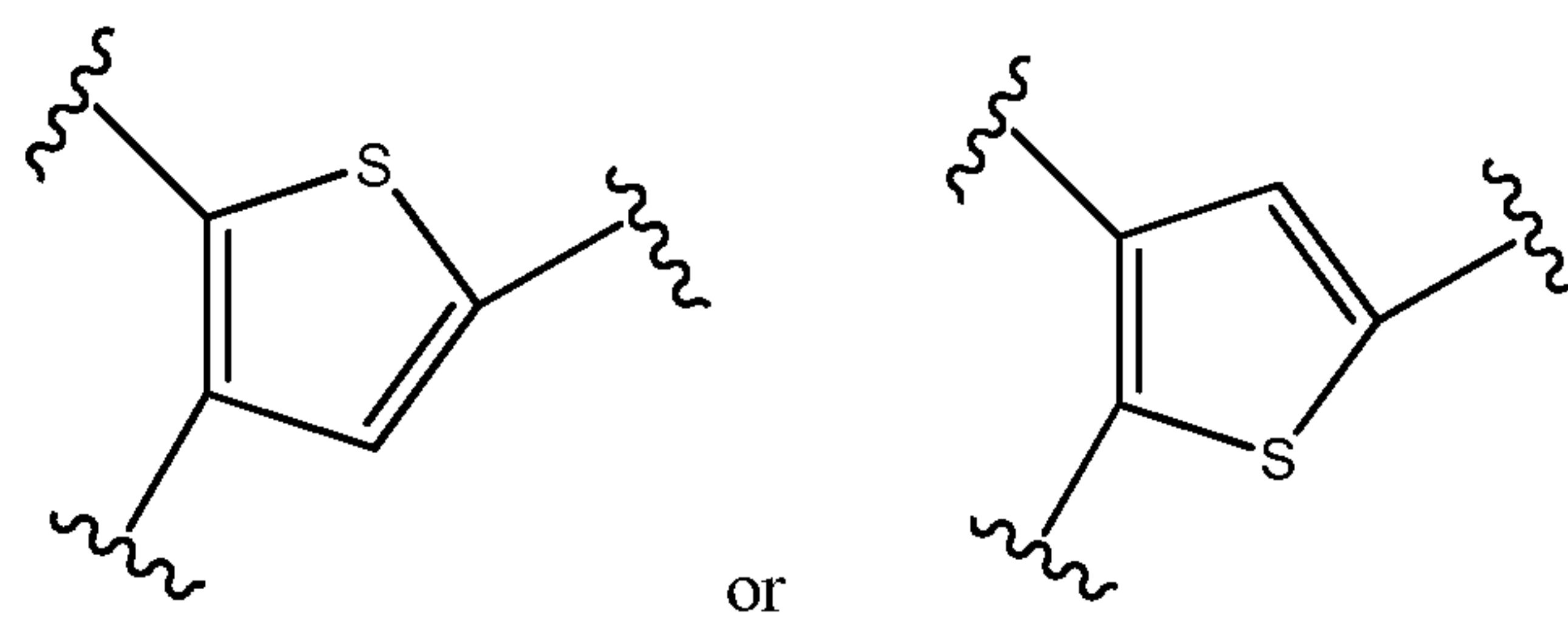


In another aspect, R₃₂, R₃₃, and R₃₅ are all -H. In one aspect, R₃₄ is selected from the group consisting of halo, cyano, haloalkyl, -C(O)OR₄, -NR₁R₂, -OR₄, -C(O)NR₁R₂, or an optionally substituted 5 or 6-membered heteroaryl, wherein R₁, R₂ and R₄ are lower alkyl. In a further aspect, R₃₄ is selected from the group consisting of Br, Cl, cyano, CF₃, -C(O)OCH₃, -C(O)OCH₂CH₃, -N(CH₃)₂, -OCH₃, -C(O)NH₂, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.

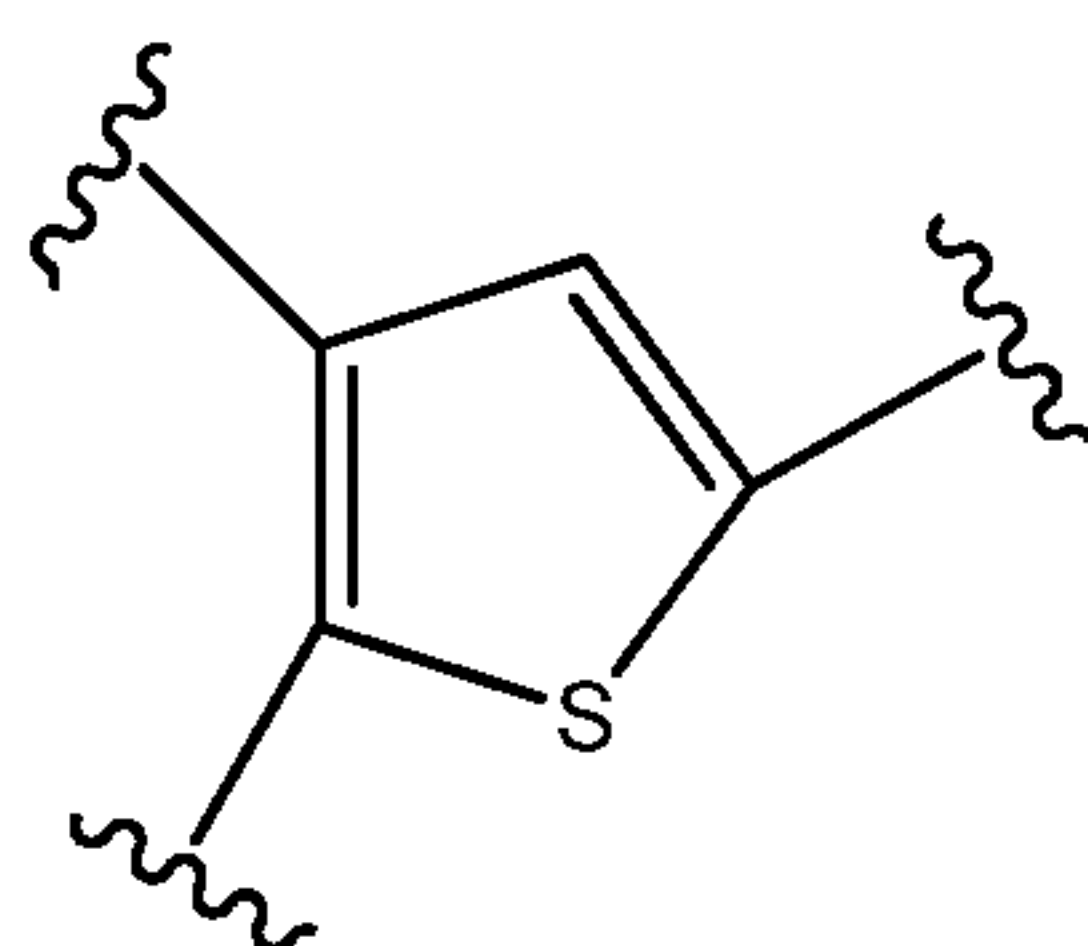
In one embodiment, in compounds represented by formula (III), Ring D is



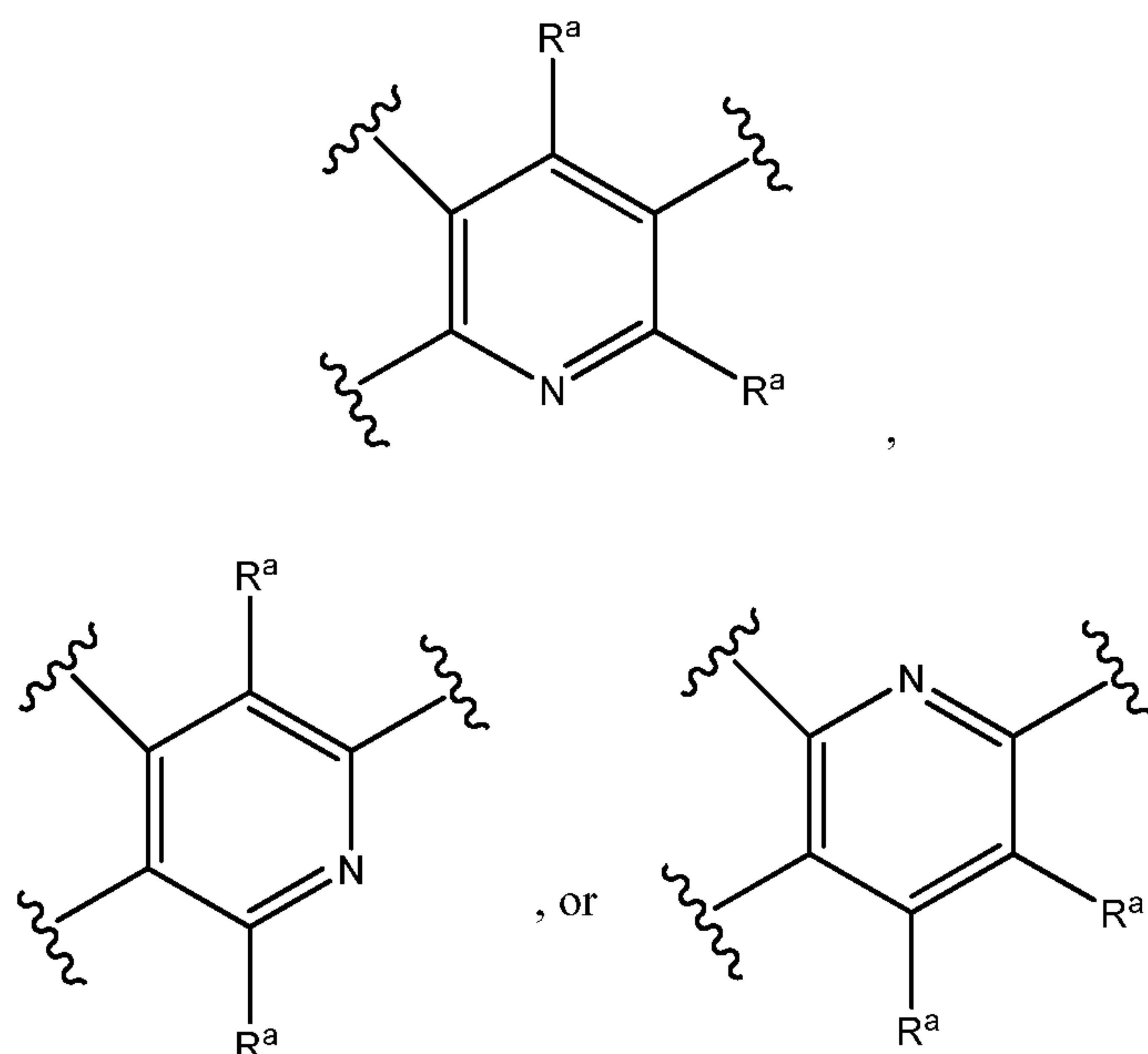
In one aspect, Ring D is



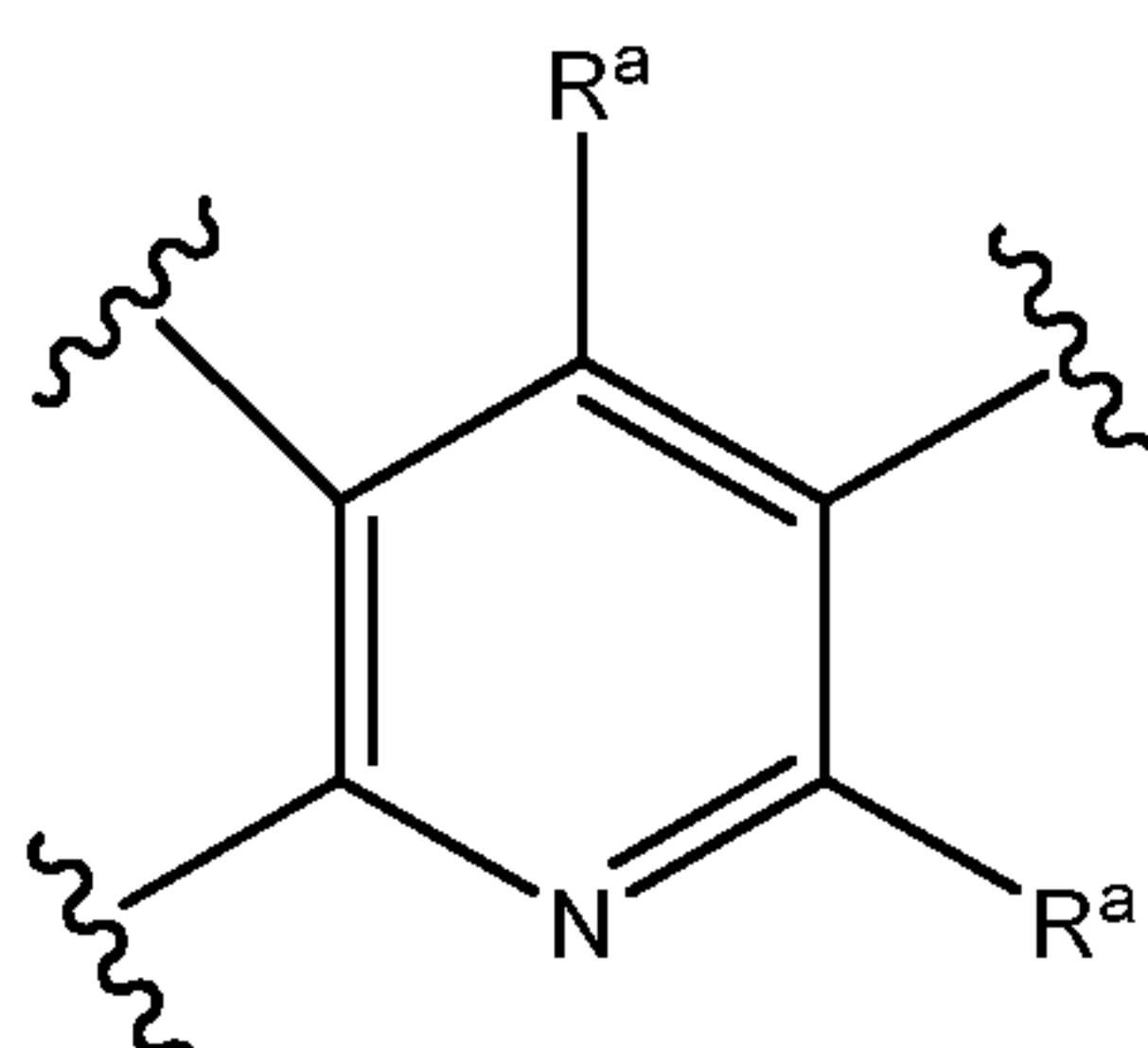
In one aspect, Ring D is



In one embodiment, in compounds represented by formula (VIII), Ring E is



In one aspect, Ring E is



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In one aspect, R_a is $-H$.

In one embodiment, in compounds represented by formula (X) or (XVII), Ring F is substituted with a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Ring F is substituted with a 5-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Ring F is attached to the heteroaromatic substituent via a C-C bond. In one aspect, Ring F is attached to the heteroaromatic substituent via a C-N bond.

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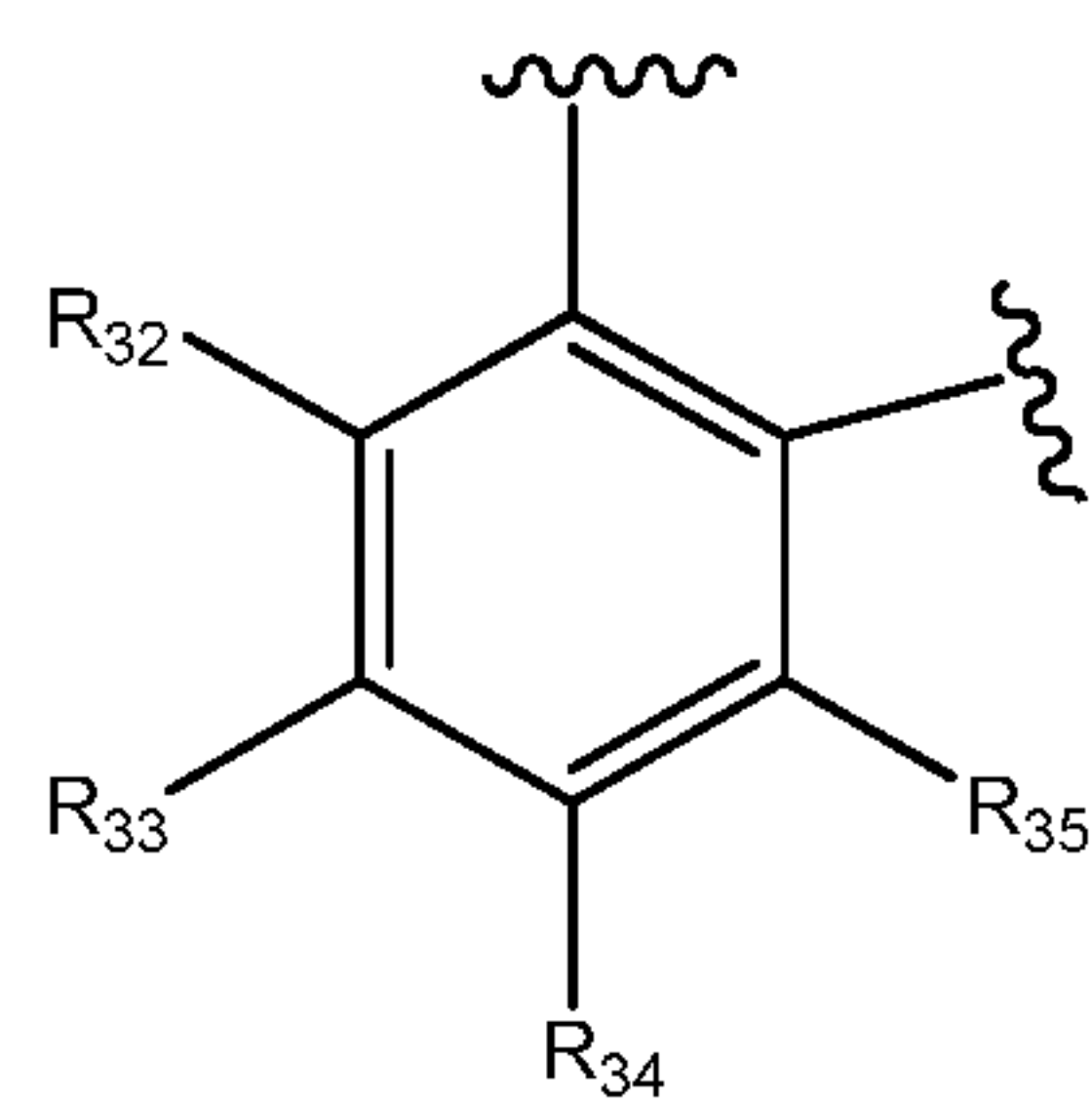
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In one embodiment, in compounds represented by formula (IA), (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), R^a is selected from the group consisting of halo, cyano, haloalkyl, $-C(O)OR_4$, $-NR_1R_2$, $-OR_4$, $-C(O)NR_1R_2$, or an optionally substituted 5 or 6-membered heteroaryl, wherein R_1 , R_2 and R_4 are lower alkyl. In one aspect, R^a is selected from the group consisting of Br, Cl, cyano, CF_3 , $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-N(CH_3)_2$, $-OCH_3$, $-C(O)NH_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally

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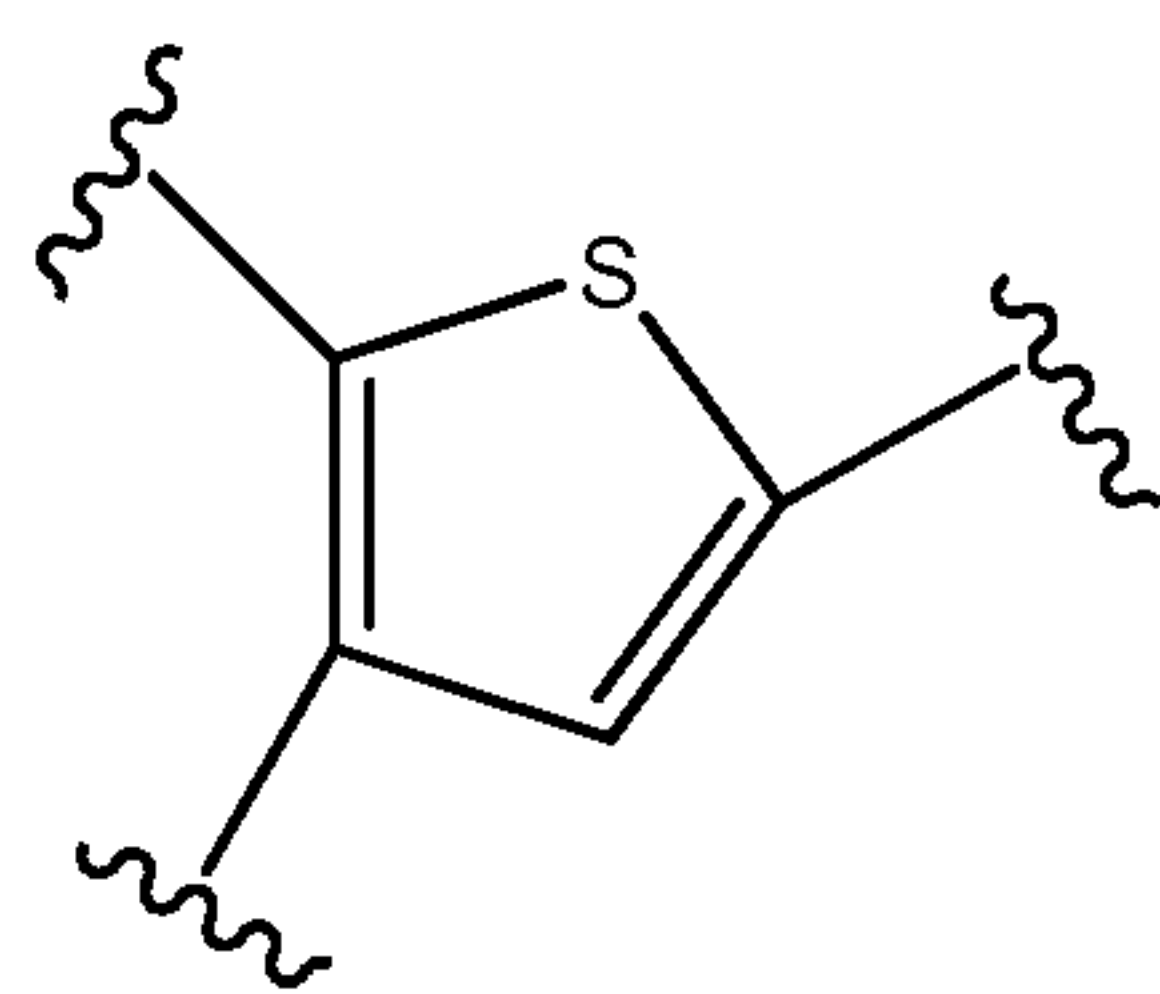
substituted imidazole, or an optionally substituted tetrazole.

In one embodiment, in compounds represented by formula (III), Ring C is:

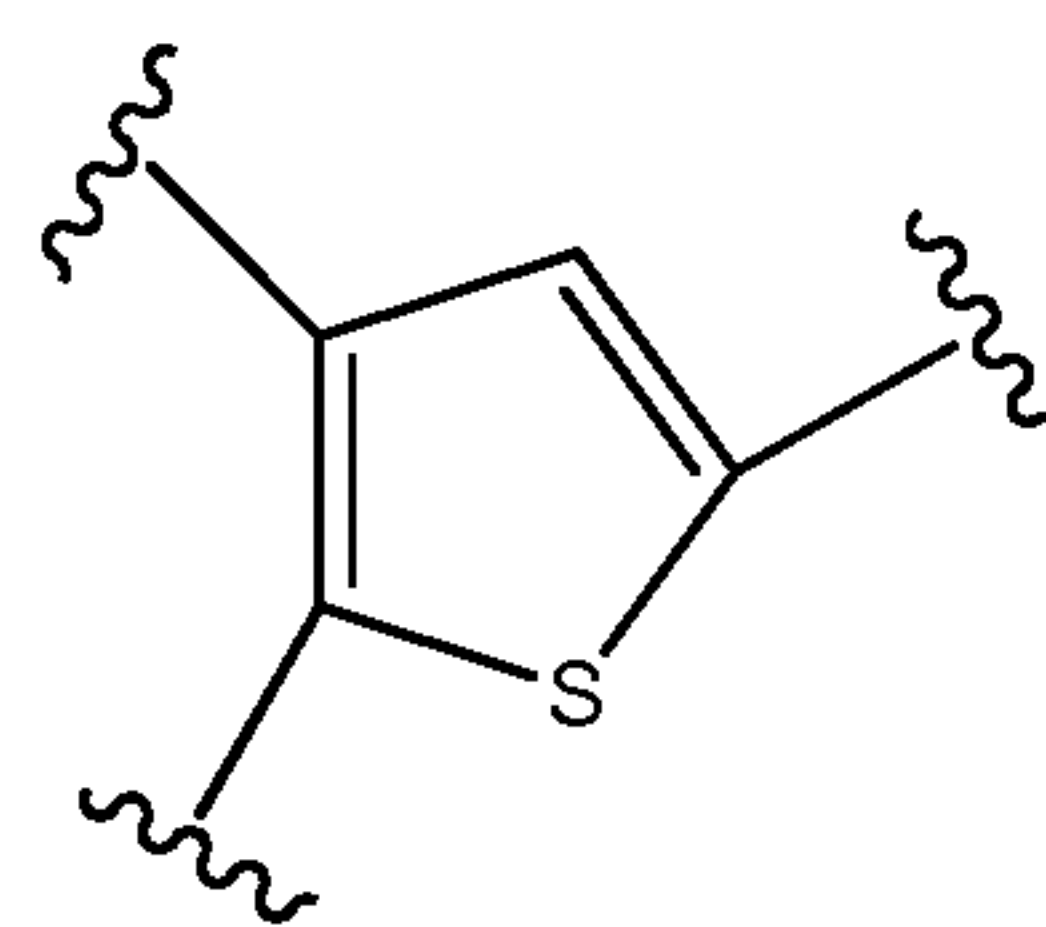


;

5 Ring D is



or

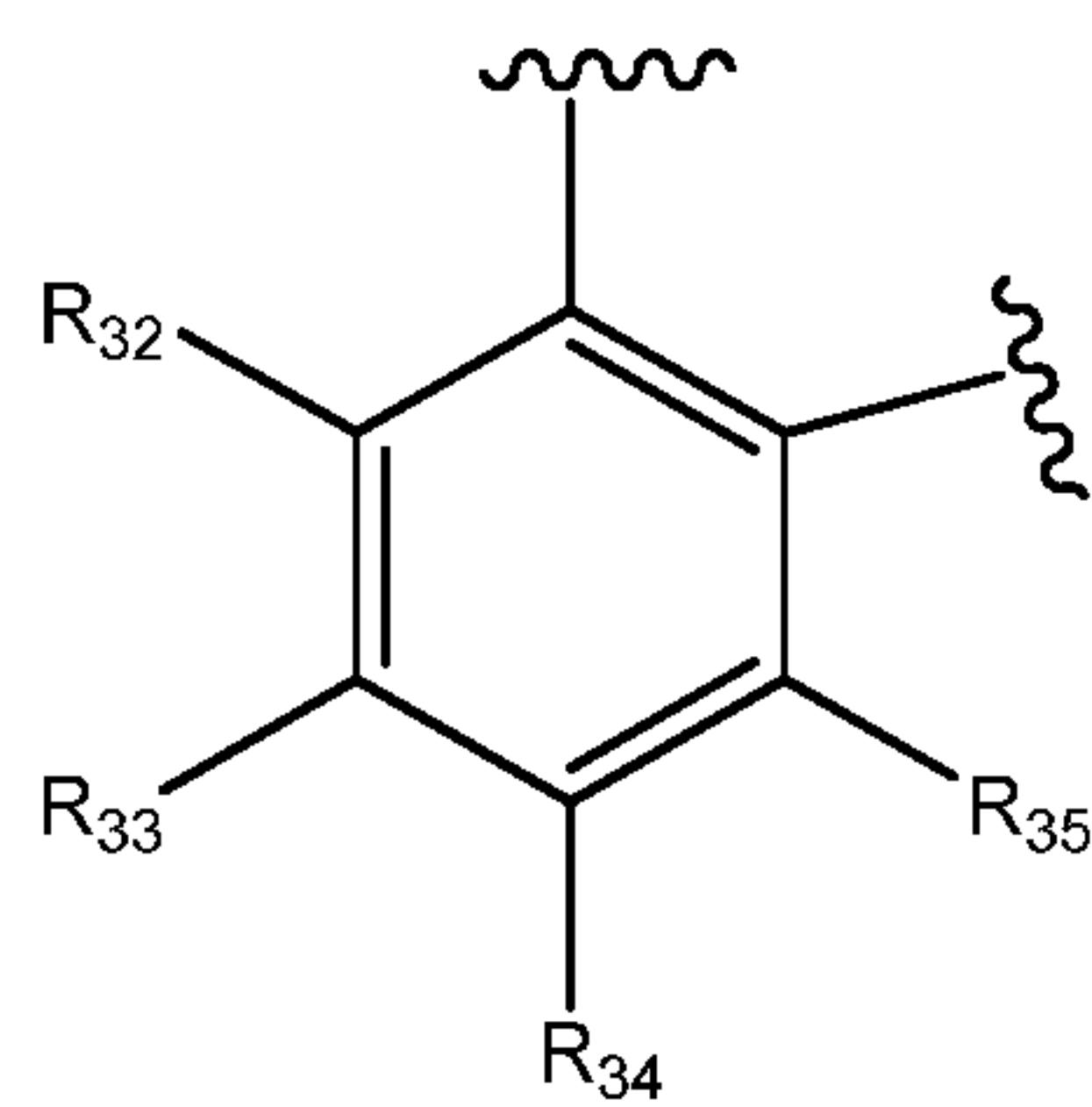


;

L₁ is -NH-C(O)- or -C(O)-NH-; and B is -CH₂-, -O-, -N(R^b)-, wherein R^b is lower alkyl.

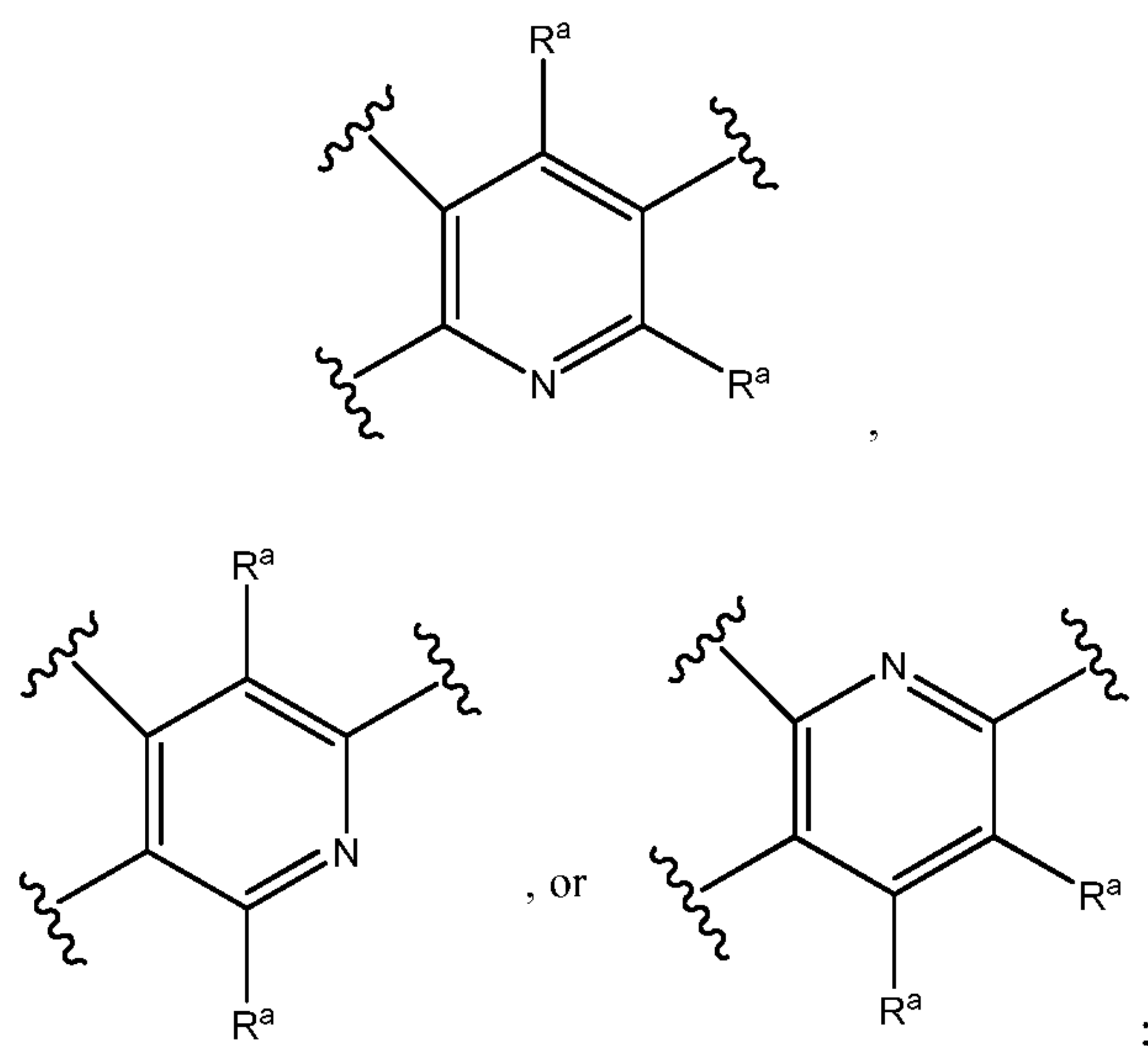
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In one embodiment, in compounds represented by formula (VIII), Ring C is:



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Ring E is



L_1 is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{C}(\text{O})-\text{NH}-$; and

B is $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{R}^b)-$, wherein R^b is lower alkyl.

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In one embodiment, in compounds represented by formula (IA) or (I), X_3 is $-\text{C}(\text{L}-\text{Y})-$. In one embodiment, in compounds represented by formula (IA) or (I), X_4 is $-\text{C}(\text{L}-\text{Y})-$. In one embodiment, in compounds represented by formula (VI), X_5 is $-\text{C}(\text{L}-\text{Y})-$. In one embodiment, in compounds represented by formula (VI), X_6 is $-\text{C}(\text{L}-\text{Y})-$. In one embodiment, in compounds represented by formula (VI), X_7 is $-\text{C}(\text{L}-\text{Y})-$.

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In one embodiment, of compounds of formulas (IX), (IXa), (IXb), (IXc), or (IXd), Z is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, $-\text{NR}_4\text{C}(\text{O})\text{R}_5$, halo, $-\text{OR}_4$, cyano, nitro, haloalkoxy, $-\text{C}(\text{O})\text{R}_4$, $-\text{NR}_1\text{R}_2$, $-\text{SR}_4$, $-\text{C}(\text{O})\text{OR}_4$, $-\text{OC}(\text{O})\text{R}_4$, $-\text{NR}_4\text{C}(\text{O})\text{NR}_1\text{R}_2$, $-\text{OC}(\text{O})\text{NR}_1\text{R}_2$, $-\text{NR}_4\text{C}(\text{O})\text{OR}_5$, $-\text{S}(\text{O})_p\text{R}_4$, or $-\text{S}(\text{O})_p\text{NR}_1\text{R}_2$. In one aspect, Z is a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, Z is a 5-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long.

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In one embodiment, of compounds of formulas (IX), (IXa), (IXb), (IXc), or (IXd), 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

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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 $-S(O)_pNR_1R_2$. In one aspect, Z is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, or a 6-membered aromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens. In one aspect, Z is a 5-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

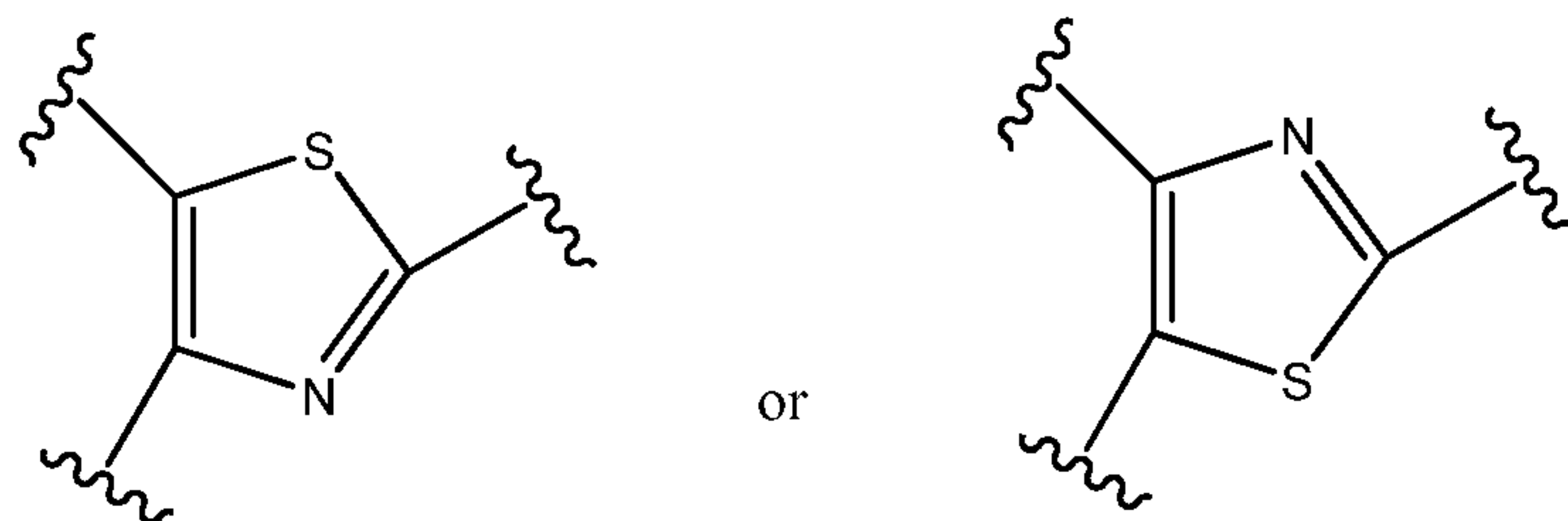
In one embodiment, in compounds represented by formula (XI), (XII), (XIV), (XV), or (XIX), when any of X_{24} , X_{25} , X_{26} or X_{27} is $-C(R^a)_2-$, one R^a is independently a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, R^a is a 5-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long.

In one embodiment, in compounds represented by formula (XI), (XII), (XIV), (XV), or (XIX), when any of X_{24} , X_{25} , X_{26} or X_{27} is $-C(R^a)_2-$, one R^a is independently a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, R^a is a 5-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

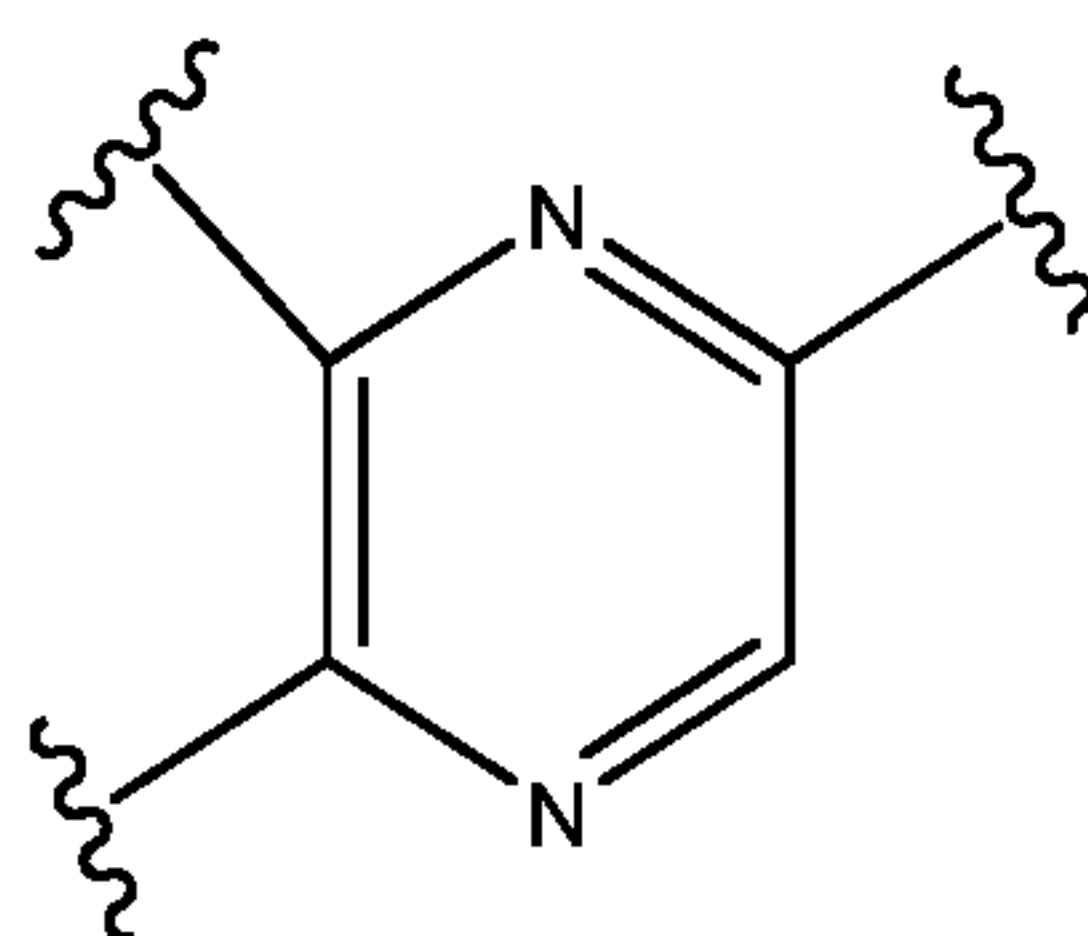
In one embodiment, in compounds represented by formula (XI), (XII), (XIV), (XV), or (XIX), when any of X_{24} , X_{25} , X_{26} or X_{27} is $-N(R^b)-$, one R^b is independently a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, R^b is a 5-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long.

In one embodiment, in compounds represented by formula (XI), (XII), (XIV), (XV), or (XIX), when any of X_{24} , X_{25} , X_{26} or X_{27} is $-N(R^b)-$, one R^b is independently a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, or a 6-membered aromatic ring with an optional substituent that is less than 5 atoms long. In one aspect, R^b is a 5-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

In one embodiment, in compounds represented by formula (XV), Ring G is:

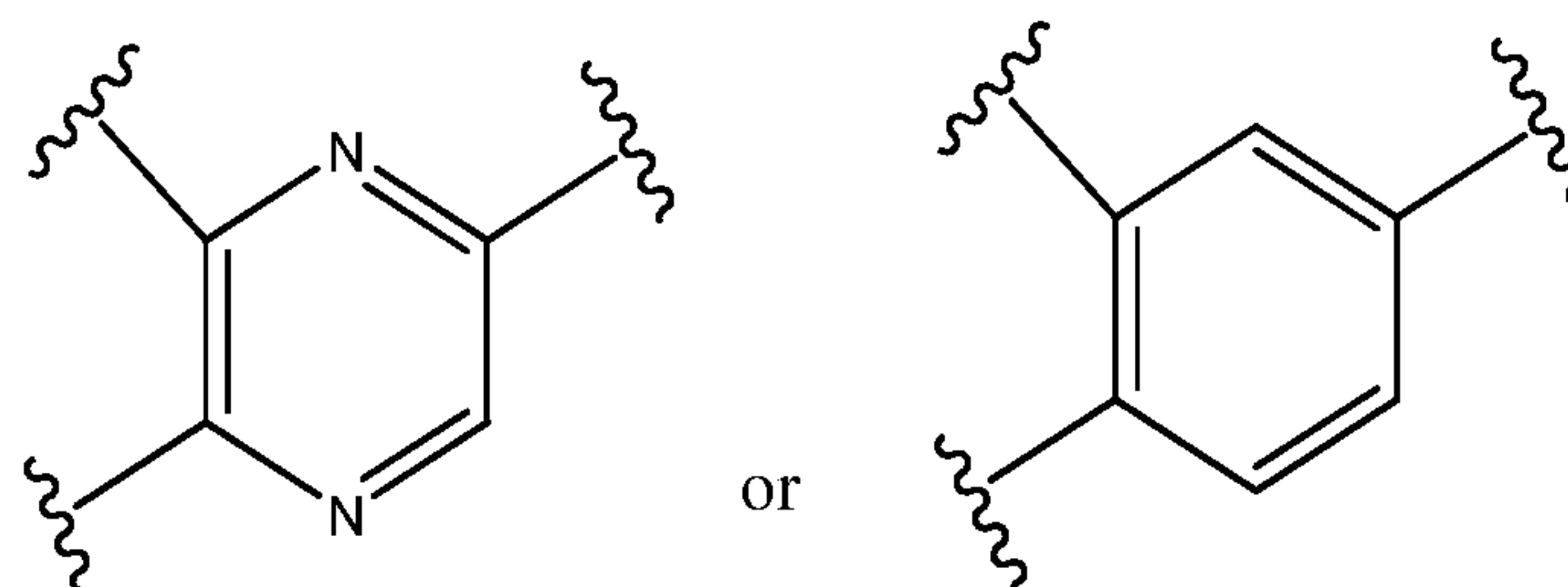


In one embodiment, in compounds represented by formula (XIX), Ring J is:

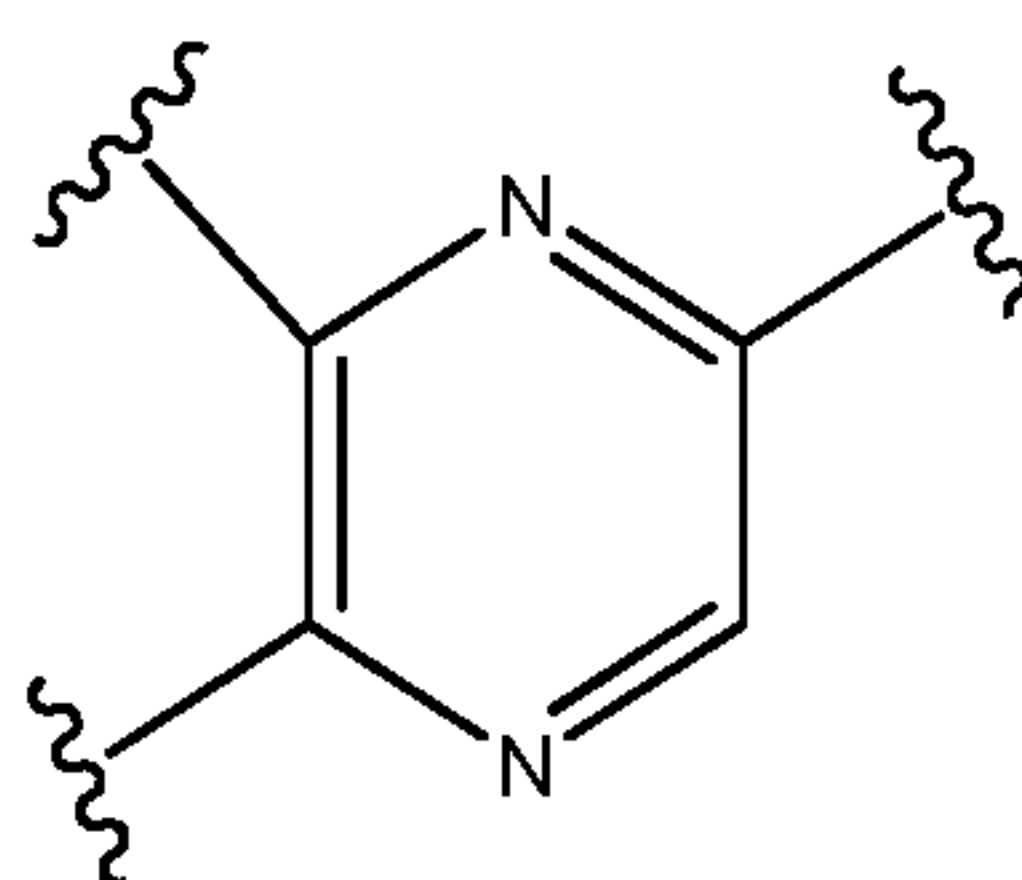


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In one embodiment, in compounds represented by formula (XVIII), the ring containing X'₇, X'₈, and X'₉ is:

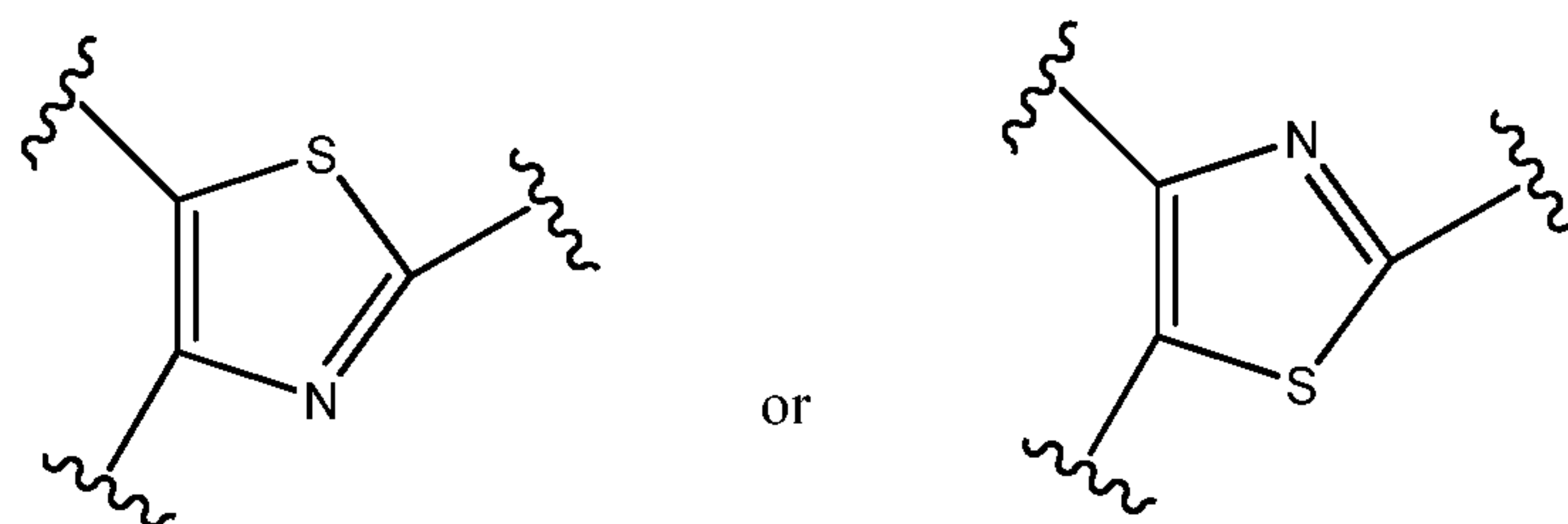


In one aspect, the ring is:



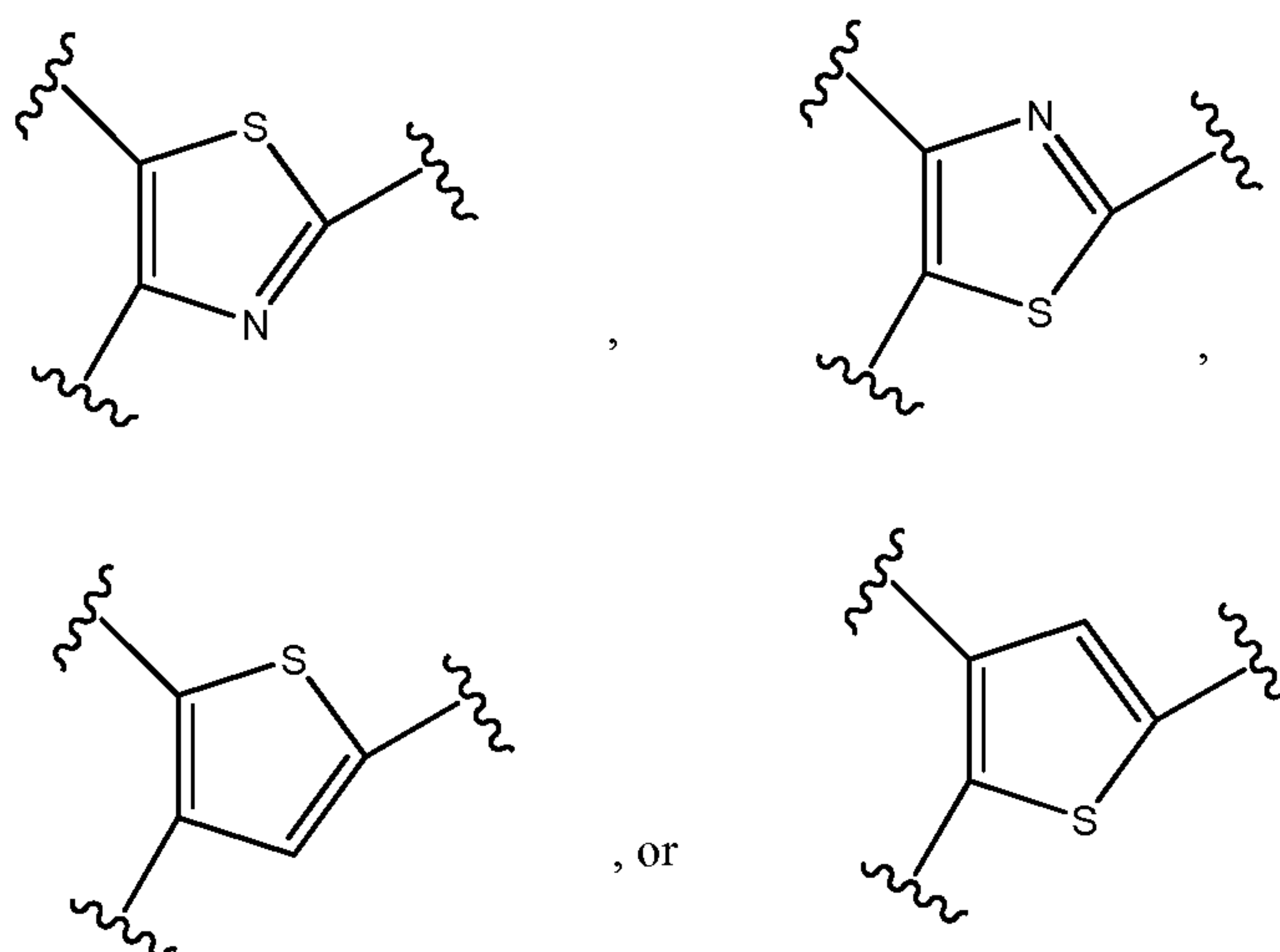
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In one embodiment, in compounds represented by formula (IA), (I), or (X), the ring containing X₂, X₃ and X₄ is:

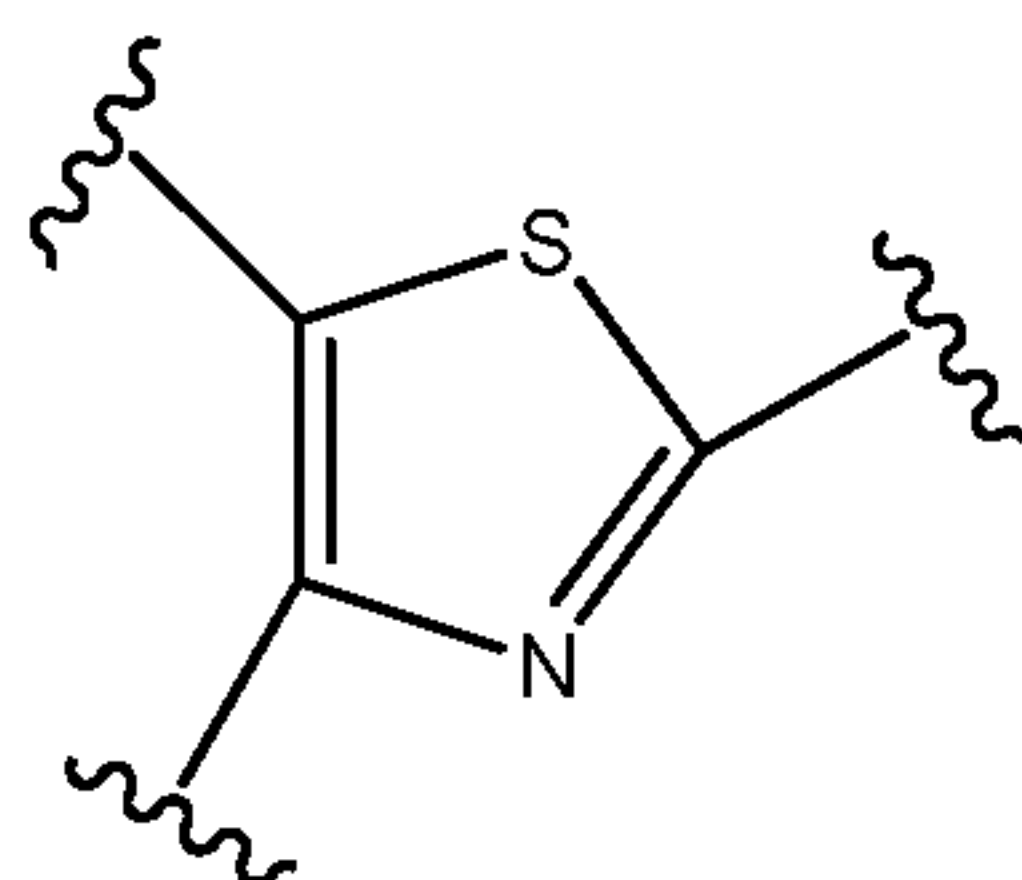


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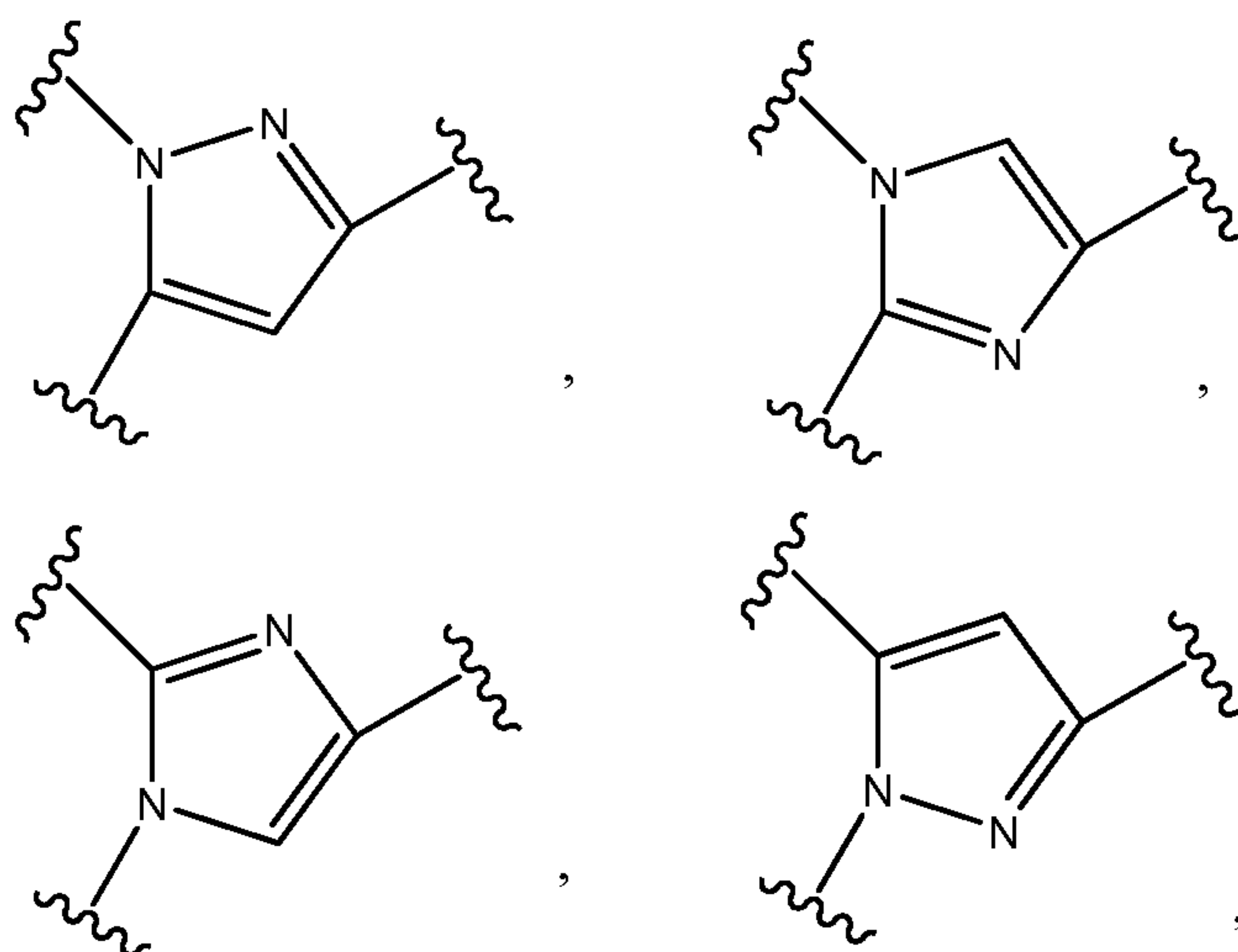
In one embodiment, in compounds represented by formula (IA), (I), or (X), the ring containing X_2 , X_3 and X_4 is:



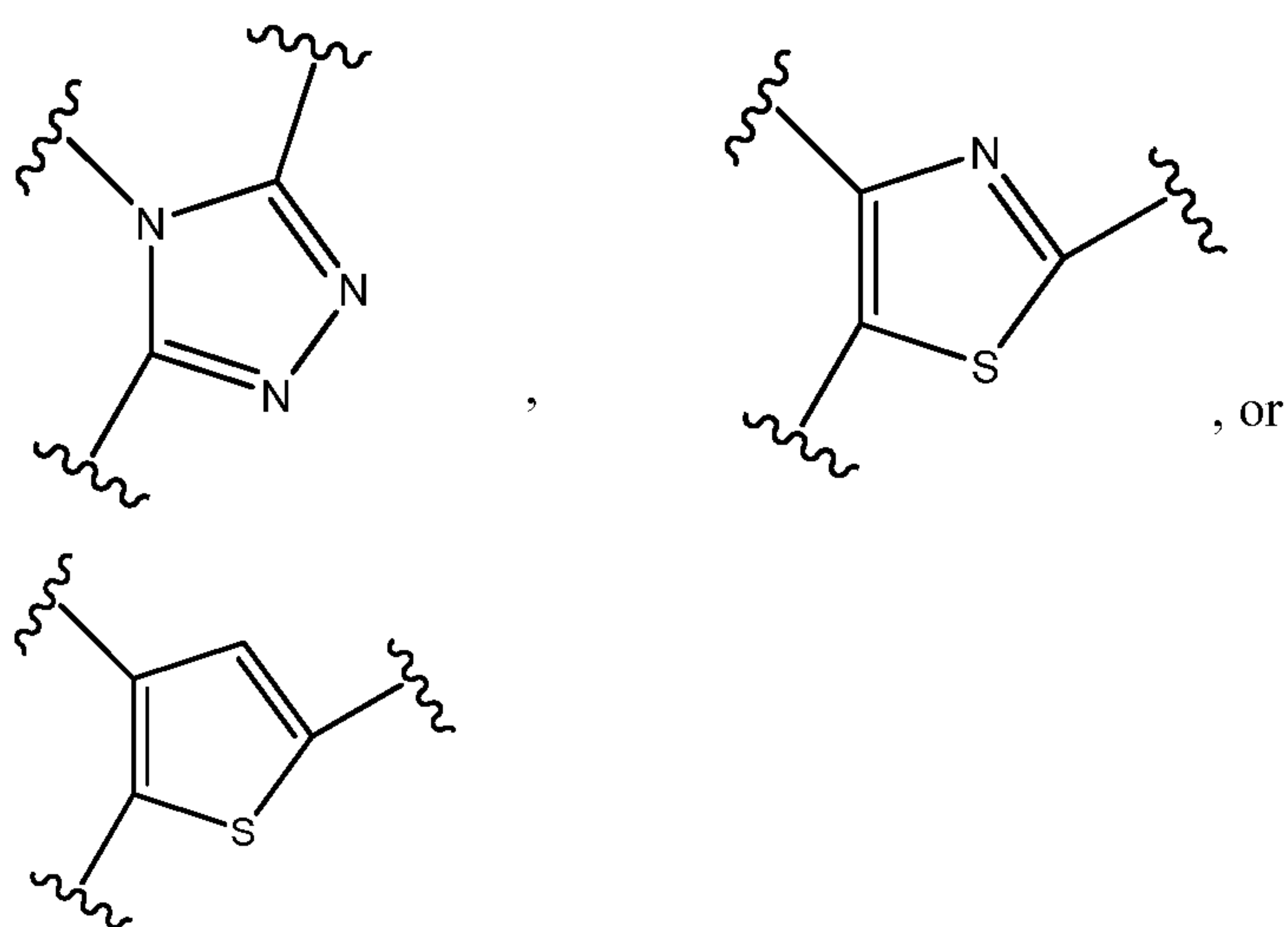
5 In one embodiment, in compounds represented by formula (IA), (I), or (X), the ring containing X_2 , X_3 and X_4 is:



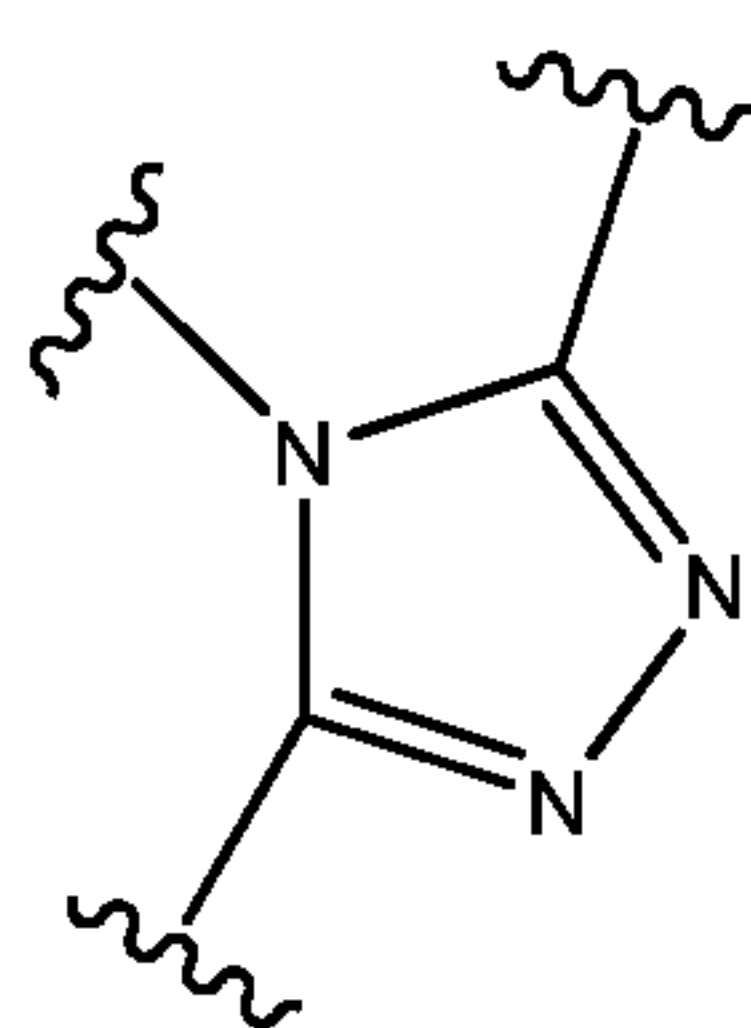
In one embodiment, in compounds represented by formula (IA) or (X), the ring containing X_2 , X_3 and X_4 is:



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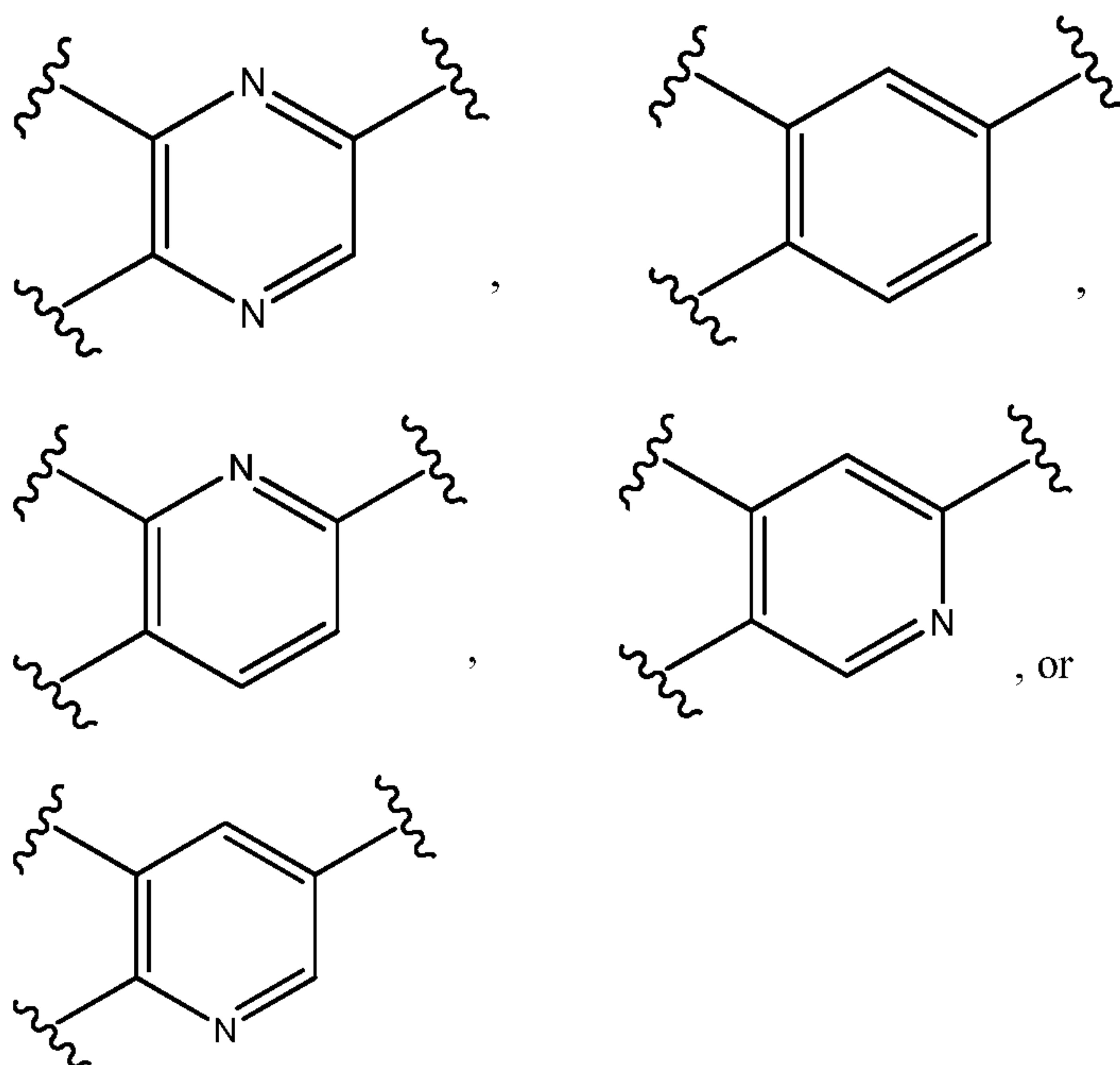


In one aspect, the ring containing X_2 , X_3 and X_4 is



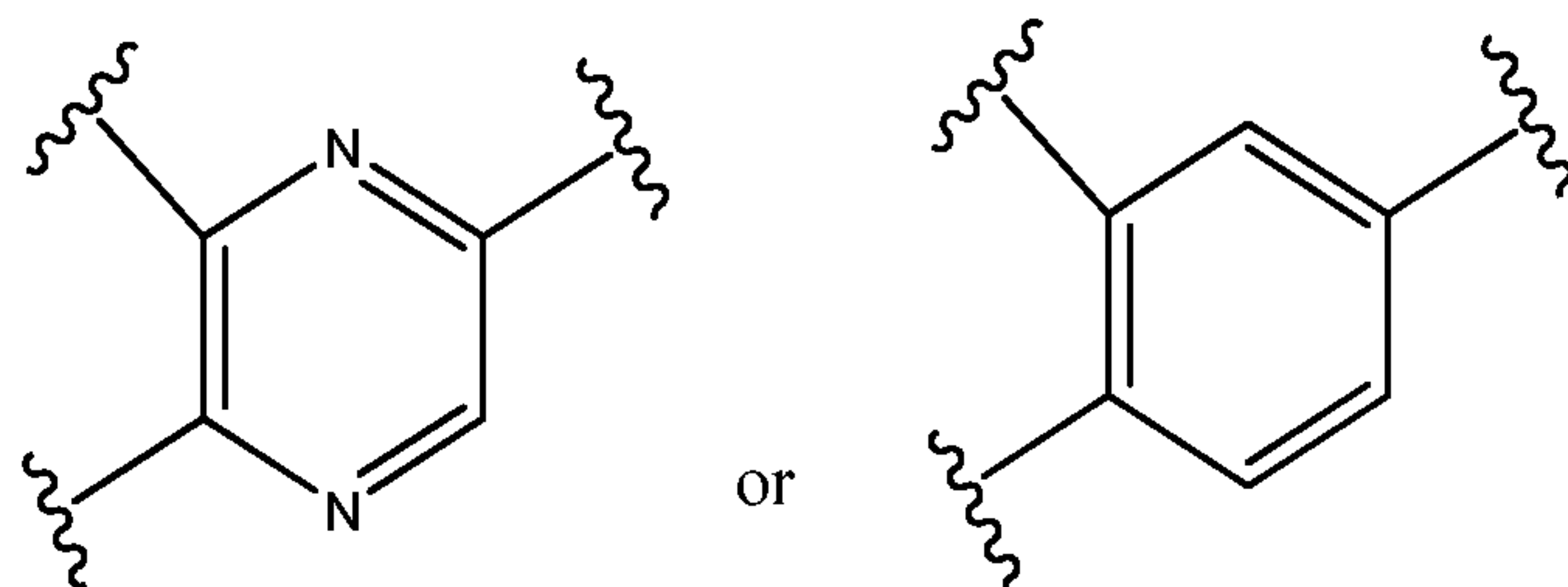
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In one embodiment, in compounds represented by formula (VI) or (XVII), the ring containing X_5 , X_6 , X_7 , and X_8 is:



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In one embodiment, in compounds represented by formula (VI) or (XVII), the ring containing X_5 , X_6 , X_7 , and X_8 is:



In one embodiment, in compounds represented by formula (XX) or (XXI), Y' is an optionally substituted C3-C5 alkyl or an optionally substituted C3-C6 cycloalkyl. In one aspect, Y' is an optionally substituted C3-C5 alkyl. In one aspect, Y' is an optionally substituted C3-C6 cycloalkyl.

In one embodiment, in compounds represented by formula (XX) or (XXI), Y' is an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl. In one aspect, Y' is an optionally substituted 5 or 6-membered aryl. In another aspect, Y' is an optionally substituted 5 or 6-membered heteroaryl. In one aspect, Y' is an optionally substituted phenyl or an optionally substituted pyridyl. In one aspect, the Y' is a 2,6-substituted phenyl. In one aspect, the substituent is selected from the group consisting of halo or lower alkyl.

In one embodiment, in compounds represented by formula (XX) or (XXI), Ring K is bonded to its substituent through a C-C bond.

In one embodiment, in compounds represented by formula (XXI), Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thienyl or a monosubstituted pyridyl.

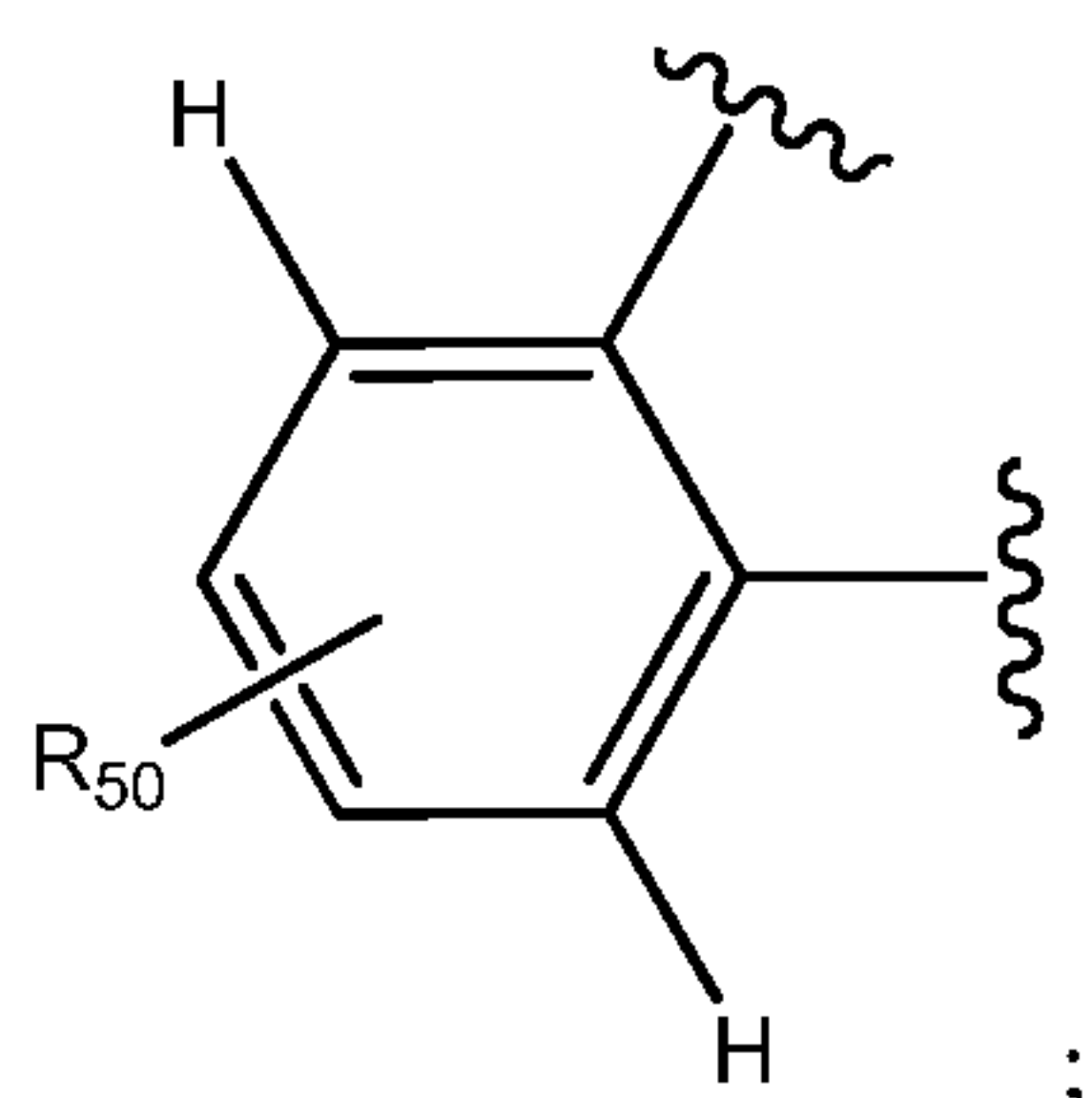
In one embodiment, in compounds represented by formula (XX) or (XXI), where Ring K is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that is less than 5 atoms long, the 5 or 6-membered heteroaromatic ring is selected from the group consisting of pyridine, pyrazole, oxazole, thiazole, imidazole, or tetrazole. In one aspect, the 5-membered heteroaromatic ring has a substituent selected from methyl or ethyl.

In one embodiment, in compounds represented by formula (XX) or (XXI), where Ring K is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, the 5 or 6-membered heteroaromatic ring is selected from the group consisting of pyridine, pyrazole, oxazole,

thiazole, imidazole, or tetrazole. In one aspect, the 5-membered heteroaromatic ring has a substituent selected from methyl or ethyl.

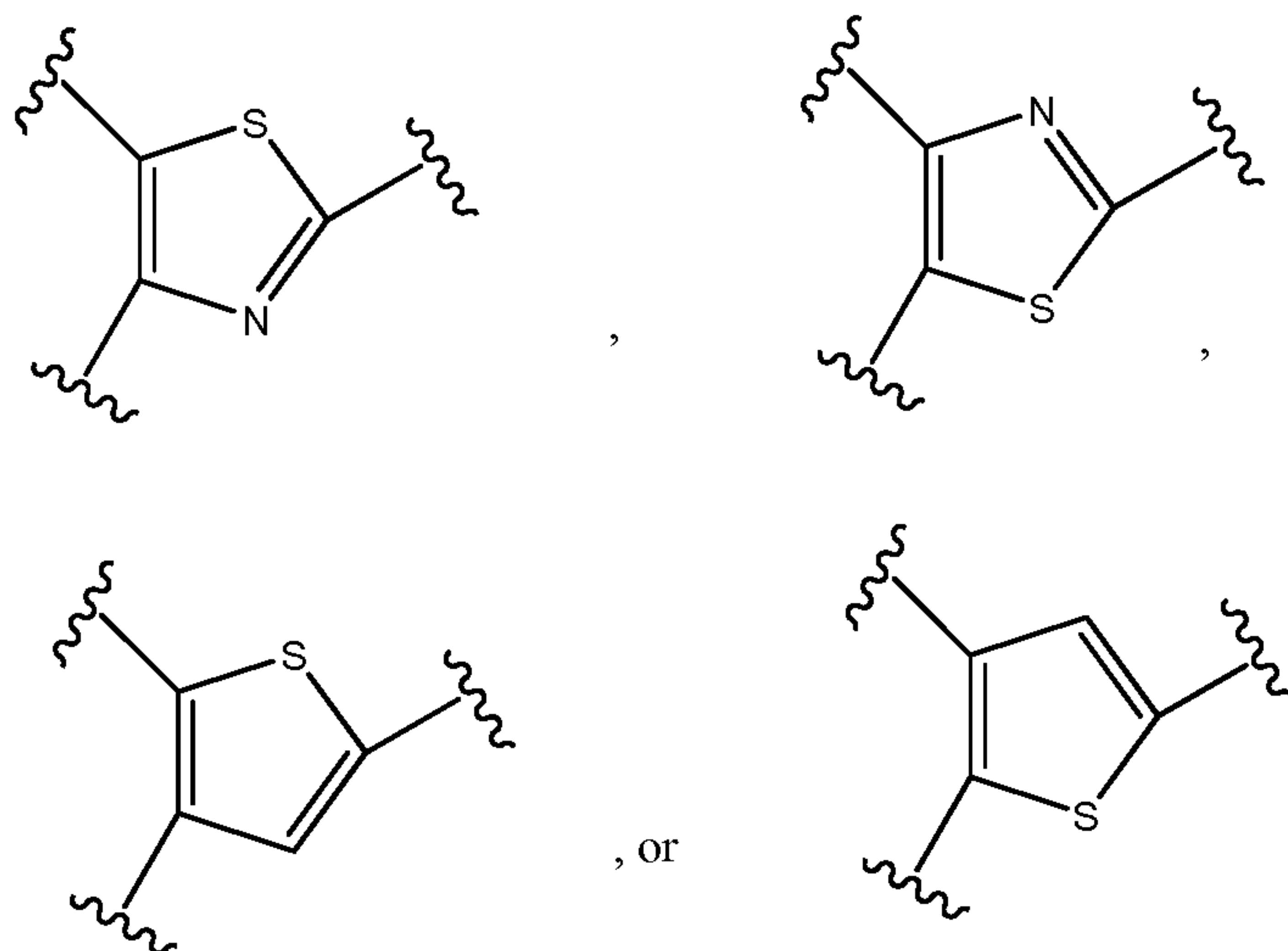
In one embodiment, in compounds represented by formula (XX) or (XXI), where Ring K is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, the substituent is a 5-membered heteroaromatic ring. In one aspect, the 5-membered heteroaromatic ring is selected from the group consisting of pyrazole, oxazole, thiazole, imidazole, or tetrazole. In one aspect, the 5-membered heteroaromatic ring has a substituent selected from methyl or ethyl.

In one embodiment, in compounds represented by formula (XX) or (XXI), Ring K is

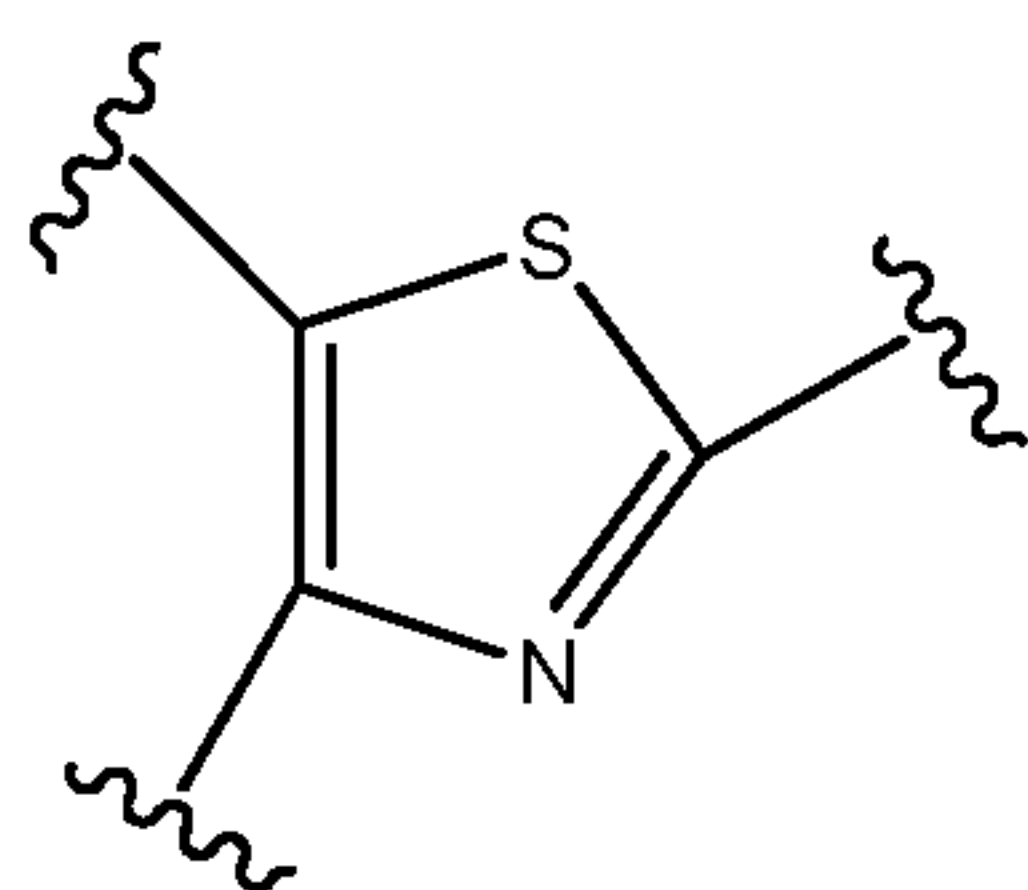


wherein R_{50} is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

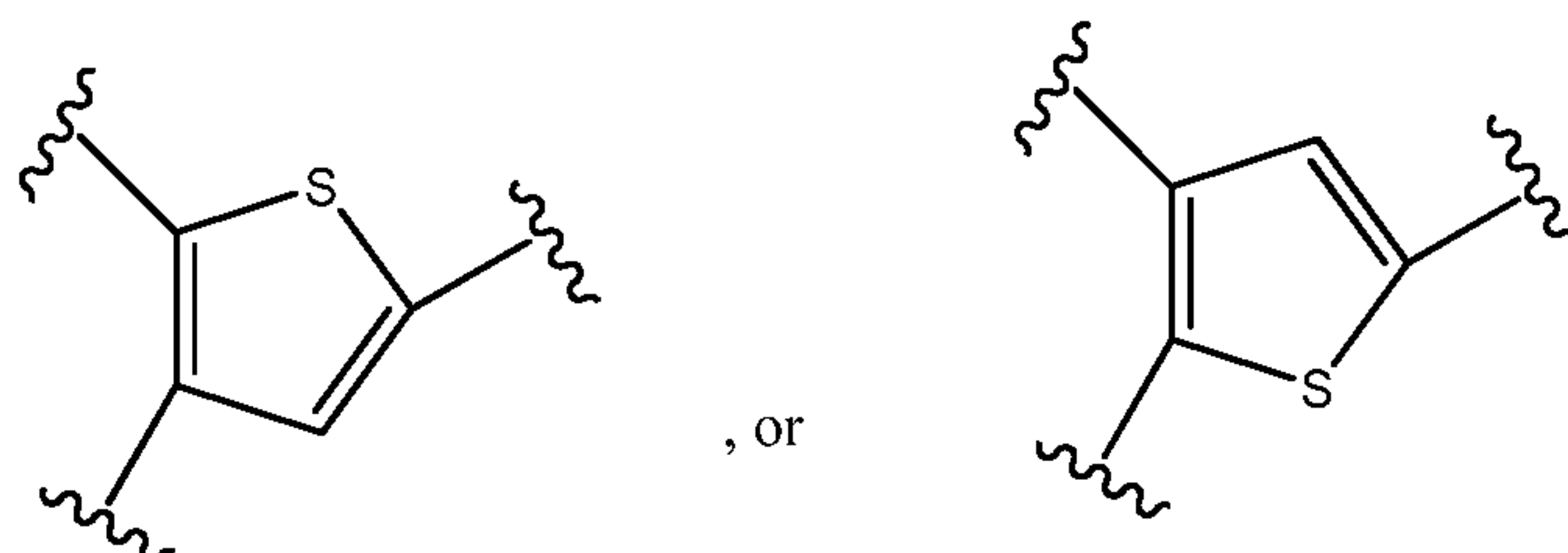
In one embodiment of compounds of formula (XX), Ring M is



In one embodiment, in compounds represented by formula (XX), Ring M is

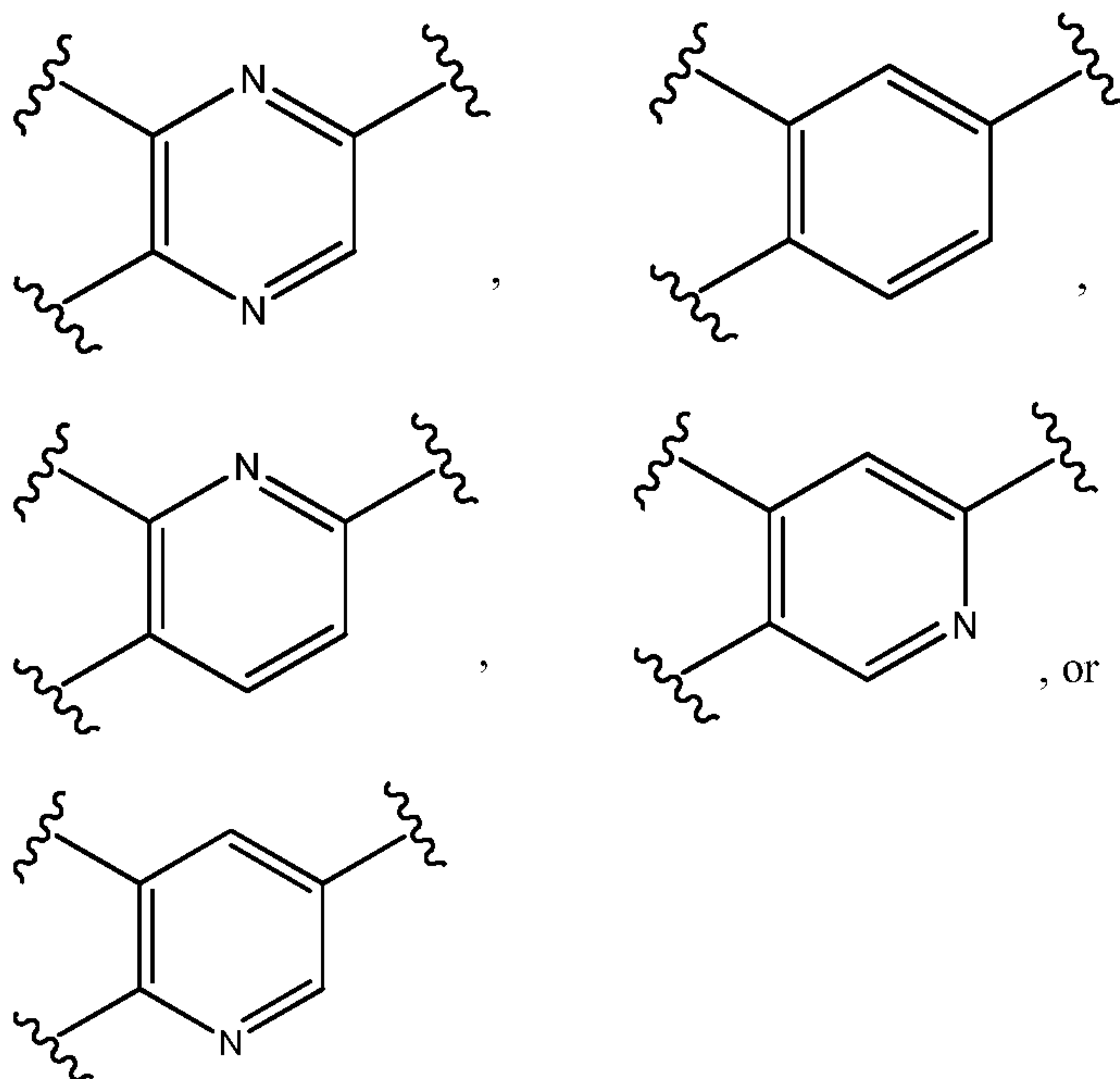


In one embodiment, in compounds represented by formula (XX), Ring M is:

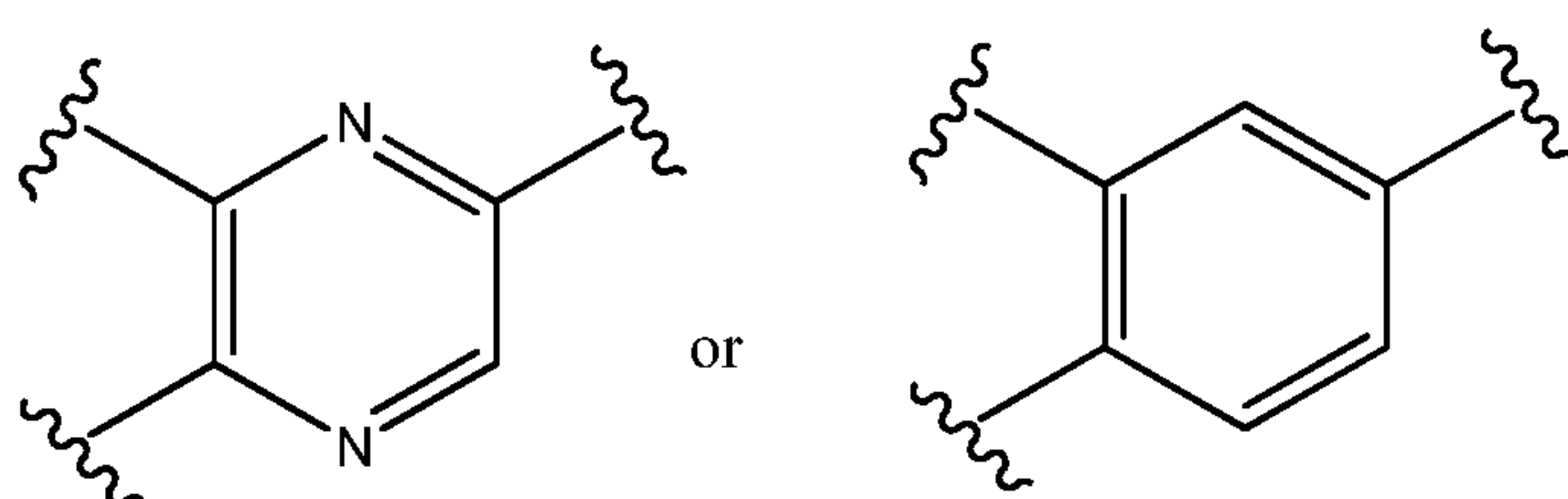


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In one embodiment, in compounds represented by formula (XXI), Ring N is:

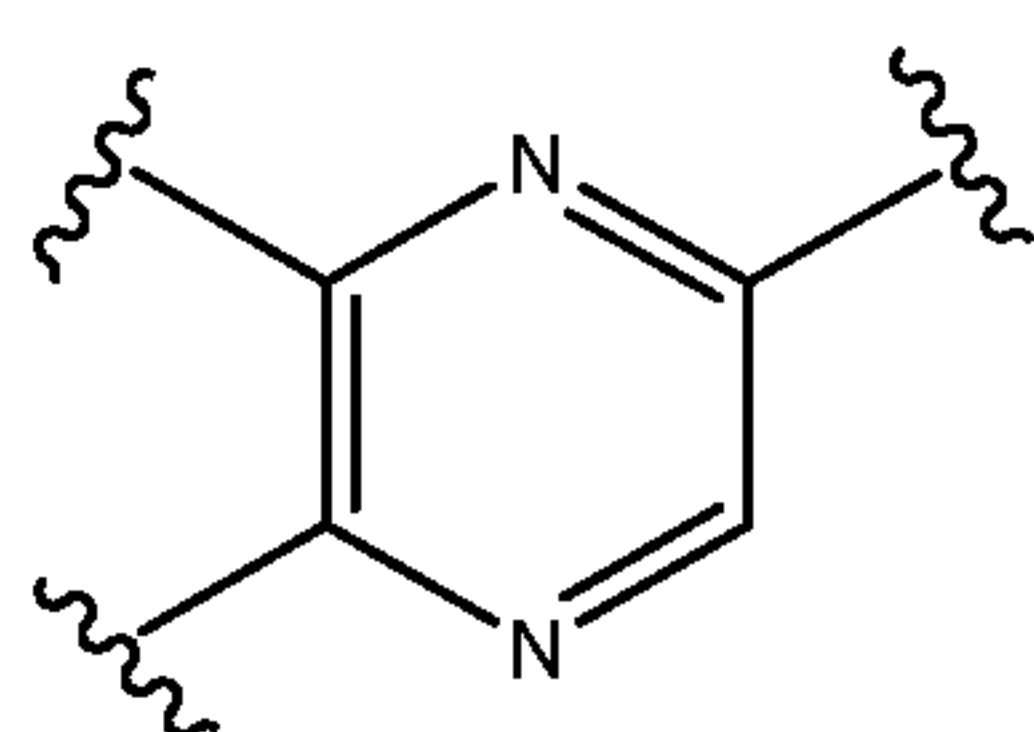


In one embodiment, in compounds represented by formula (XXI), Ring N is:

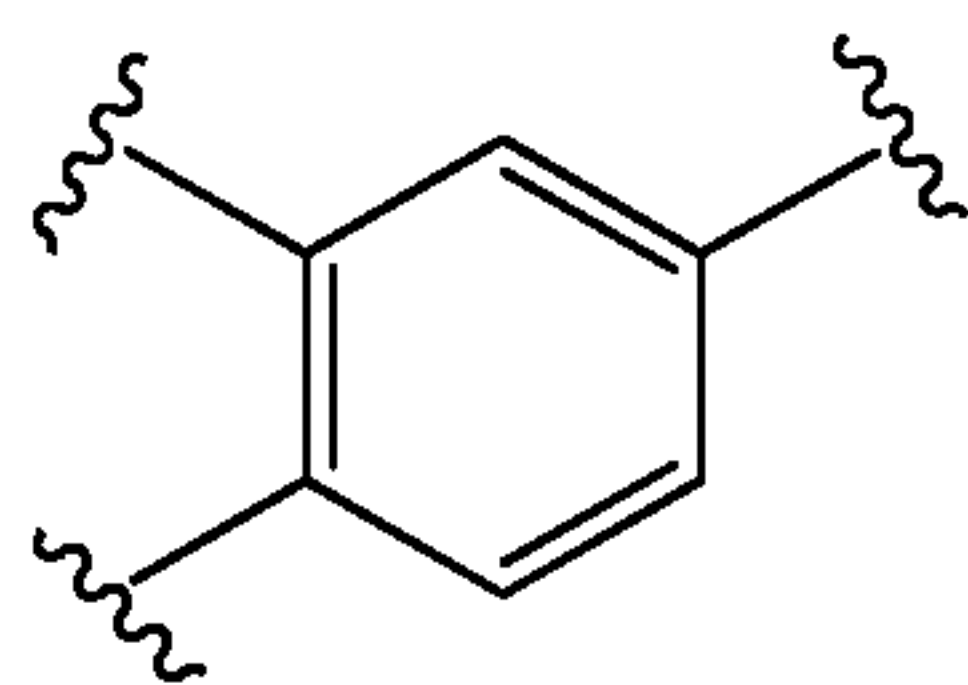


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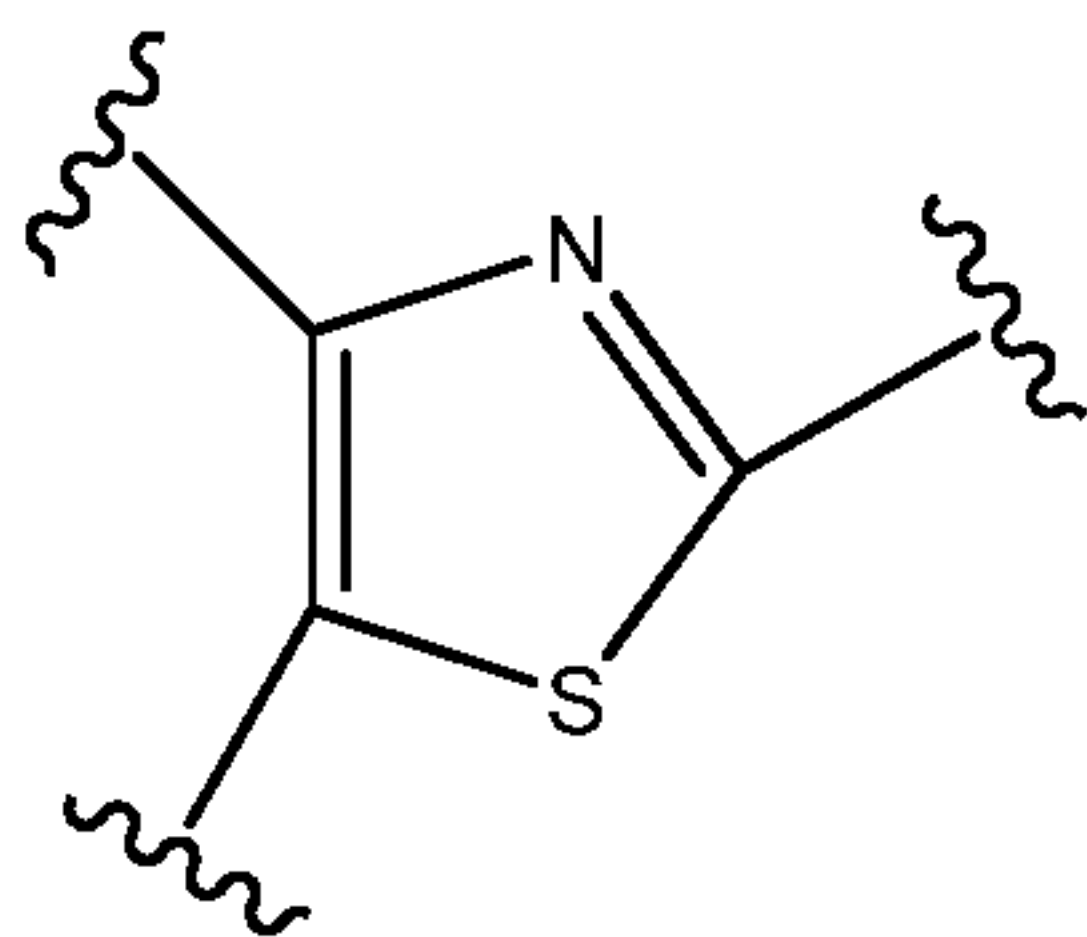
In one aspect, Ring N is



In another aspect, Ring N is



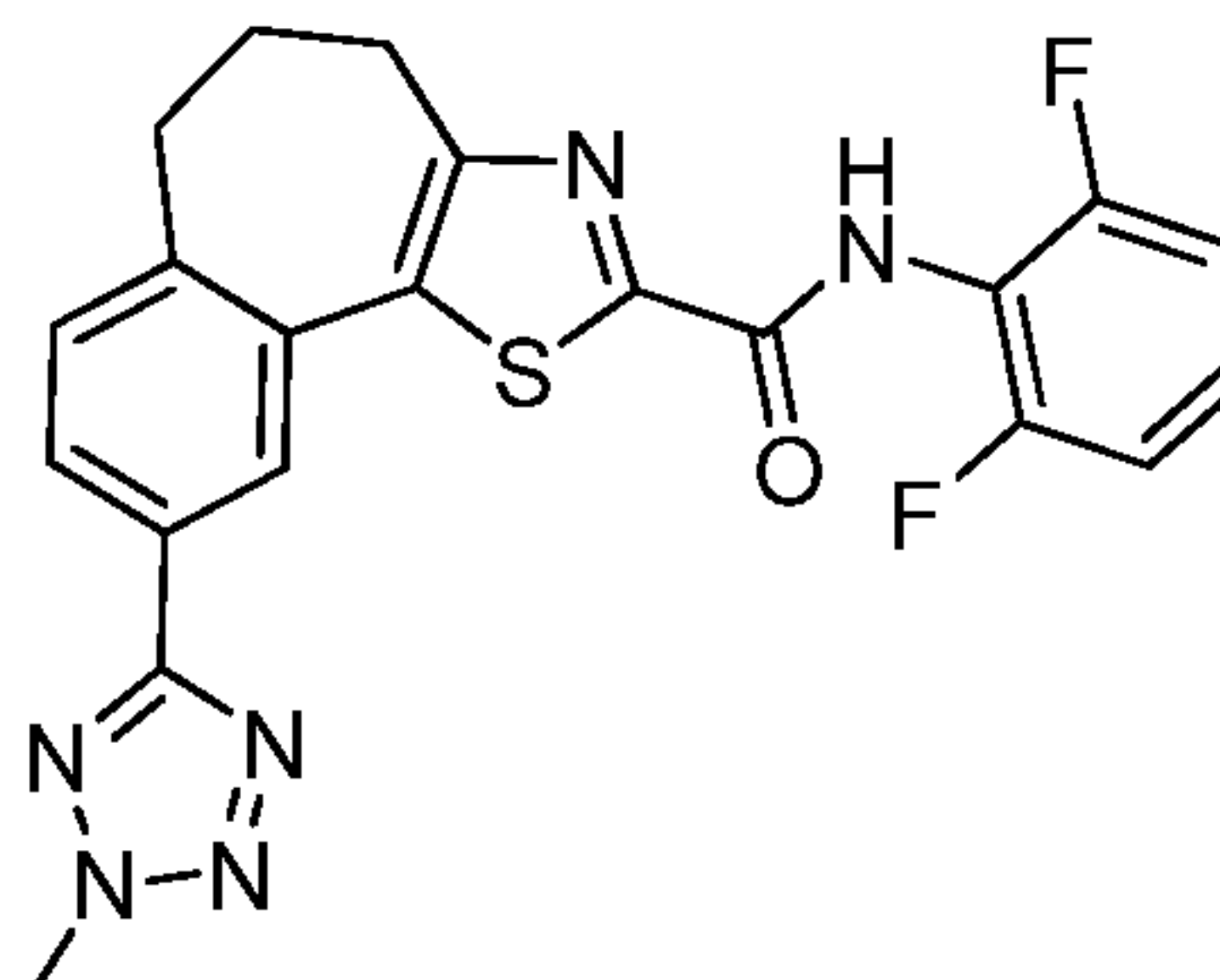
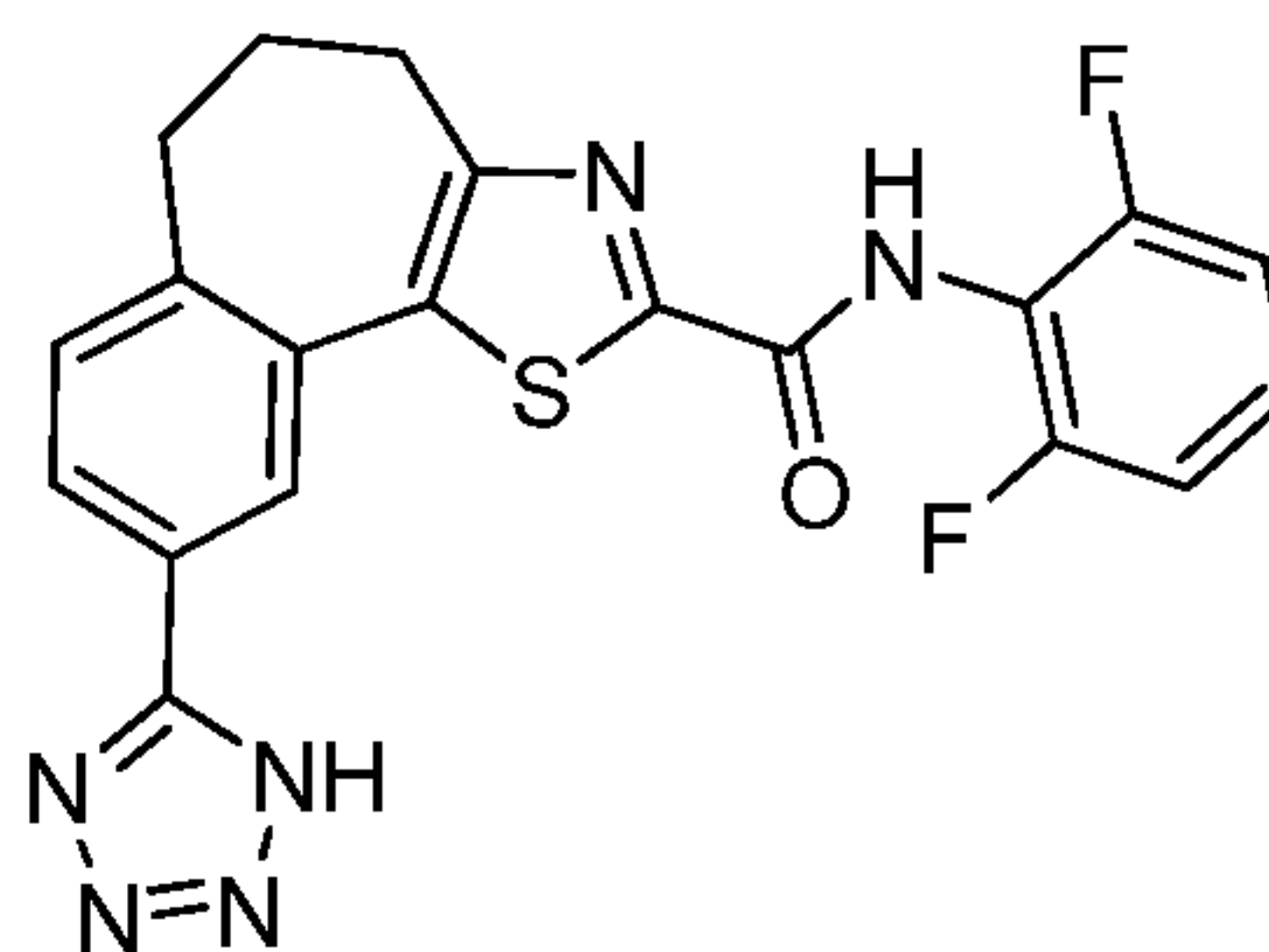
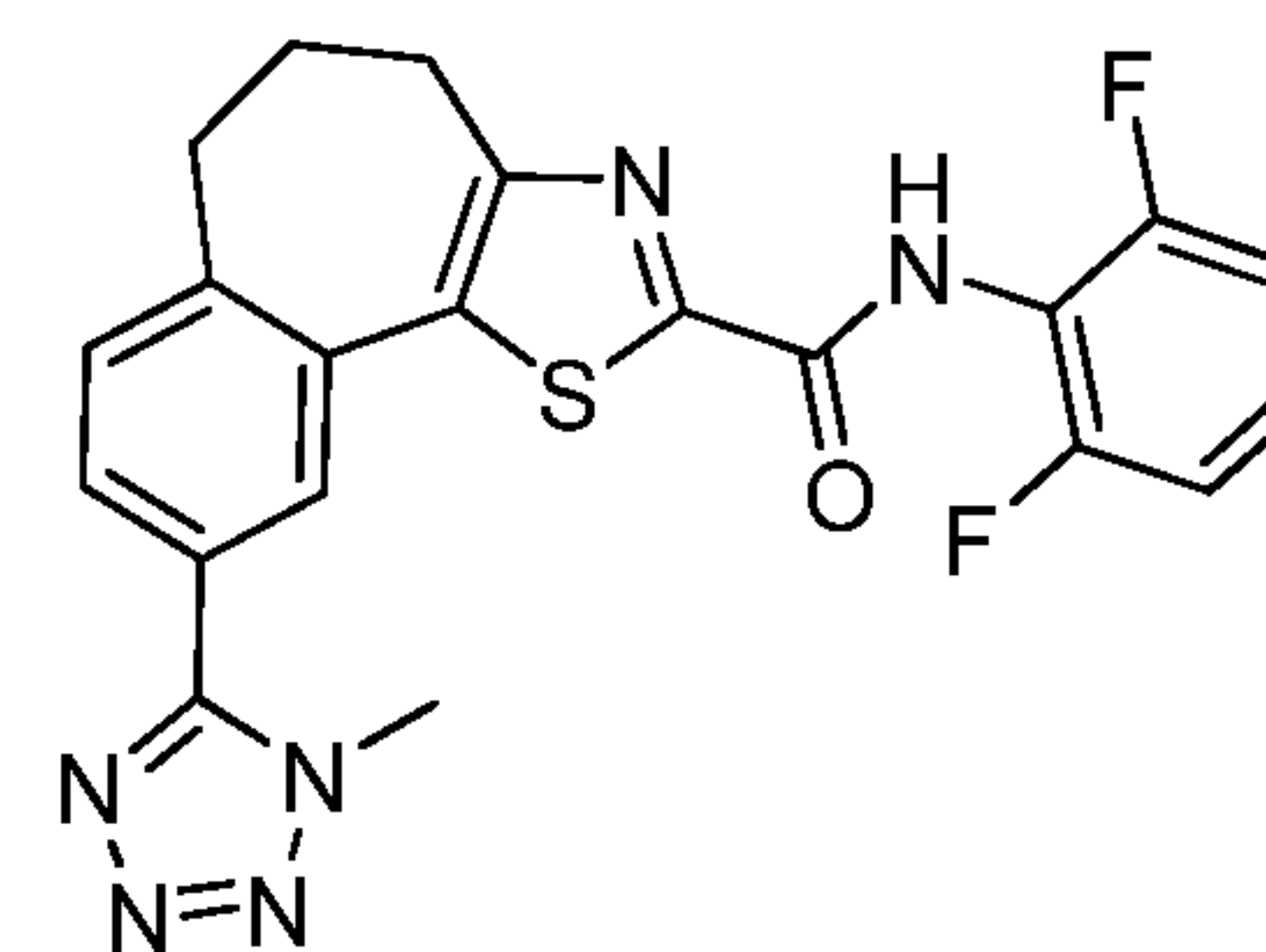
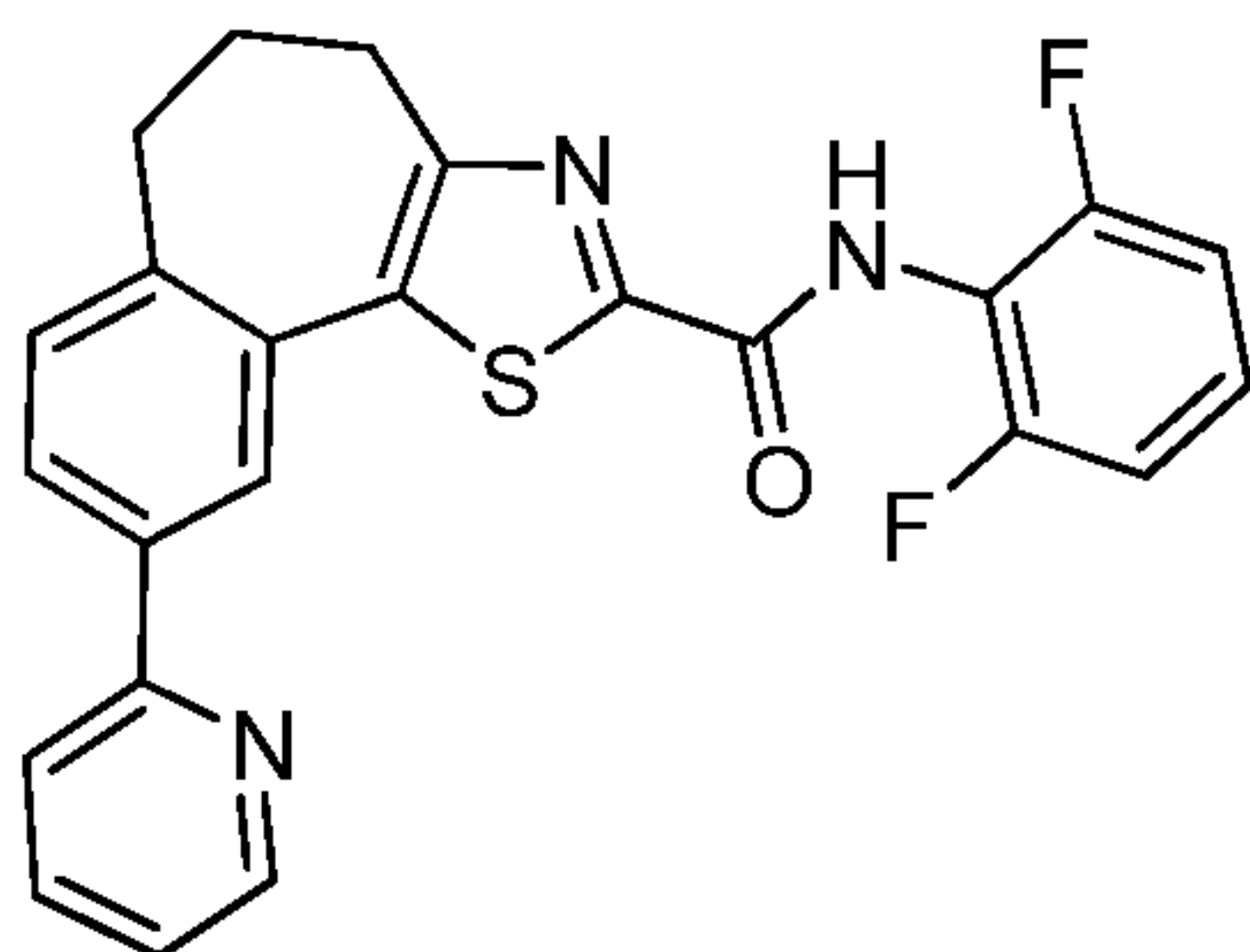
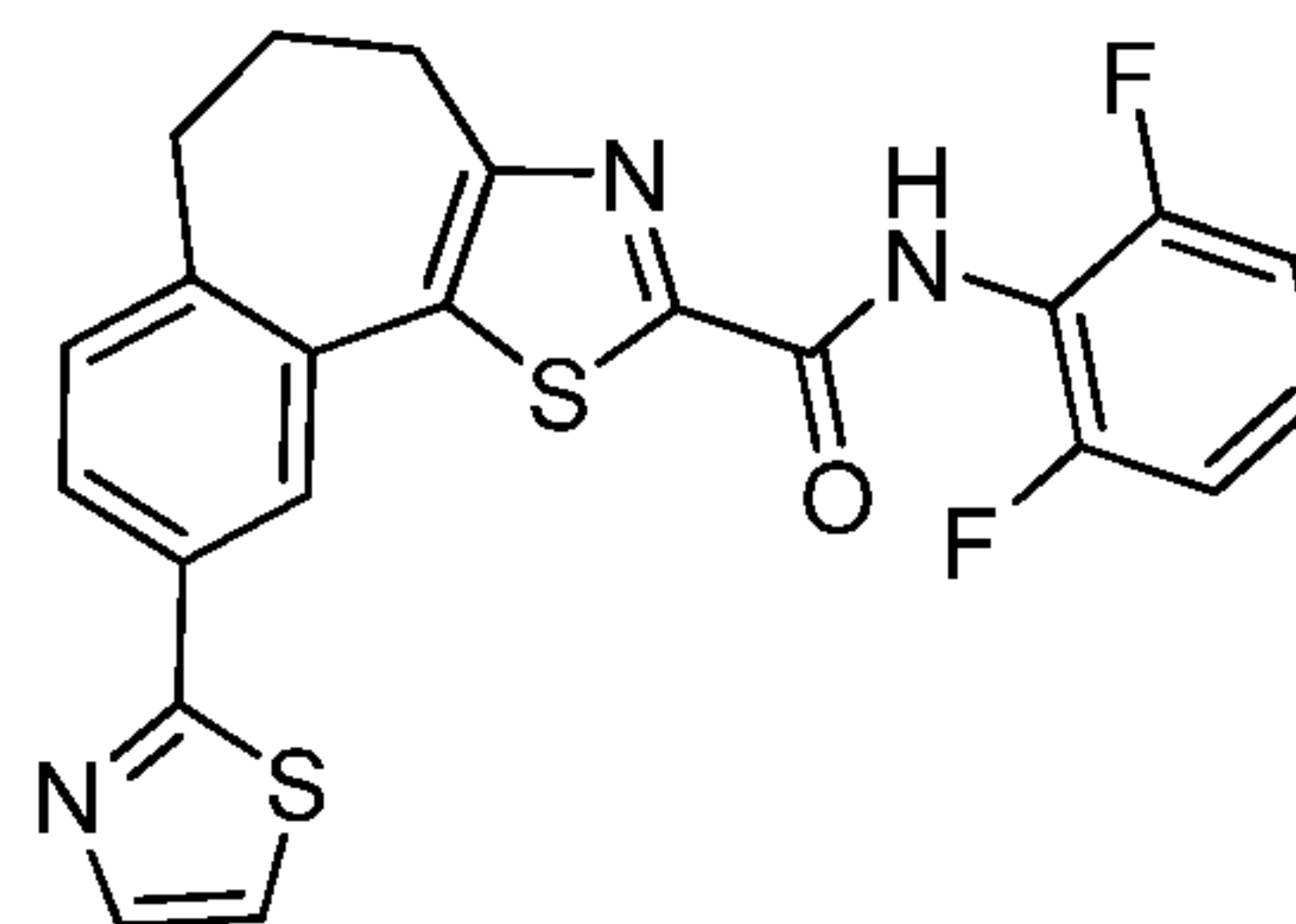
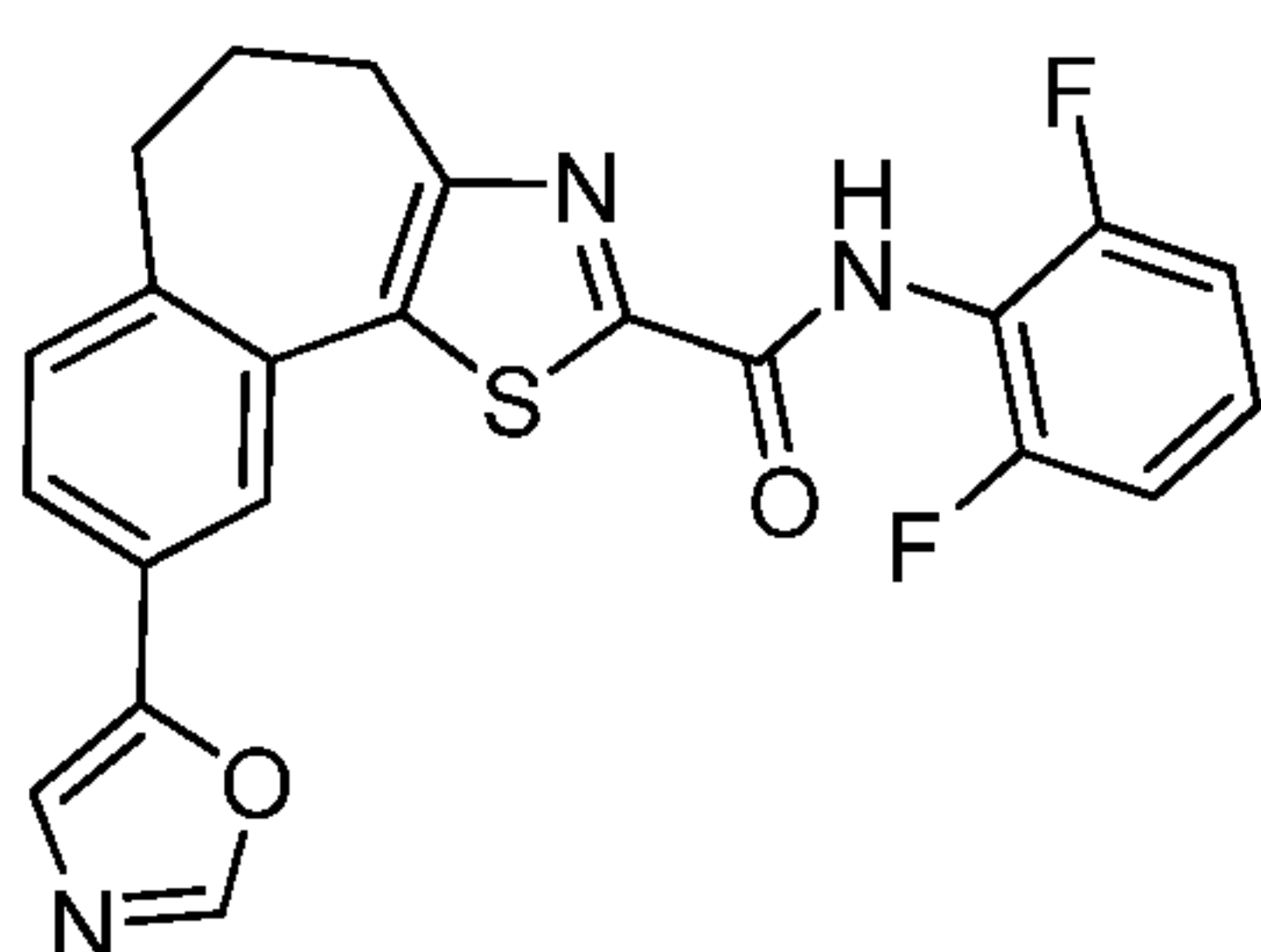
In one embodiment of compounds of formula (XX), Y' is an optionally substituted C3-C5 alkyl or an optionally substituted C3-C6 cycloalkyl and Ring M is:

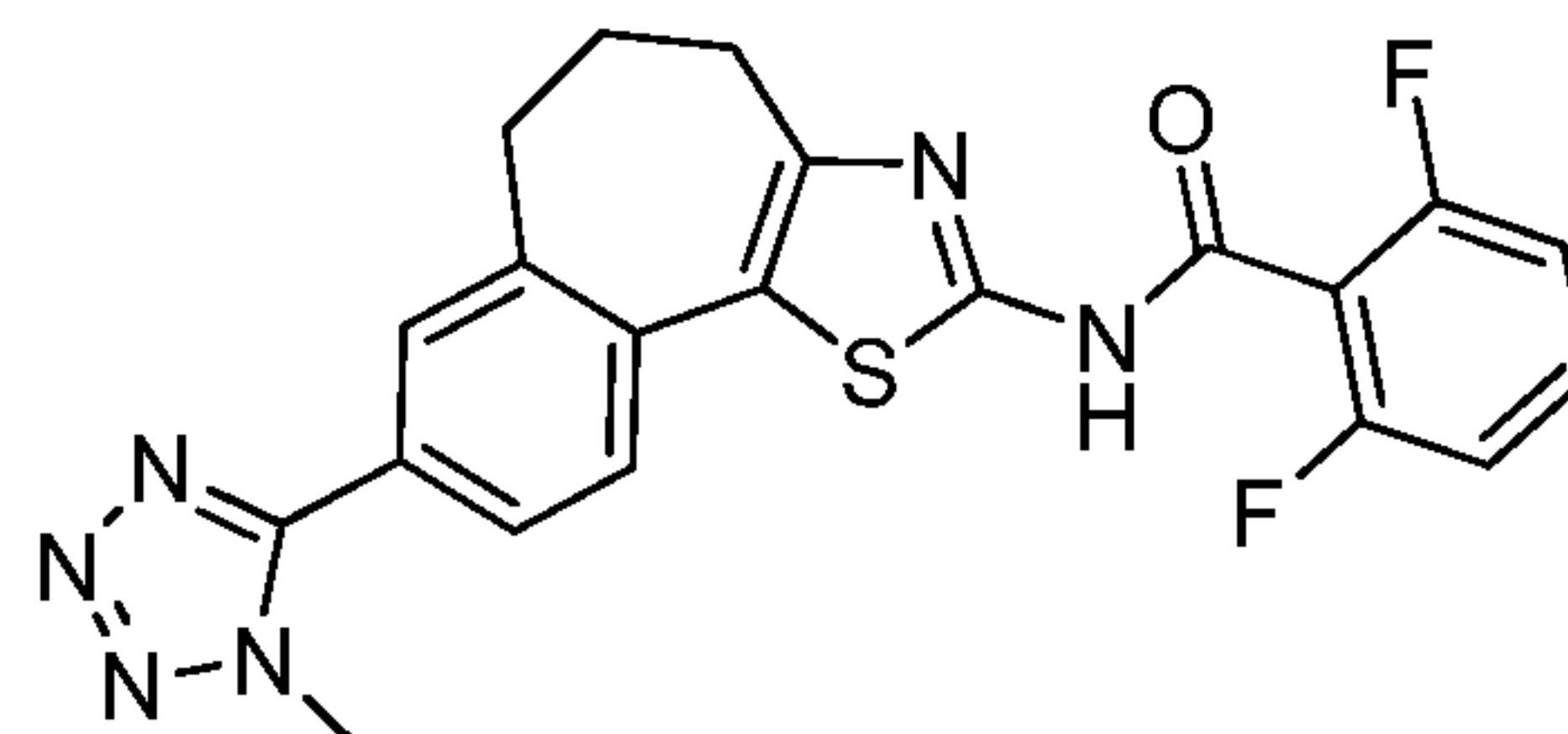
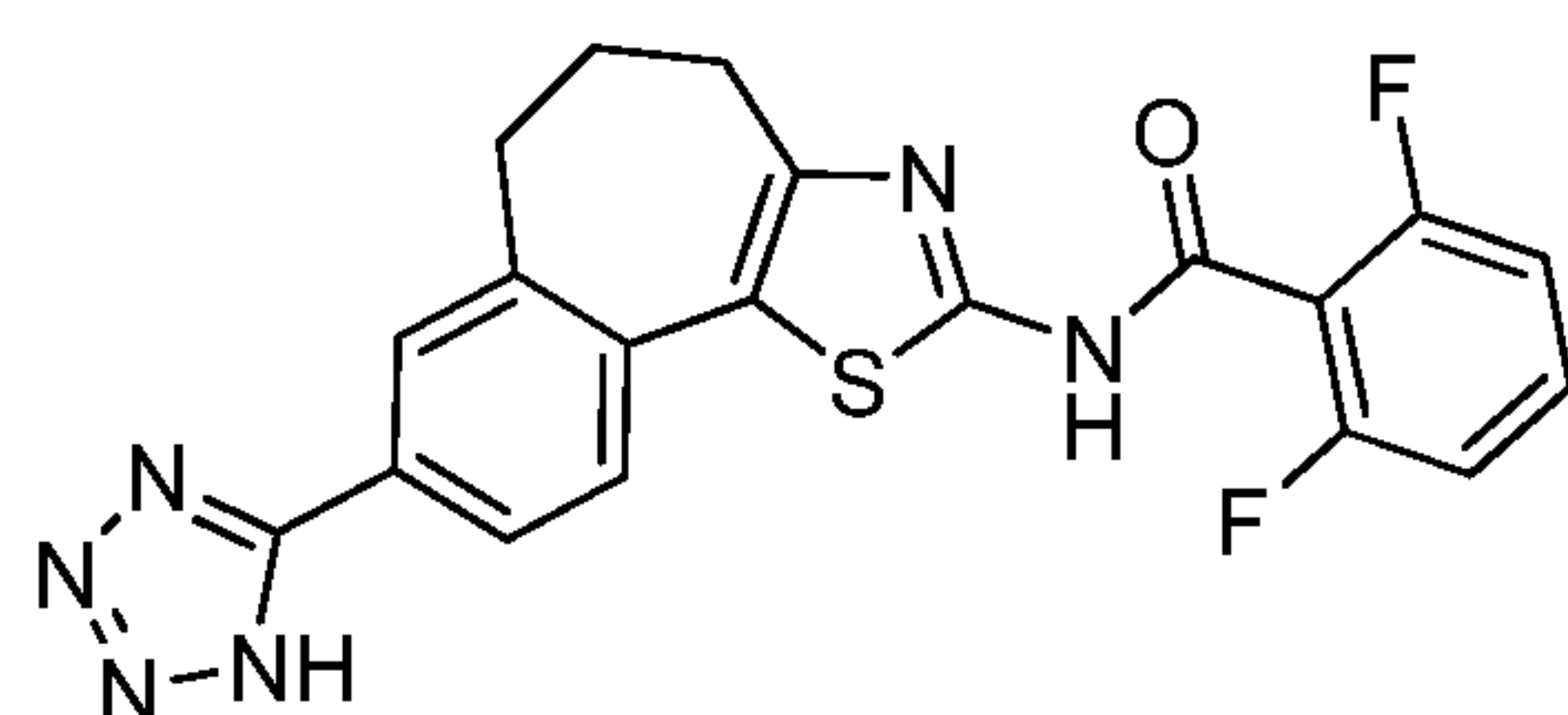
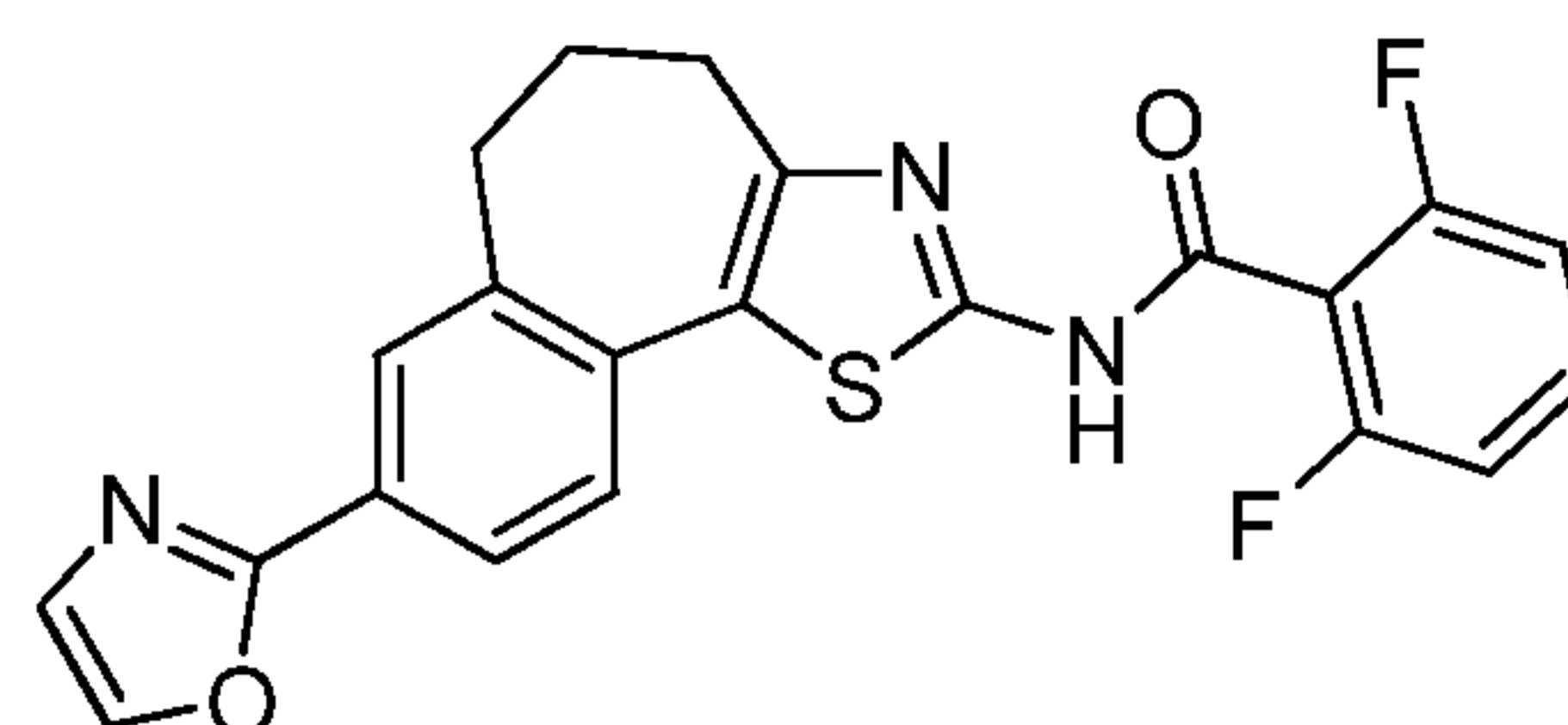
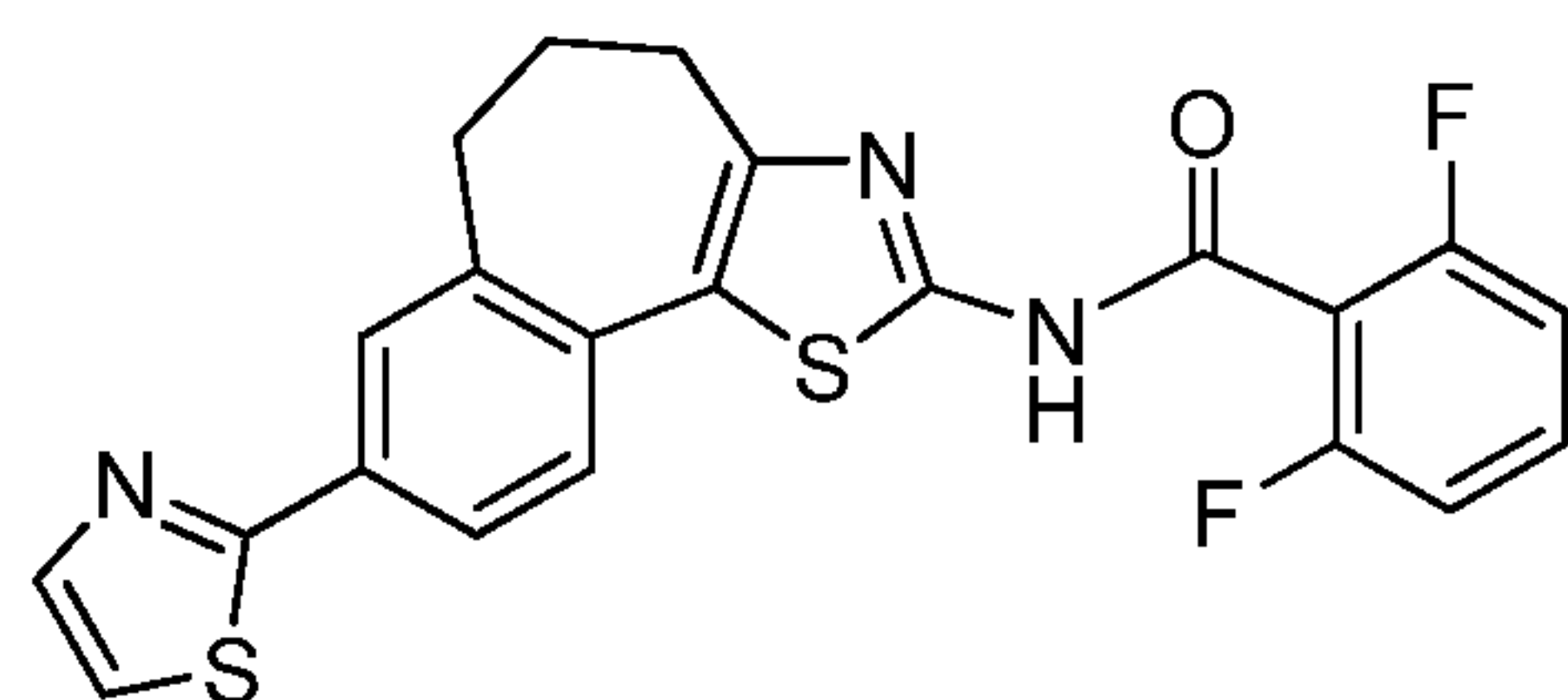
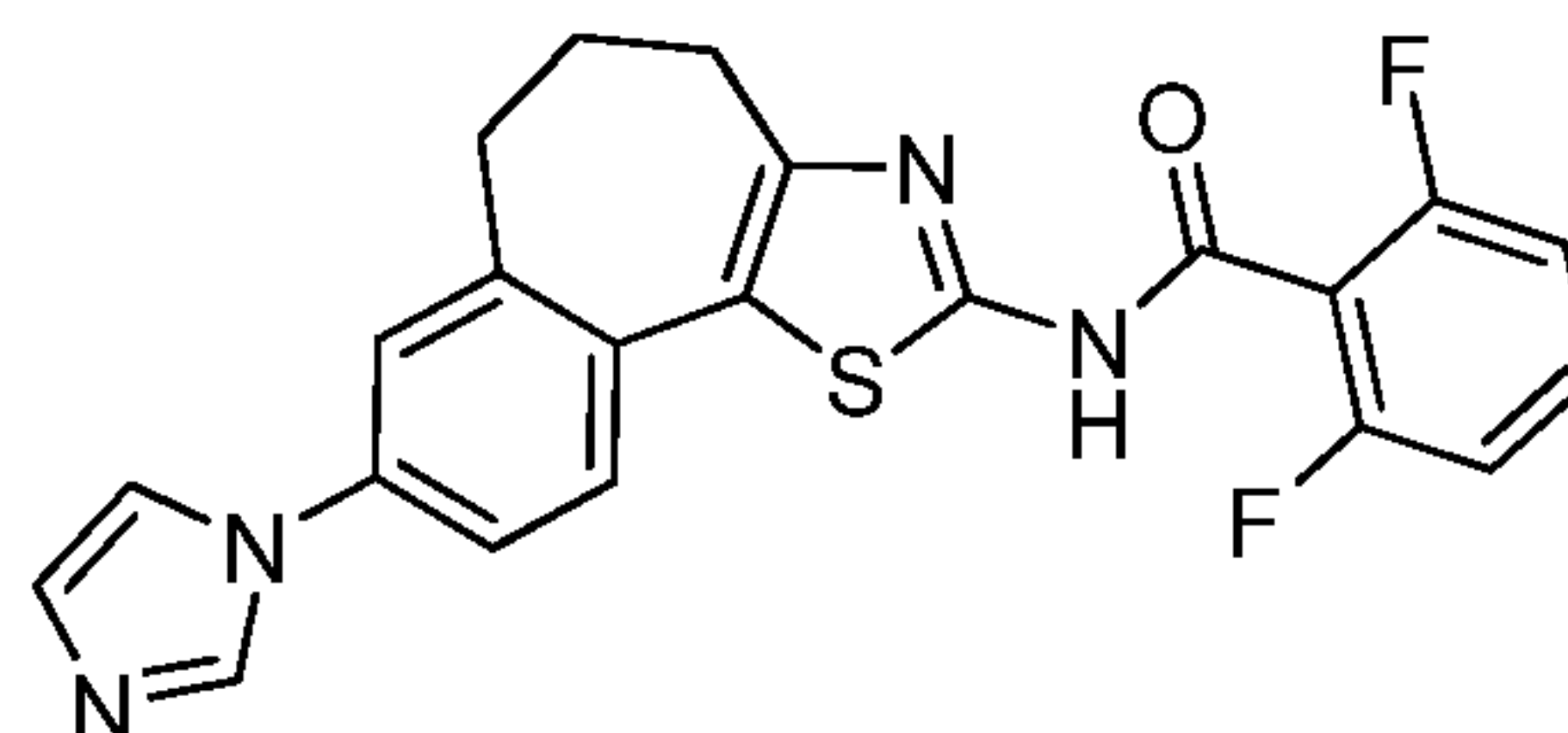
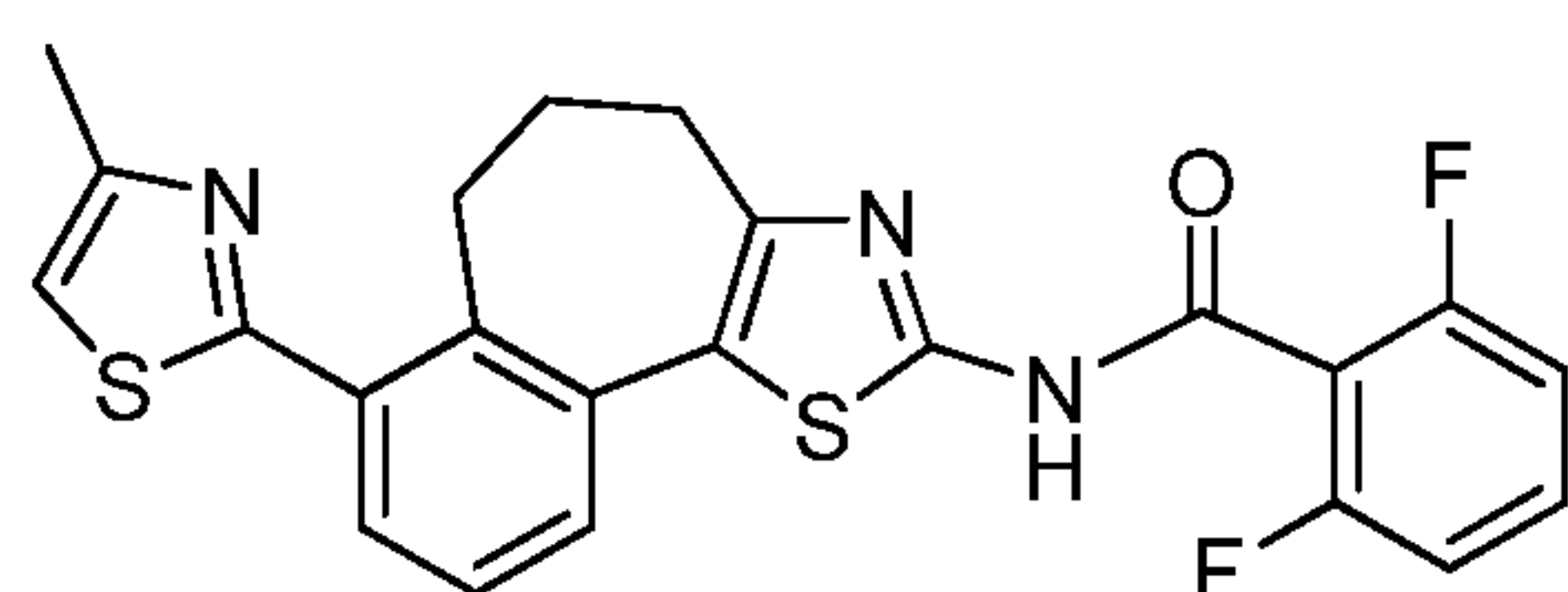
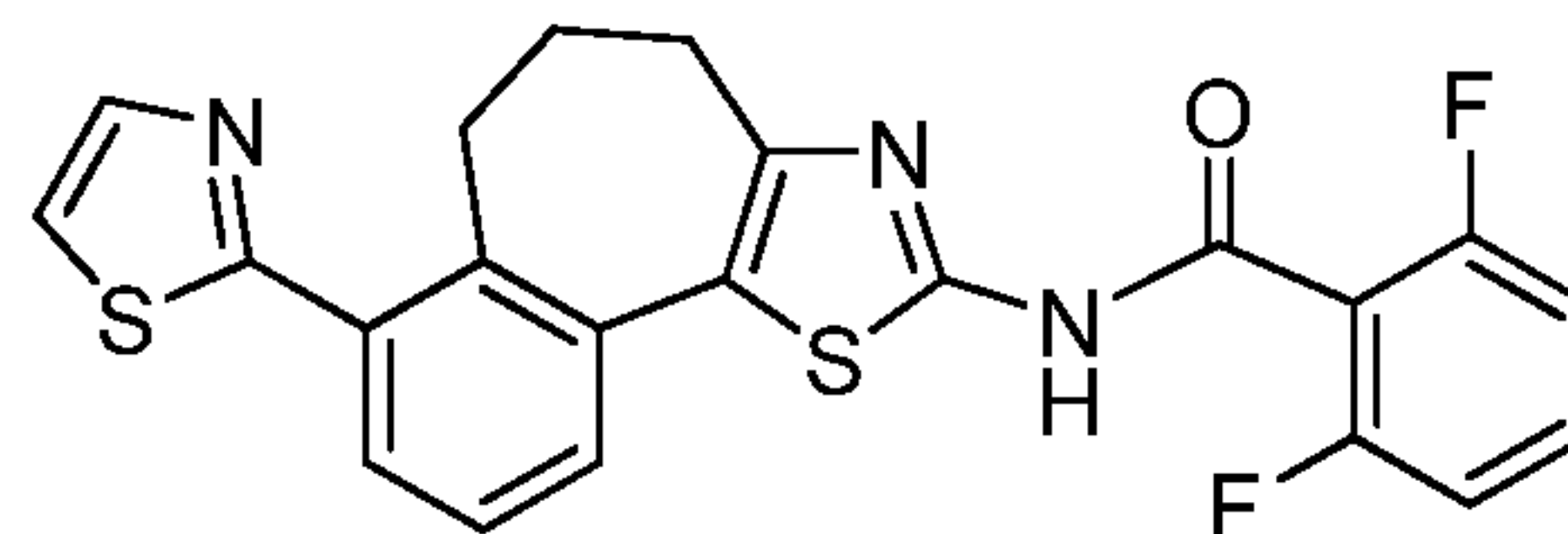
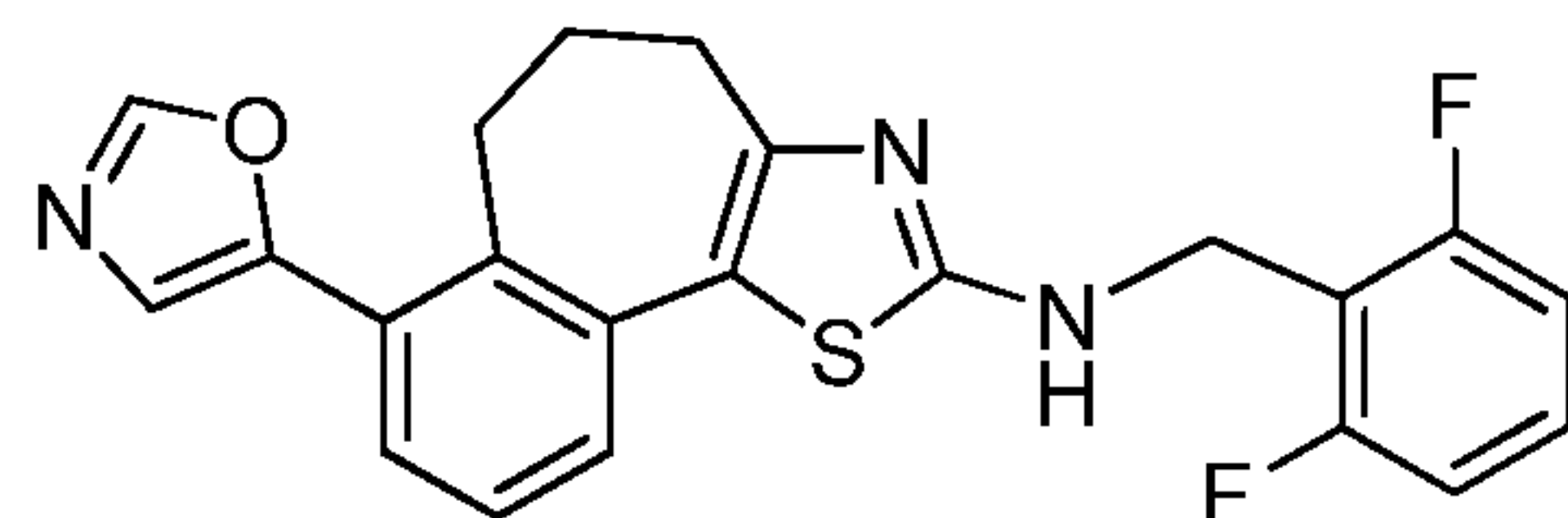
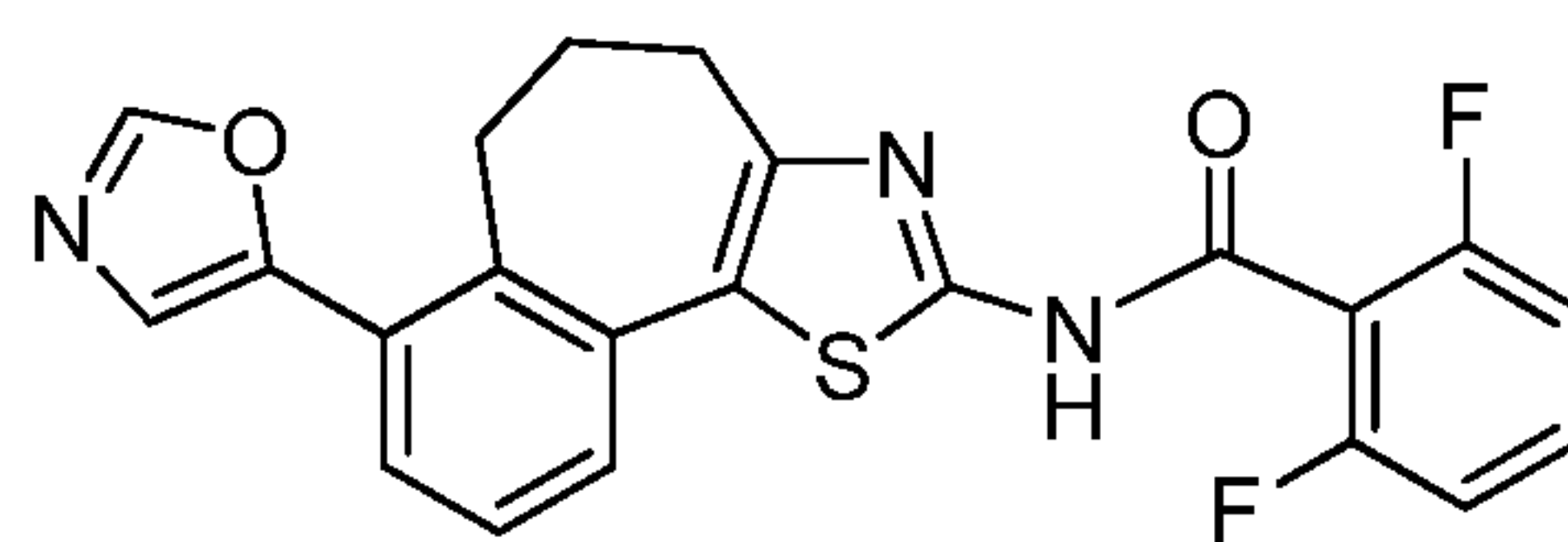
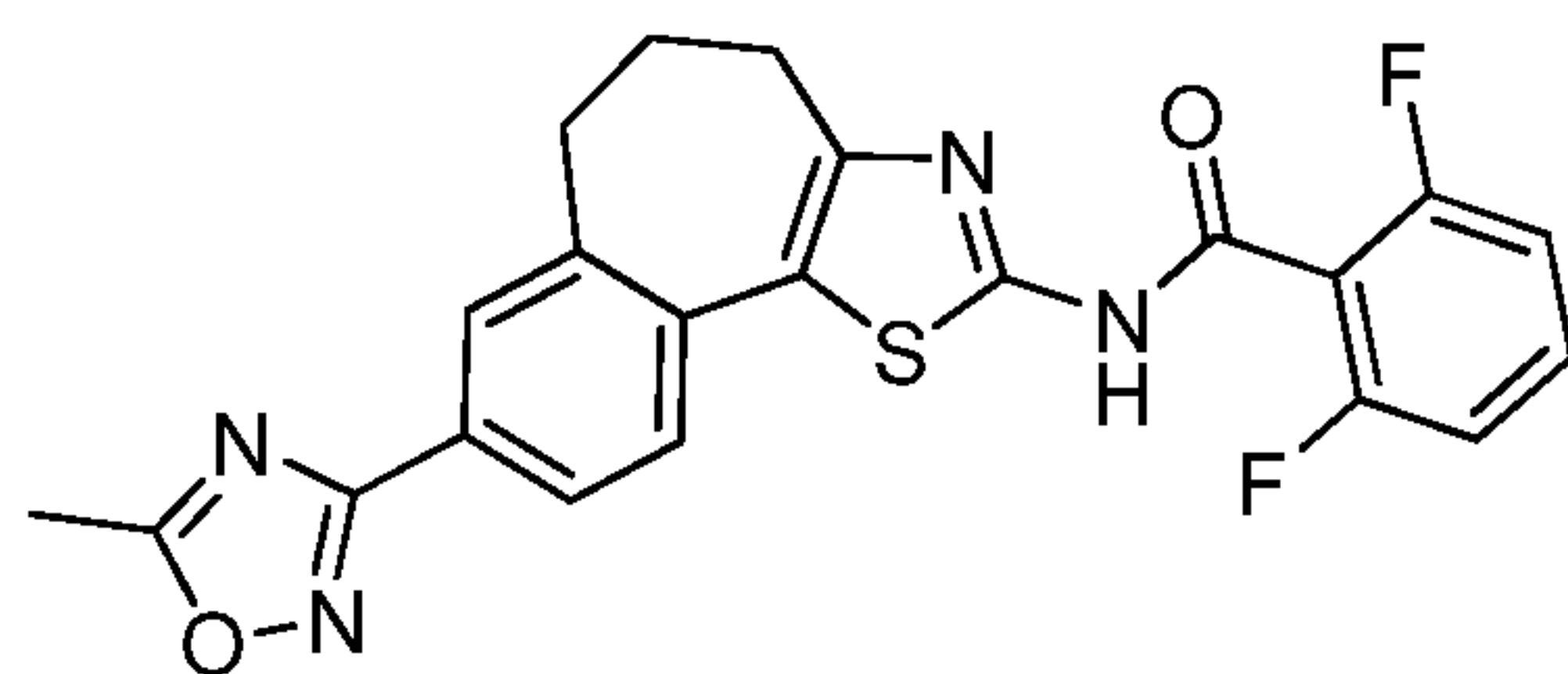


and

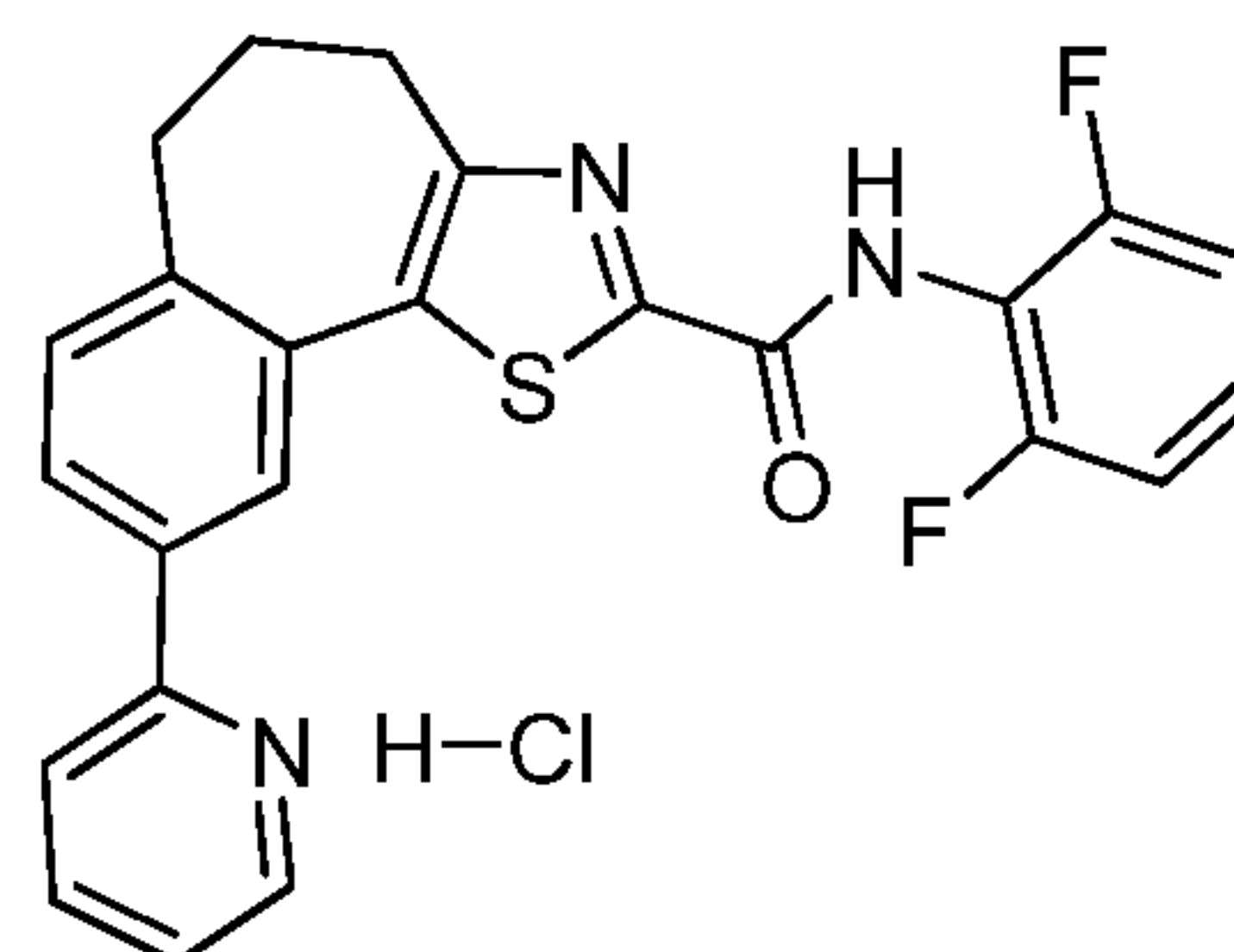
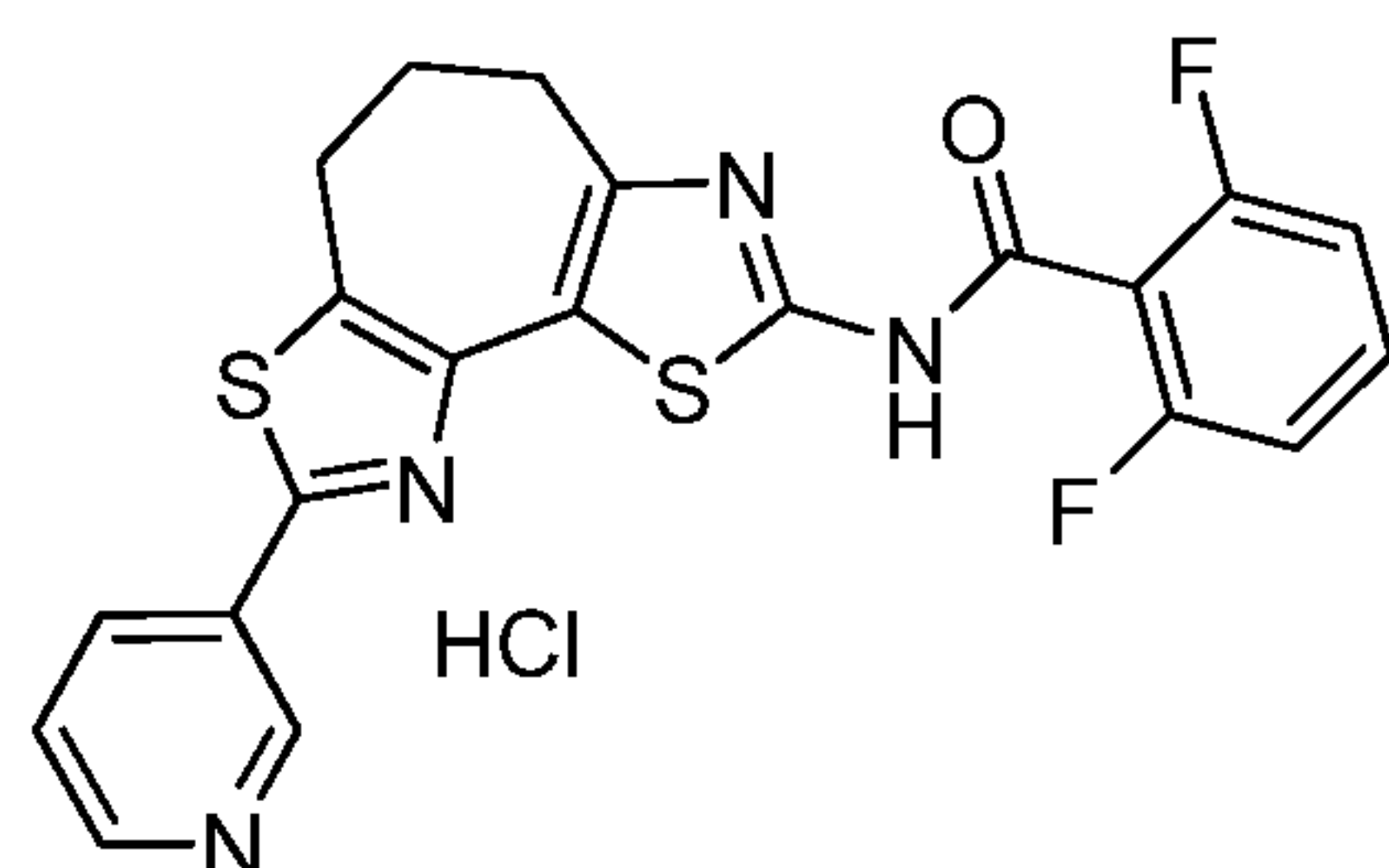
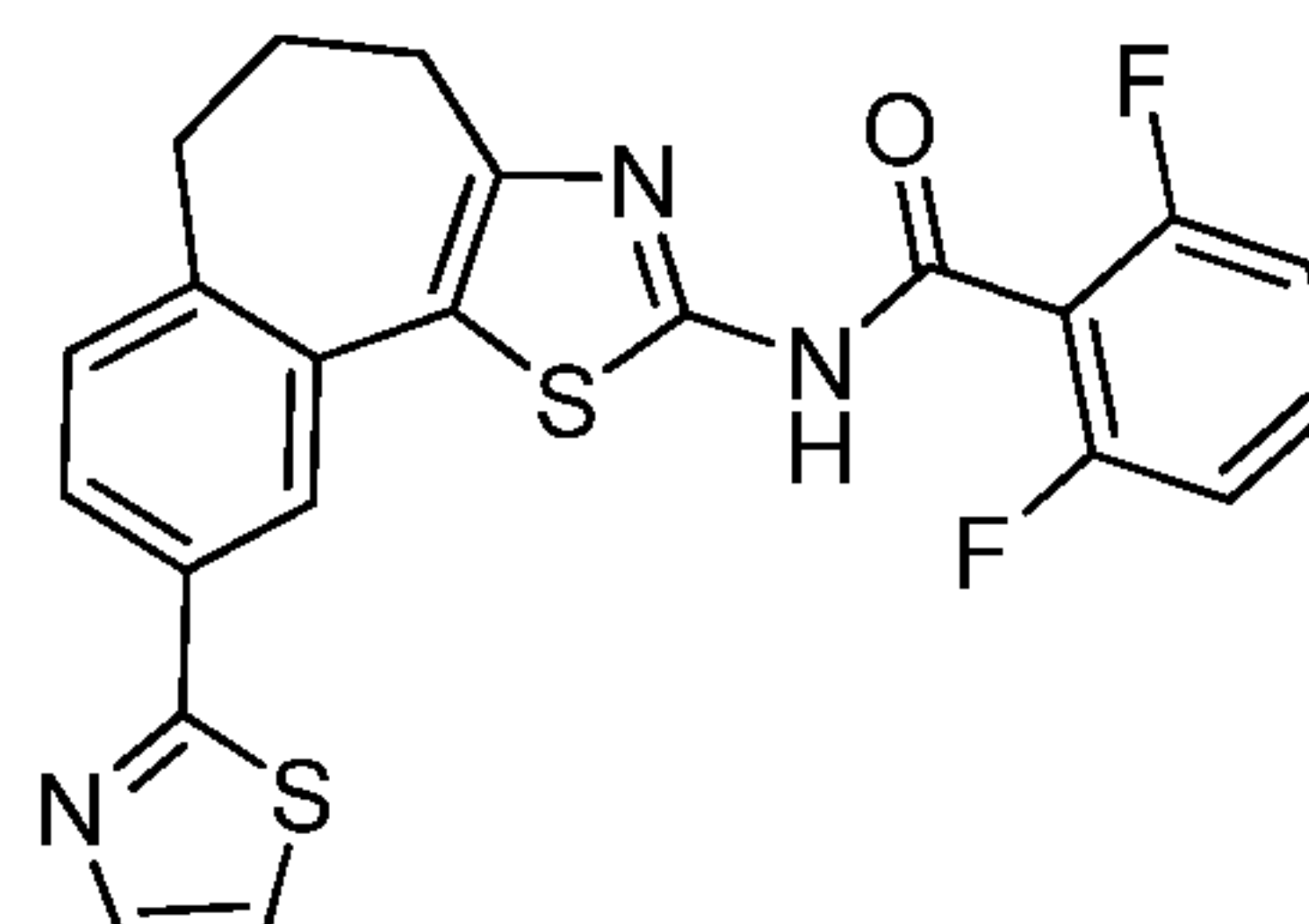
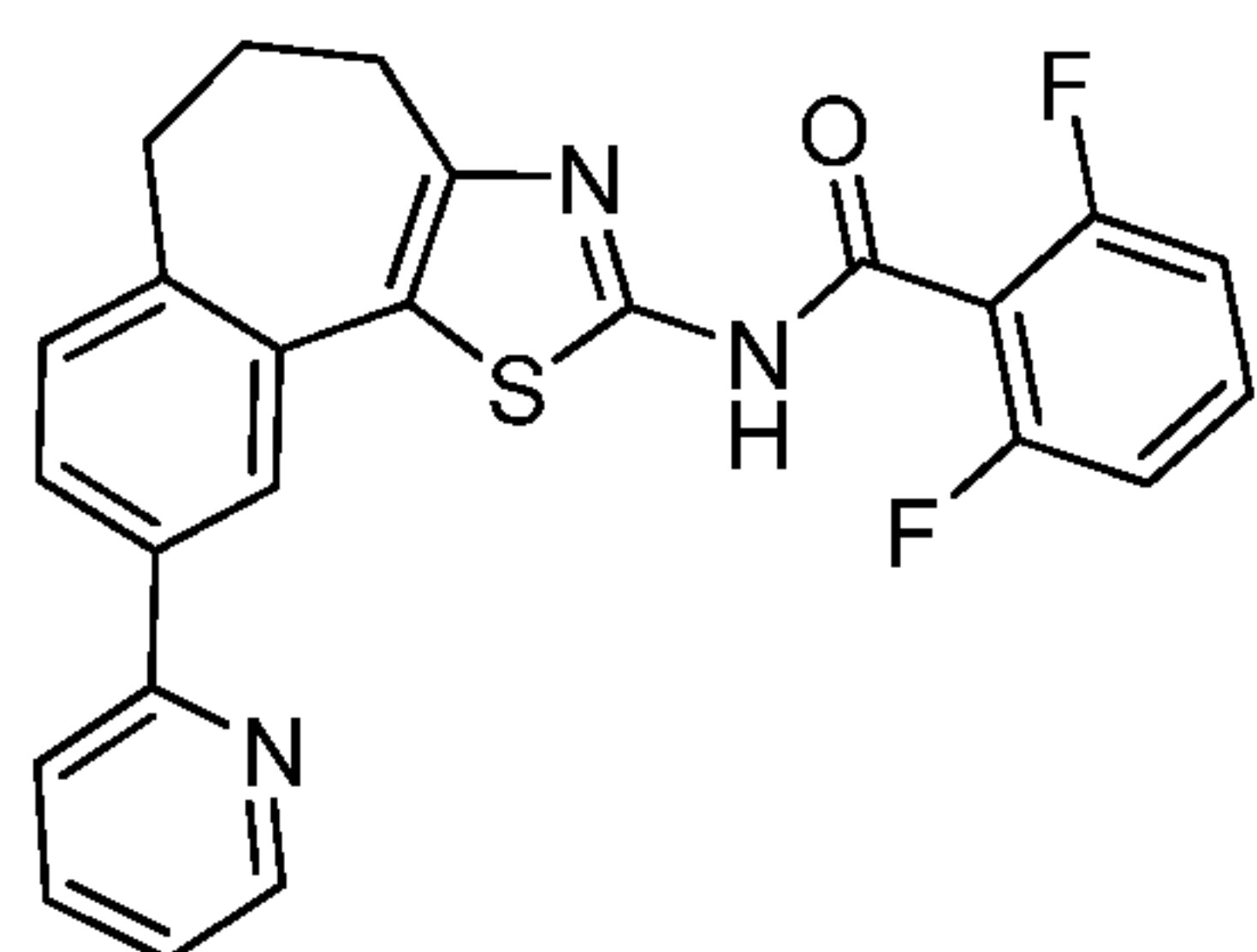
Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl for all other Rings M.

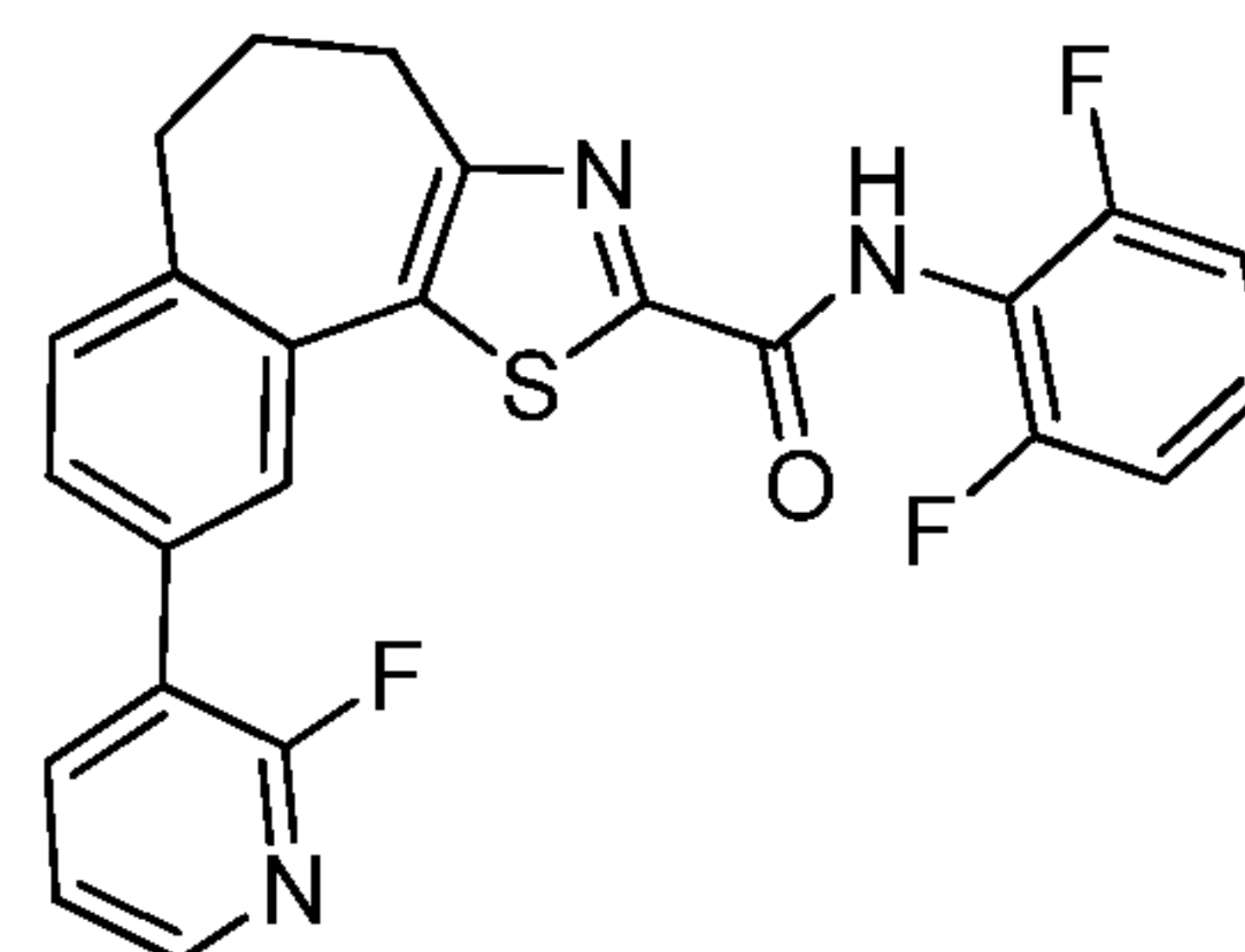
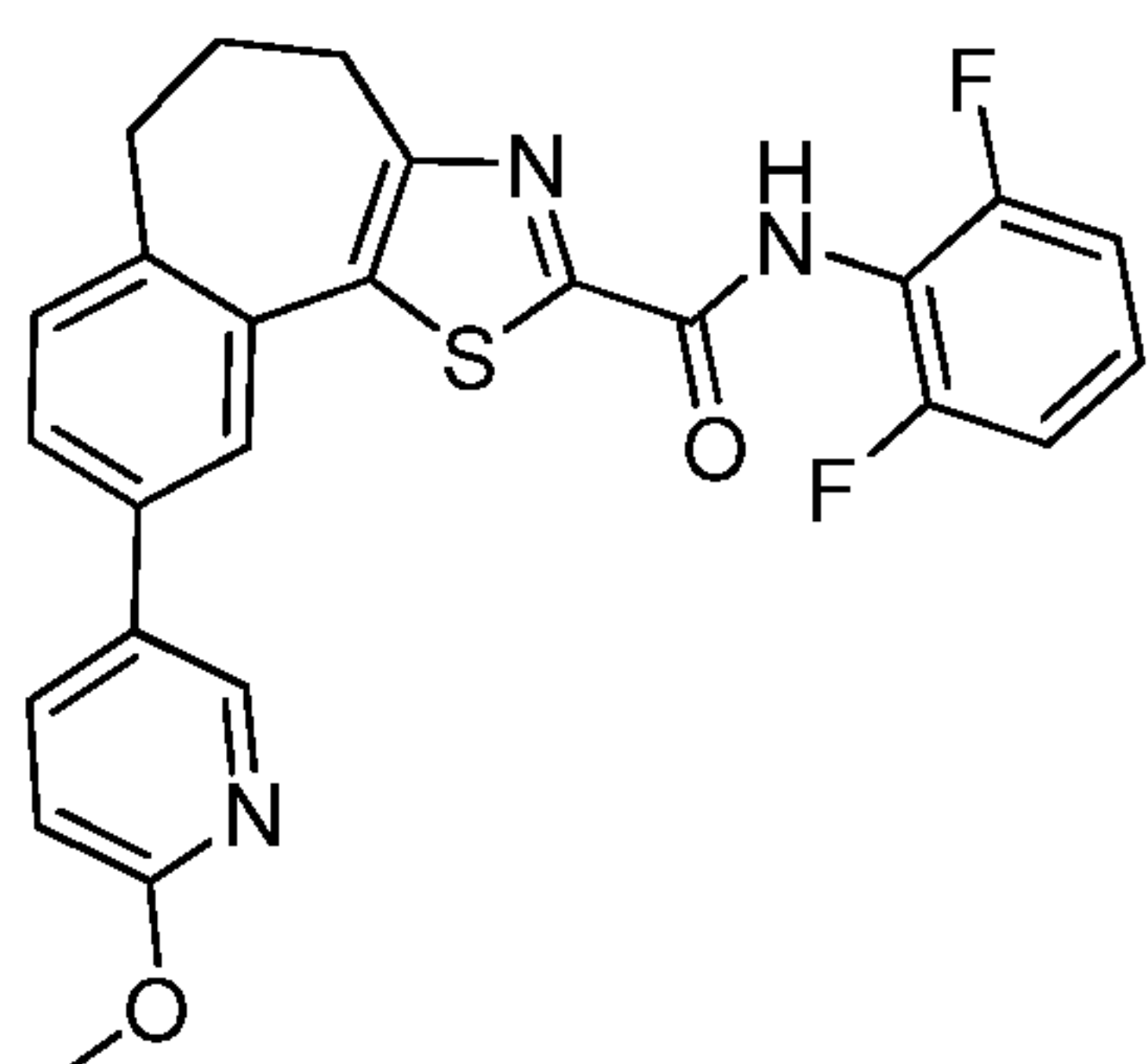
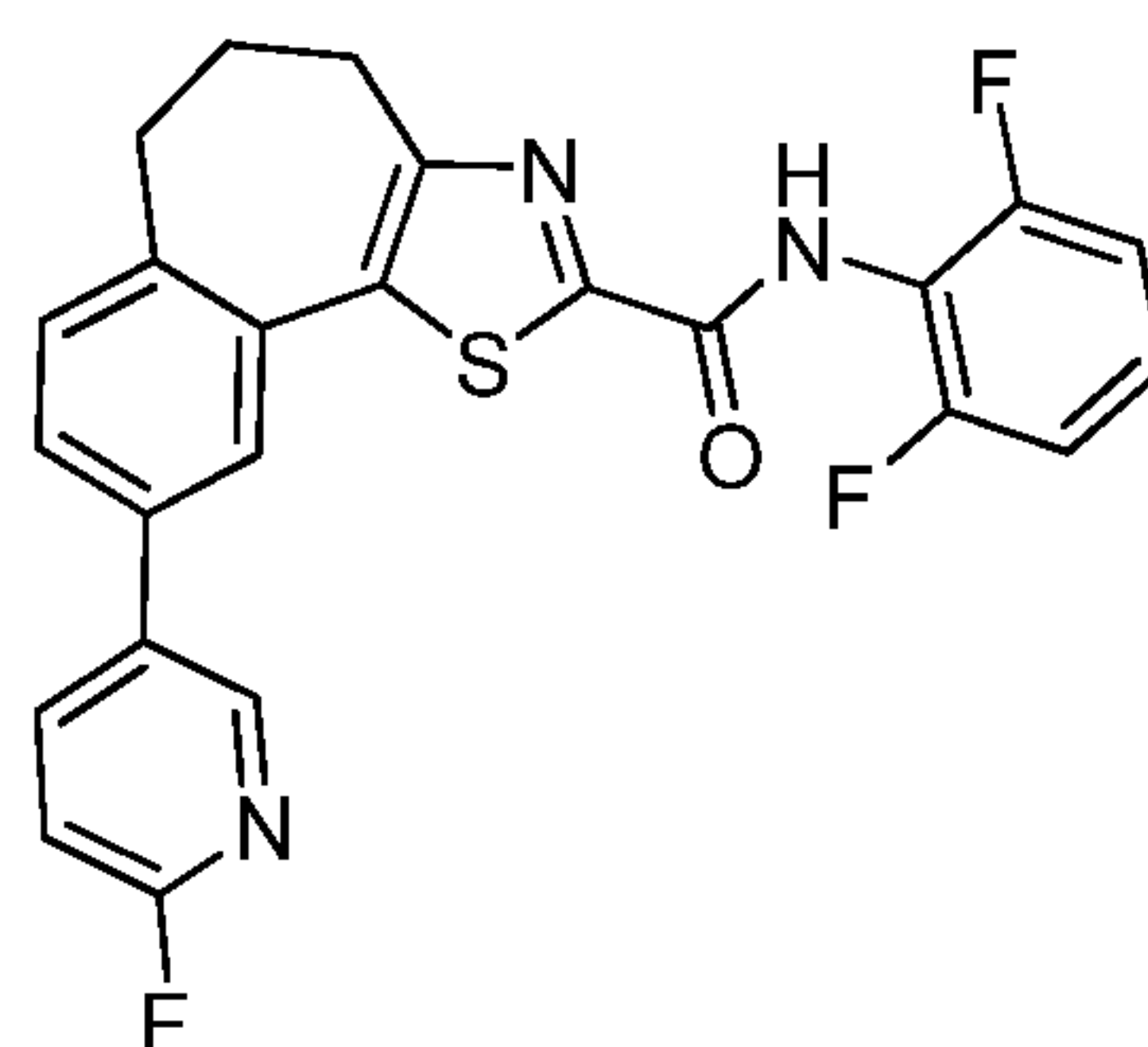
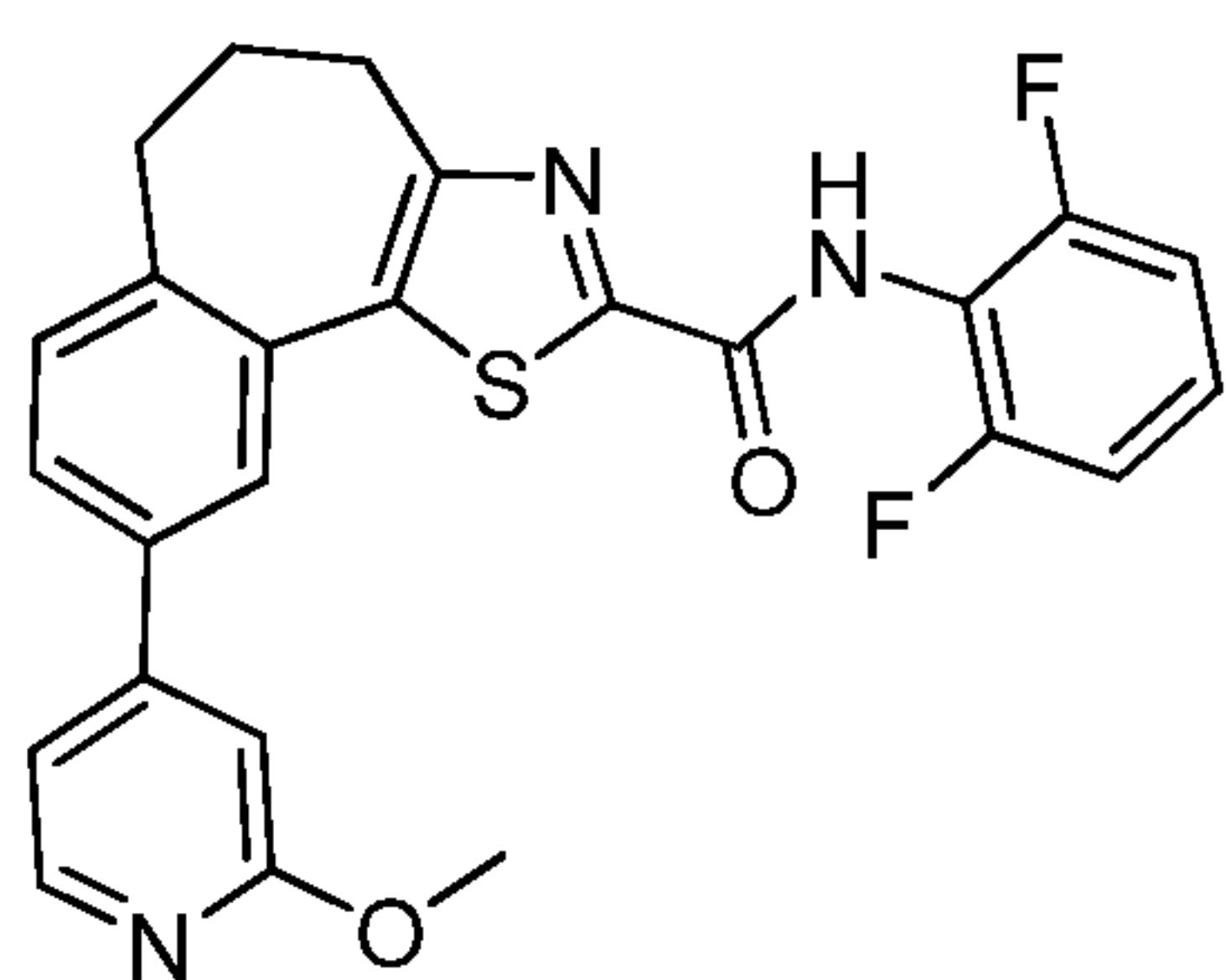
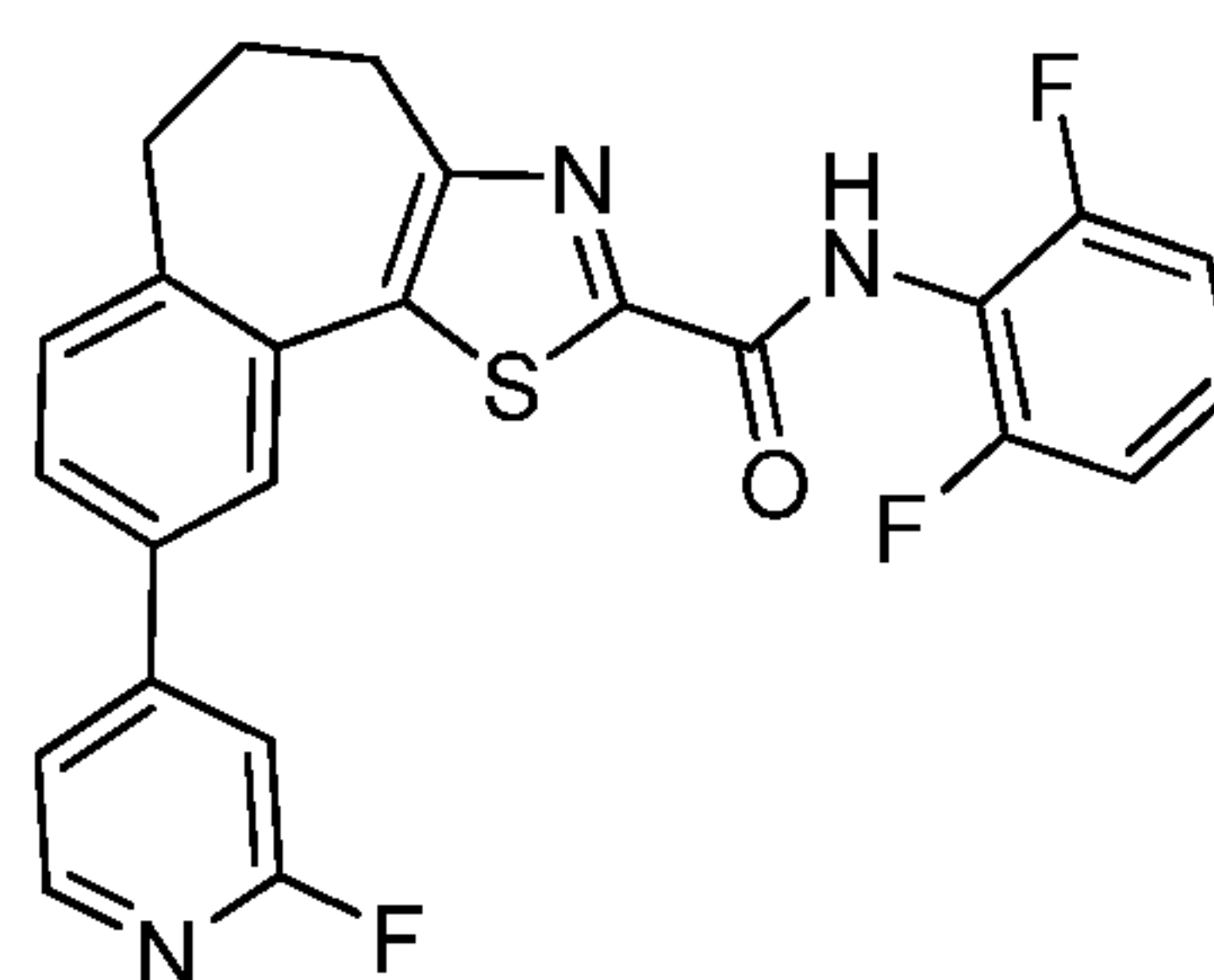
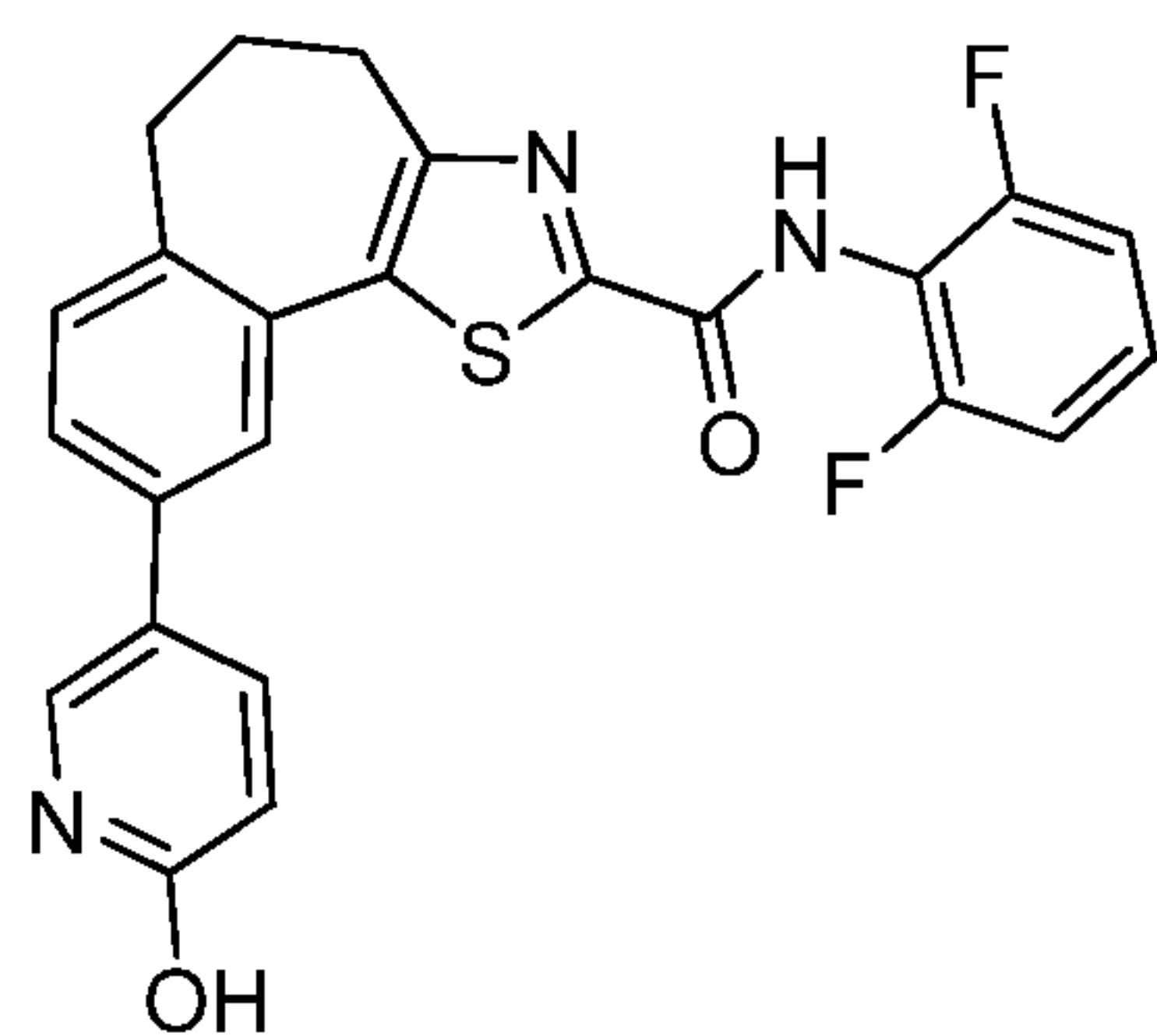
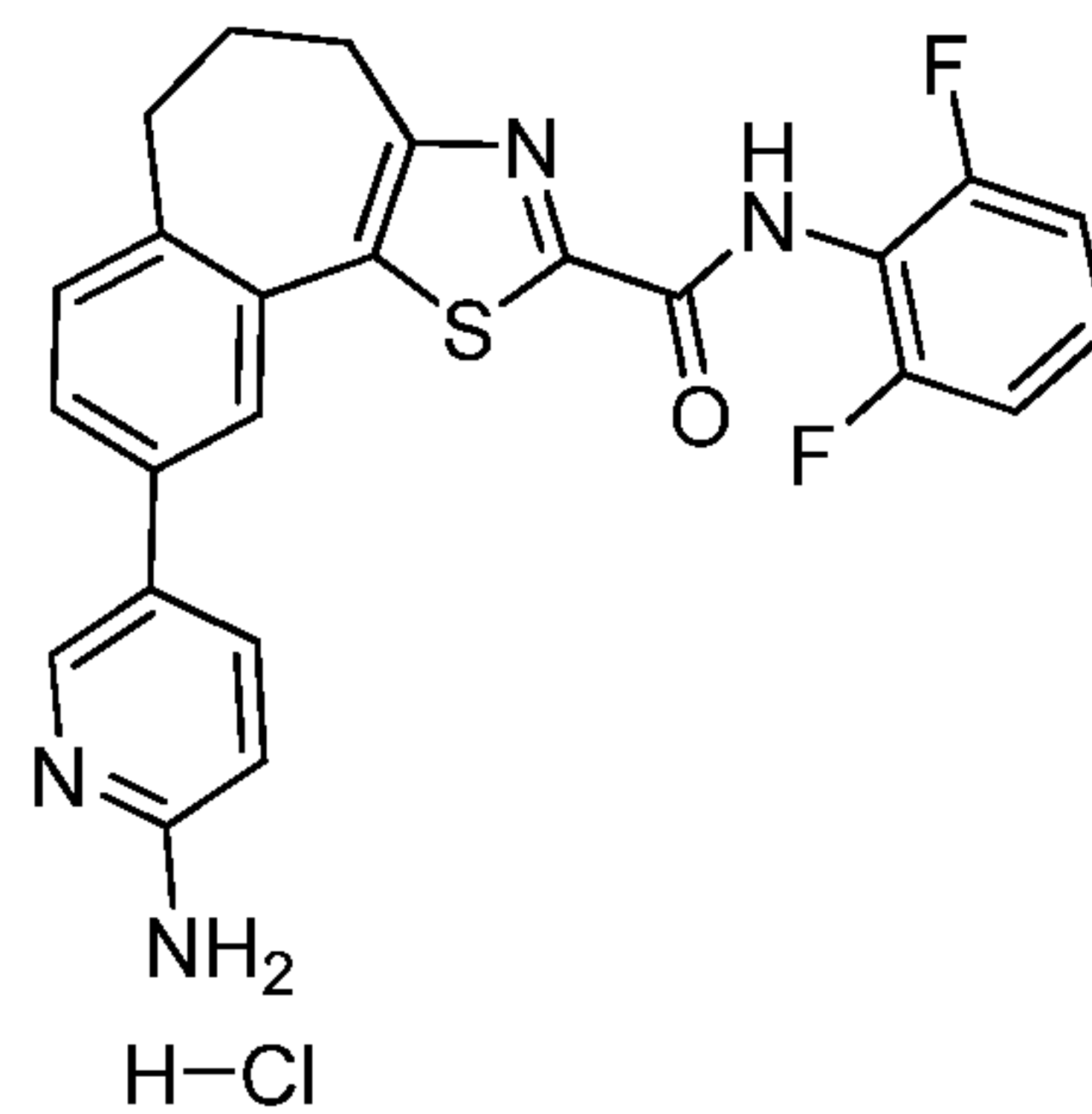
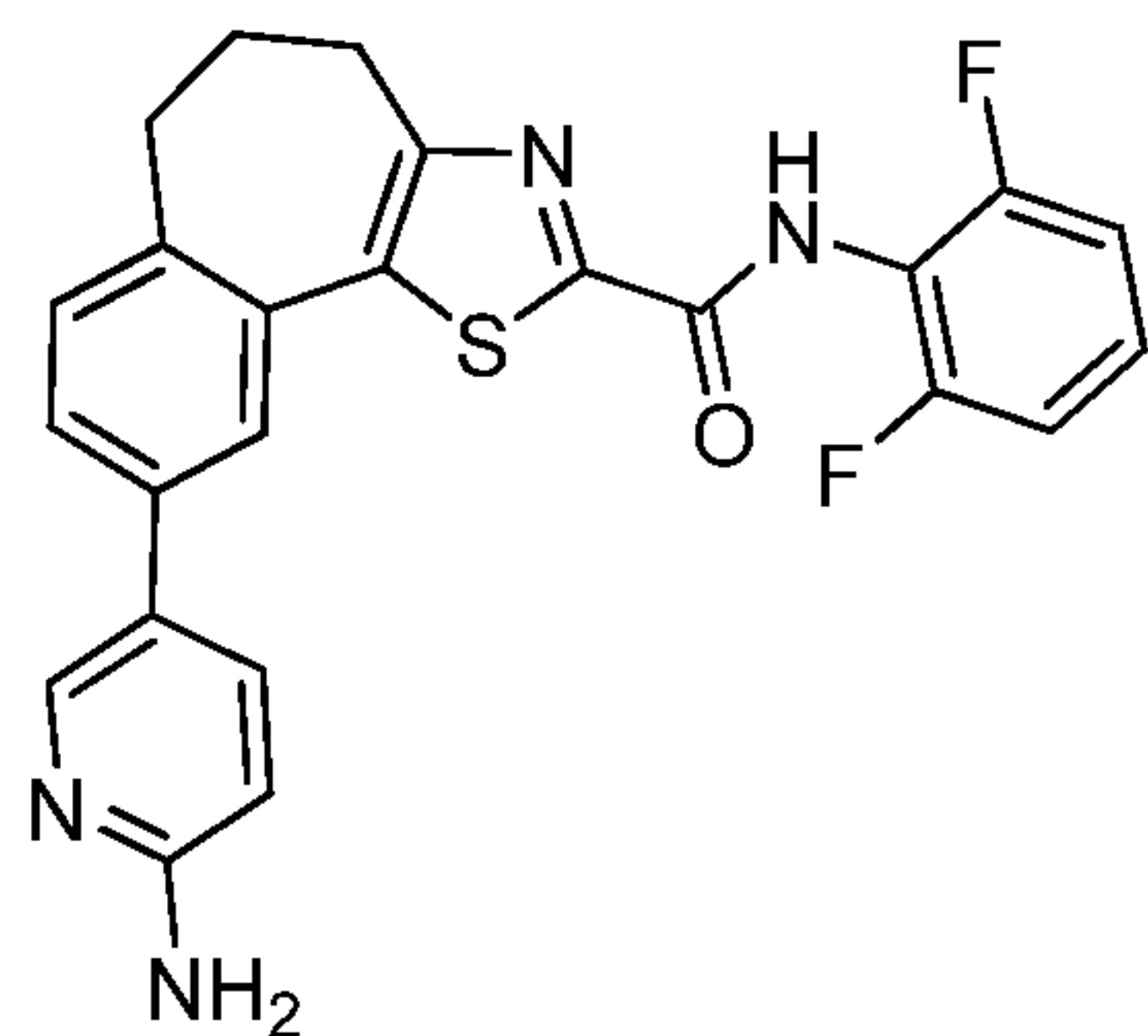
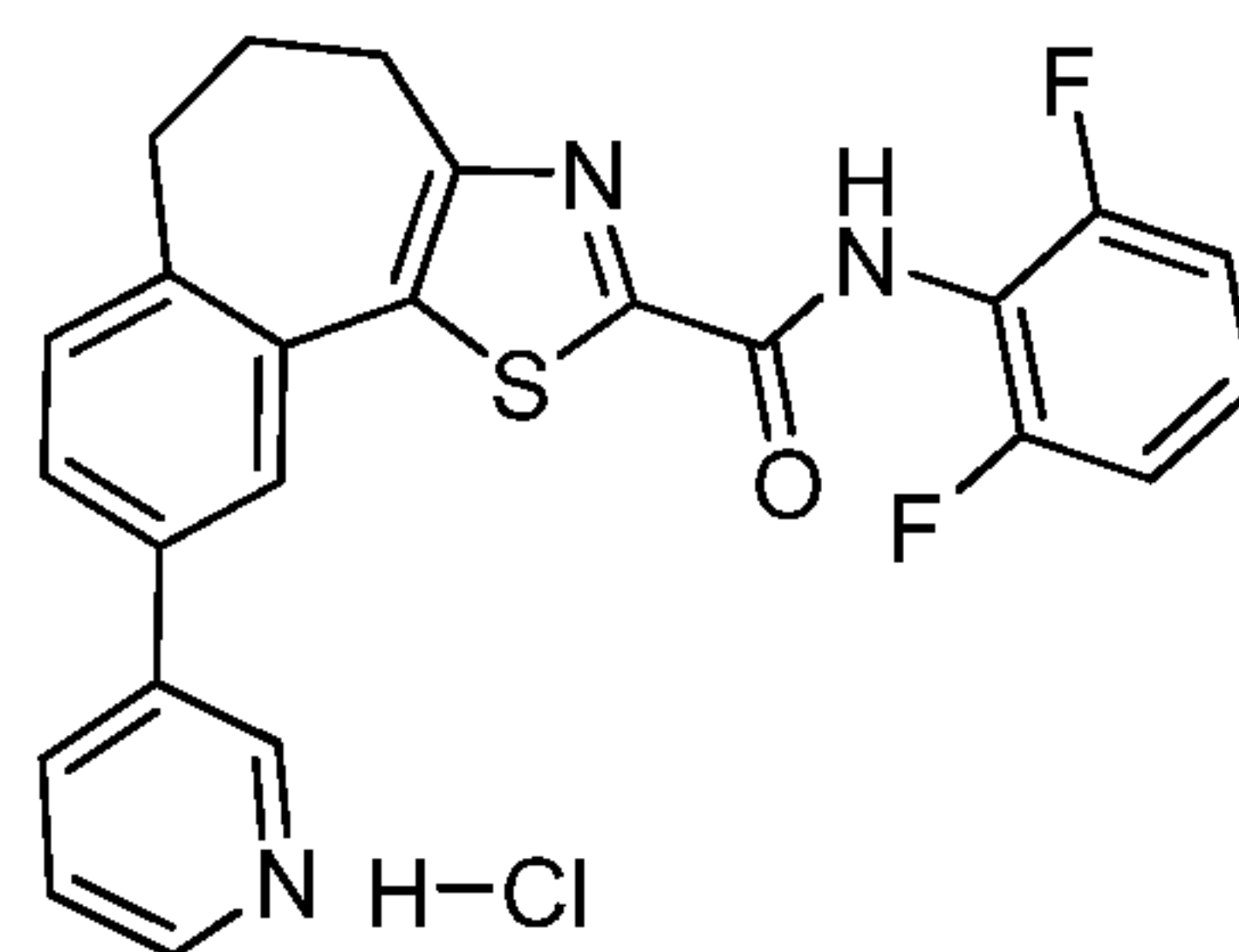
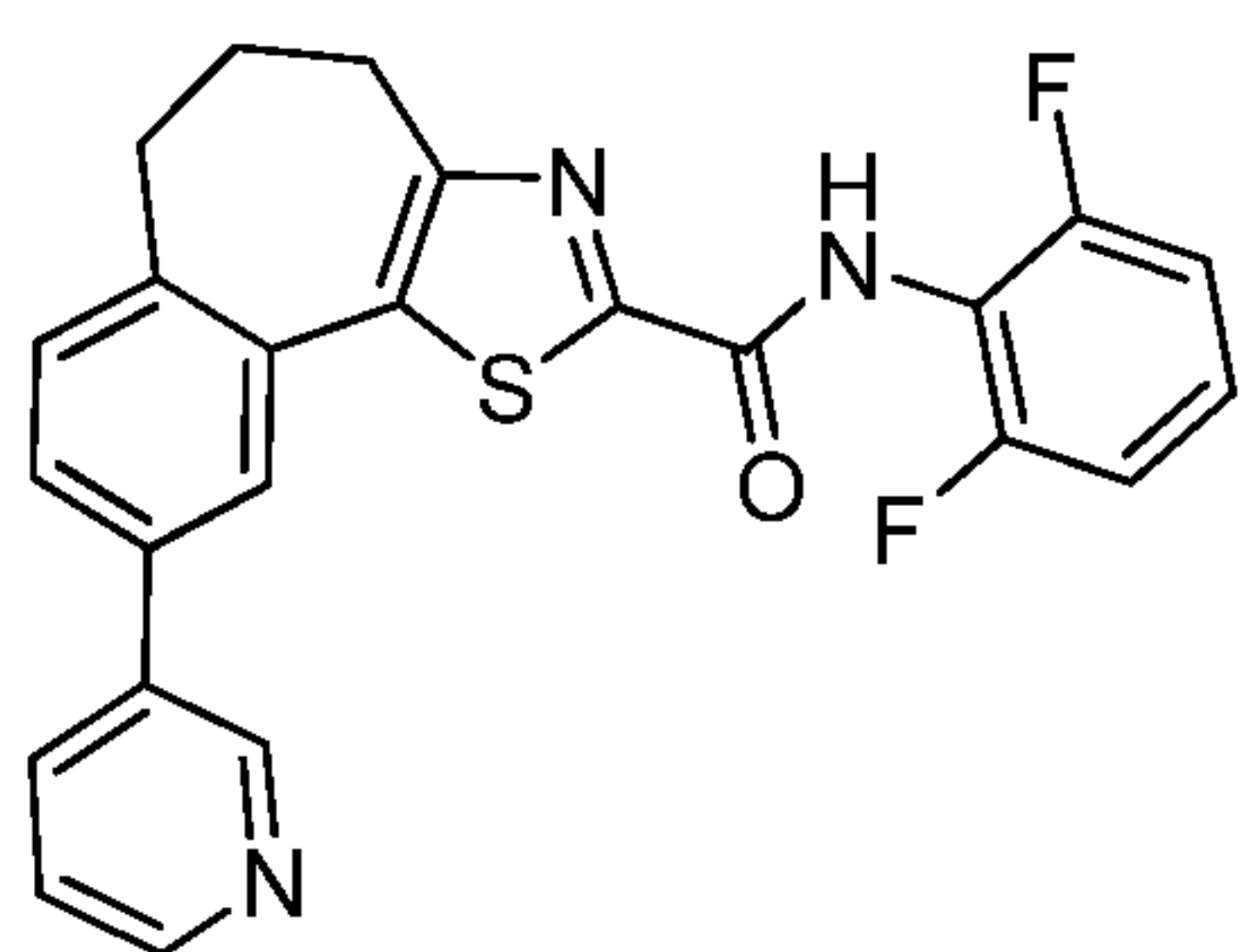
In one embodiment of compounds of formula (XX), the following compounds are specifically excluded:

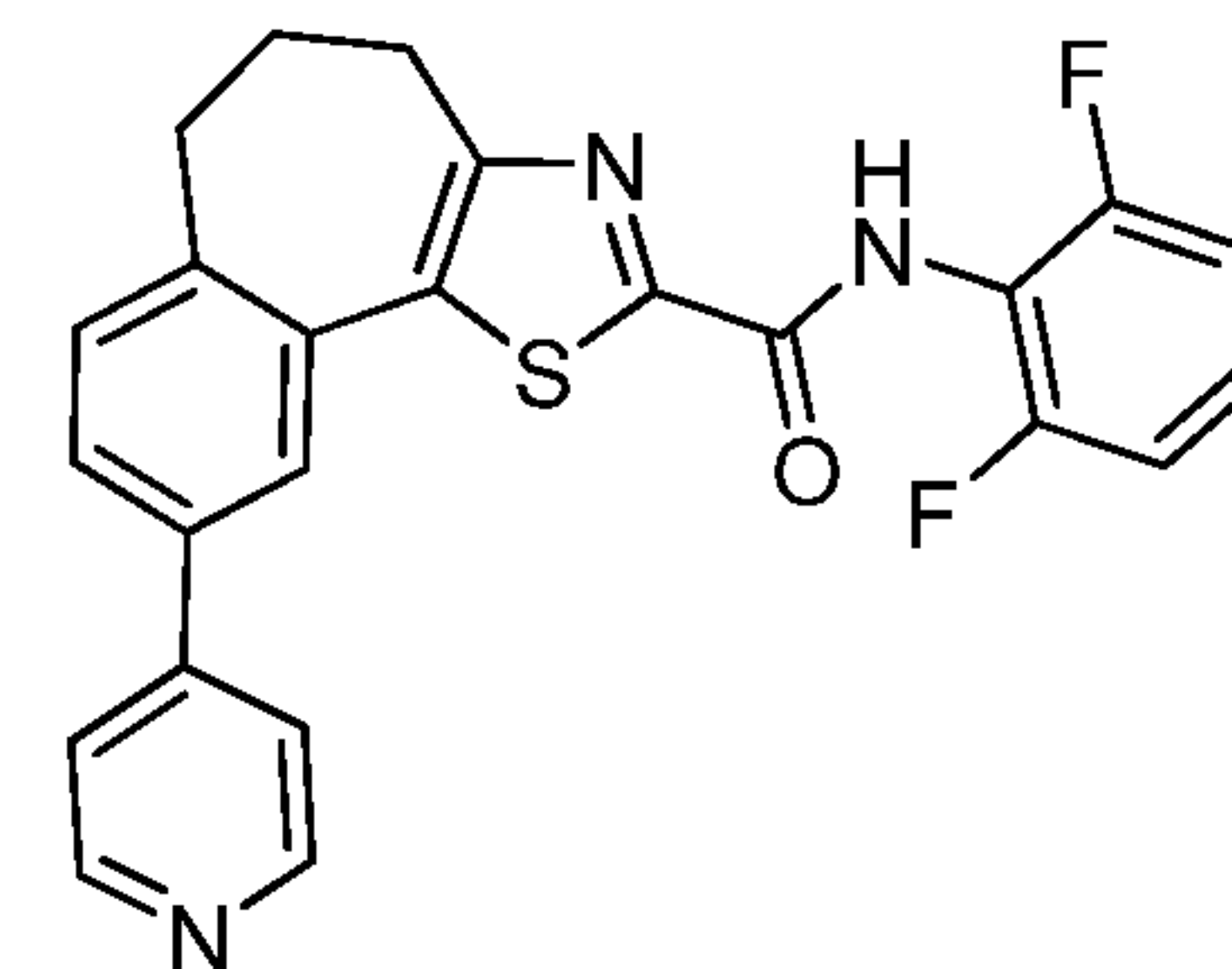
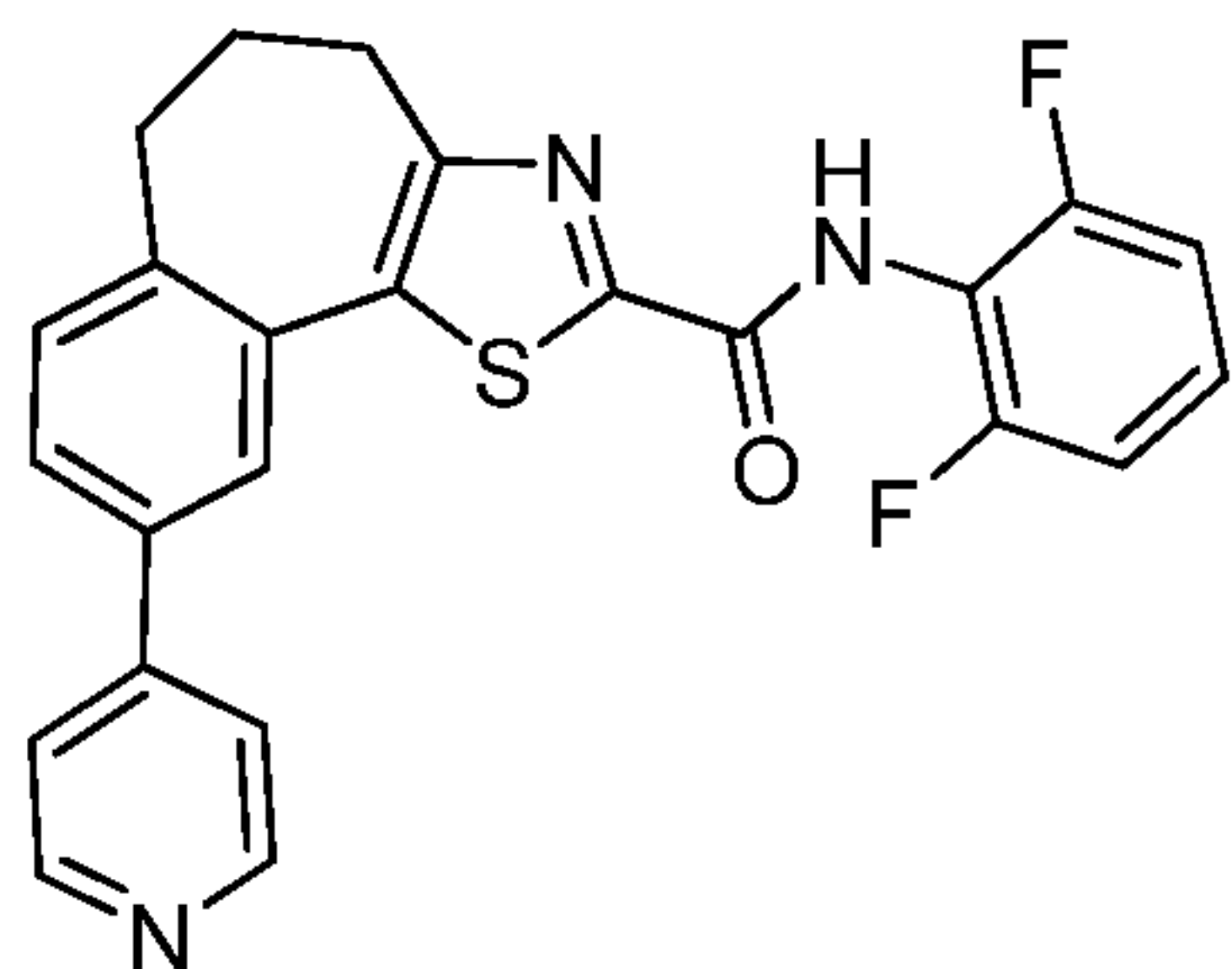
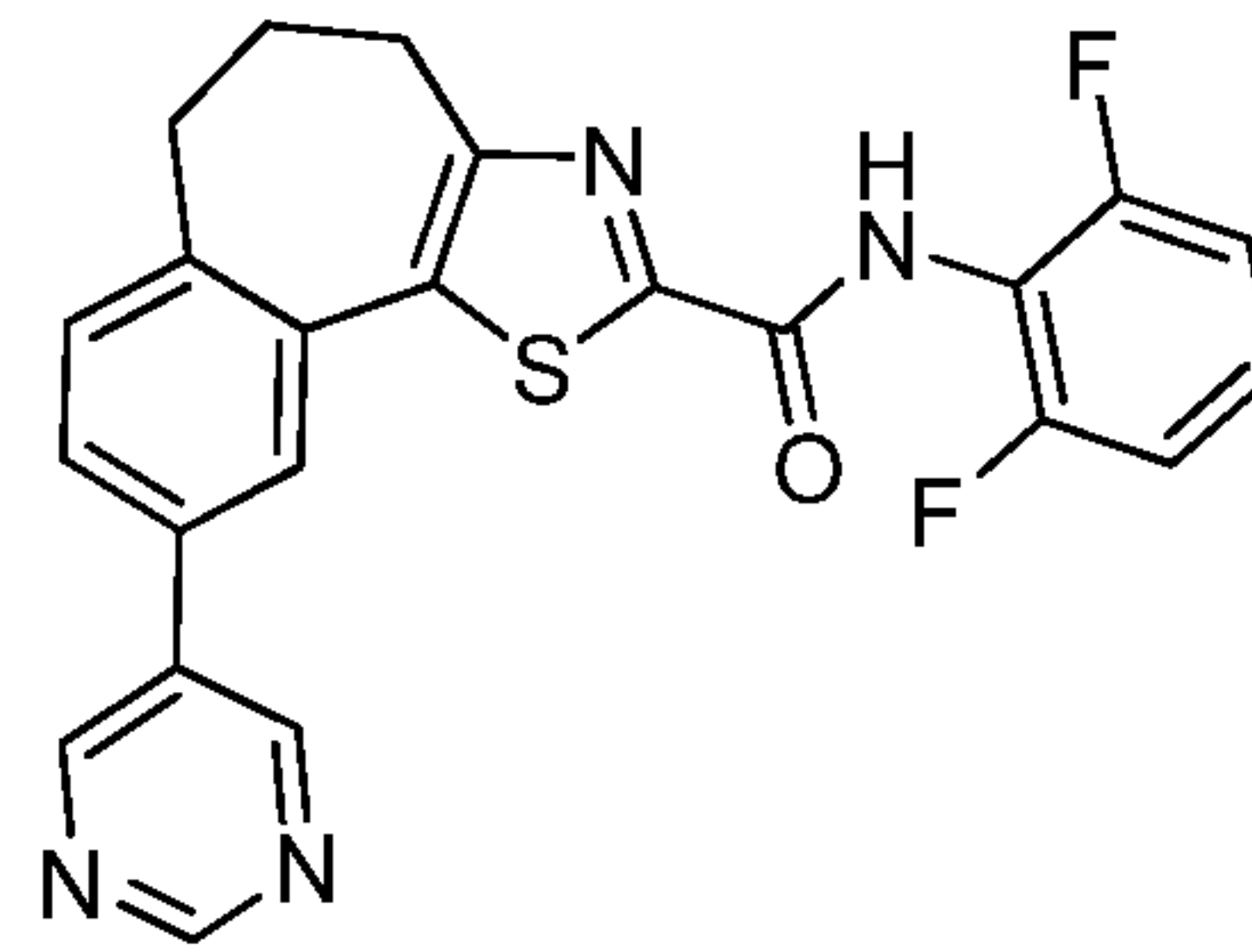
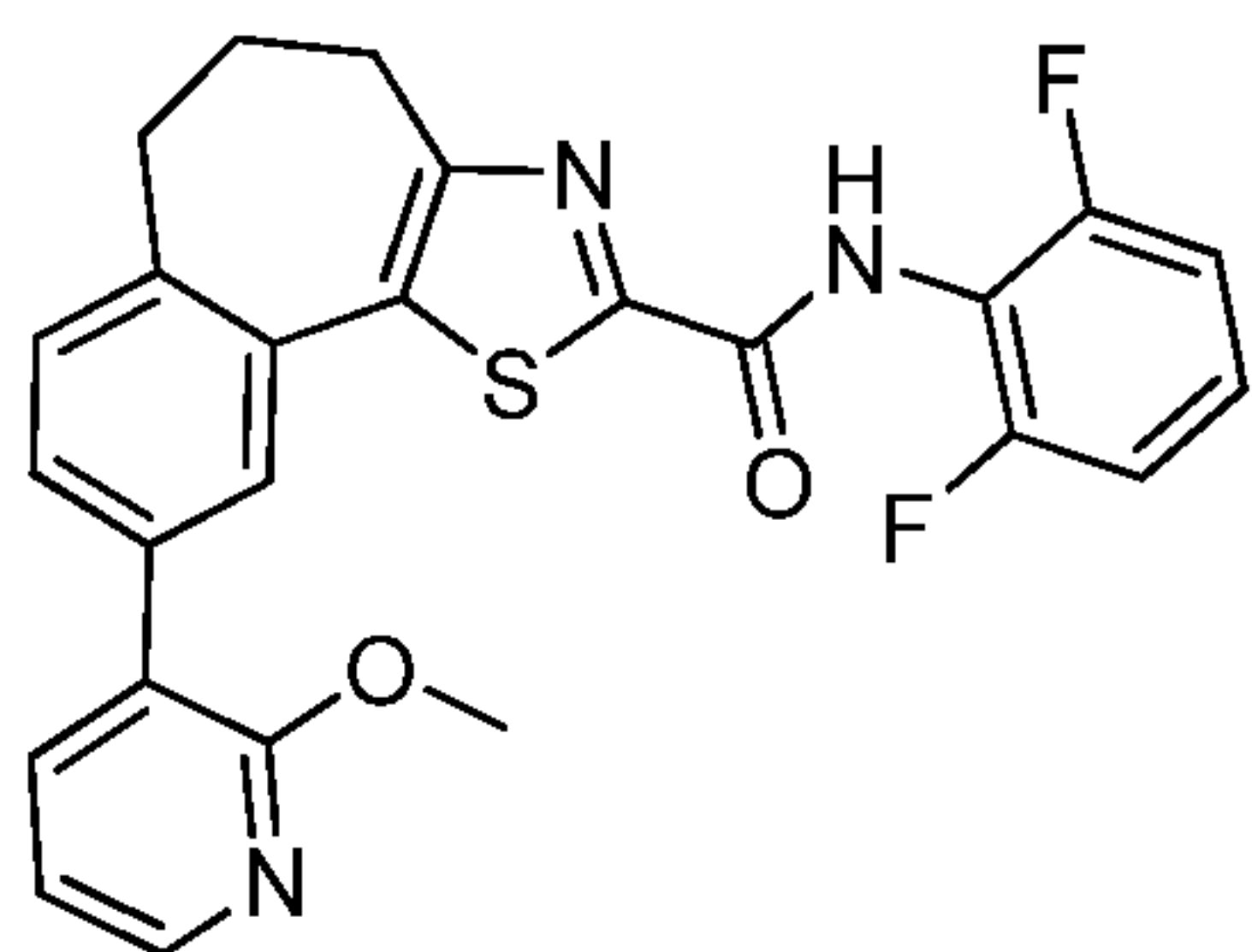




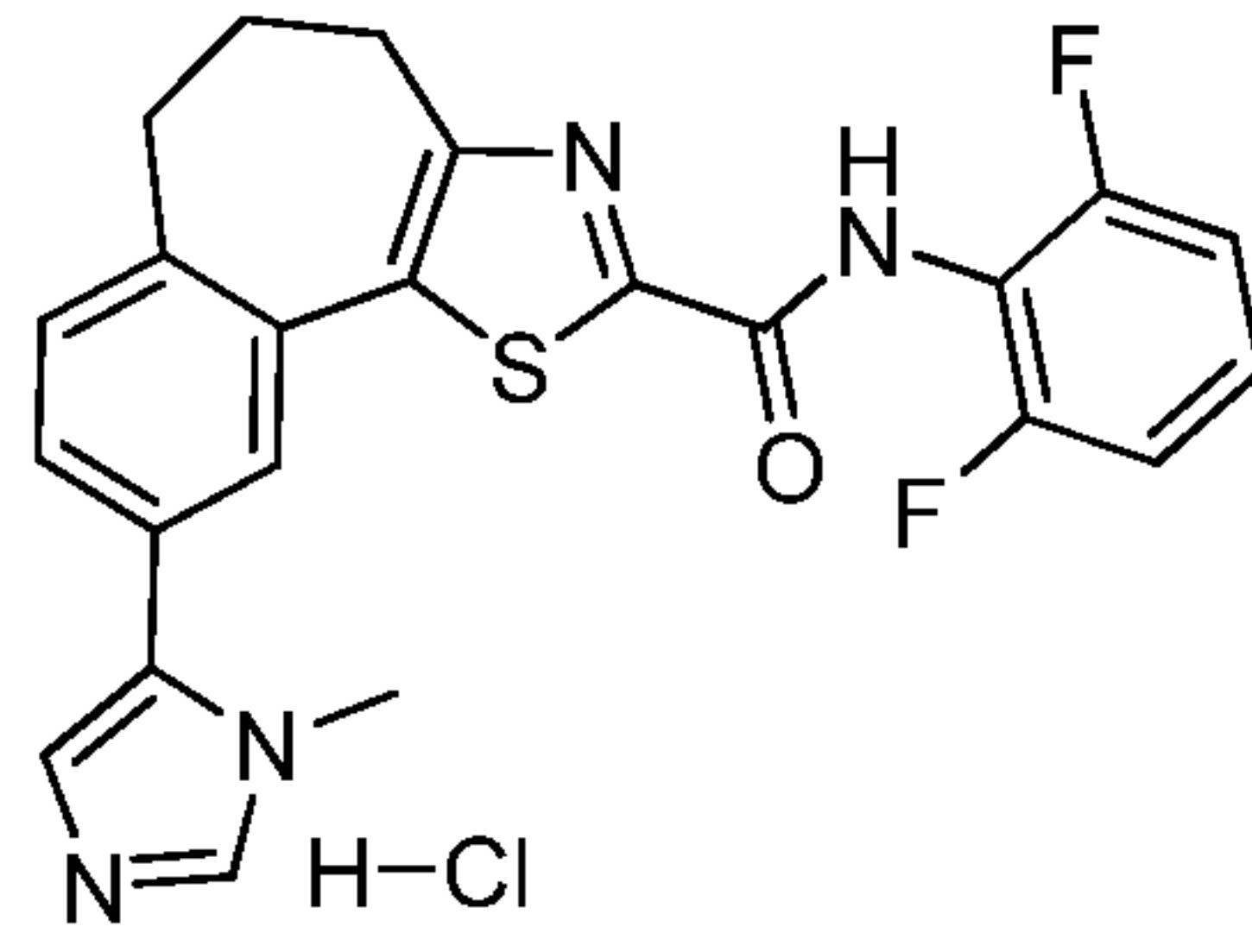
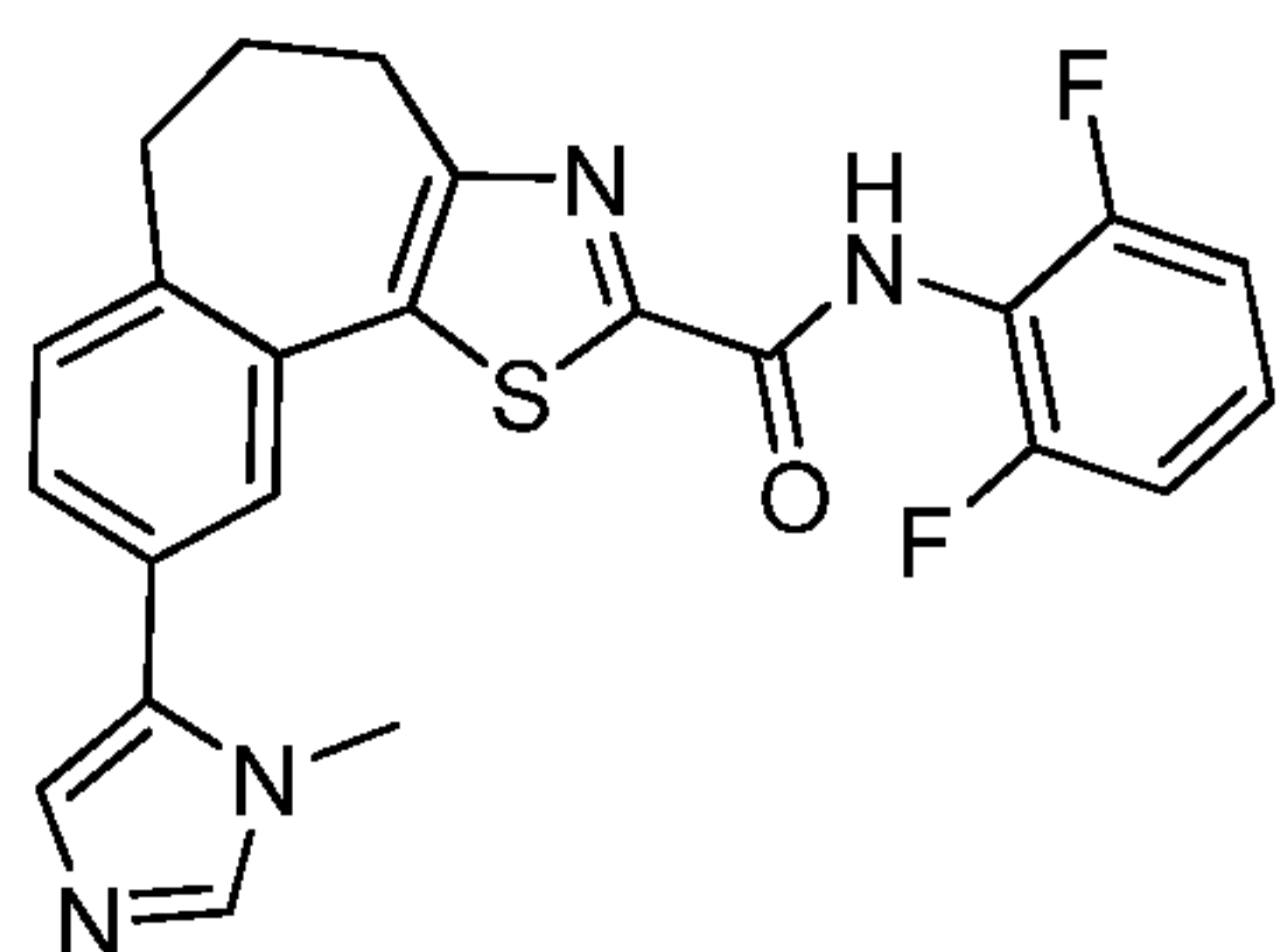
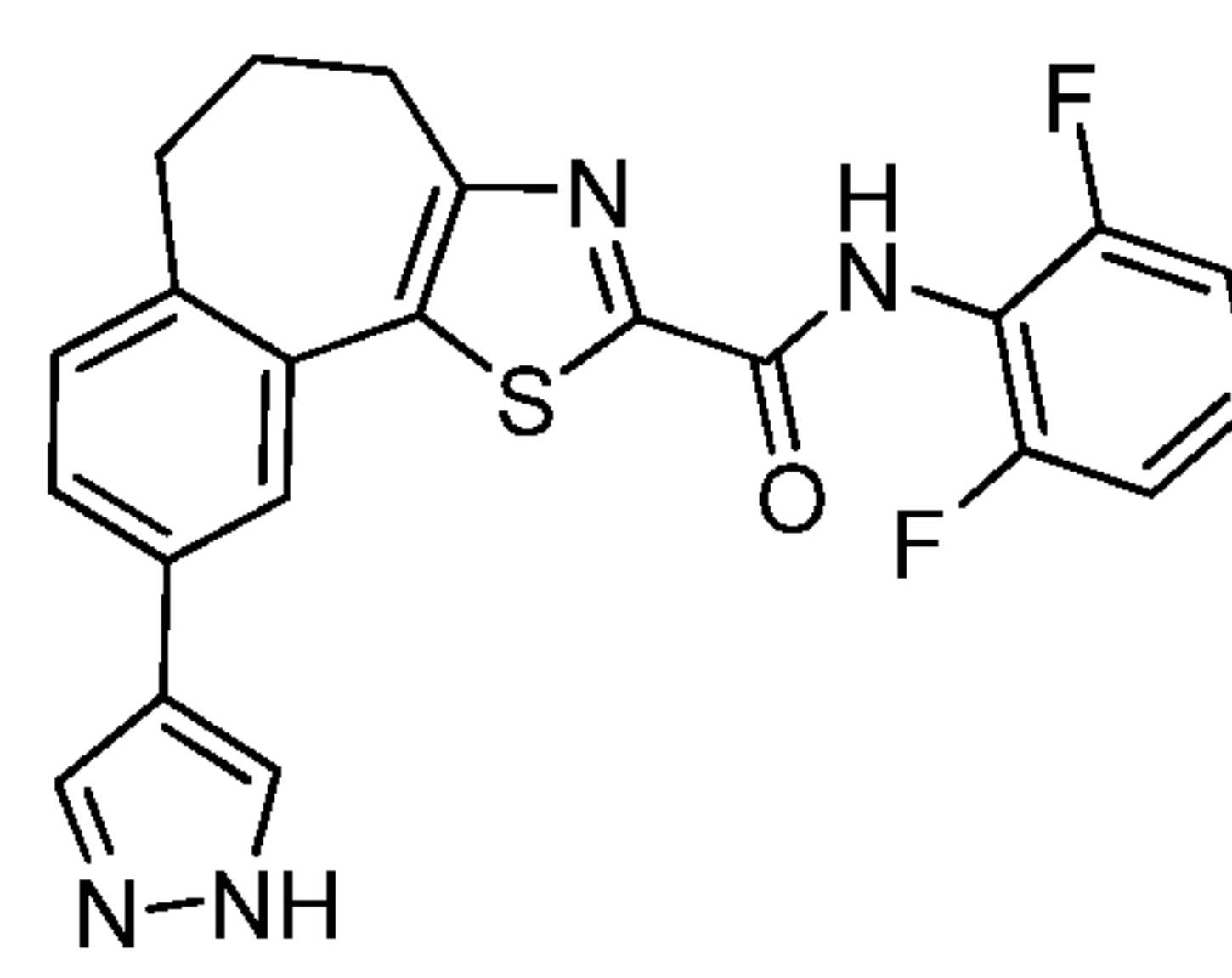
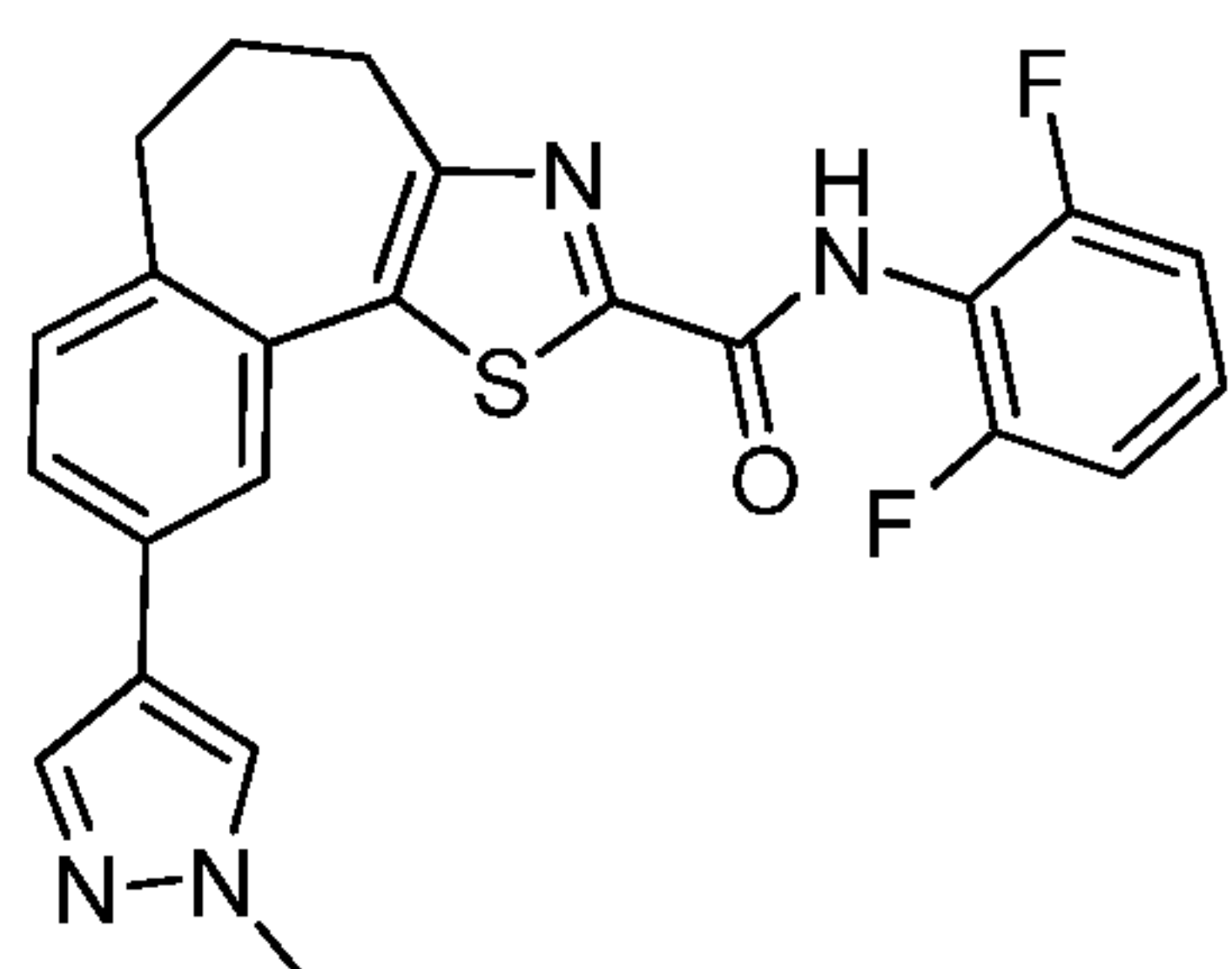
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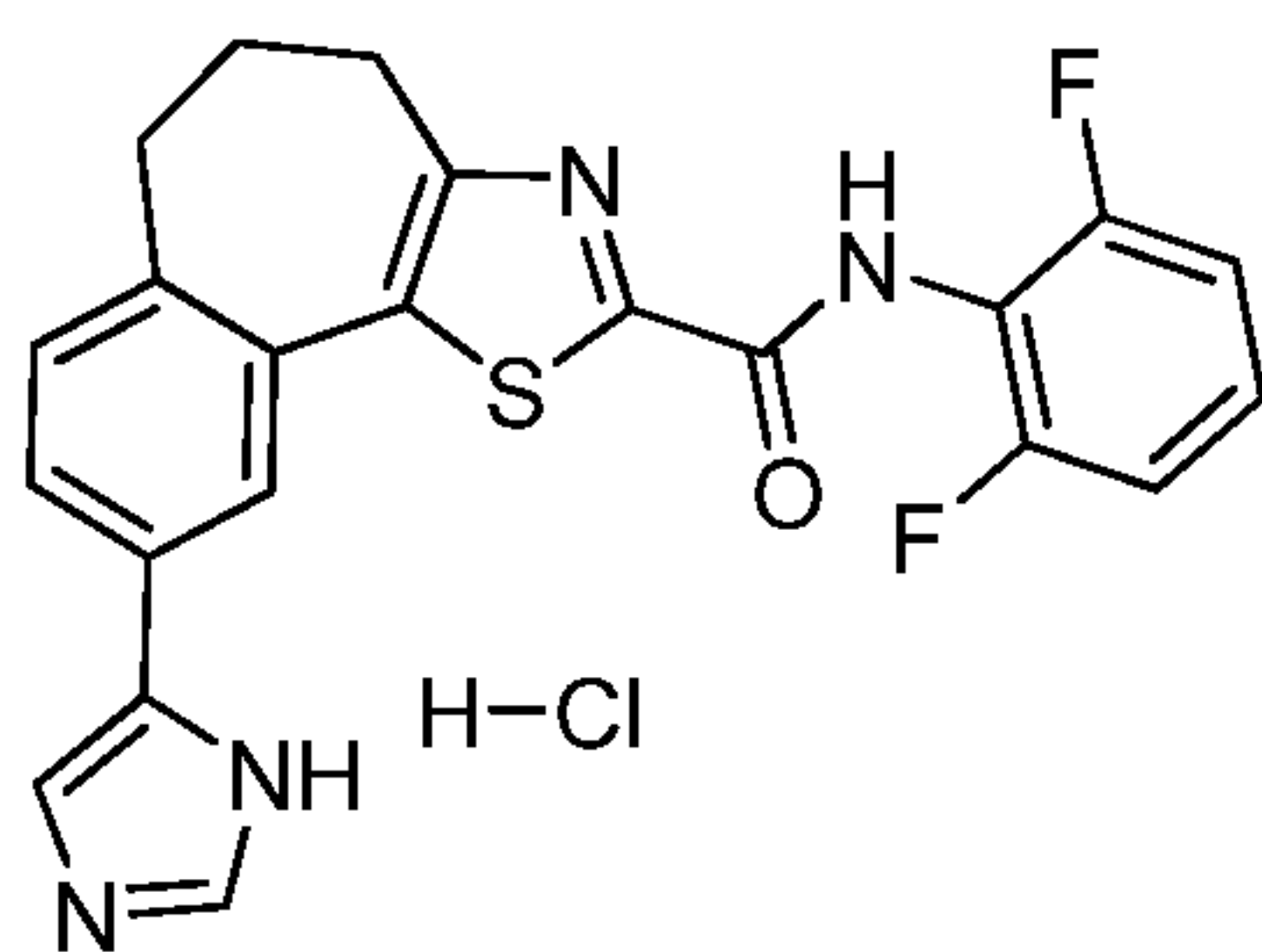
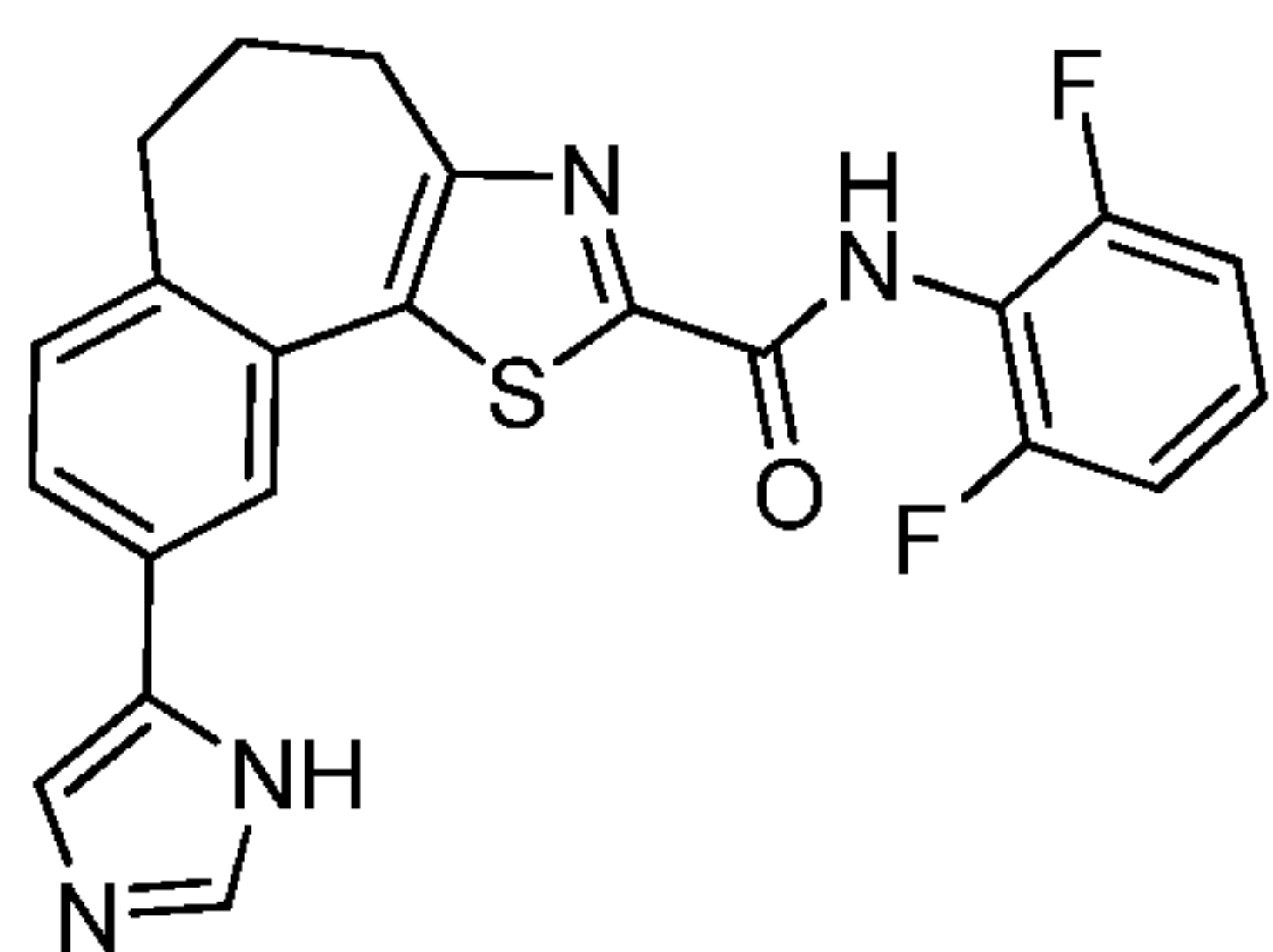




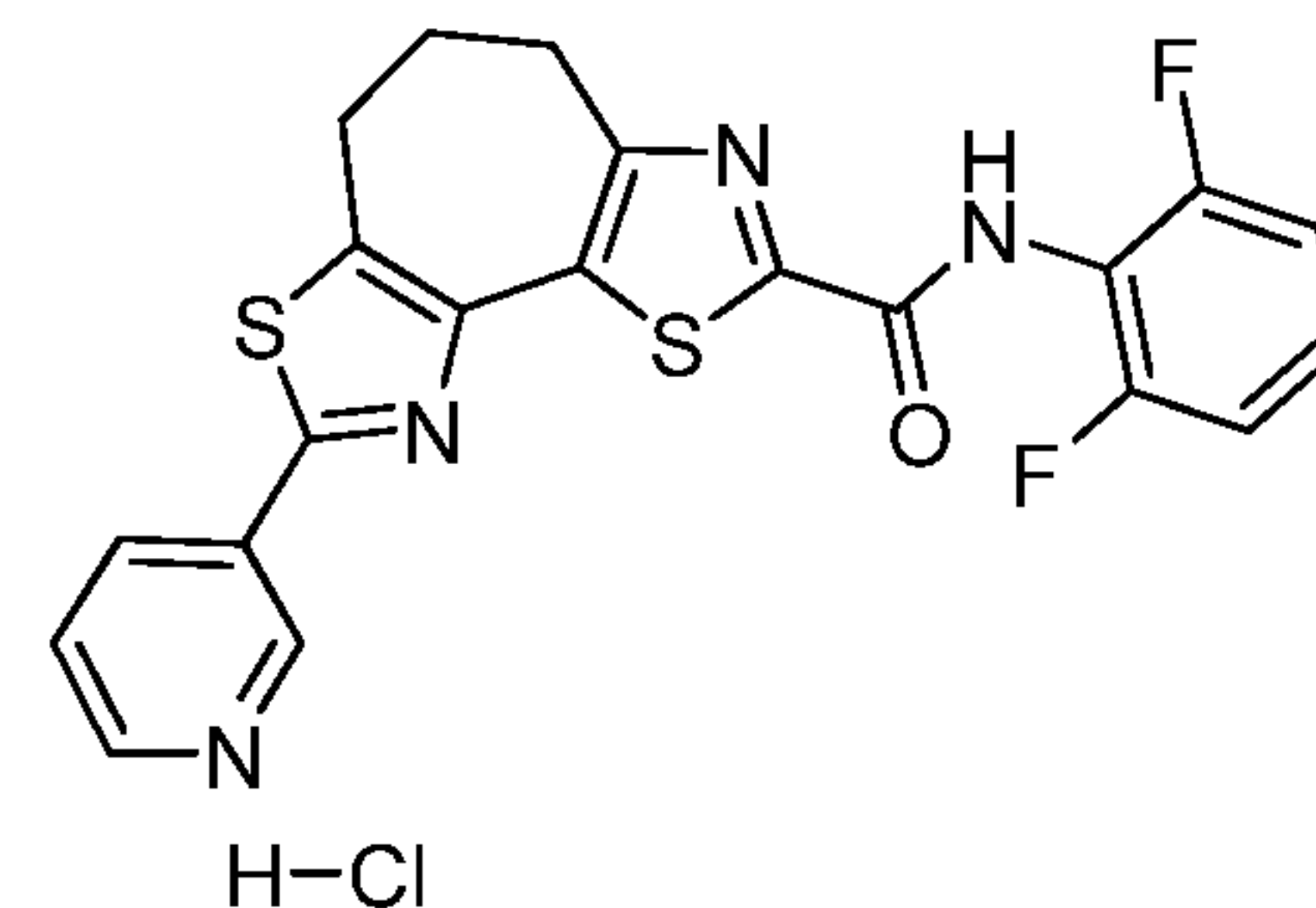
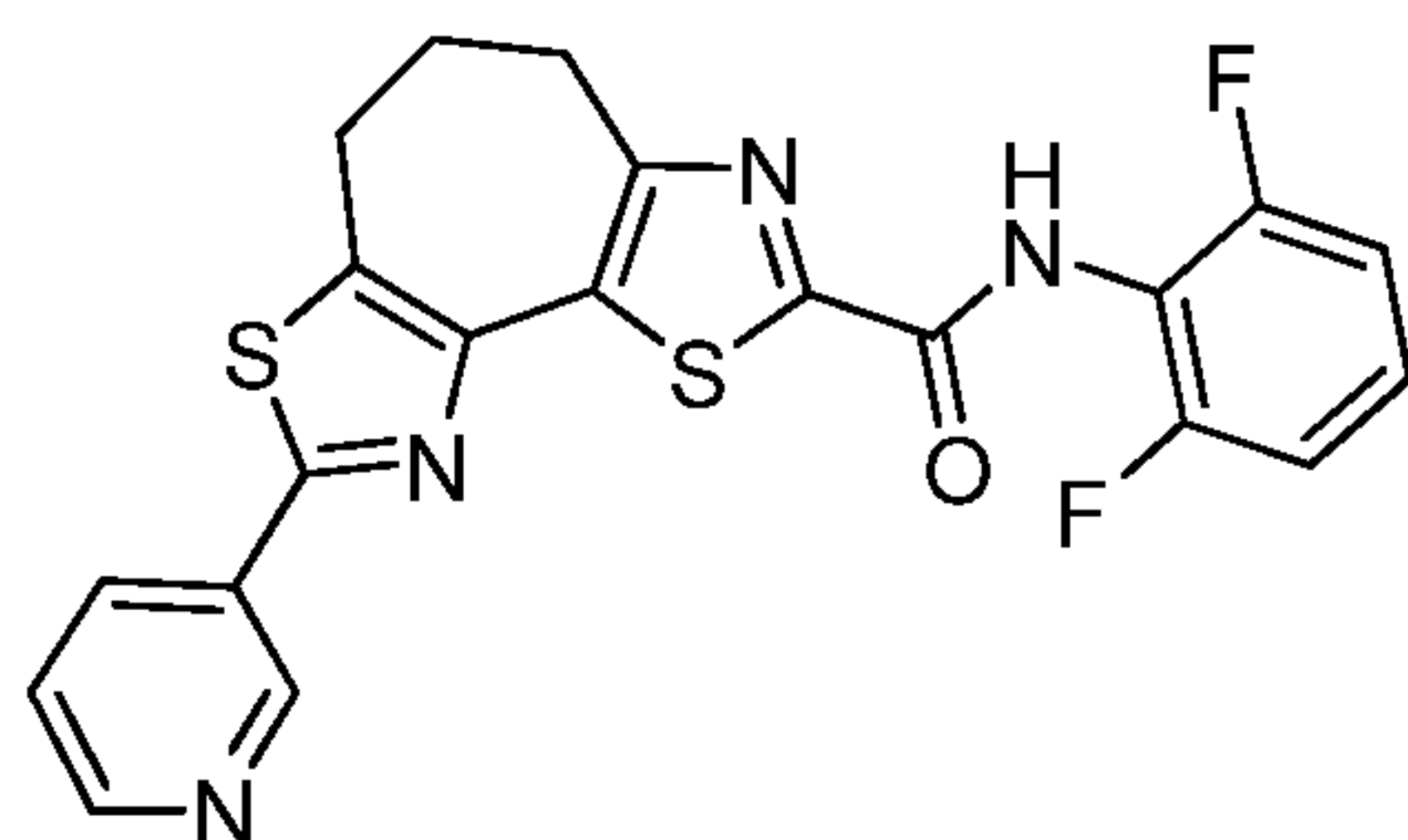
H-Cl



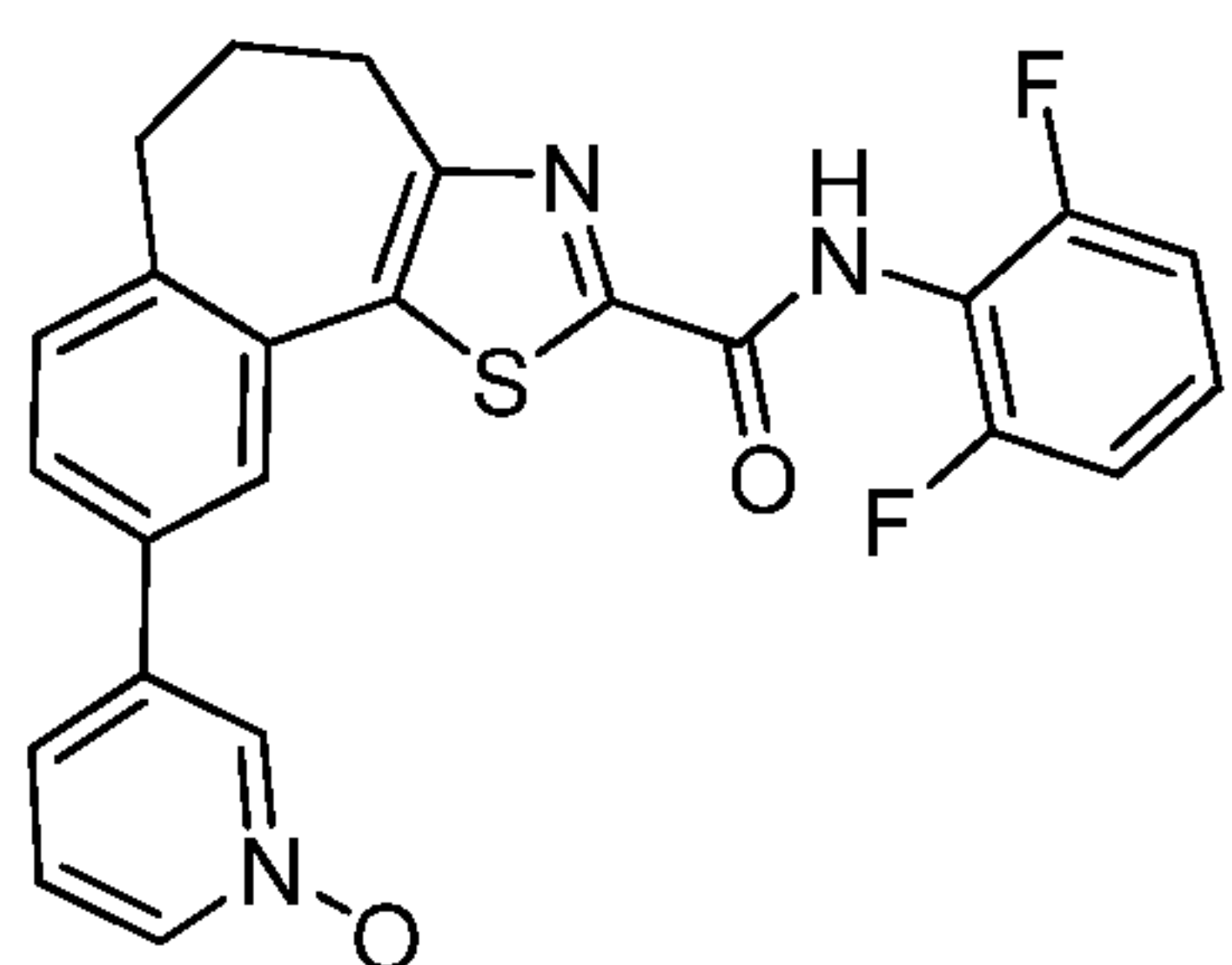
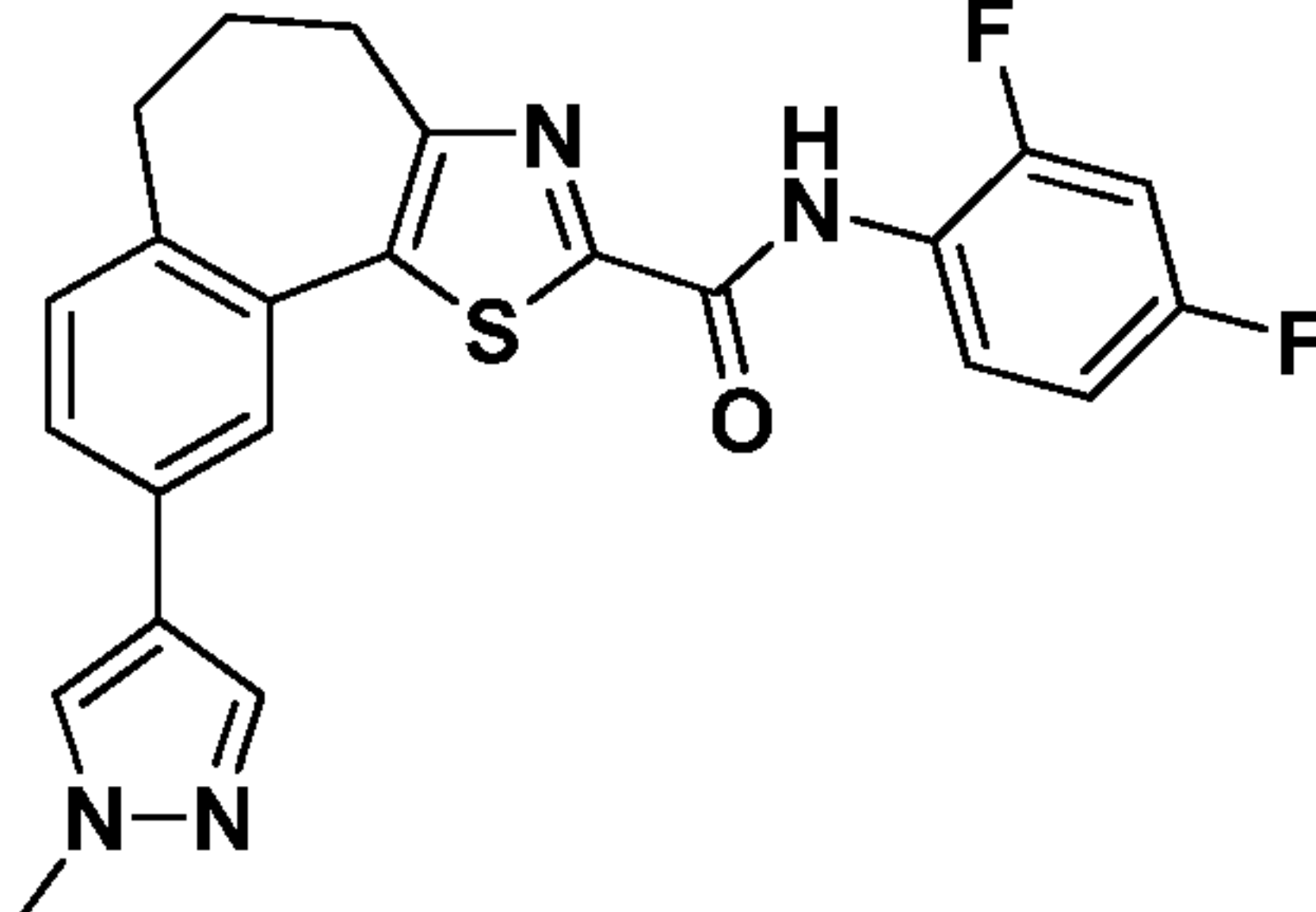
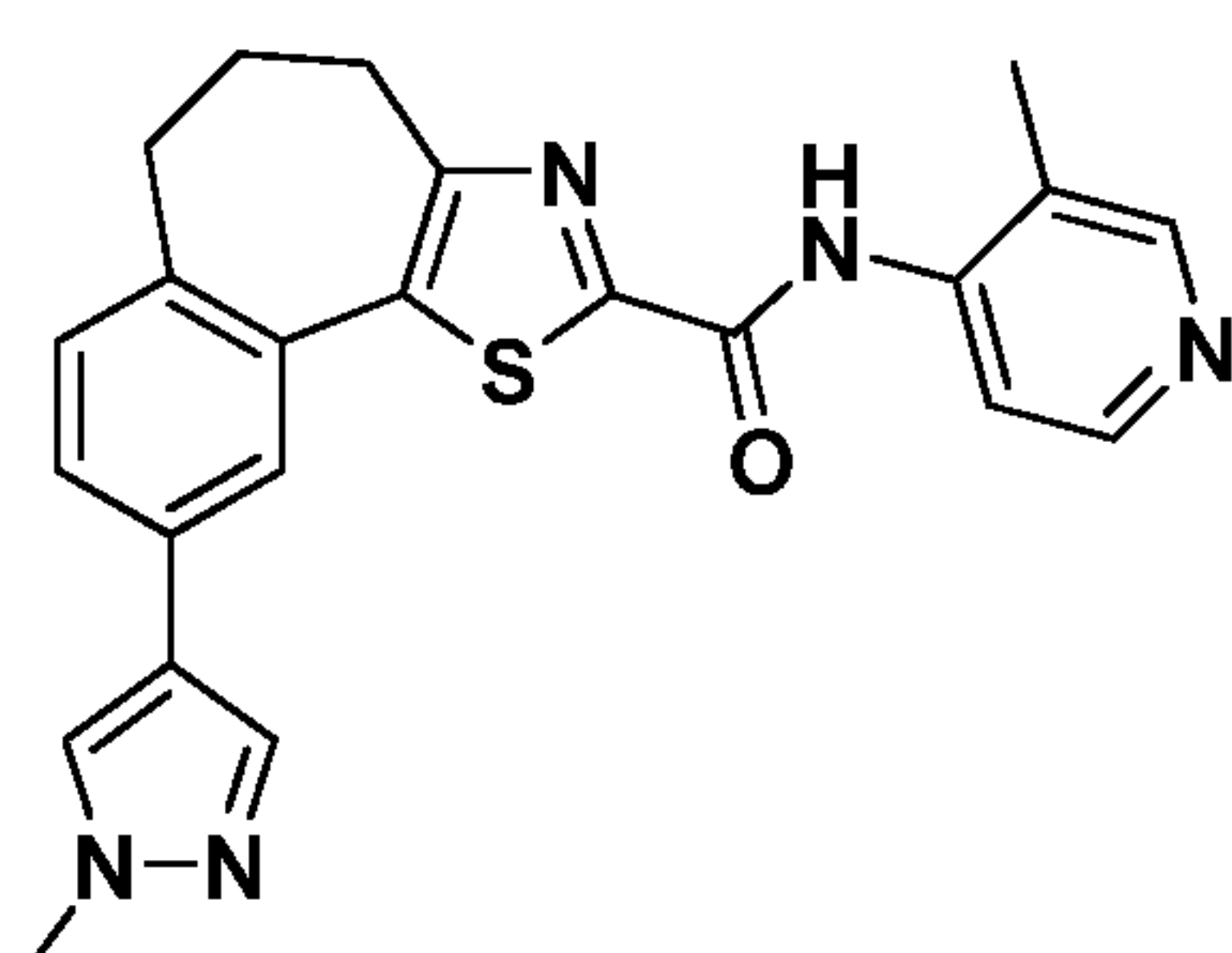
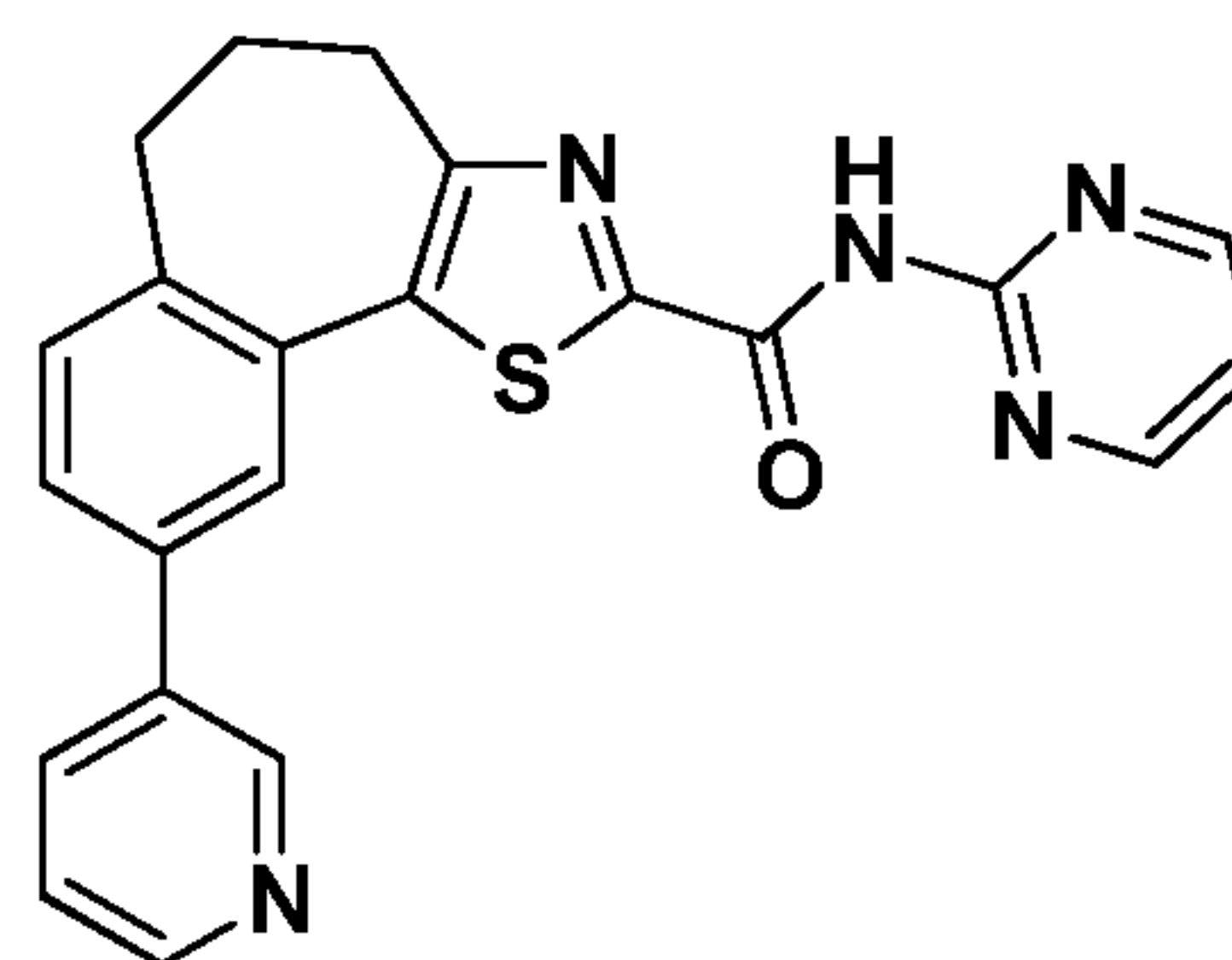
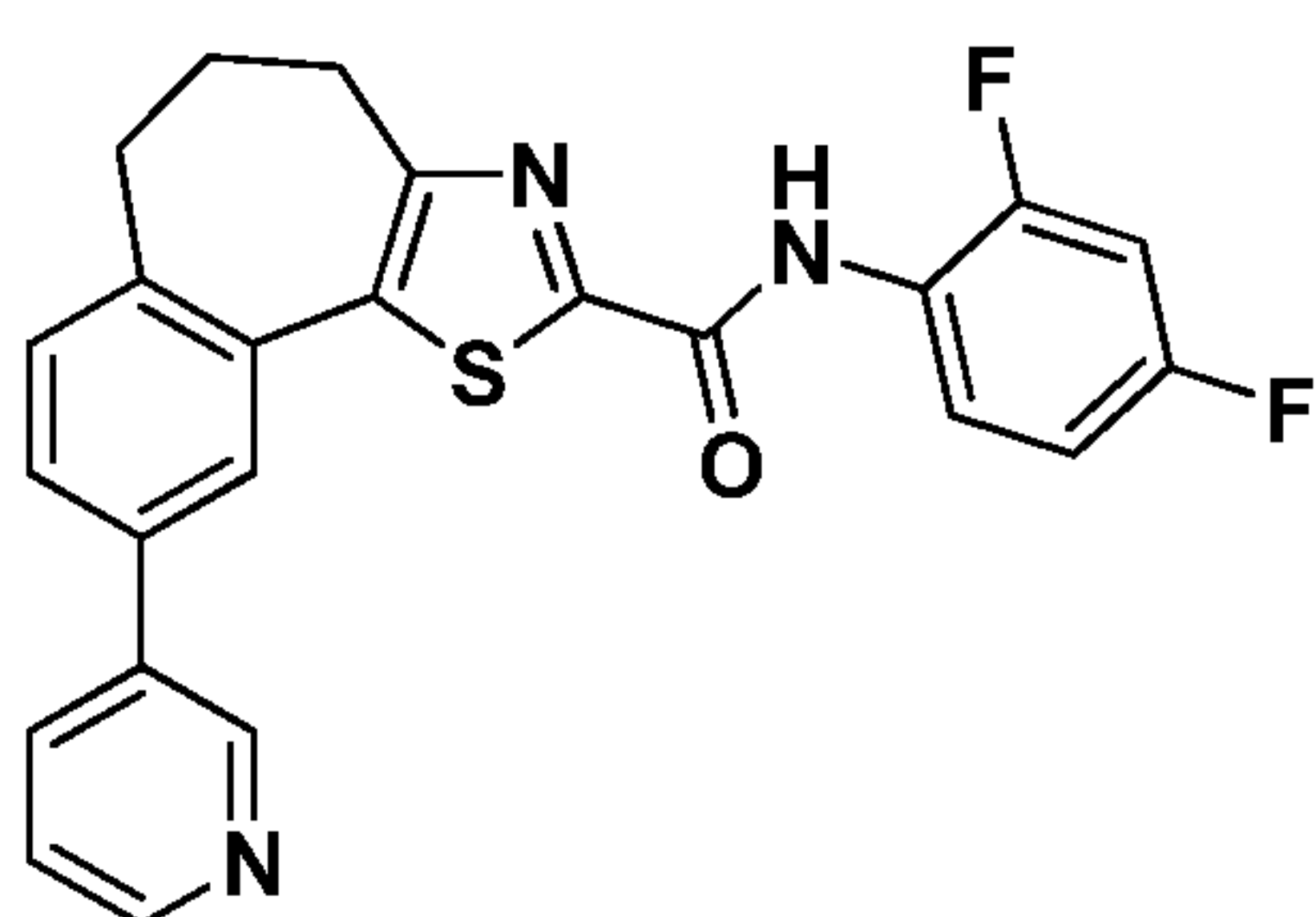
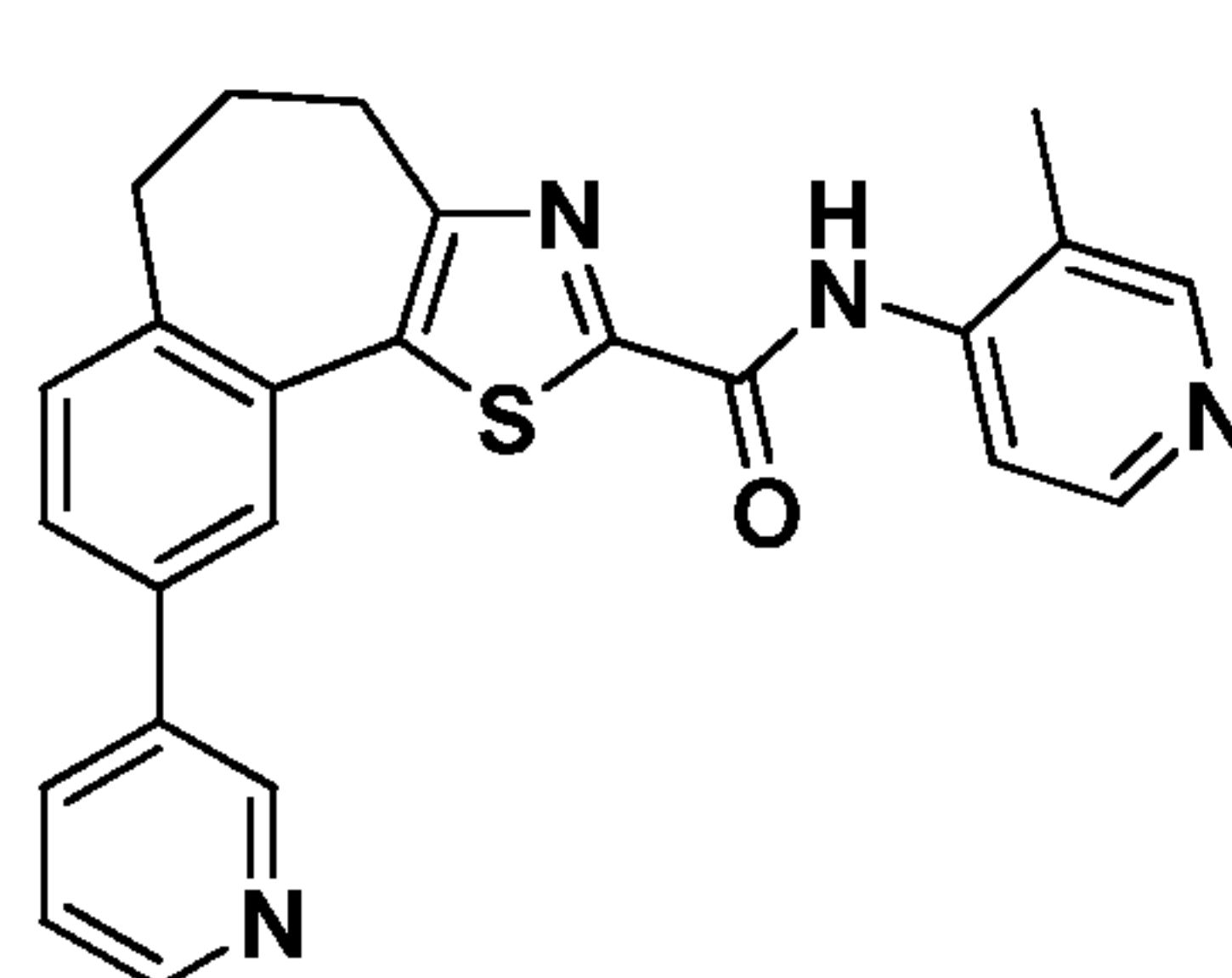
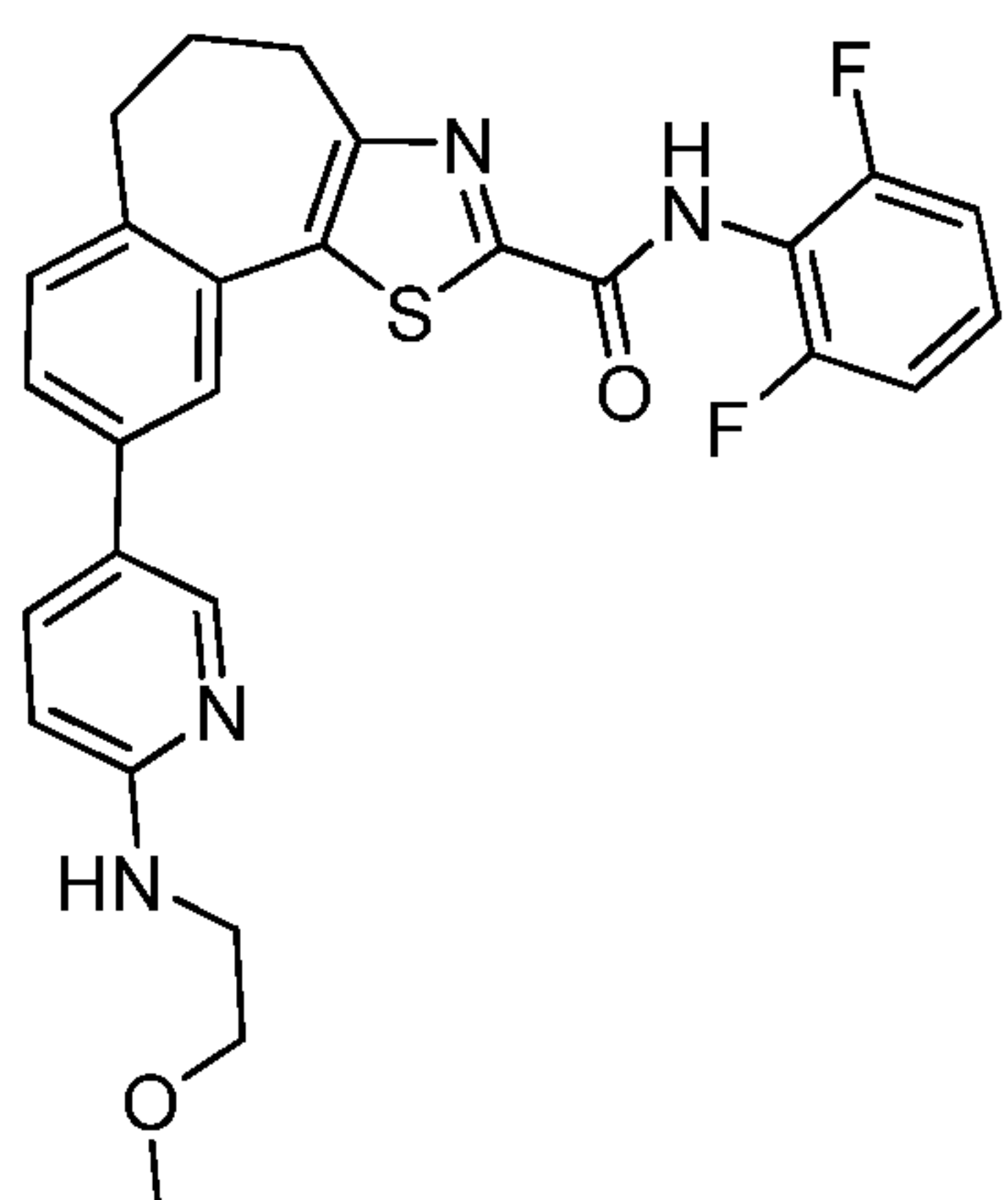
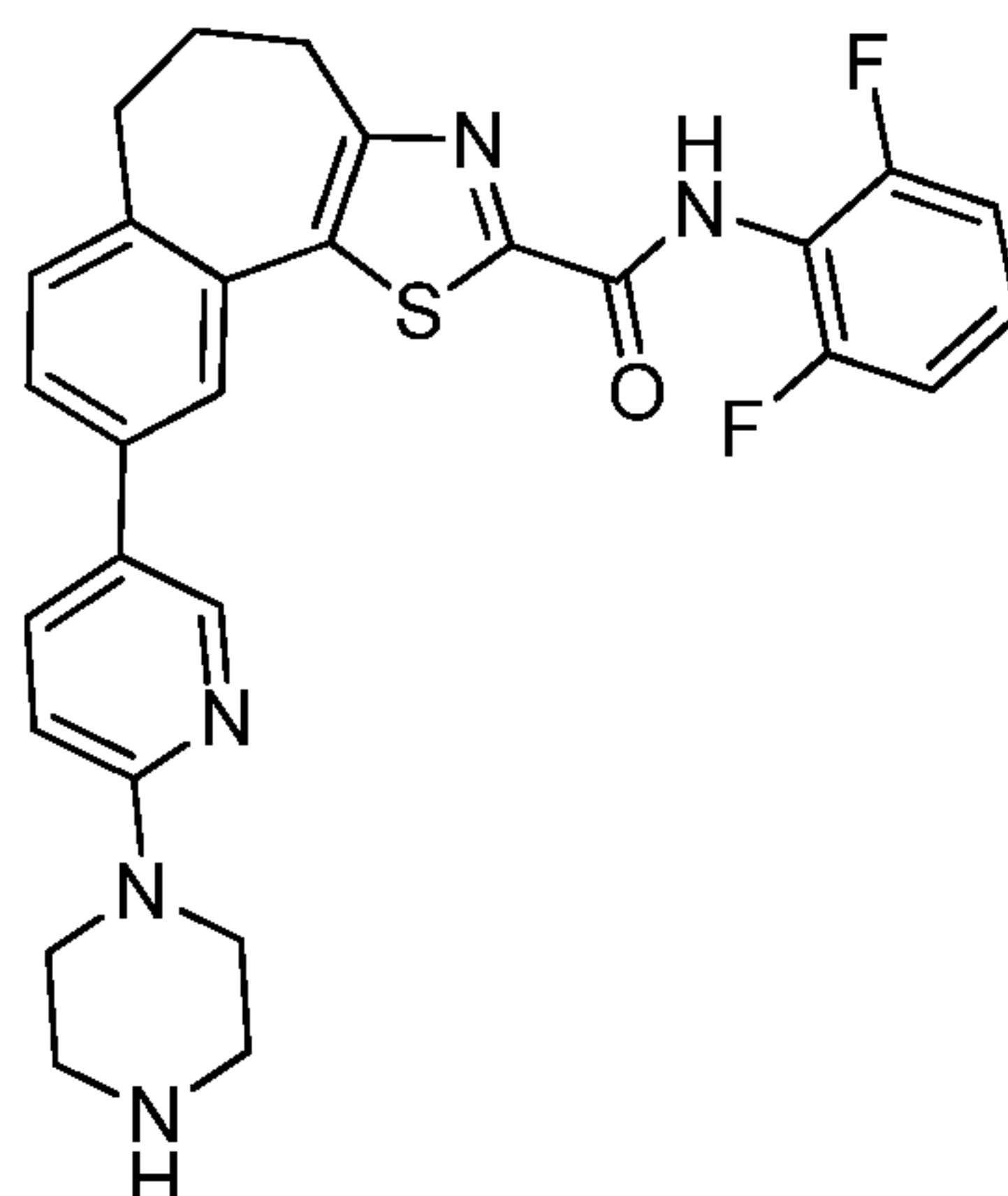
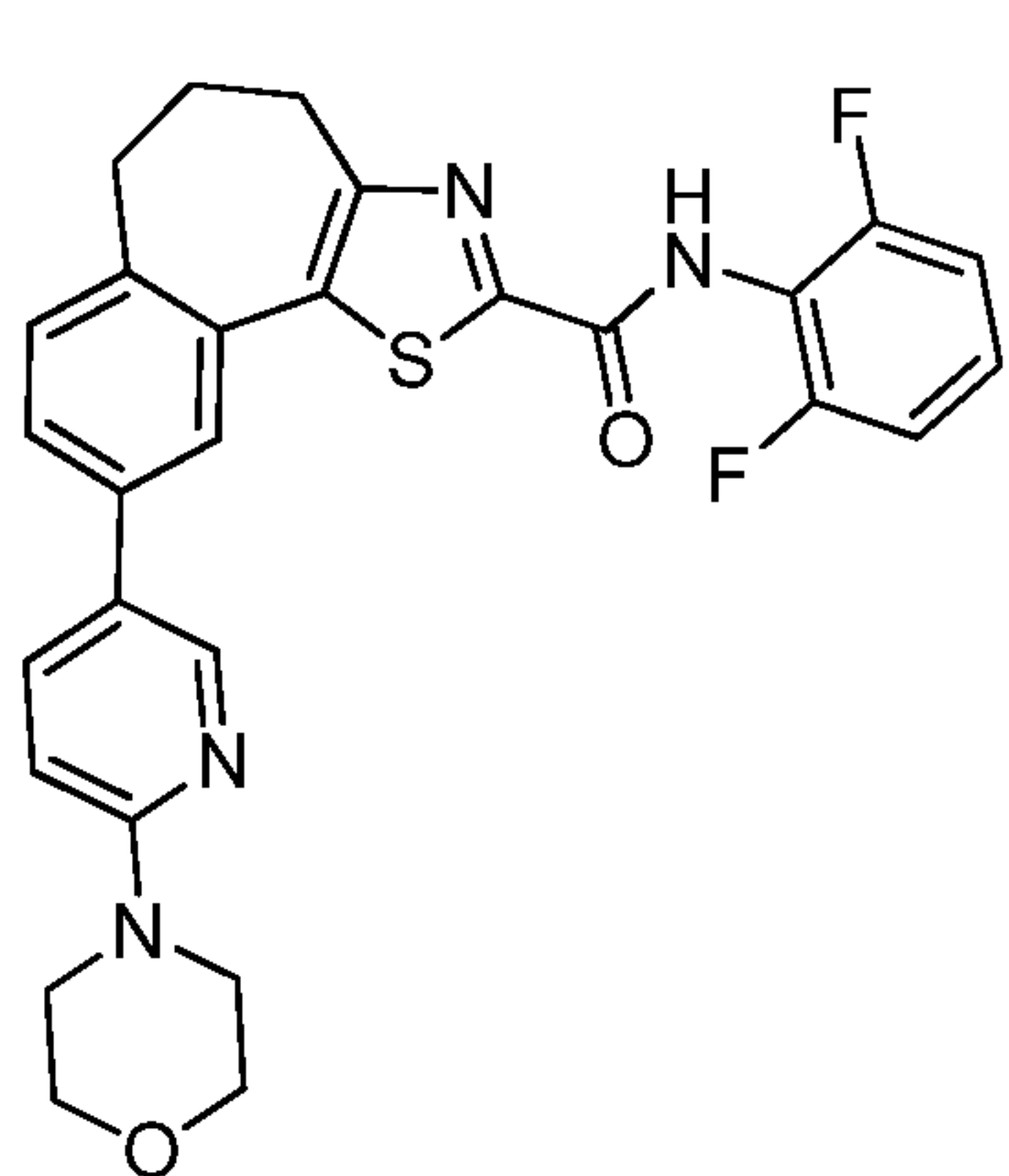
H-Cl



H-Cl

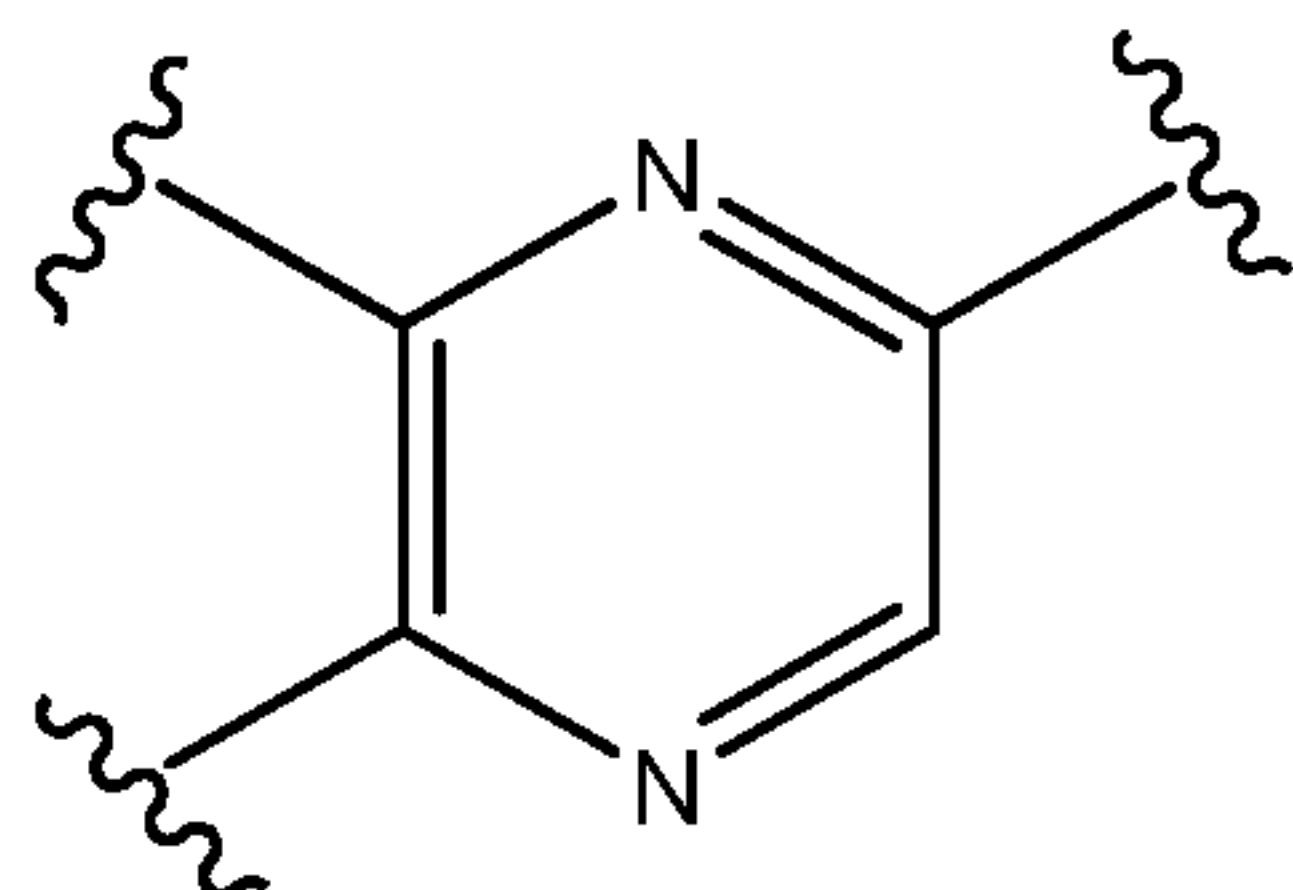


H-Cl



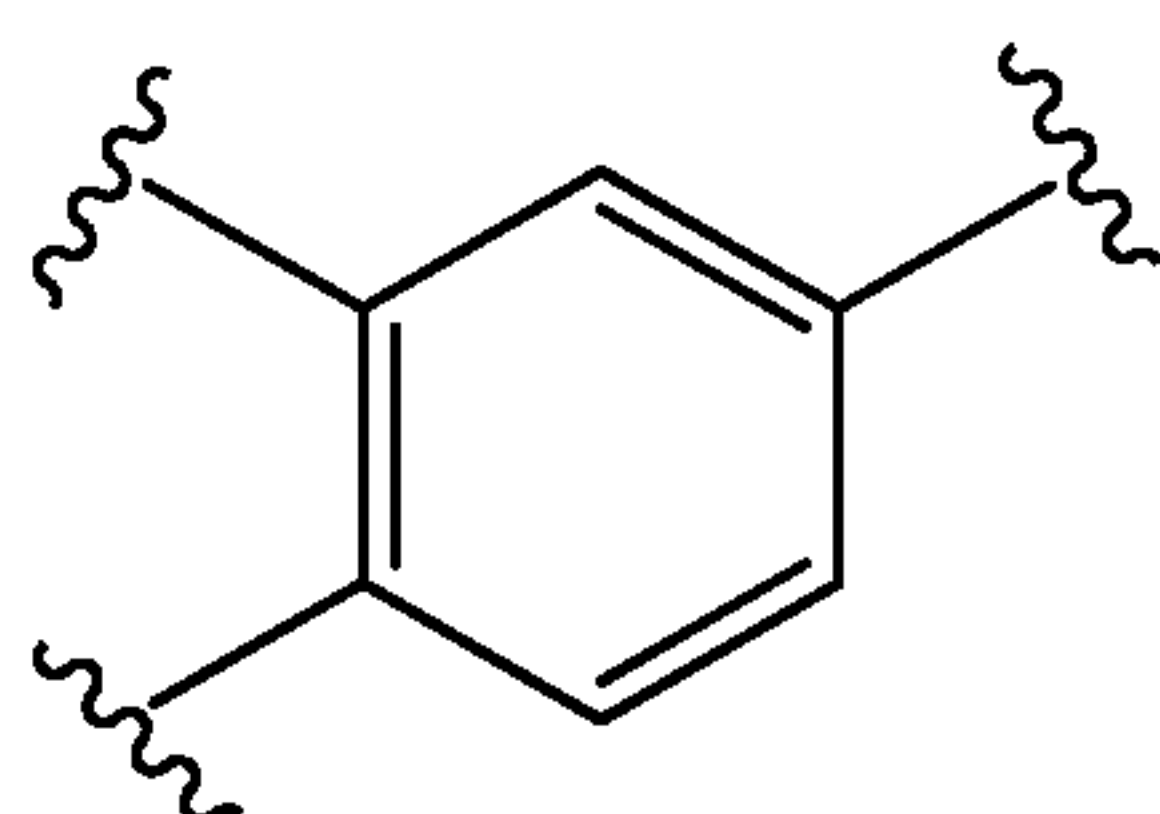
In one embodiment of compounds of formula (XXI), Y' is an optionally substituted C3-C5

alkyl or an optionally substituted C3-C6 cycloalkyl; Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens; and Ring N is:



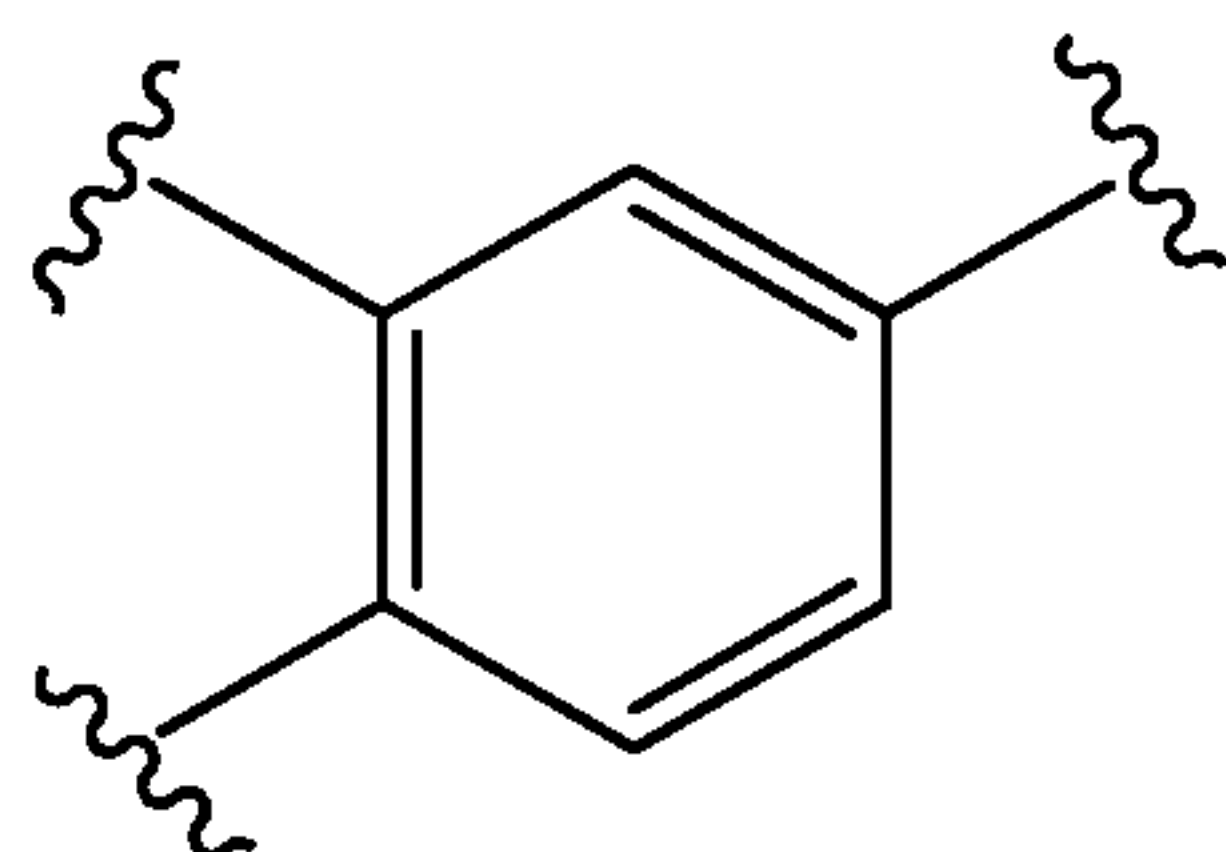
and

Y' is an optionally substituted C3-C5 alkyl or an optionally substituted C3-C6 cycloalkyl; Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens; and Ring N is:



or

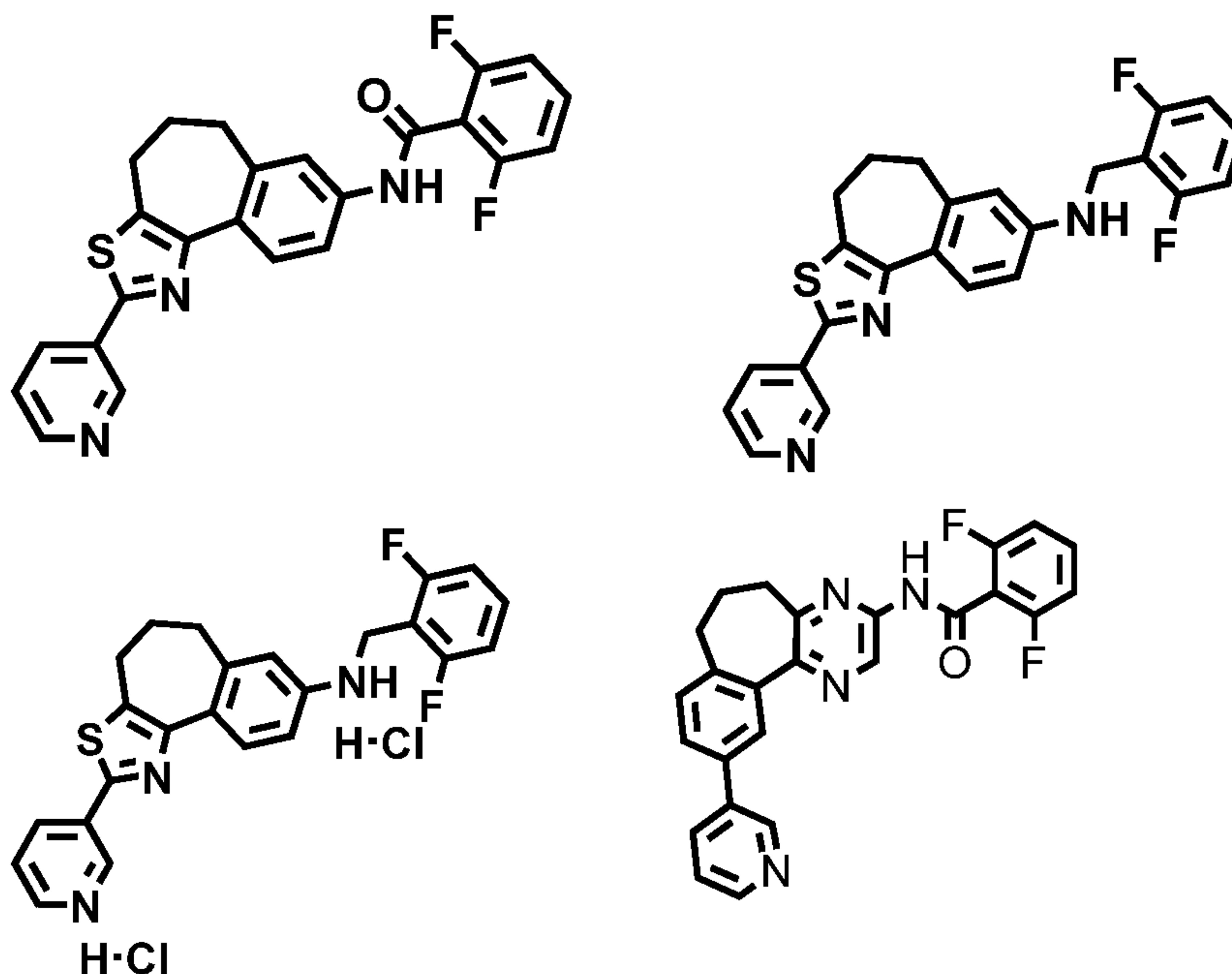
Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl; Ring K is a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens; and Ring N is:



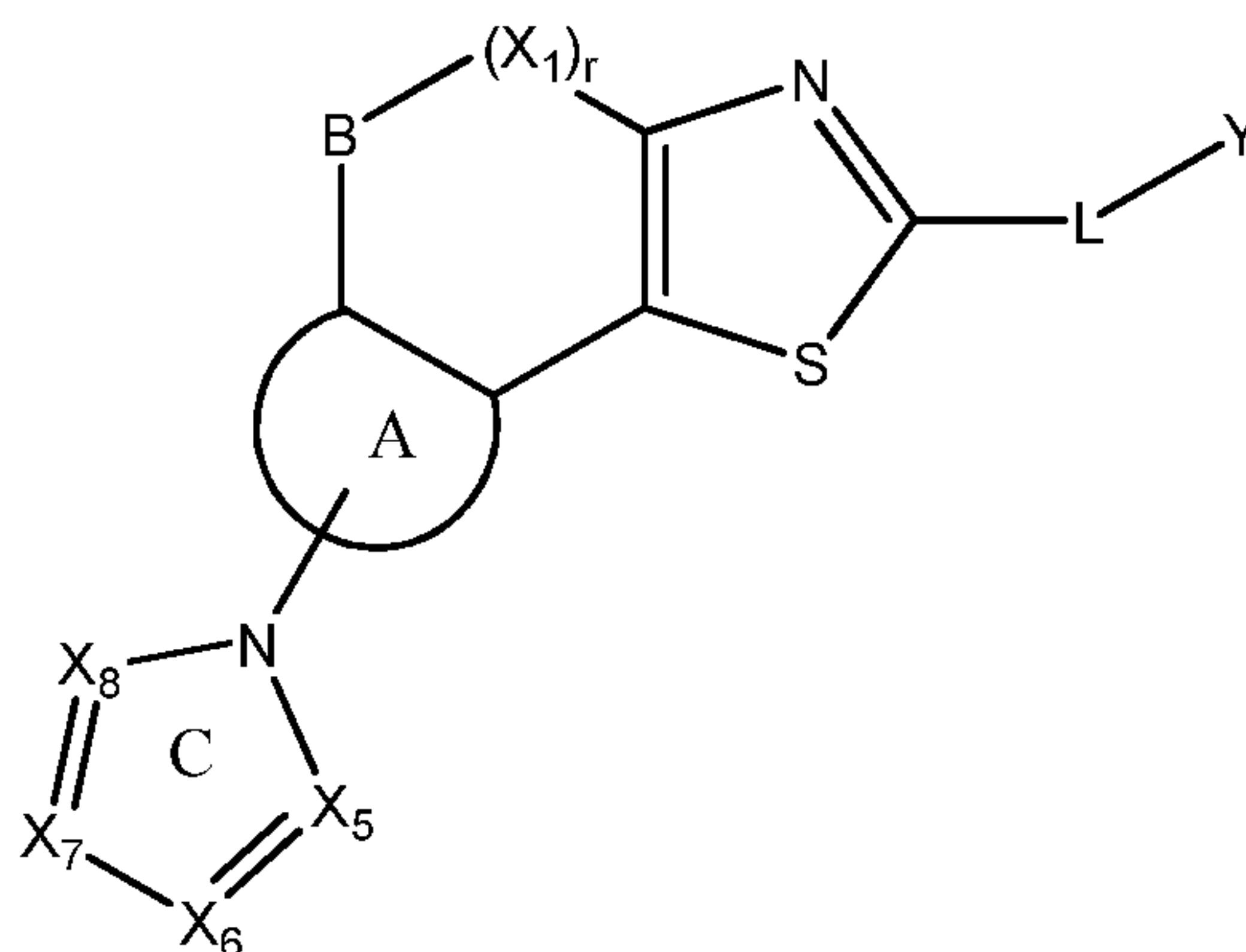
and

Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl; Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens, for all other Rings N.

In one embodiment of compounds of formula (XXI), the following compounds are specifically excluded:



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



(XXII)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl wherein the ring atoms are selected from the group consisting of C, S, O, or N, and wherein Ring A contains at least one C atom that is bonded to Ring C;

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

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

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

each of X_5 , X_6 , X_7 , and X_8 is independently $-\text{N}-$ or $-\text{C}(\text{R}^c)-$;

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)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)_pR₄, or -S(O)_pNR₁R₂;

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)NR₁R₂, -C(O)R₄, or -C(O)OR₄;

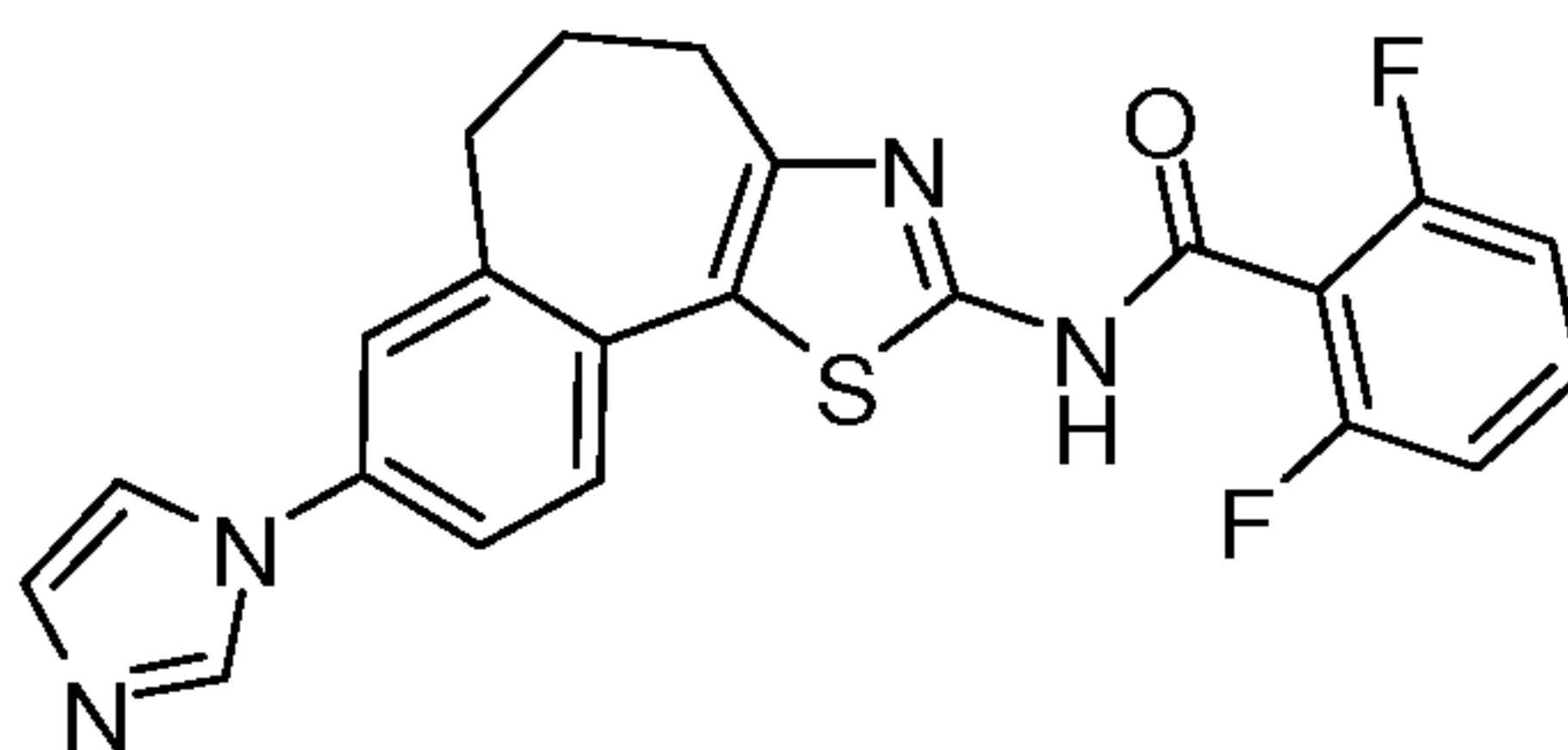
each R^c is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, nitro, or cyano;

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

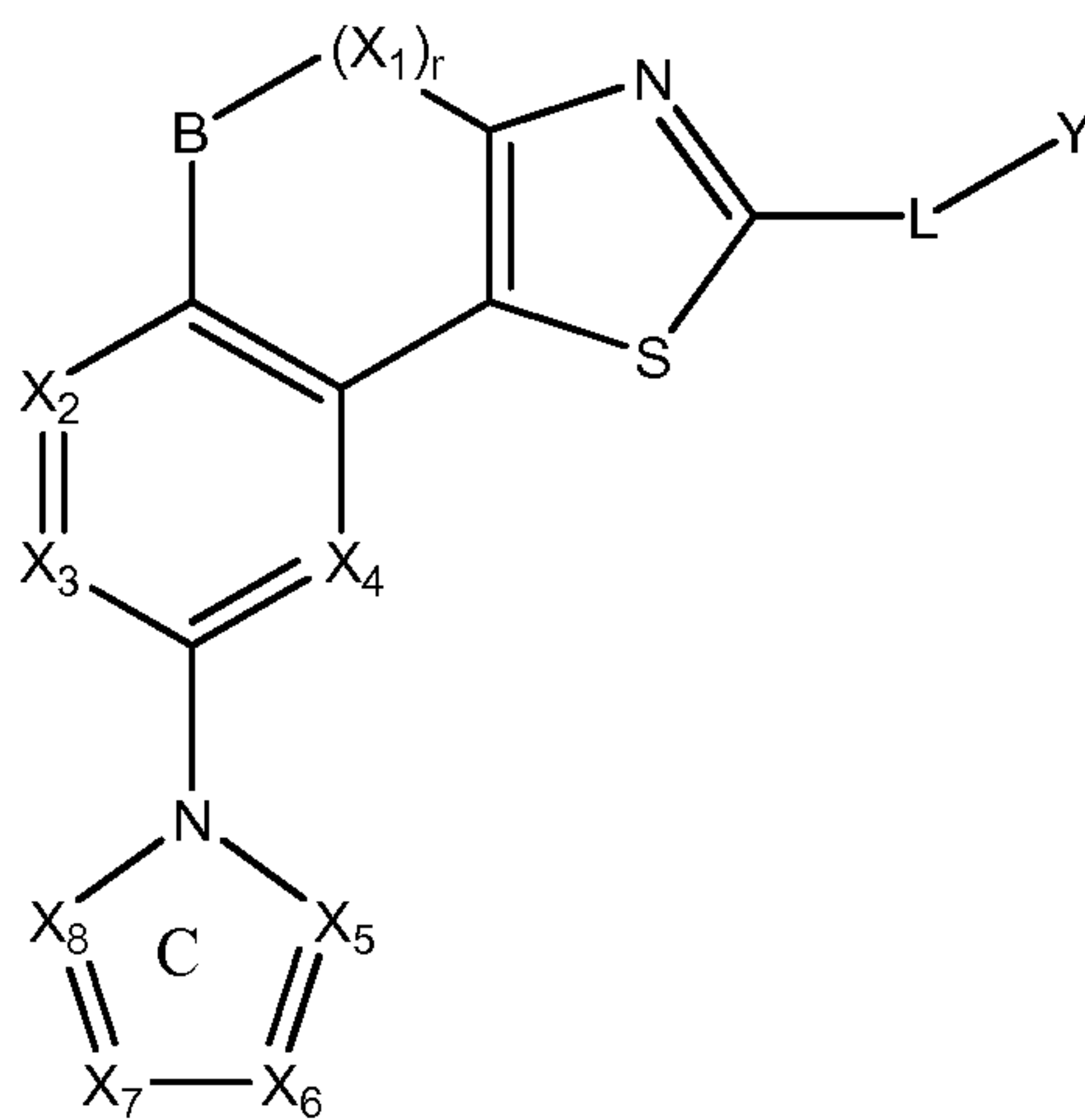
R₄ and R₅, for each occurrence is, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl,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

r is 1, 2, 3, or 4; and p is 0, 1, or 2.

In one embodiment of compounds of formula (XXII), the compound is not:



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

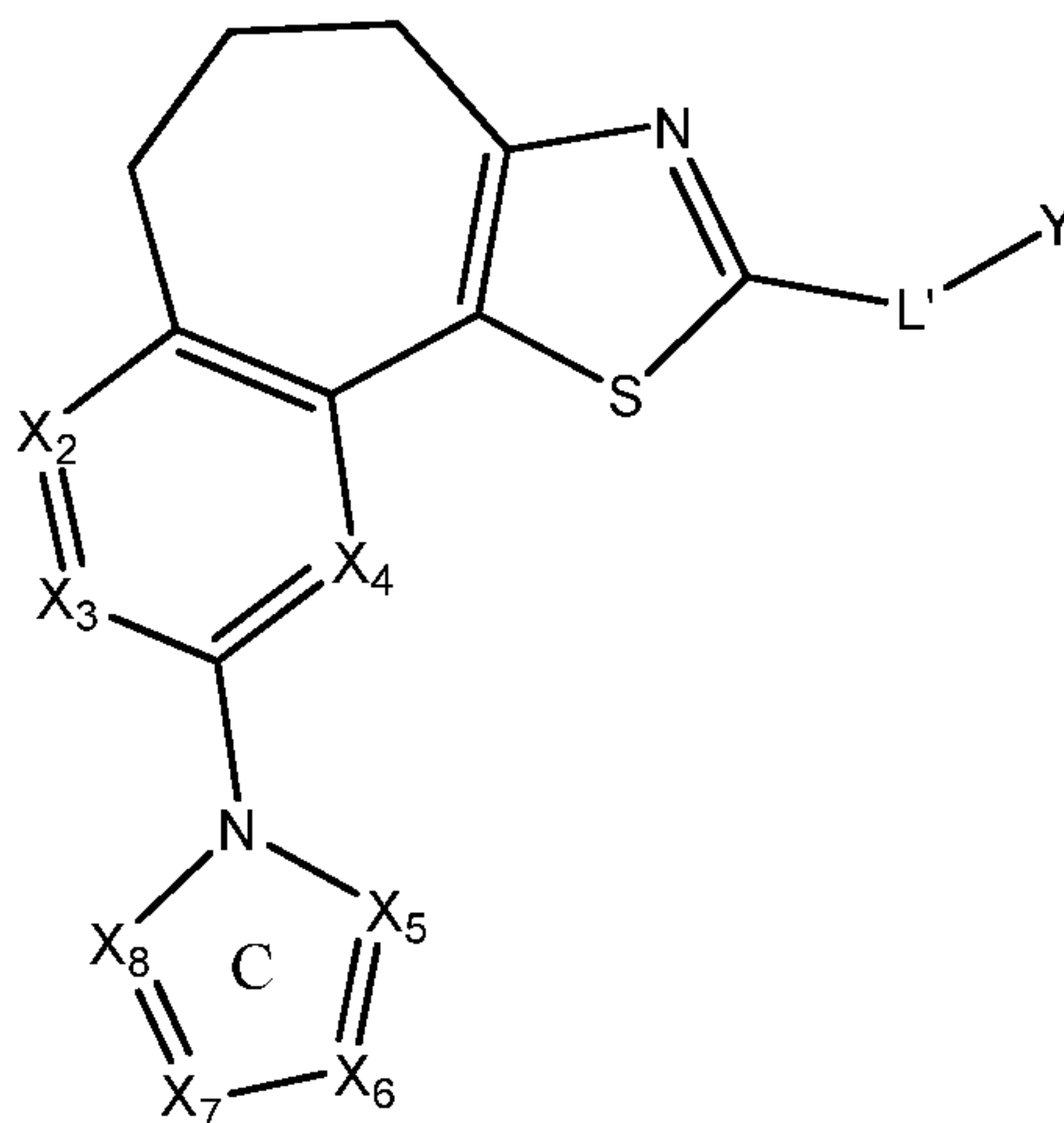


(XXIII)

or a pharmaceutically acceptable salt thereof, wherein:

- 5 each of X_2 , X_3 , and X_4 is independently $-\text{CH}-$ or $-\text{N}-$; and X_1 , X_5 , X_6 , X_7 , X_8 , r , B , L and Y are defined as for formula (XXII).

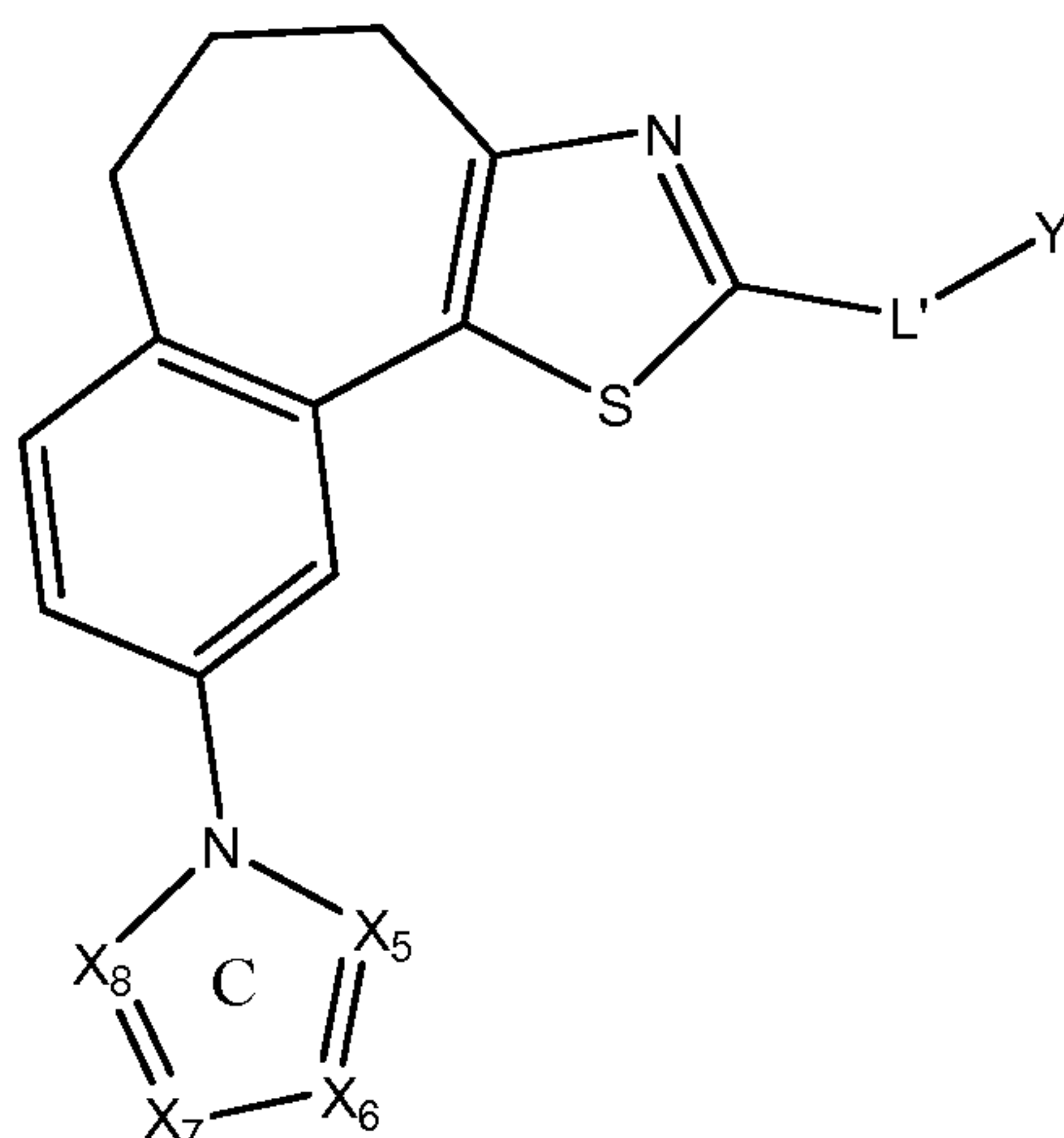
Another embodiment of the invention relates to compounds of formula (XXIV):



(XXIV)

or a pharmaceutically acceptable salt thereof, wherein: L' is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NHC(O)NH}-$, $-\text{NH-C(O)}-$, or $-\text{C(O)-NH}-$; and Y , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , and X_8 are defined as for formula (XXIII).

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

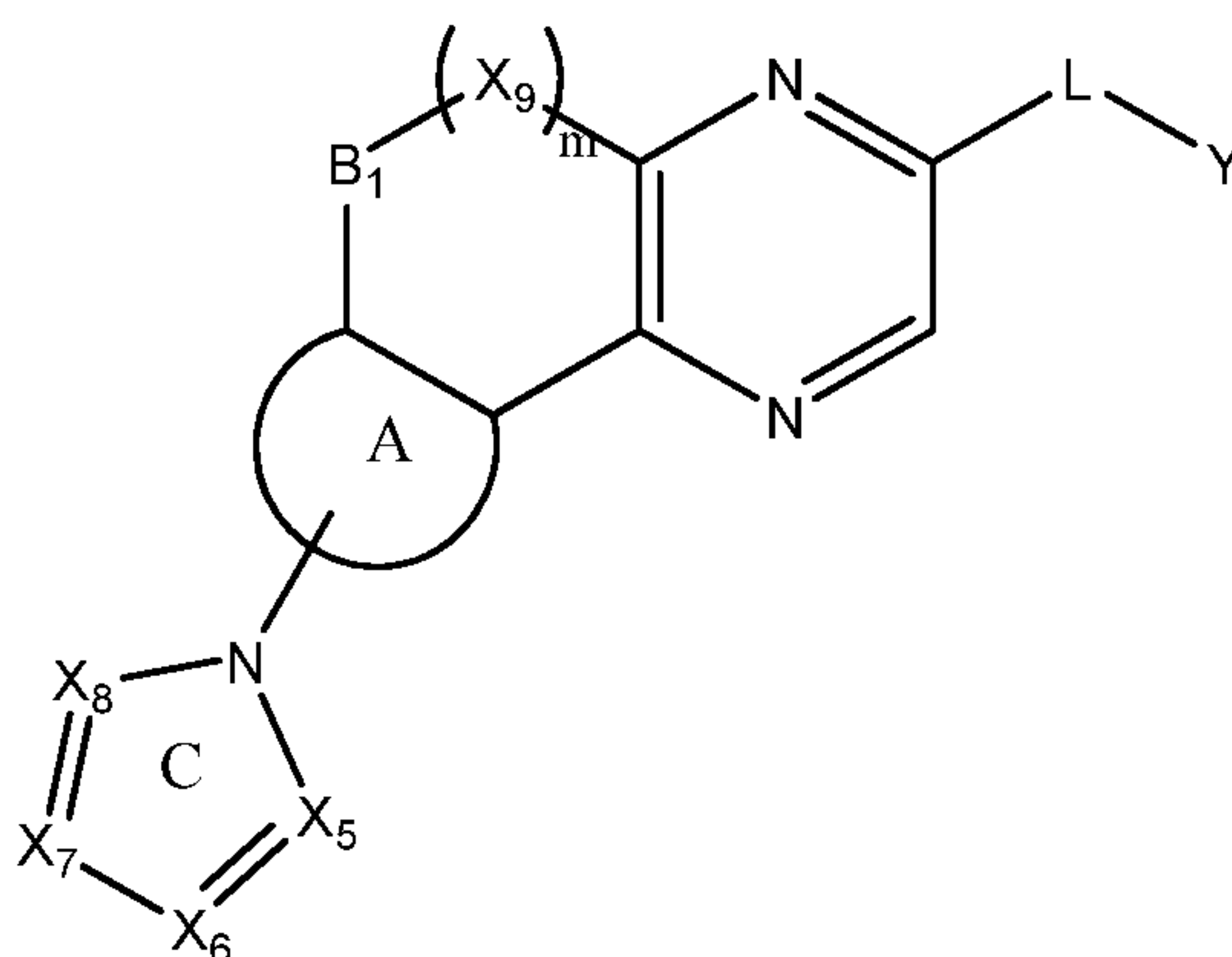


(XXV)

or a pharmaceutically acceptable salt thereof, wherein: L' is defined as for formula (XXIV); and Y, X₅, X₆, X₇, and X₈ are defined as for formula (XXIII).

5

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



(XXVI)

or a pharmaceutically acceptable salt thereof, wherein:

10

X₉ is -C(R^a)₂-;

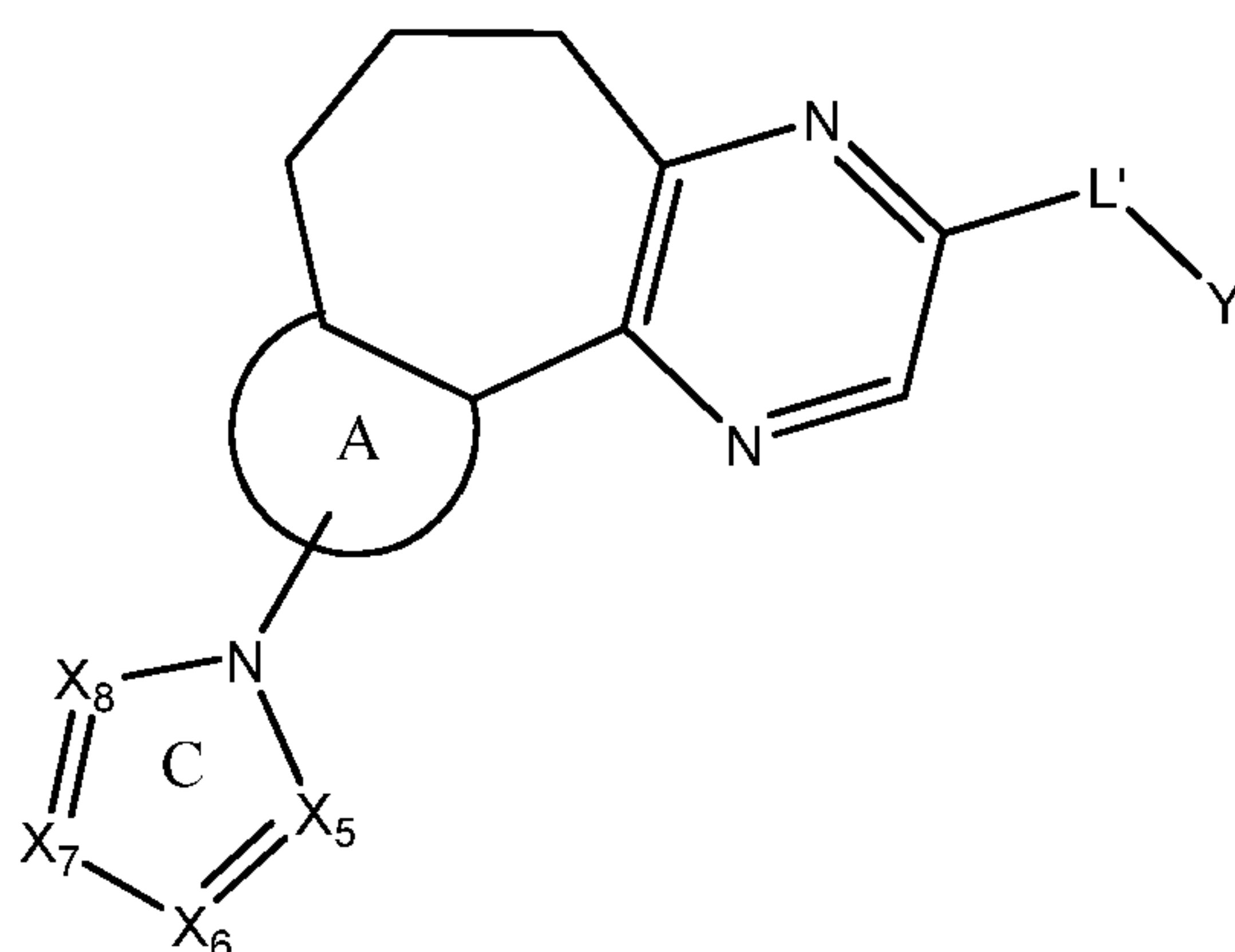
B₁ is -C(R^a)₂-, -C(O)-; or -O-;

m is 1 or 2; and

X_5, X_6, X_7, X_8 , Ring A, L and Y are defined as for formula (XXII).

15

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

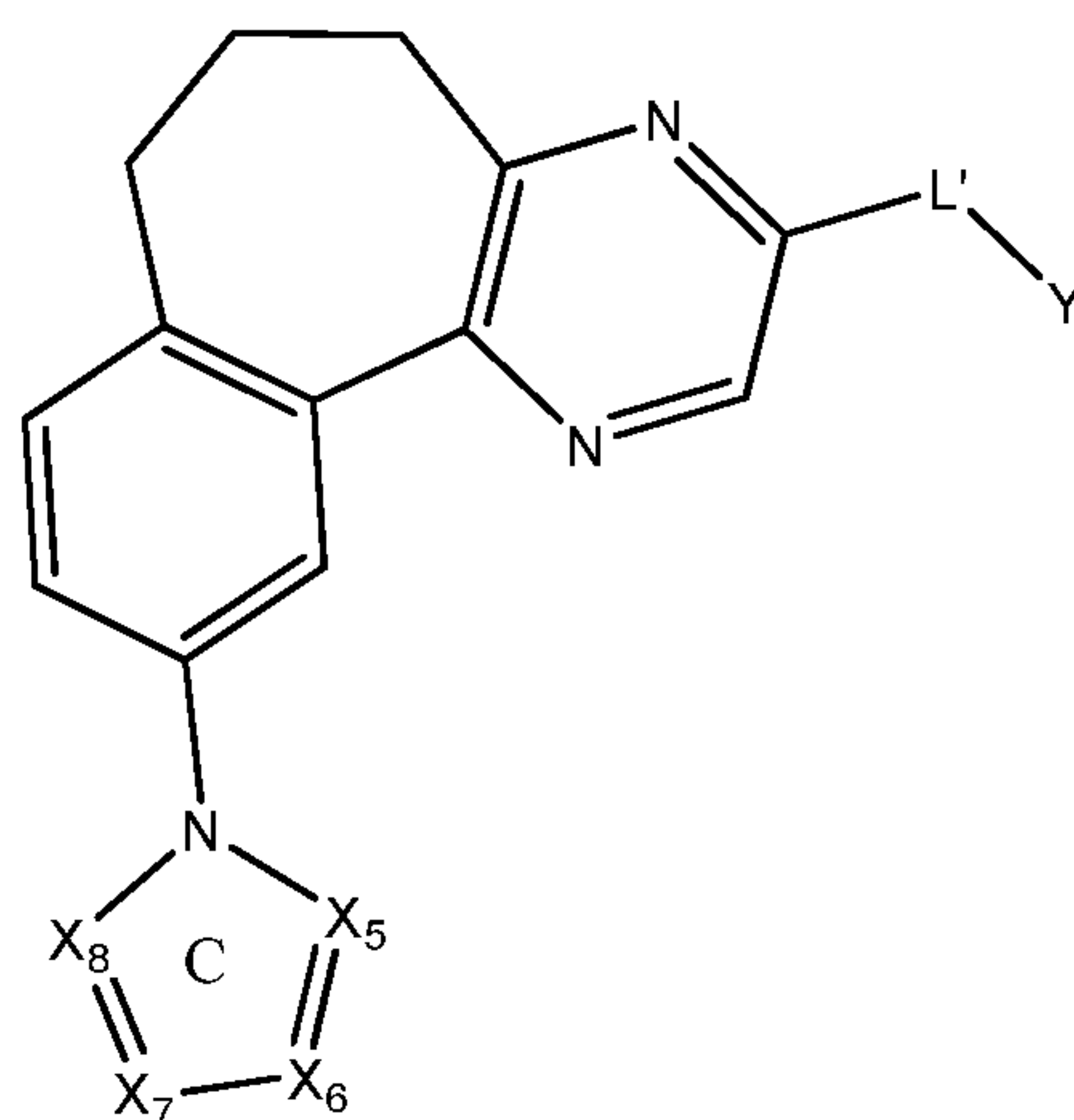


(XXVII)

or a pharmaceutically acceptable salt thereof, wherein: L' is defined as for formula (XXIV) and X₅, X₆, X₇, X₈, Ring A, and Y are defined as for formula (XXII).

5

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

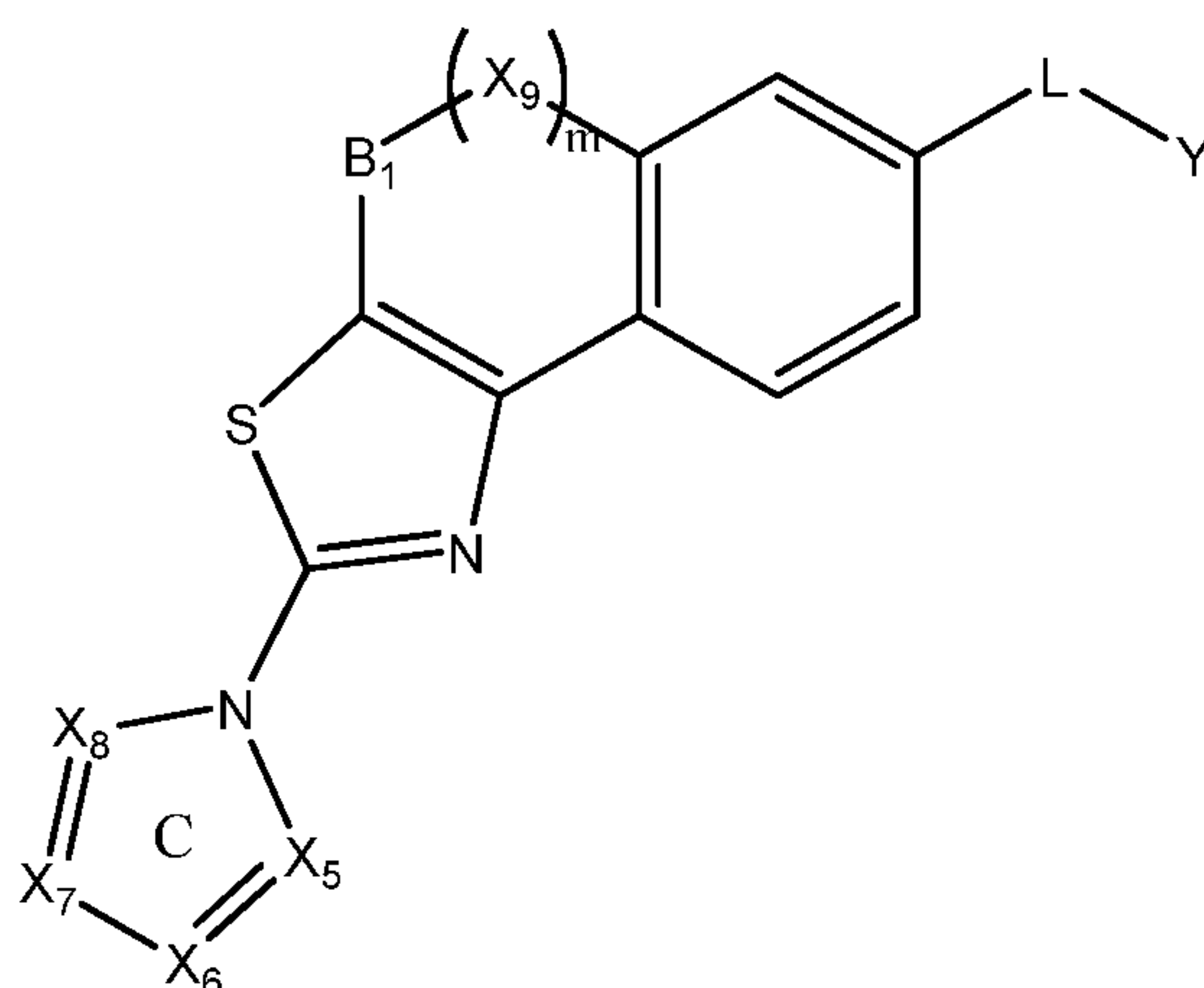


(XXVIII)

or a pharmaceutically acceptable salt thereof, wherein: L' is defined as for formula (XXIV) and X₅, X₆, X₇, X₈, and Y are defined as for formula (XXII).

10

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



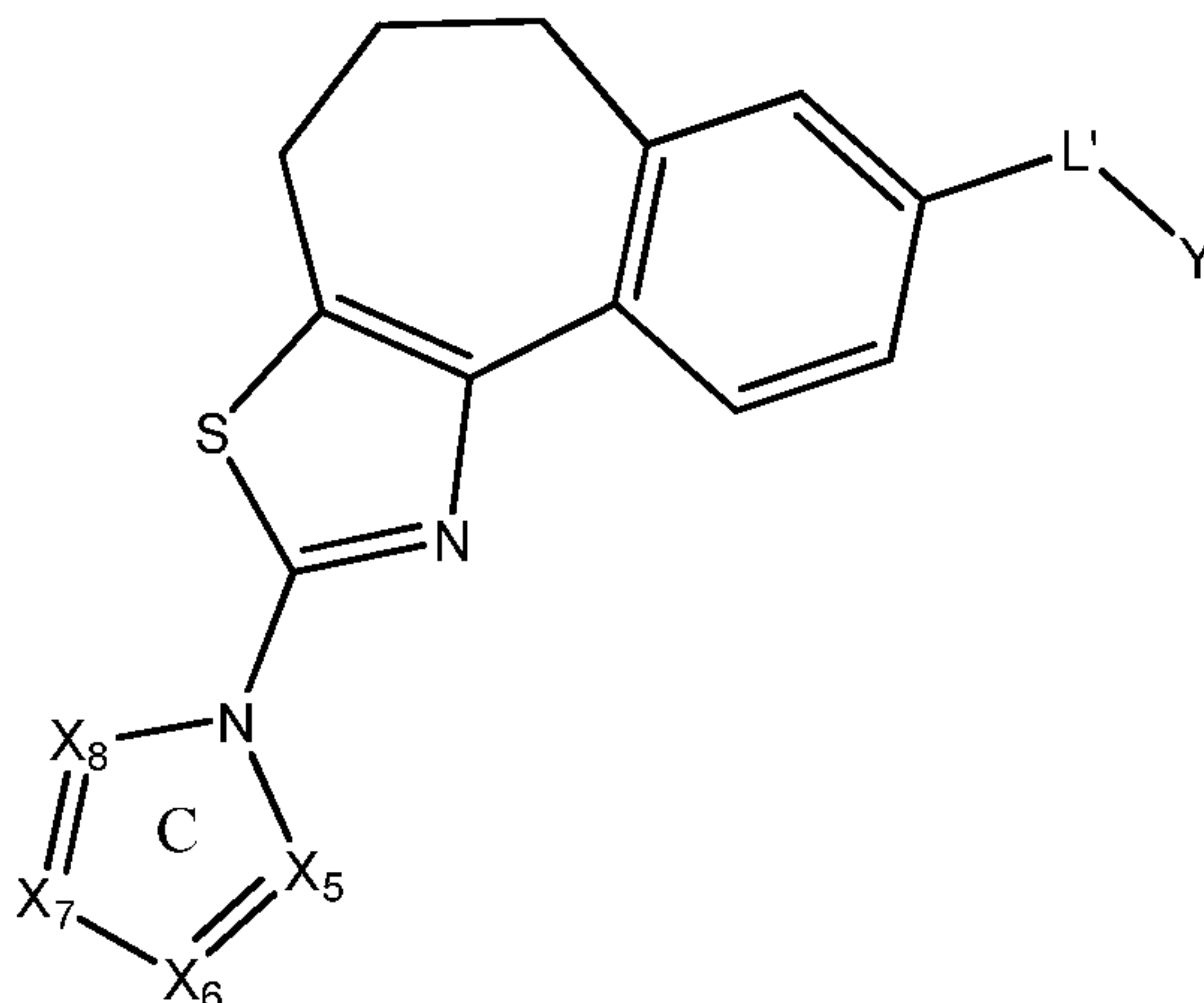
(XXIX)

or a pharmaceutically acceptable salt thereof, wherein:

B₁, X₉, and m are defined as for formula (XXVI) and X₅, X₆, X₇, X₈, Ring A, L and Y are defined as for formula (XXII).

5

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



(XXX)

or a pharmaceutically acceptable salt thereof, wherein: L' is defined as for formula (XXIV) and

10 X₅, X₆, X₇, X₈, and Y are defined as for formula (XXII).

In one embodiment, in compounds represented by formula (XXII), (XXIII), (XXVI), or (XXIX), L is -NRCH₂-, -CH₂NR-, -C(O)-, -NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, -NR-C(S)-, -C(S)-NR-, -NRC(NR₉)- or -C(NR₉)NR-;

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

R₉, for each occurrence, is independently -H, halo, an alkyl, -OR₇, -NR₁₁R₁₂, -C(O)R₇, -C(O)OR₇, or -C(O)R₁₁R₁₂;

20 R₇, for each occurrence, is independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

25 R₁₁ and R₁₂, 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 R₁₁ and R₁₂ 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 (XXII), (XXIII), (XXVI), or (XXIX), L is $-\text{NRCH}_2-$, $-\text{CH}_2\text{NR}-$, $-\text{NR}-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{NR}-$. In another aspect, R is $-\text{H}$. In a further aspect, L is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{C}(\text{O})-\text{NH}-$. In another aspect, L is $-\text{NH}-\text{C}(\text{O})-$. In another aspect, L is $-\text{C}(\text{O})-\text{NH}-$.

5

In one embodiment, in compounds represented by formula (XXII), (XXIII), (XXVI), or (XXIX), L is $-\text{NRS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{NR}-$, $-\text{NRS}(\text{O})_2\text{NR}-$, $-\text{NRC}(\text{O})\text{NR}-$, $-\text{NRC}(\text{NR})\text{NR}-$, $-\text{NRC}(\text{S})\text{NR}-$, $-\text{NRCH}_2\text{NR}-$, $-\text{NRN}=\text{CR}_6-$, $-\text{C}(\text{NR})-$, or $-\text{CR}_6=\text{NNR}-$;

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

10

R_6 , for each occurrence, is $-\text{H}$ or alkyl; and

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

15

In one aspect, in compounds represented by formula (XXII), (XXIII), (XXVI), or (XXIX), R is $-\text{H}$; and R_6 is $-\text{H}$. In another aspect, L is $-\text{NHS}(\text{O})_2-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NHC}(\text{S})\text{NH}-$, or $-\text{NHN}=\text{CH}-$. In one aspect, L is $-\text{NHC}(\text{O})\text{NH}-$.

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In one aspect, in compounds represented by formula (XXII), (XXIII), (XXVI), or (XXIX), L is $-\text{C}(=\text{NR}_{20})\text{NR}-$. R_{20} is $-\text{H}$, alkyl, $-\text{C}(\text{O})-\text{R}_7$, $-\text{OR}_7$, or $-\text{C}(\text{O})\text{OR}_7$. In one aspect, R is $-\text{H}$.

In one embodiment, in compounds represented by formula (XXII), (XXIII), (XXVI), or (XXIX), L is $-\text{NRCH}_2-$, $-\text{CH}_2\text{NR}-$, $-\text{NRC}(\text{O})\text{NR}-$, $-\text{NR}-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{NR}-$. In one aspect, L is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{NH}-$. In one aspect, L is $-\text{NHCH}_2-$. In one aspect, L is $-\text{CH}_2\text{NH}-$. In one aspect, L is $-\text{NHC}(\text{O})\text{NH}-$. In one aspect, L is $-\text{NH}-\text{C}(\text{O})-$. In one aspect, L is $-\text{C}(\text{O})-\text{NH}-$.

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In one embodiment, in compounds represented by any of formula (XXIV), (XXV), (XXVII), (XVIII), or (XXX), L' is $-\text{NRCH}_2-$. In one embodiment, in compounds represented by any of formula (XXIV), (XXV), (XXVII), (XVIII), or (XXX), L' is $-\text{CH}_2\text{NR}-$. In one embodiment, in compounds represented by any of formula (XXIV), (XXV), (XXVII), (XVIII), or (XXX), L' is $-\text{NRC}(\text{O})\text{NR}-$. In one embodiment, in compounds represented by any of formula (XXIV), (XXV), (XXVII), (XVIII), or (XXX), L' is $-\text{NR}-\text{C}(\text{O})-$. In one embodiment, in compounds represented by formula (XXIV), (XXV), (XXVII), (XVIII), or (XXX), L' is $-\text{C}(\text{O})-\text{NR}-$.

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In one embodiment, in compounds represented by any of formulae (XXII) – (XXX), Y is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substituted 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, two, or three substituents. In a further aspect, Y is substituted with one to two substituents. In another aspect, the substituents on Y are each independently a lower alkyl or a halo. In another aspect, the substituents on Y are each halo. In another aspect, the substituents on Y are each fluoro. 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 any of formulae (XXII) – (XXX), Y is an optionally substituted 5 or 6-membered aryl. In one embodiment, in compounds represented by any of formulae (XXII) – (XXX), Y is an optionally substituted 5 or 6-membered heteroaryl.

In one embodiment, in compounds represented by formula (XXII) or (XXIII), r is 3. In one embodiment, in compounds represented by formula (XXII) or (XXIII), r is 4. In one embodiment, in compounds represented by formula (XXII) or (XXIII), r is 2.

In one embodiment, in compounds represented by formula (XXII) or (XXIII), 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 (XXII) or (XXIII), 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 (XXVI) or (XXIX), 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 (XXVI) or (XXIX), X_9 is $-CH_2-$. In one aspect, m is 2.

In one embodiment, in compounds represented by formula (XXVI) or (XXIX), m is 1. In one

embodiment, in compounds represented by formula (XXVI) or (XXIX), m is 2.

In one embodiment, in compounds represented by formula (XXVI) or (XXIX), B₁ is -C(R^a)₂- or -O- and each X₉ is -CH₂-.

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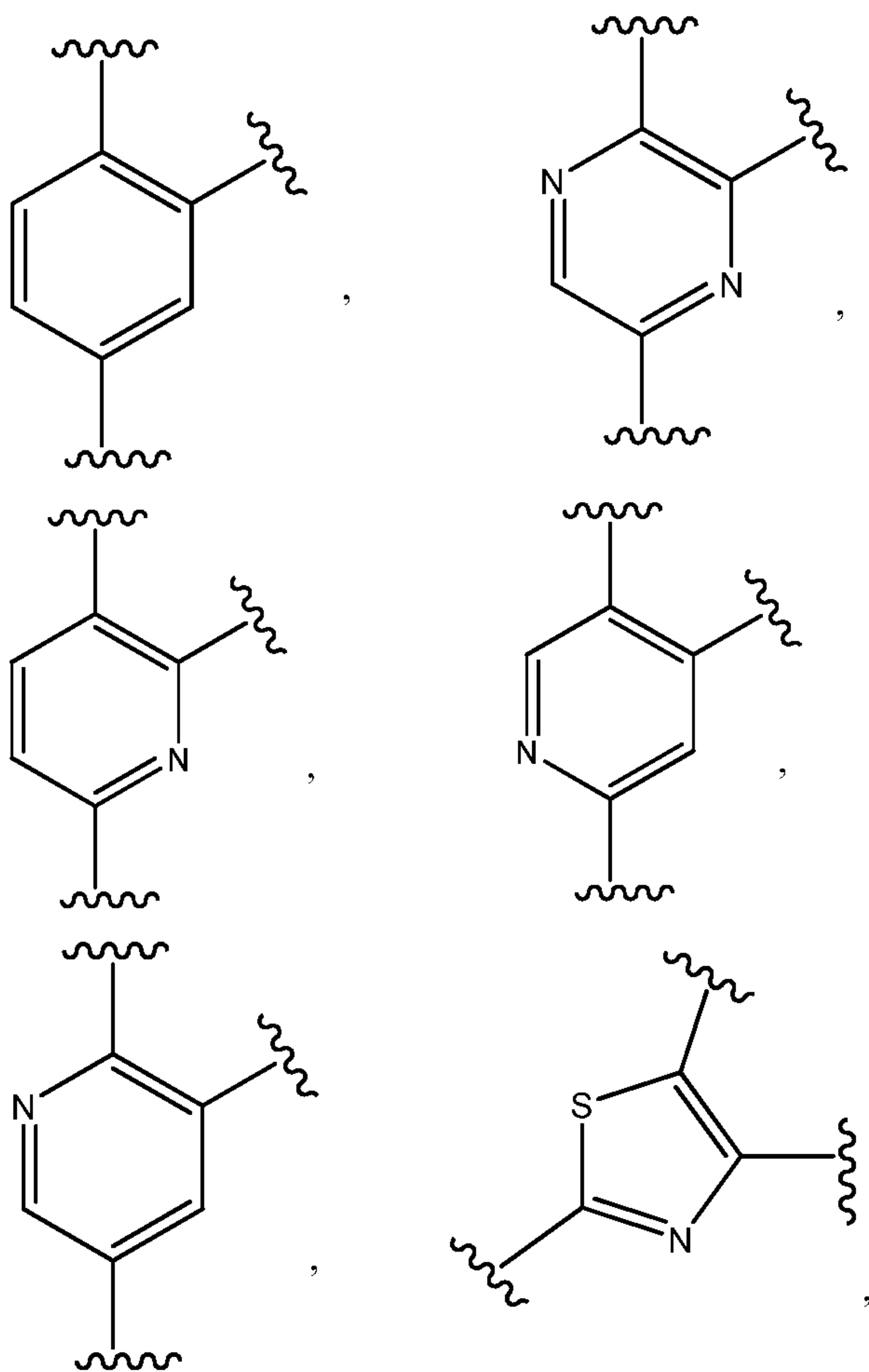
In one embodiment, in compounds represented by formula (XXVI) or (XXIX), B₁ is -C(R^a)₂- and each X₉ is -CH₂-.

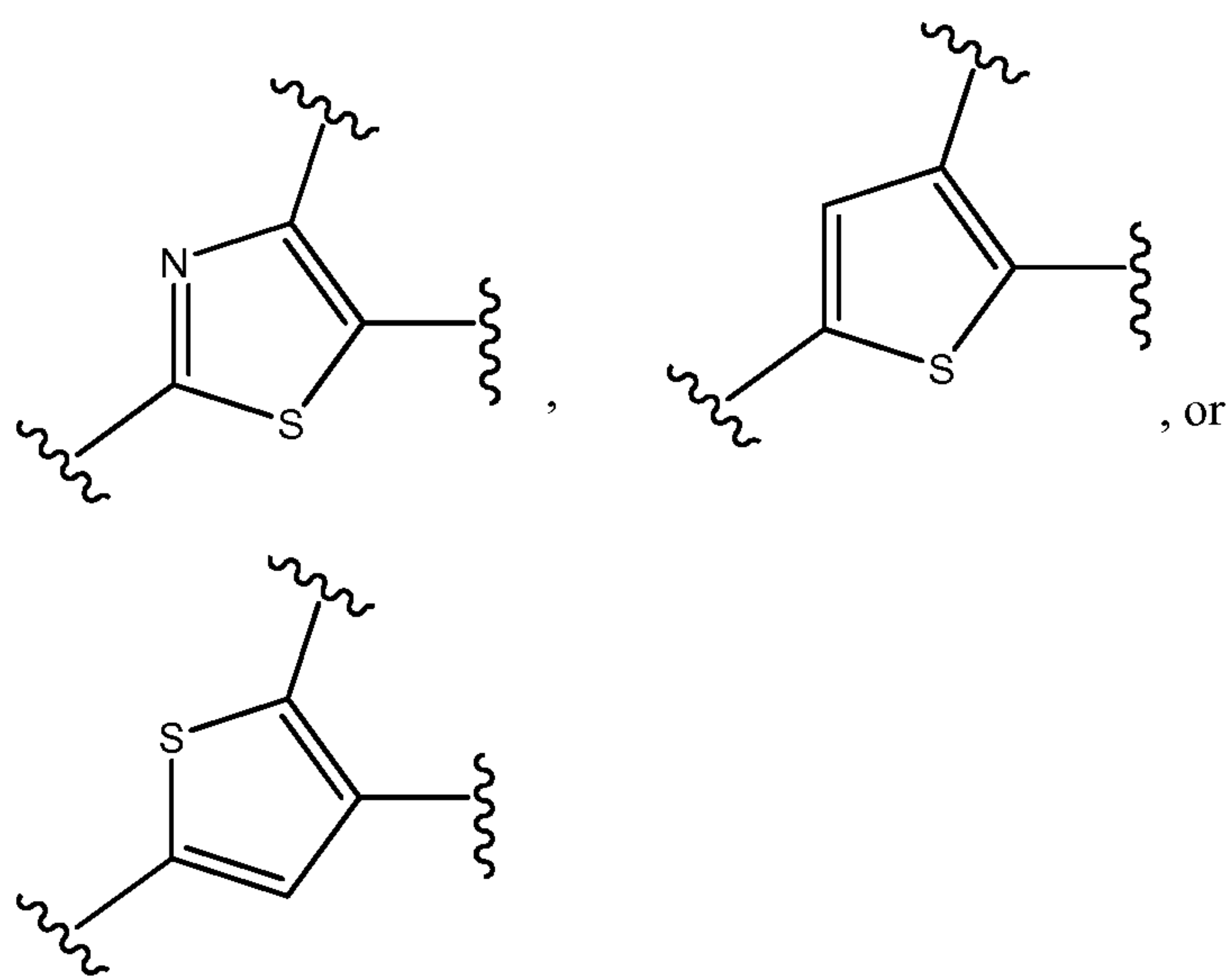
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In one embodiment, in compounds represented by formula (XXII), (XXVI), or (XXVII), Ring A is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl.

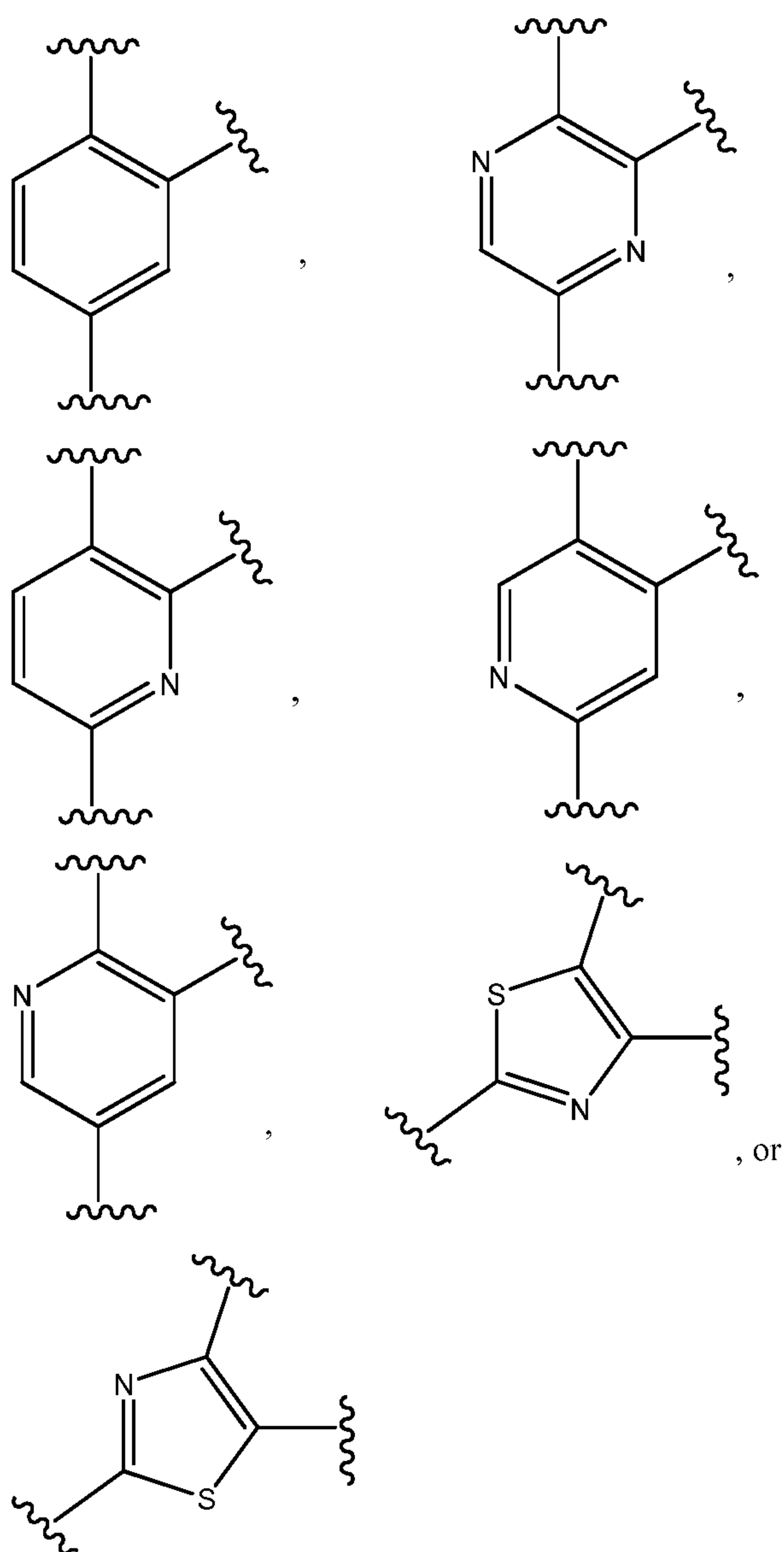
In one embodiment, in compounds represented by formula (XXII), (XXVI), or (XXVII), Ring A is:

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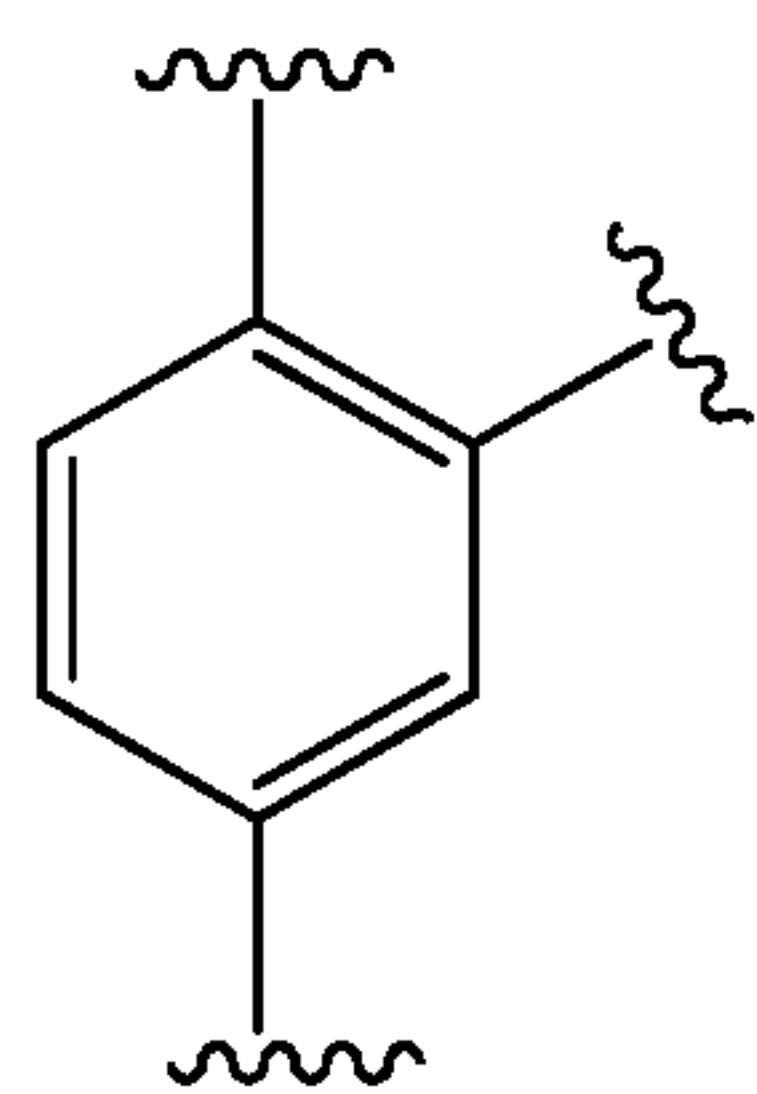




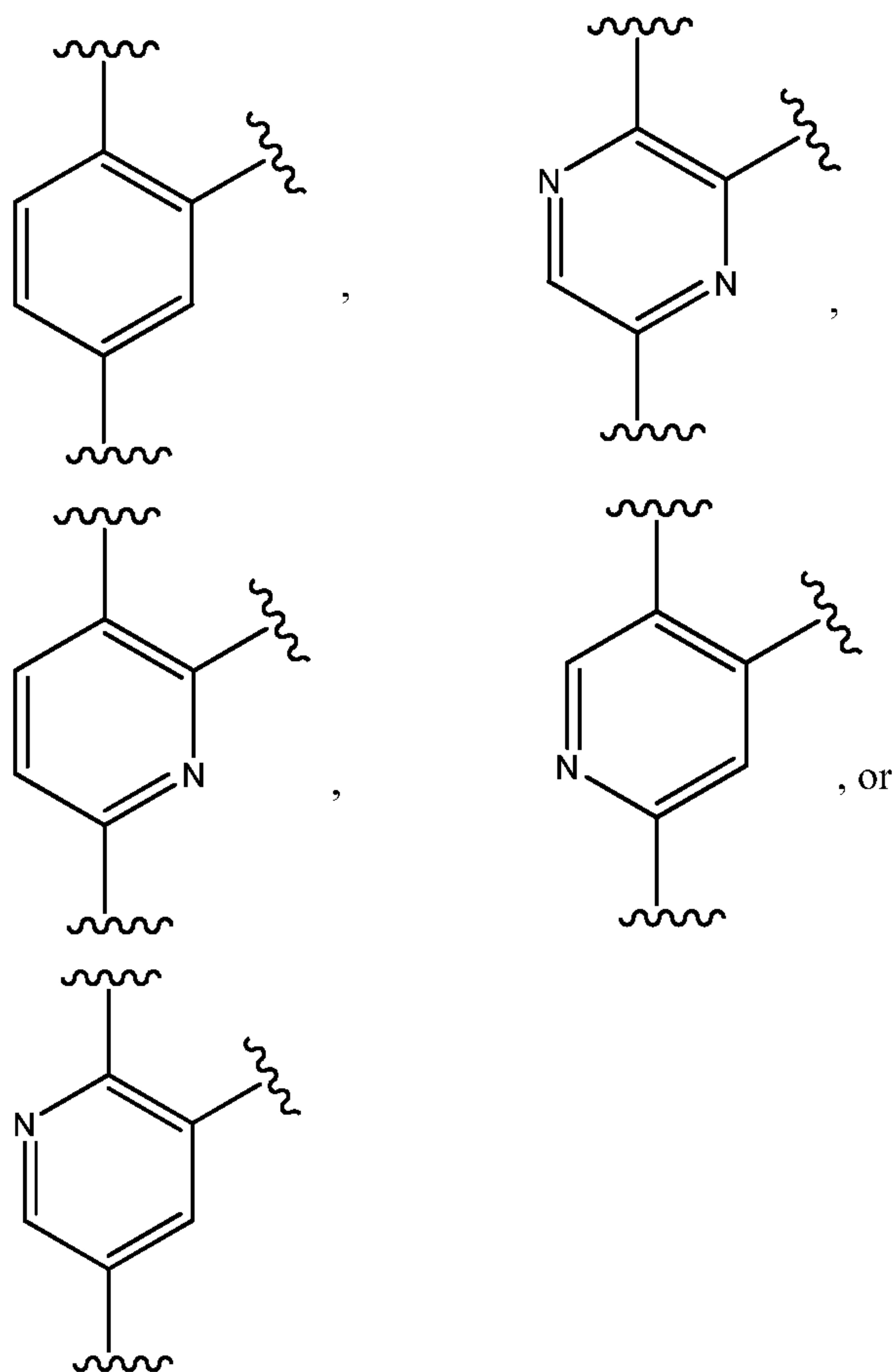
In one embodiment, in compounds represented by formula (XXII), (XXVI), or (XXVII), Ring A is:



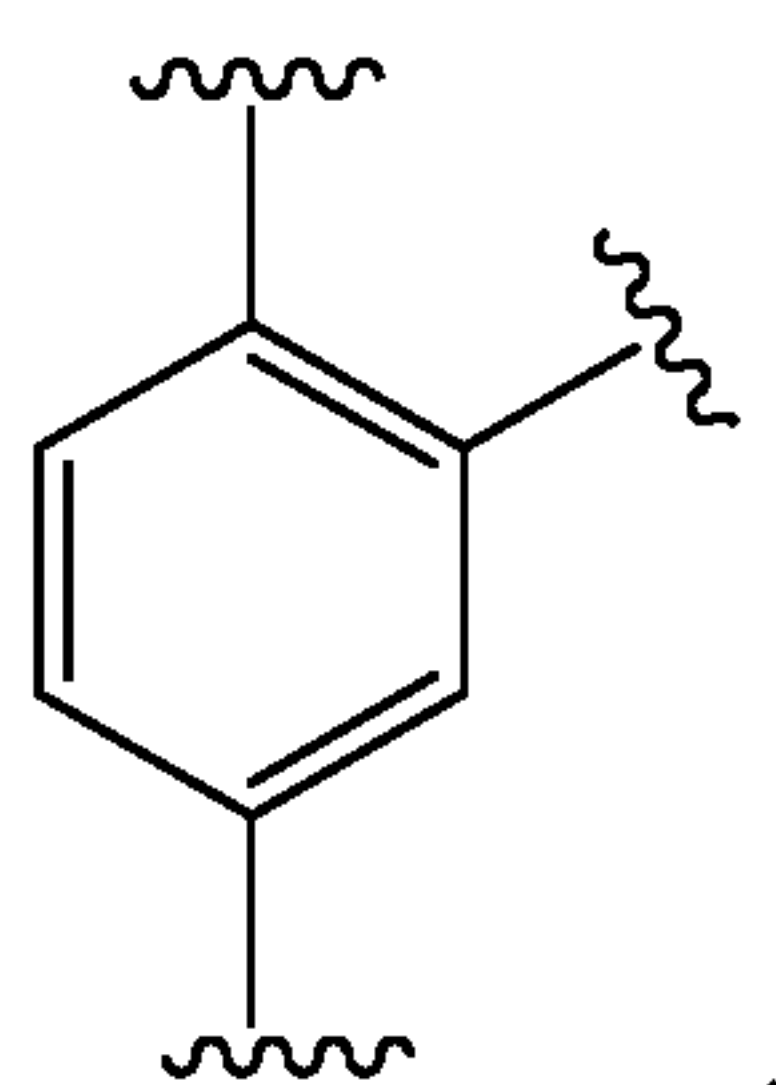
In one embodiment, in compounds represented by formula (XXII), (XXVI), or (XXVII), Ring A is:



In one embodiment, in compounds represented by formula (XXIII) or (XXIV), the ring containing X_2 , X_3 and X_4 is:



In one embodiment, in compounds represented by formula (XXIII) or (XXIV), the ring containing X_2 , X_3 and X_4 is:



In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), the Ring C has at least one $-C(R^c)-$ wherein R^c is a substituent that contains 6 or fewer atoms, excluding any hydrogens.

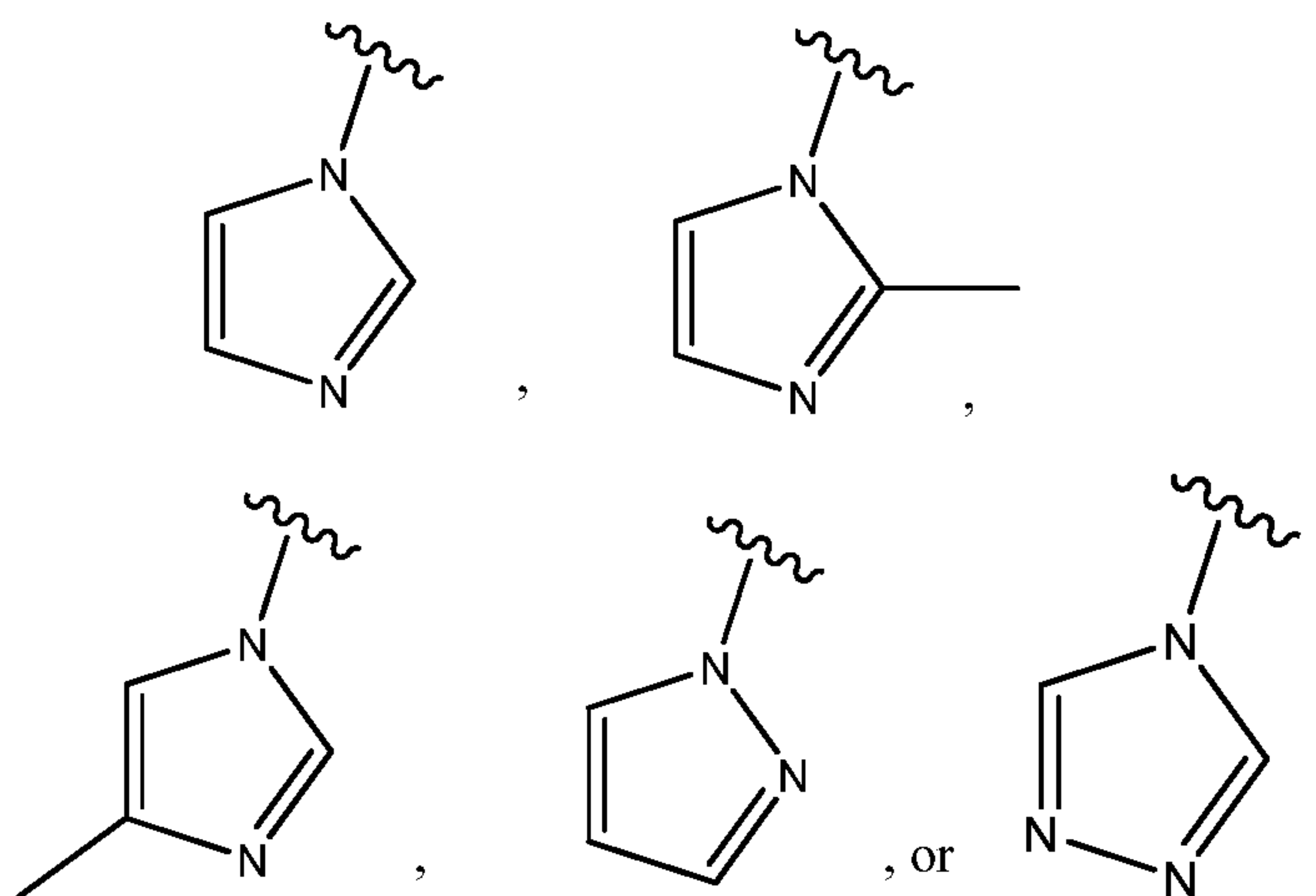
In one aspect, the substituent contains 5 or fewer atoms. In one aspect, the substituent is selected from methyl or ethyl.

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In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), one of X_5 , X_6 , X_7 or X_8 is $-N-$. In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), two of X_5 , X_6 , X_7 or X_8 are $-N-$. In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), three of X_5 , X_6 , X_7 or X_8 are $-N-$. In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), all of X_5 , X_6 , X_7 or X_8 are $-N-$.

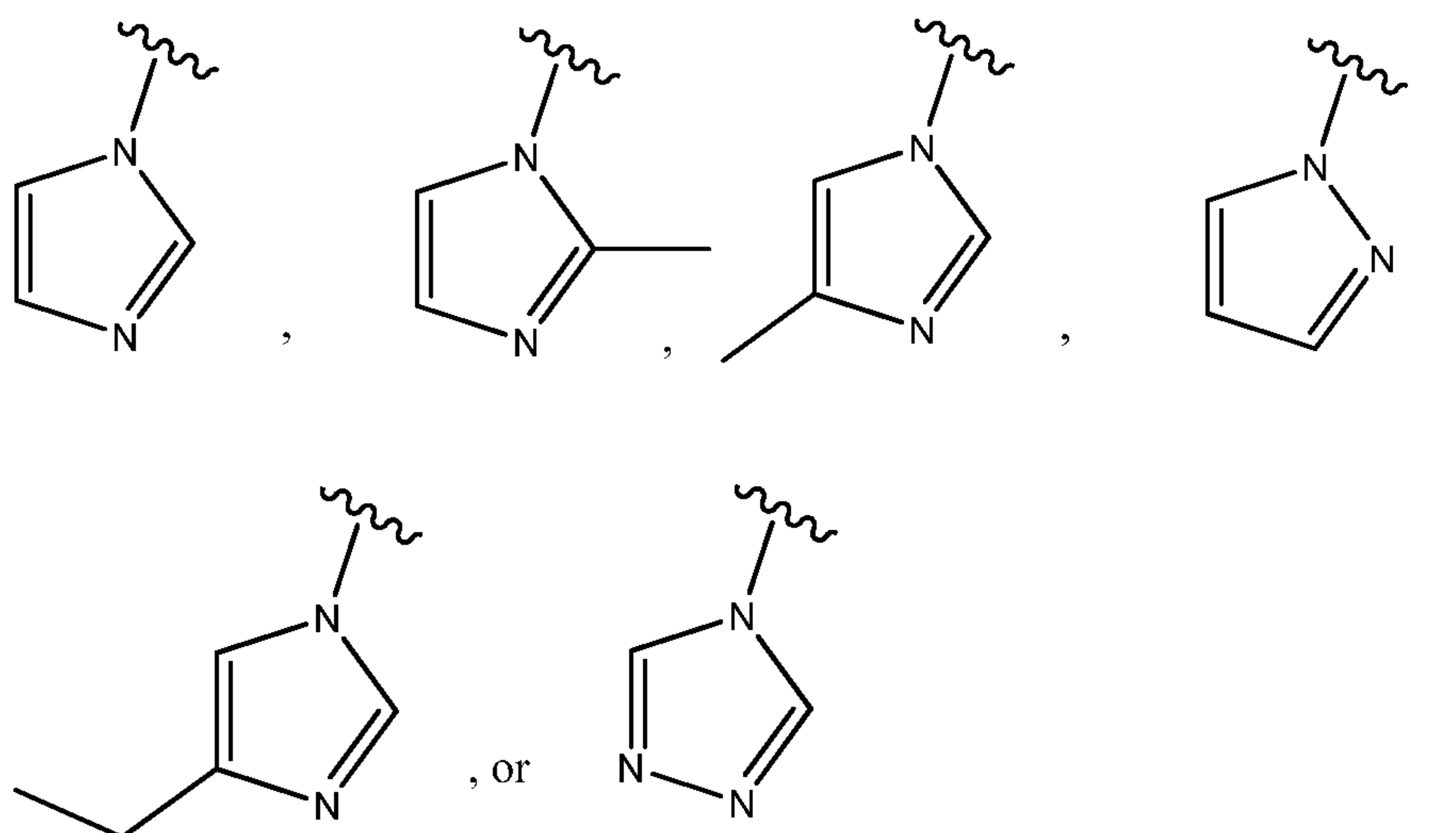
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In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), Ring C is:



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In one embodiment, in compounds represented by any of formulae (XXII) - (XXX), Ring C is:



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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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt thereof.

In another embodiment, compounds of any one of formulas (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt 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 (IA), (I) through (XXX) or Tables 1-3, 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt thereof, can inhibit the production of certain cytokines that regulate immune cell activation. For example, compounds of any one of formulas (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt 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 (IA), (I) through (XXX), or Tables 1-3, inhibits cytokine production in a mammal (*e.g.*, a human).

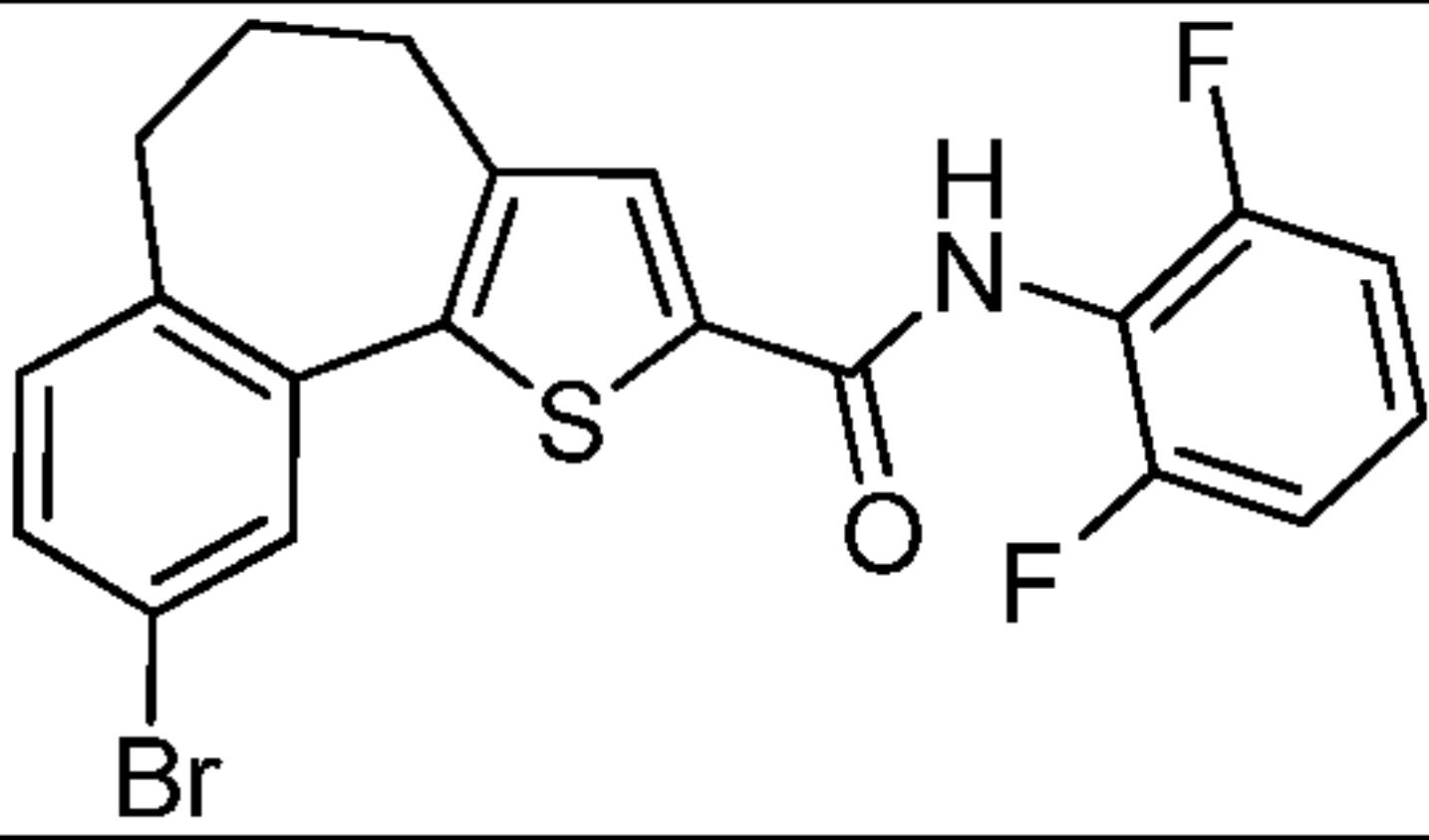
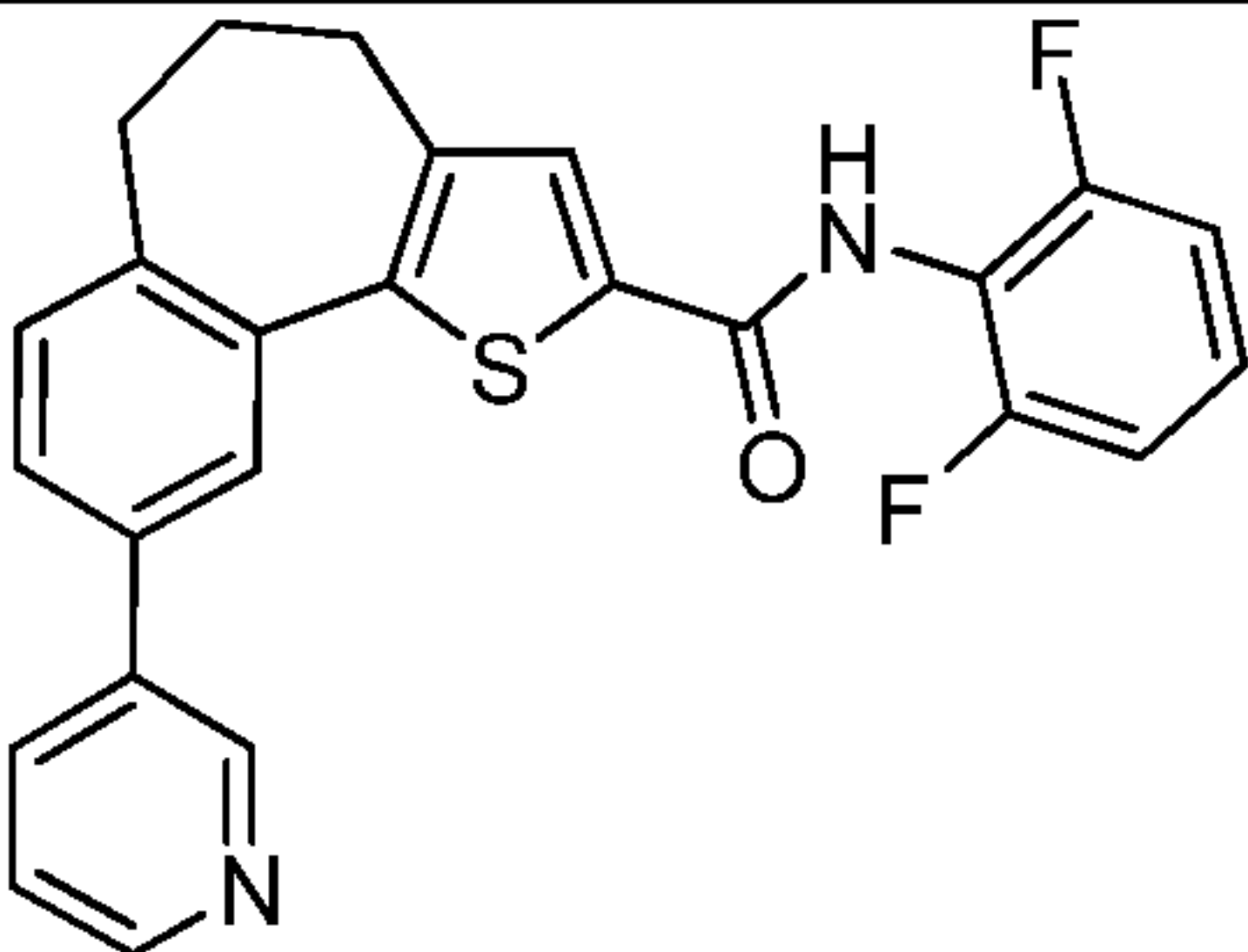
In another embodiment, compounds of any one of formulas (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt thereof, can modulate the activity of one or more ion channel involved in activation of immune cells, such as CRAC ion channels.

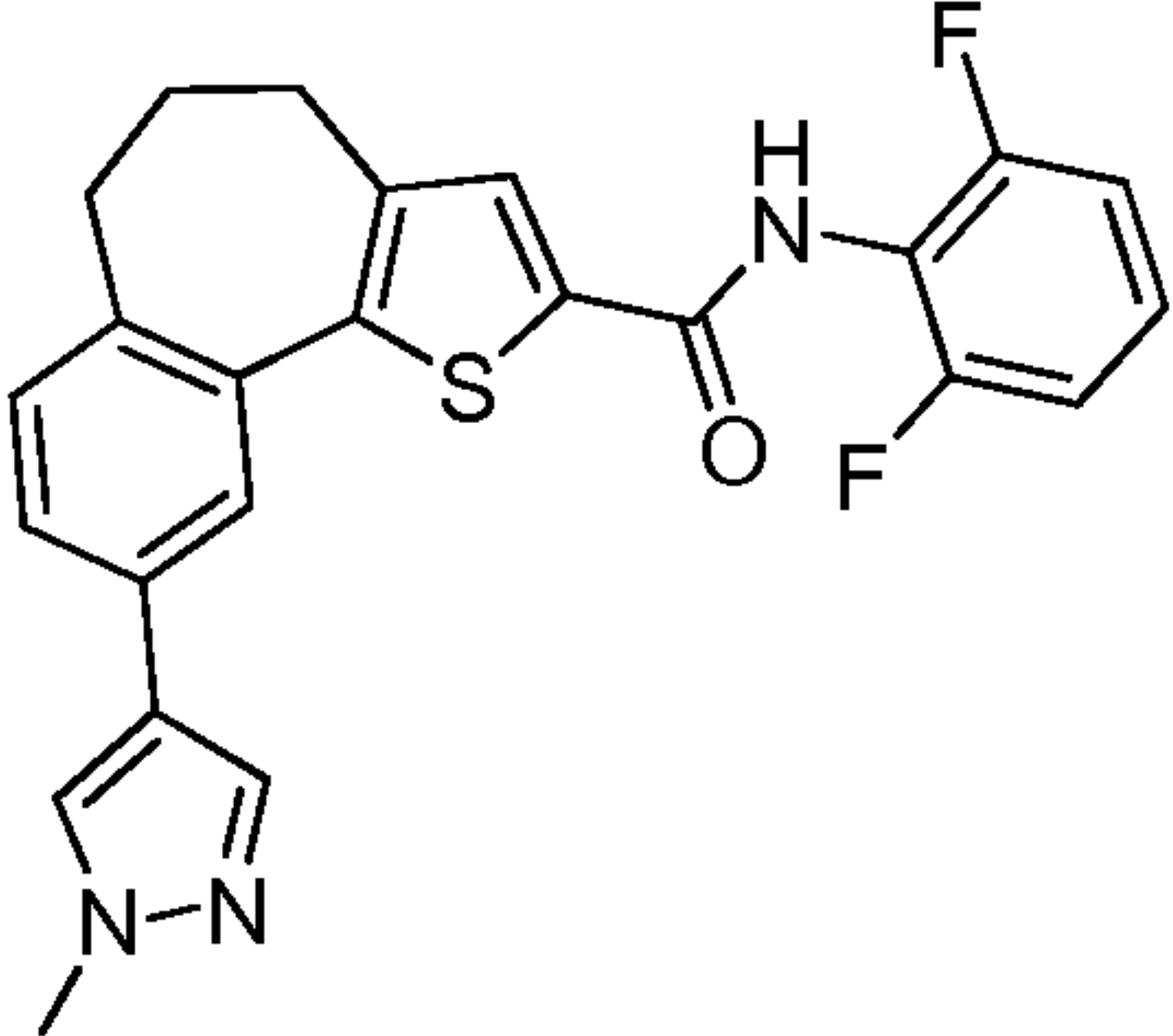
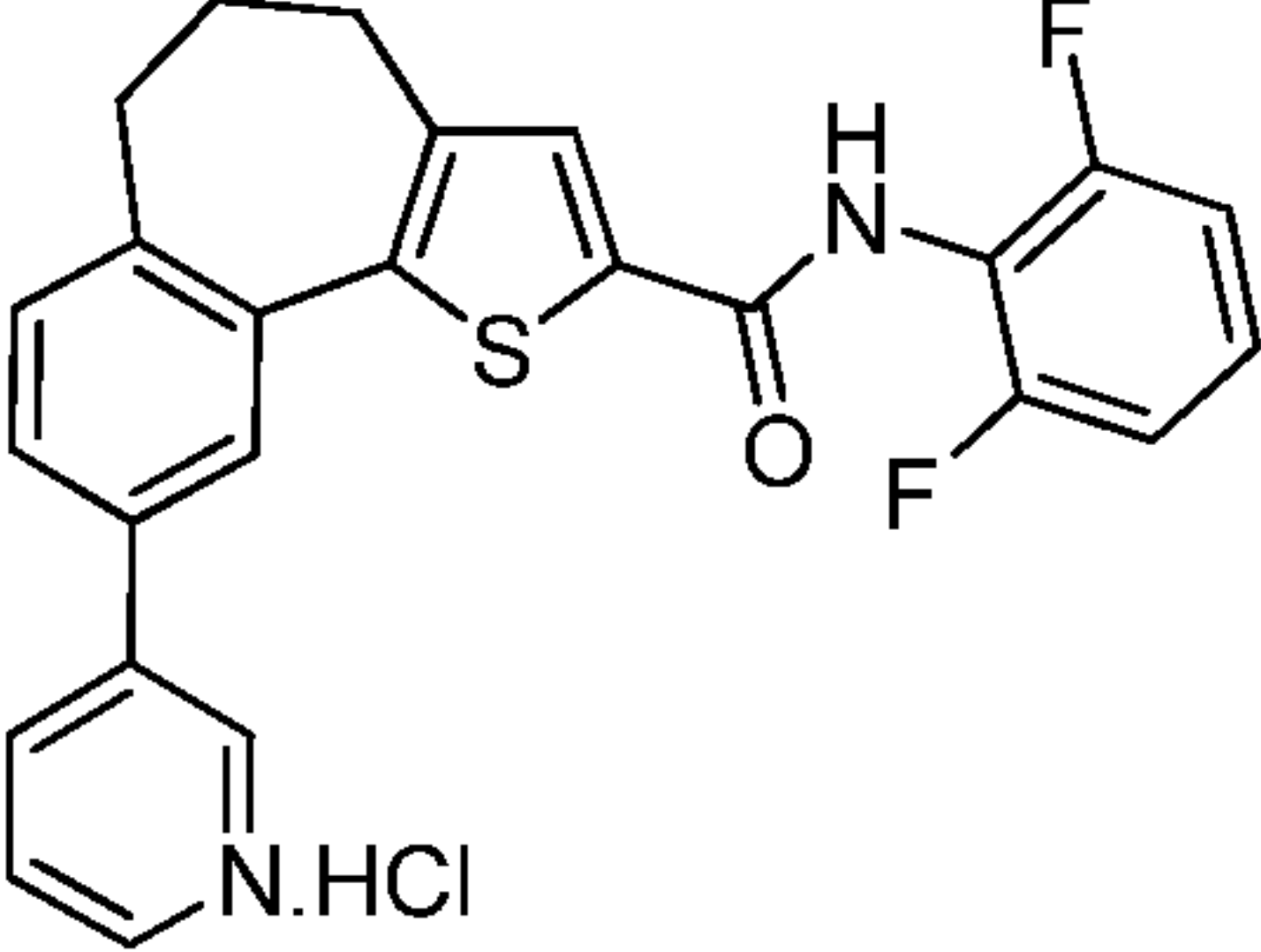
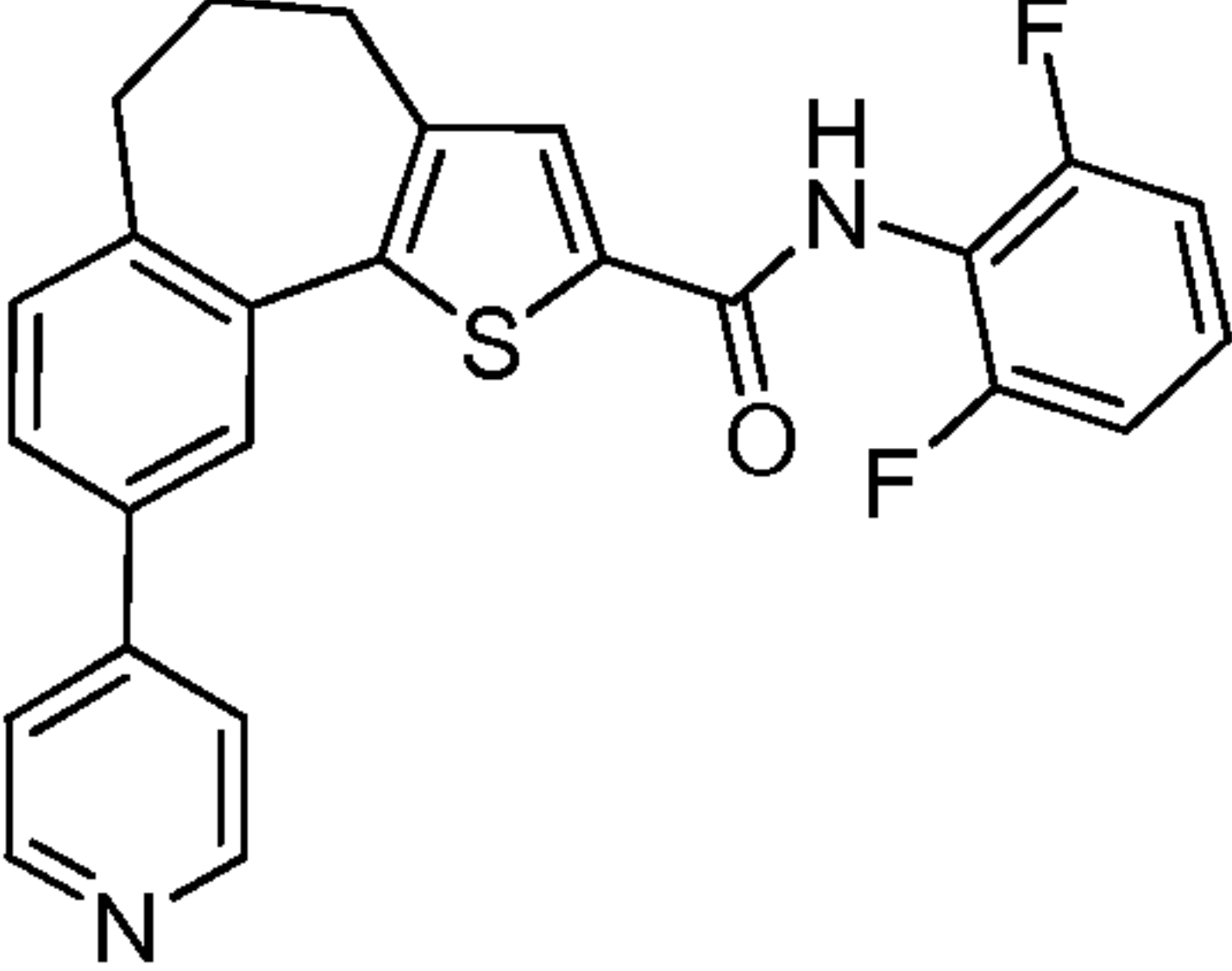
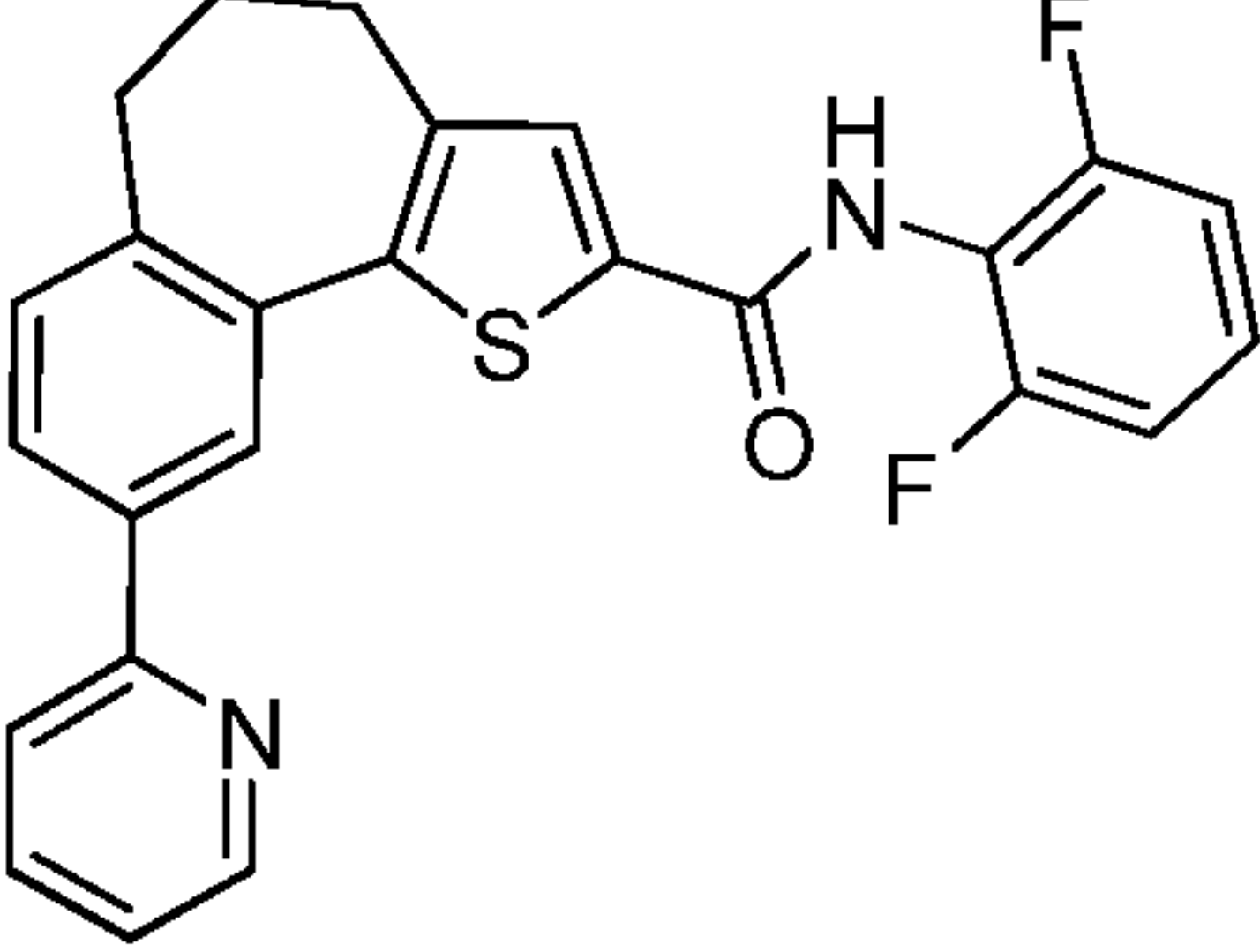
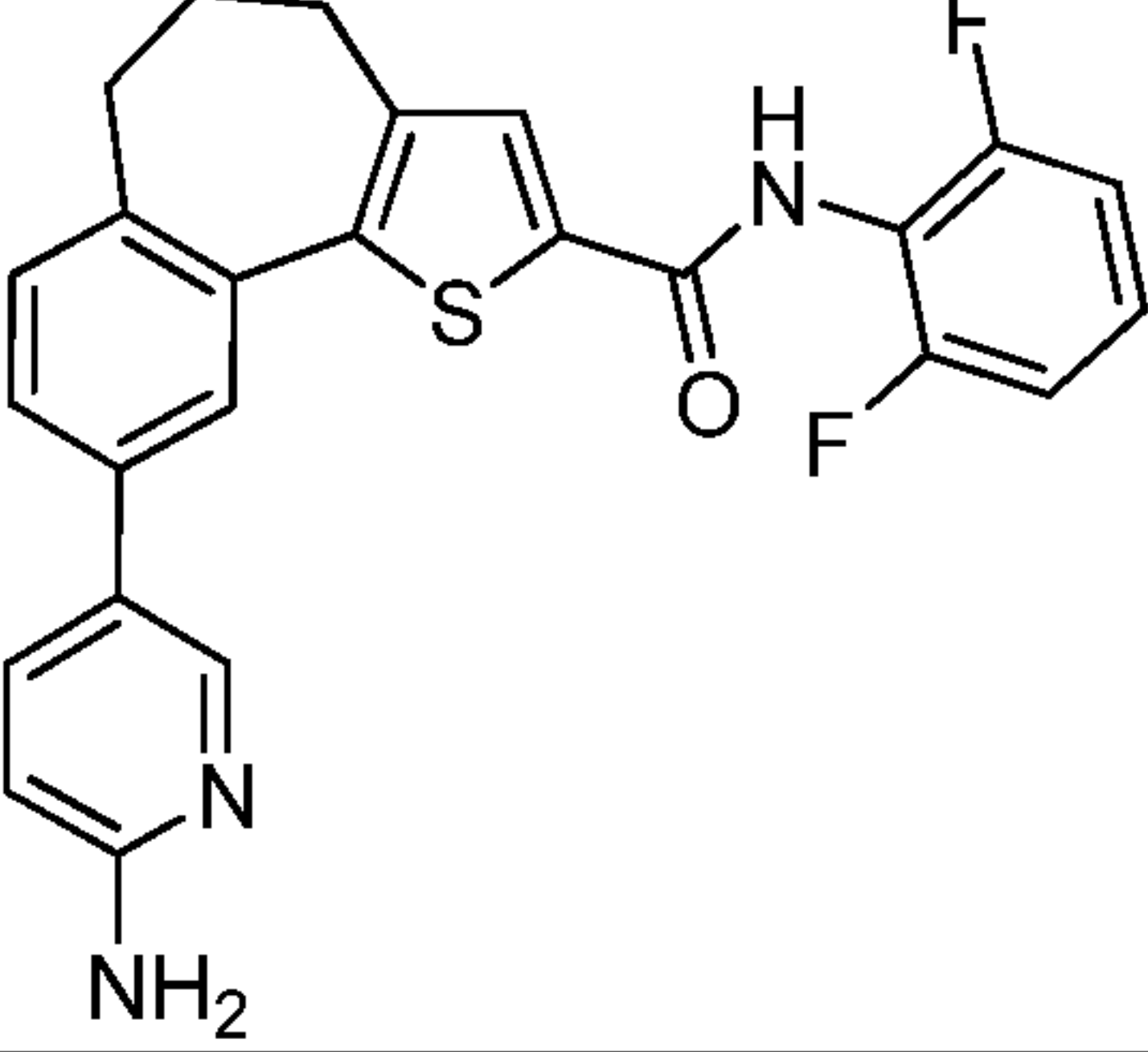
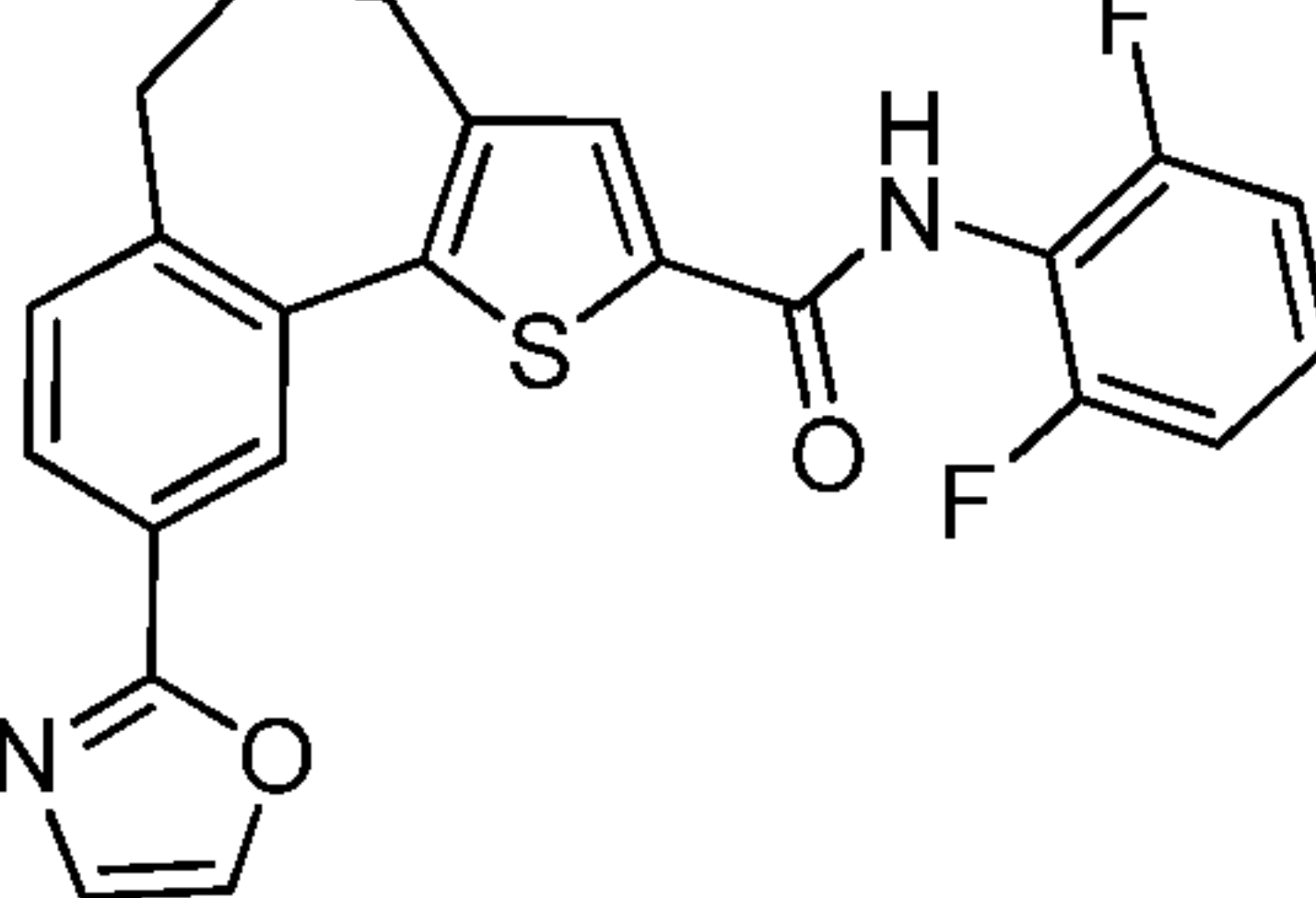
In one embodiment, a compound of any one of formulas (IA), (I) through (XXX), or Tables 1-3, can inhibit the influx of calcium ions into an immune cell (*e.g.*, T cells and/or B cells) by inhibiting the action of CRAC ion channels. In general, a decrease in I_{CRAC} current upon contacting a cell with 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 (IA), (I) through (XXX), or Tables 1-3, modulates an ion channel in a mammal (*e.g.*, a human).

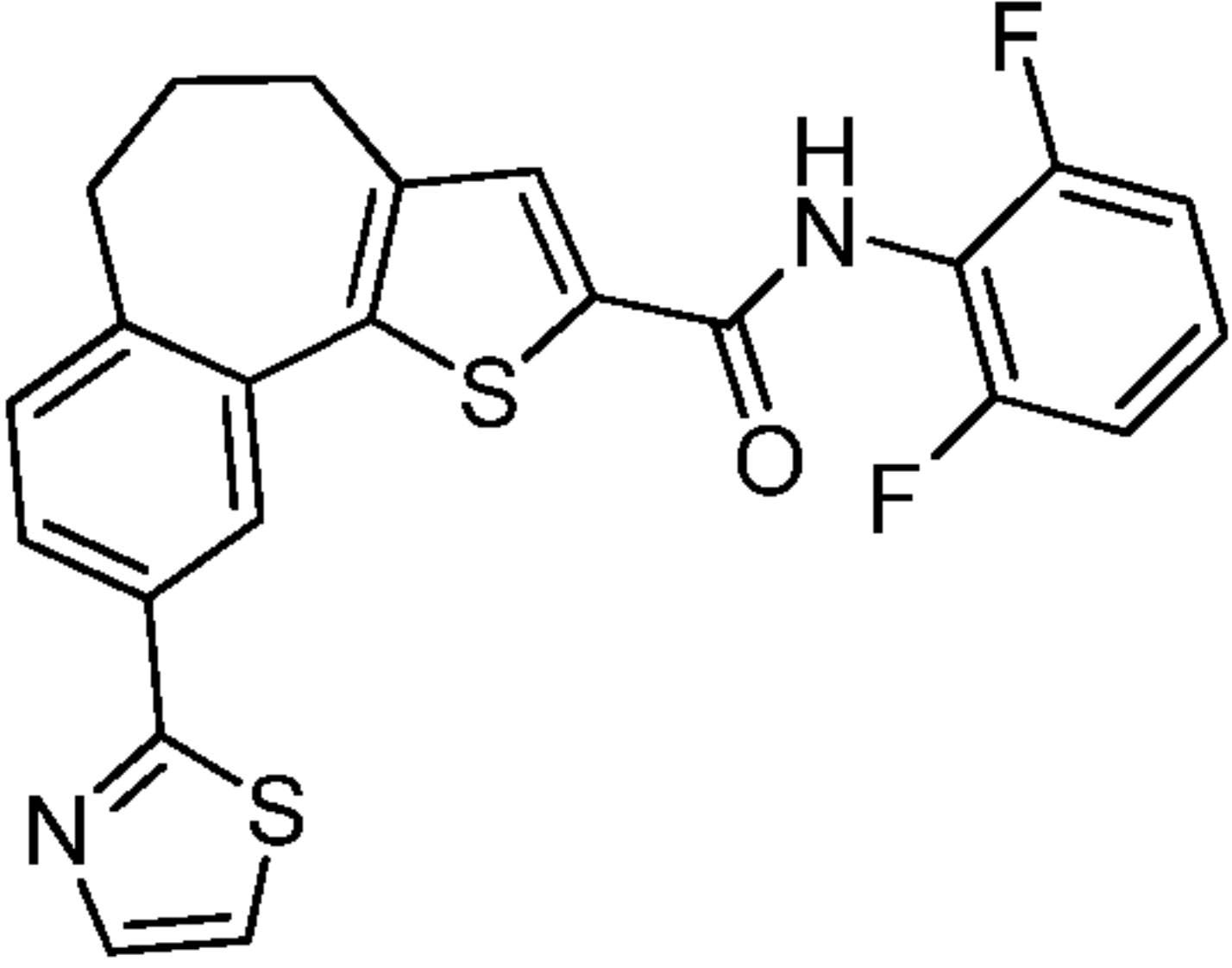
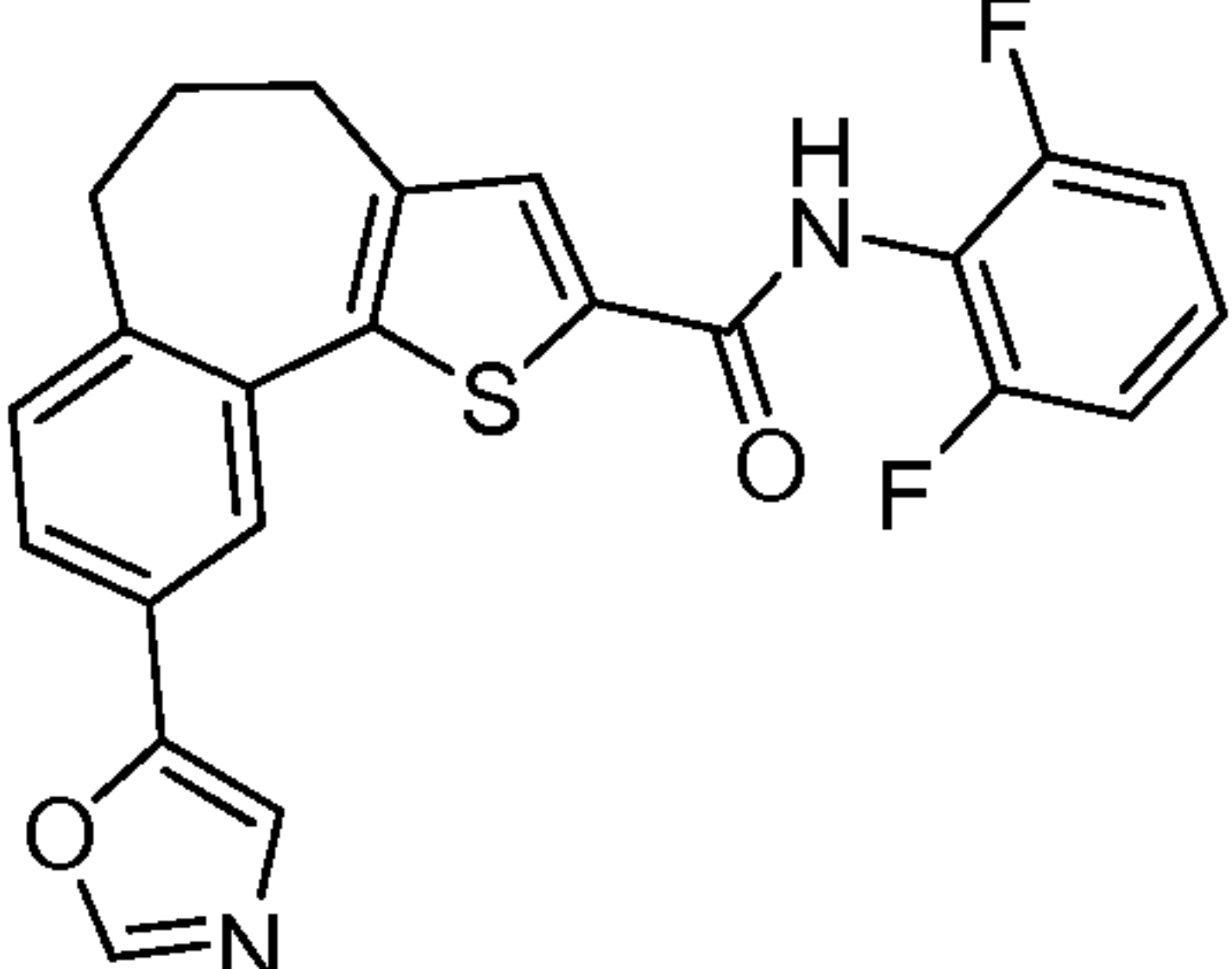
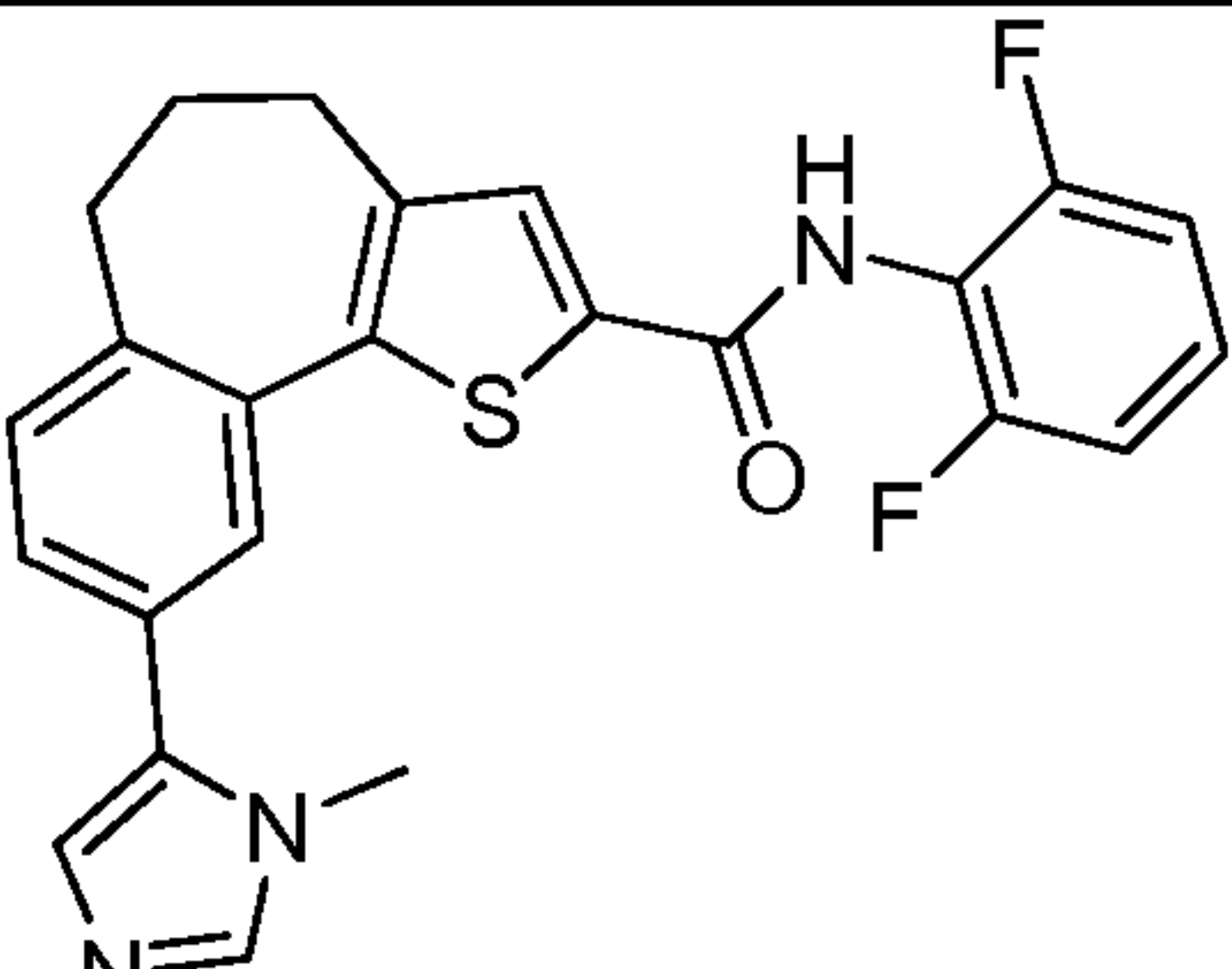
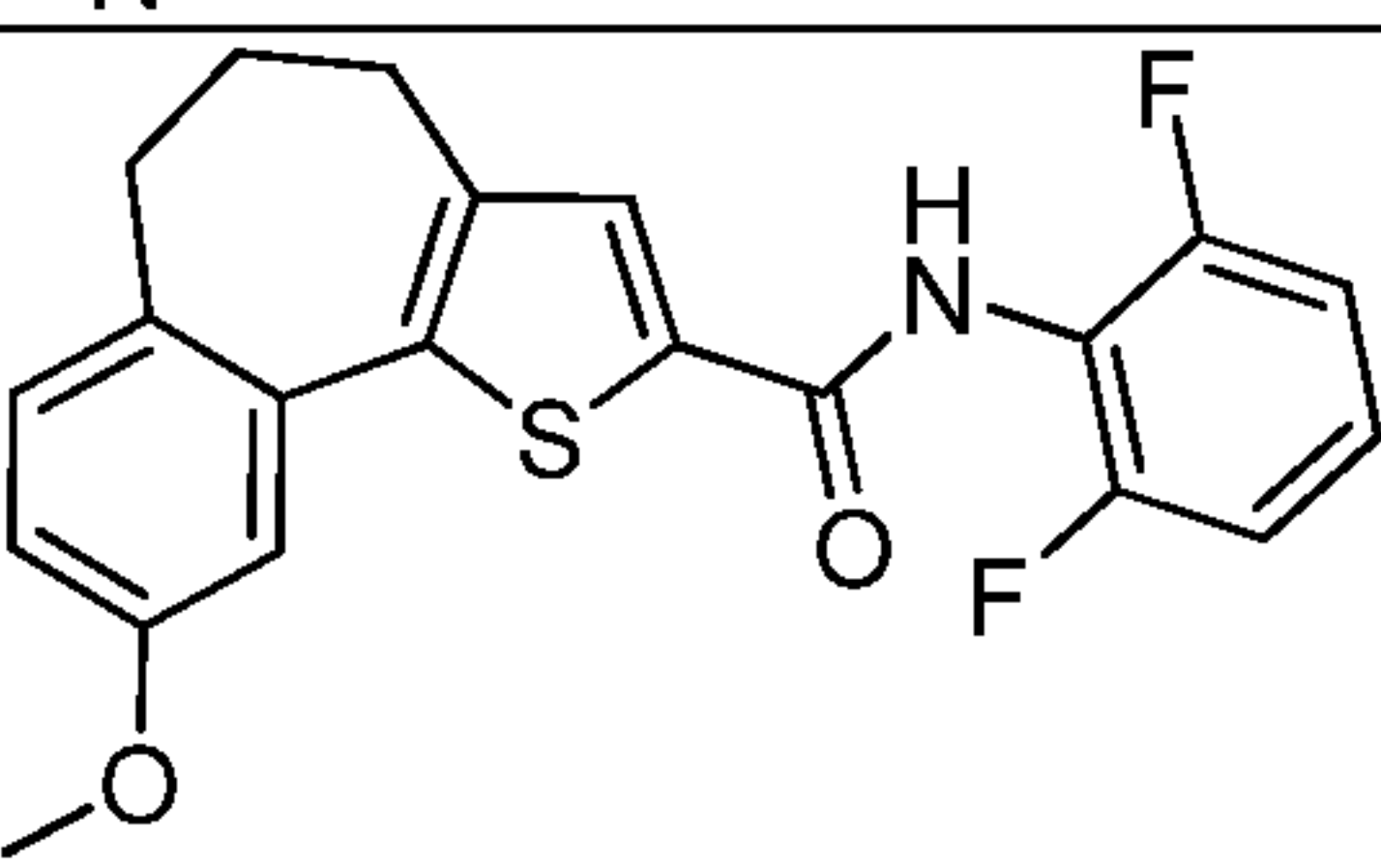
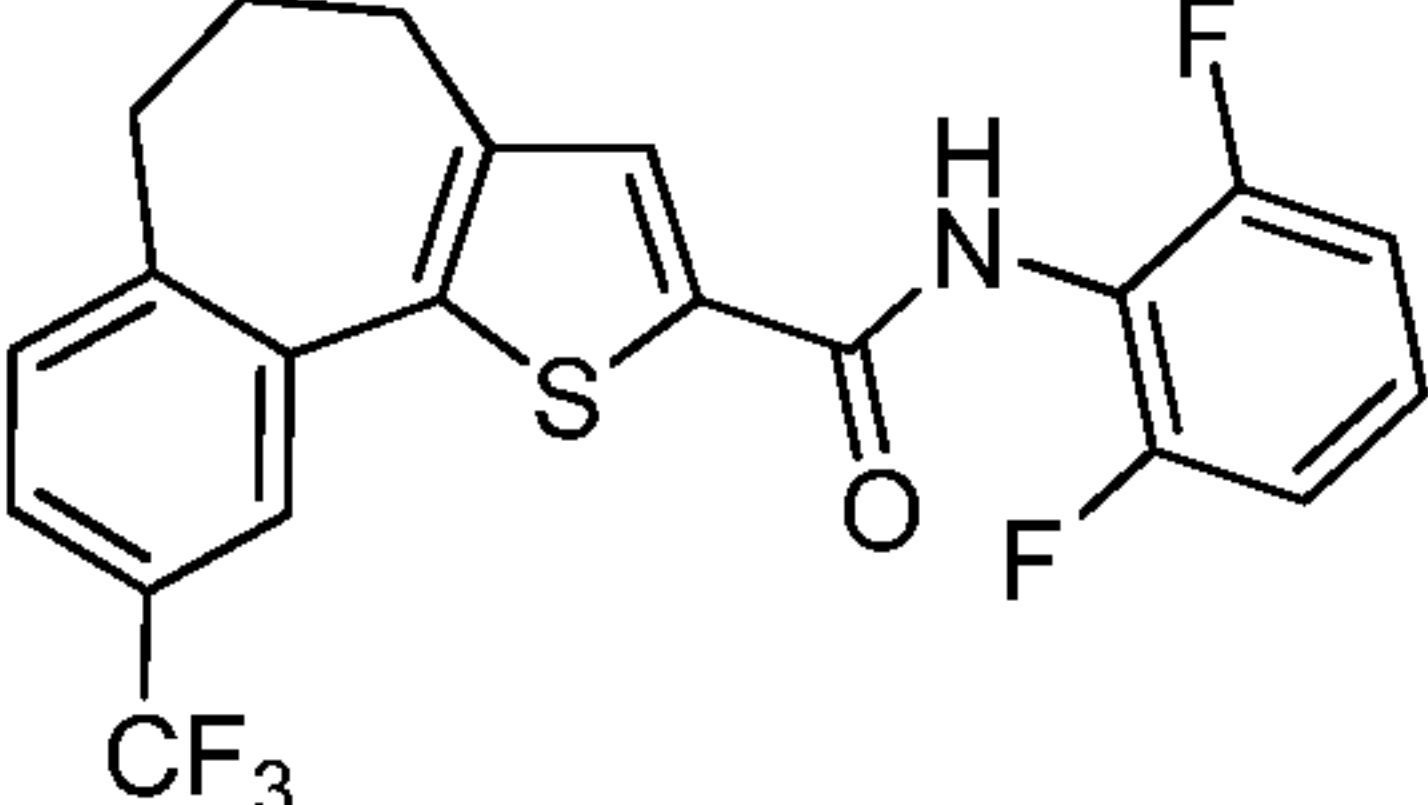
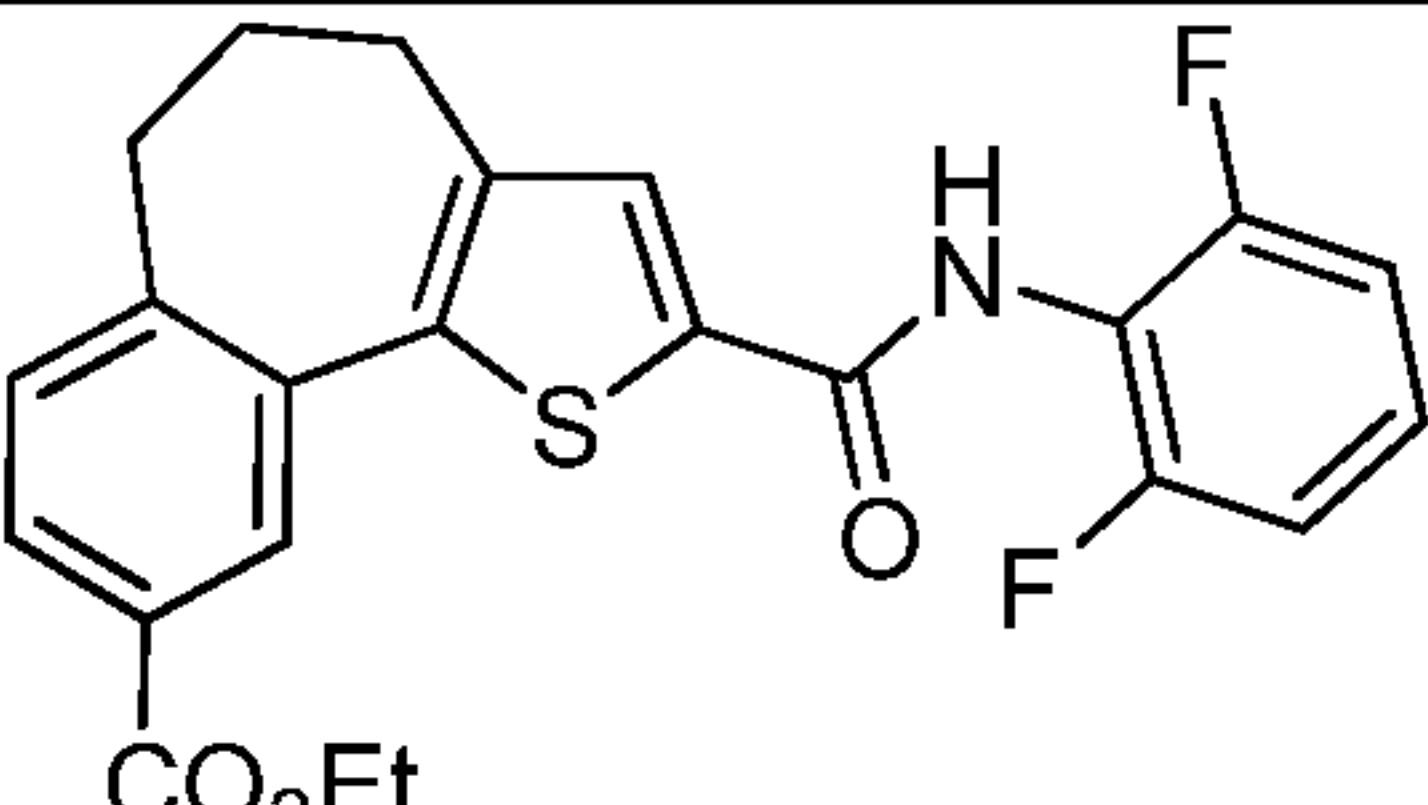
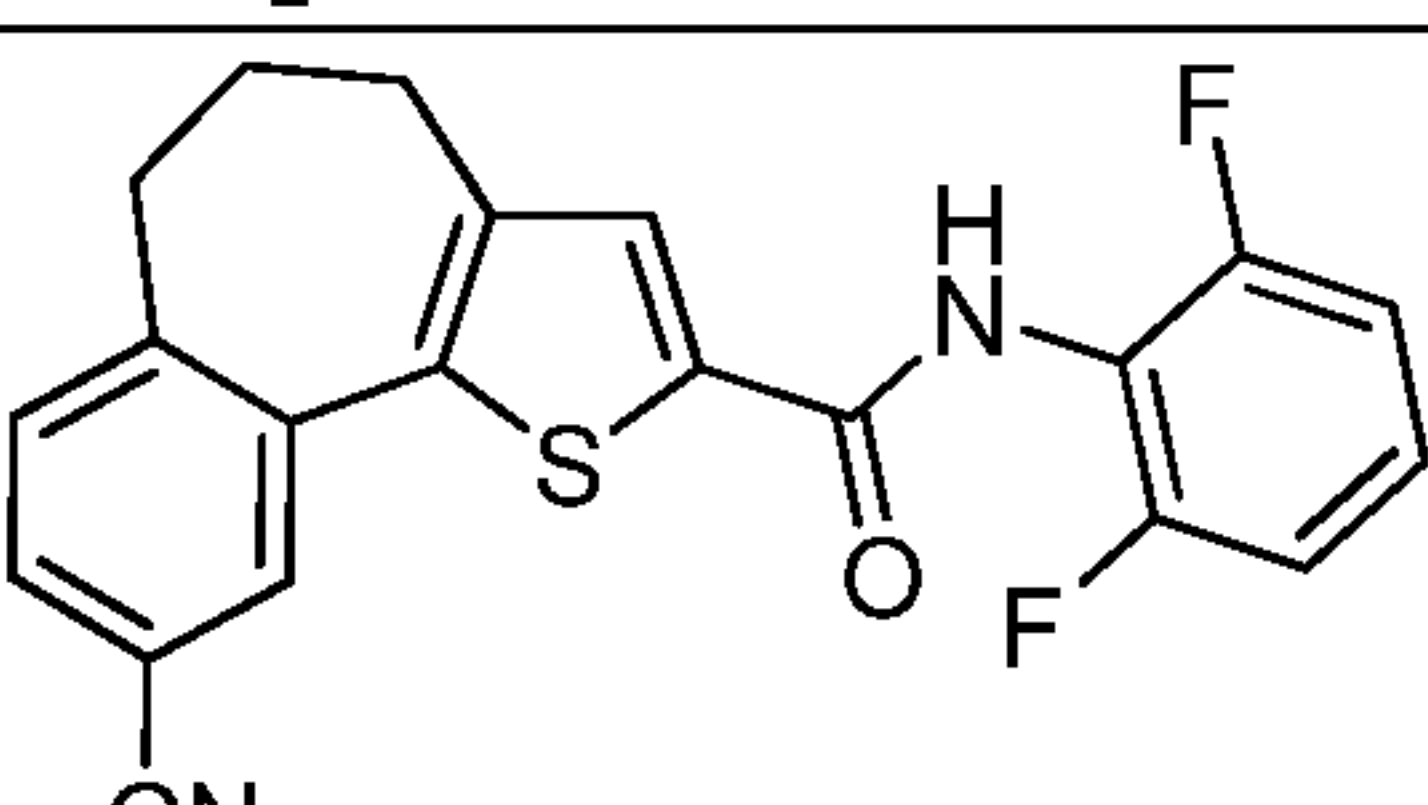
EXEMPLARY COMPOUNDS OF THE INVENTION

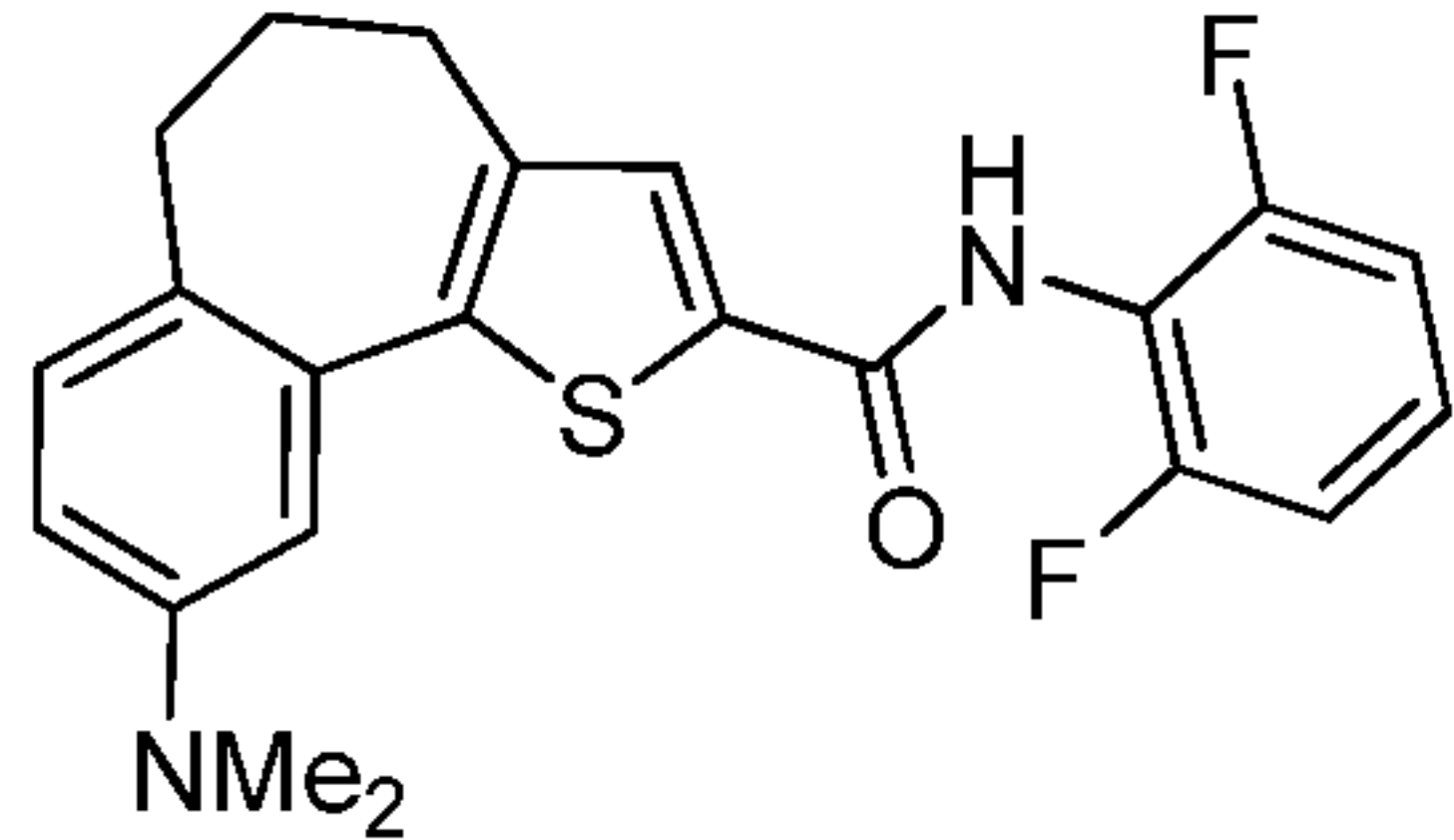
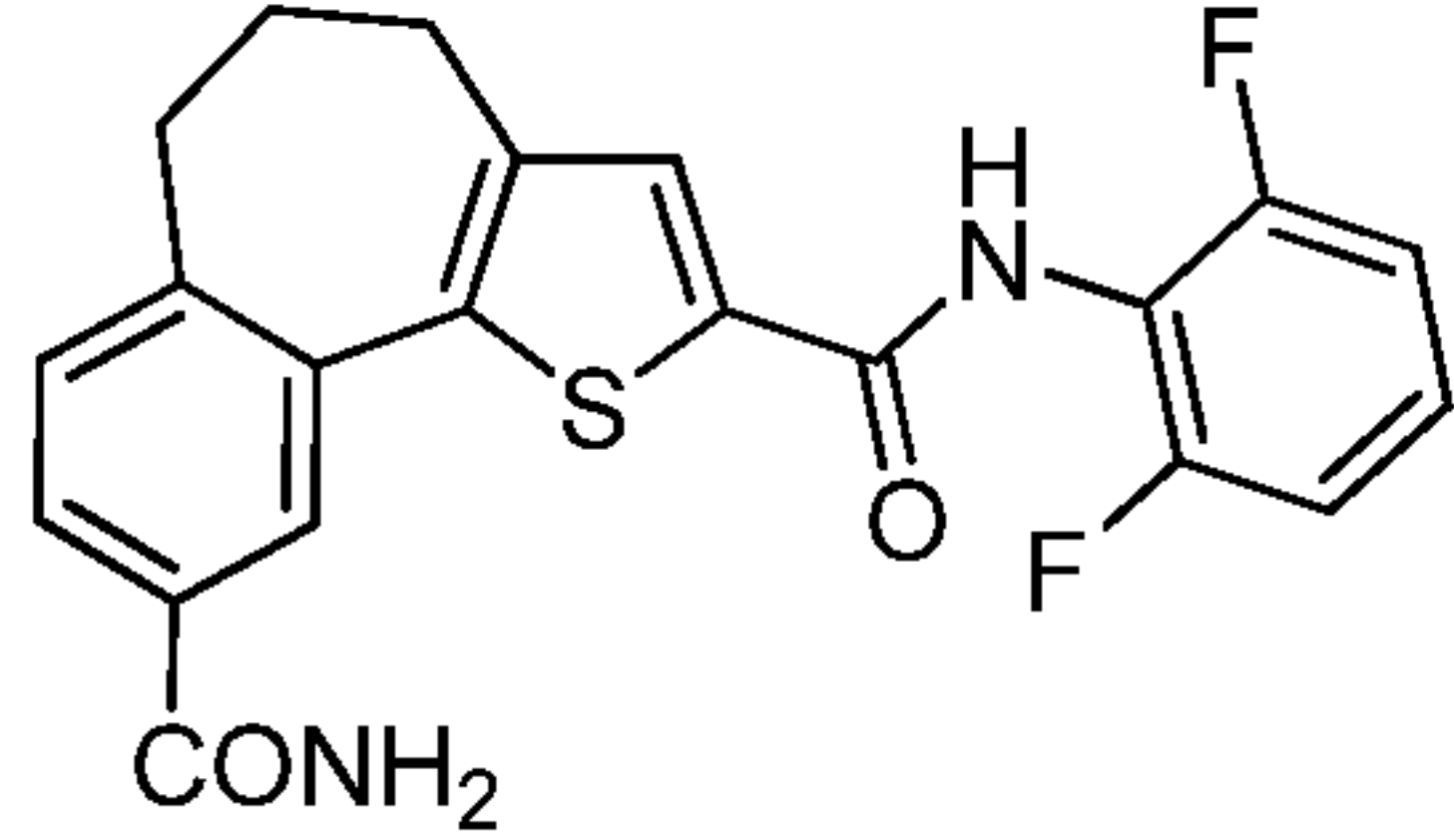
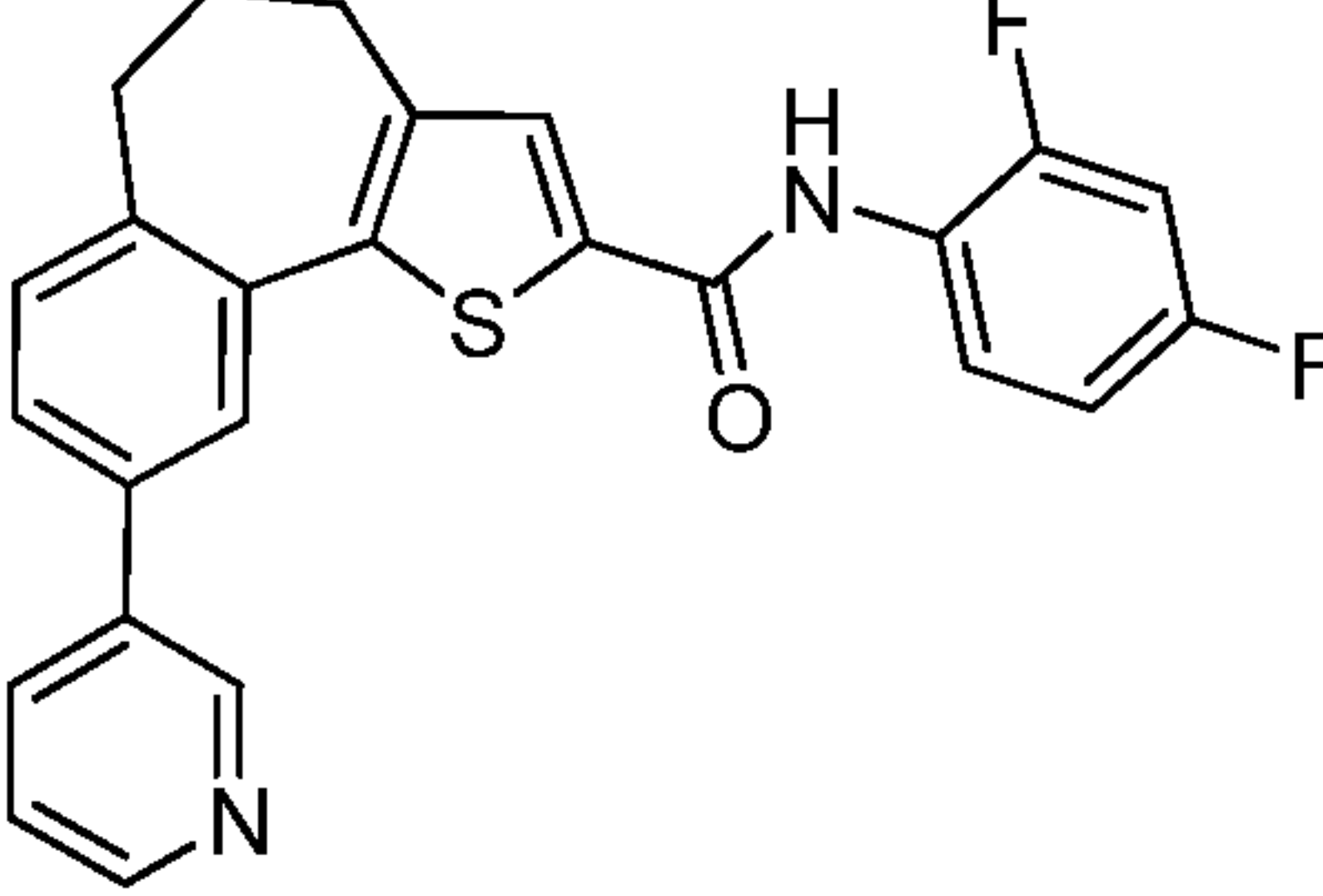
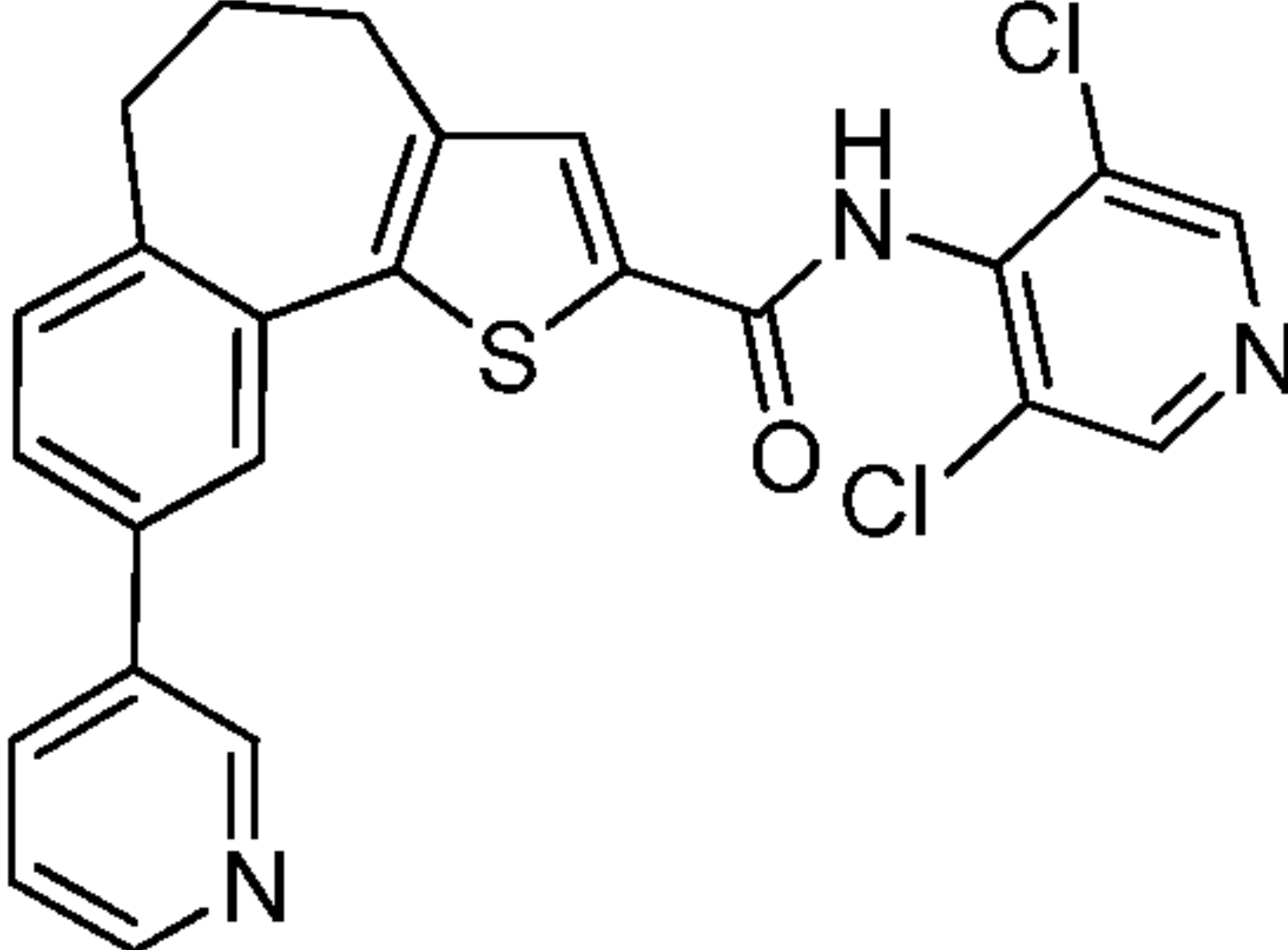
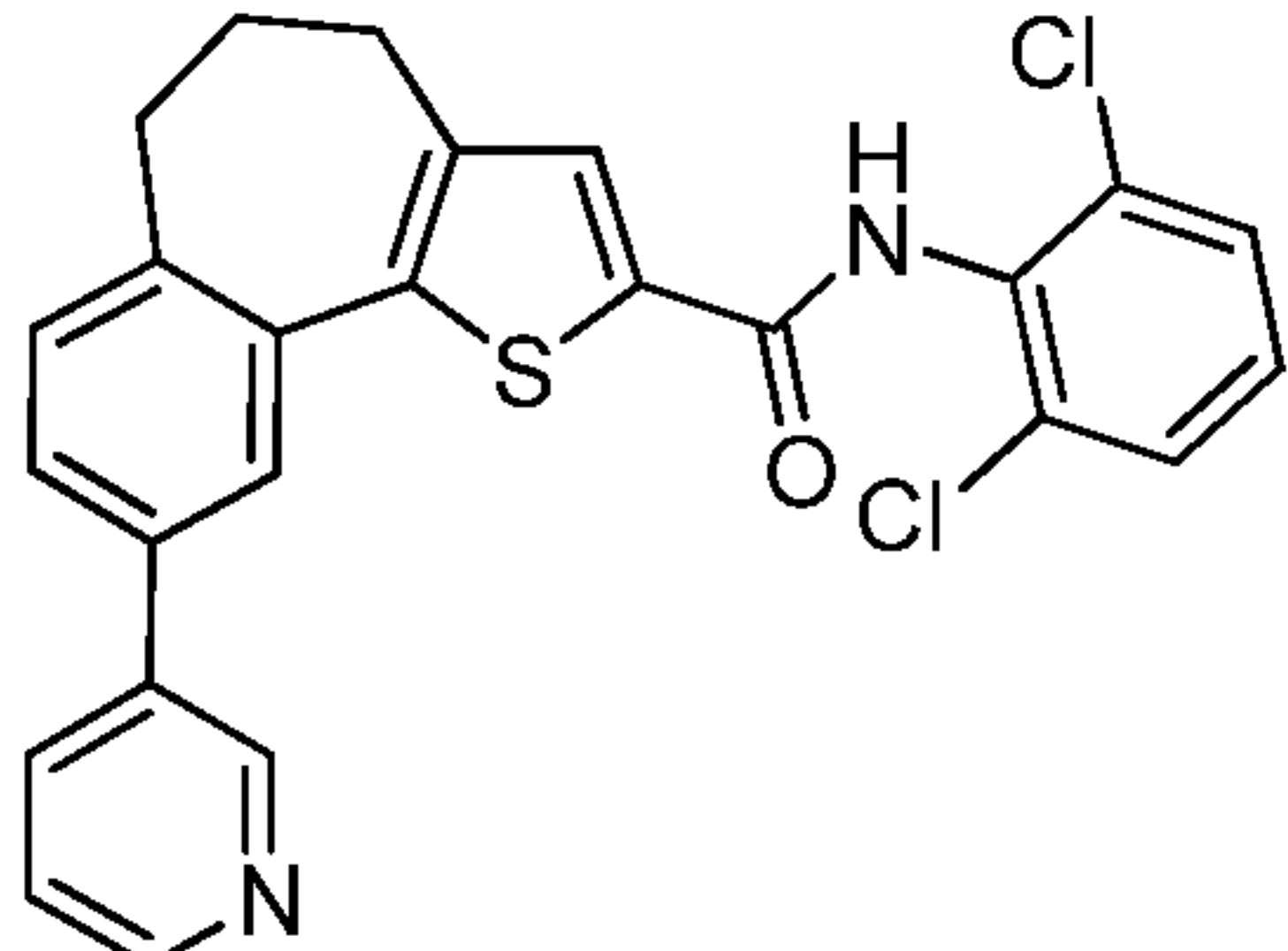
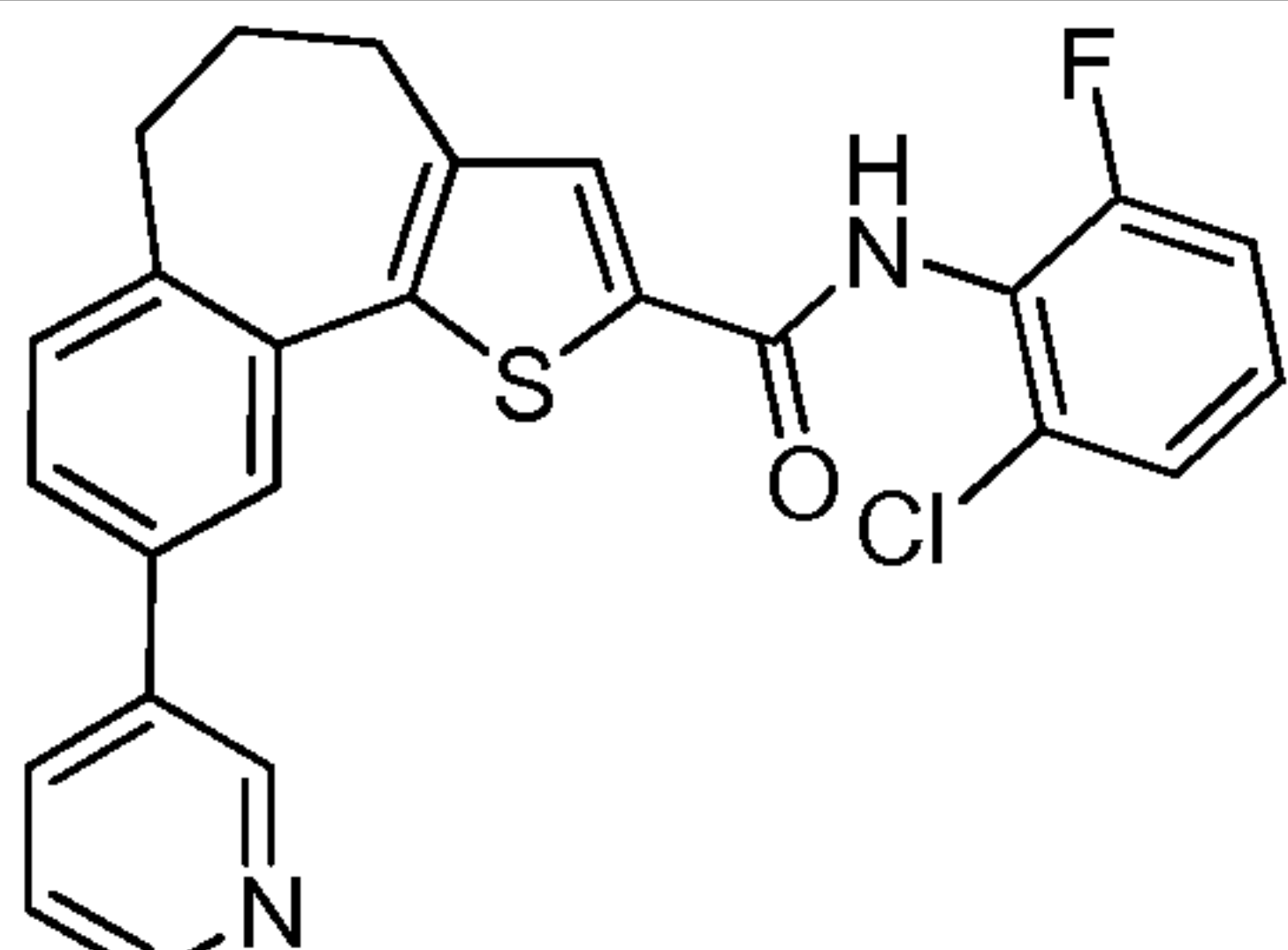
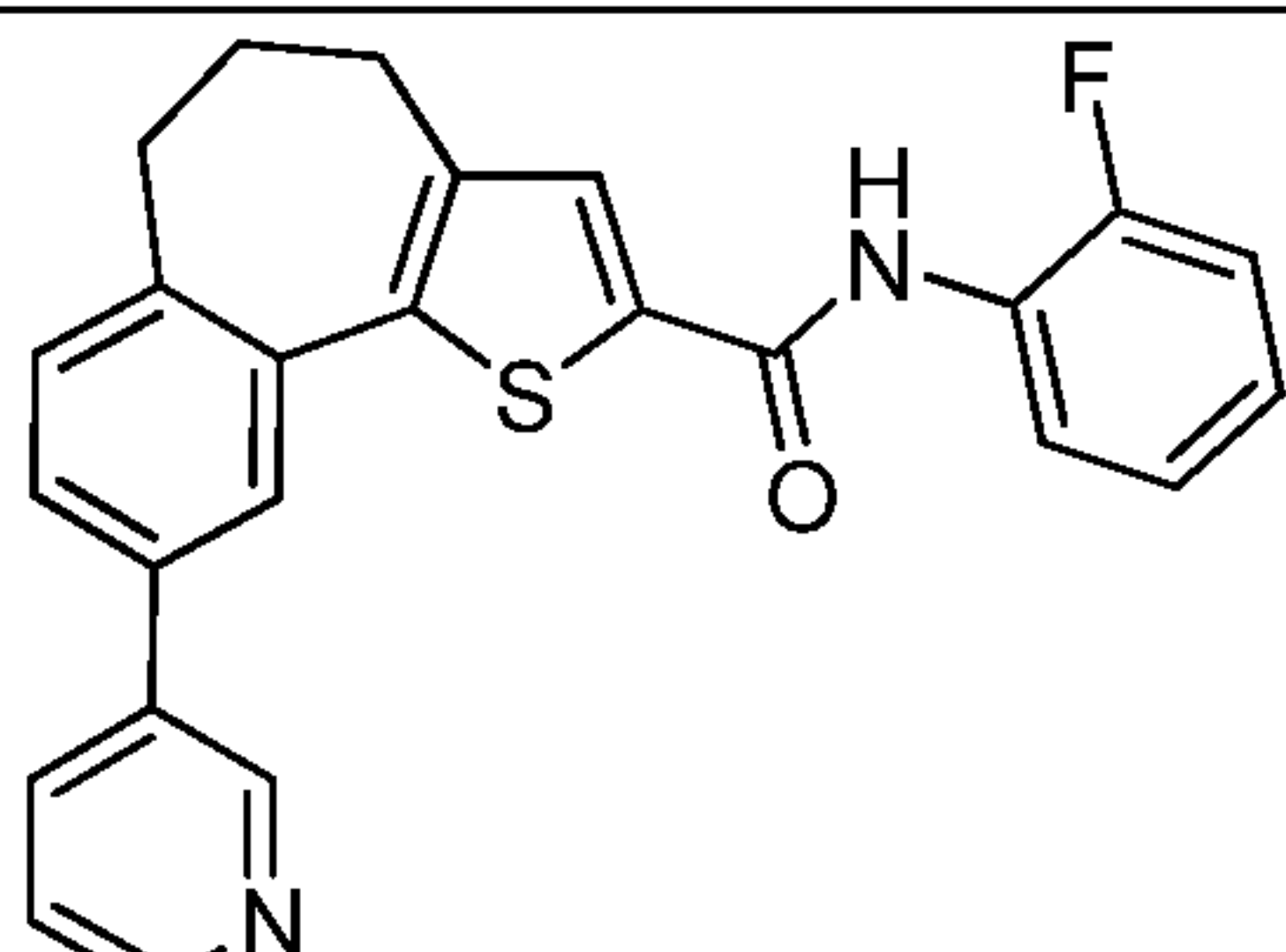
Exemplary compounds of the invention are depicted in Table 1 below.

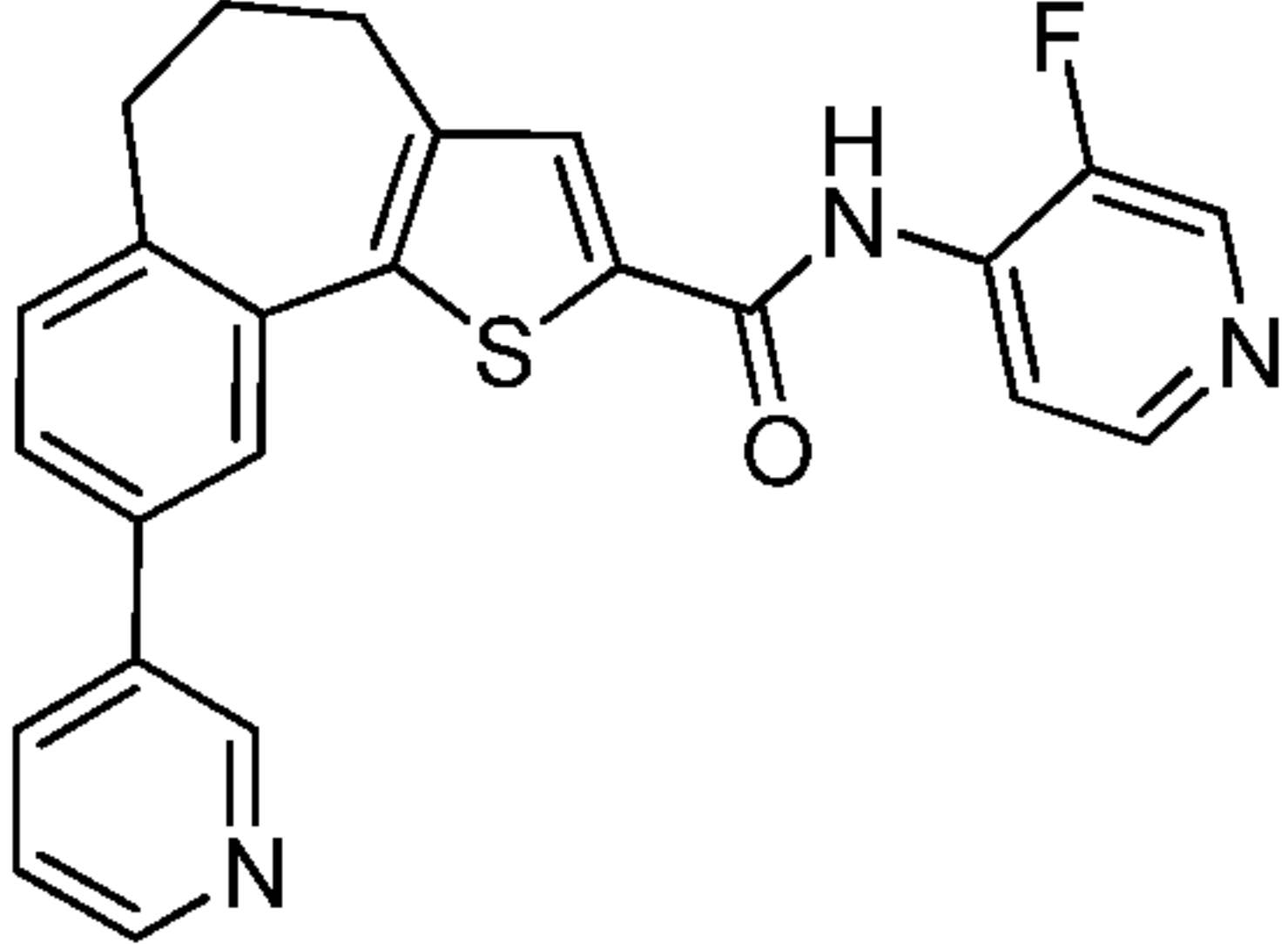
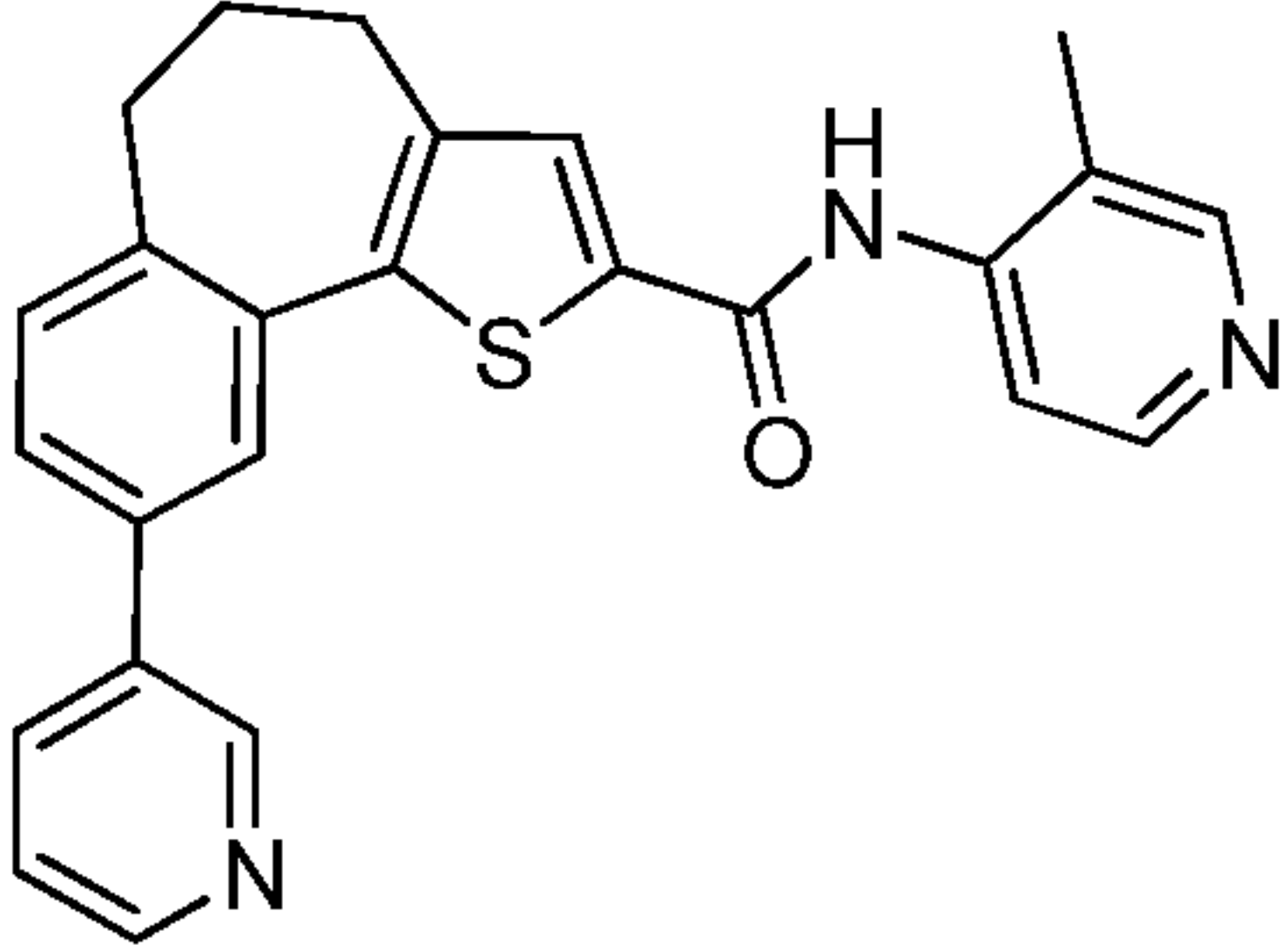
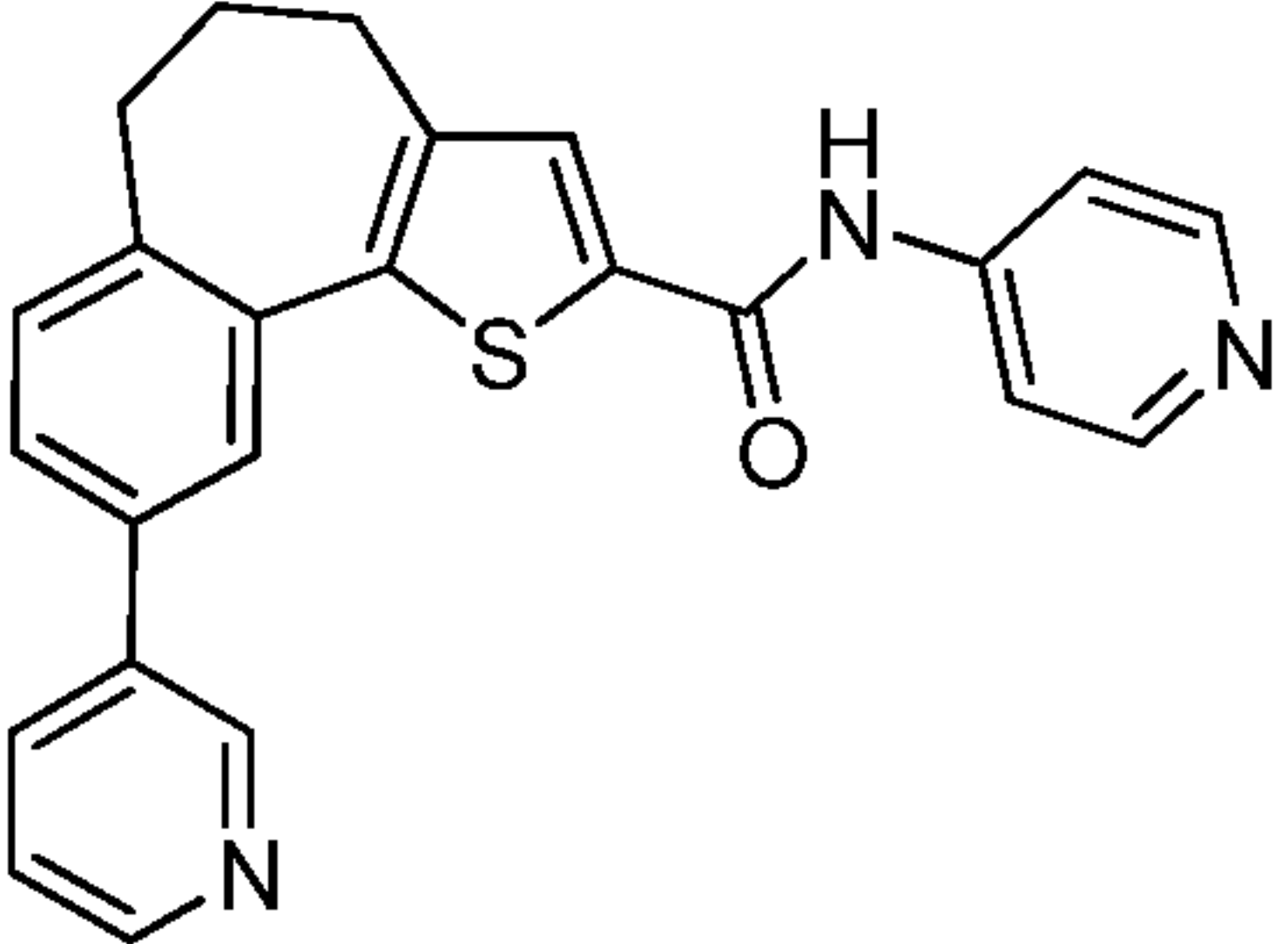
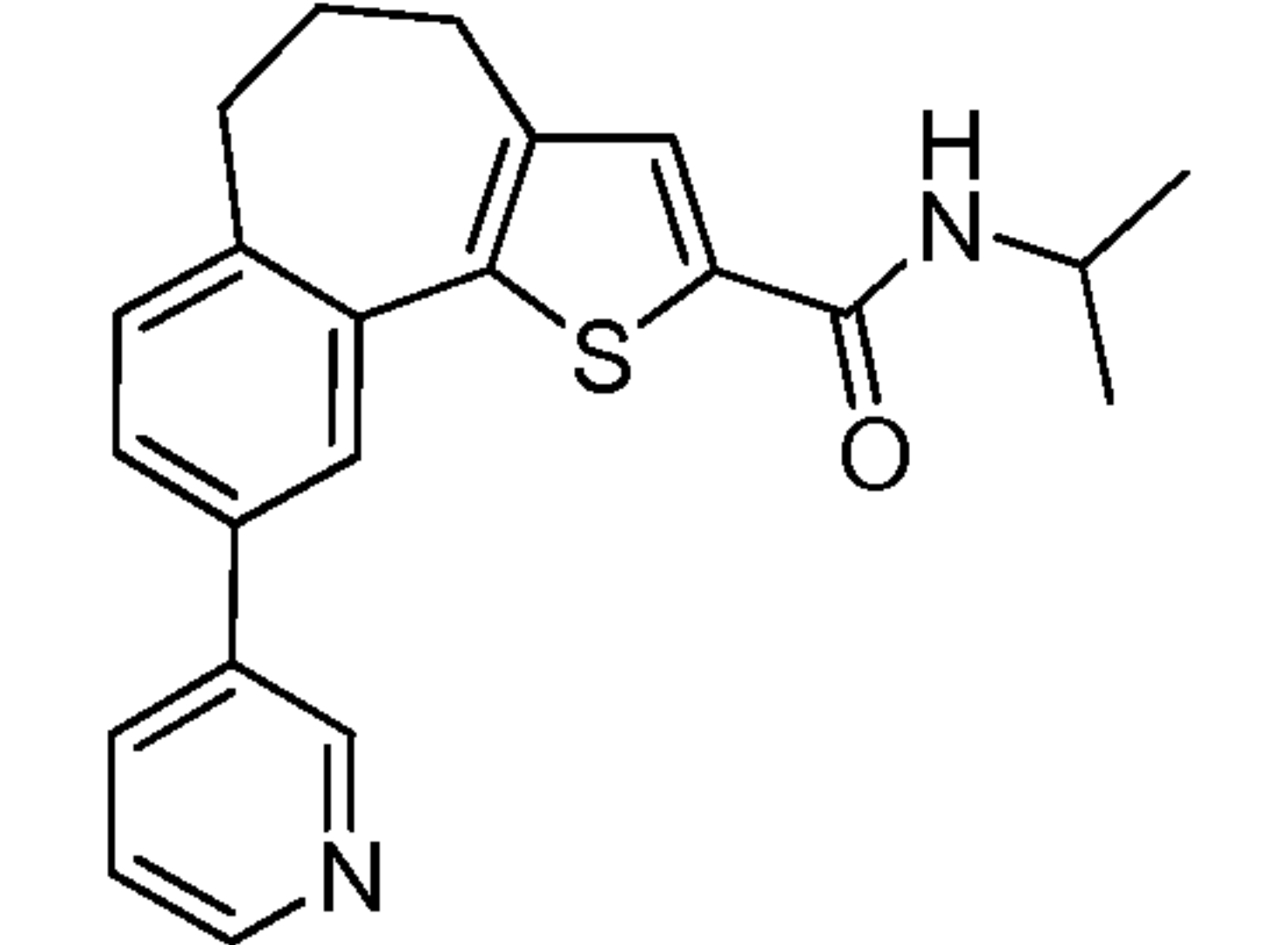
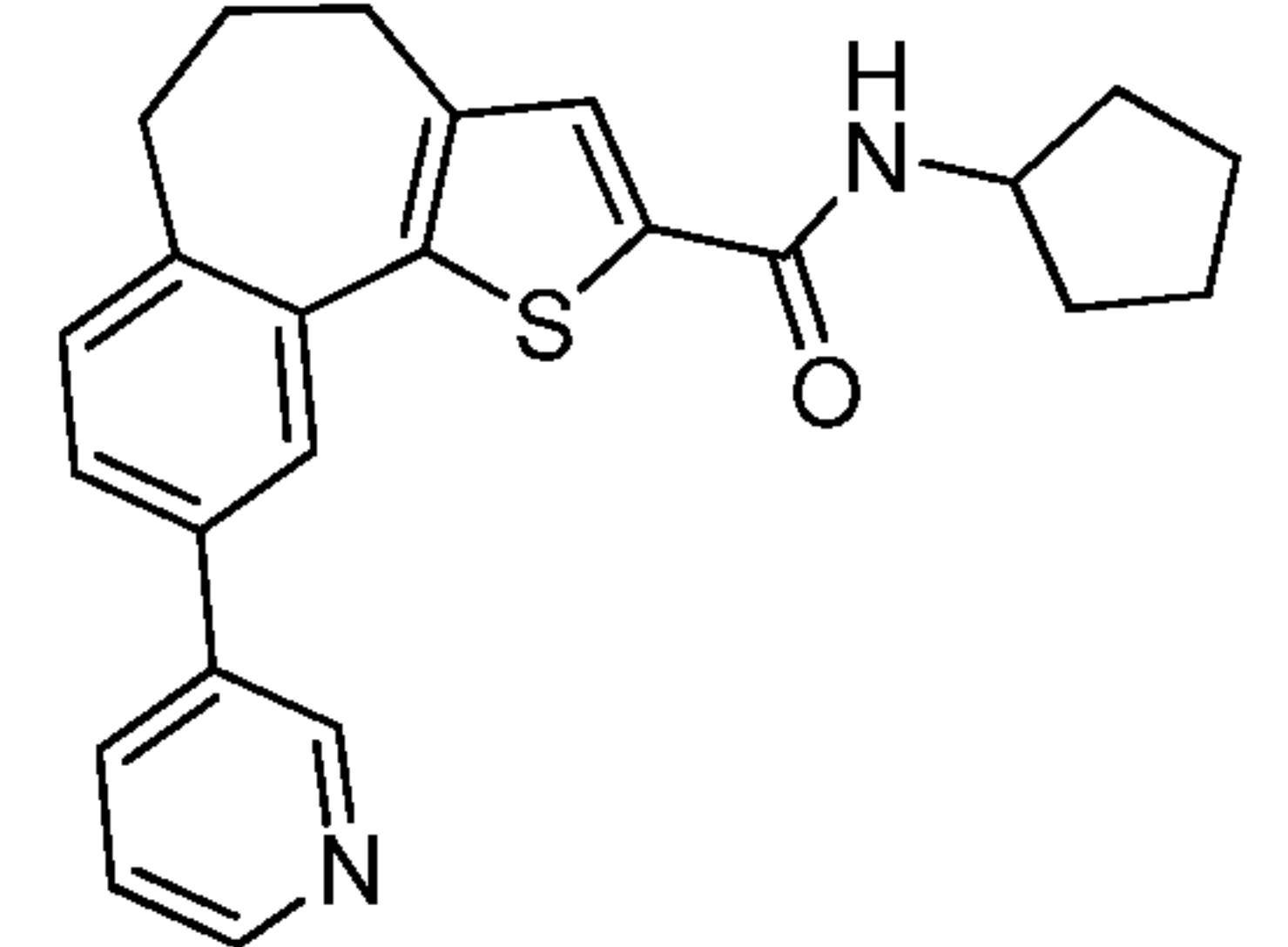
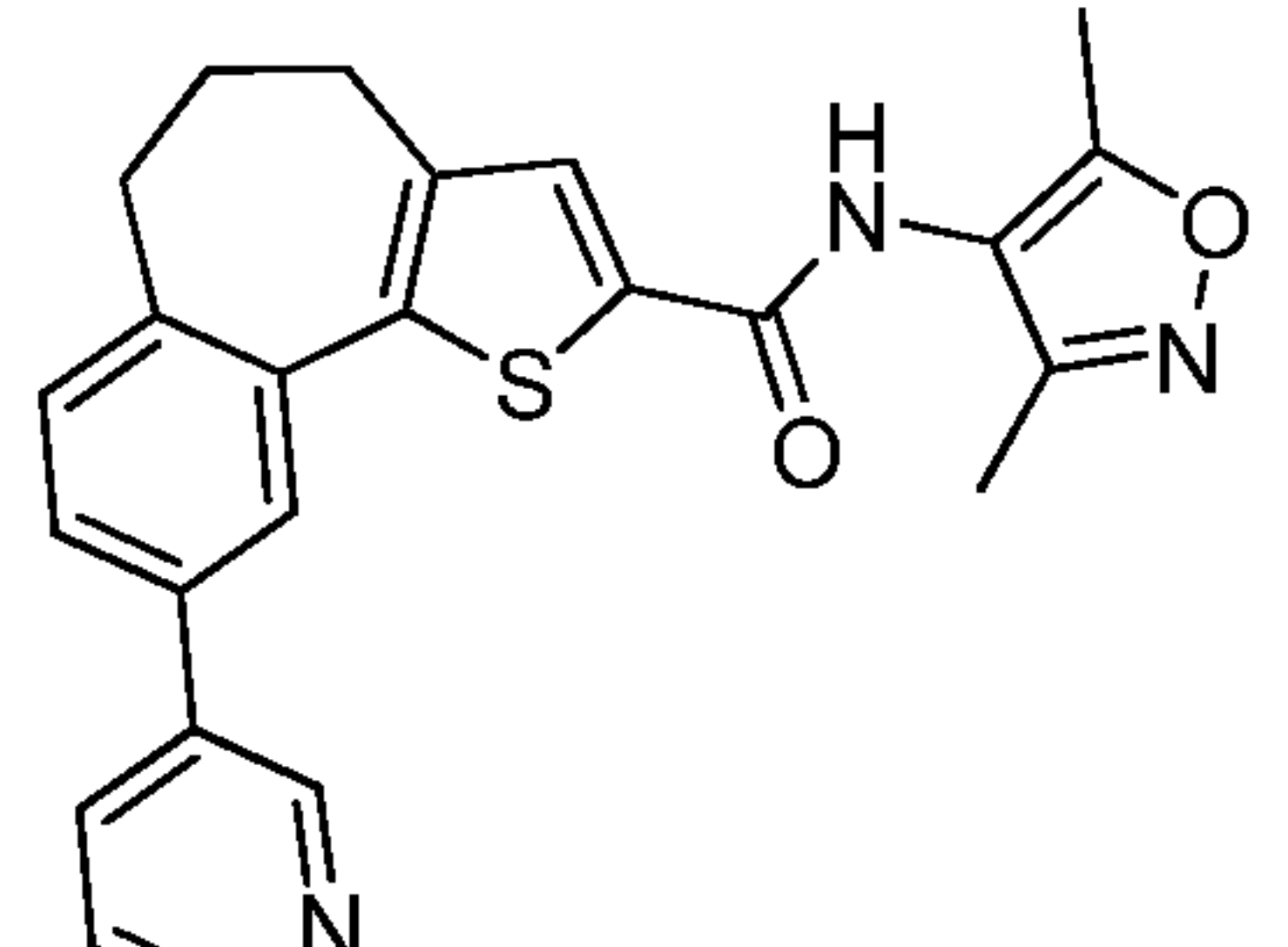
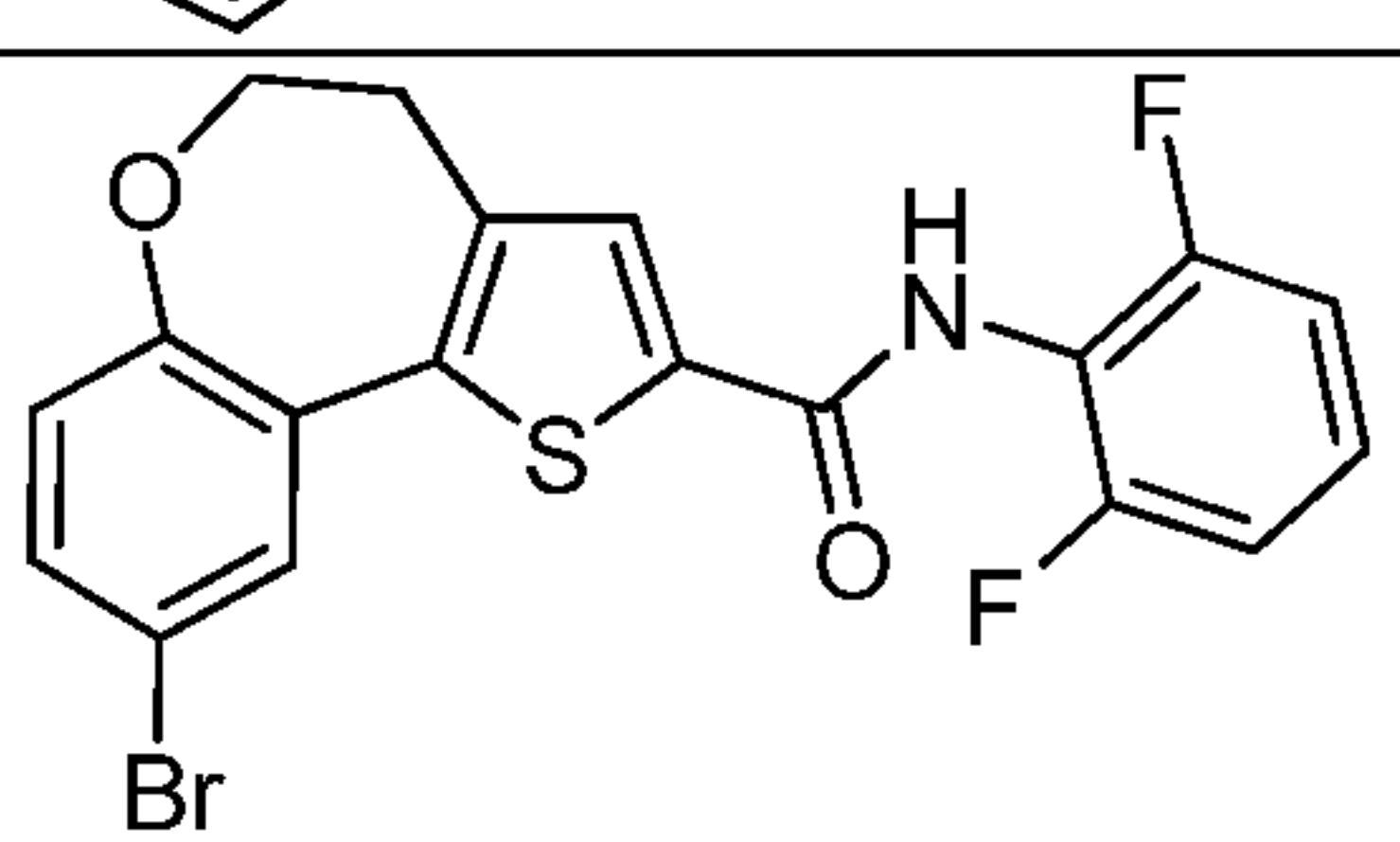
Table 1

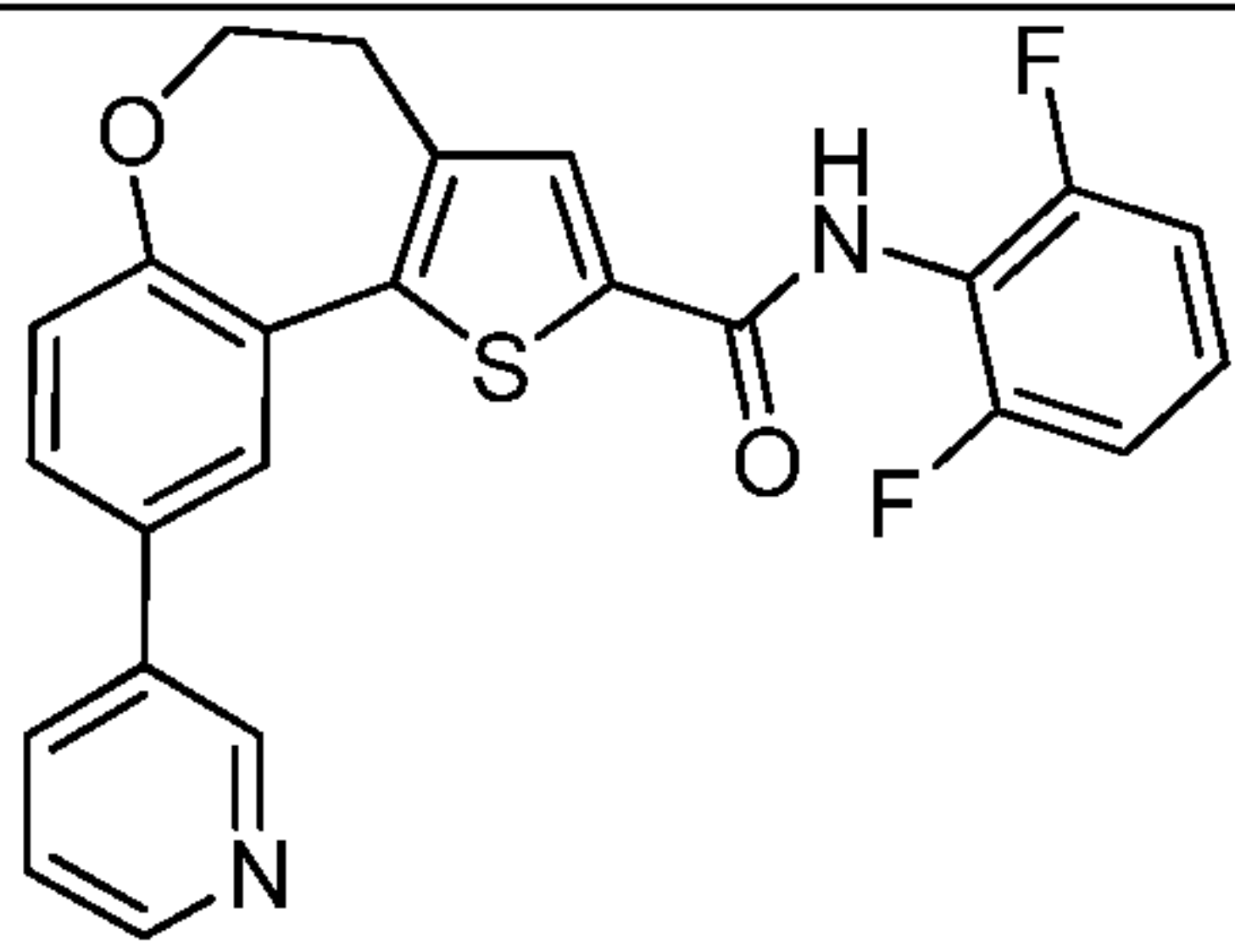
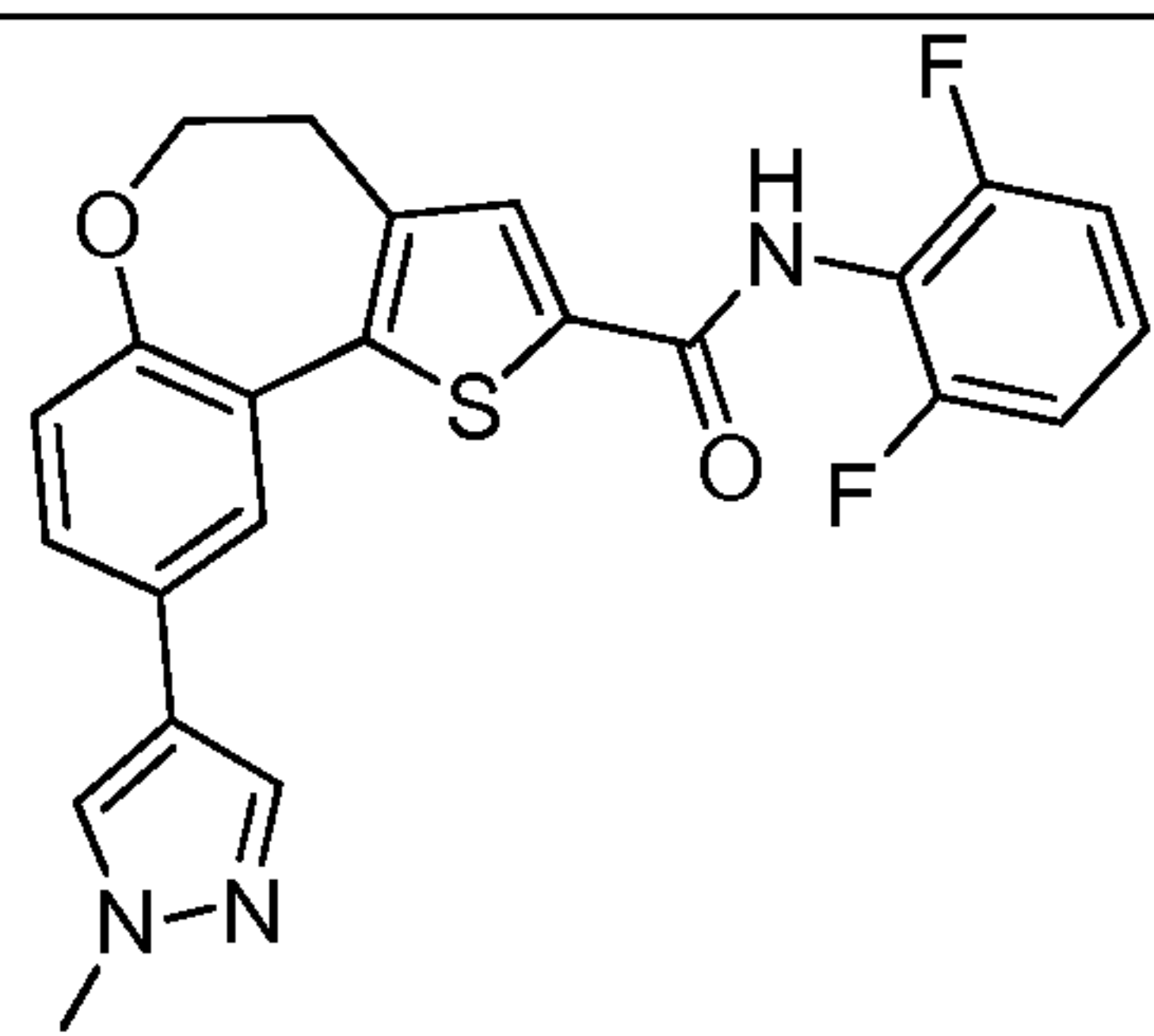
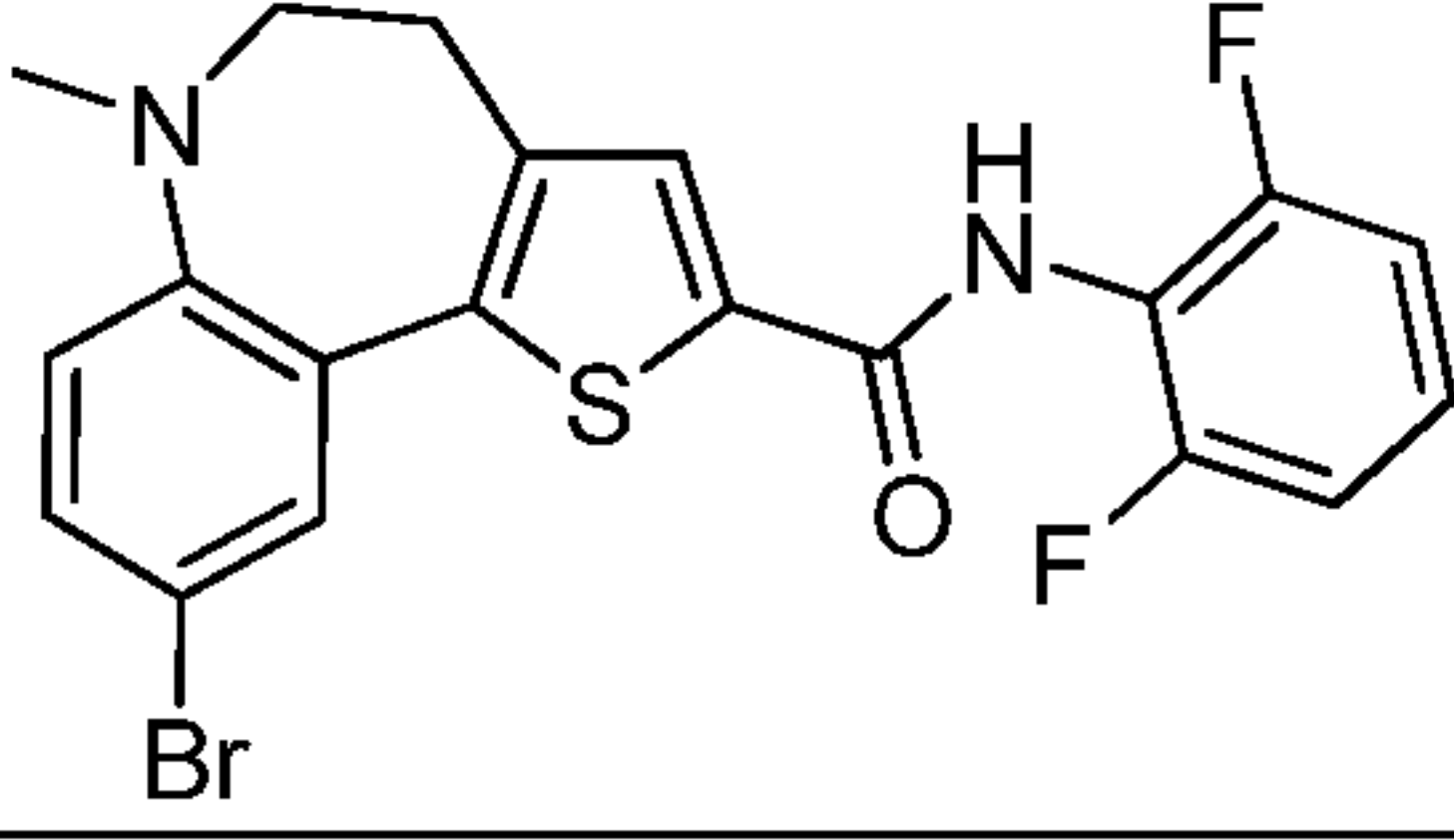
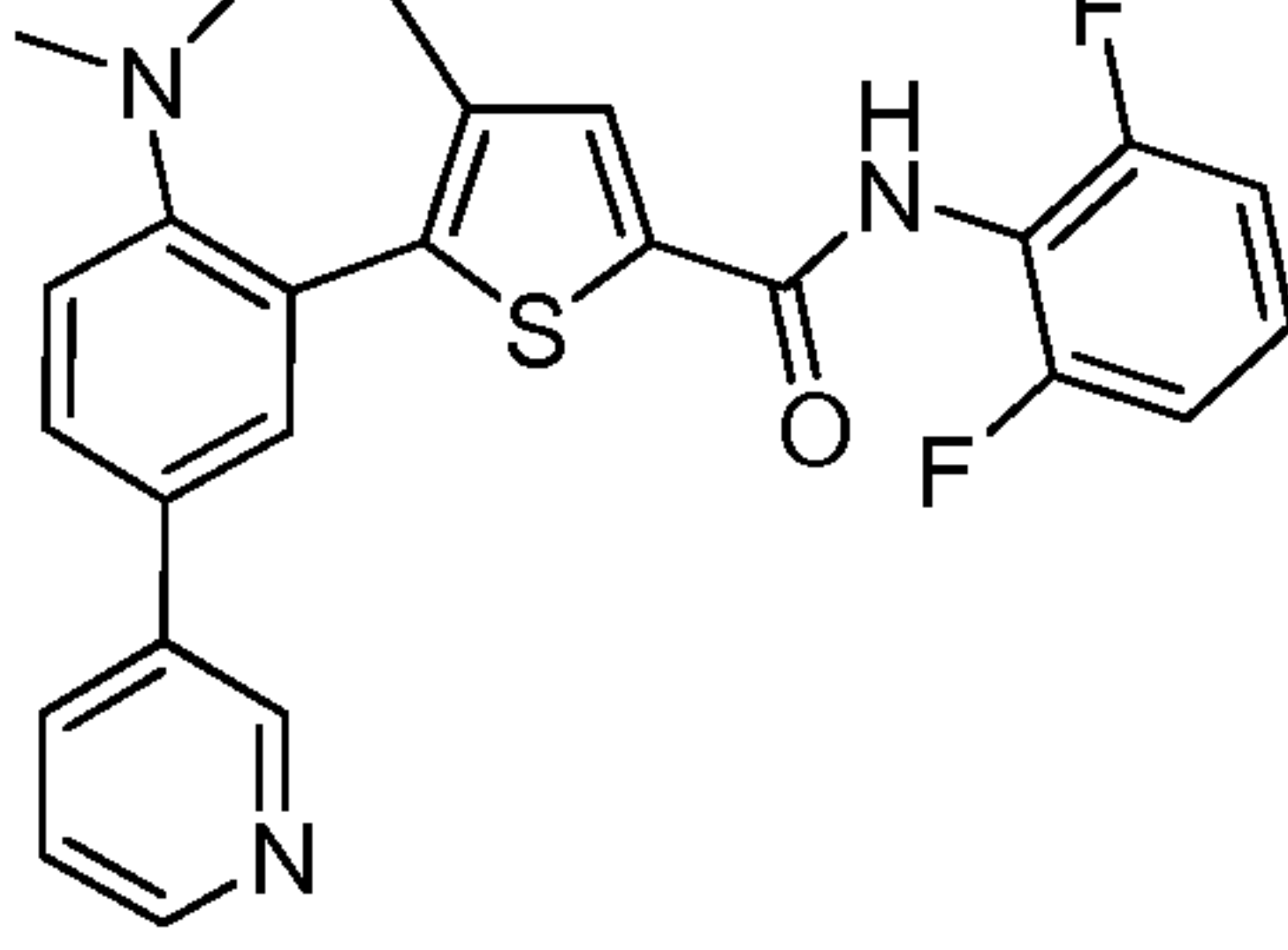
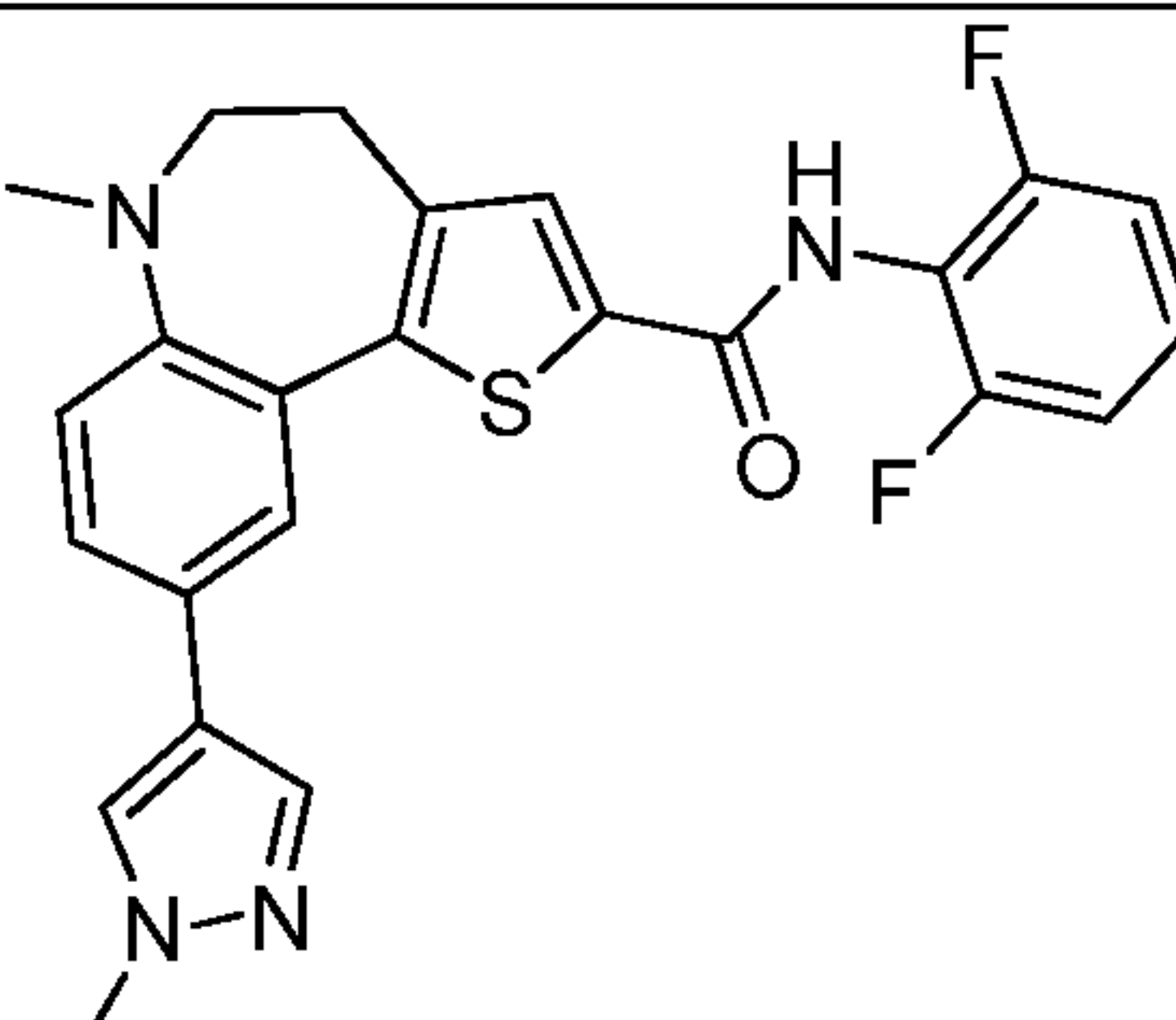
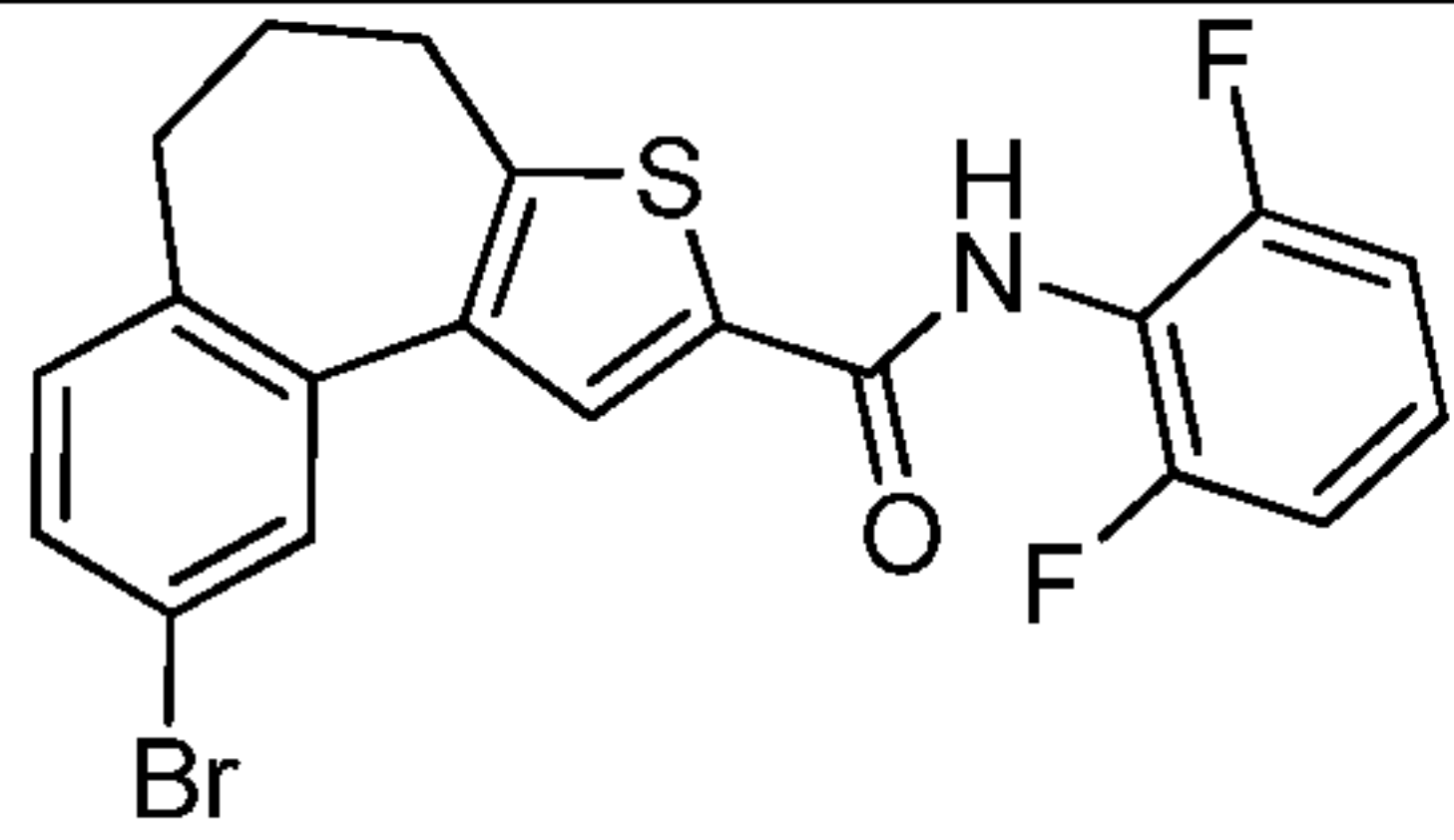
Compound No.	Structure
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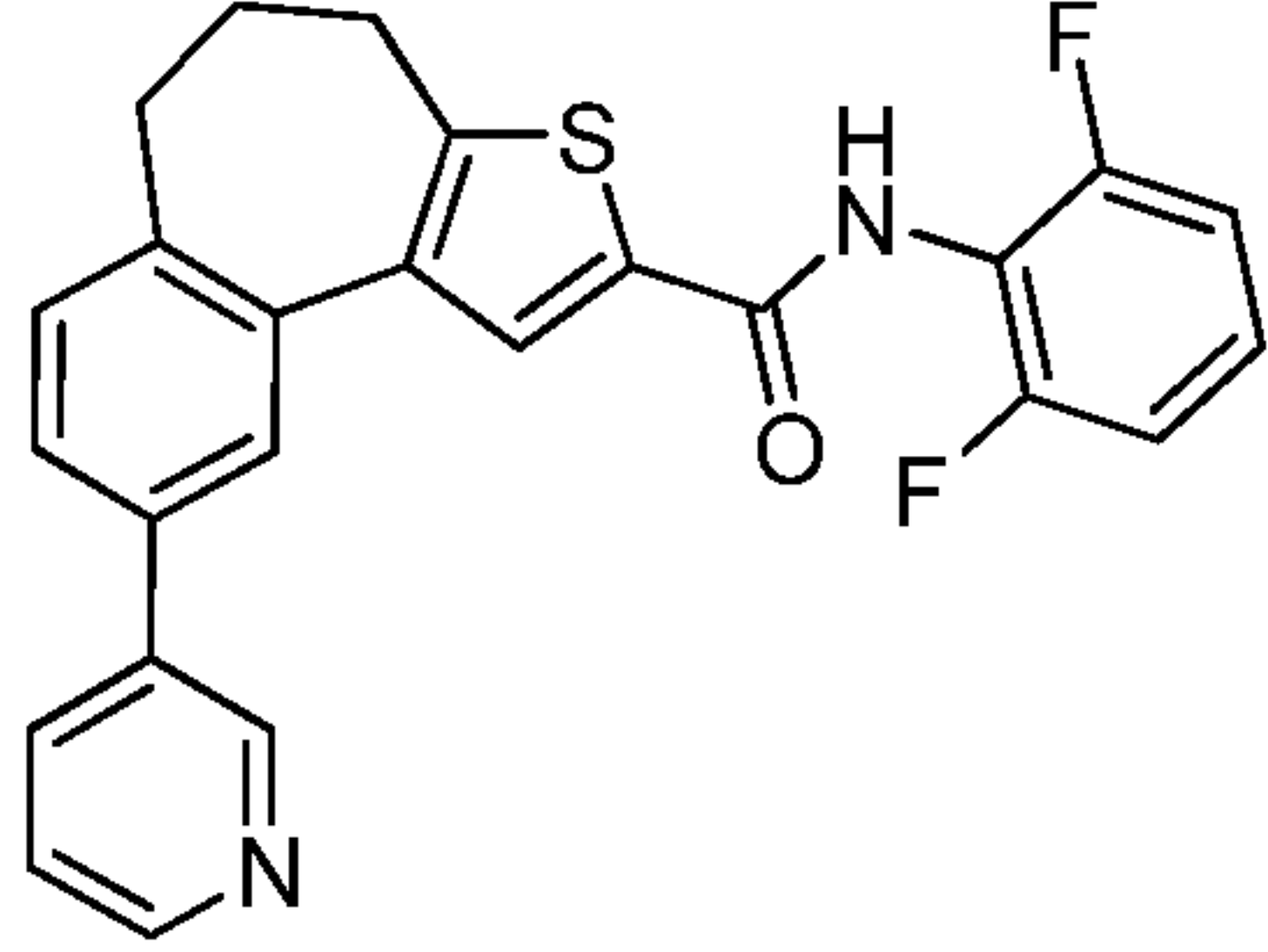
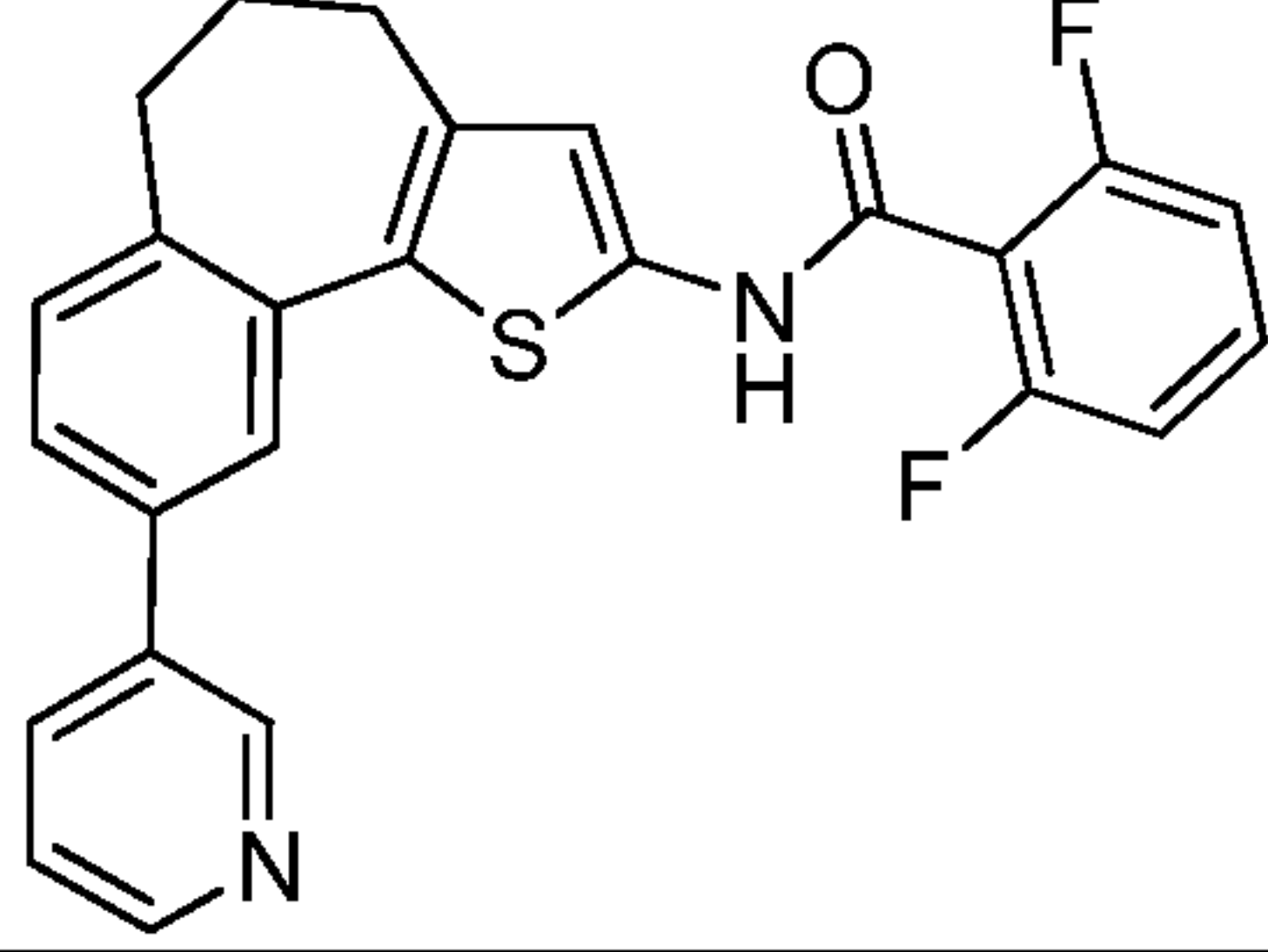
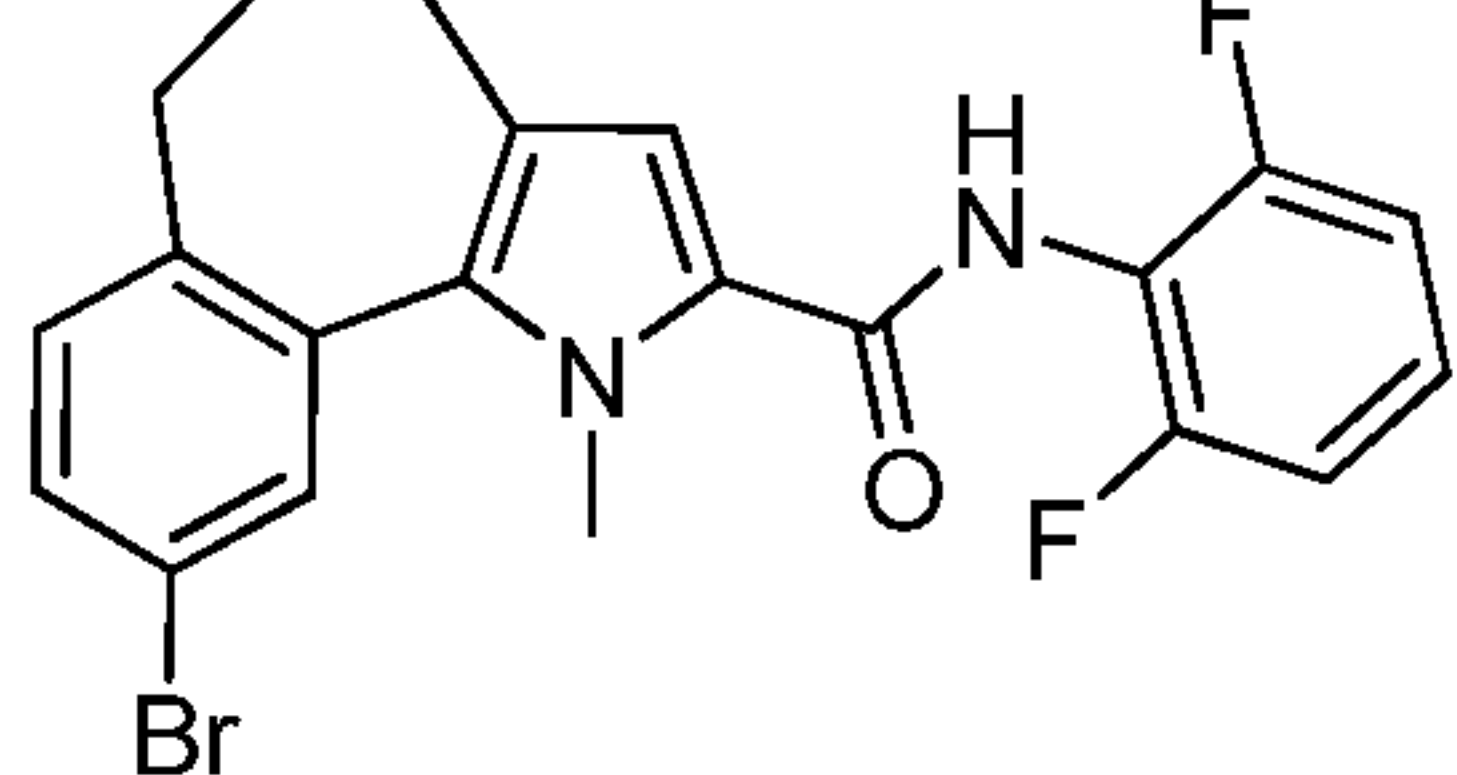
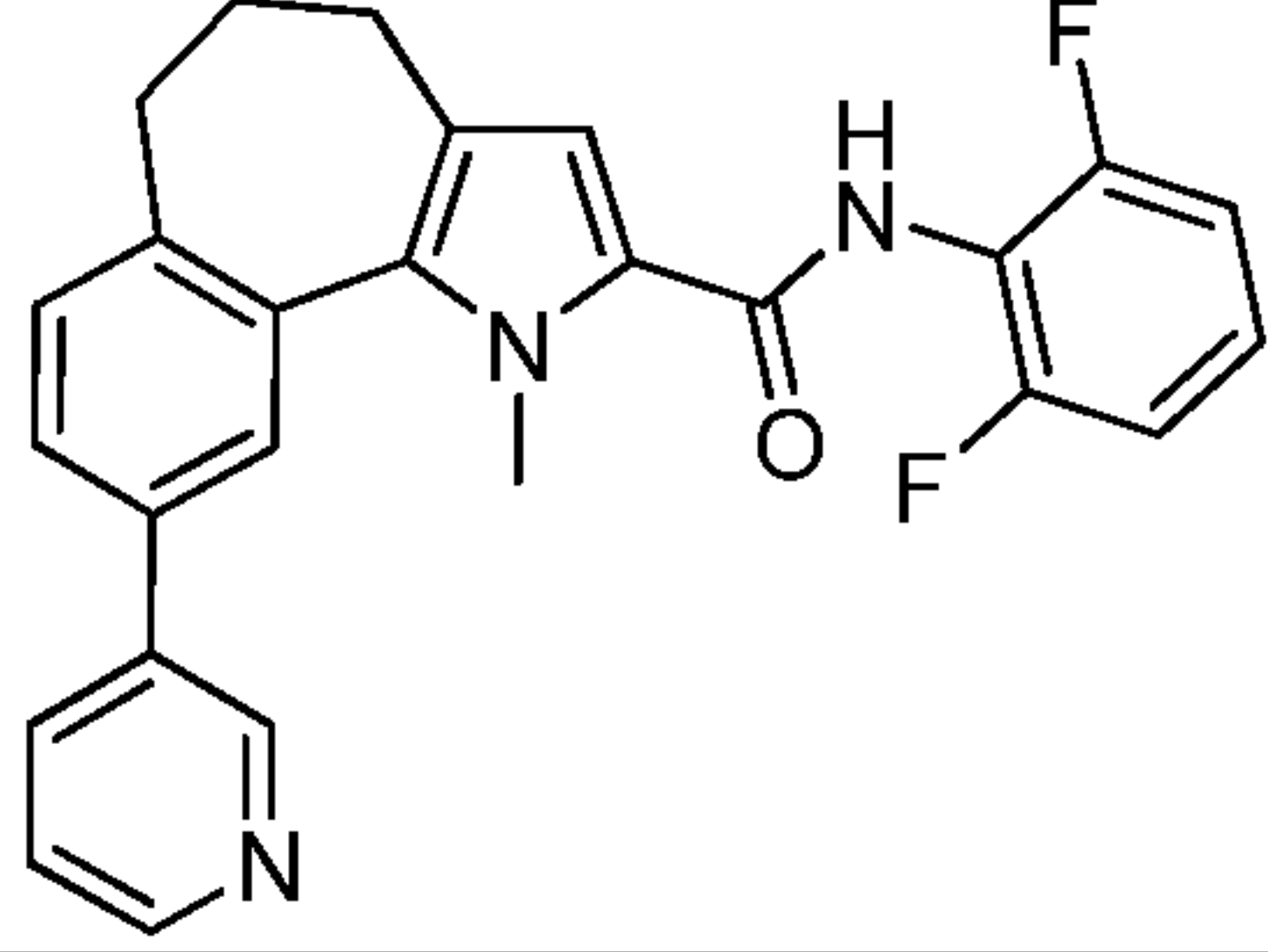
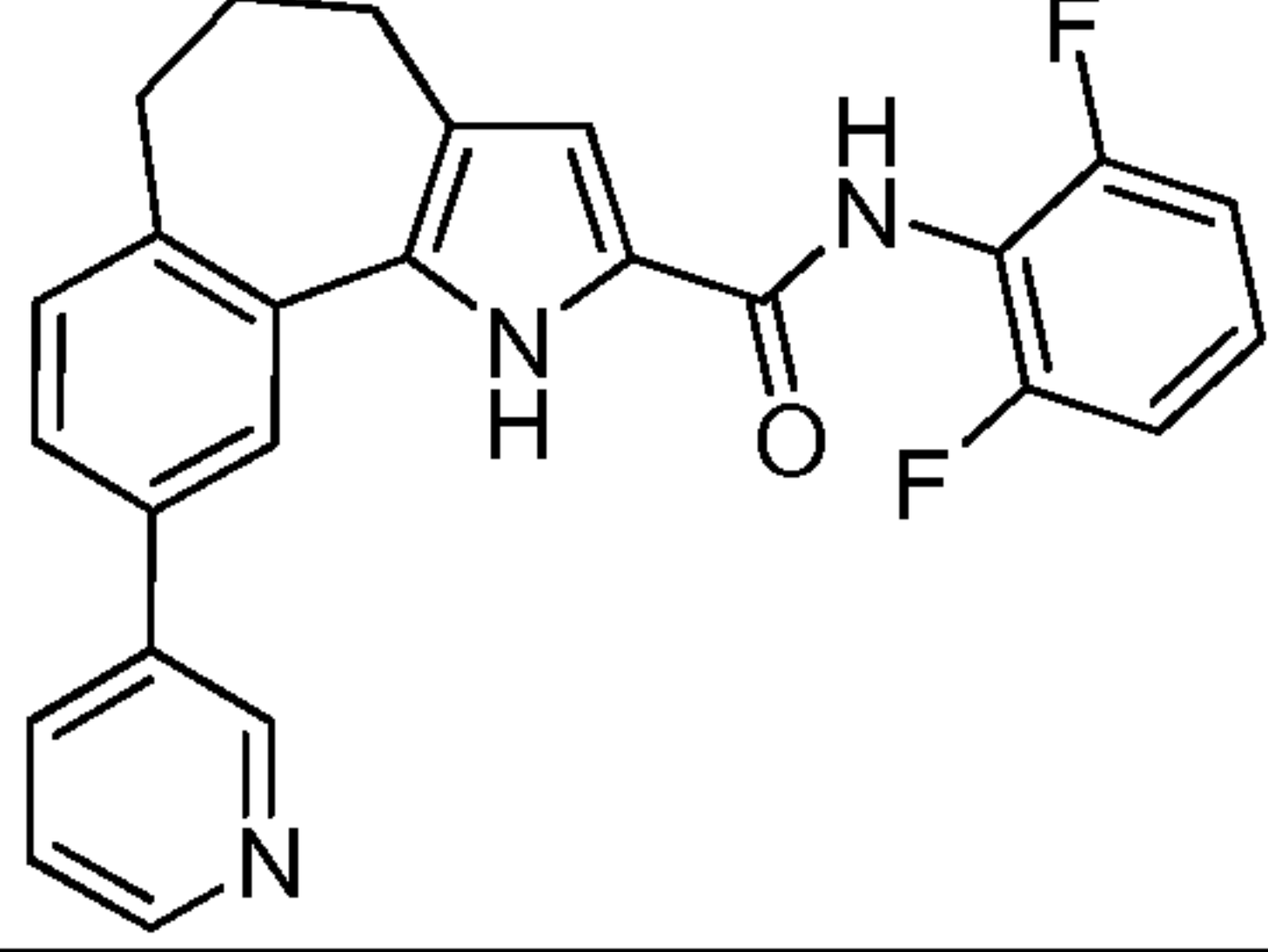
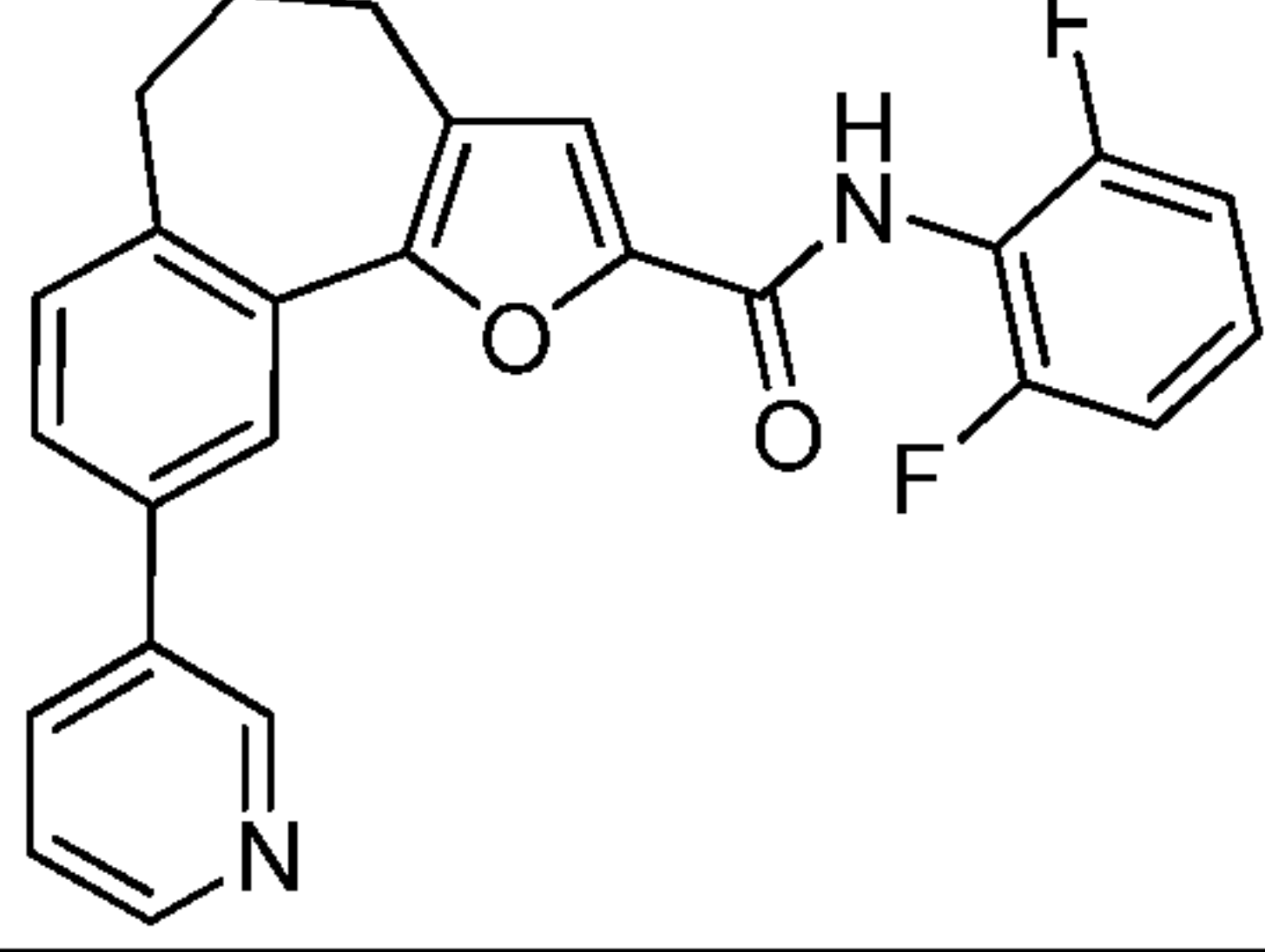
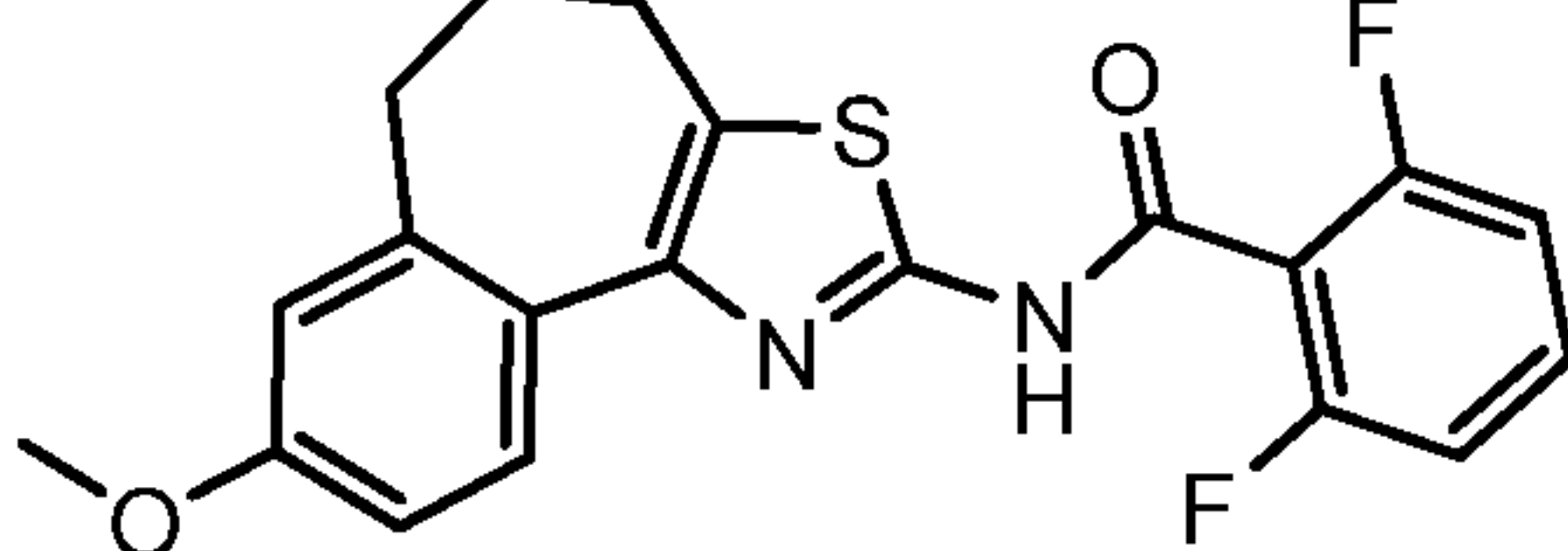
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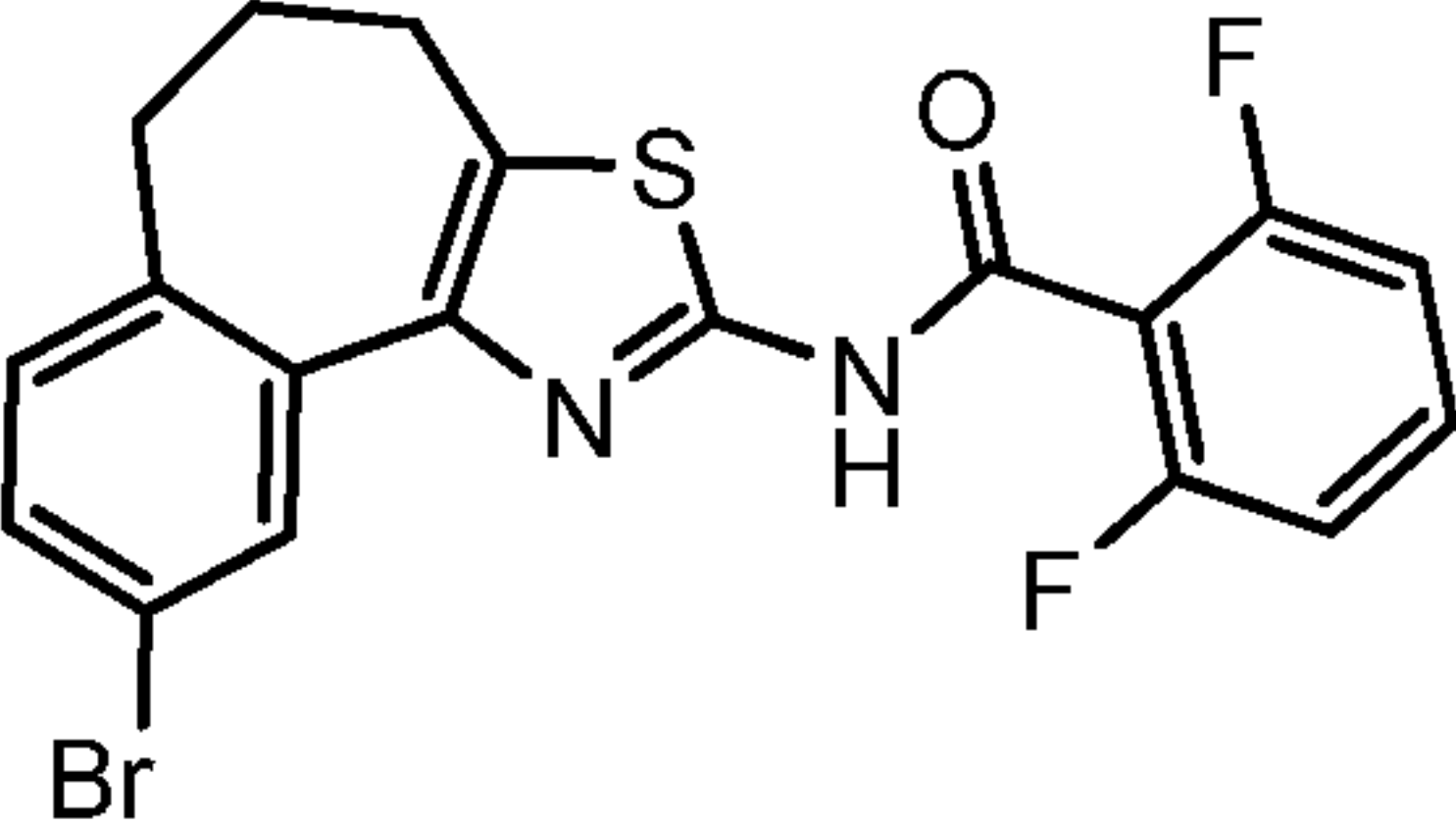
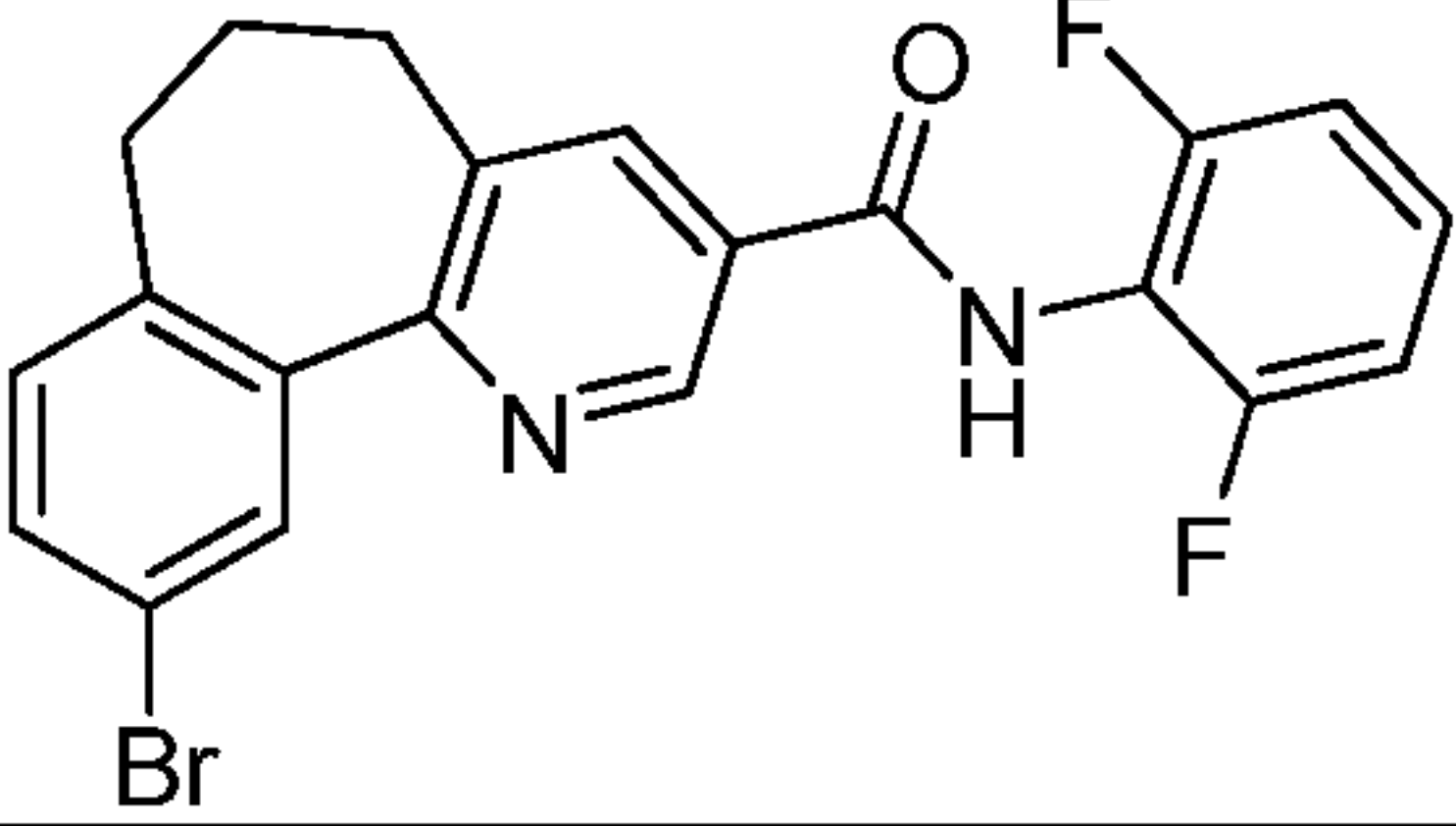
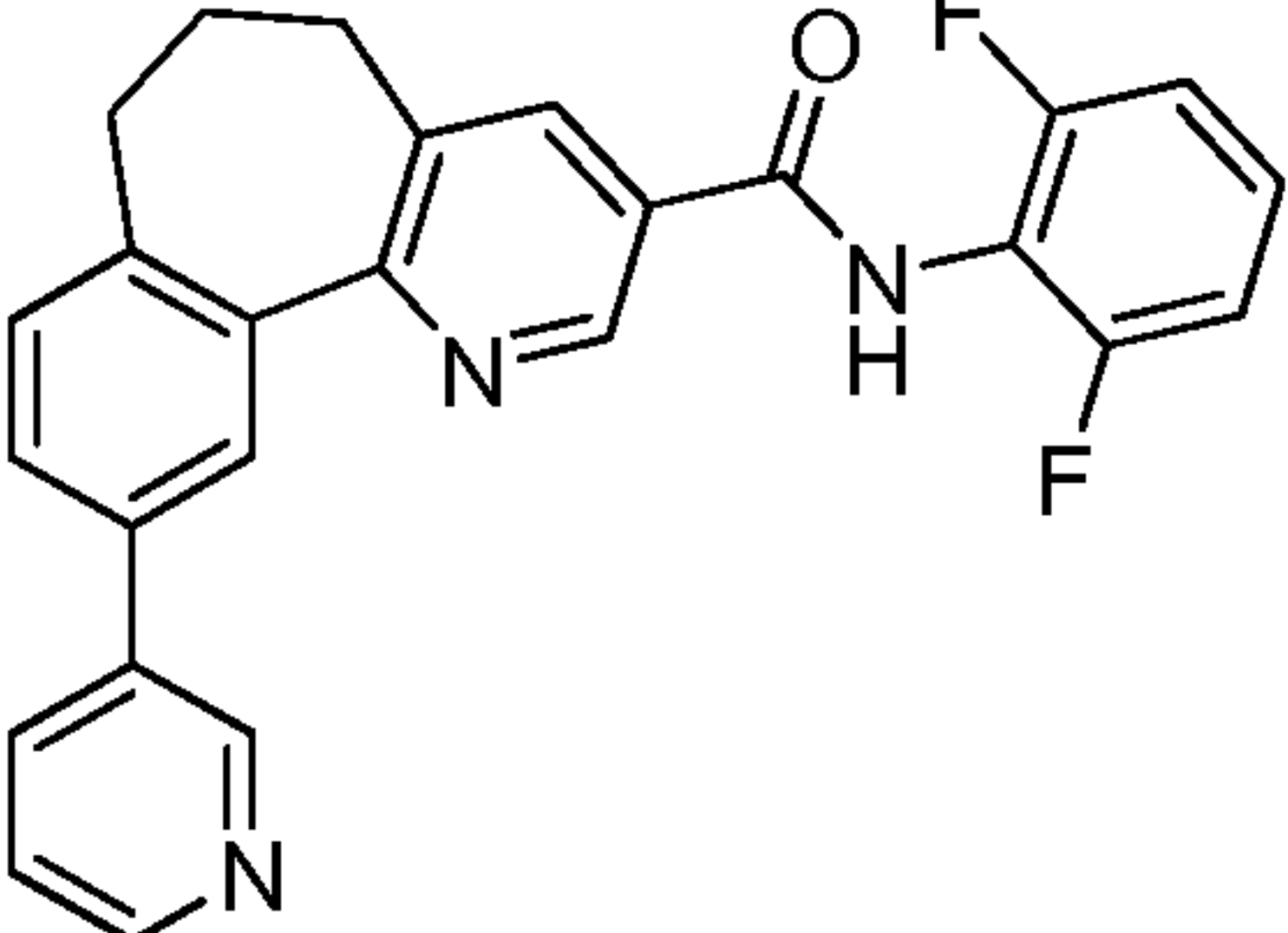
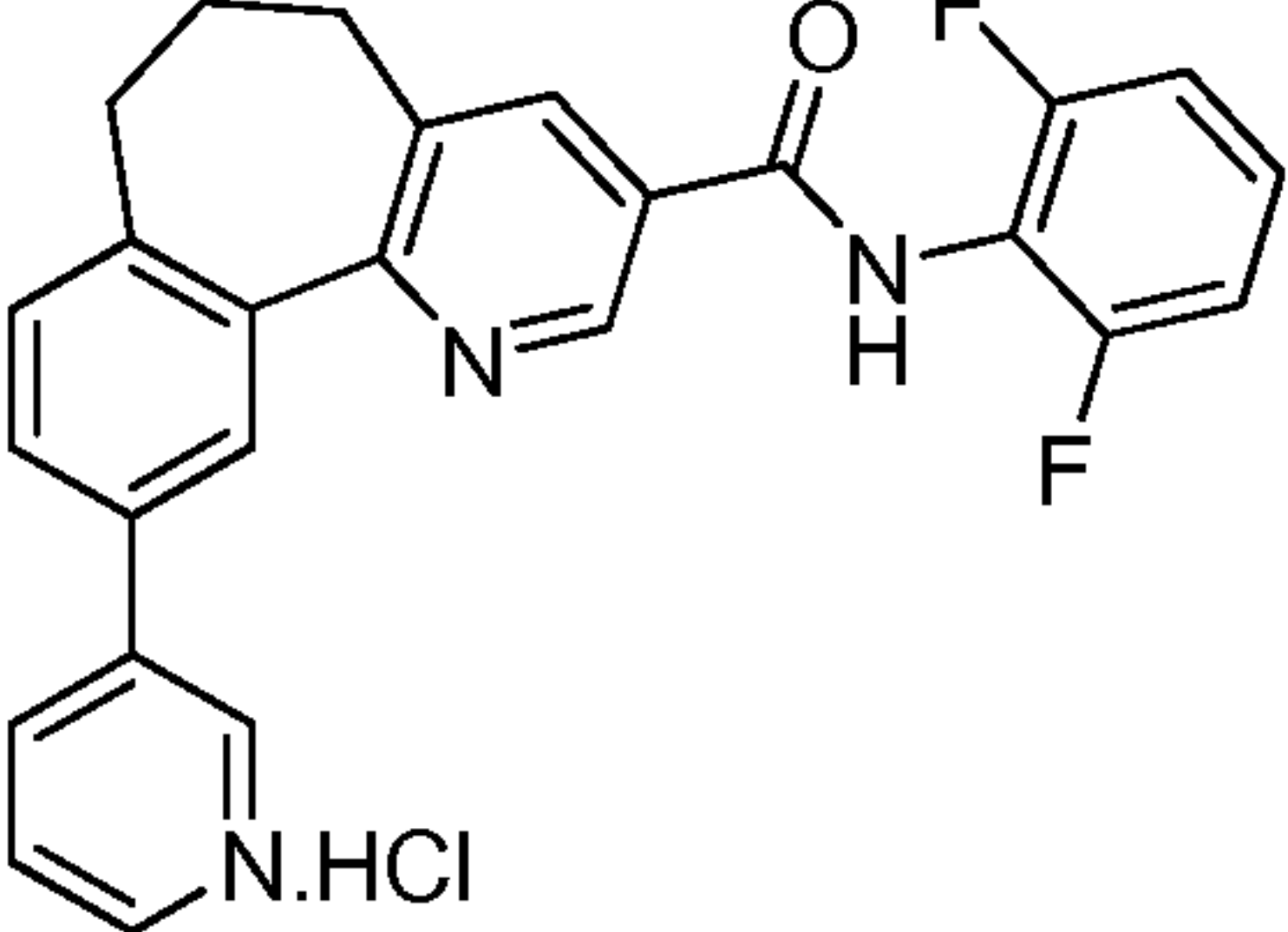
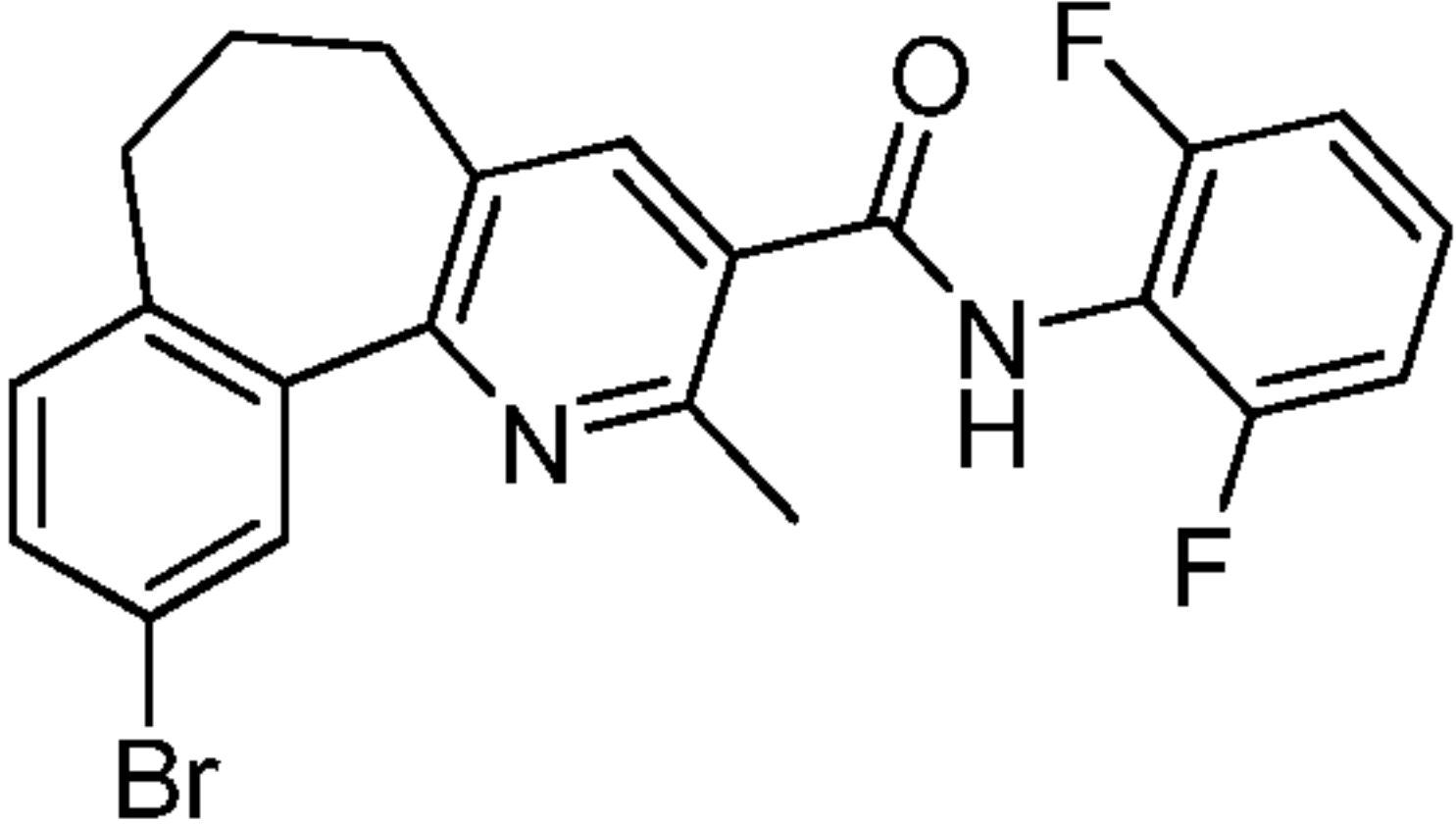
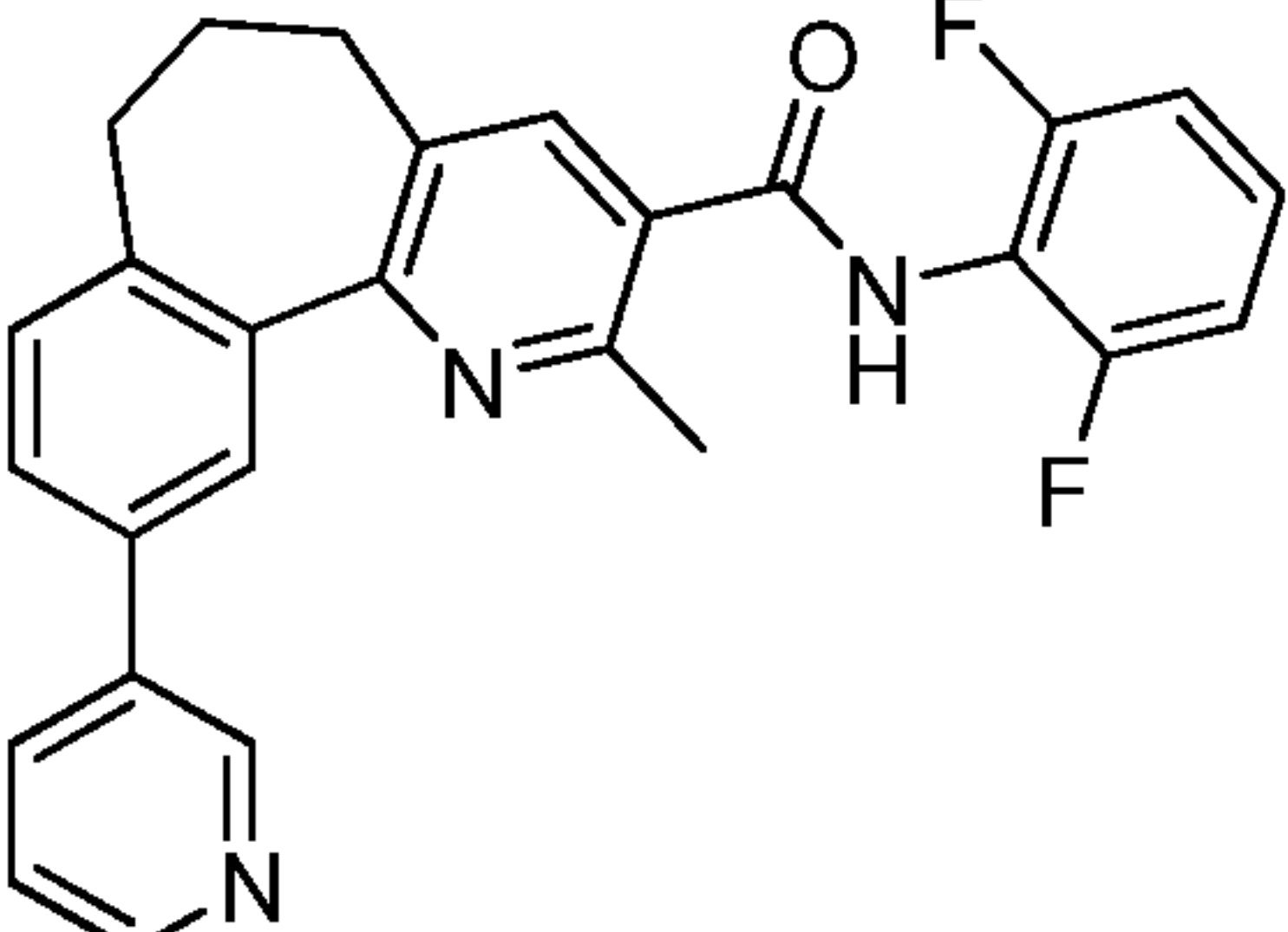
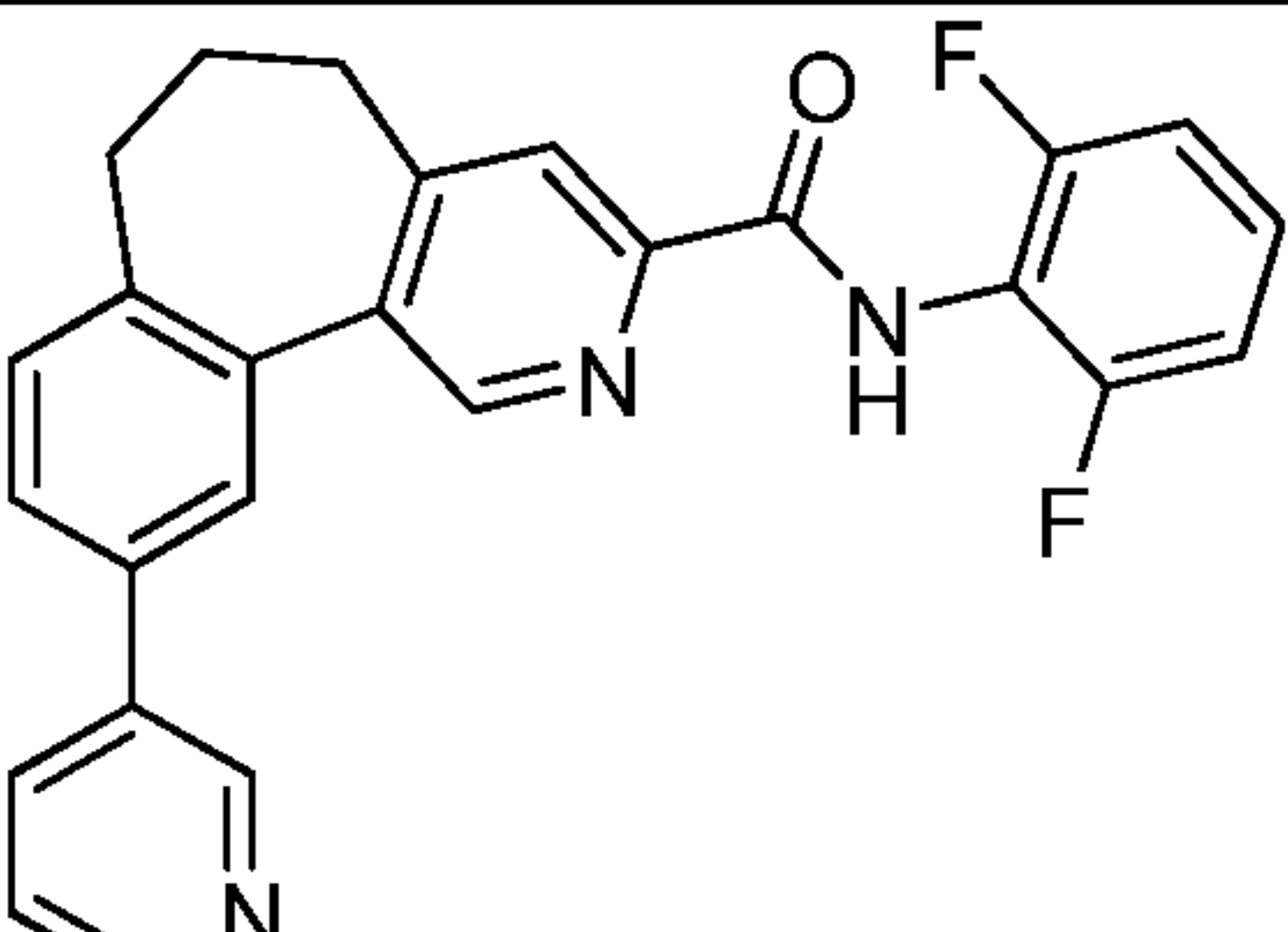
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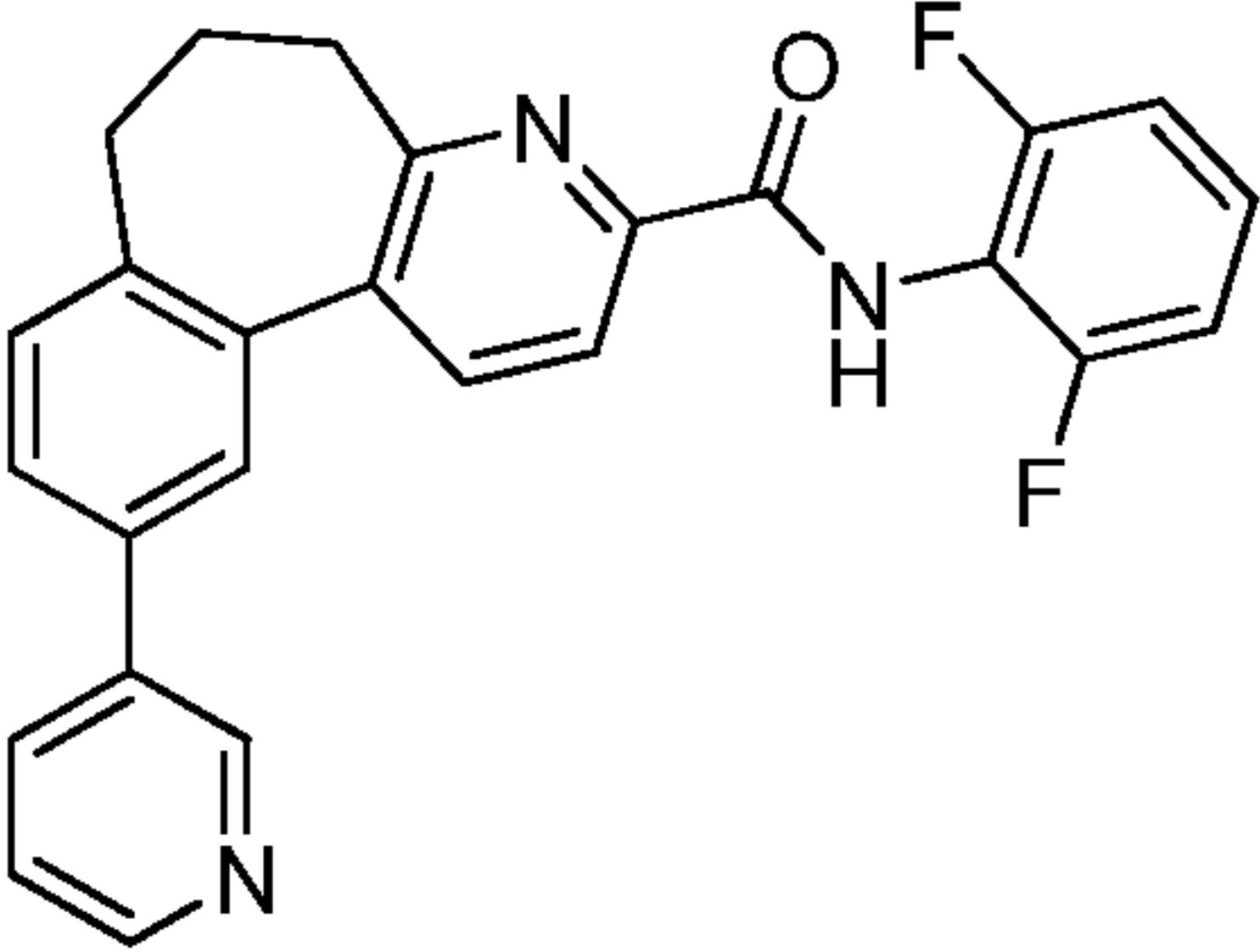
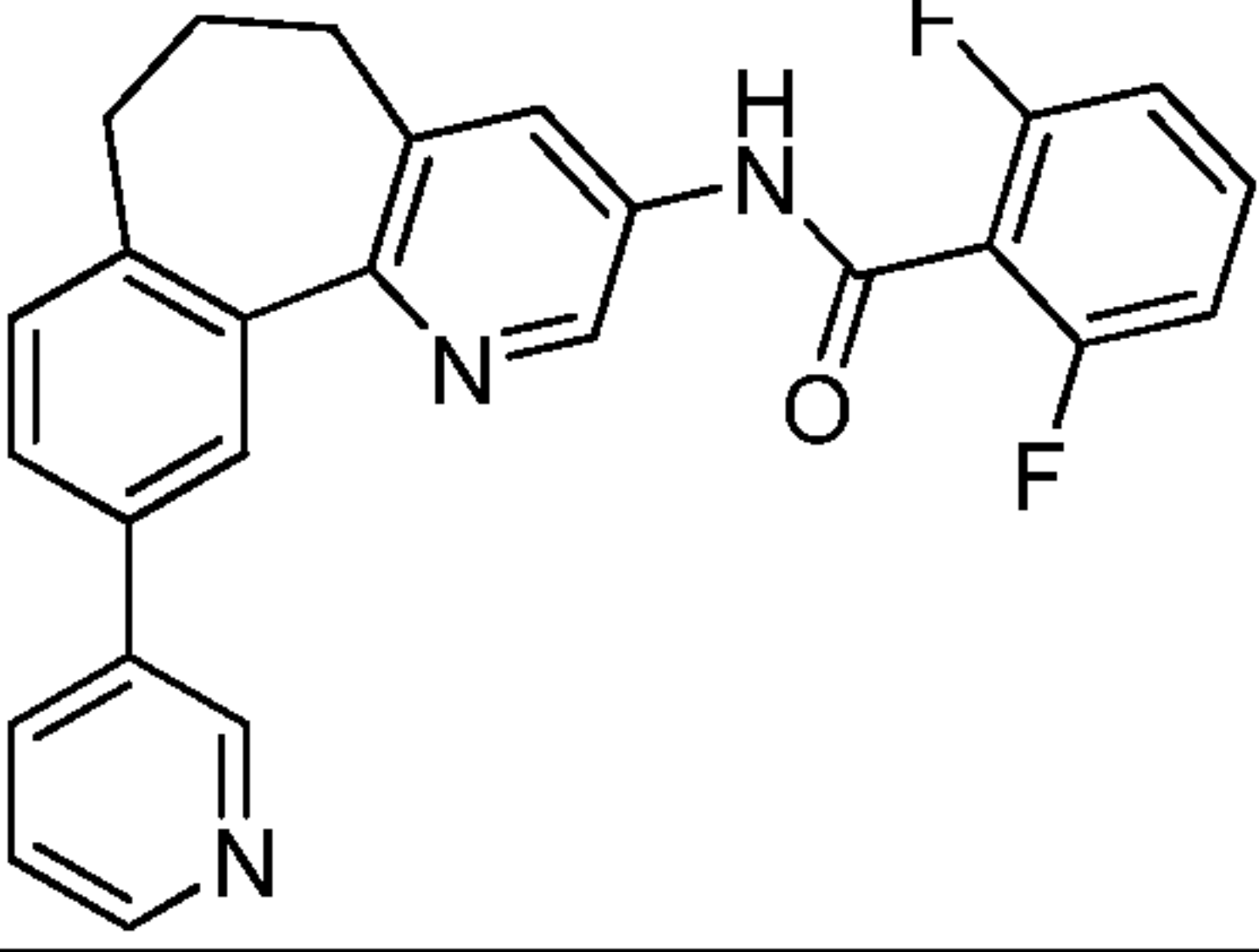
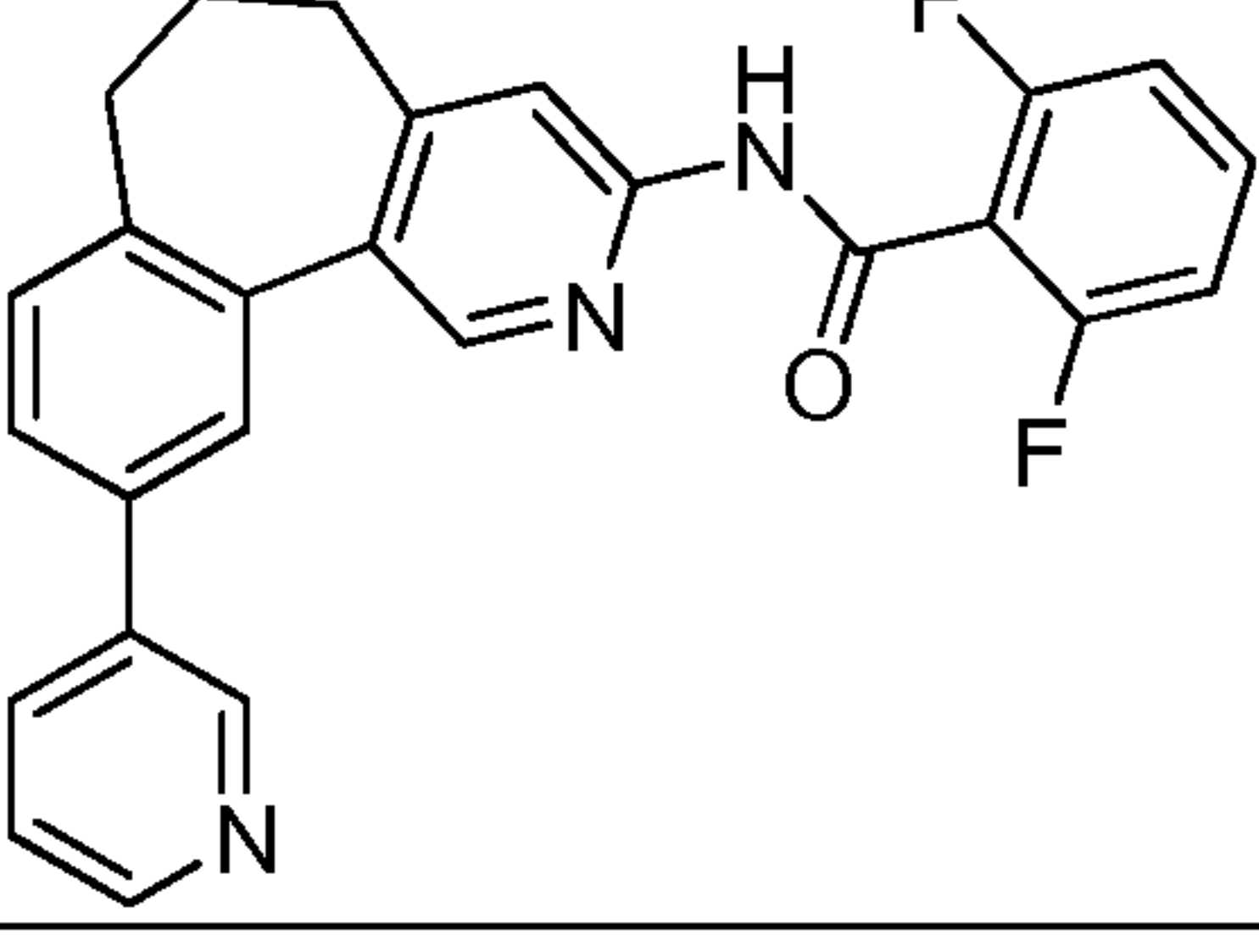
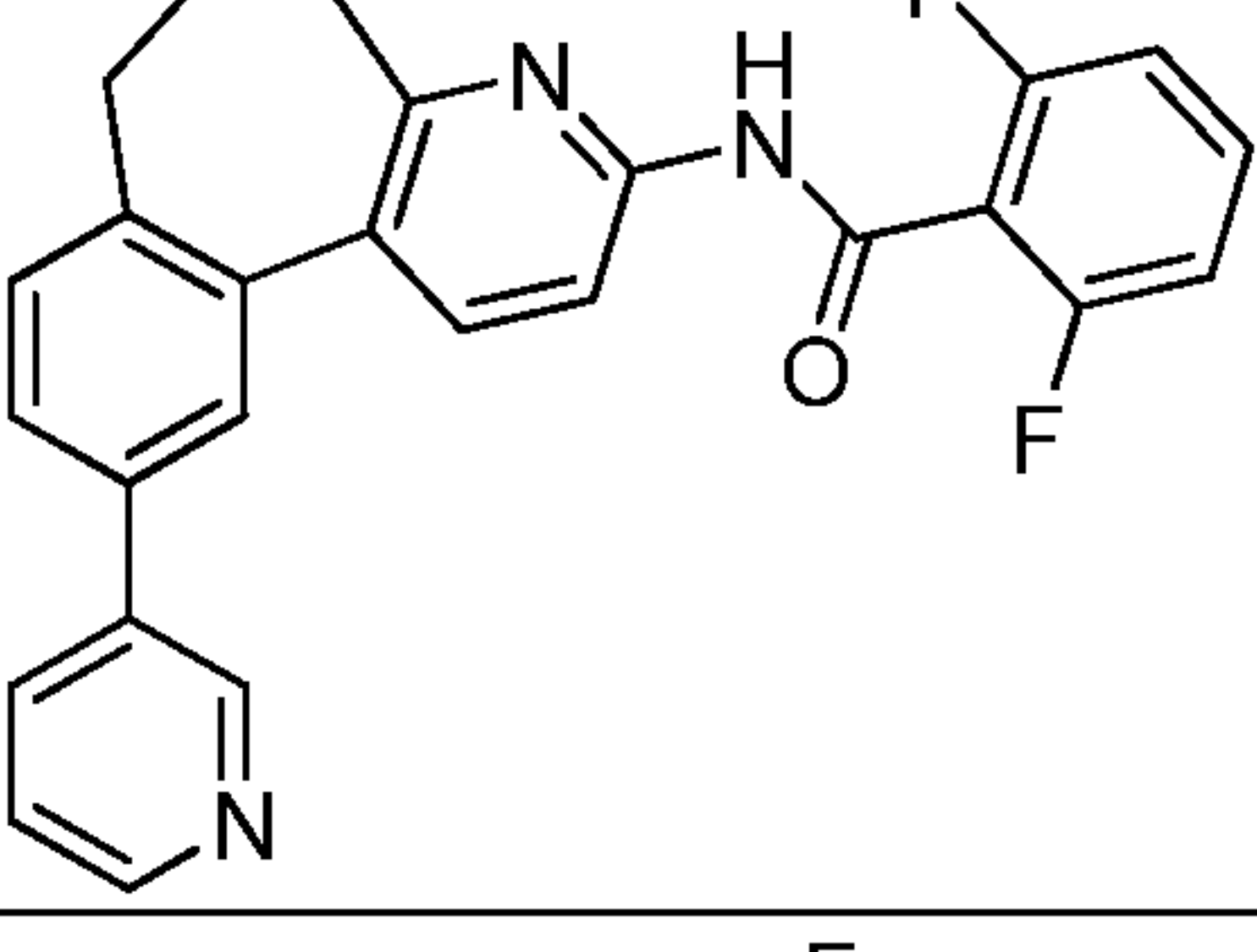
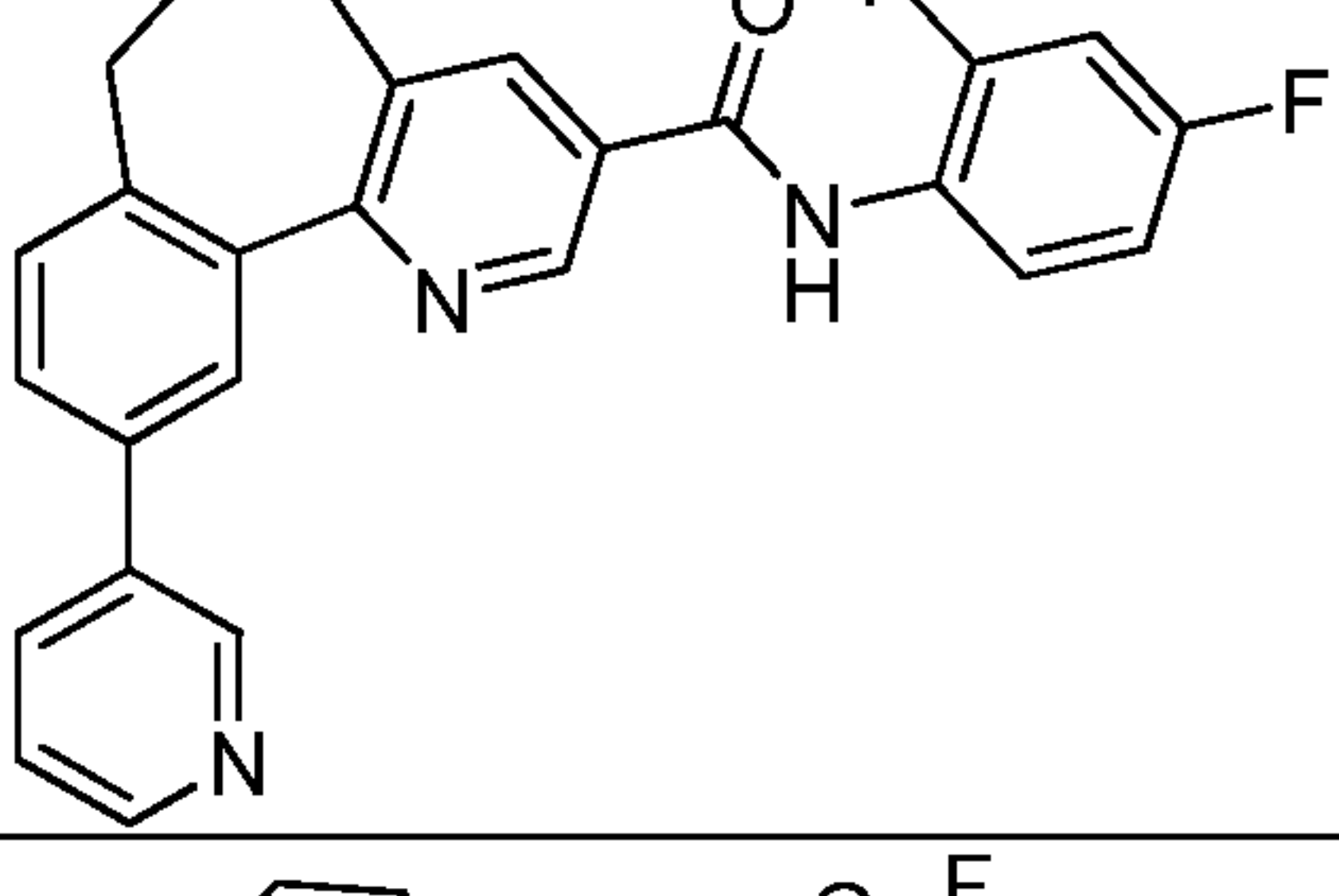
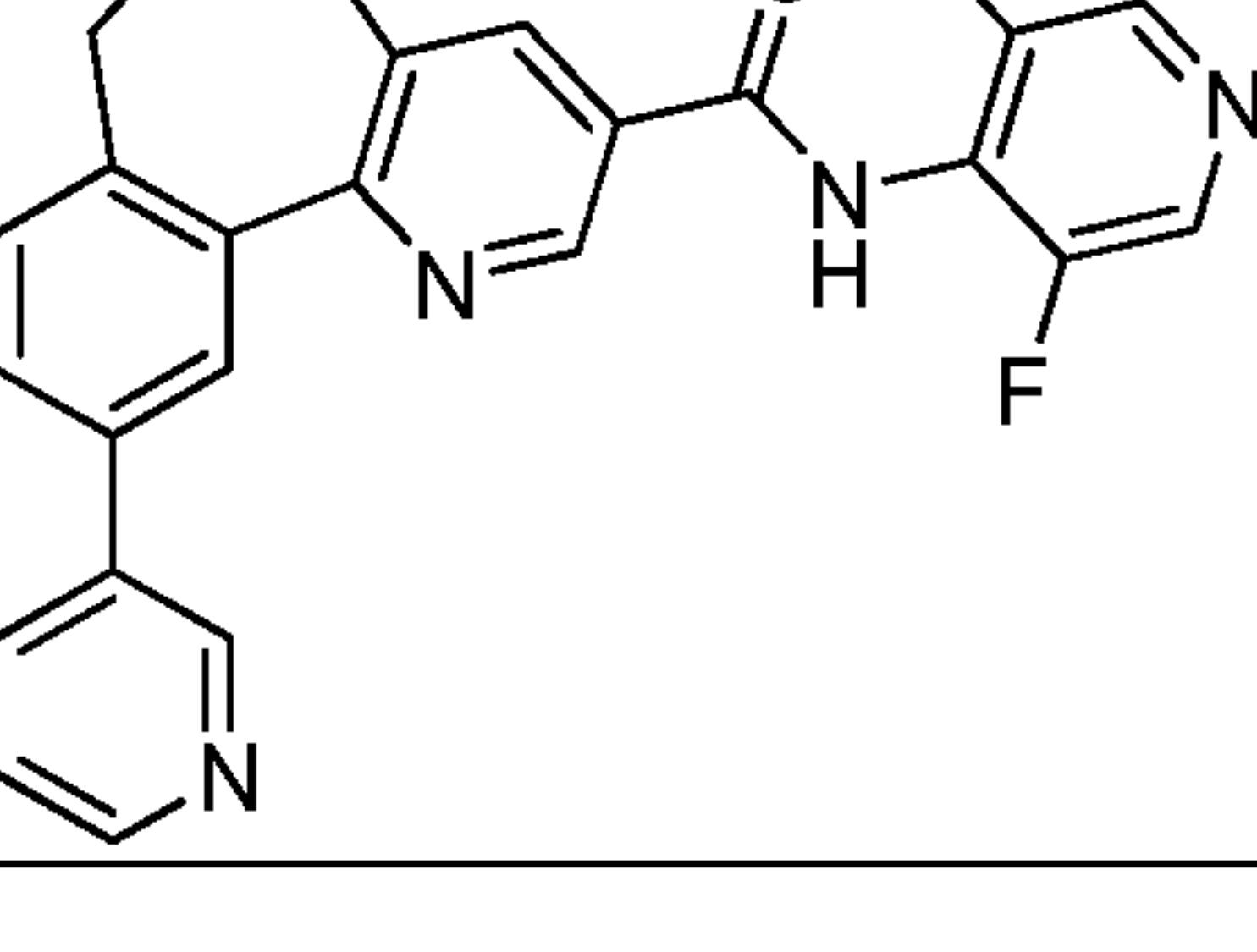
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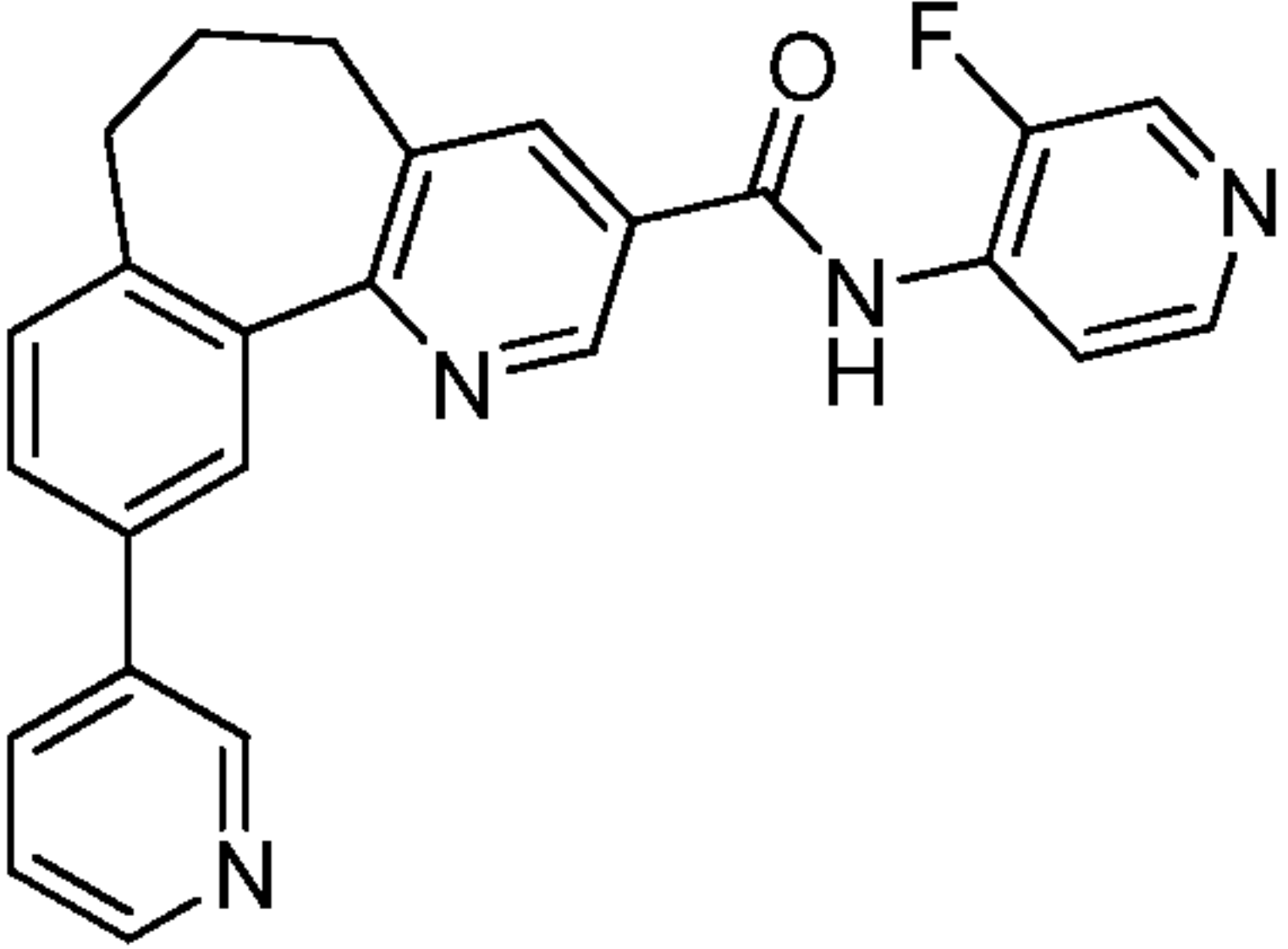
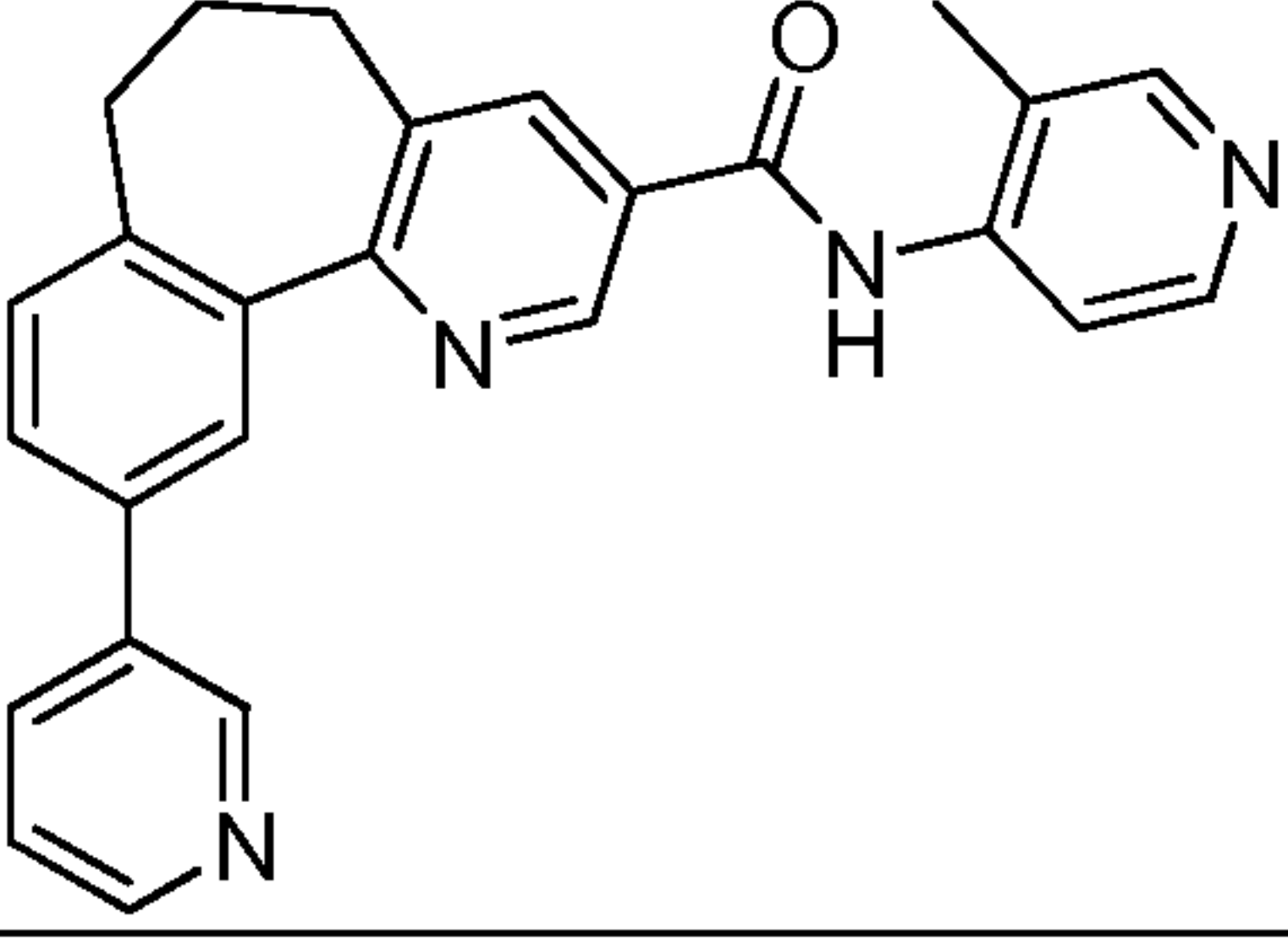
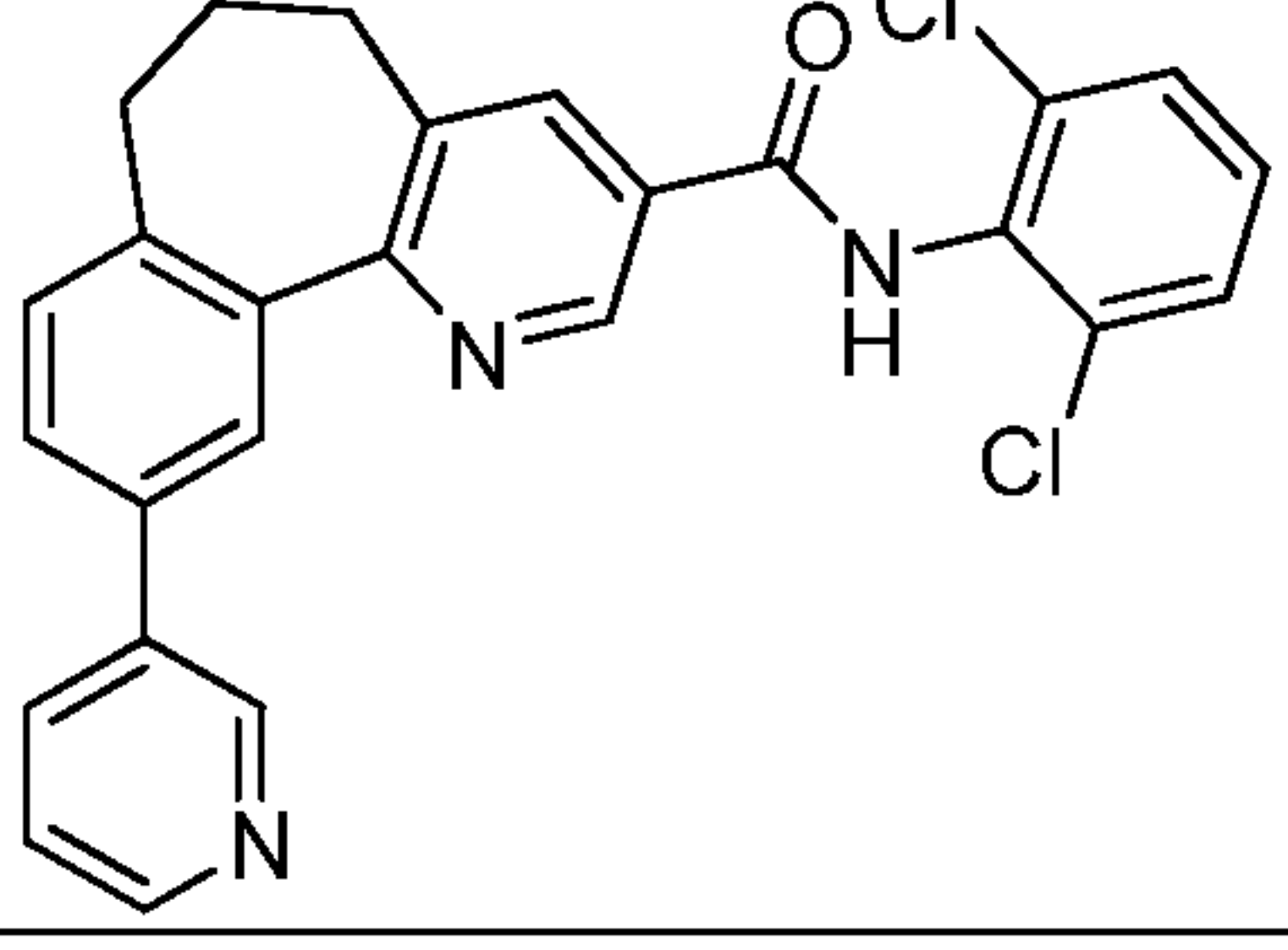
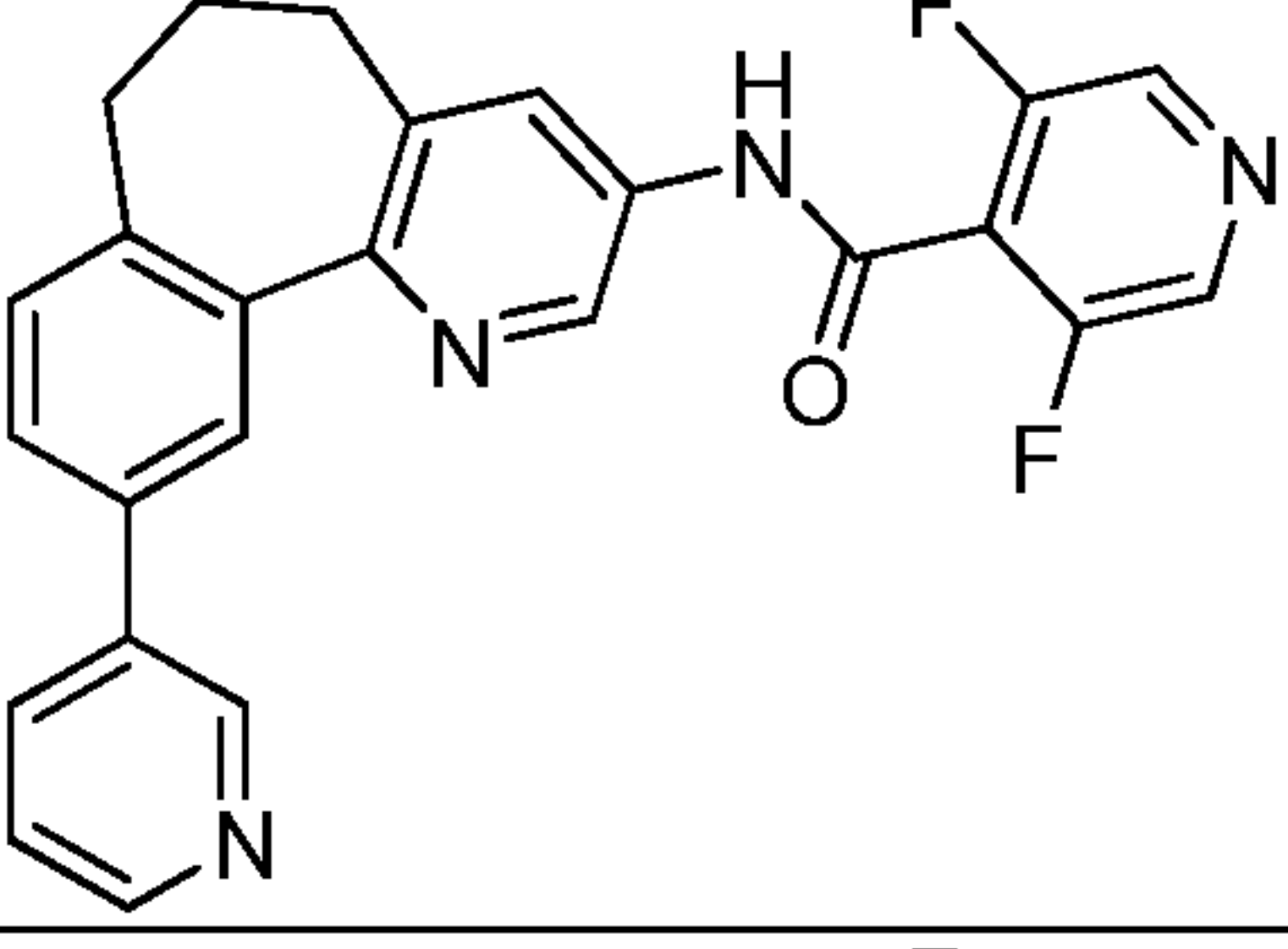
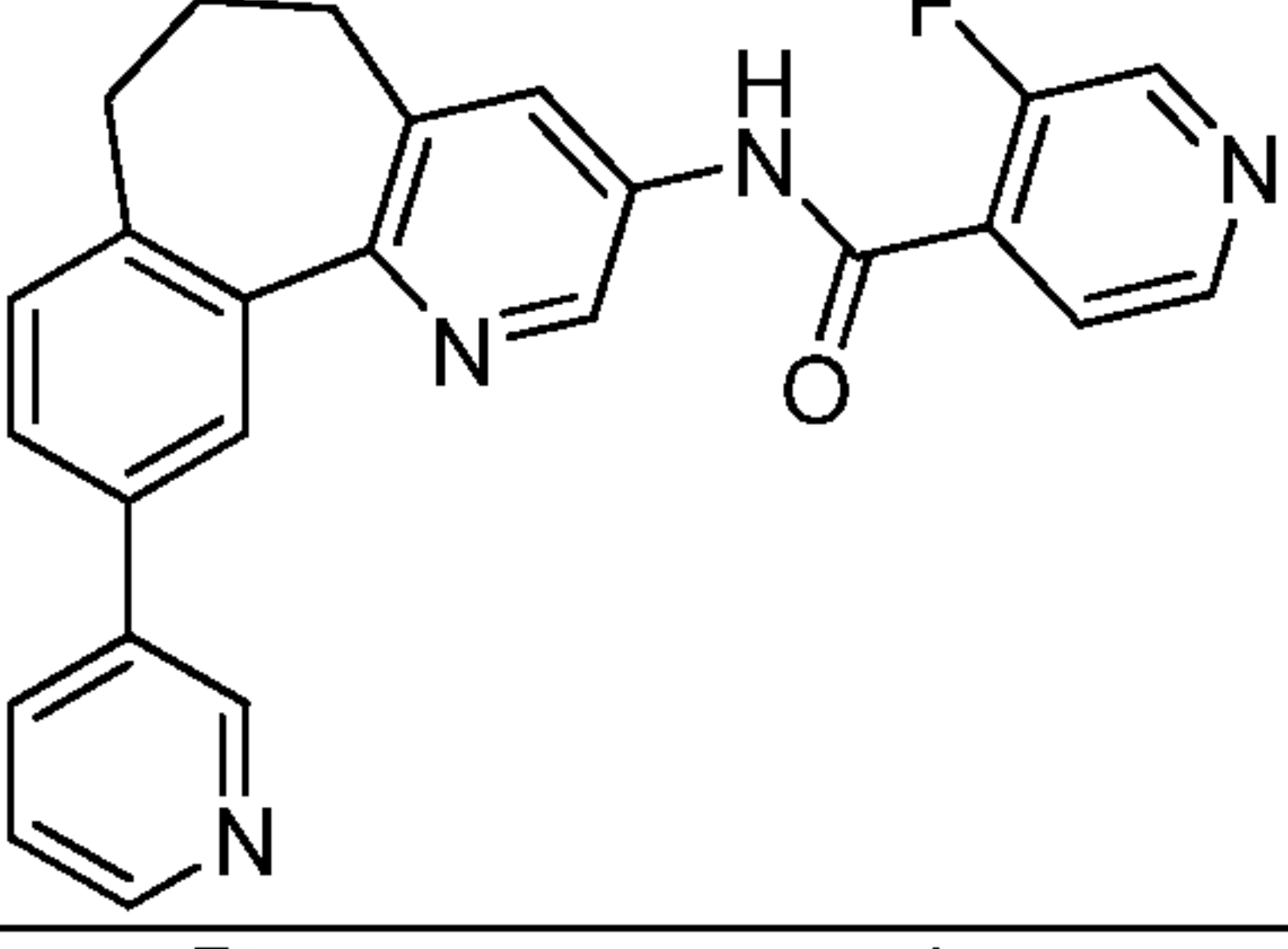
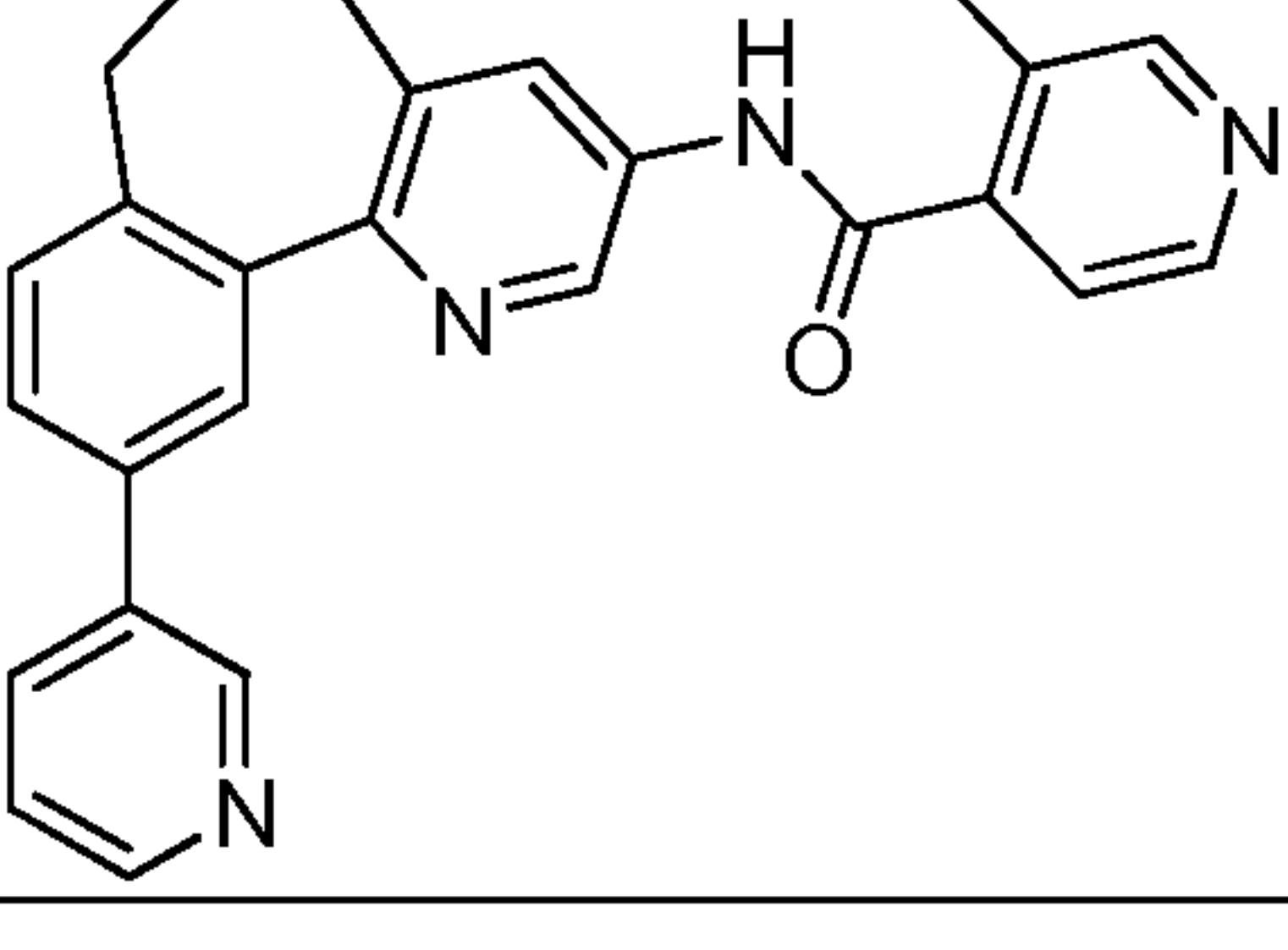
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24	 <chem>C1=CC=C(C=C1C2=CC=CC=C2C3=CC=CC=C3S4C=CC(=C4)C(=O)NC5=CC=C(N)C=C5C)S6</chem>
25	 <chem>C1=CC=C(C=C1C2=CC=CC=C2C3=CC=CC=C3S4C=CC(=C4)C(=O)NC5=CC=CC=C5N)S6</chem>
26	 <chem>CC(C)NC(=O)c1sc2c(c1)C3=CC=CC=C3C4=CC=CC=C4N=C5C=CC=CC=C5S2</chem>
27	 <chem>C1CCC(CC1)NC(=O)c2sc3c(c2)C4=CC=CC=C4C5=CC=CC=C5N=C6C=CC=CC=C6S3</chem>
28	 <chem>Cc1c(C)nn(c1)NC(=O)c2sc3c(c2)C4=CC=CC=C4C5=CC=CC=C5N=C6C=CC=CC=C6S3</chem>
29	 <chem>Fc1cc(F)ccc1NC(=O)c2sc3c(c2)C4=CC=CC=C4C5=CC=CC=C5N=C6C=CC=CC=C6S3</chem>

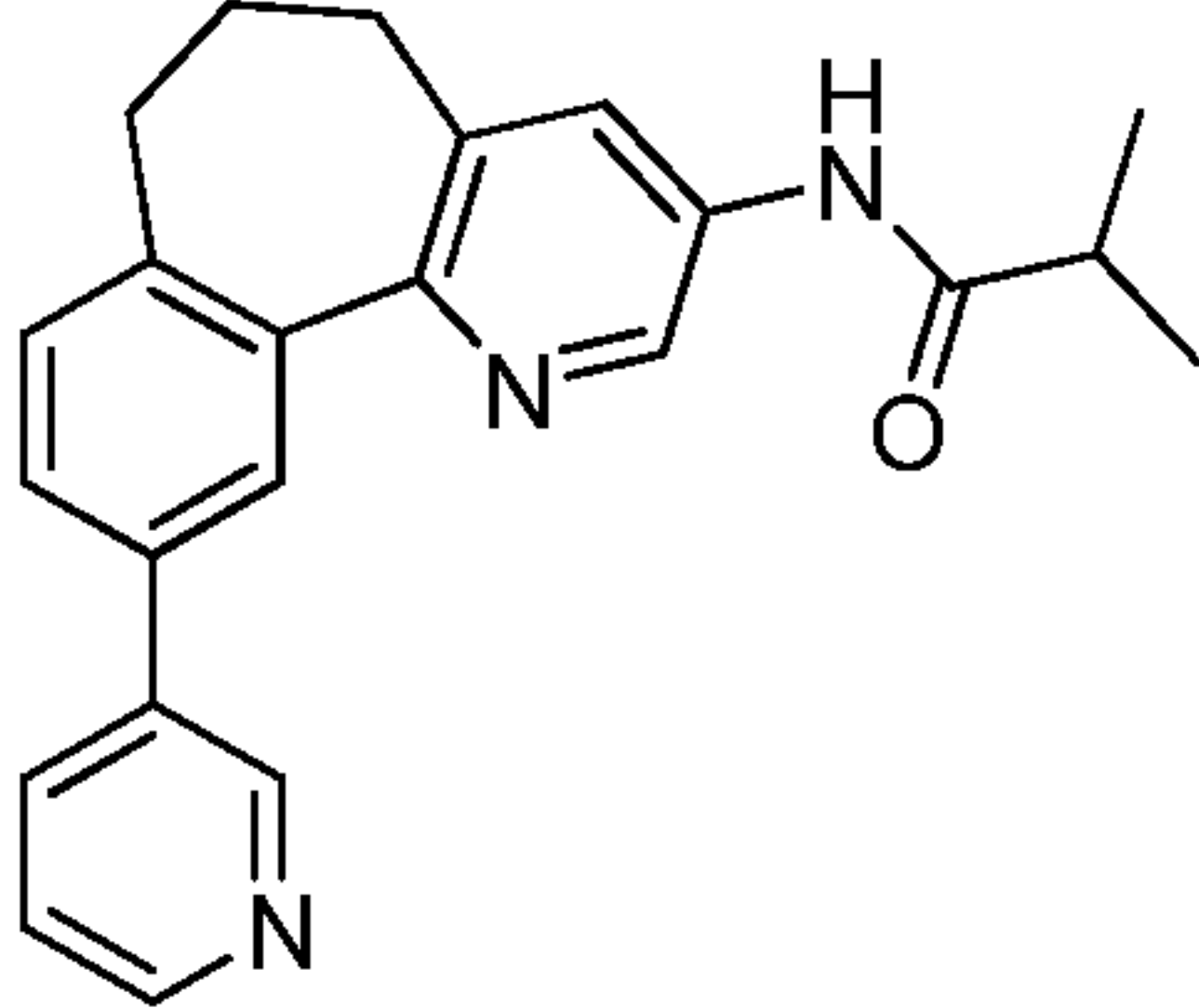
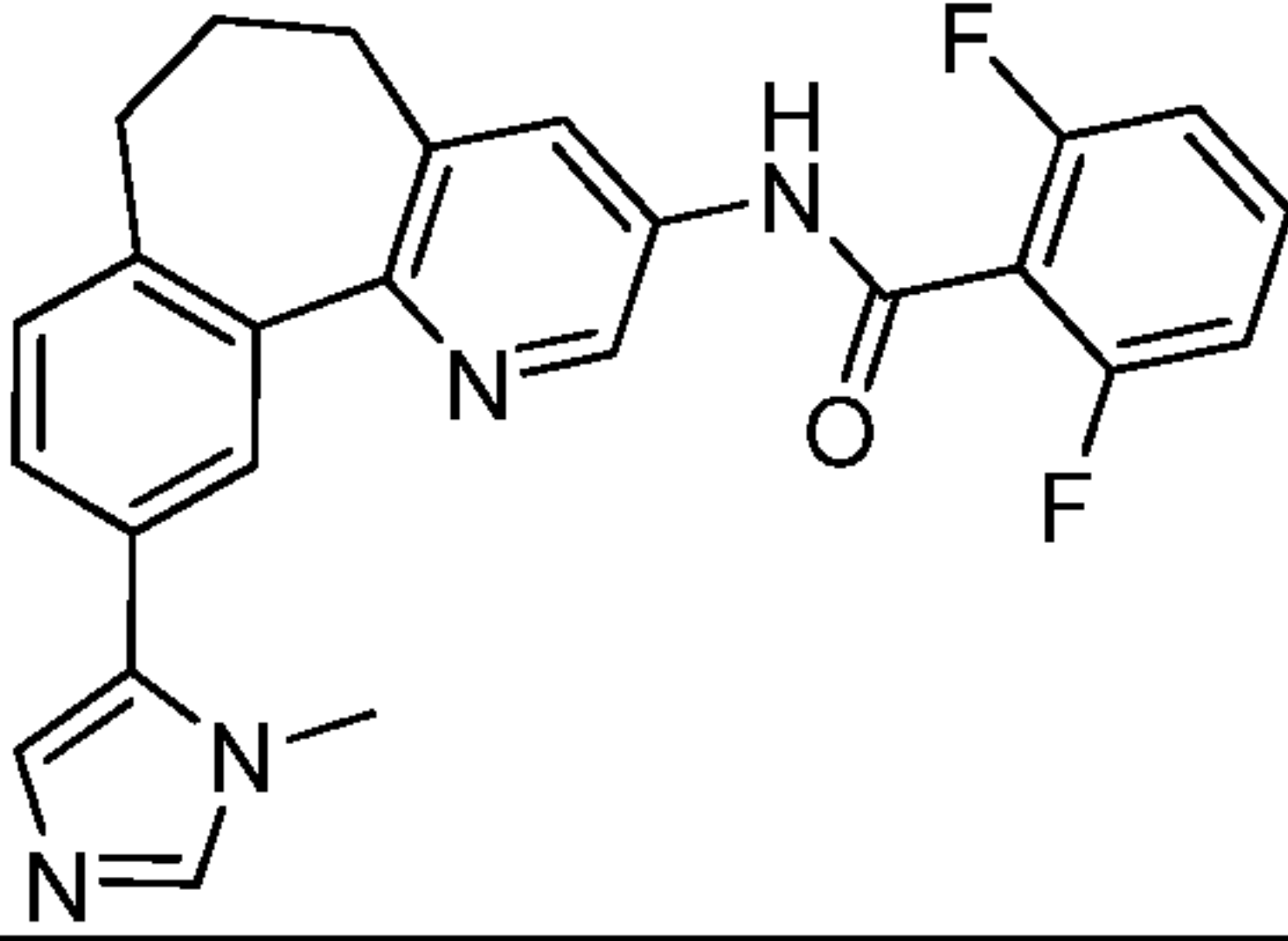
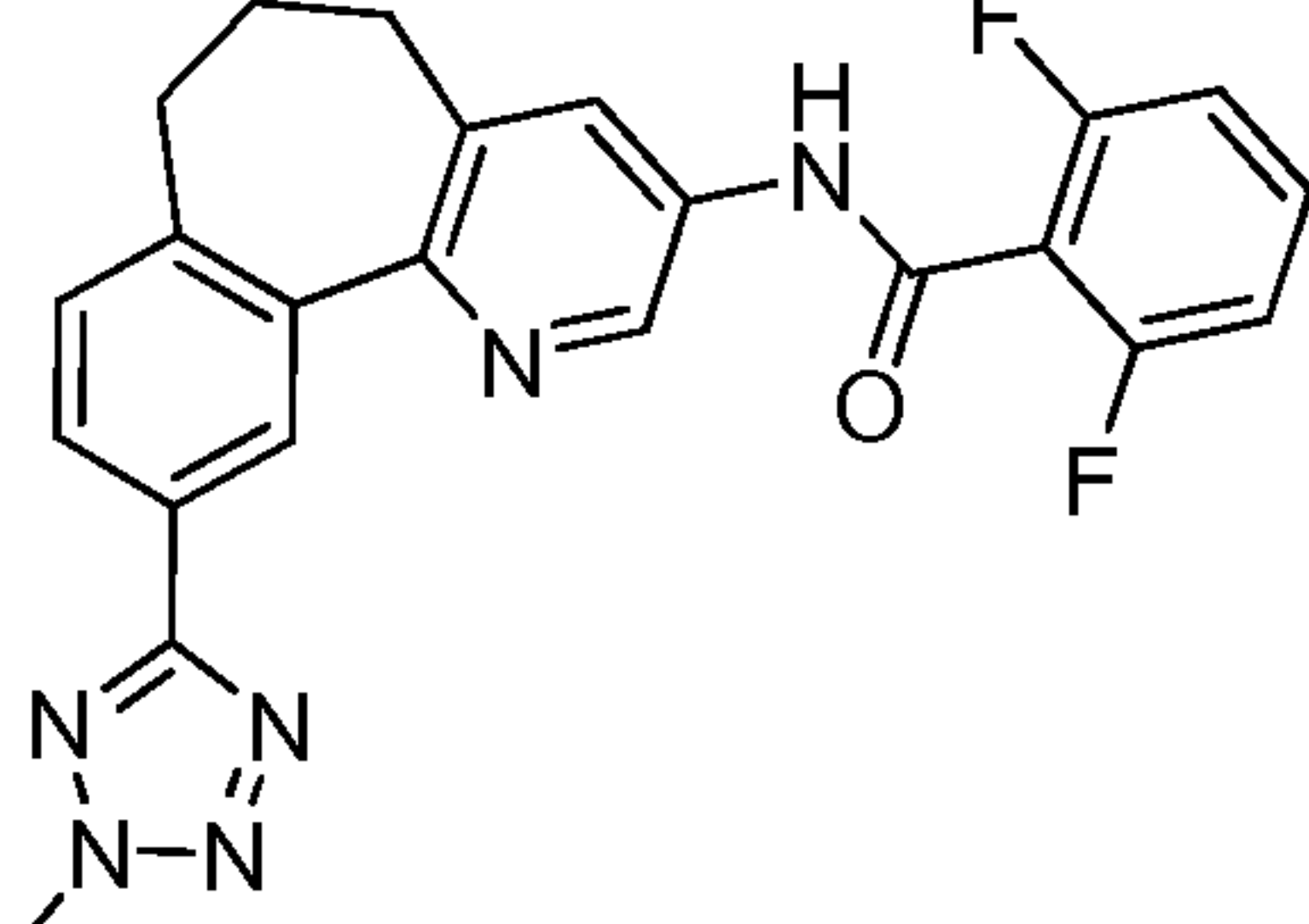
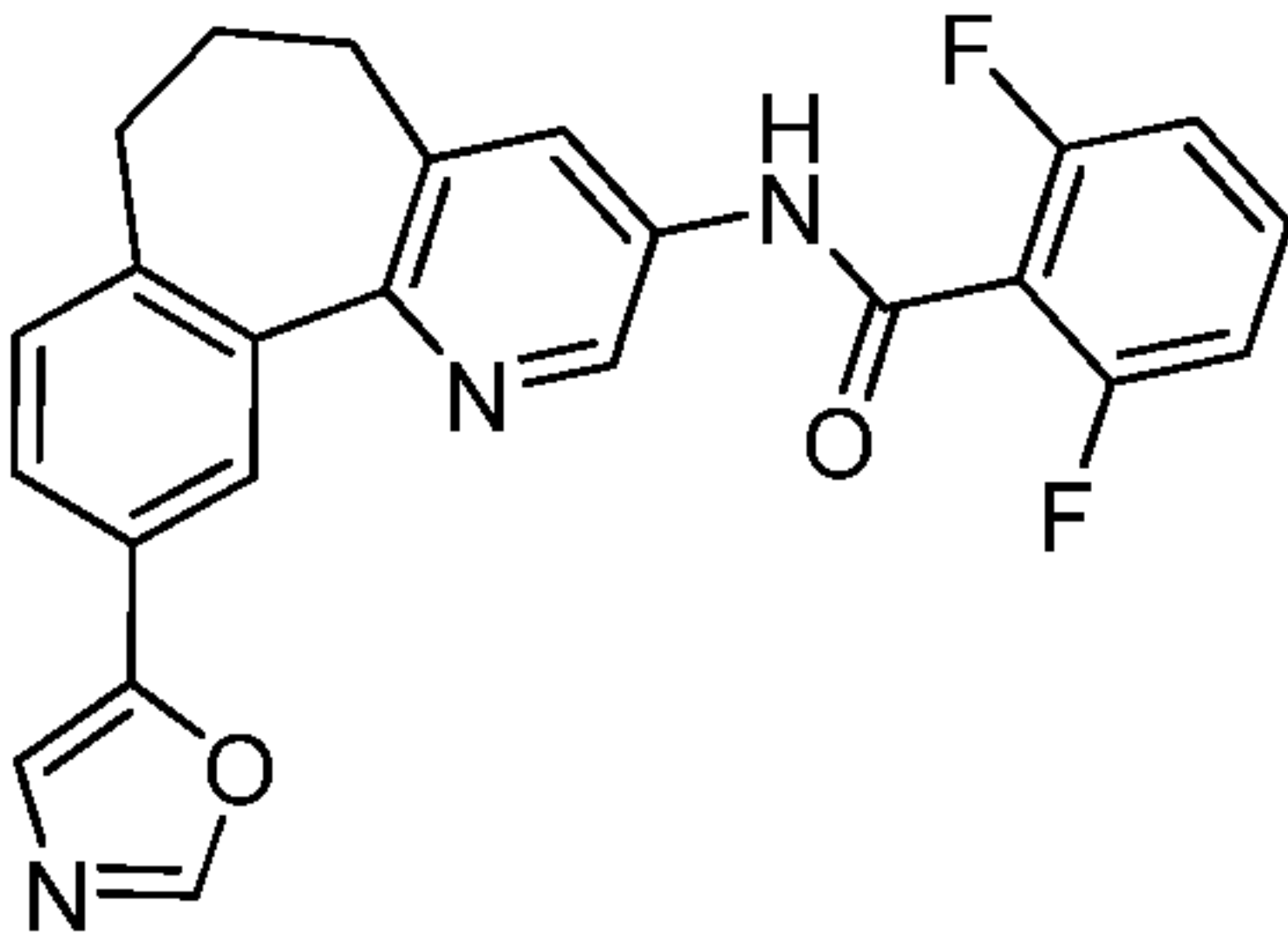
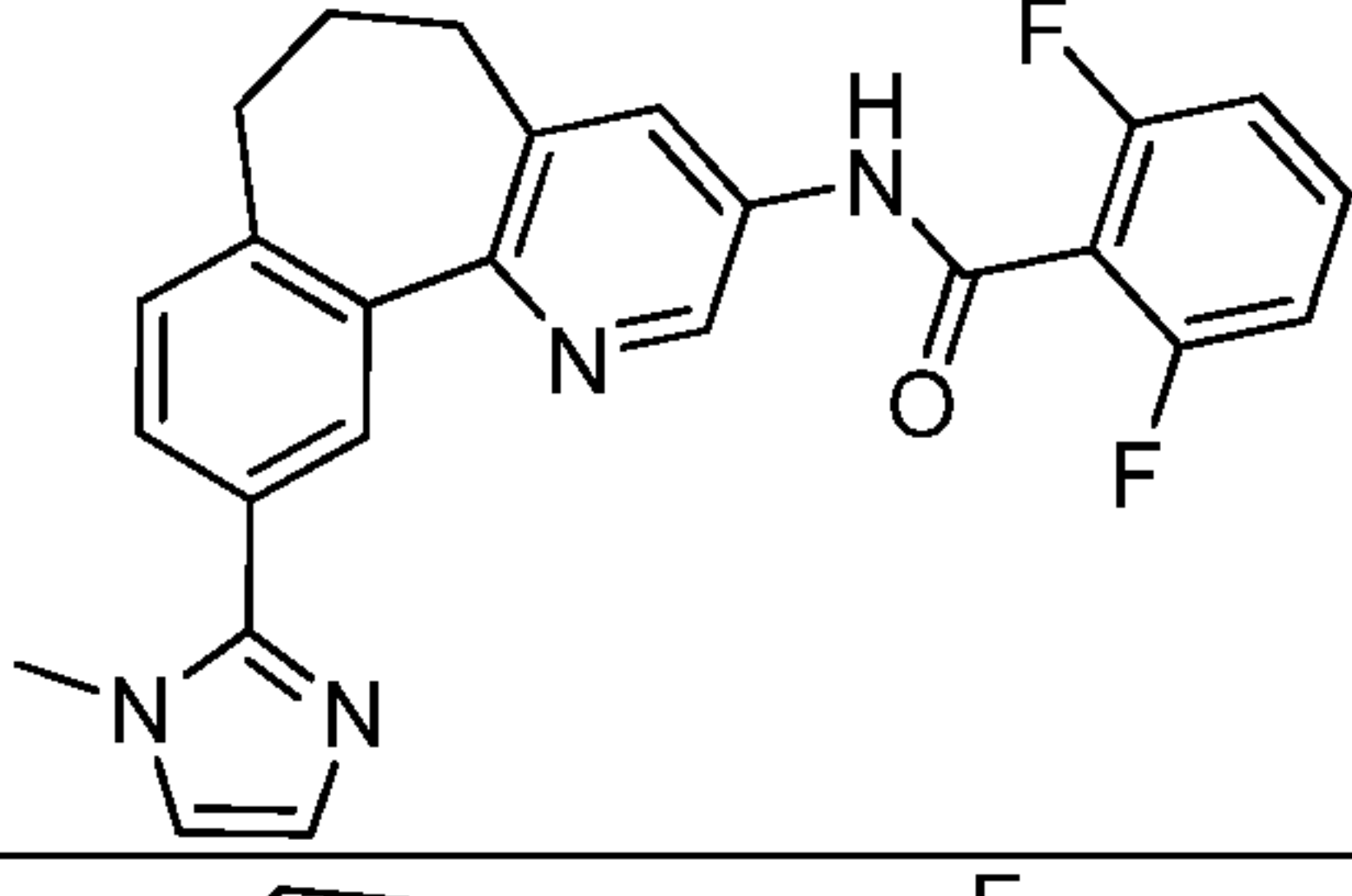
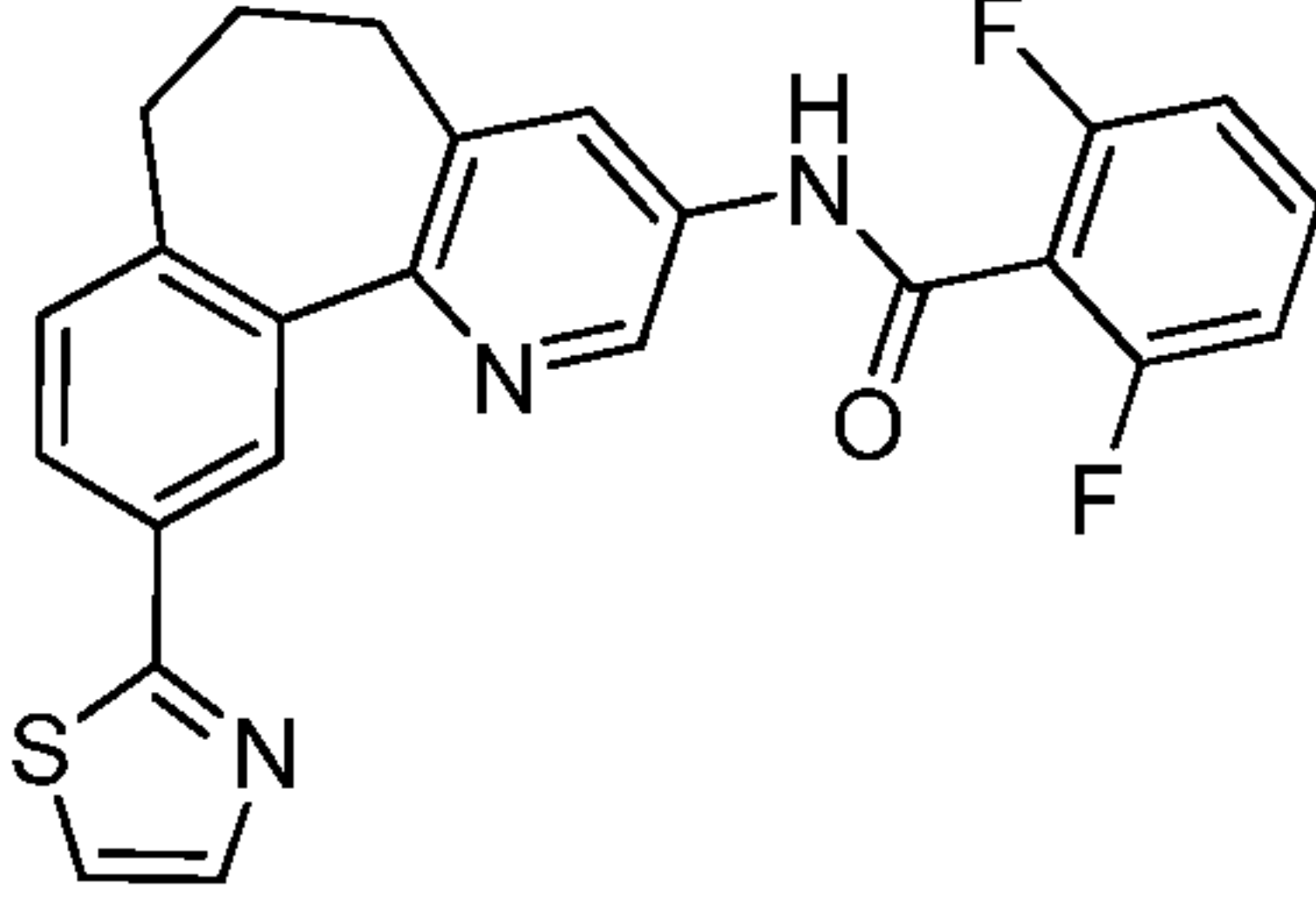
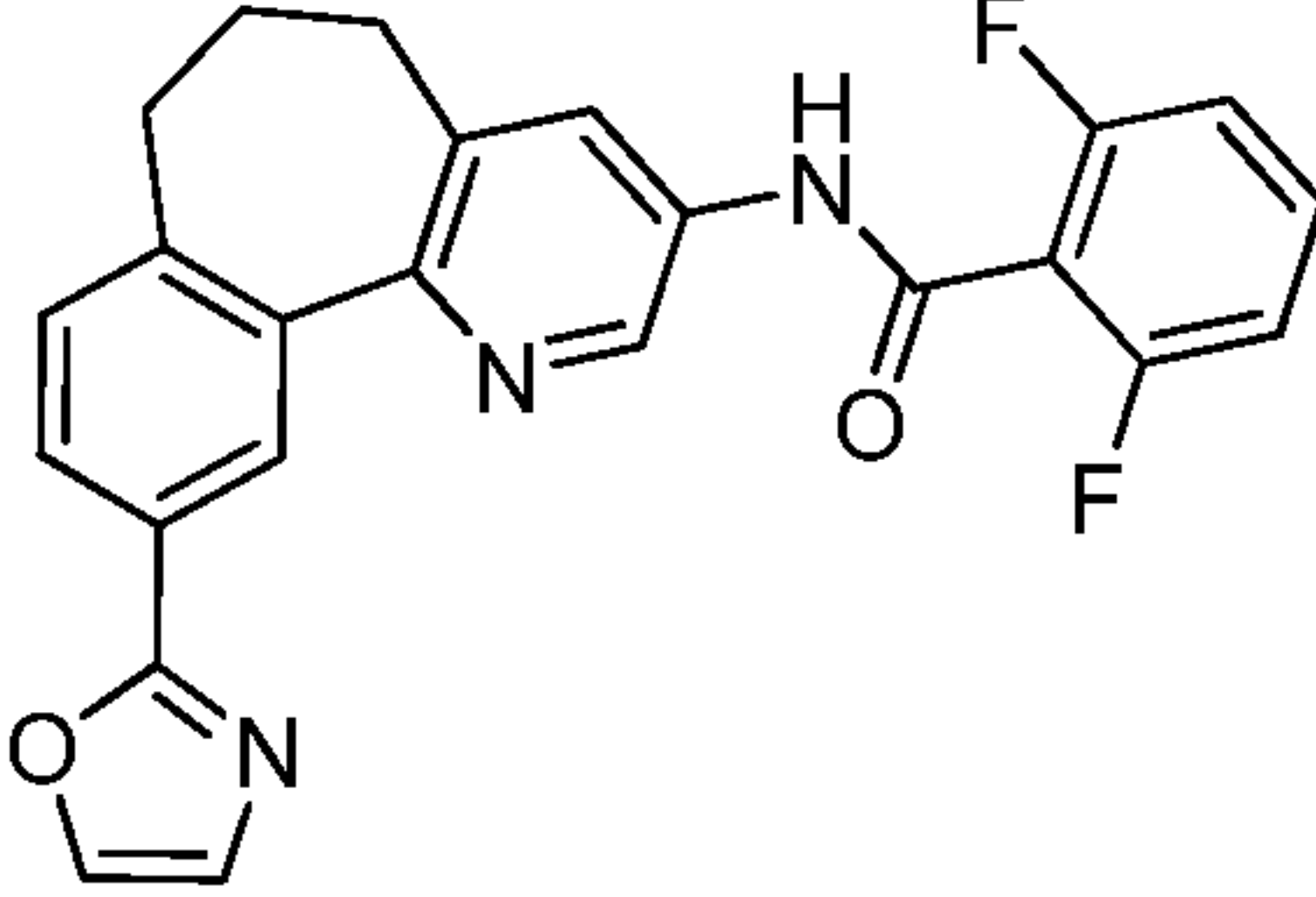
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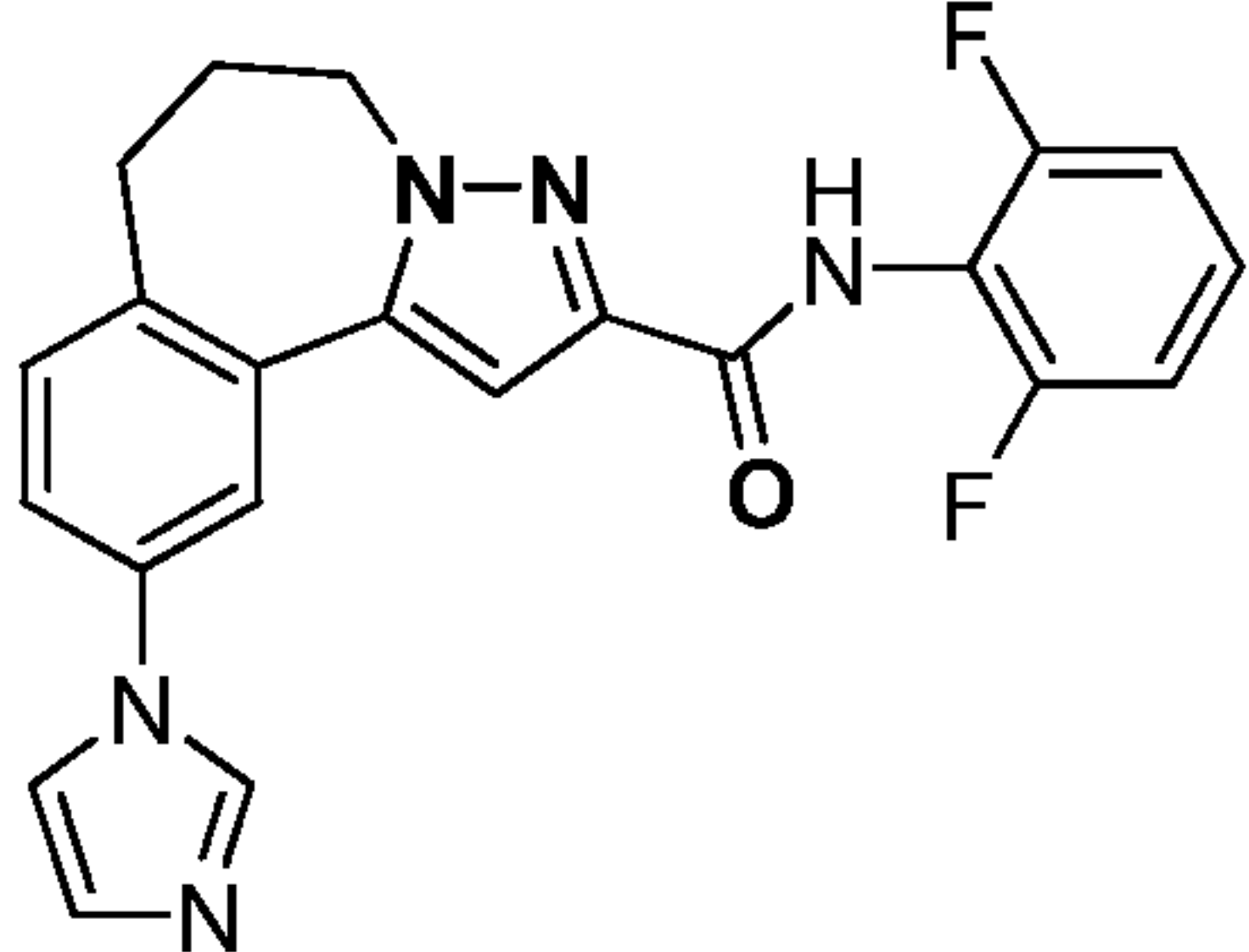
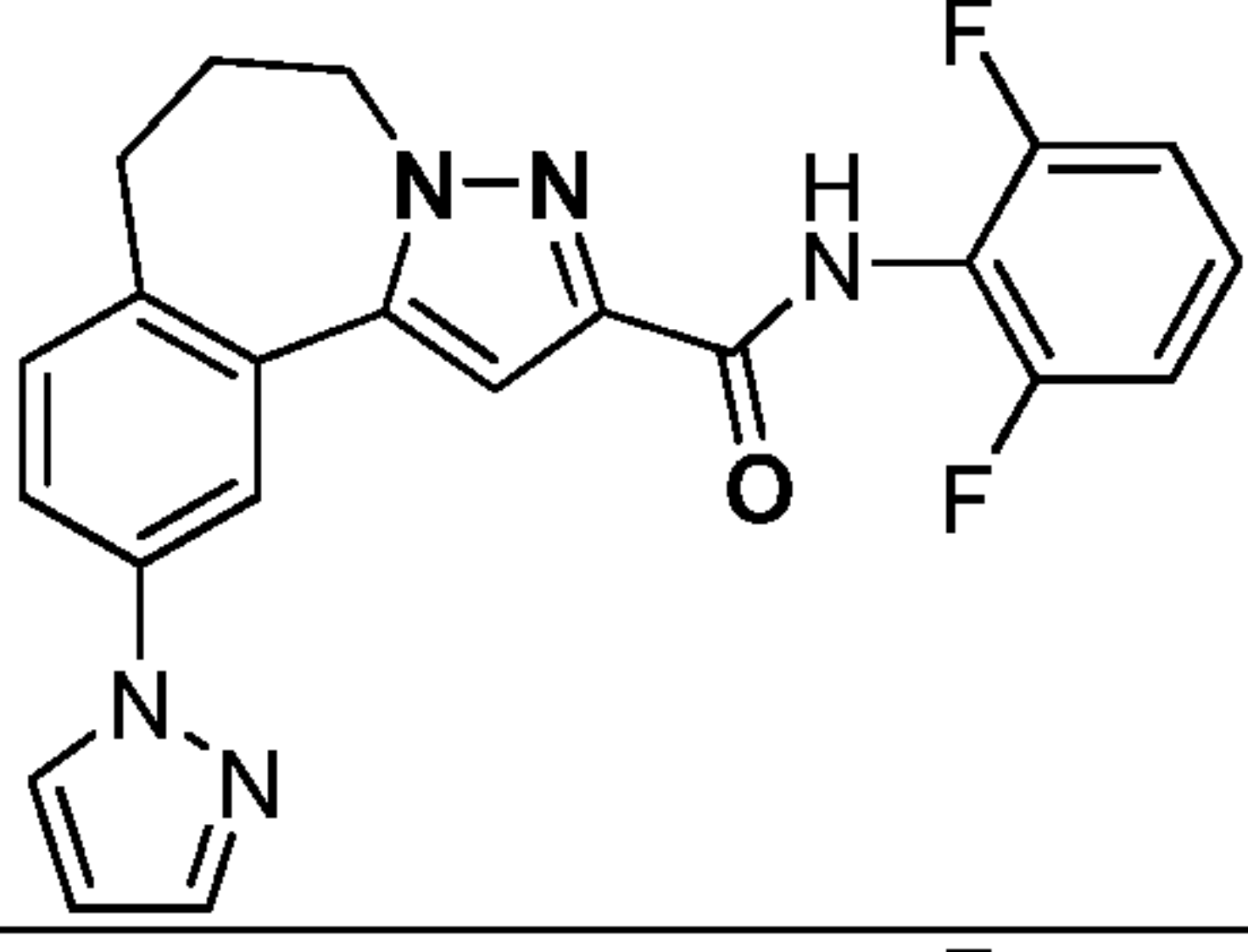
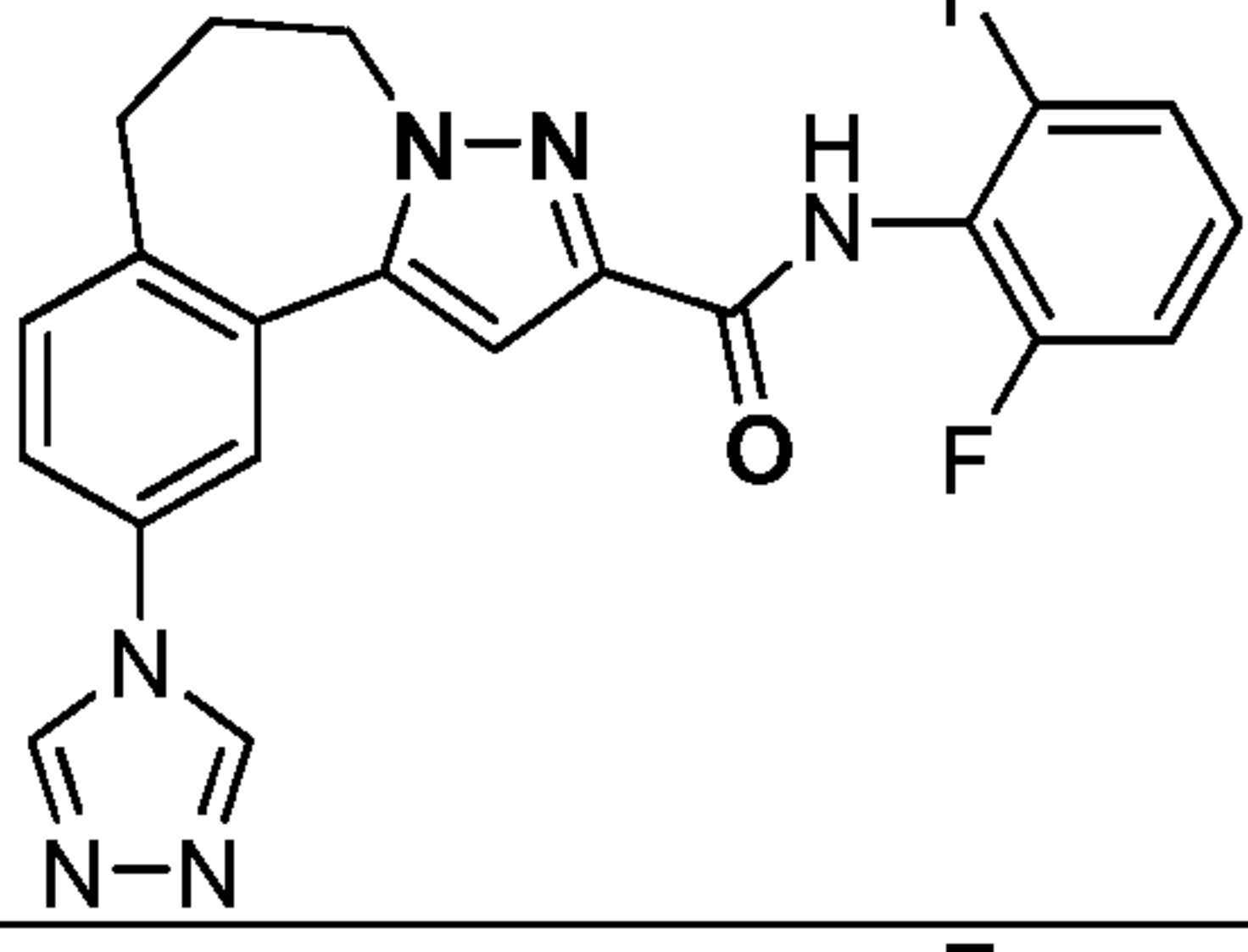
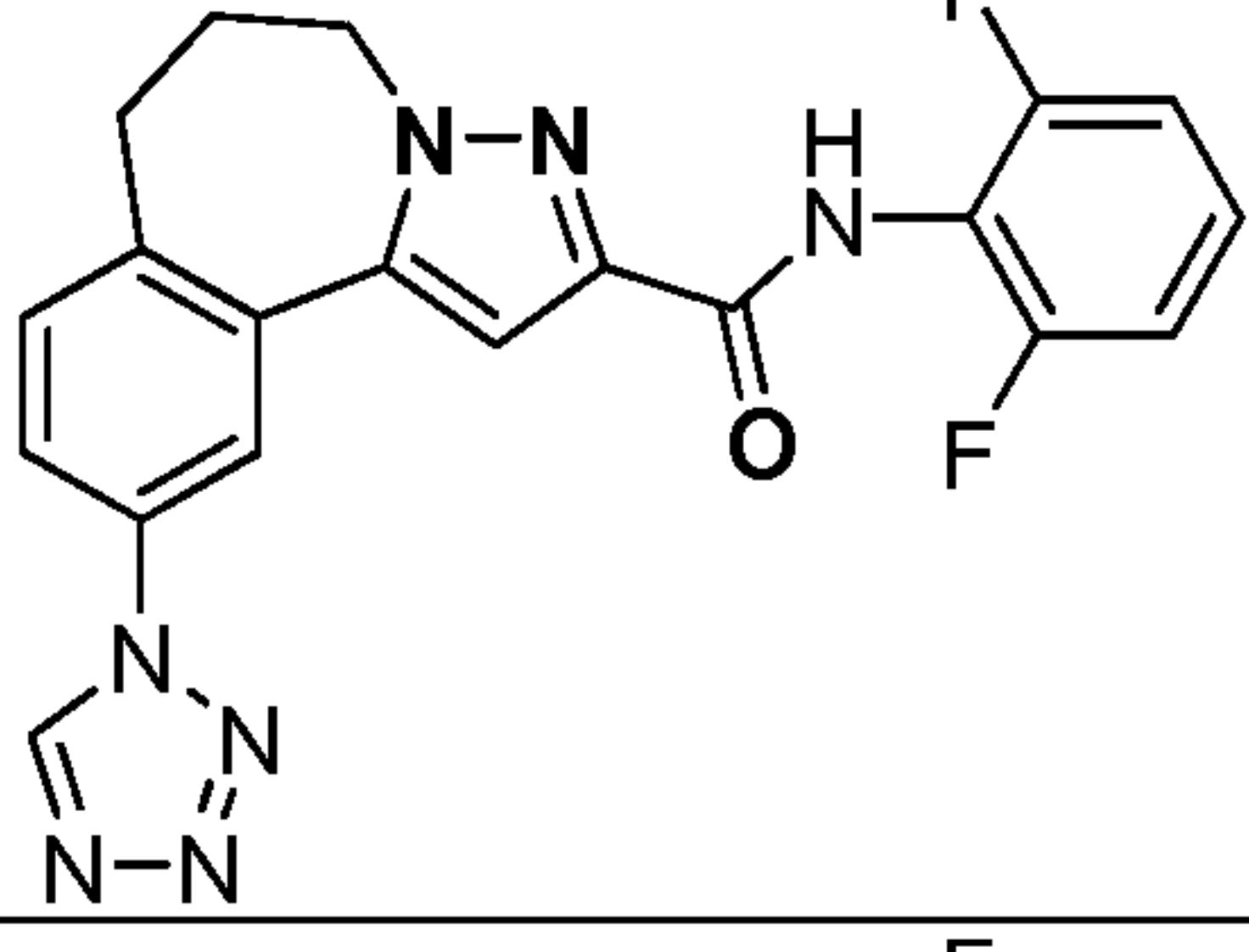
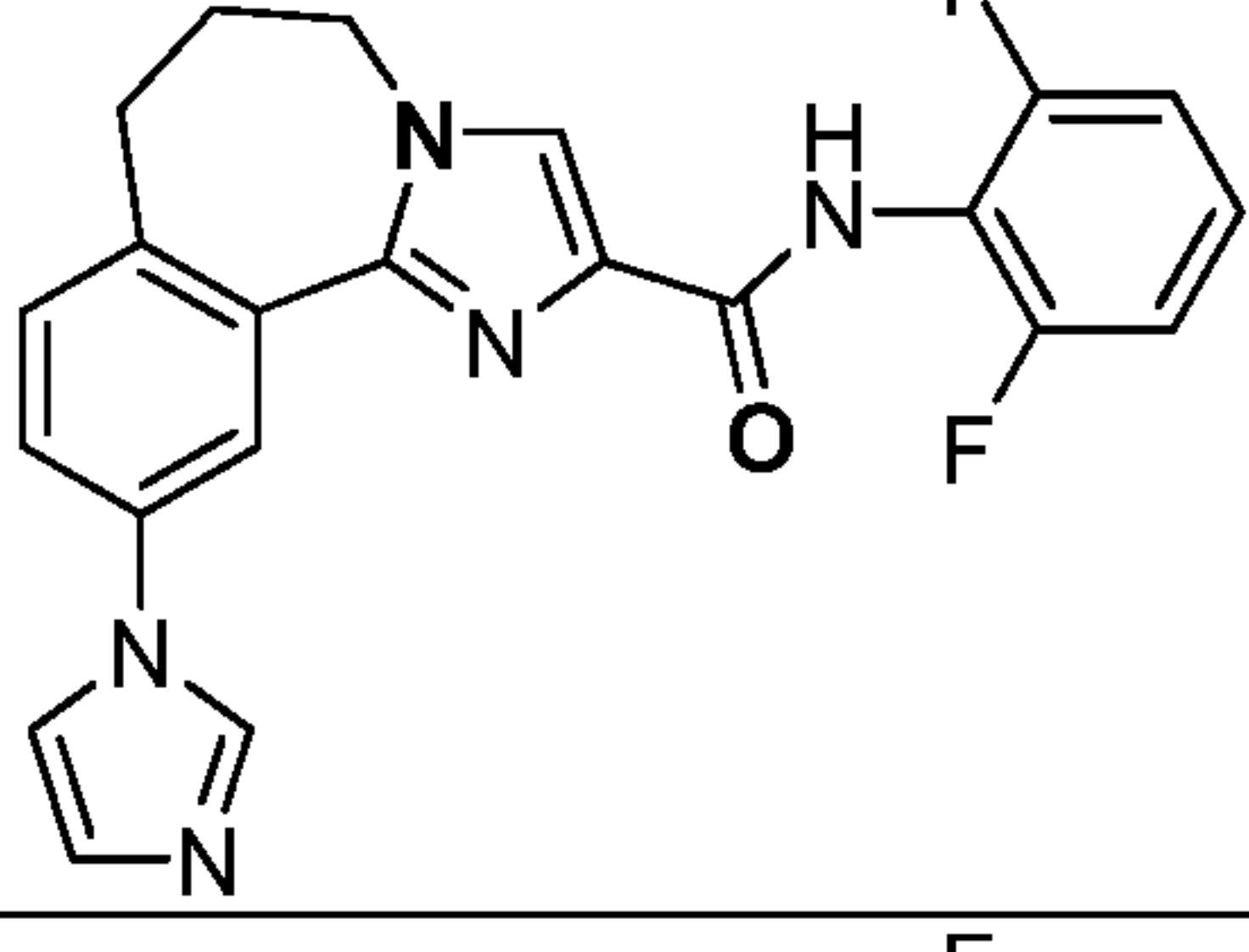
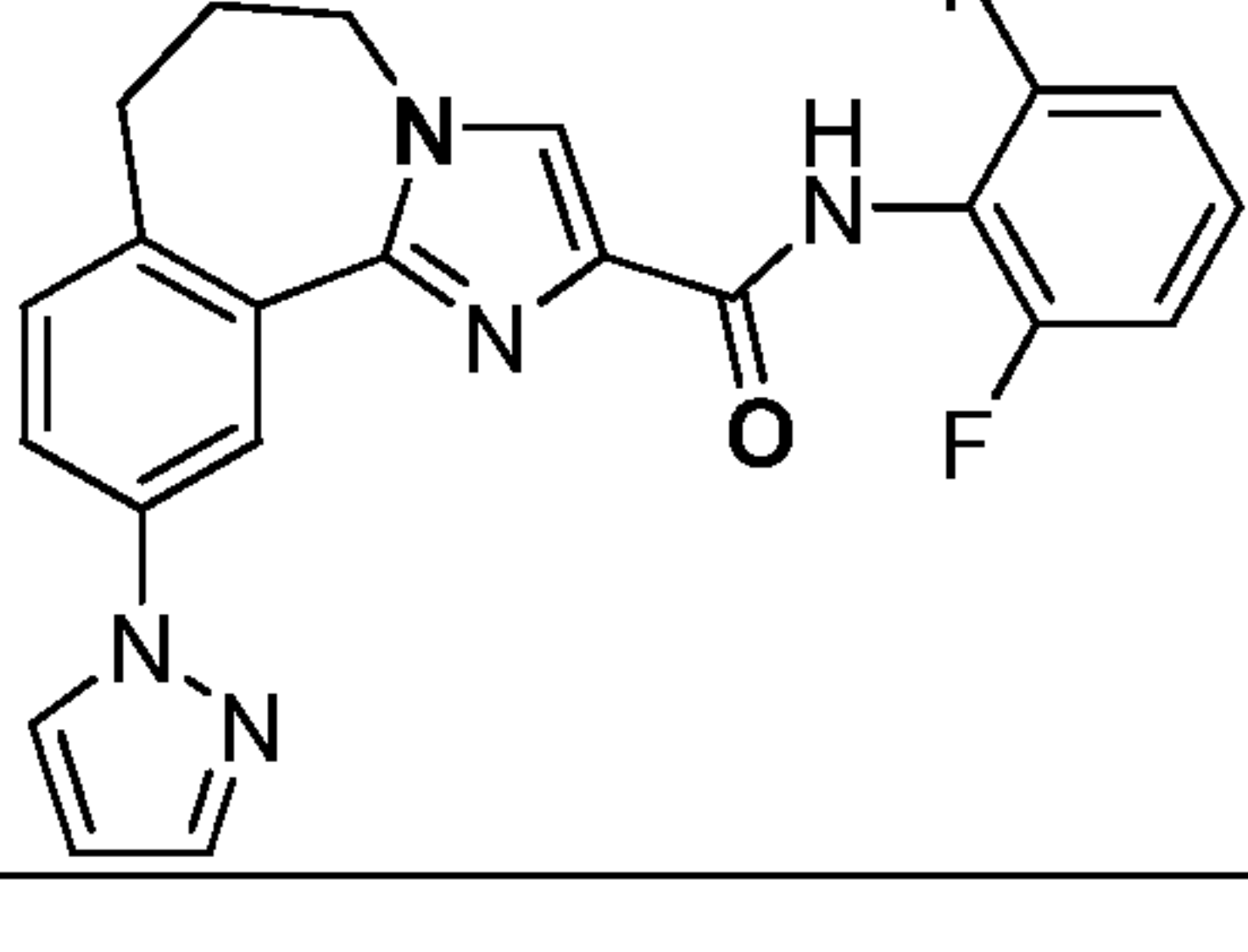
36	 <chem>C1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)SC(=C4)C(=O)Nc5cc(F)c(F)cc5</chem>
37	 <chem>C1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)SC(=C4)C(=O)Nc5cc(F)c(F)cc5</chem>
38	 <chem>BrC1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)N(C)C(=O)Nc5cc(F)c(F)cc5</chem>
39	 <chem>C1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)N(C)C(=O)Nc5cc(F)c(F)cc5</chem>
40	 <chem>C1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)N(C)C(=O)Nc5cc(F)c(F)cc5</chem>
41	 <chem>C1=CC=C2C(=C1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)OC(=C4)C(=O)Nc5cc(F)c(F)cc5</chem>
42	 <chem>COc1ccc2c(c1)C(=CC=C2)C3=CC(=CC=C3N)C=C4C(=CC=C4)SC(=N4)C(=O)Nc5cc(F)c(F)cc5</chem>

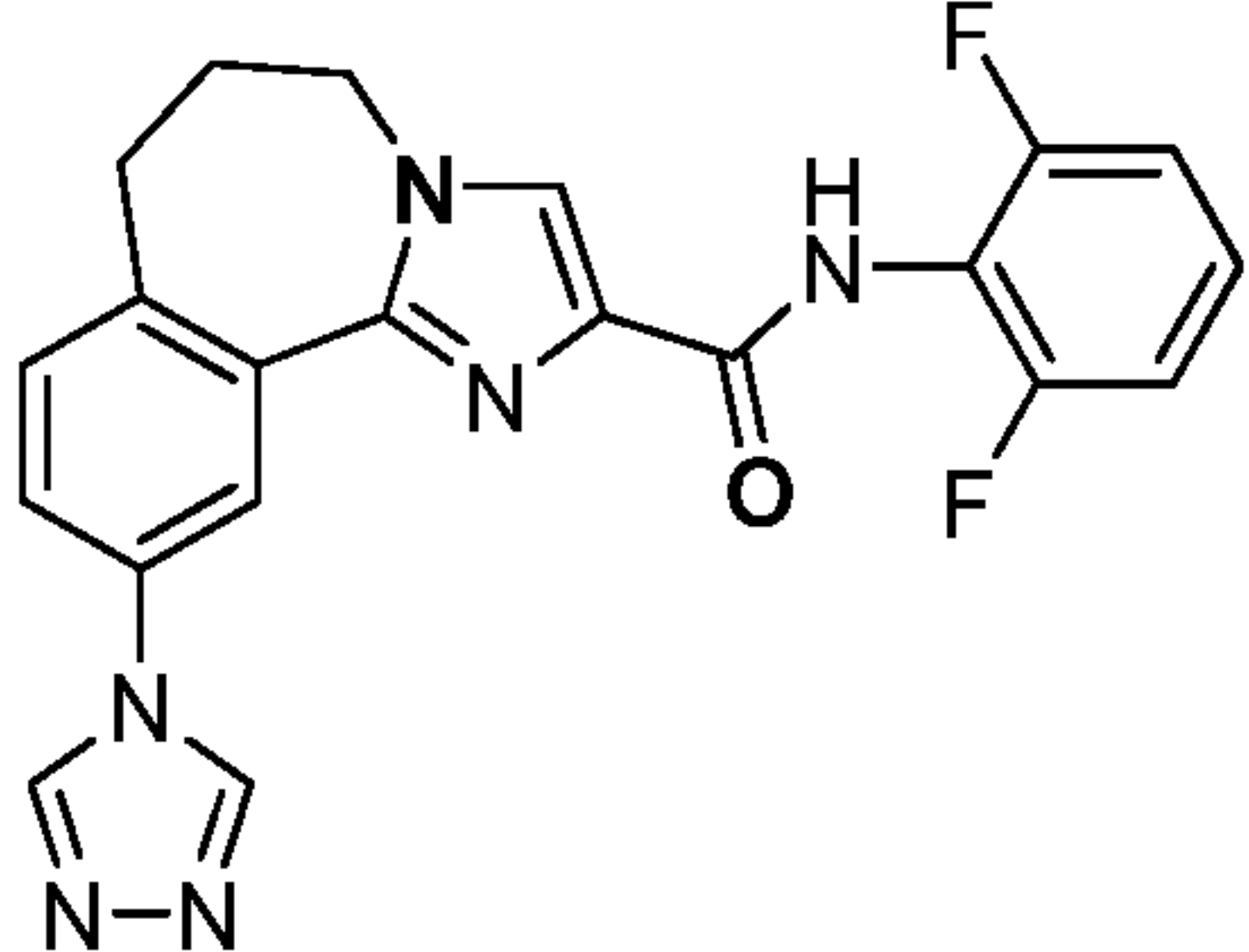
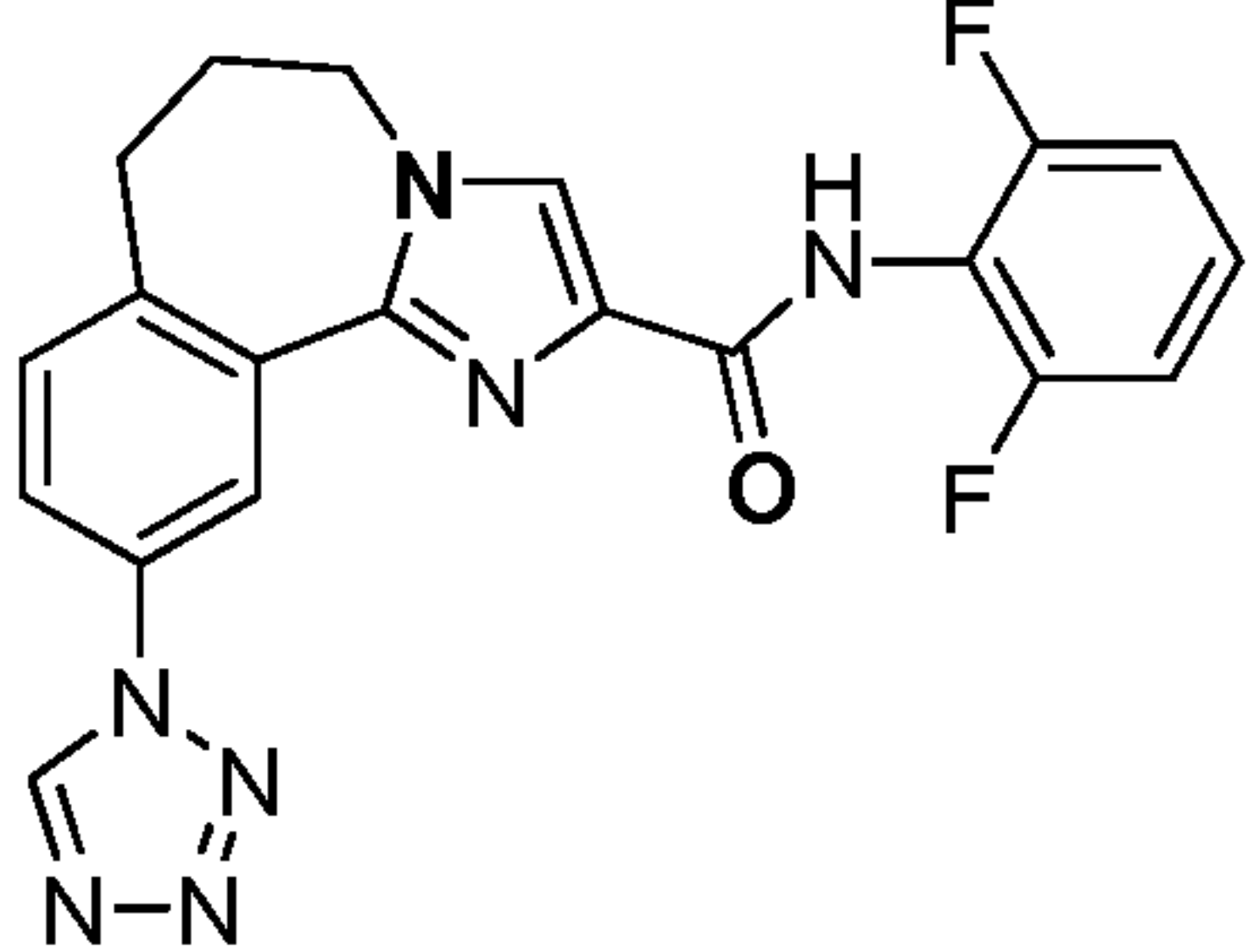
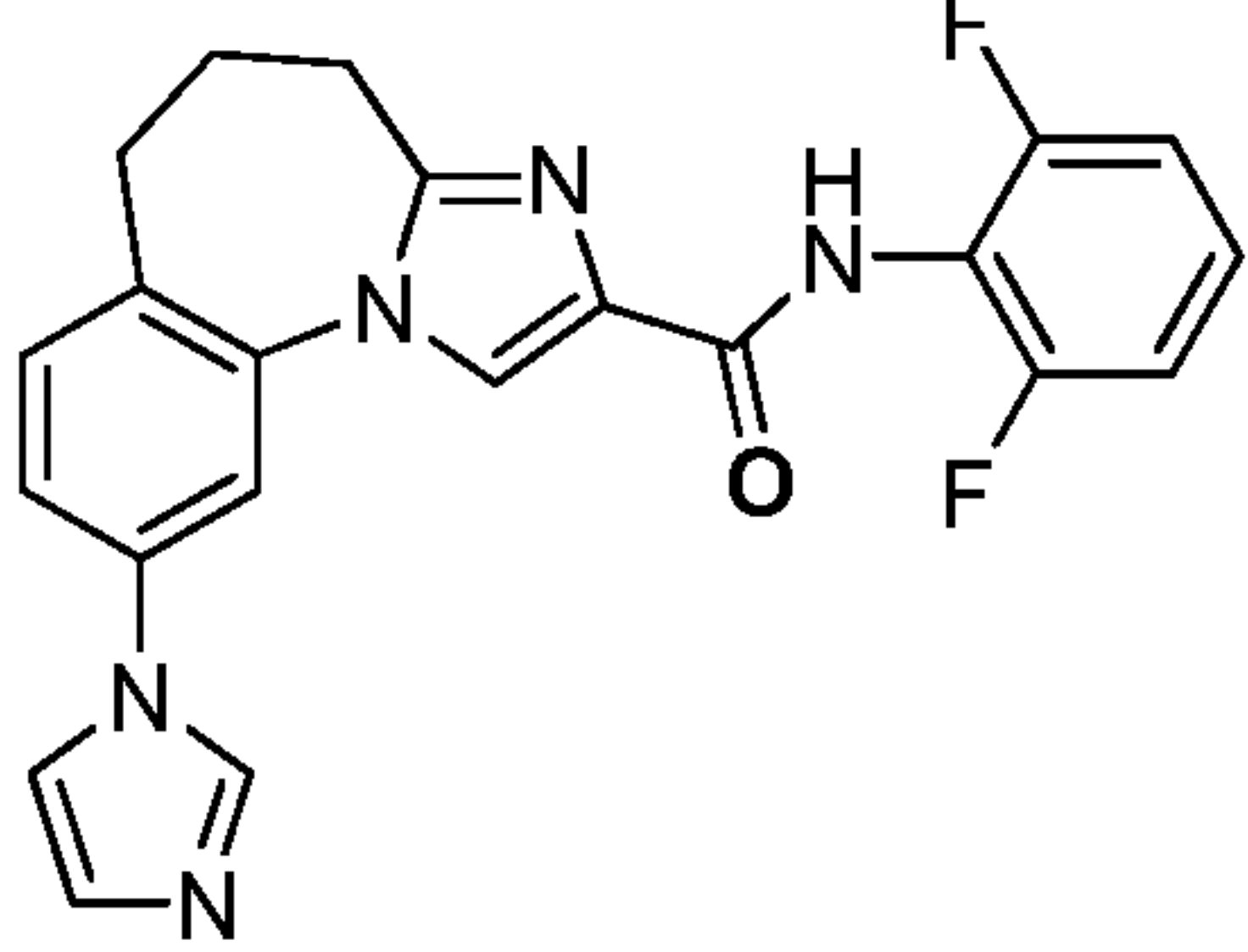
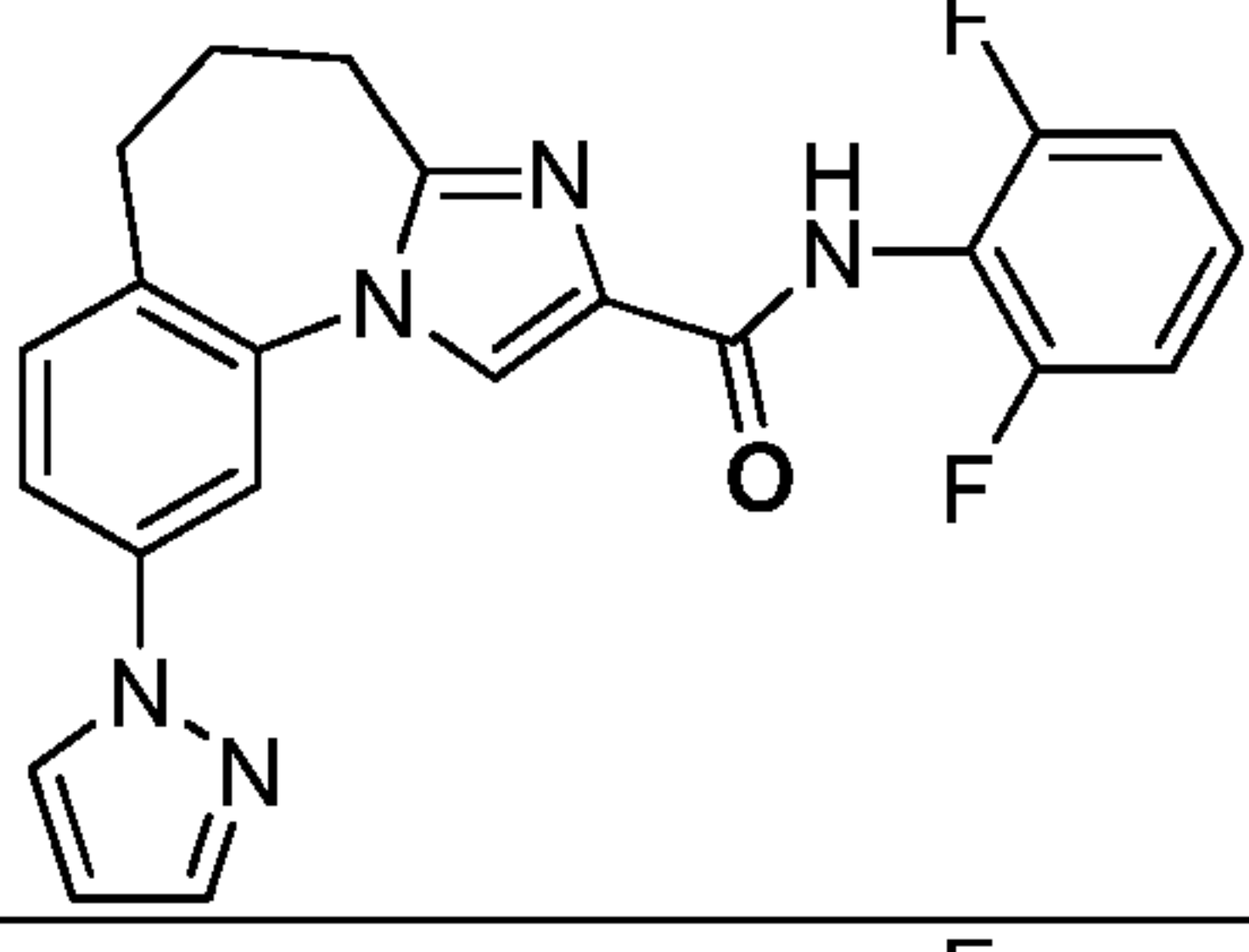
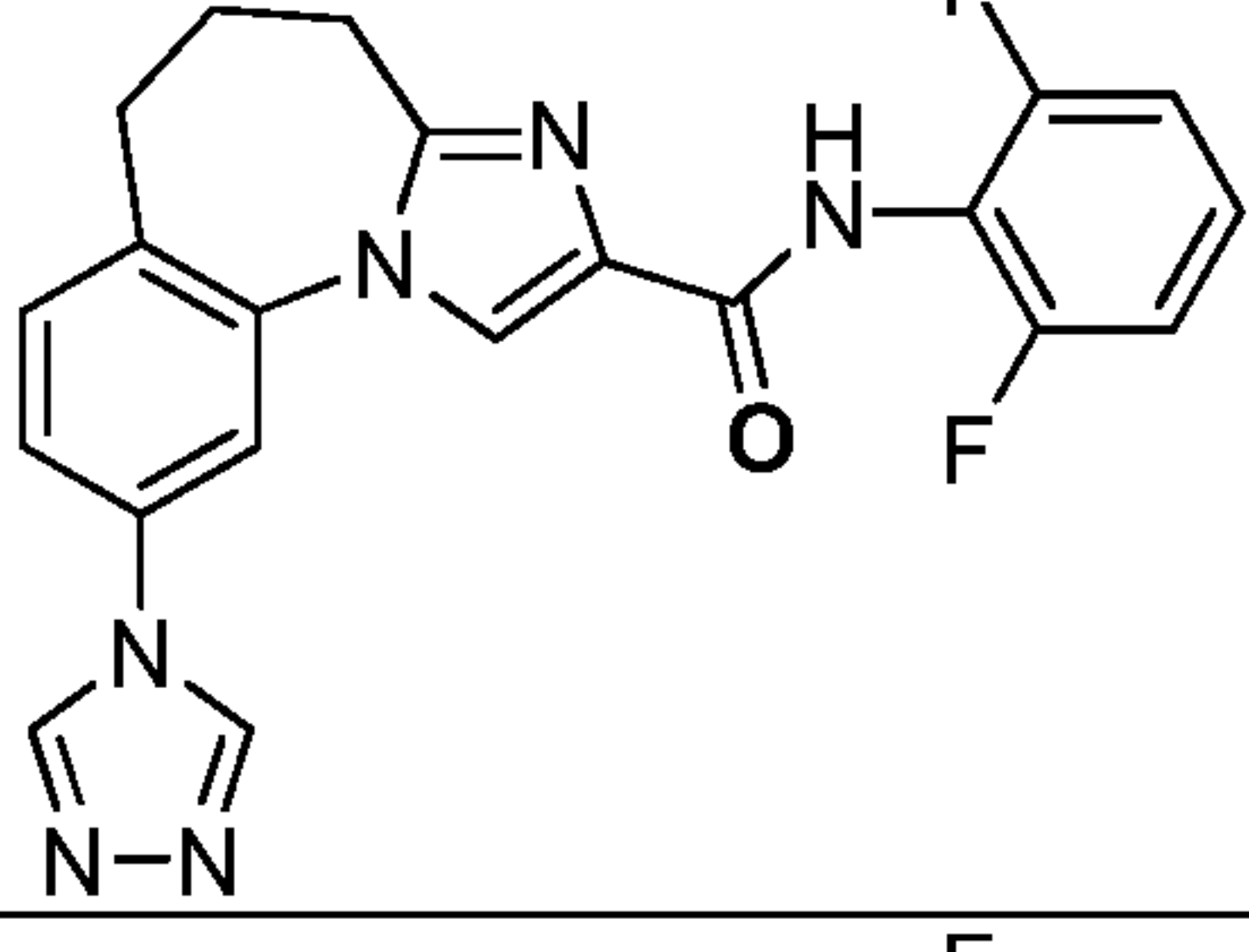
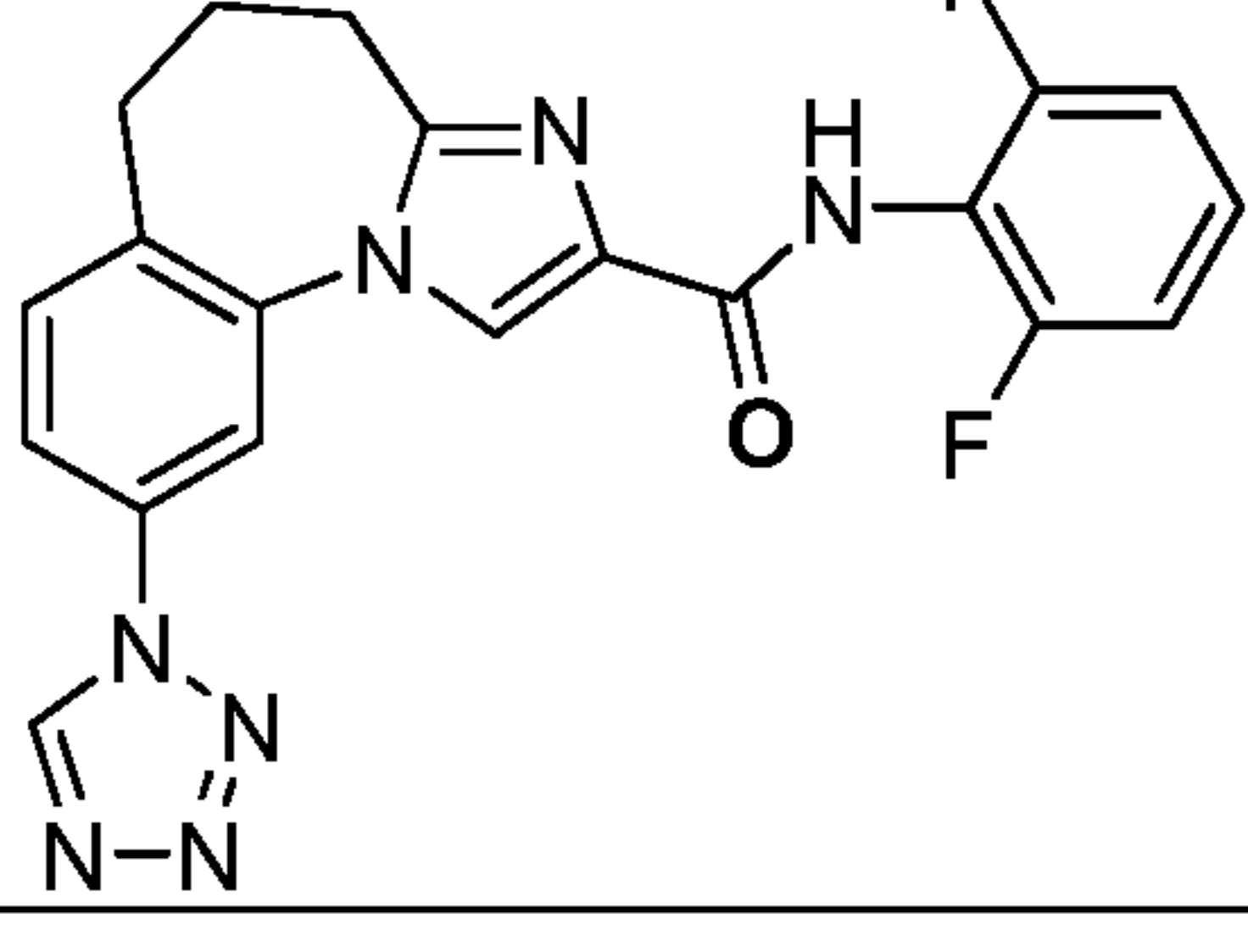
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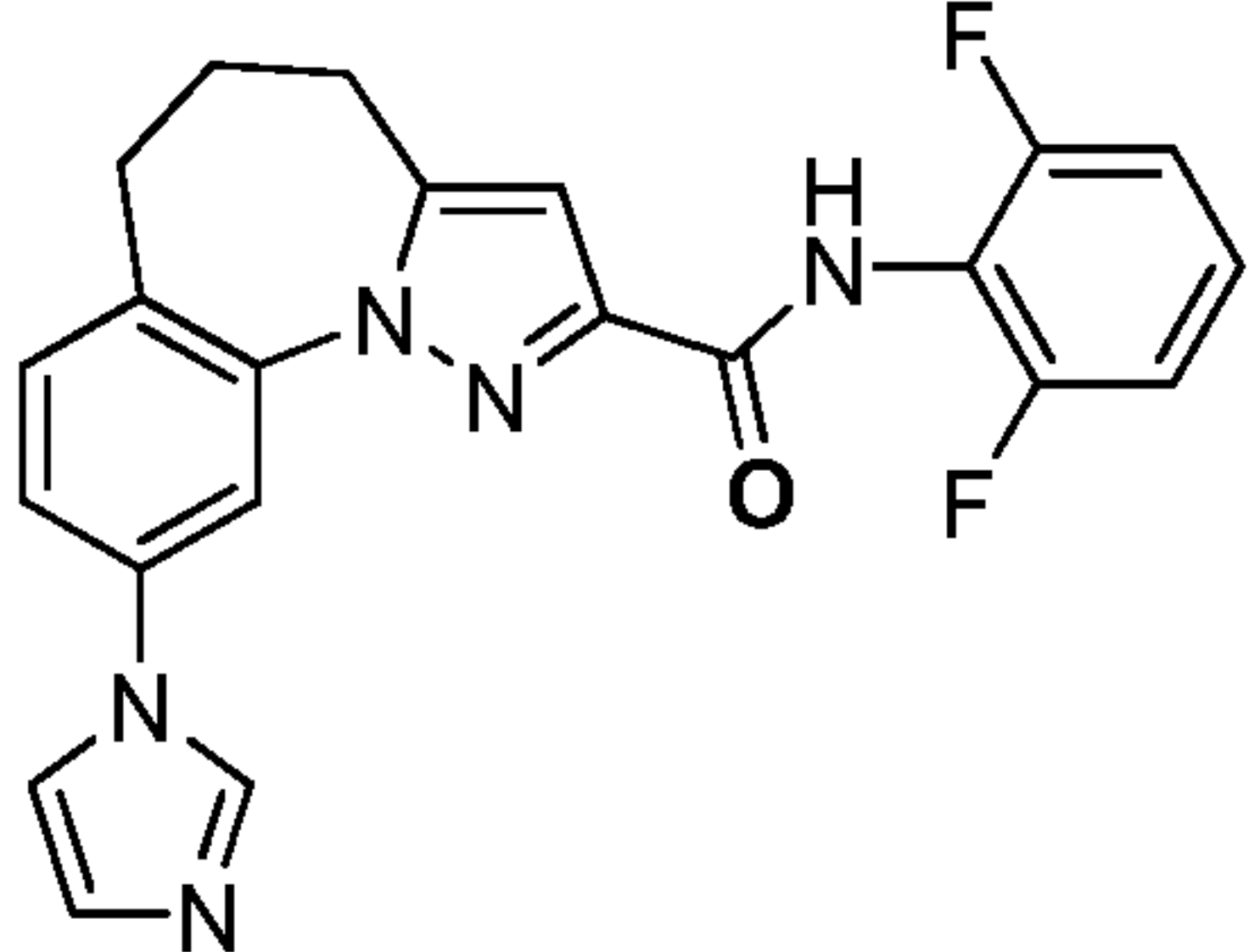
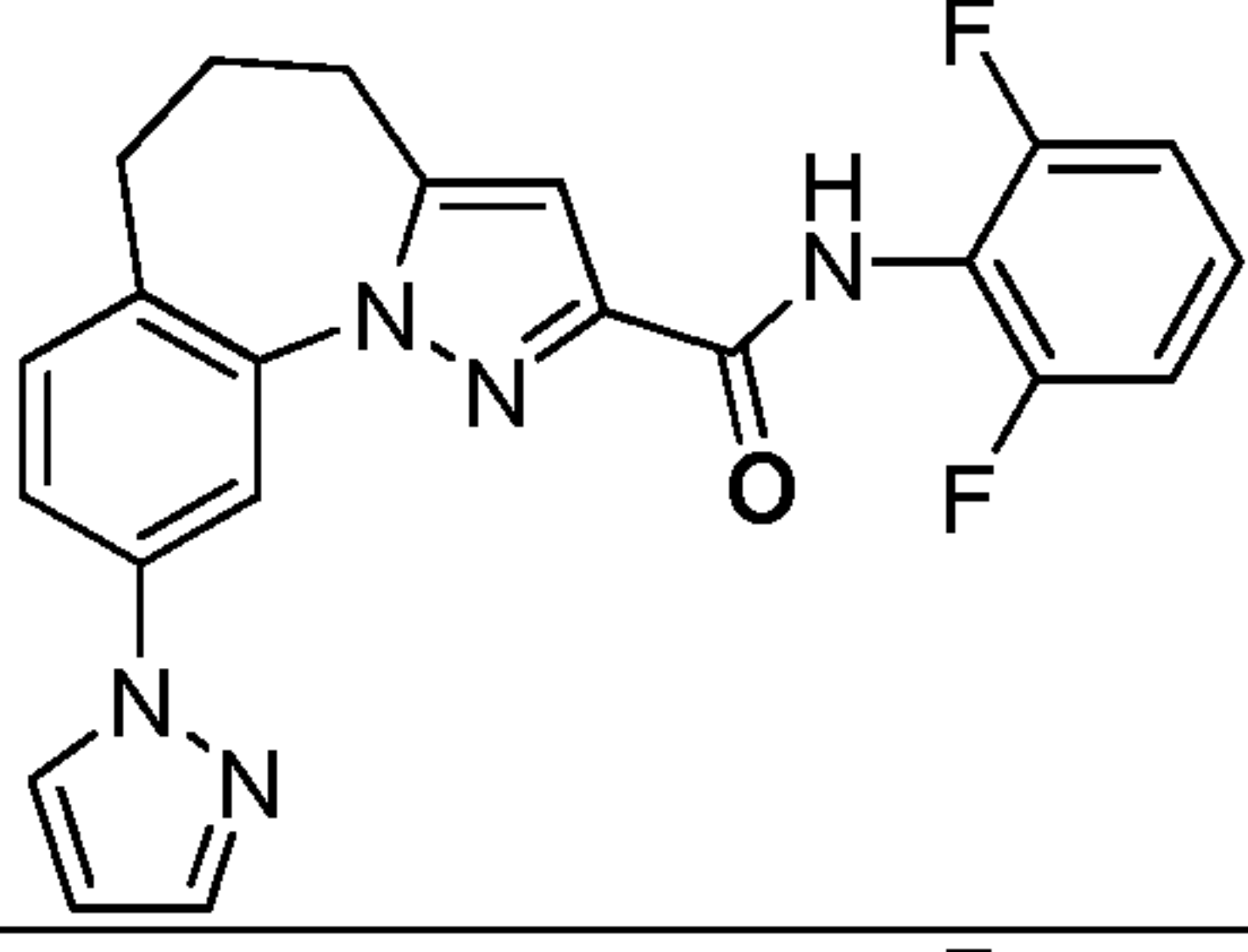
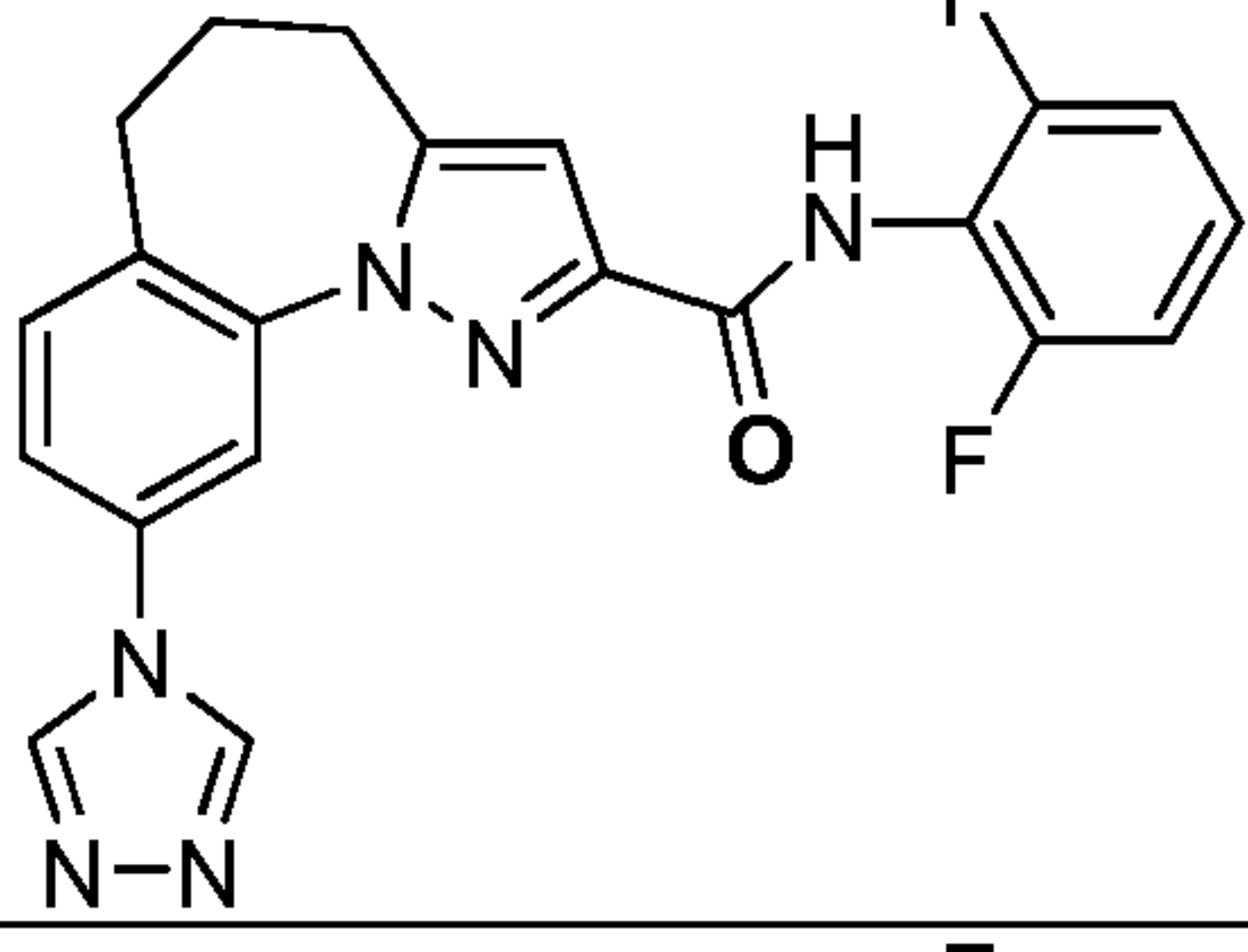
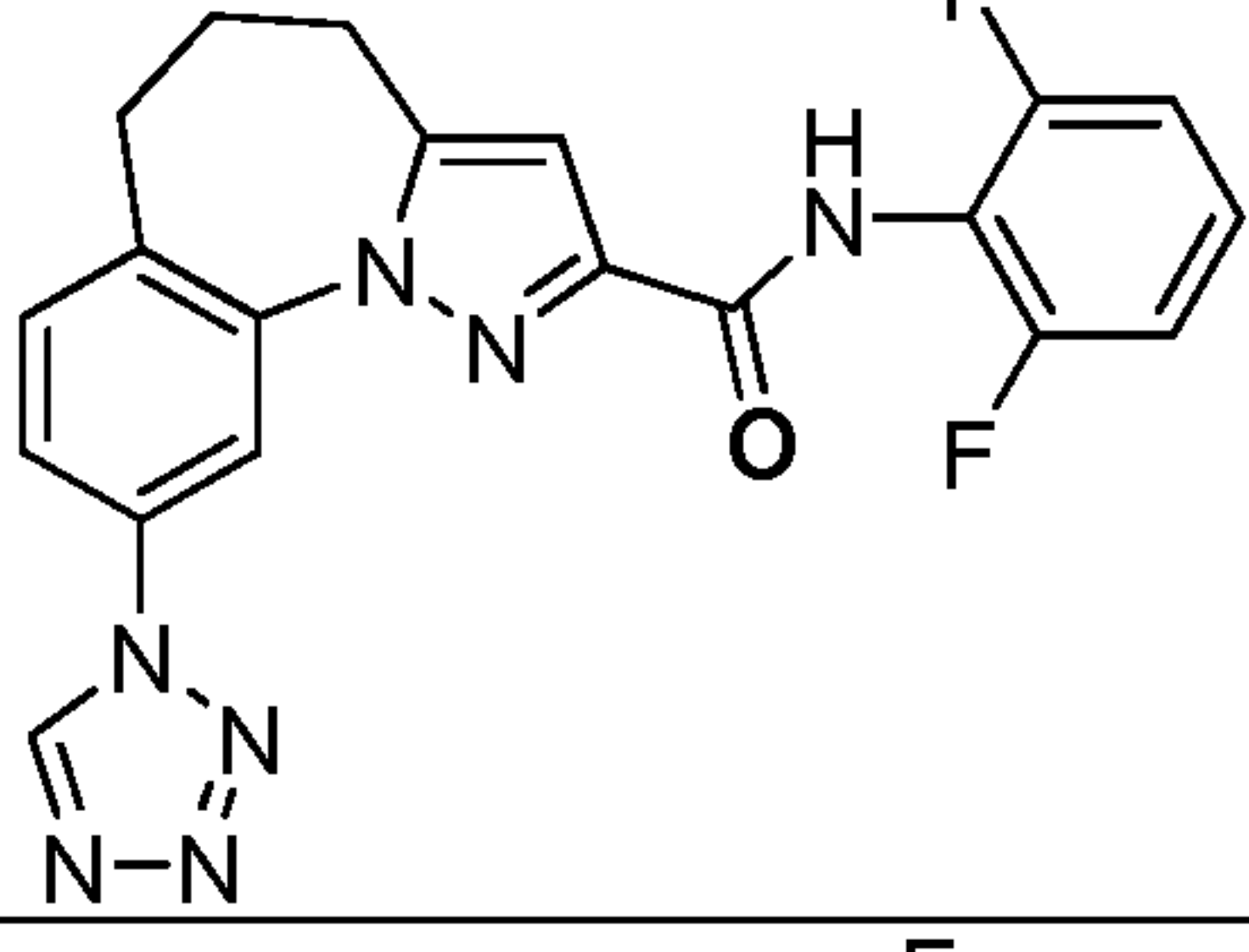
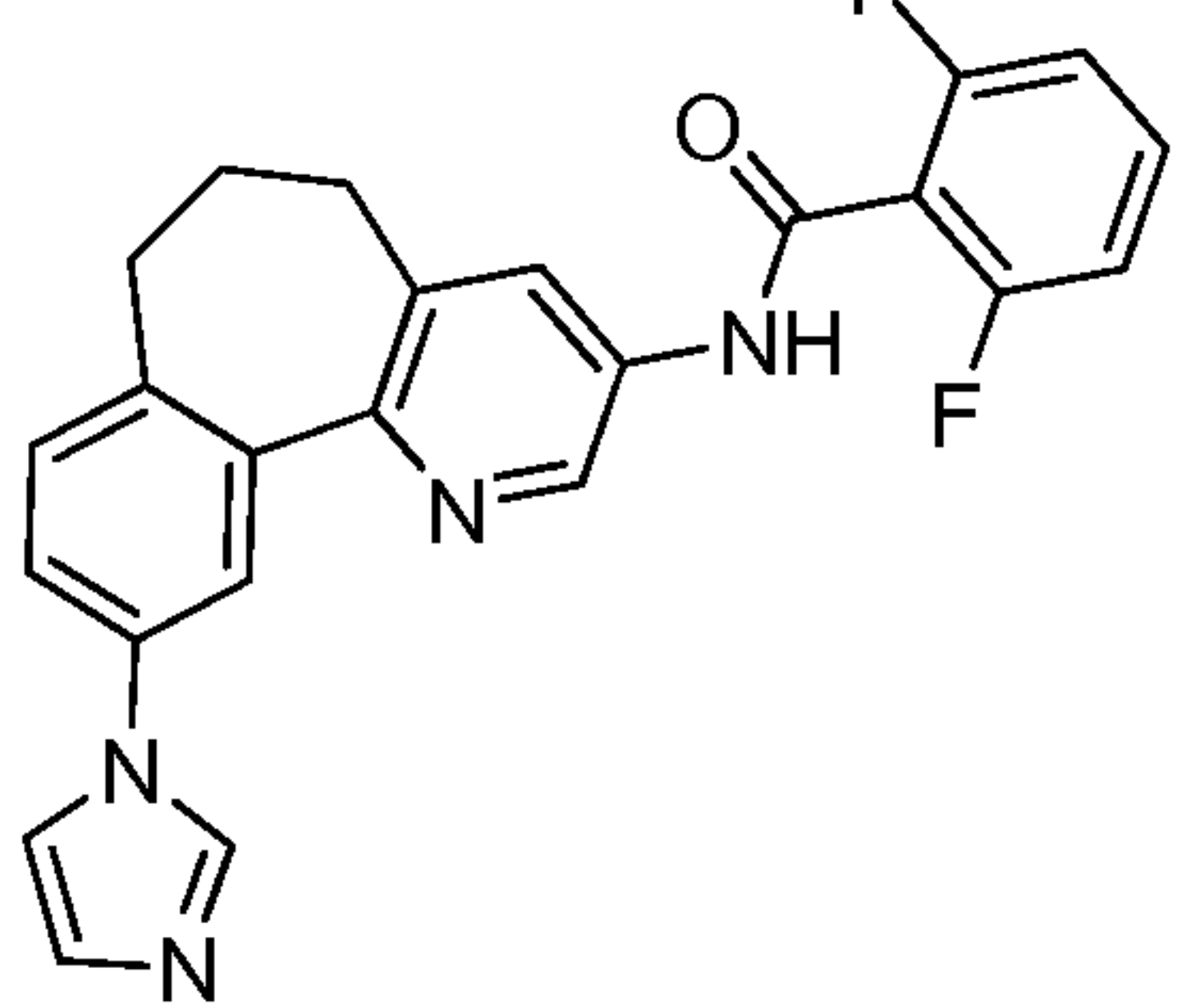
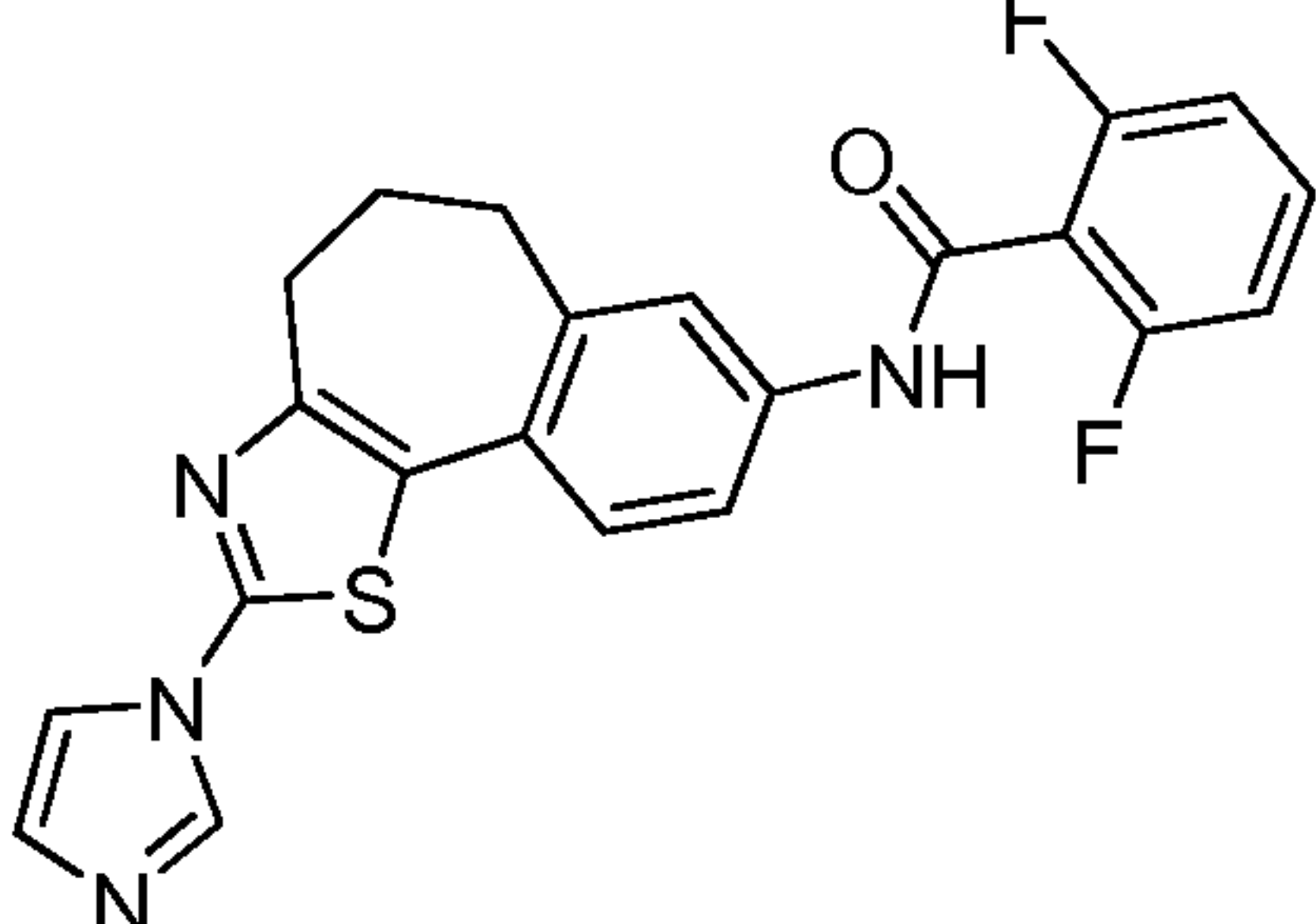
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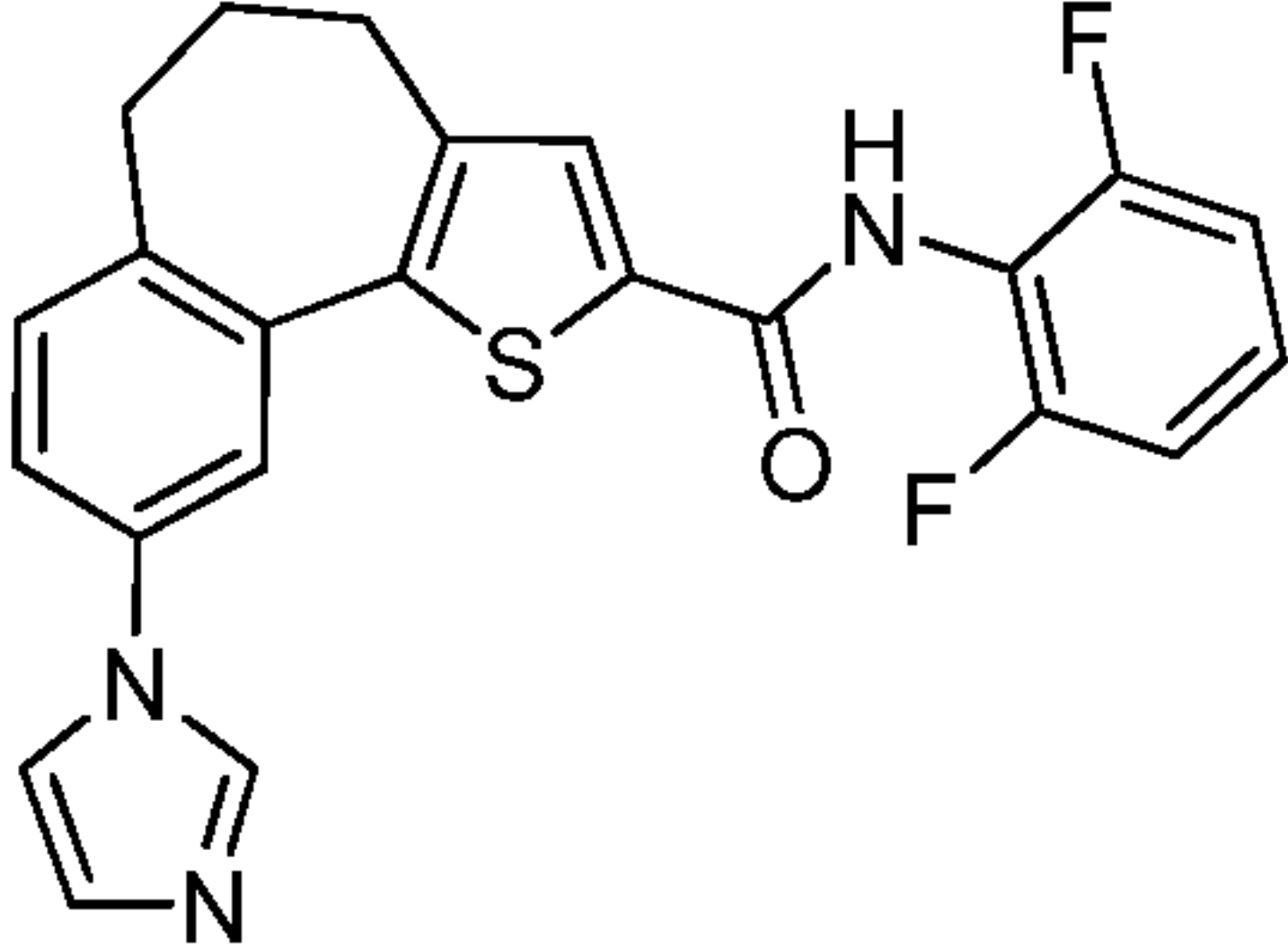
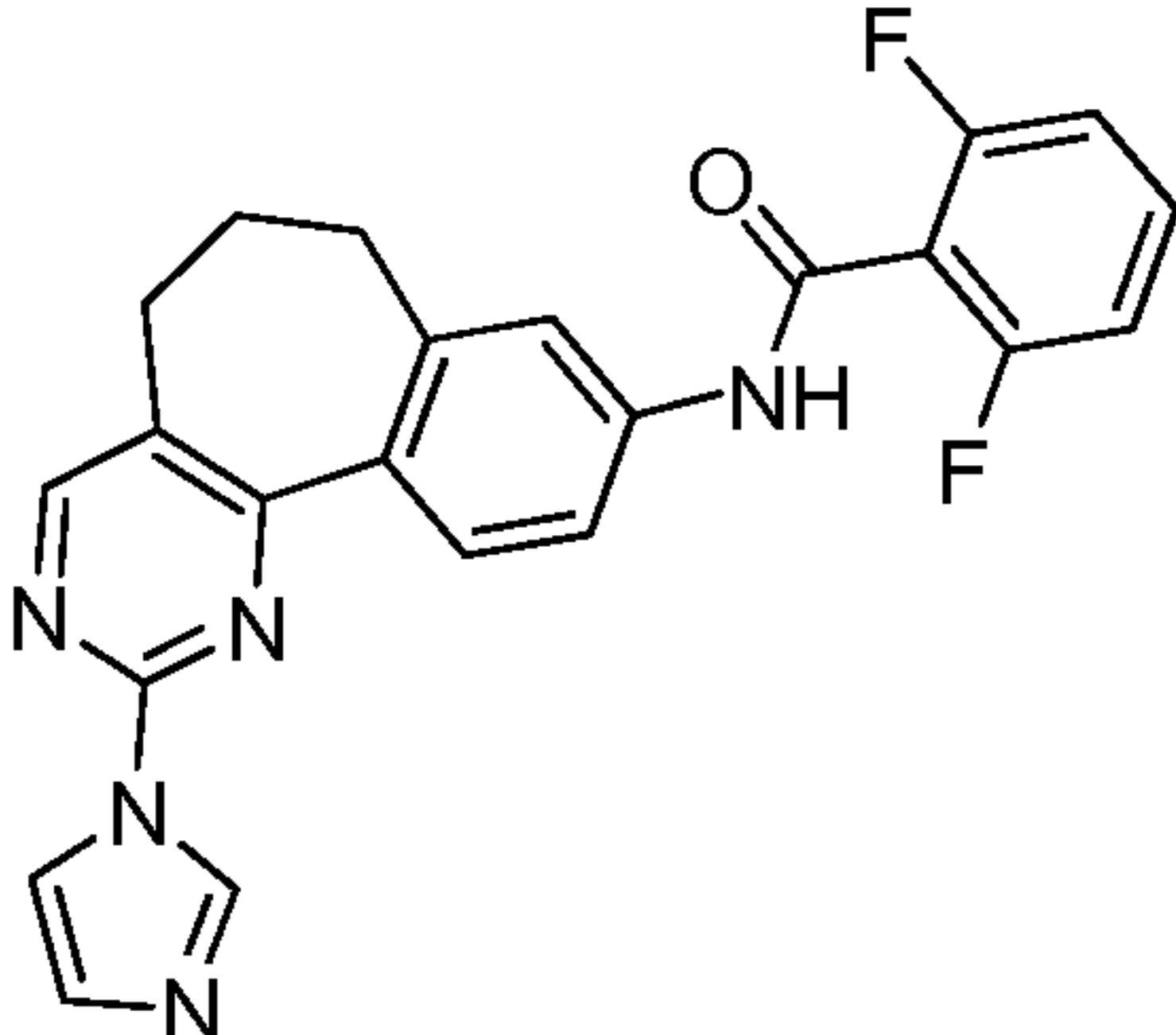
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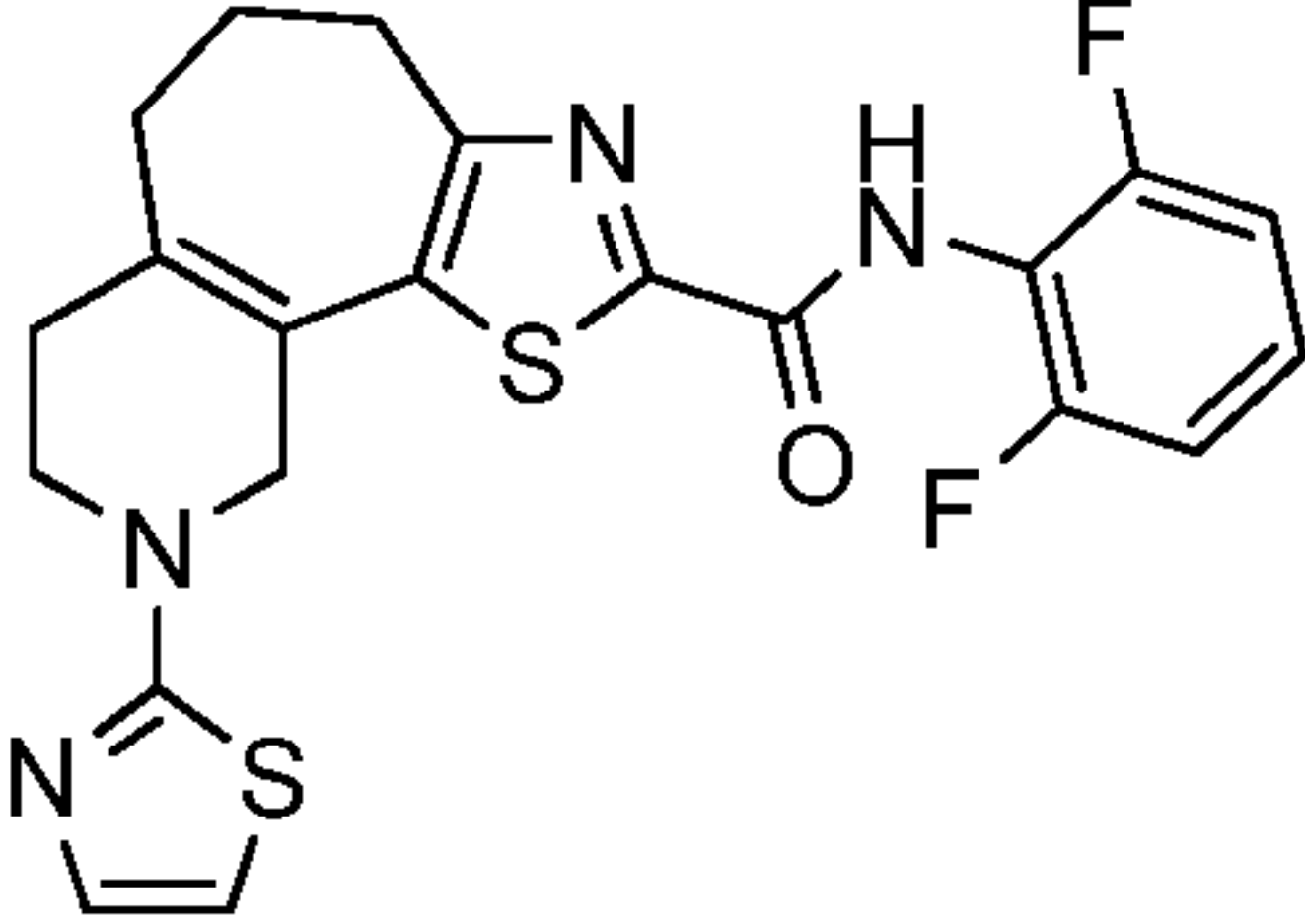
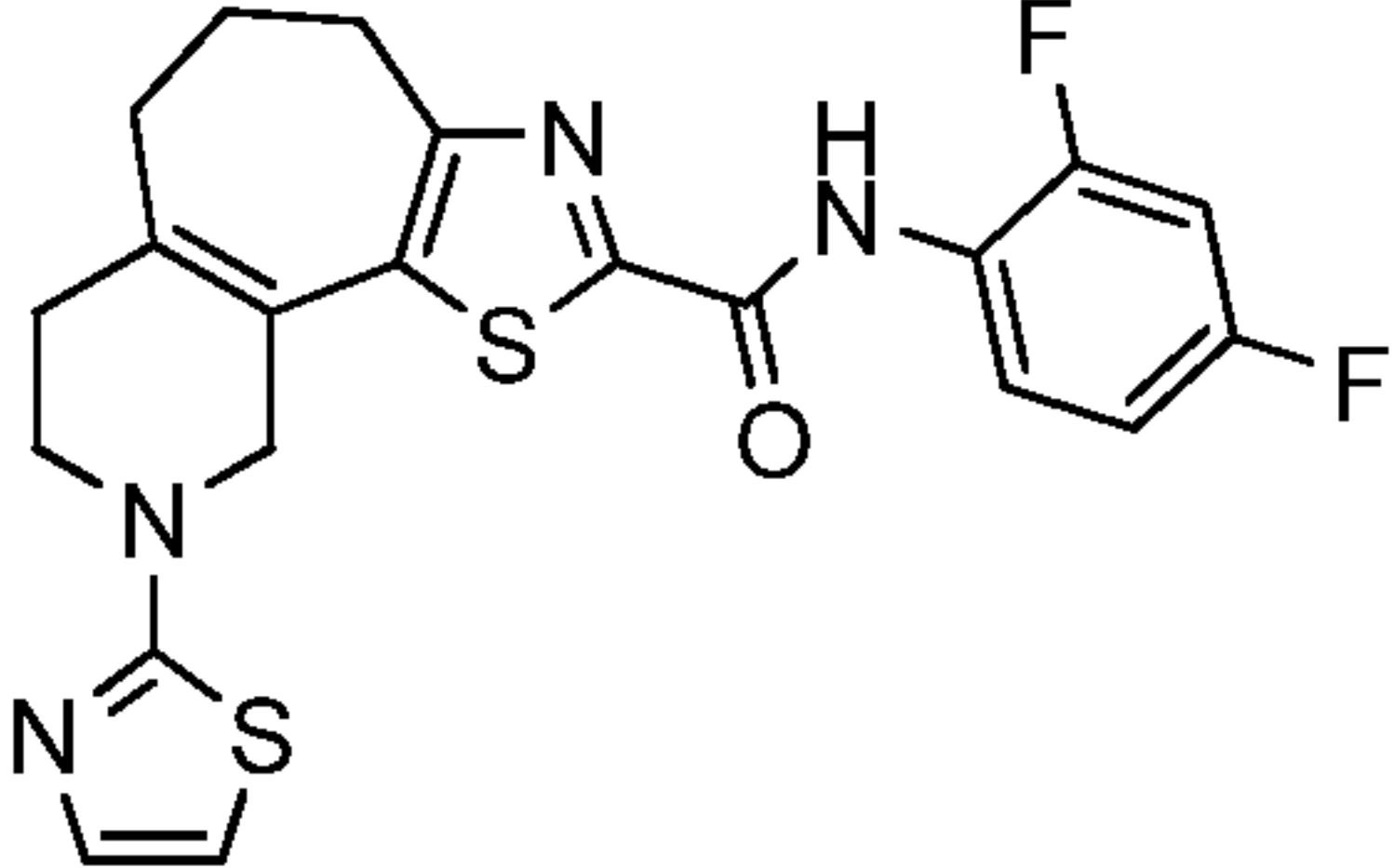
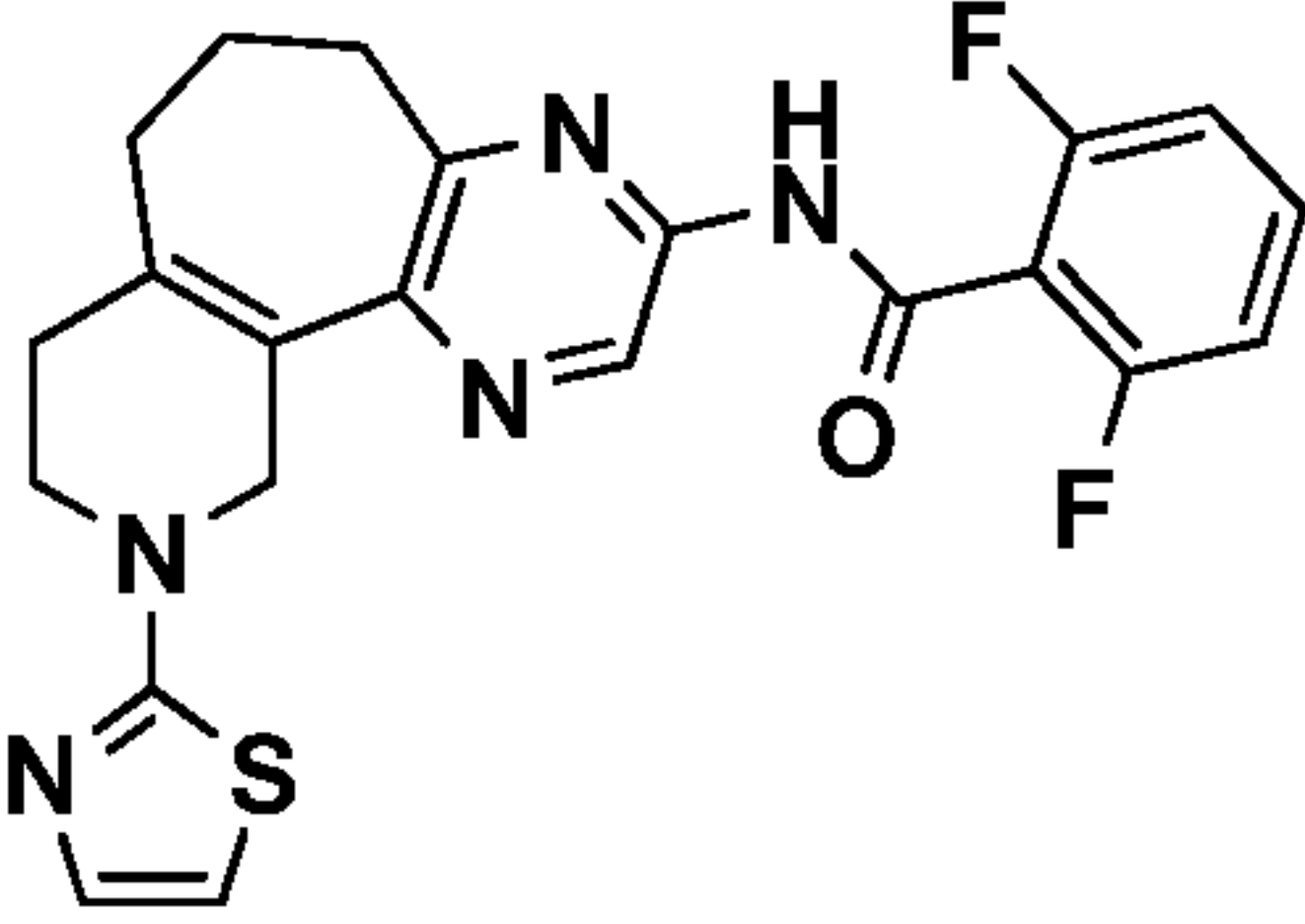
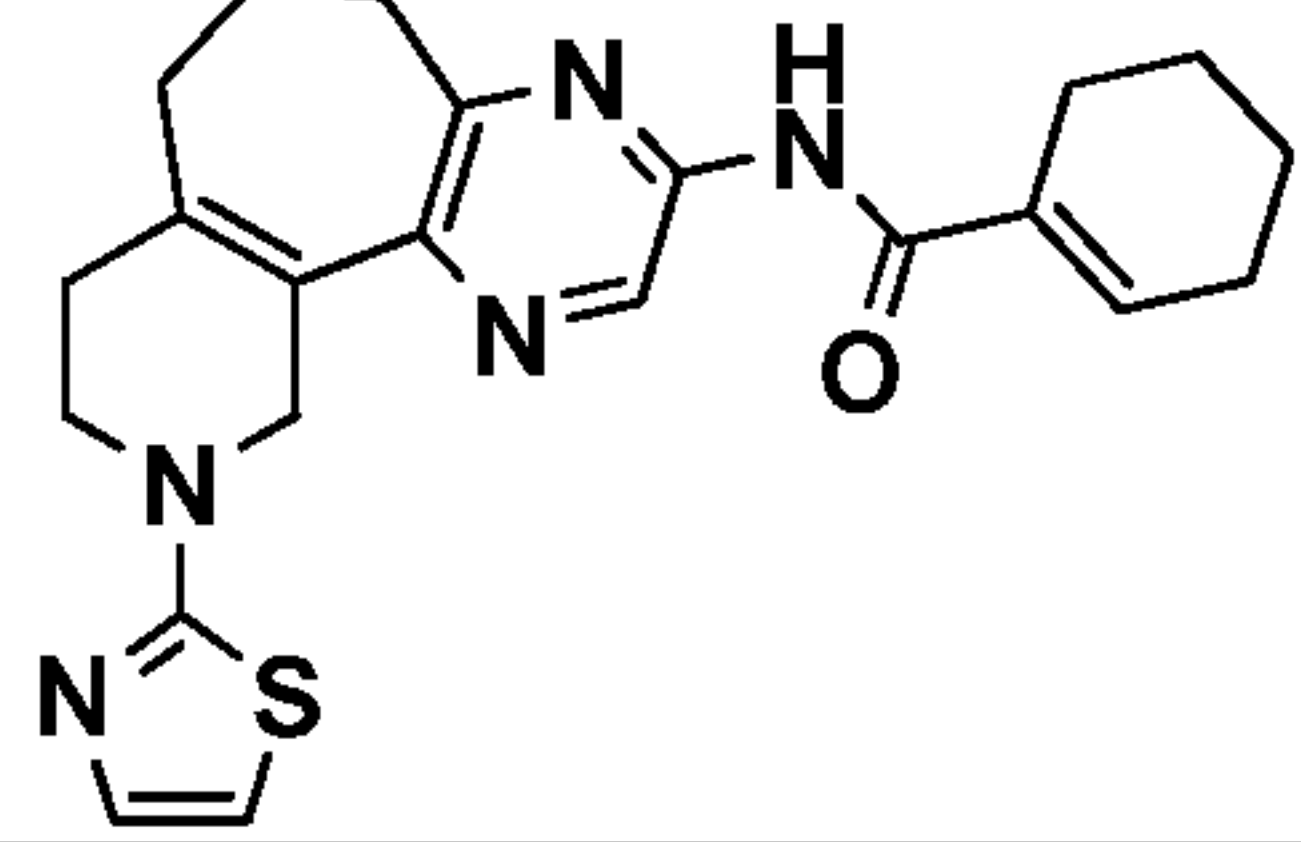
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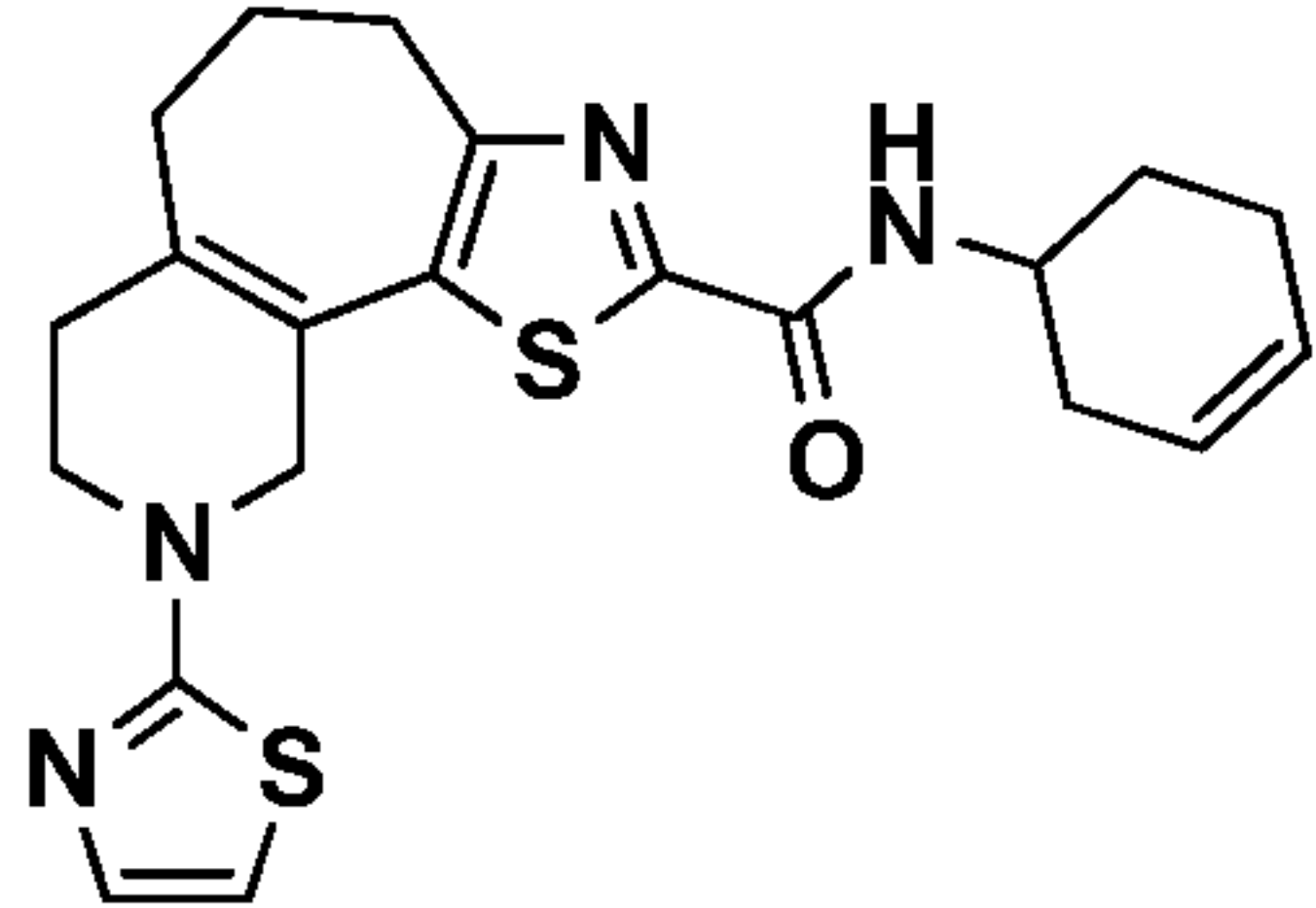
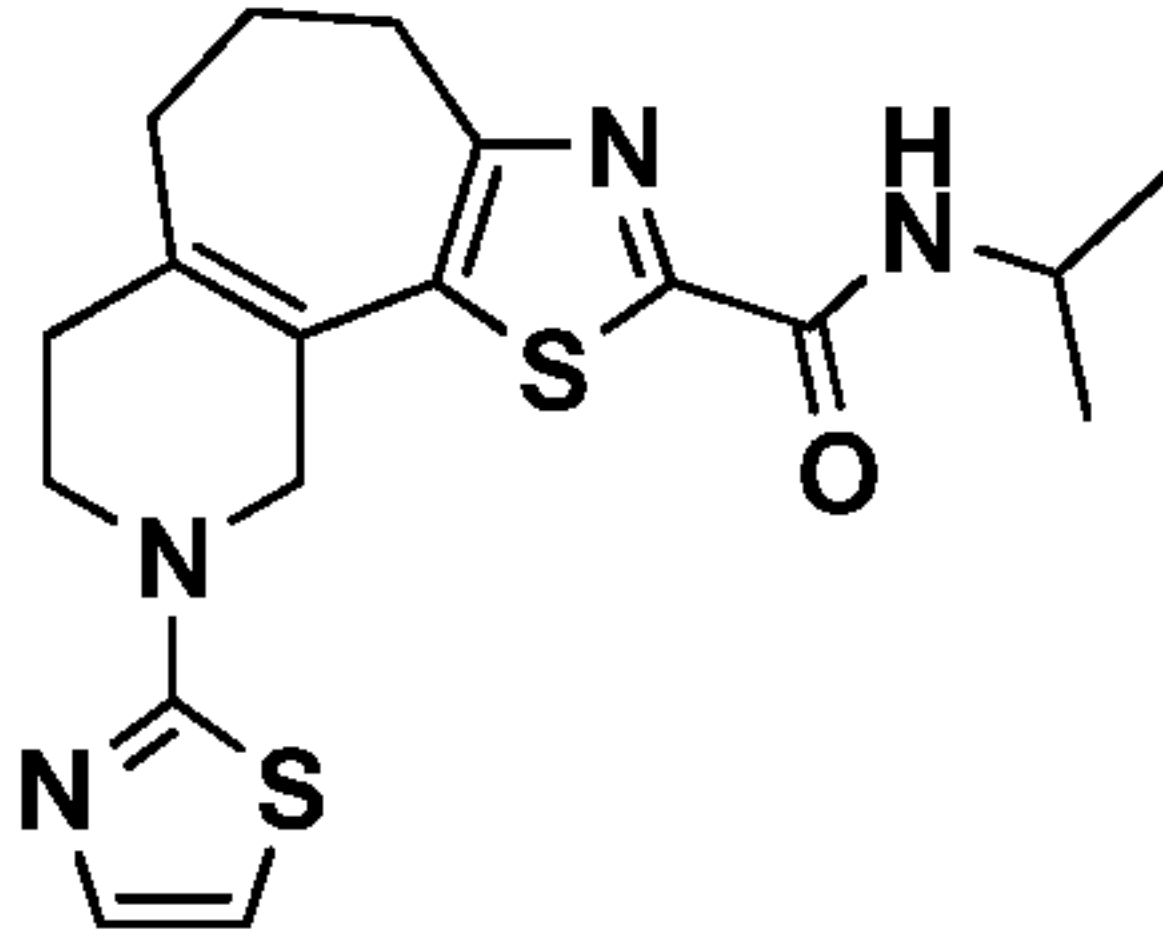
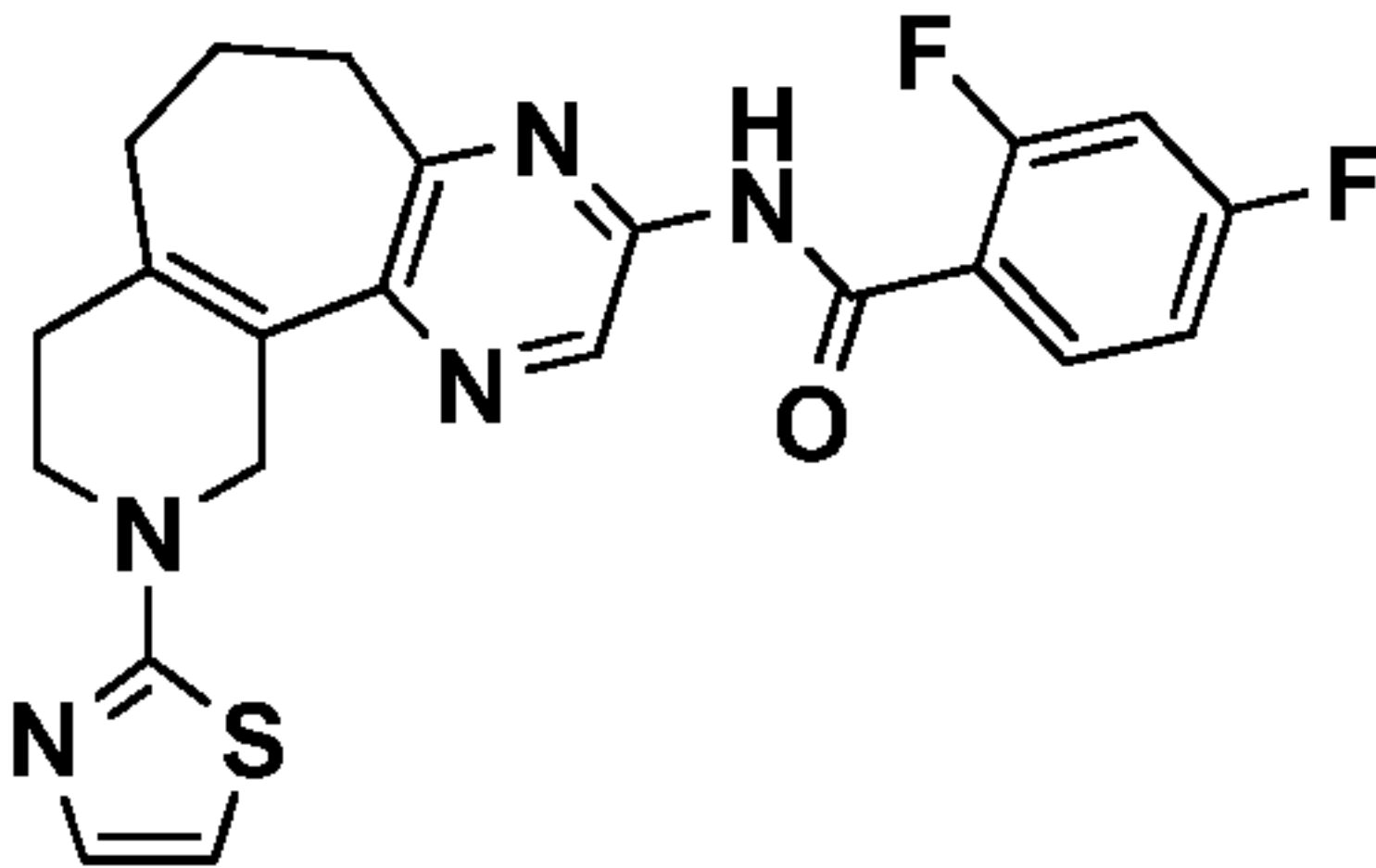
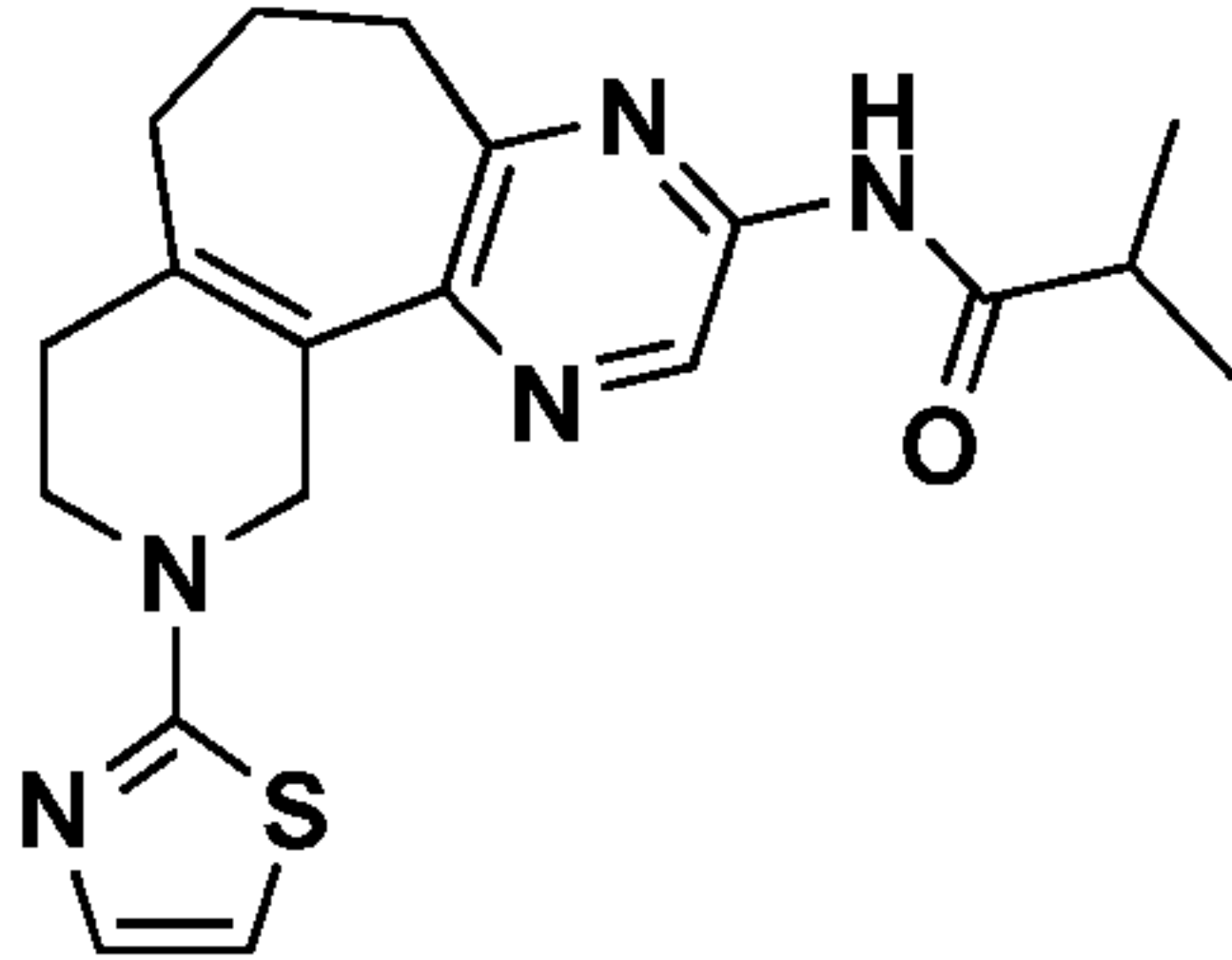
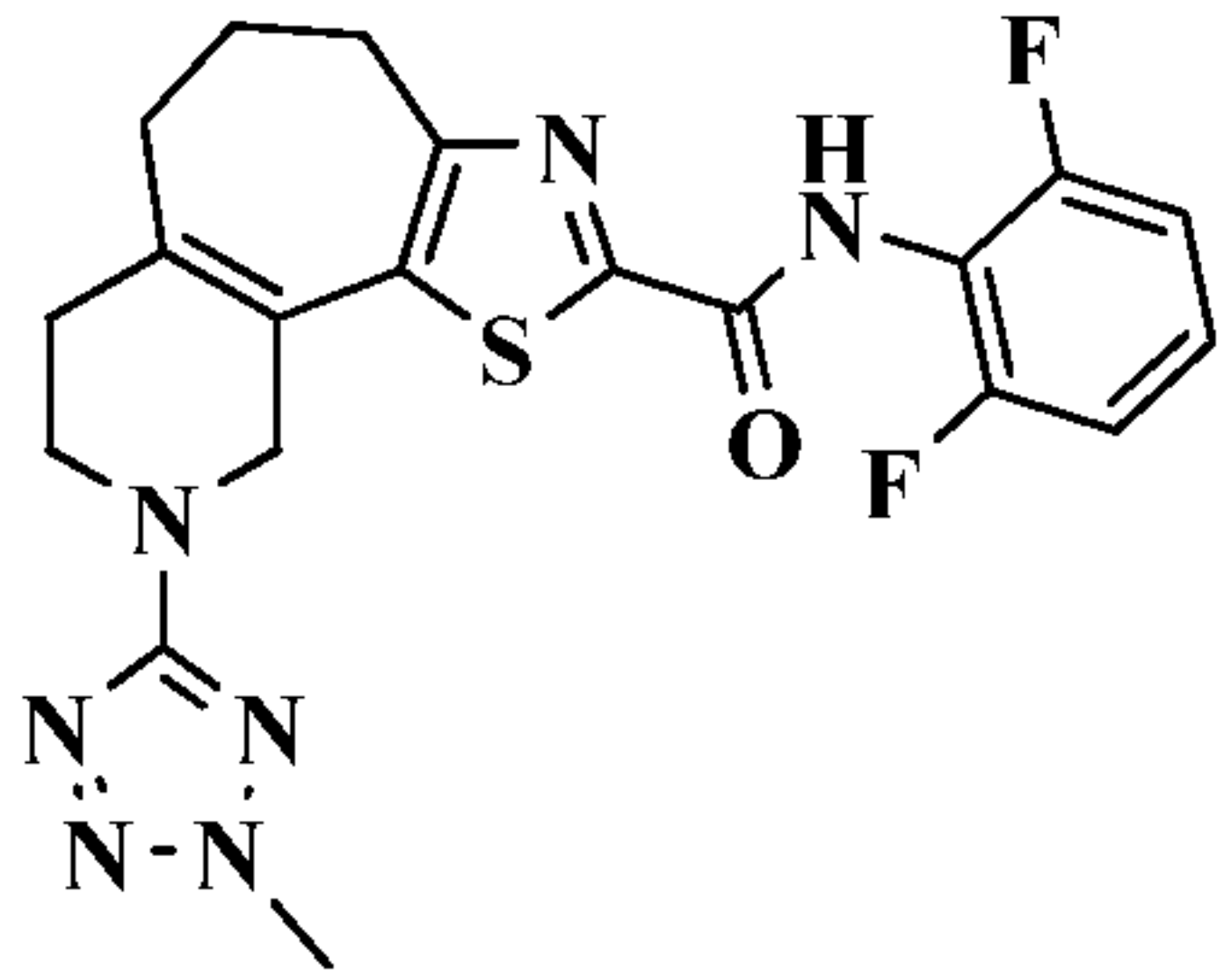
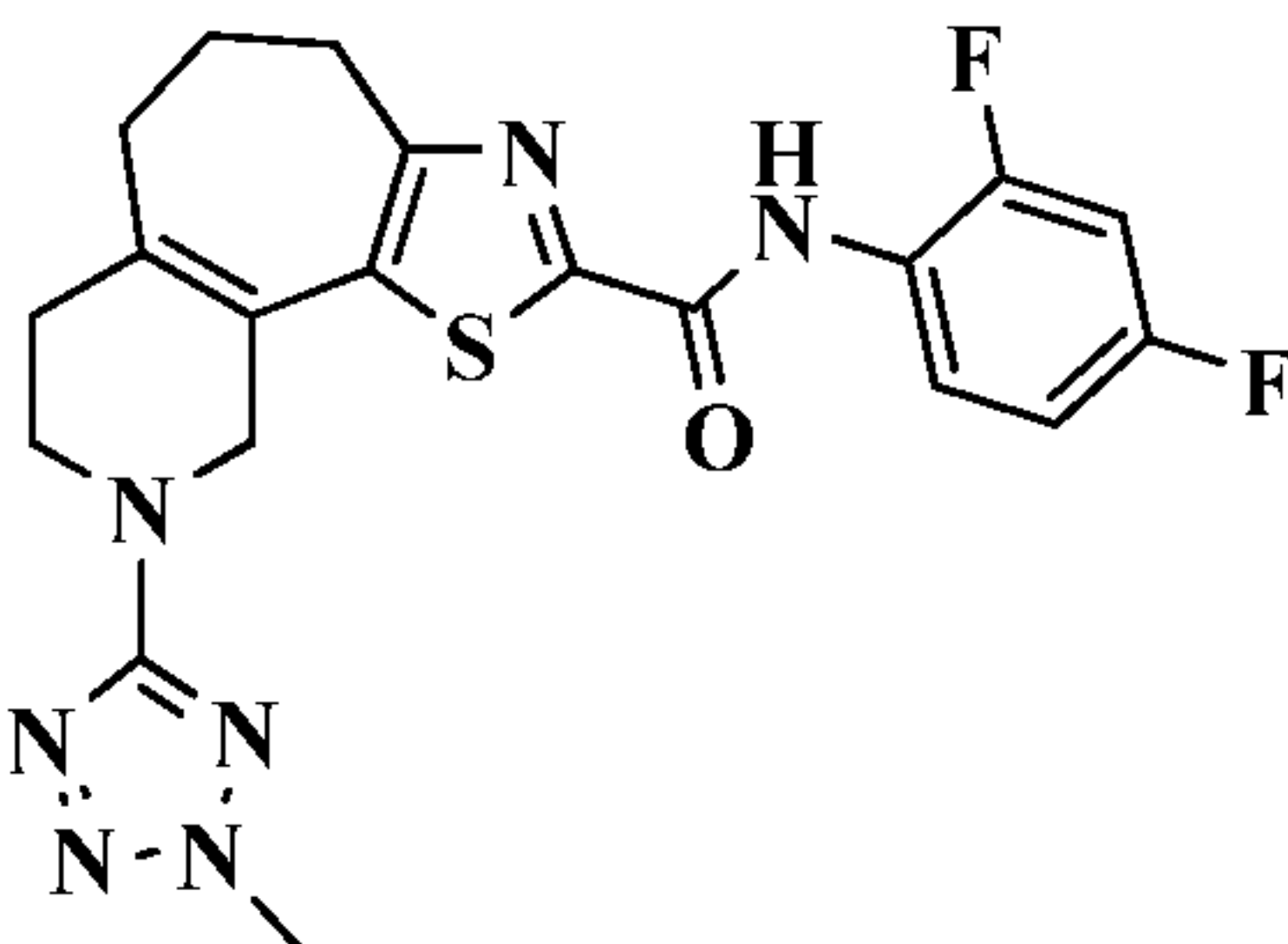
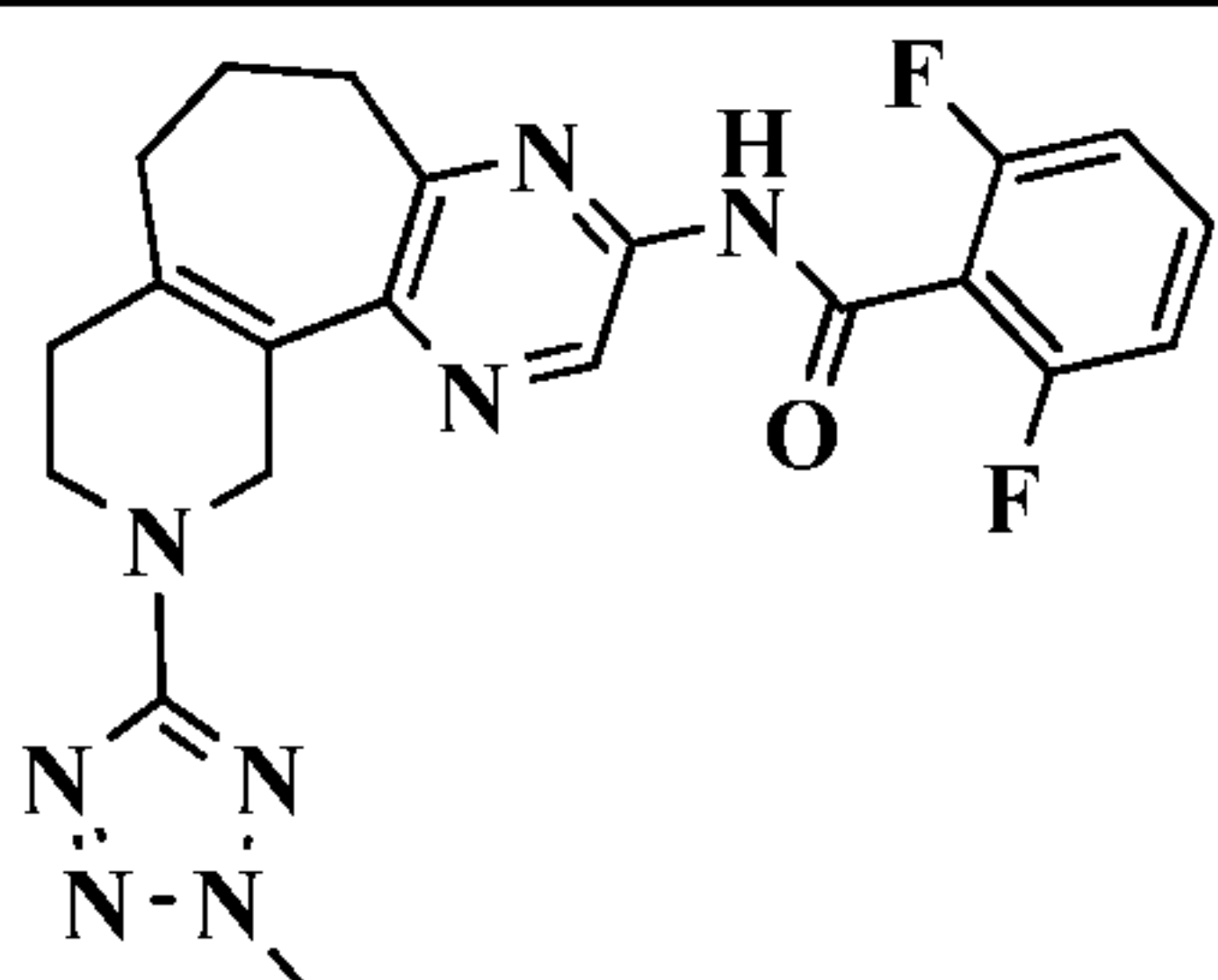
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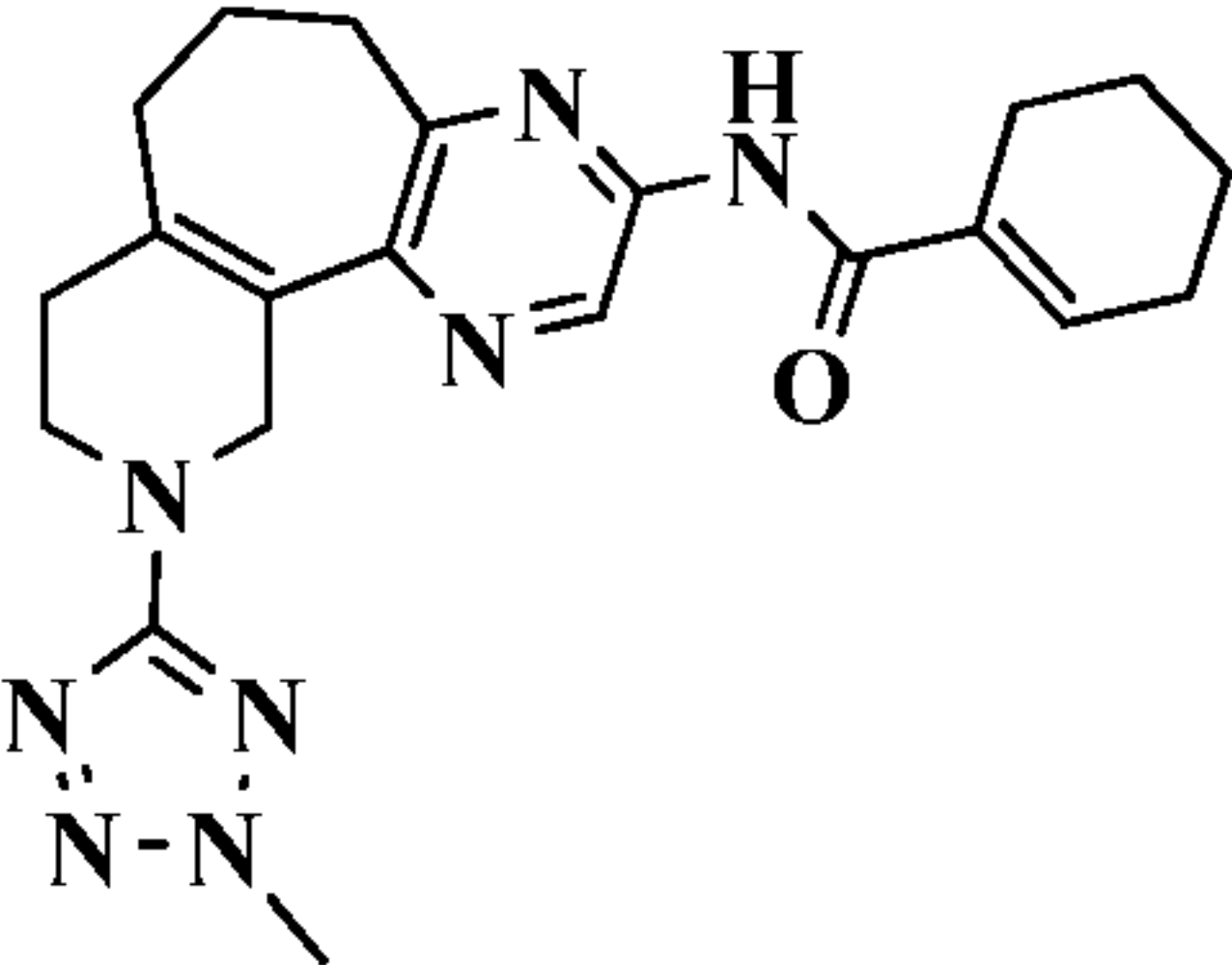
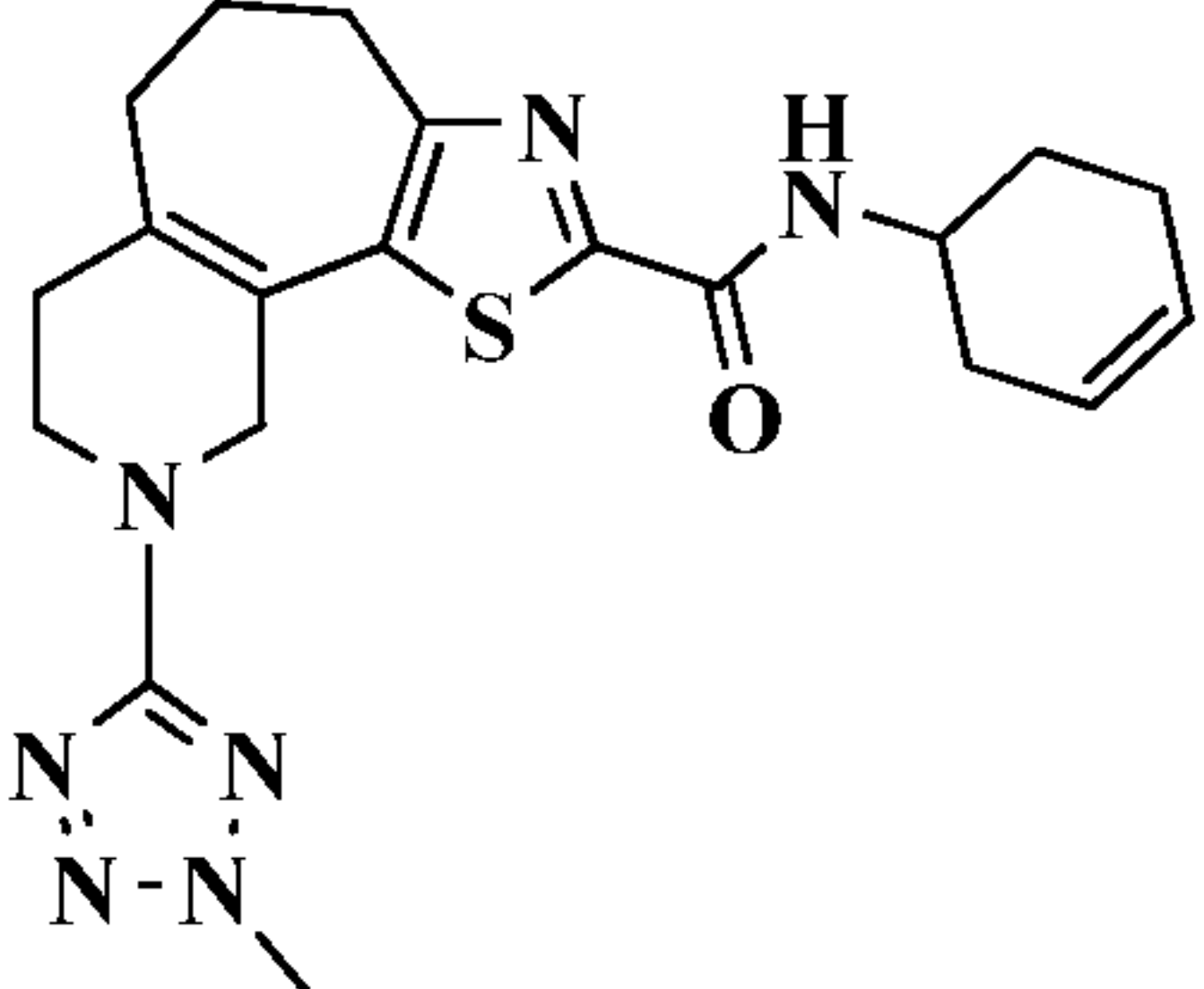
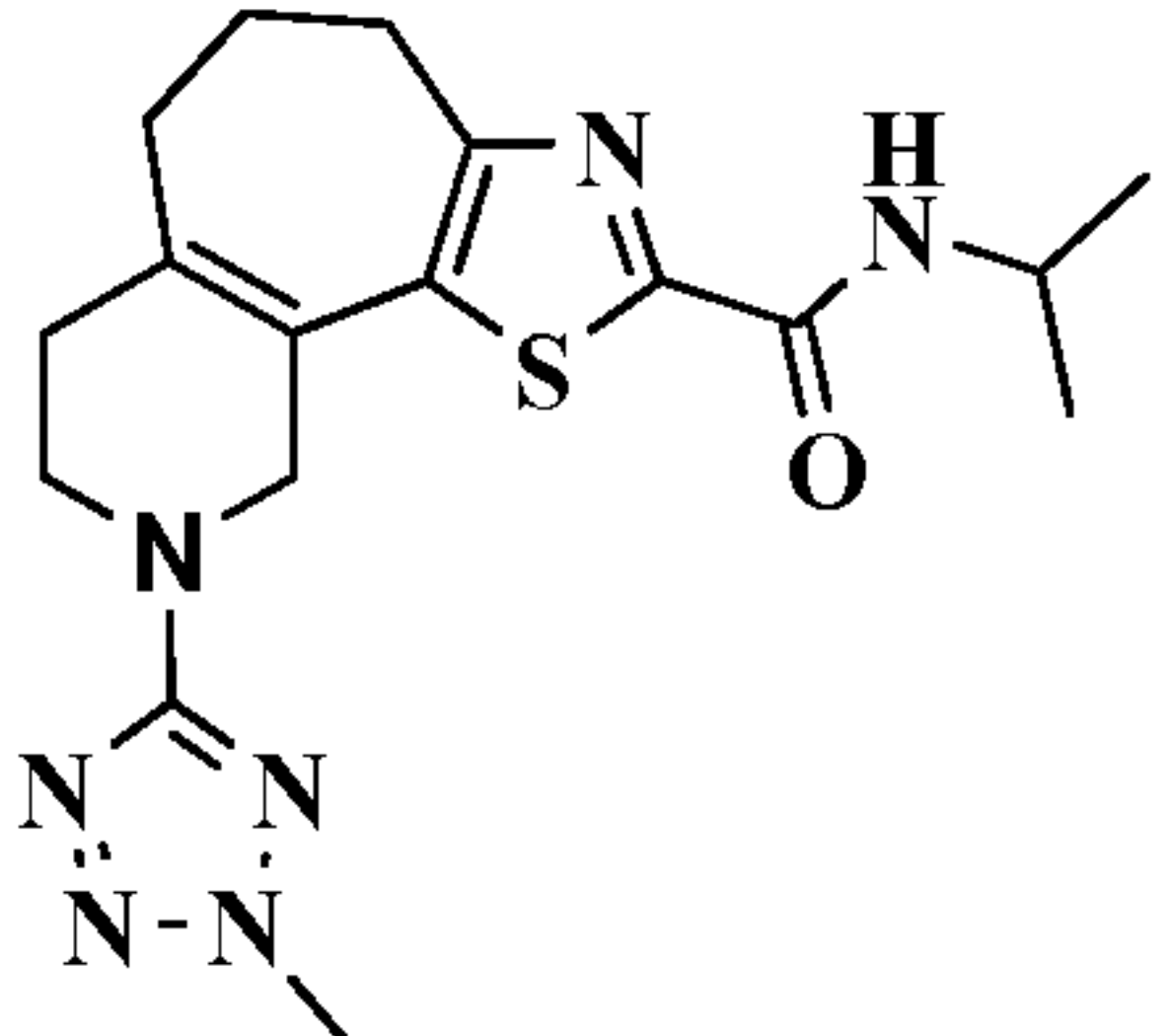
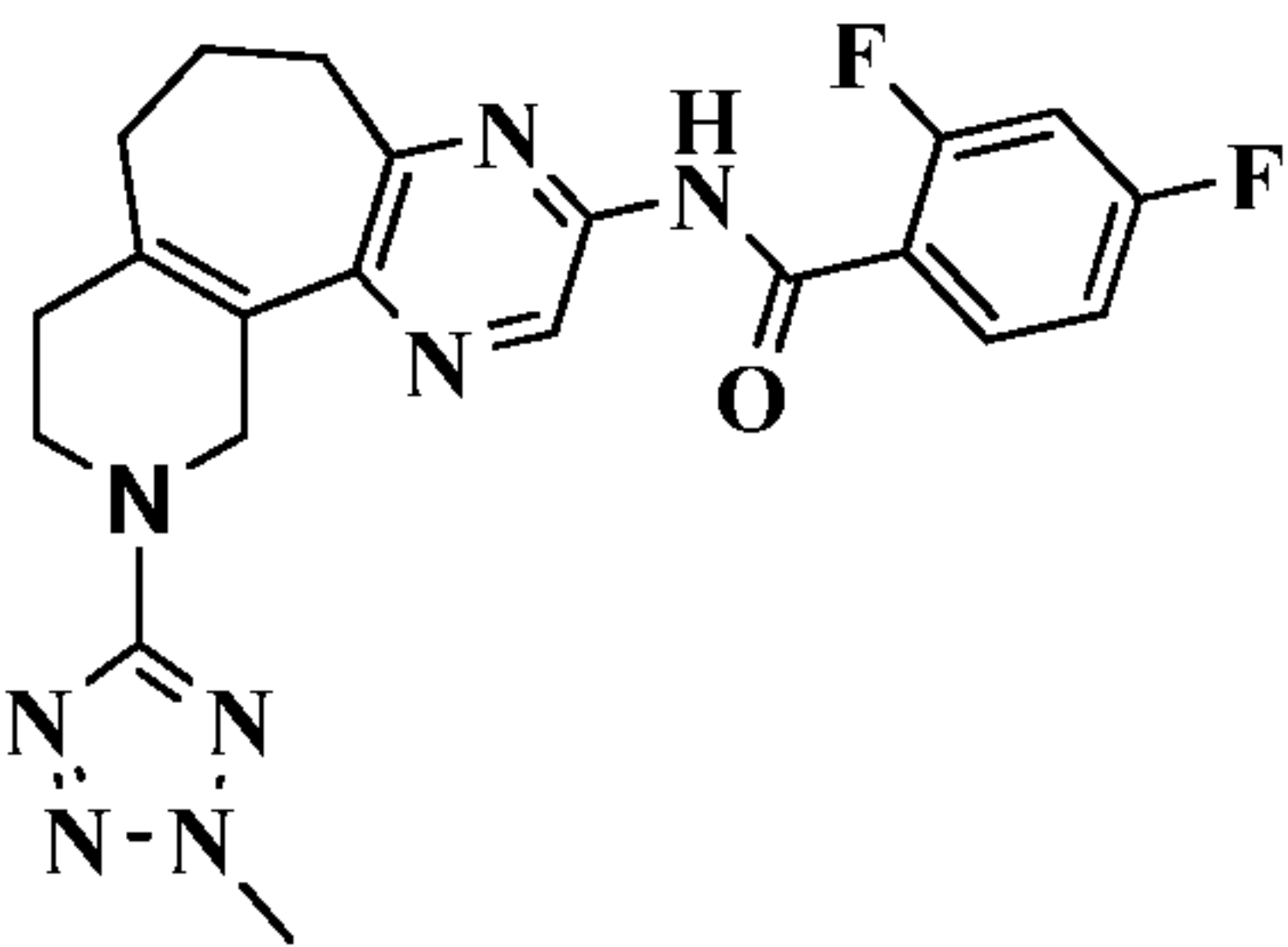
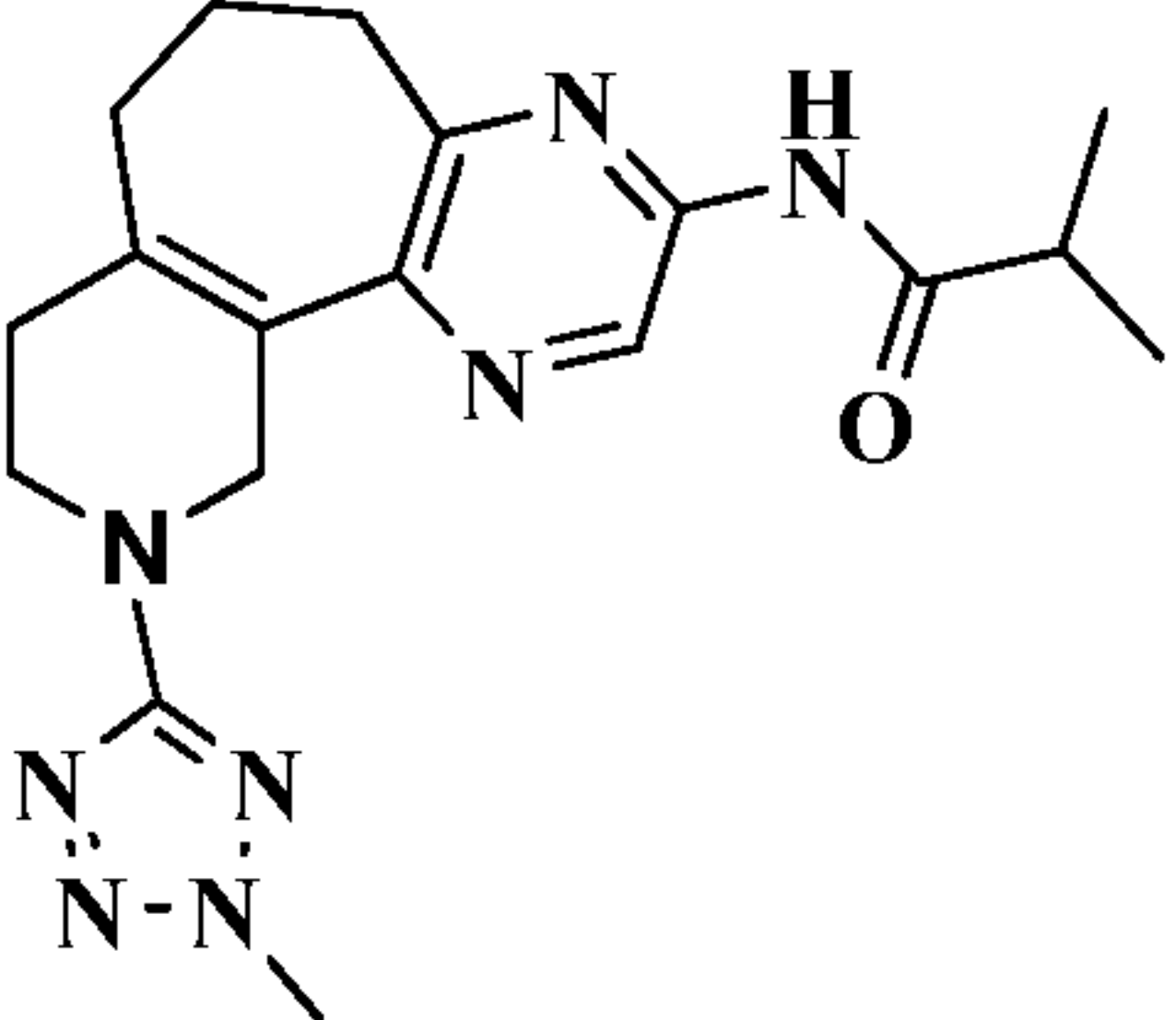
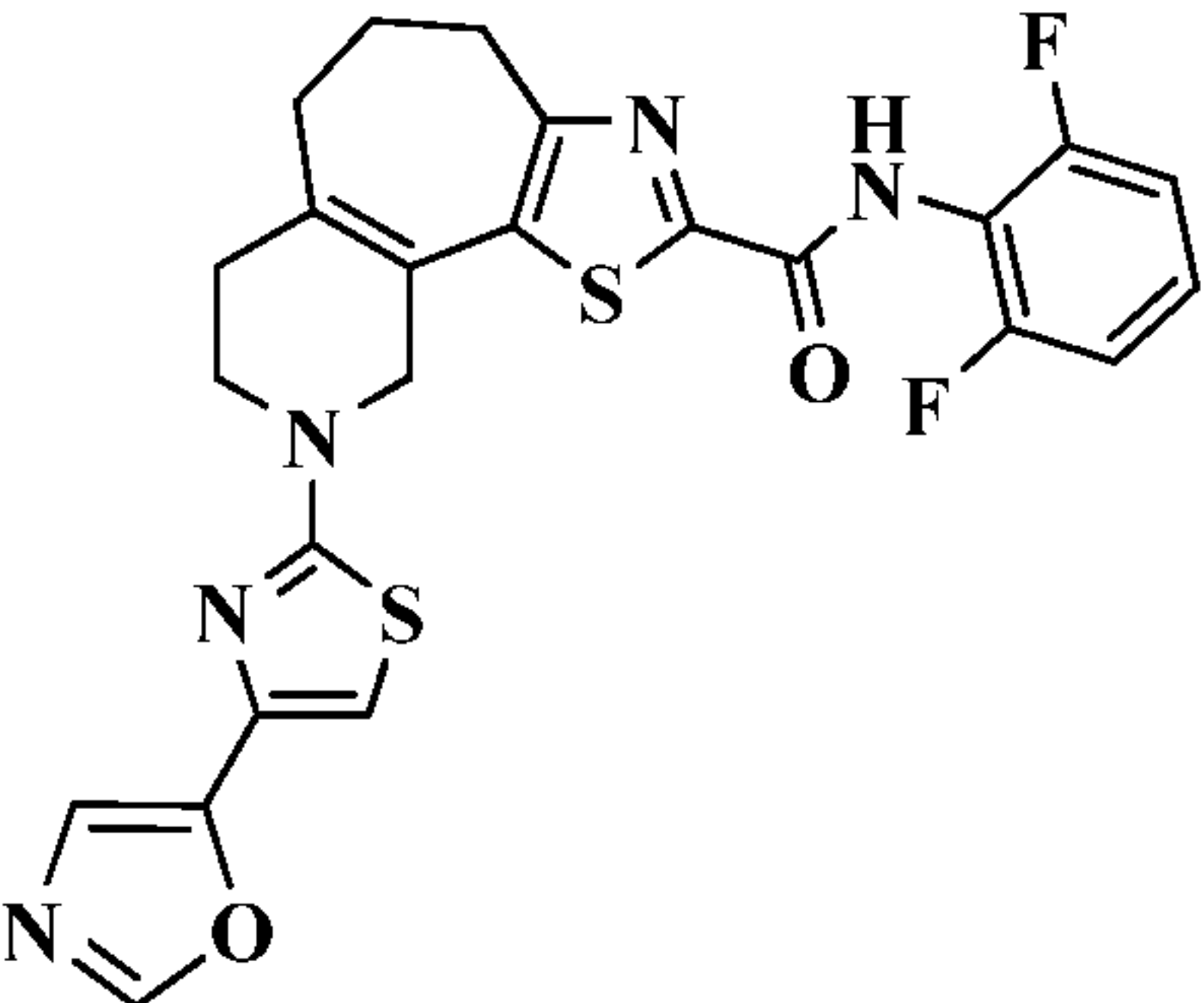
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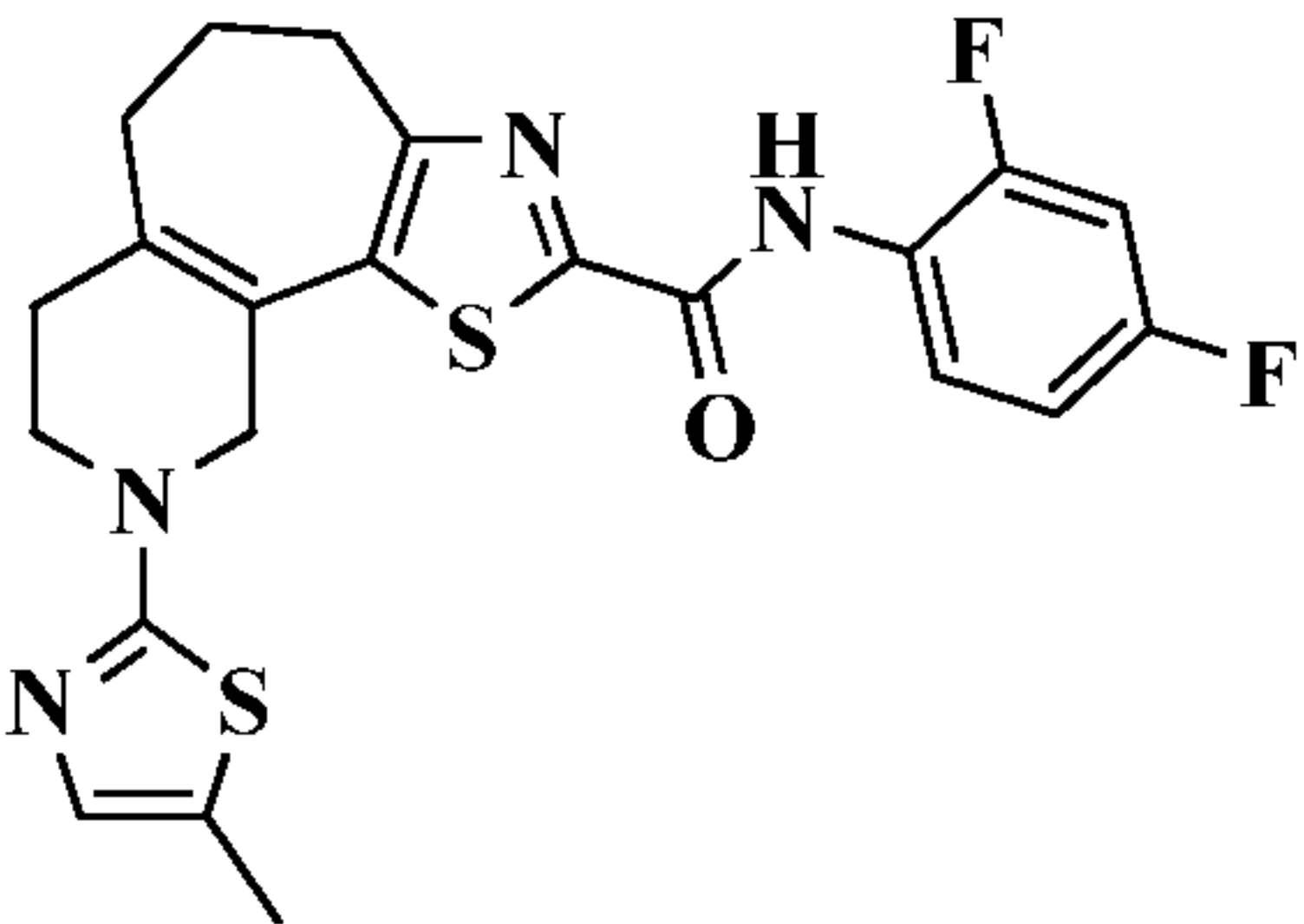
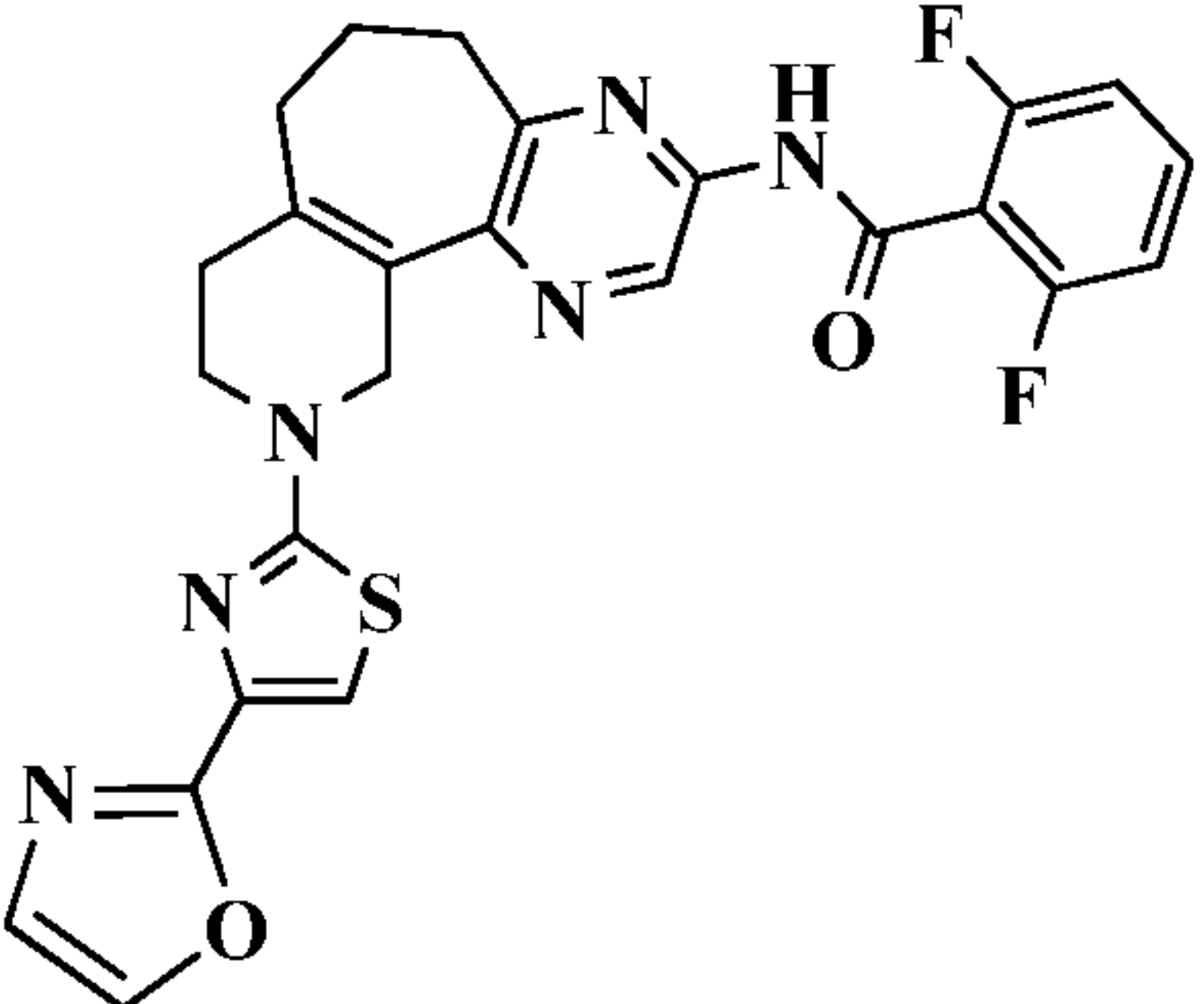
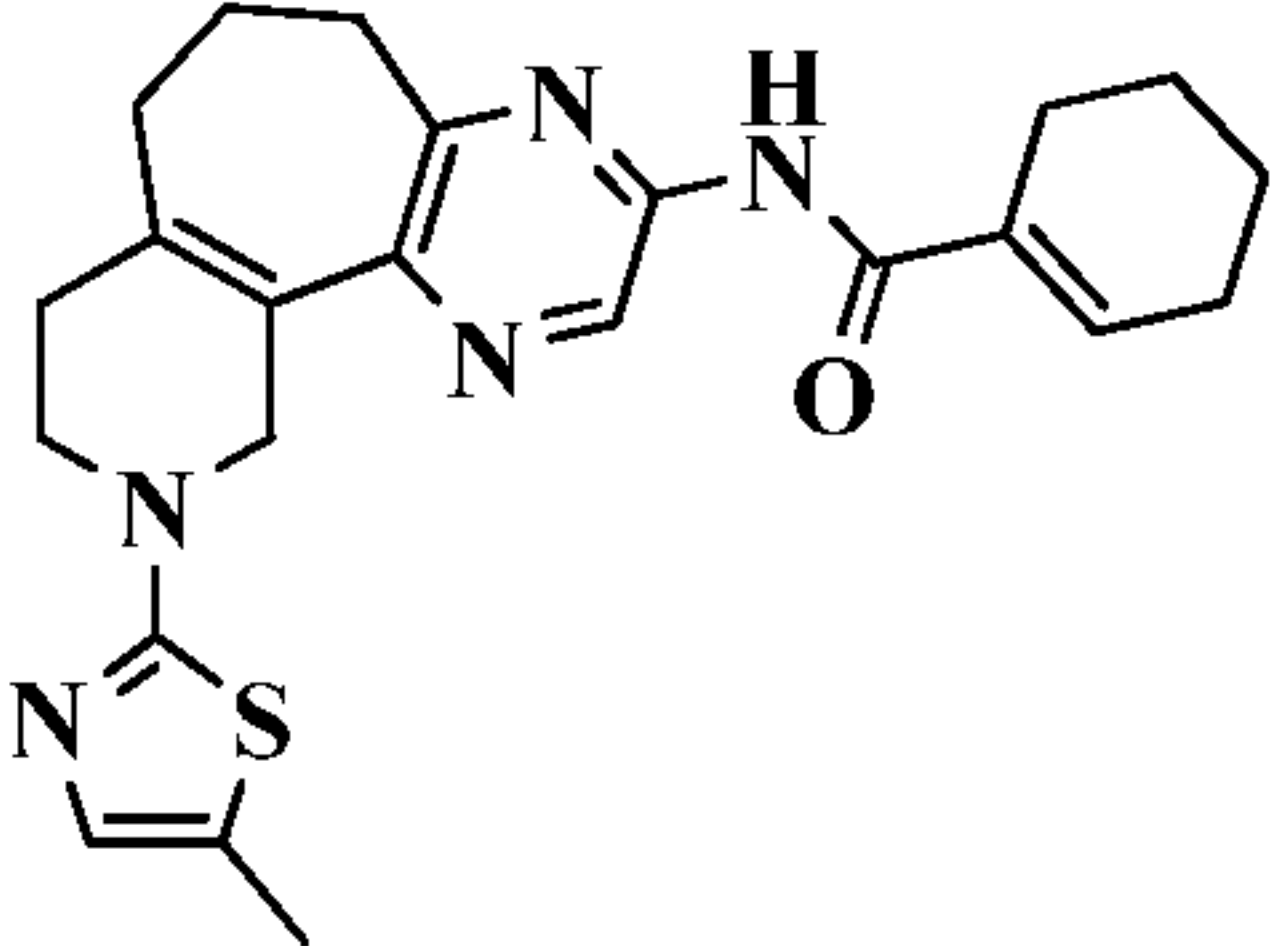
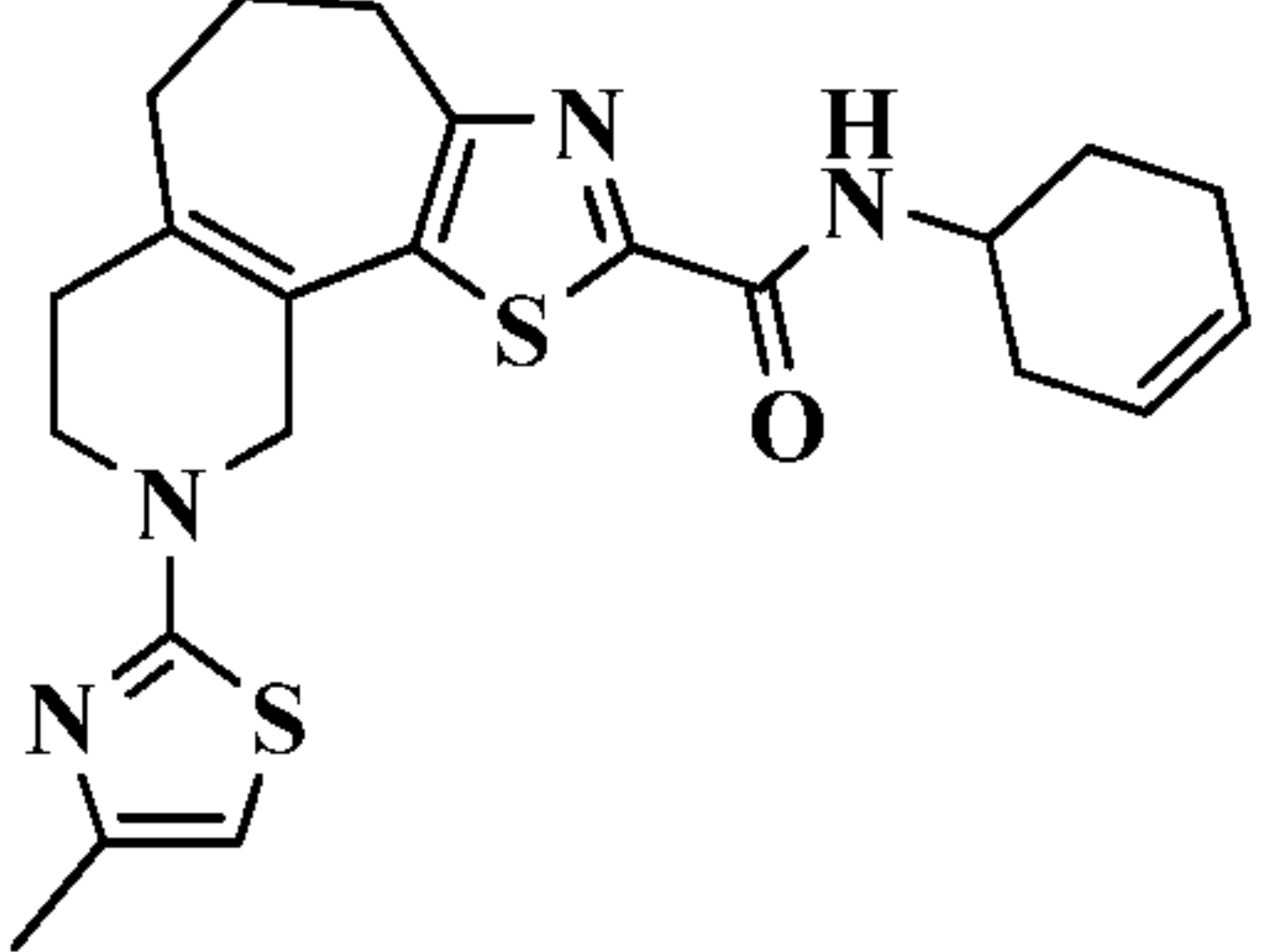
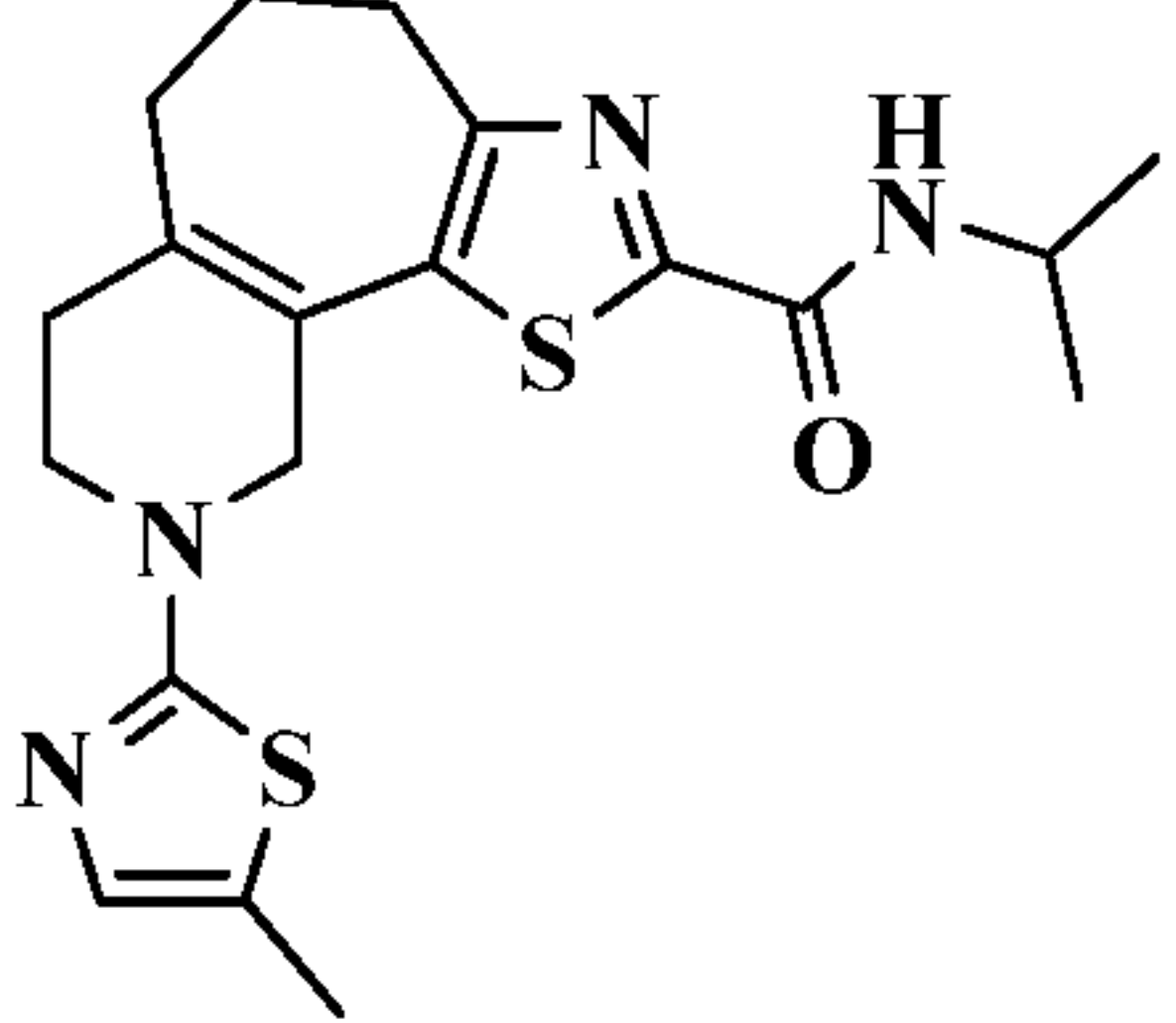
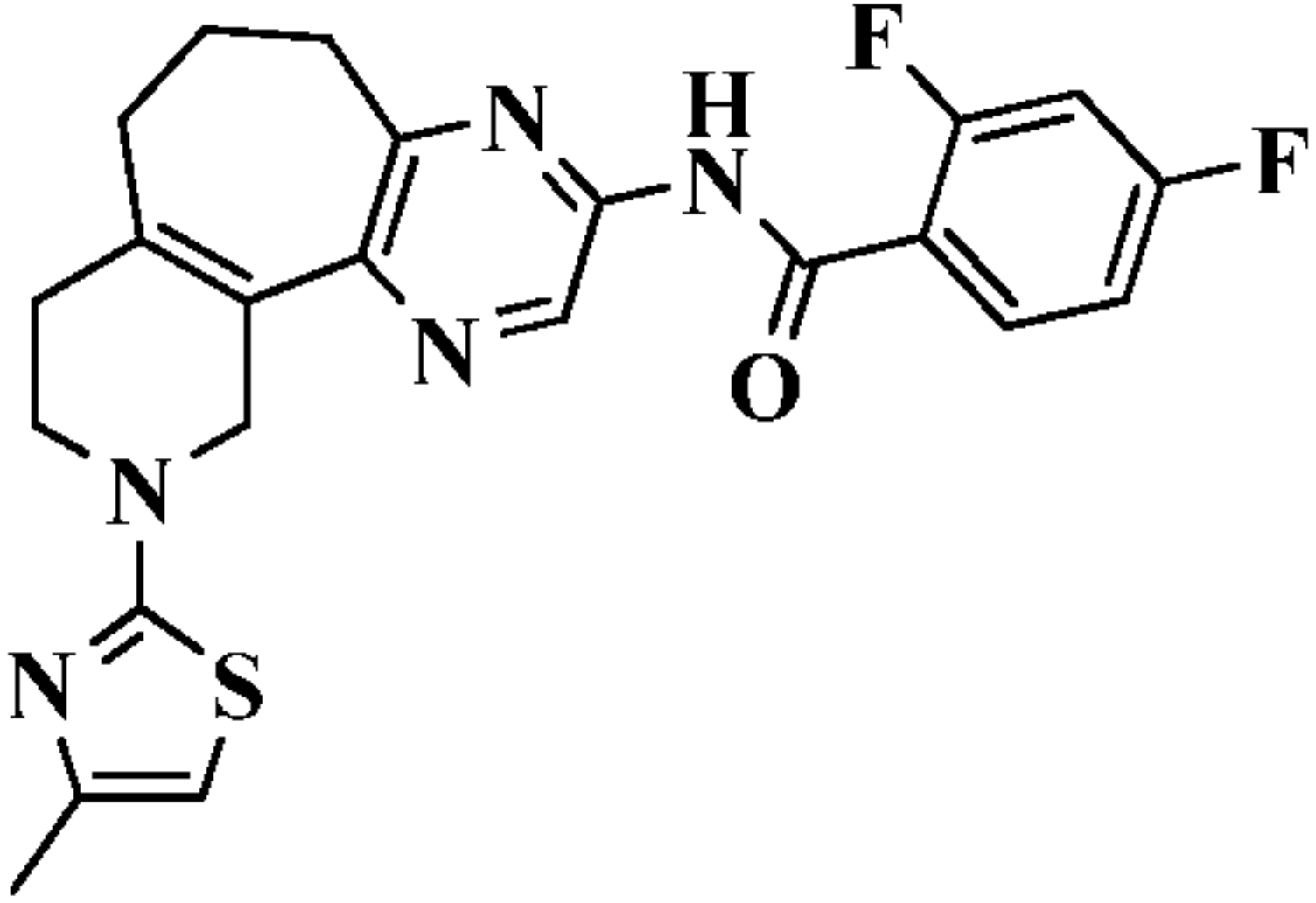
Exemplary compounds of the invention are also depicted in Table 2 below.

Table 2

Compound No.	Structure
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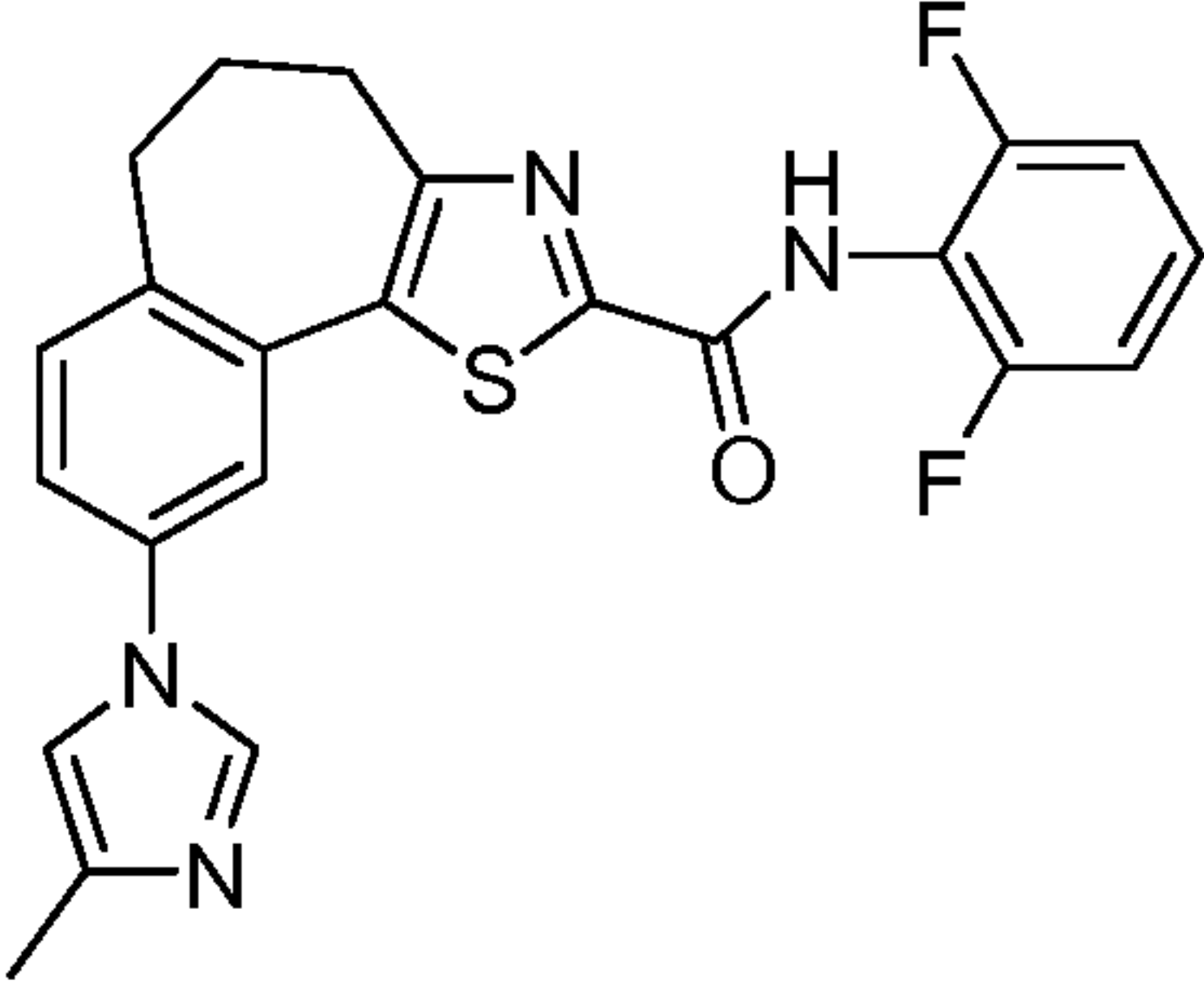
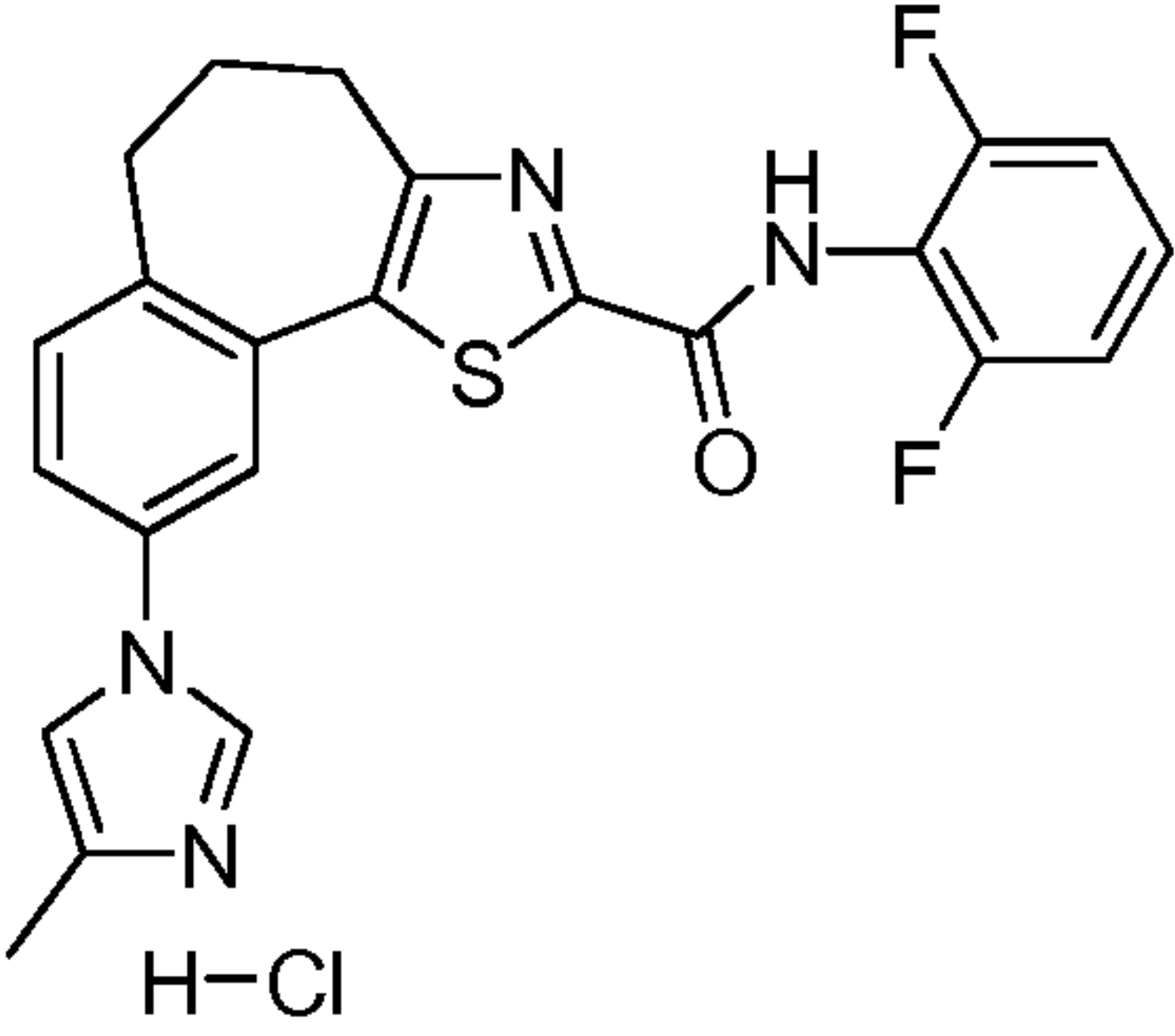
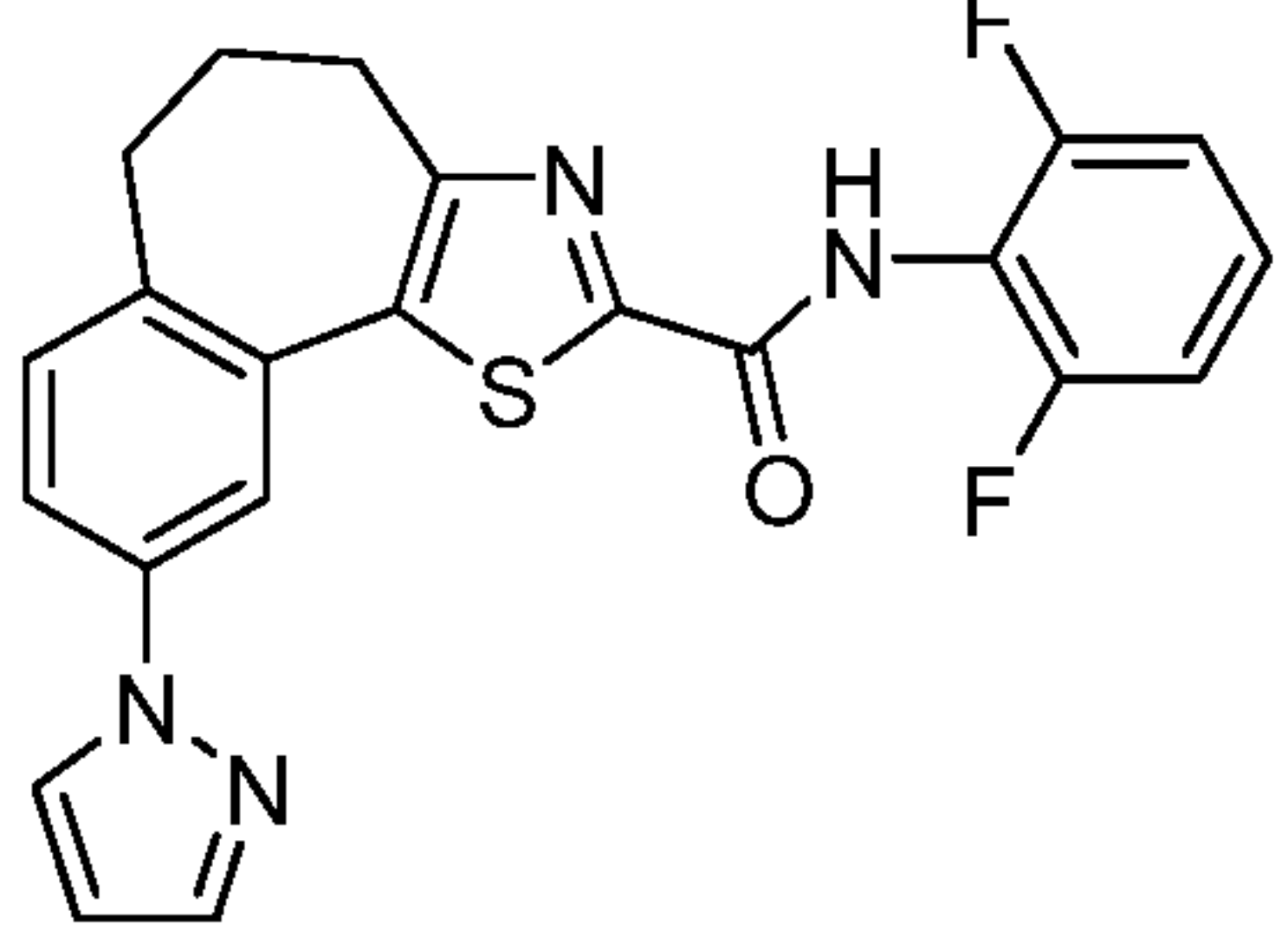
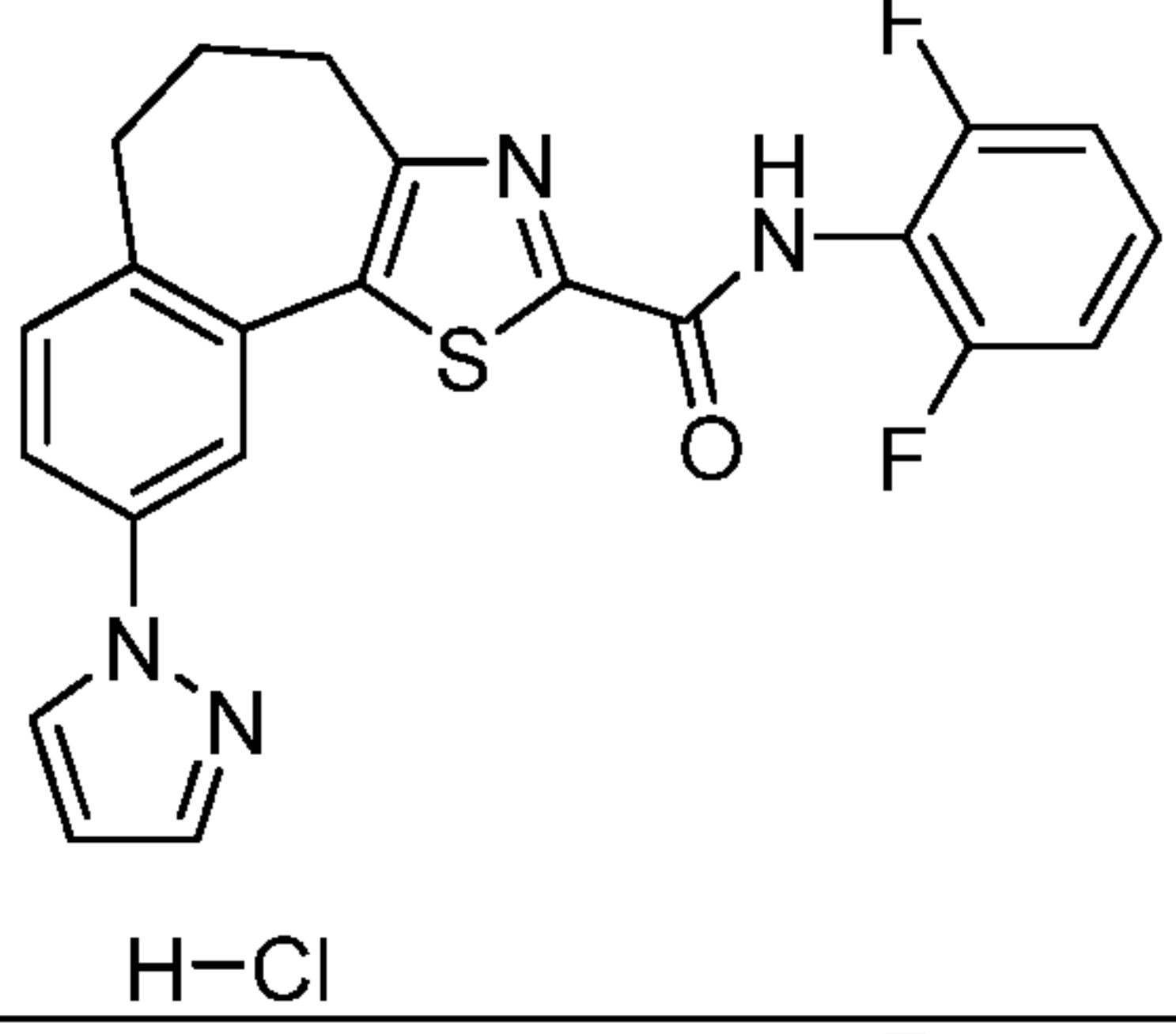
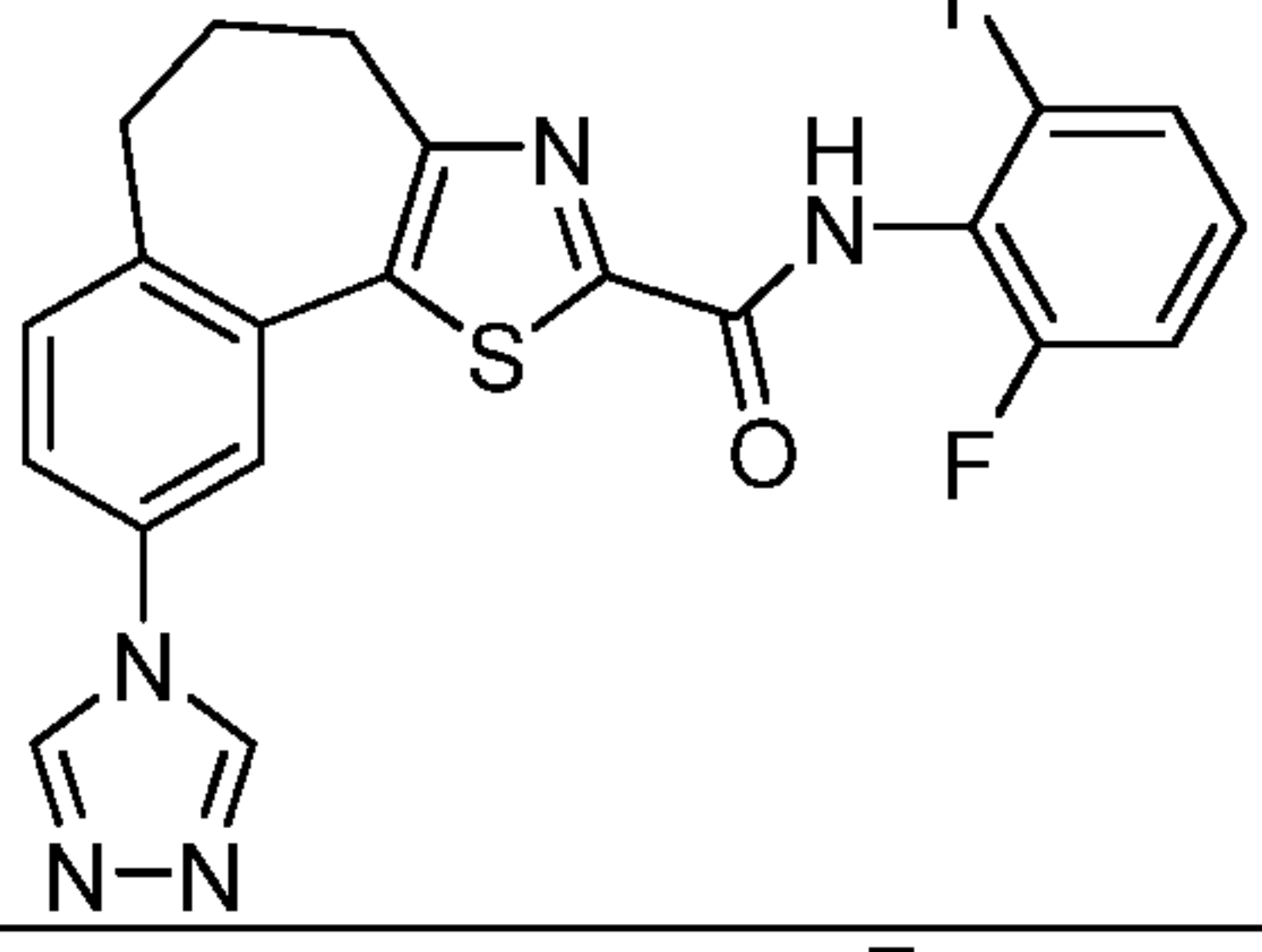
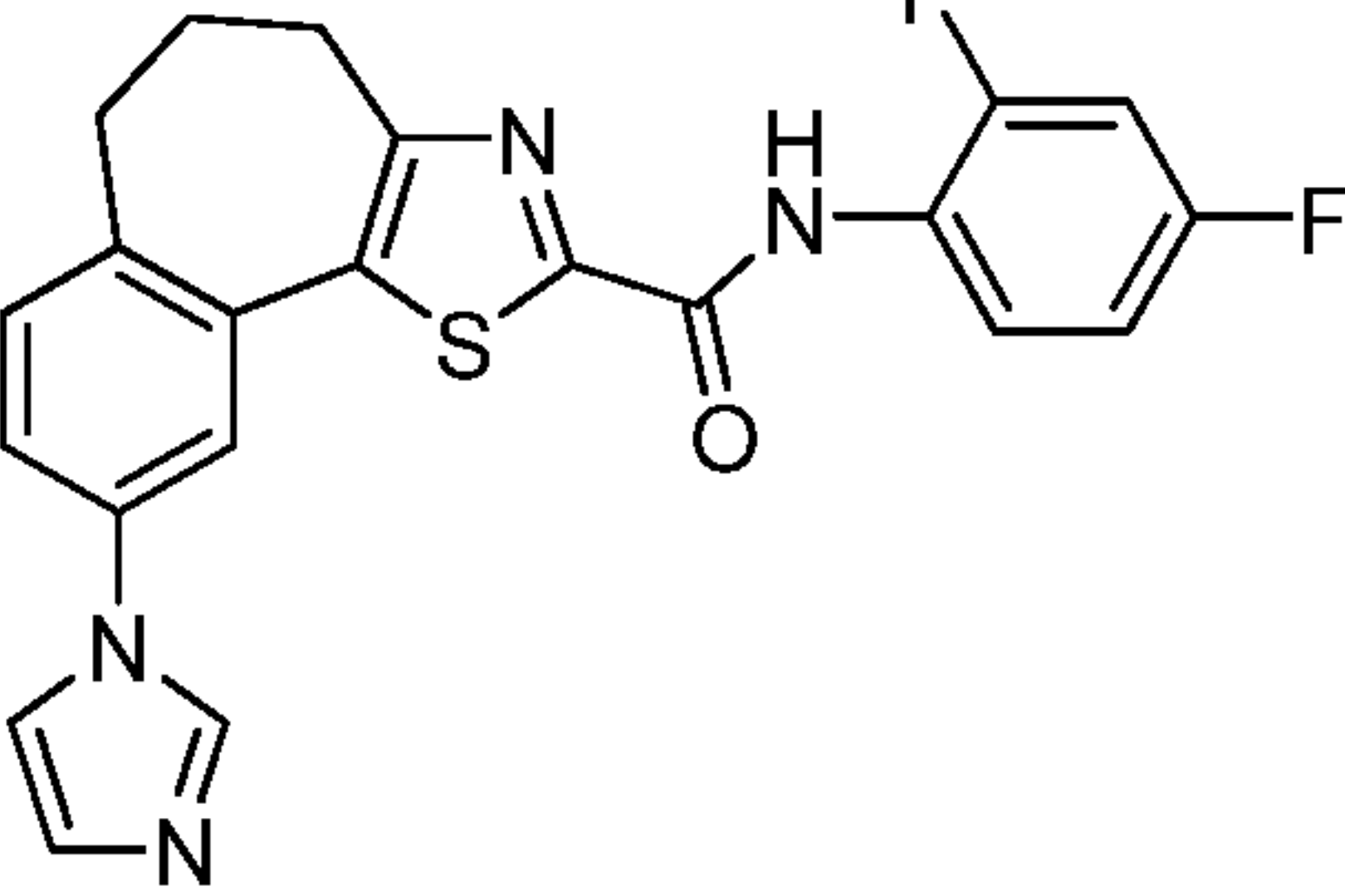
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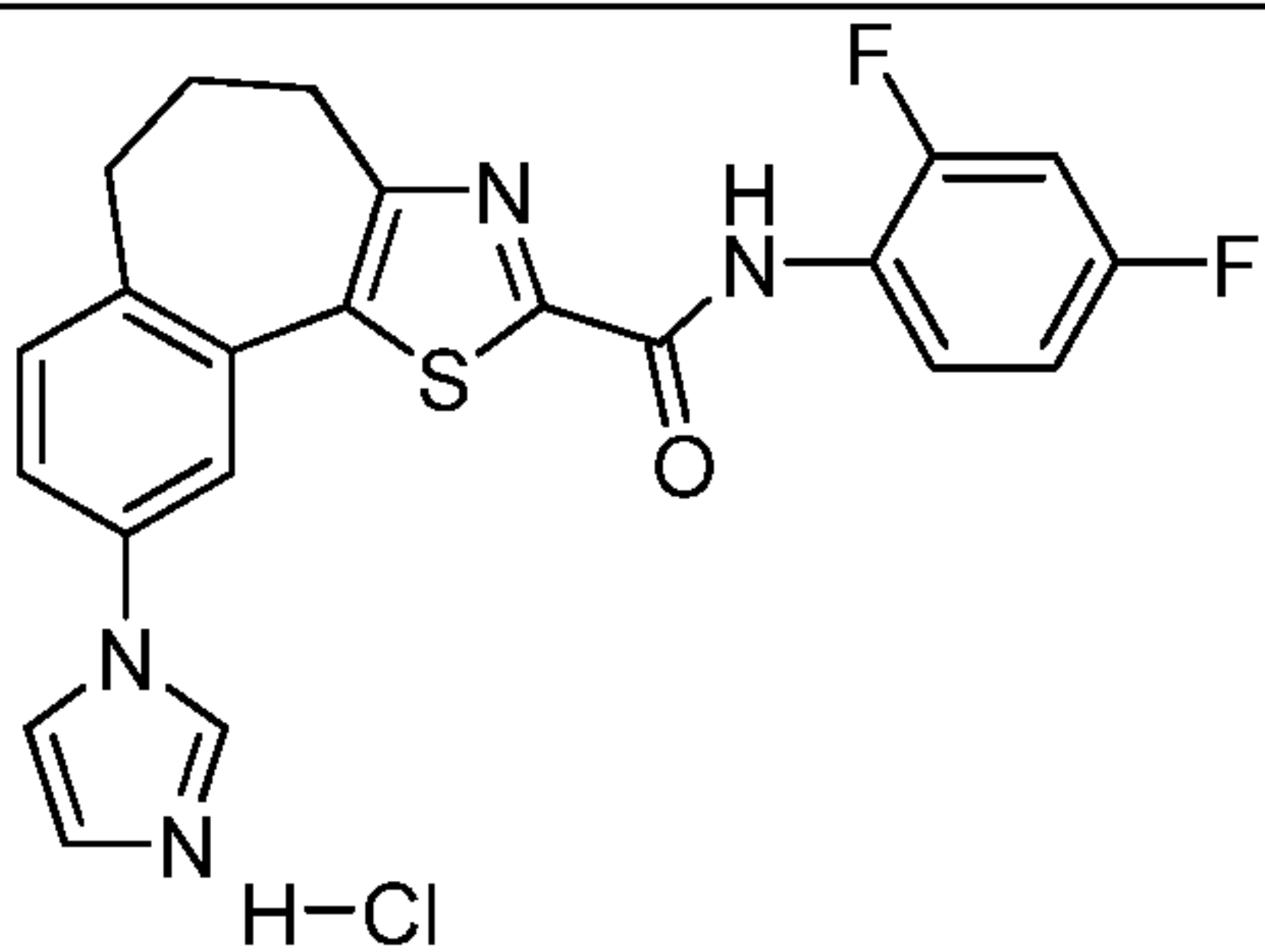
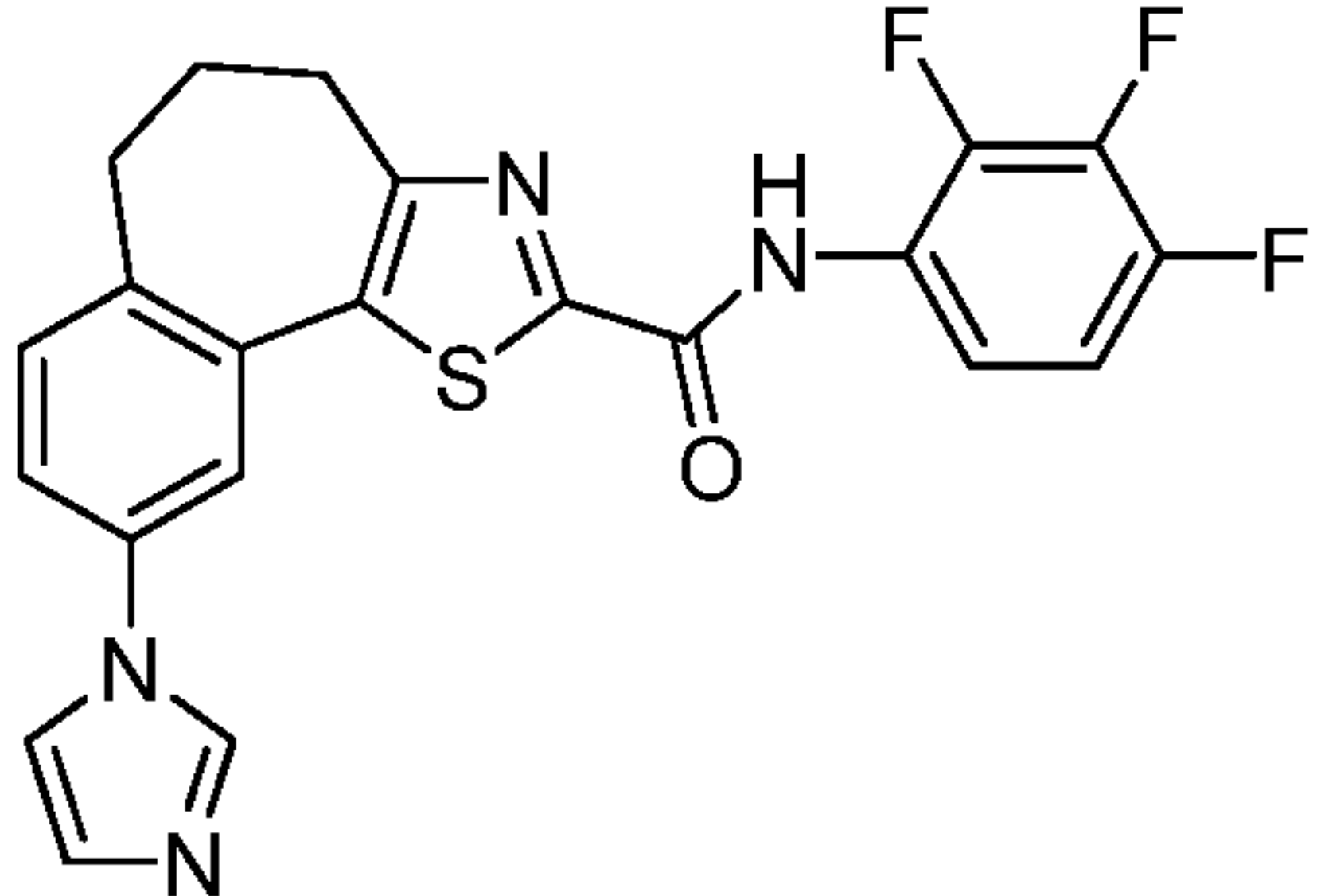
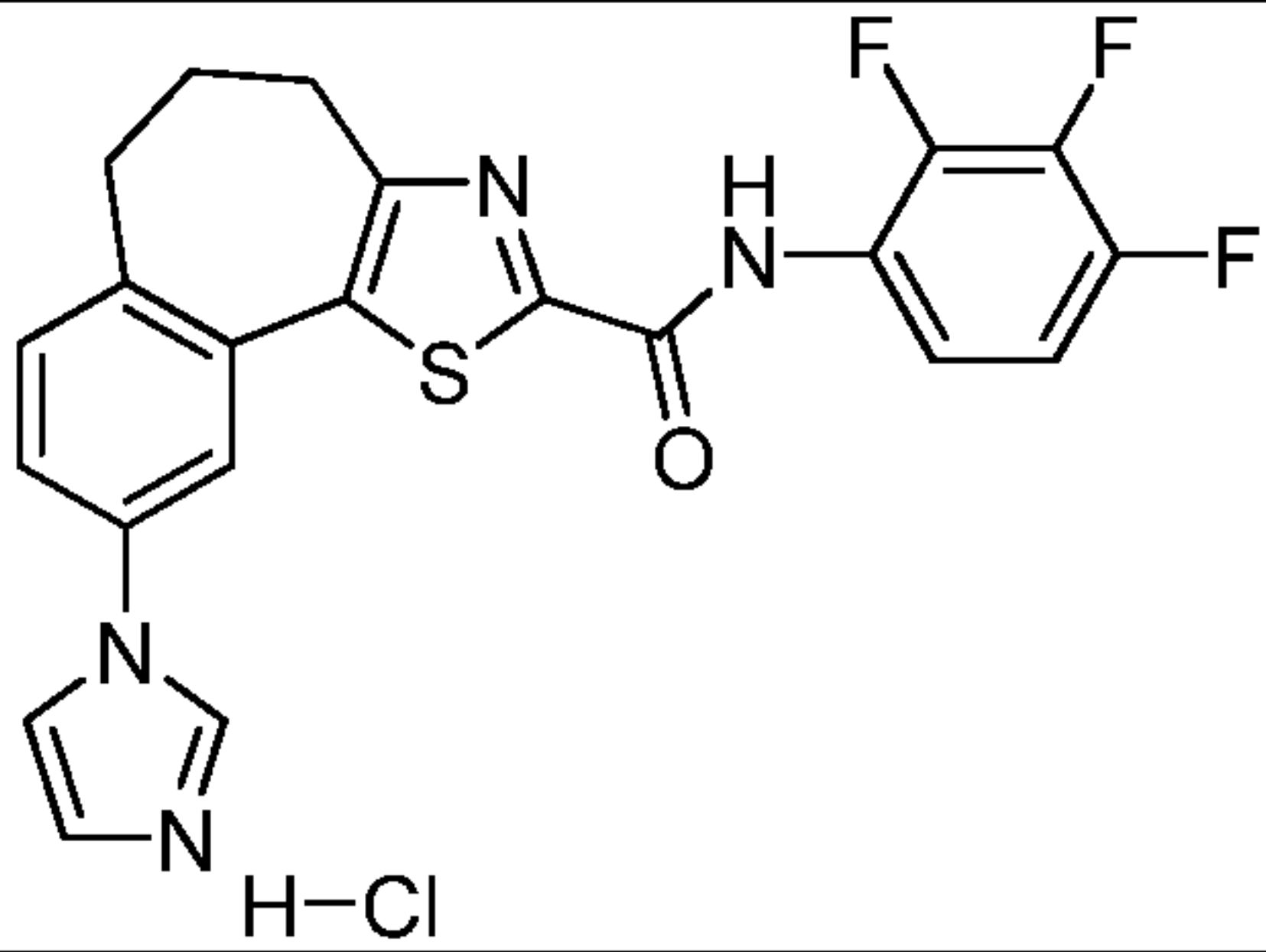
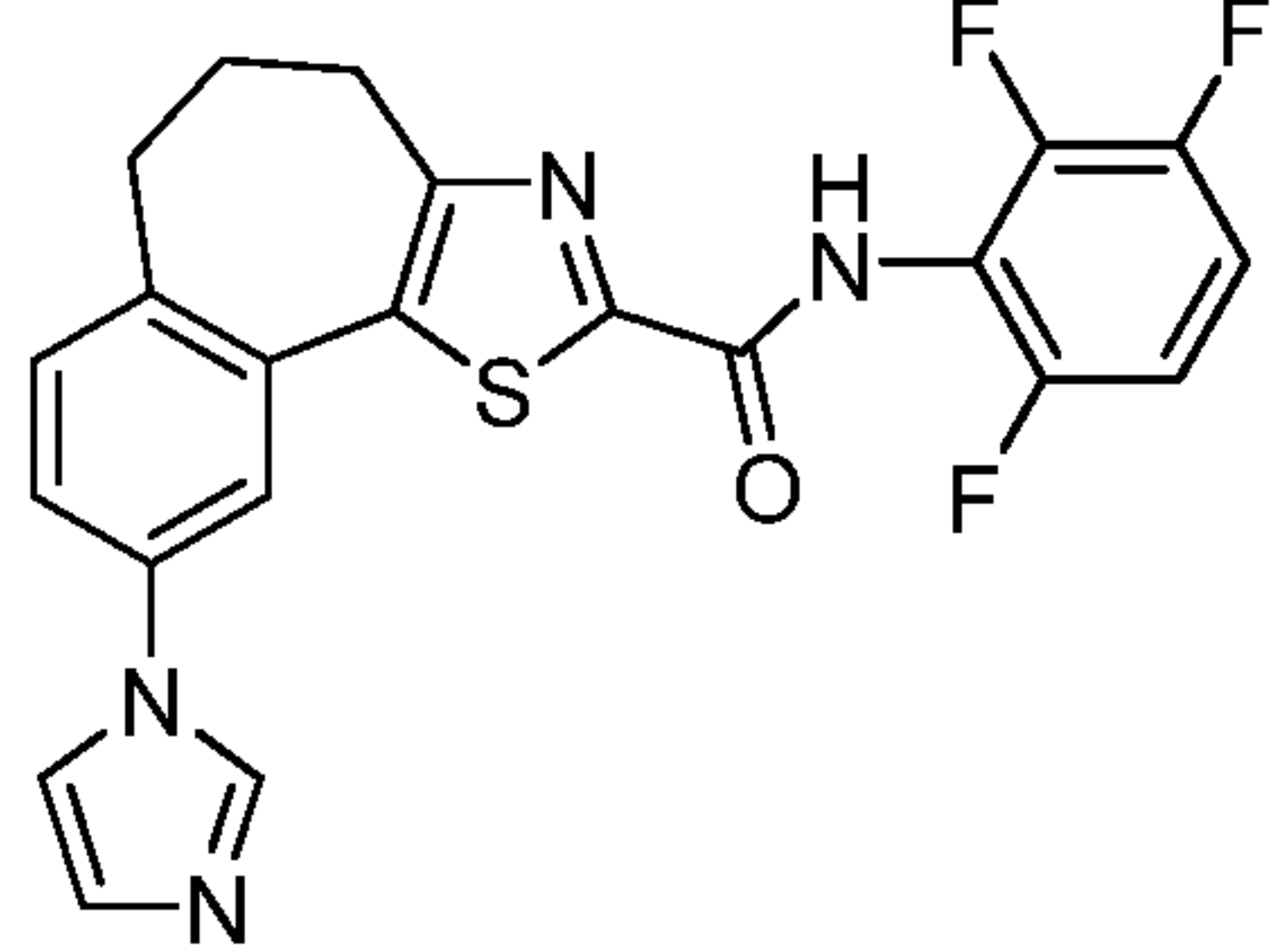
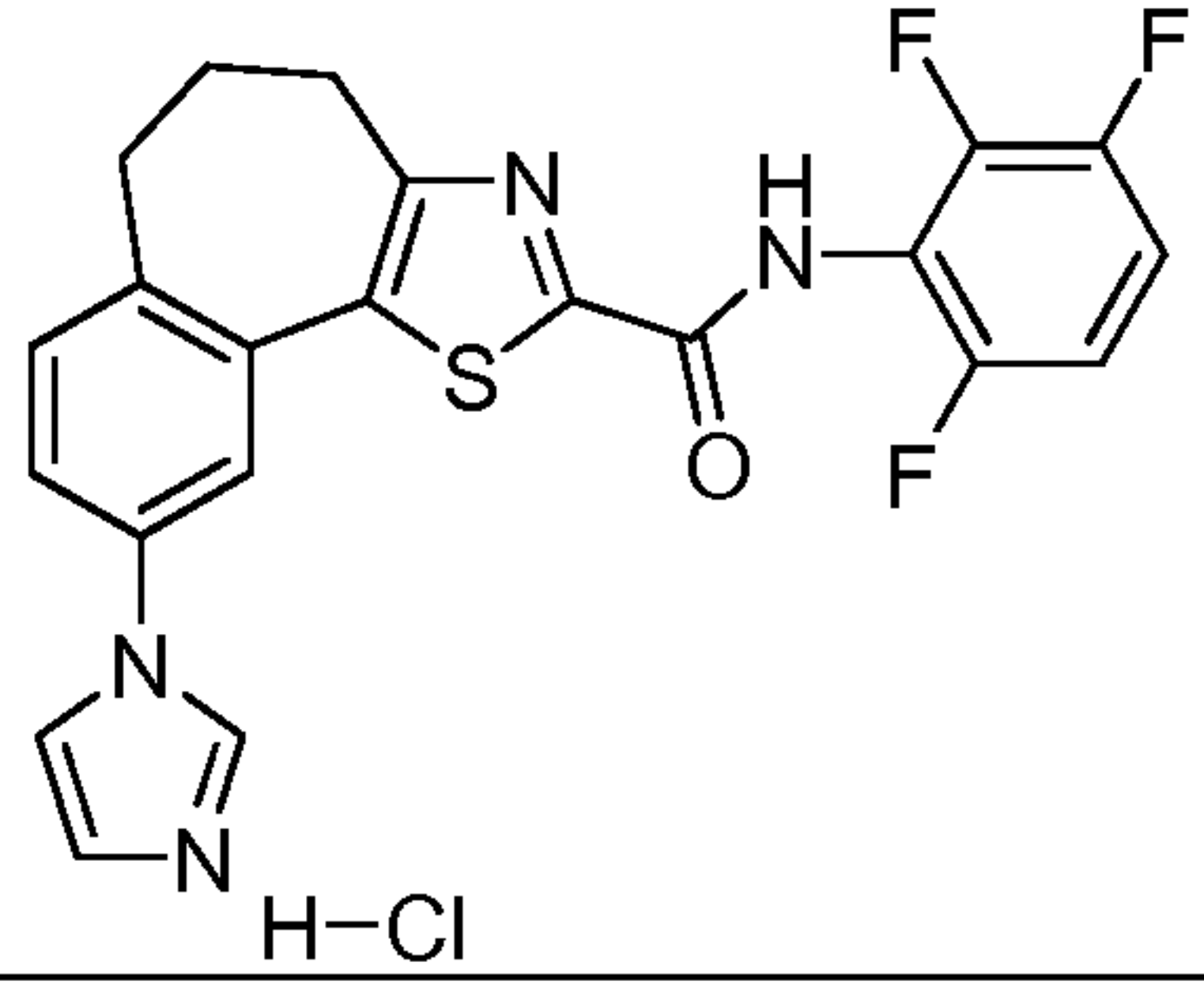
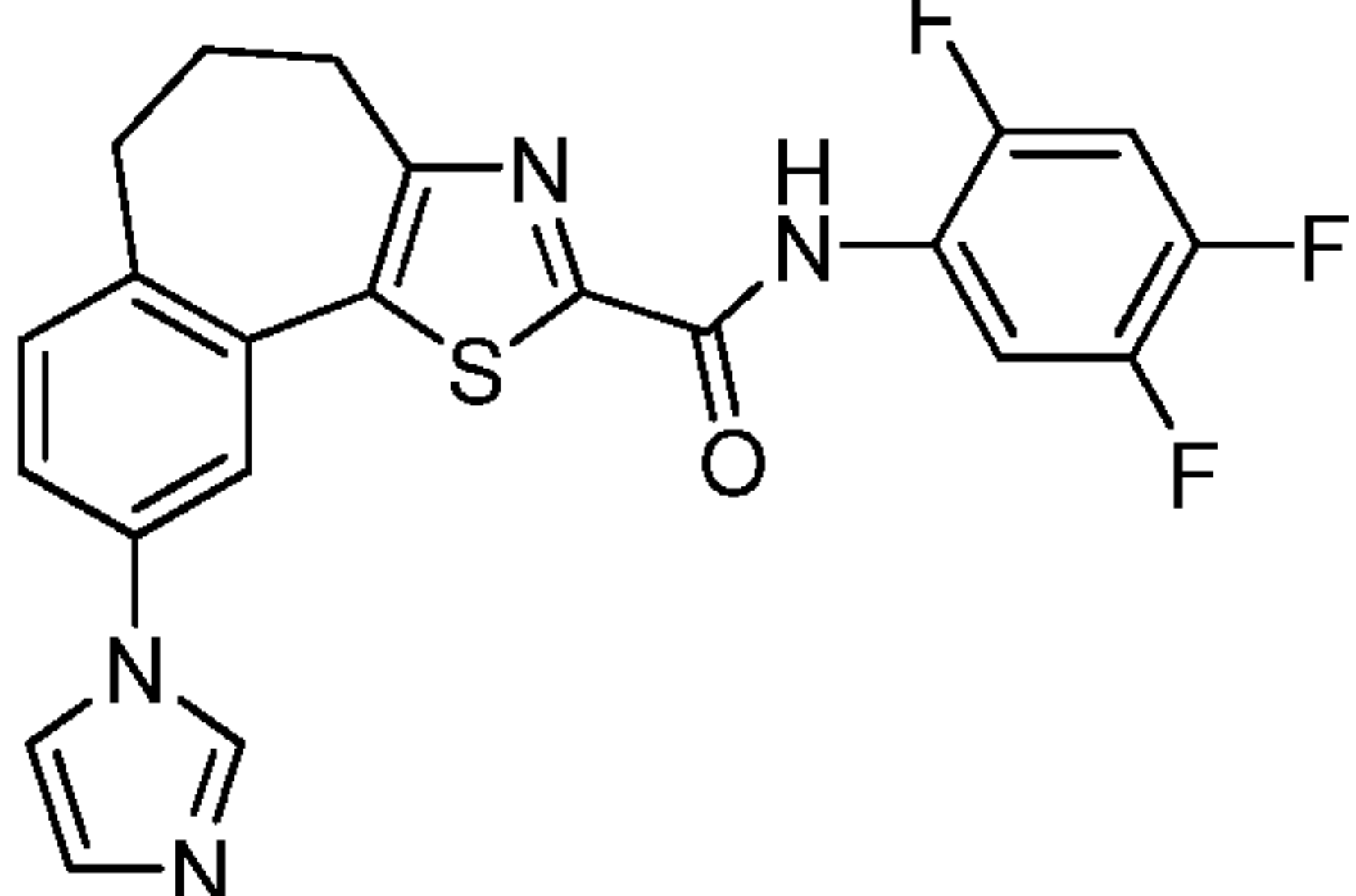
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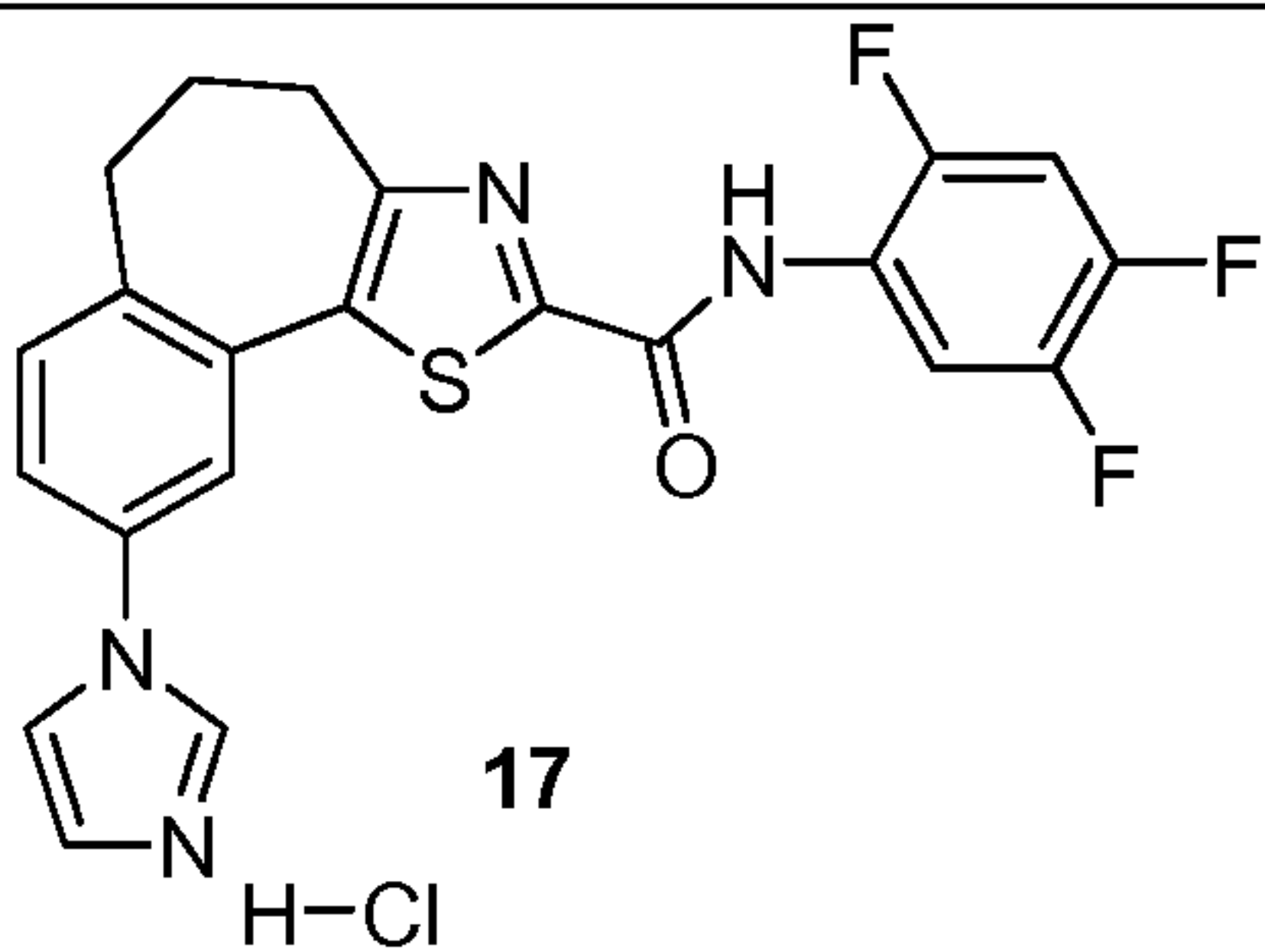
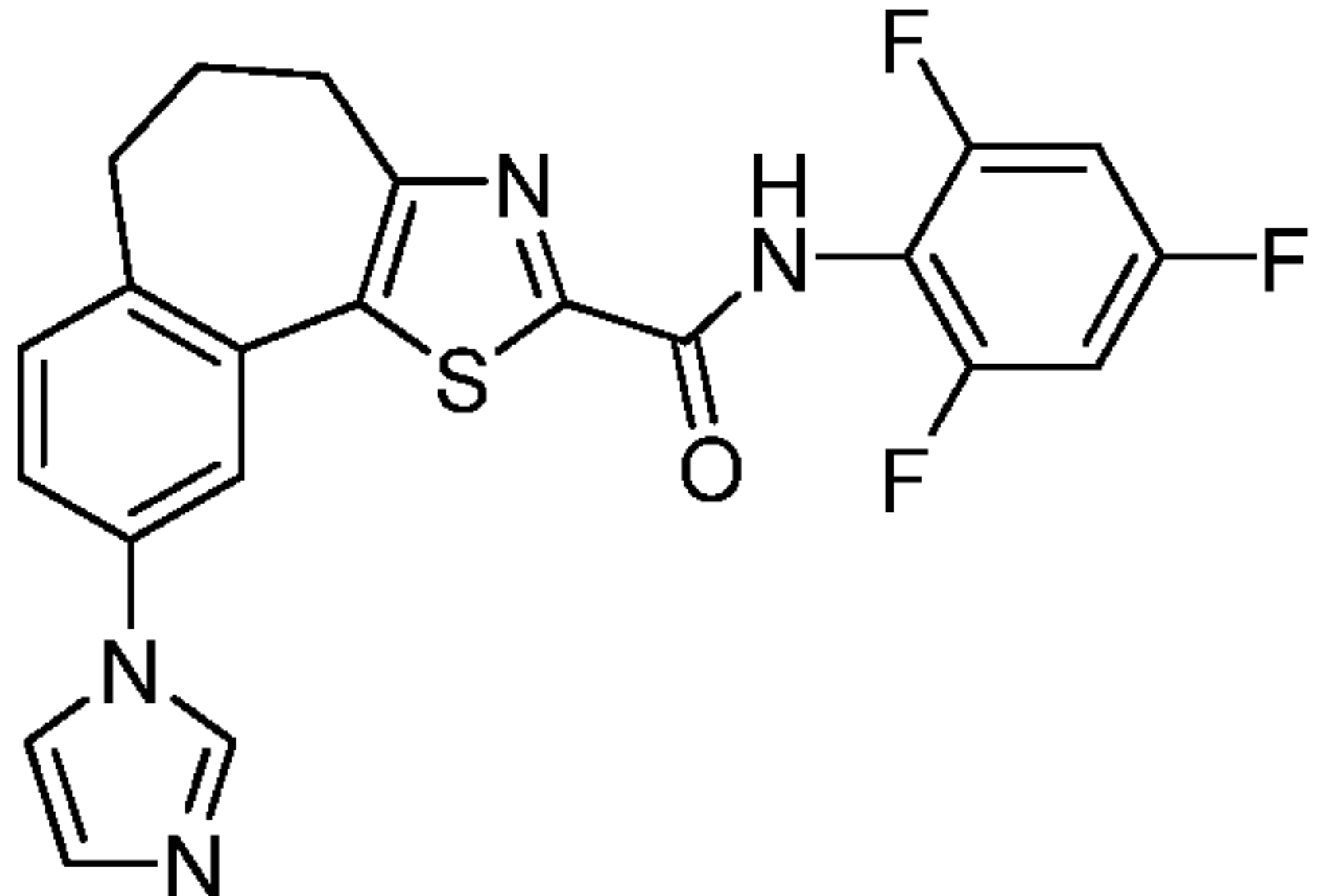
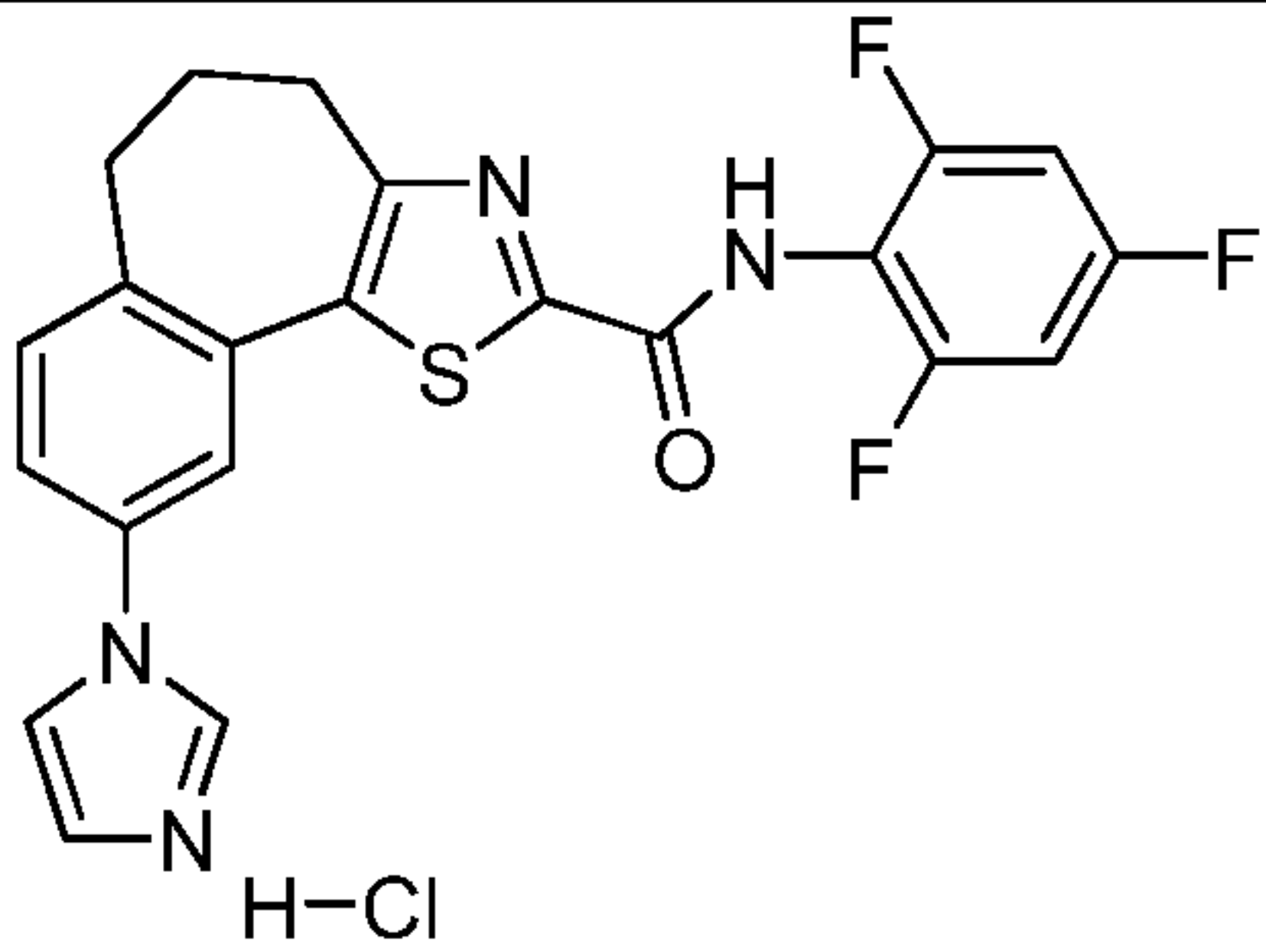
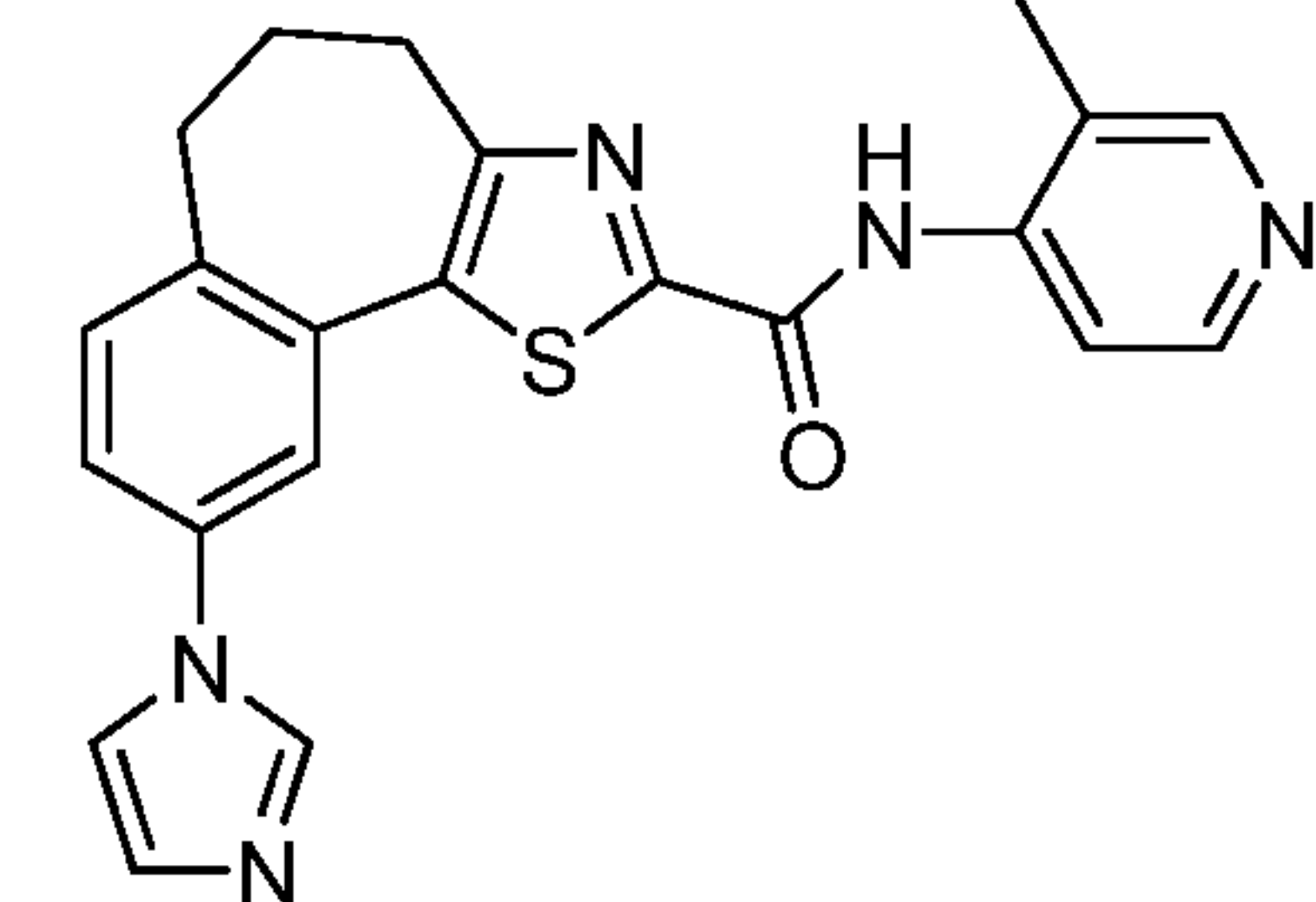
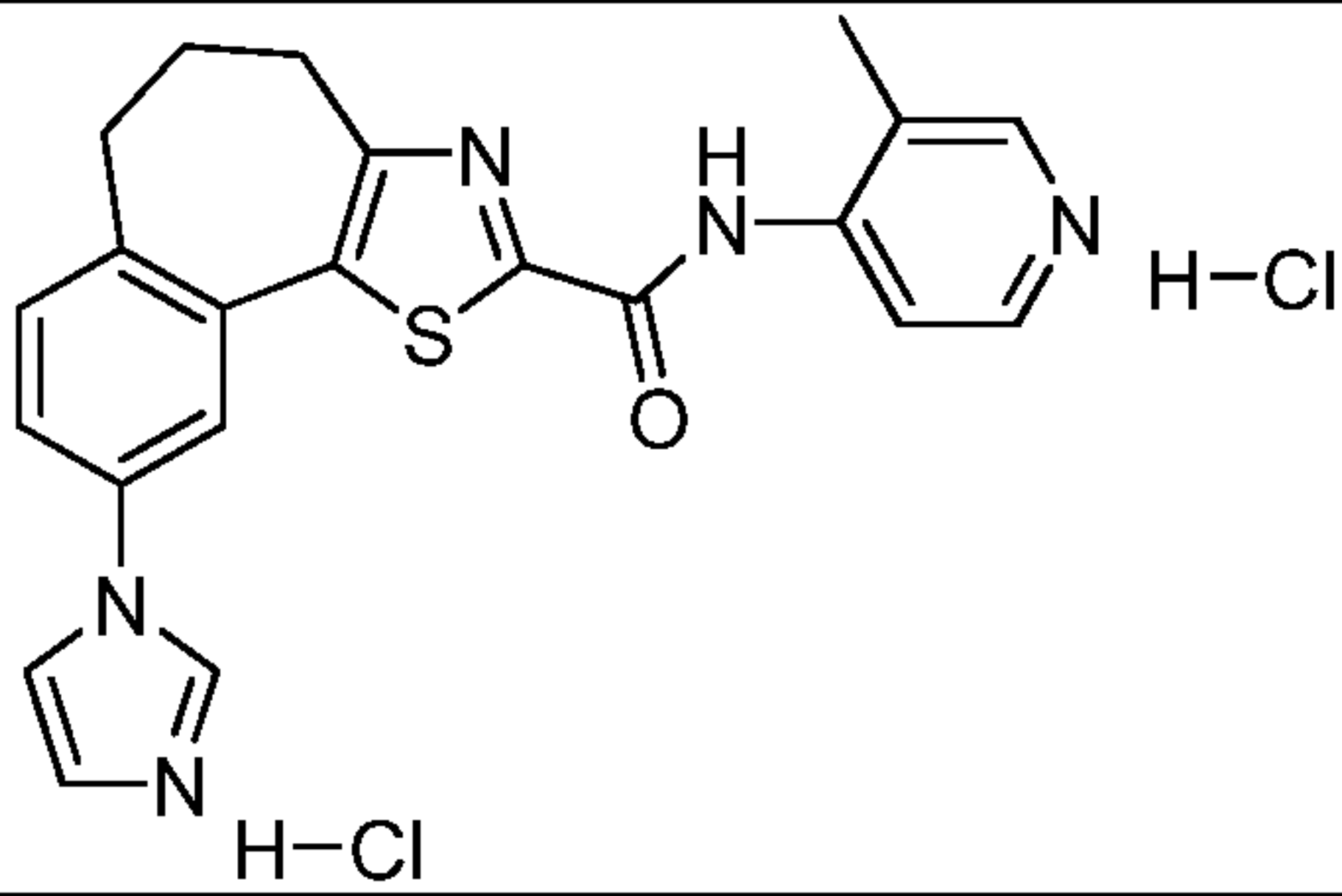
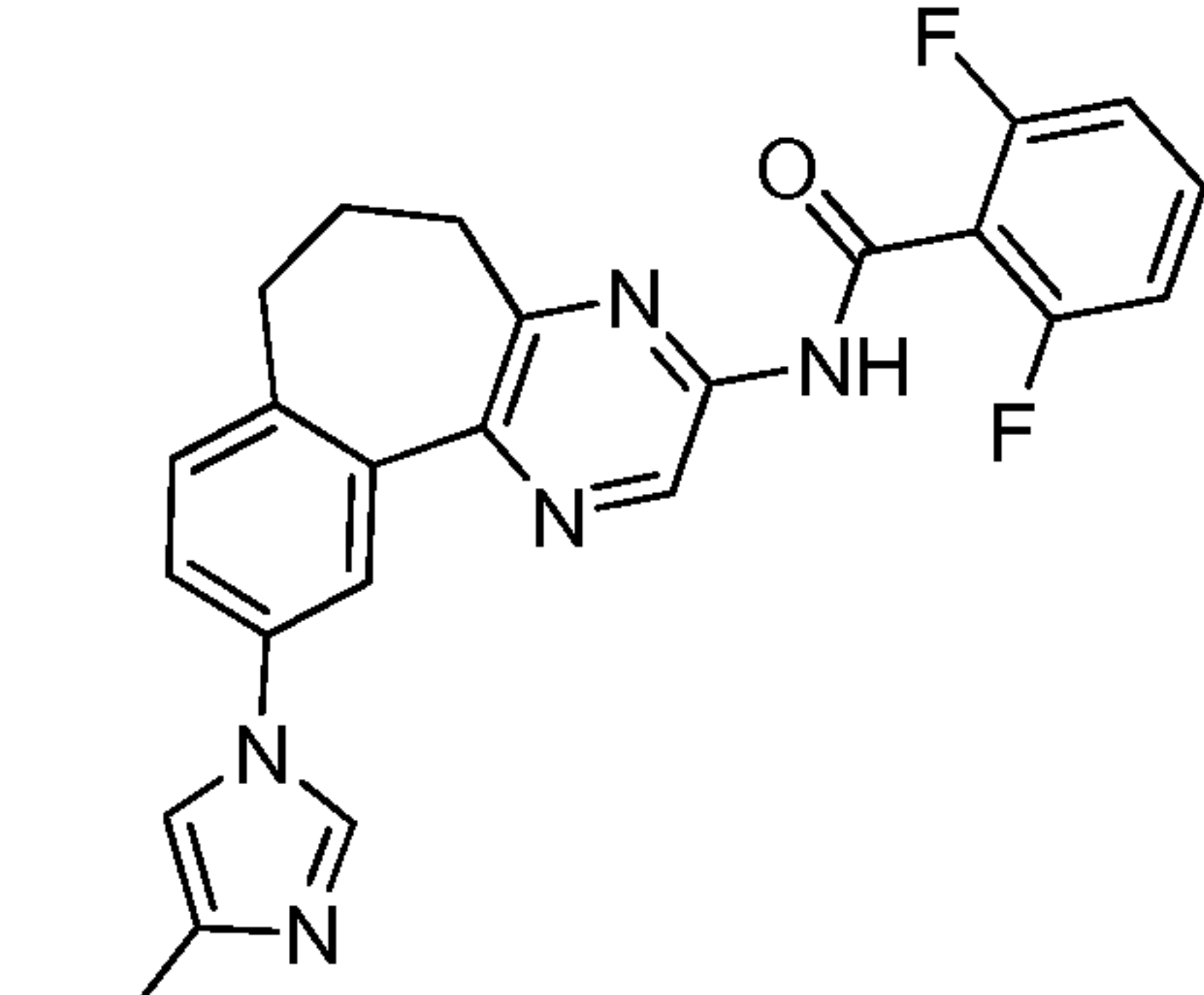
Additional exemplary compounds of the invention are also depicted in Table 3 below.

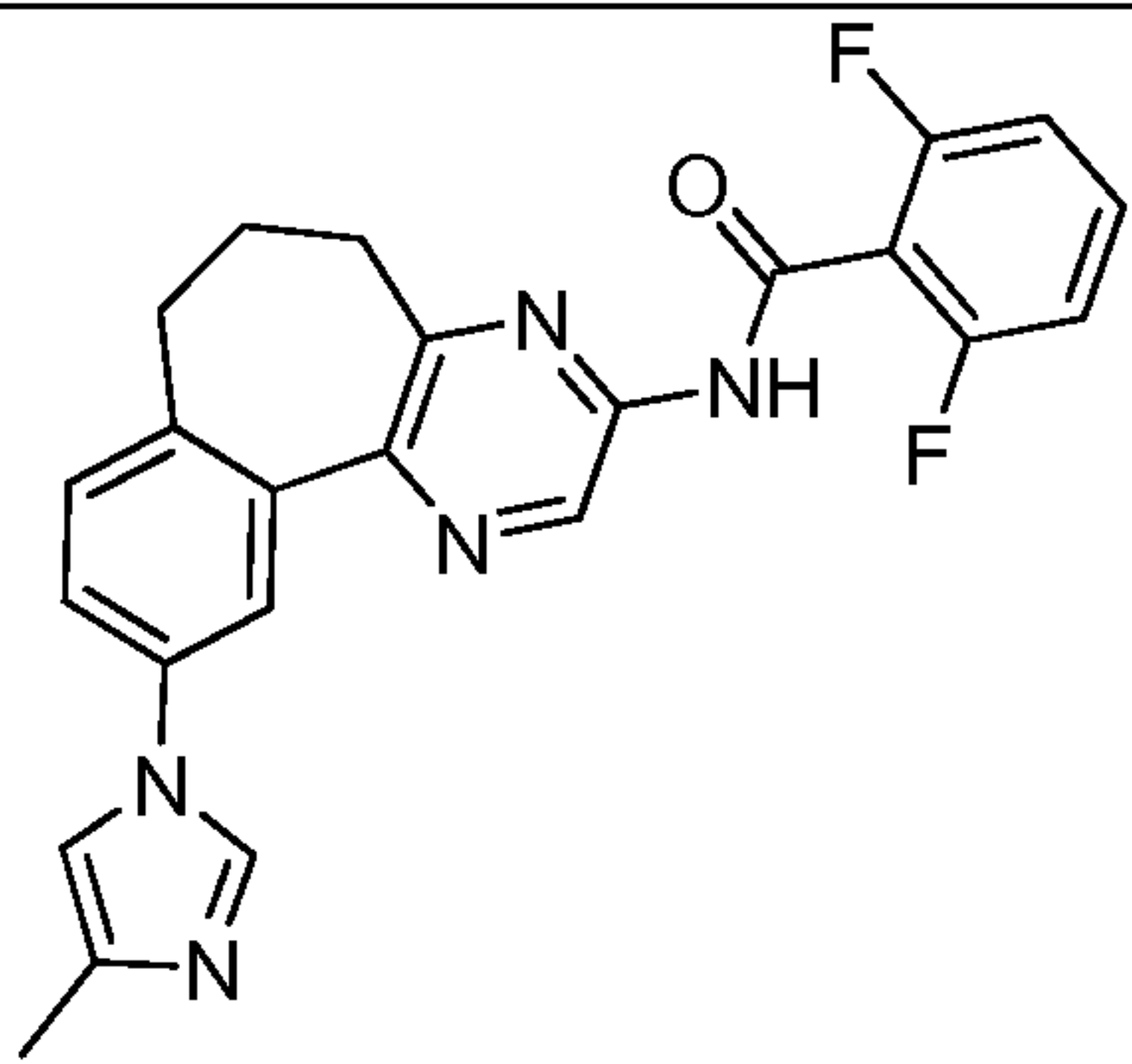
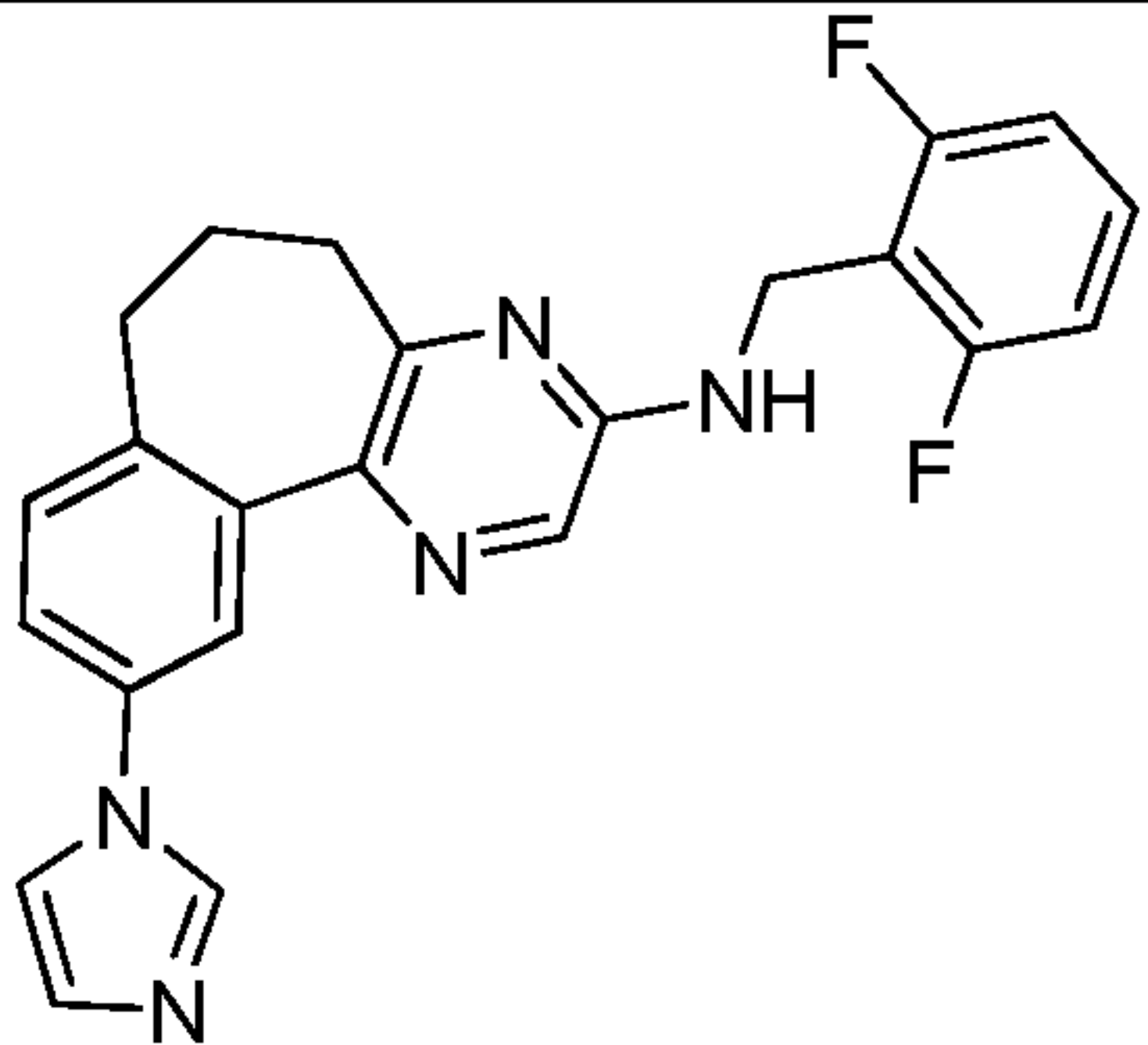
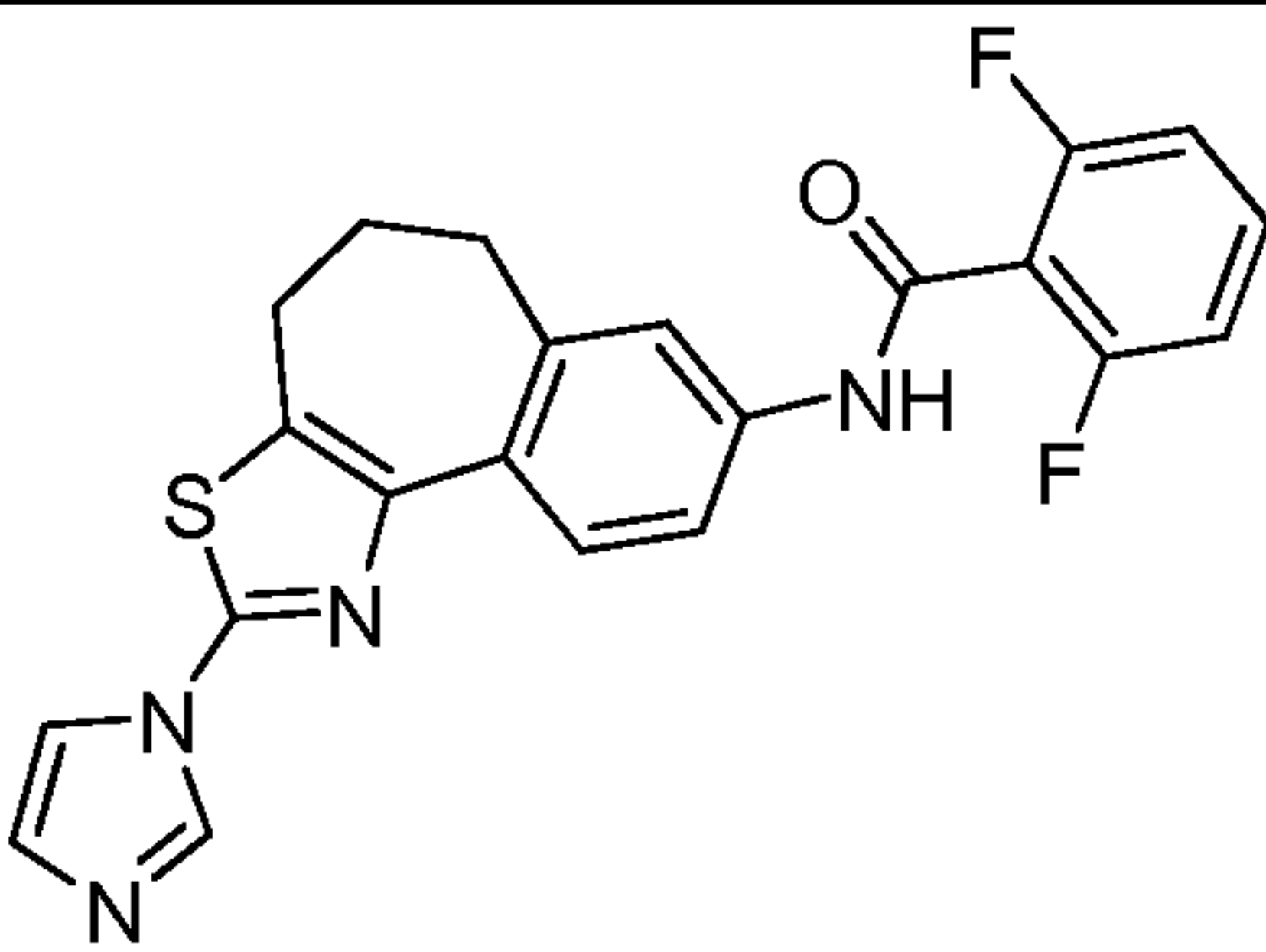
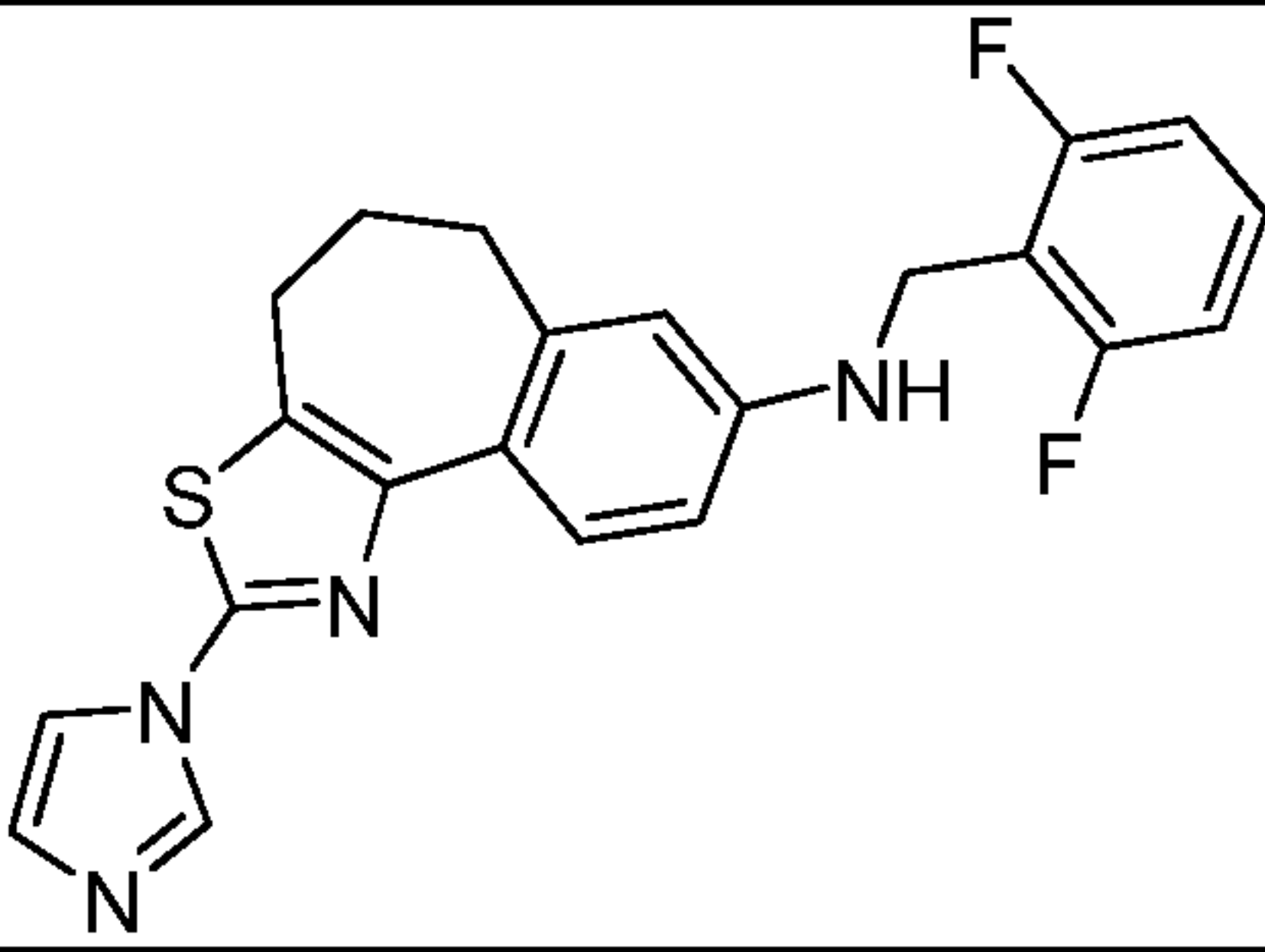
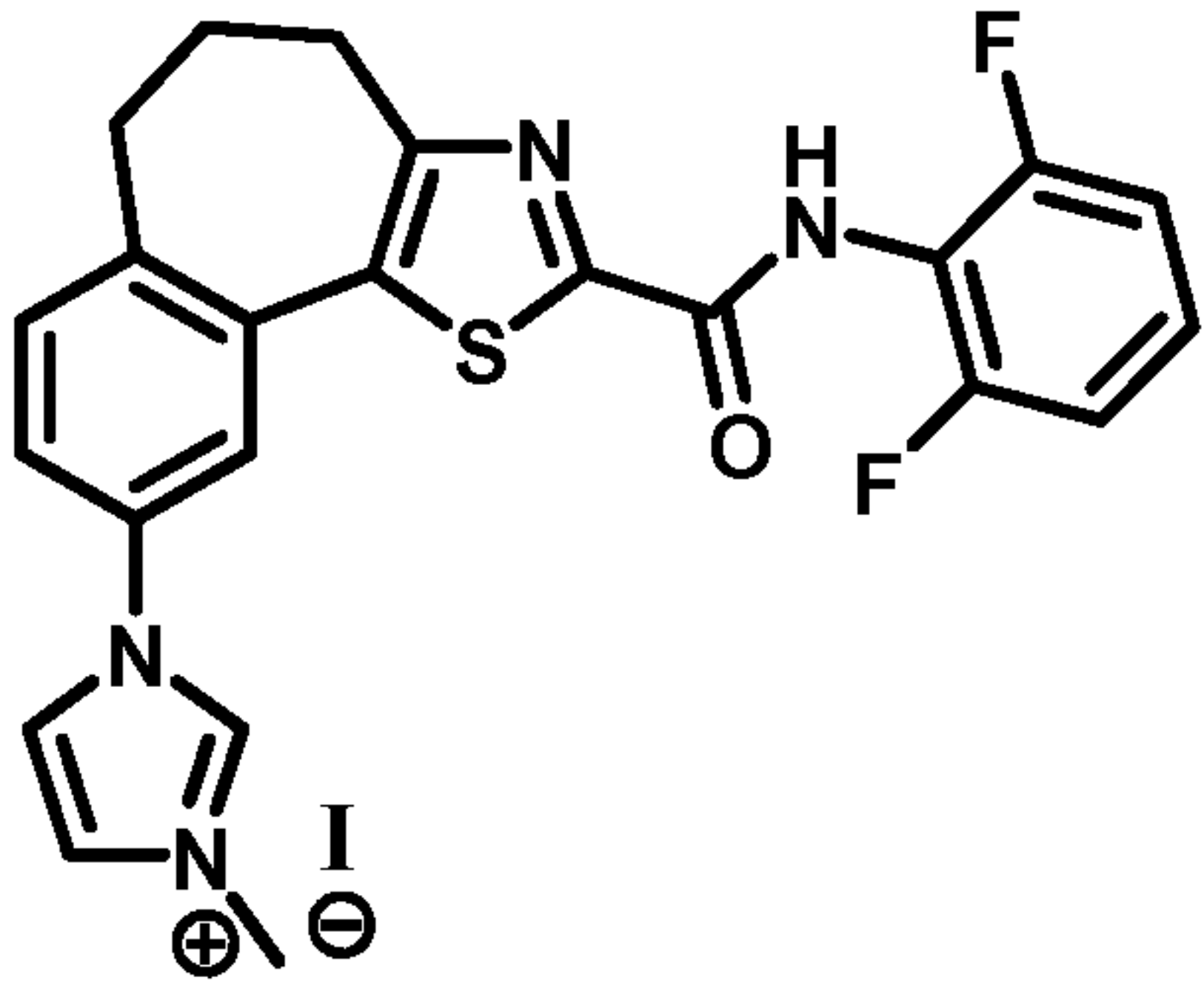
Table 3

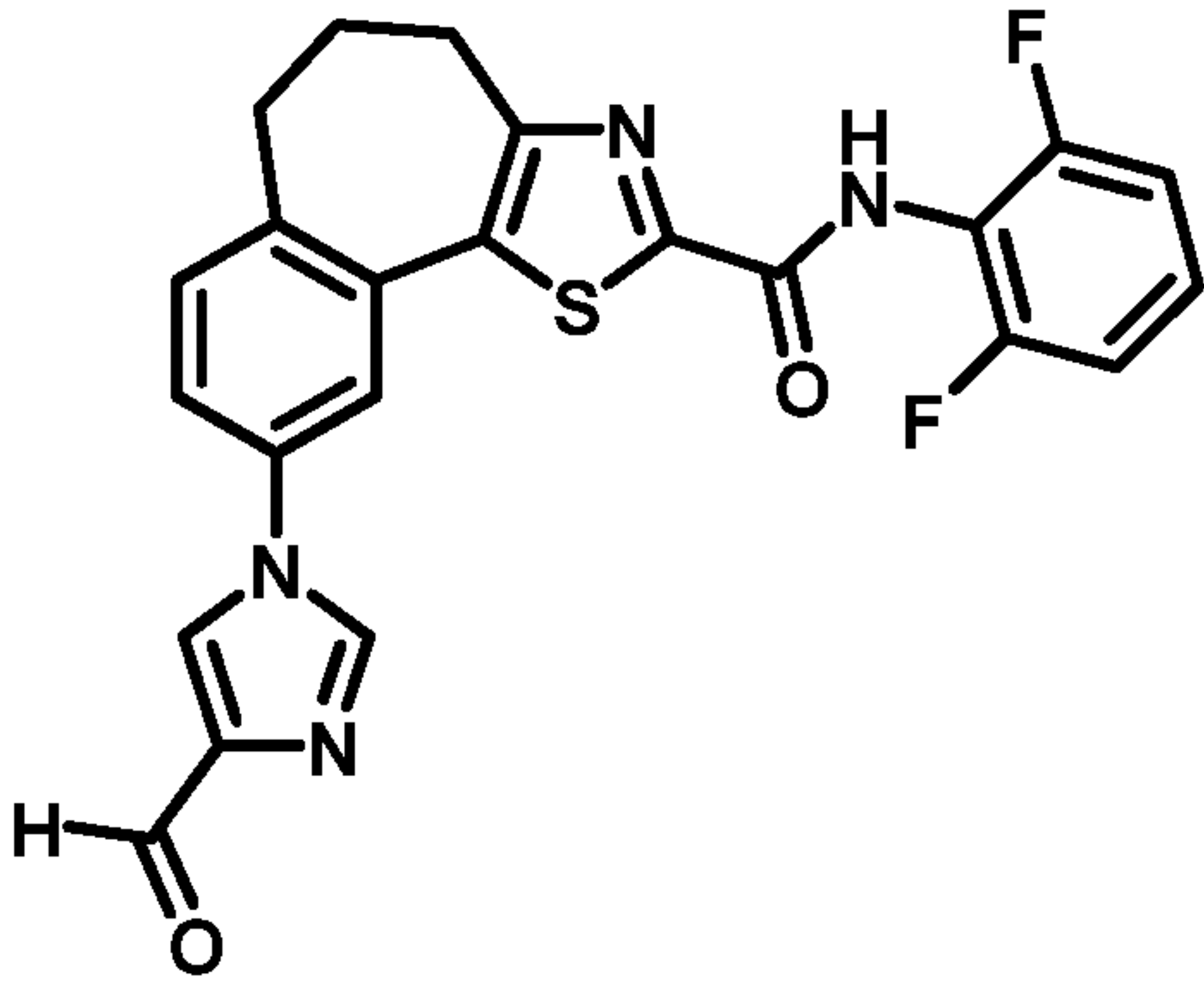
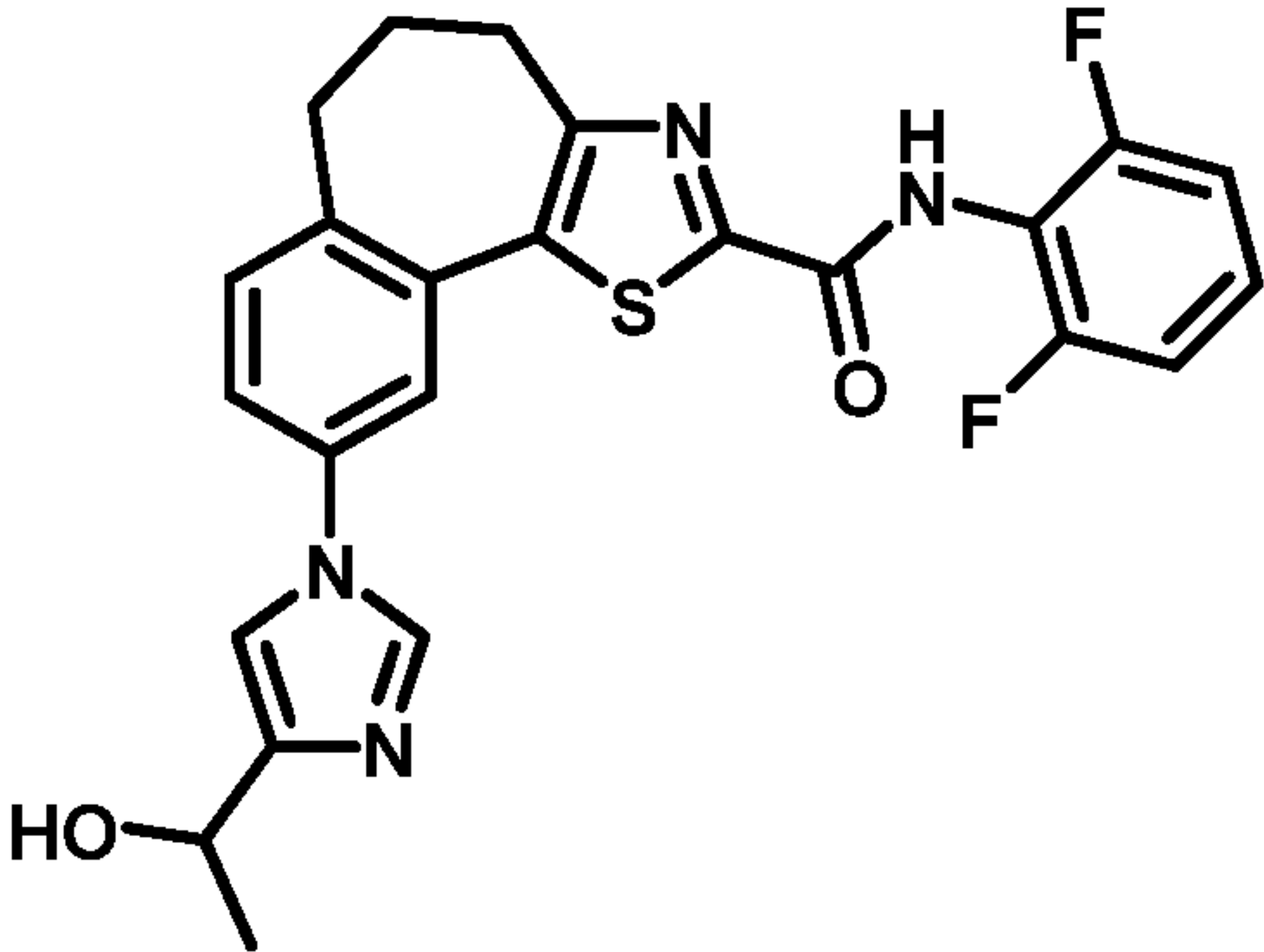
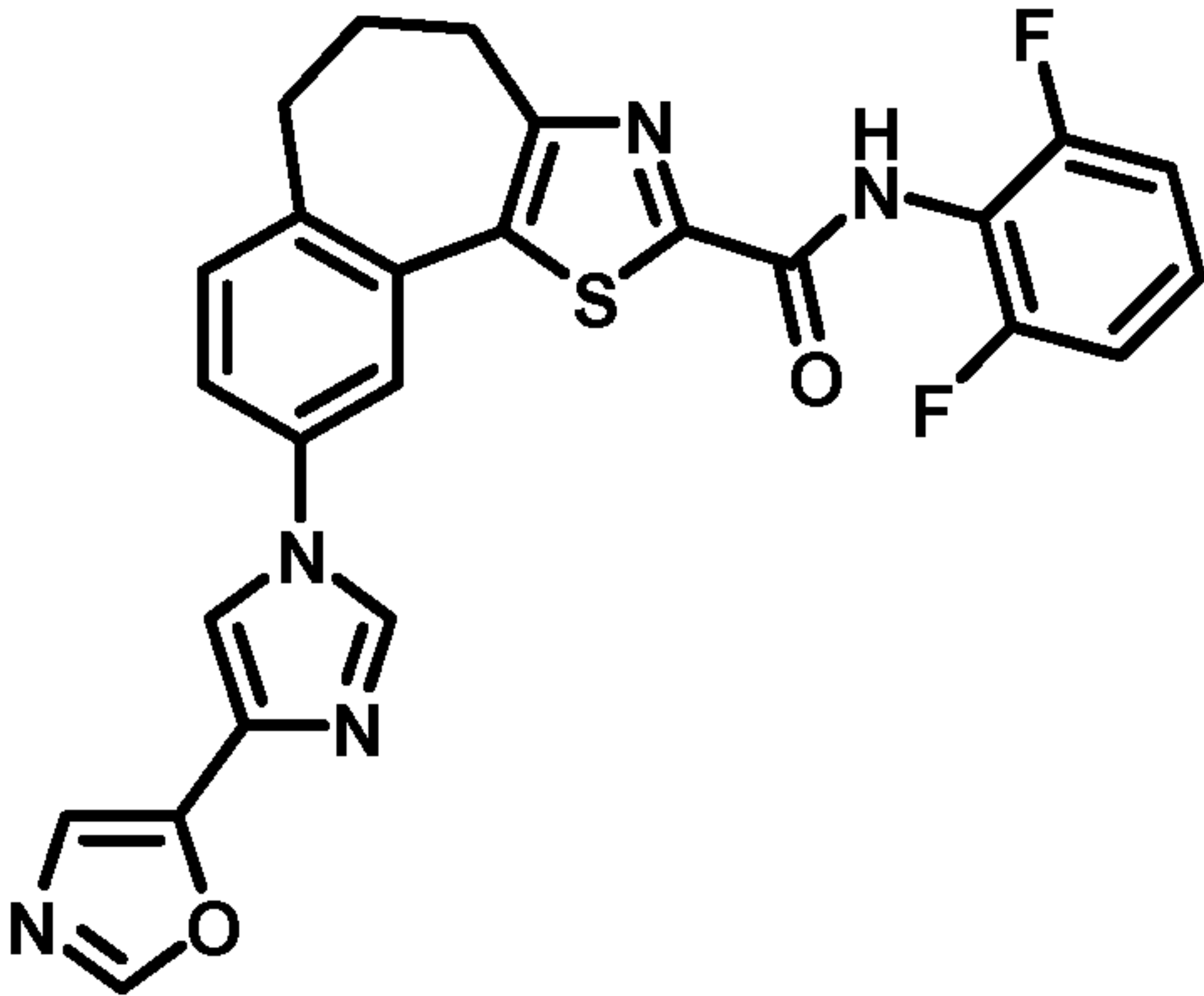
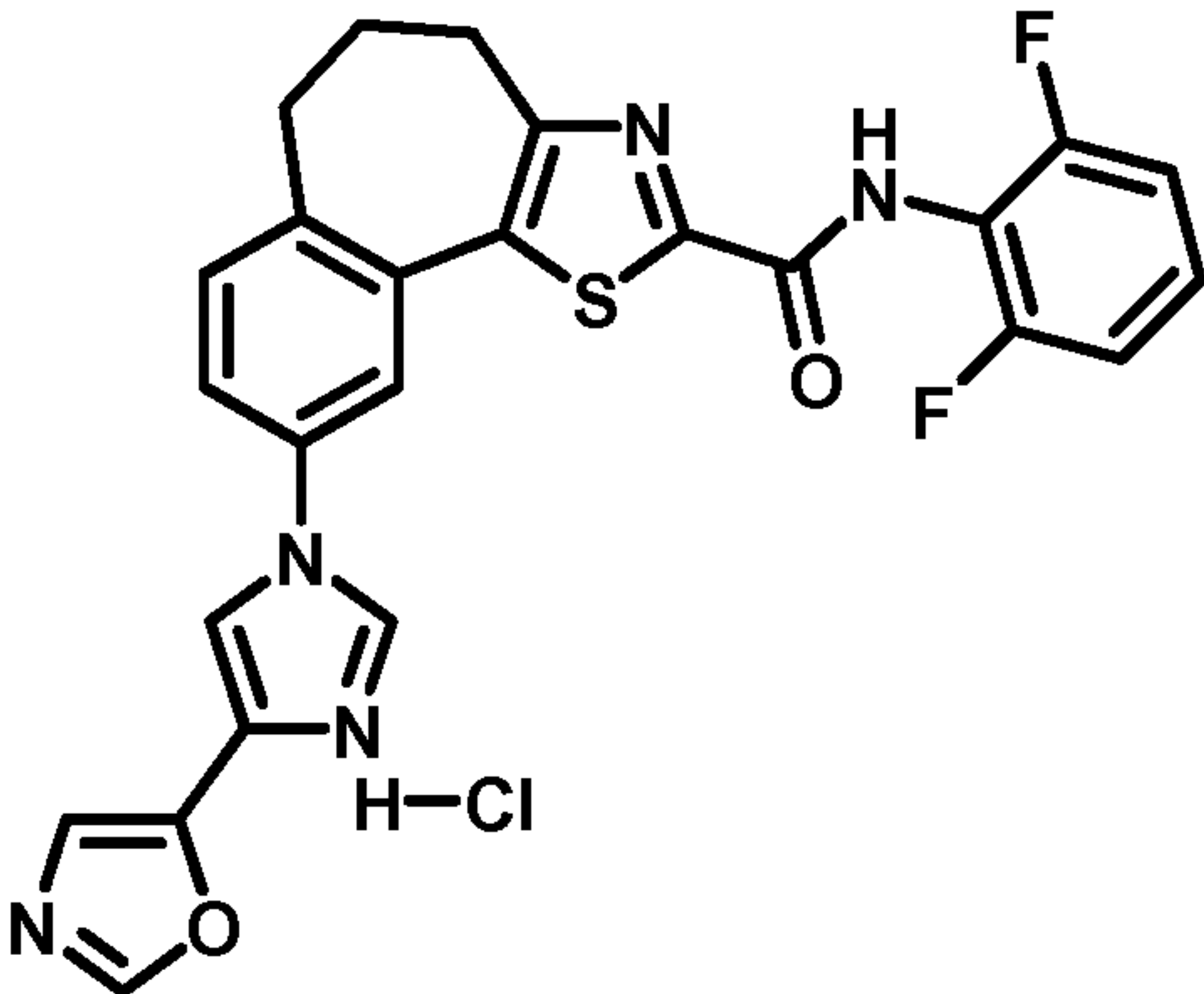
- 100 -

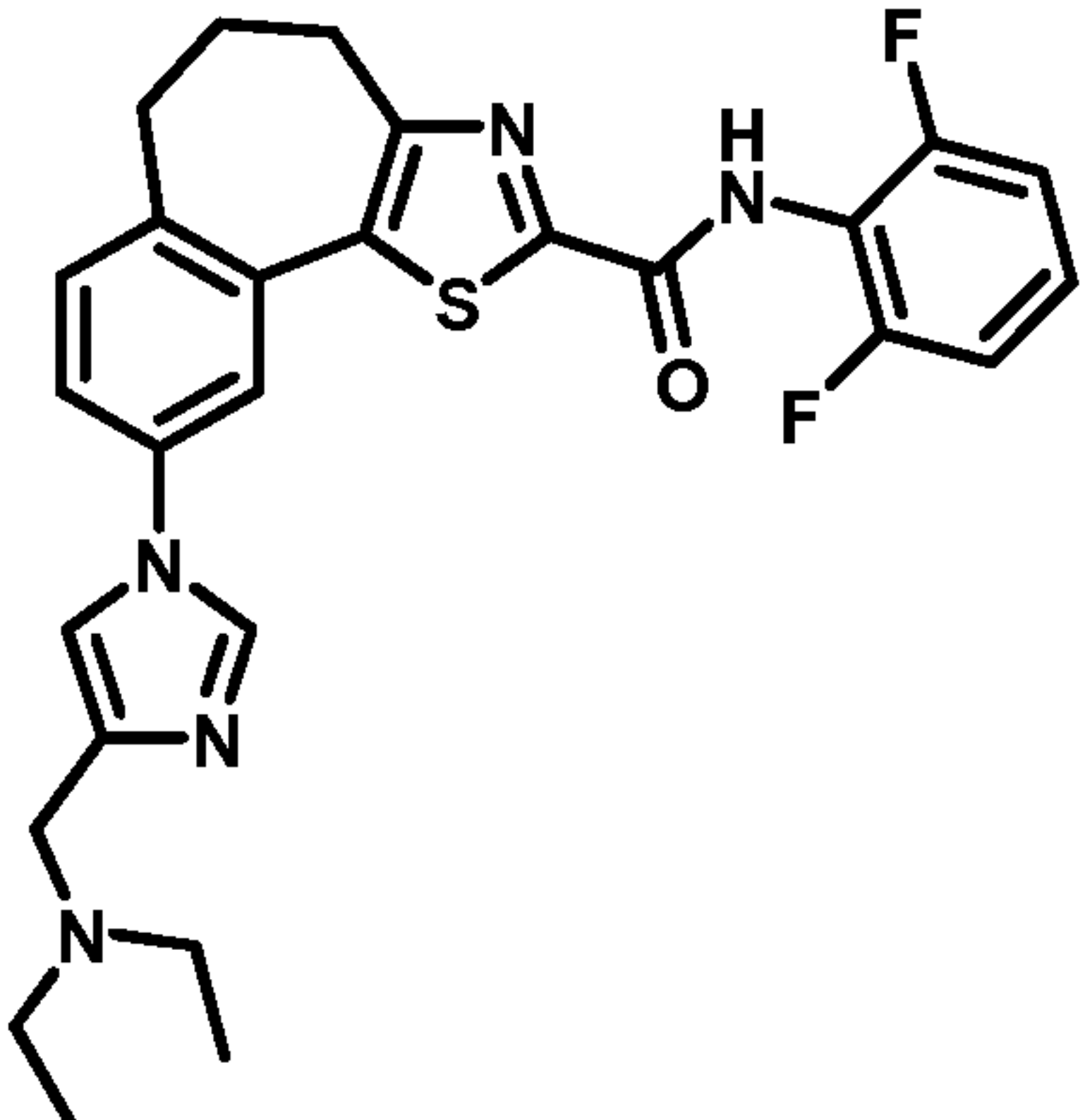
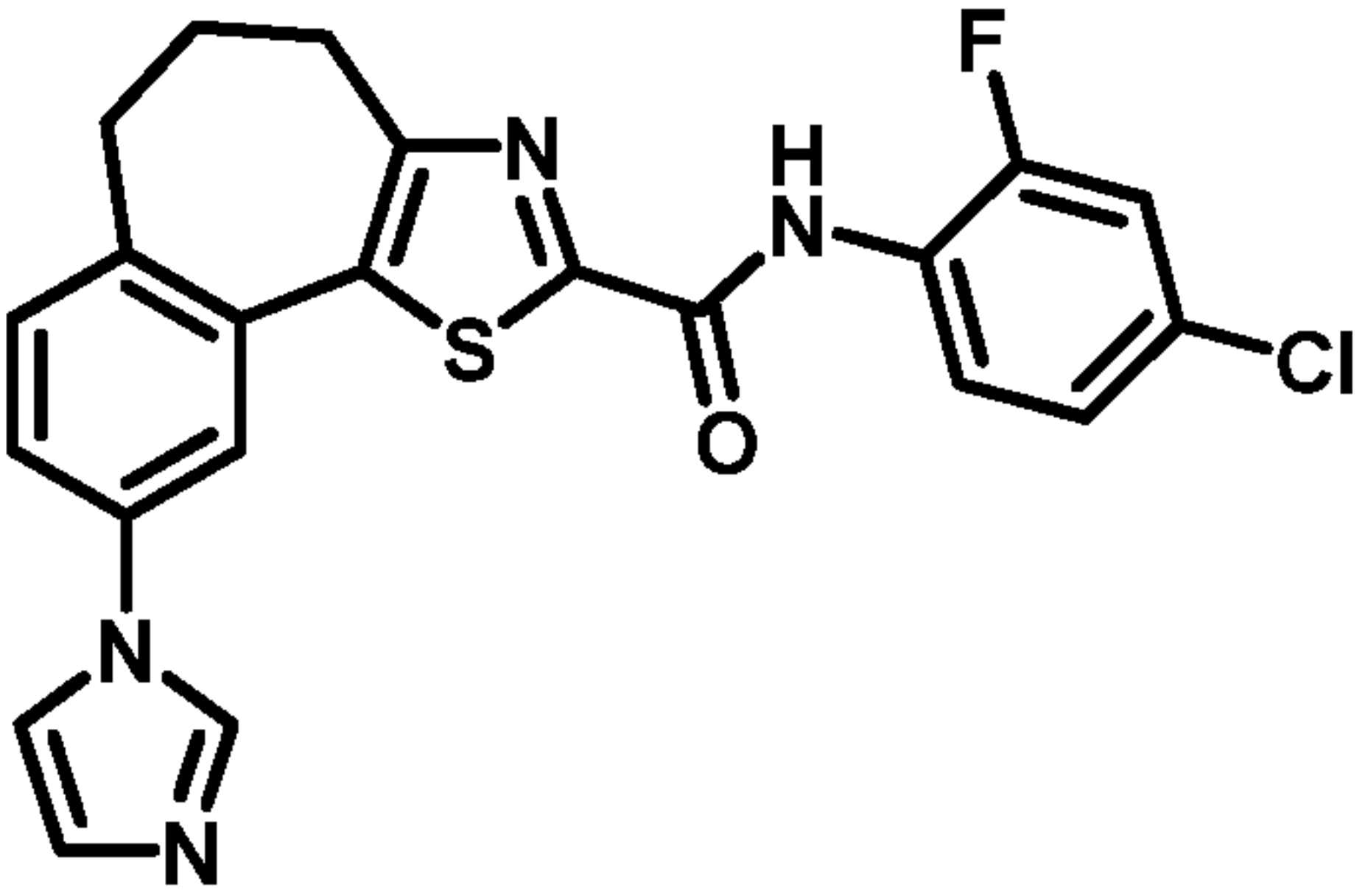
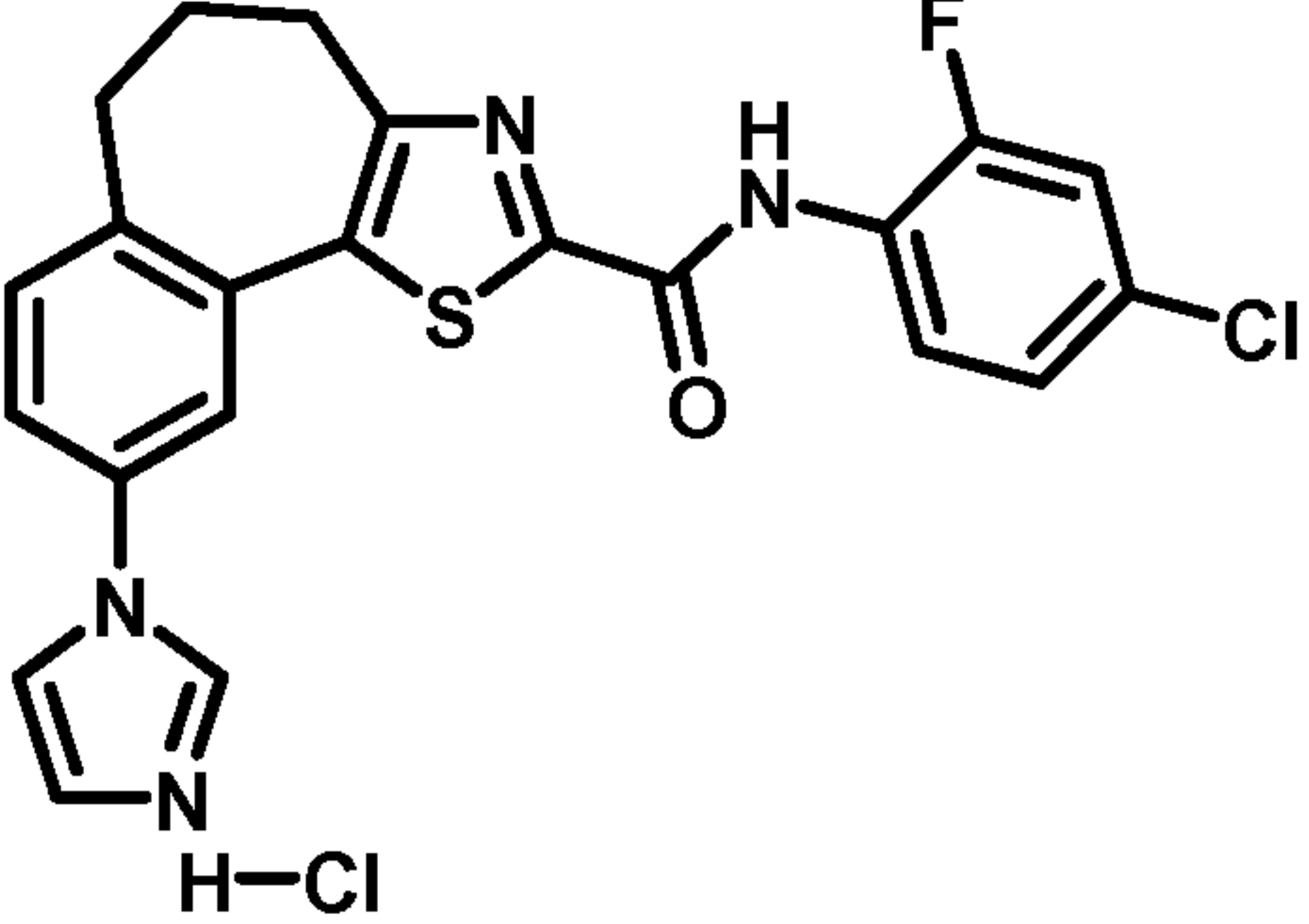
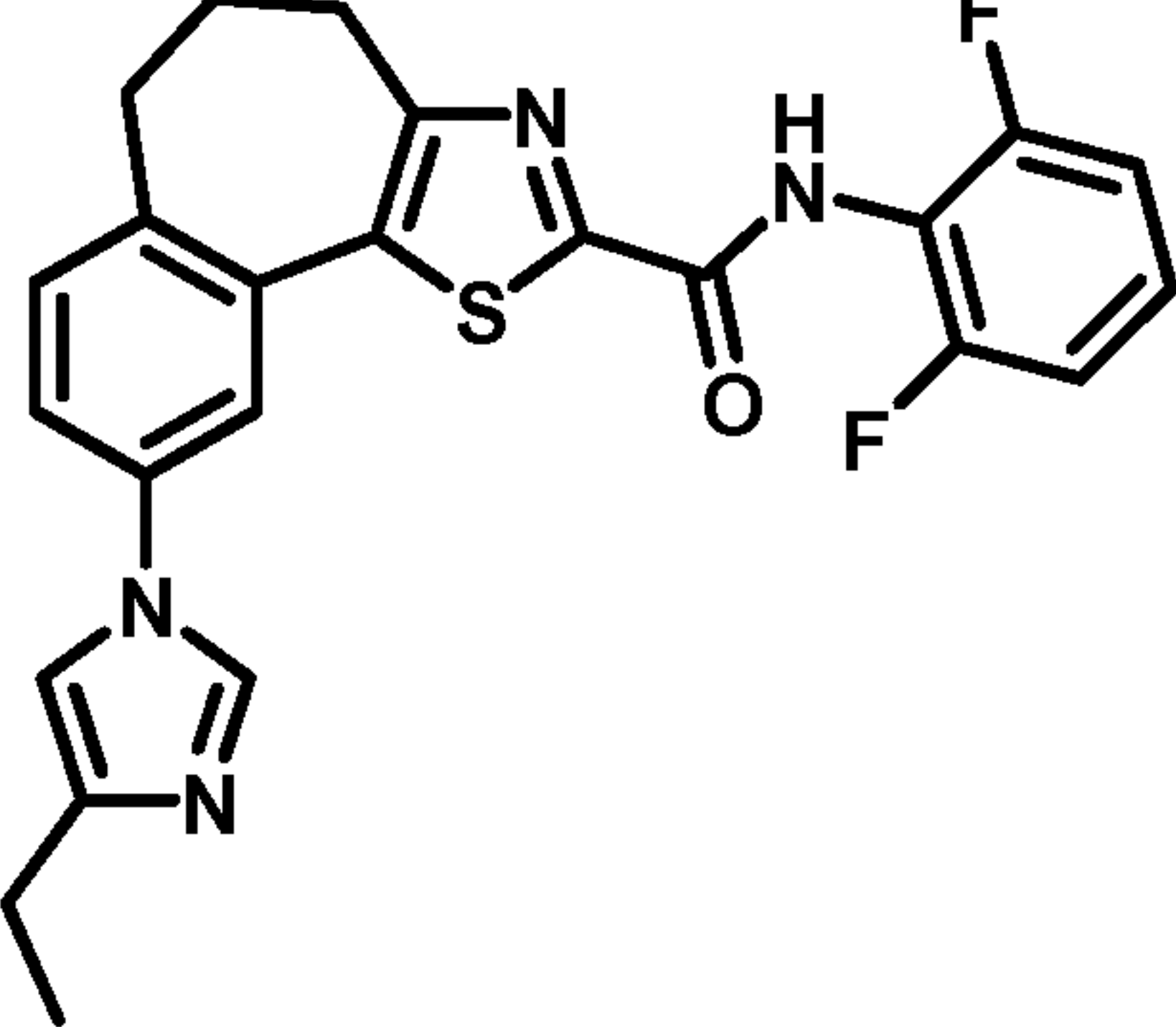
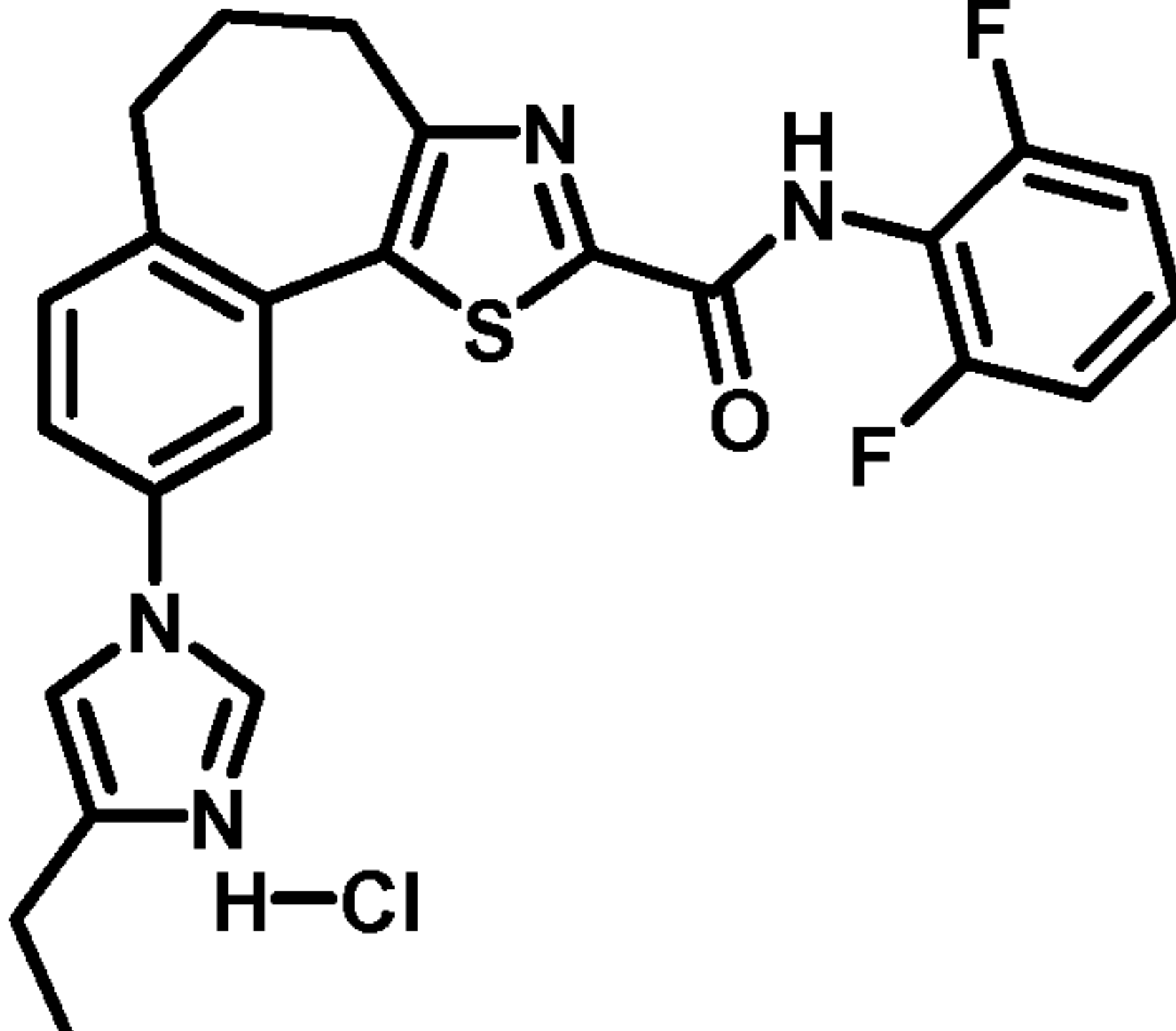
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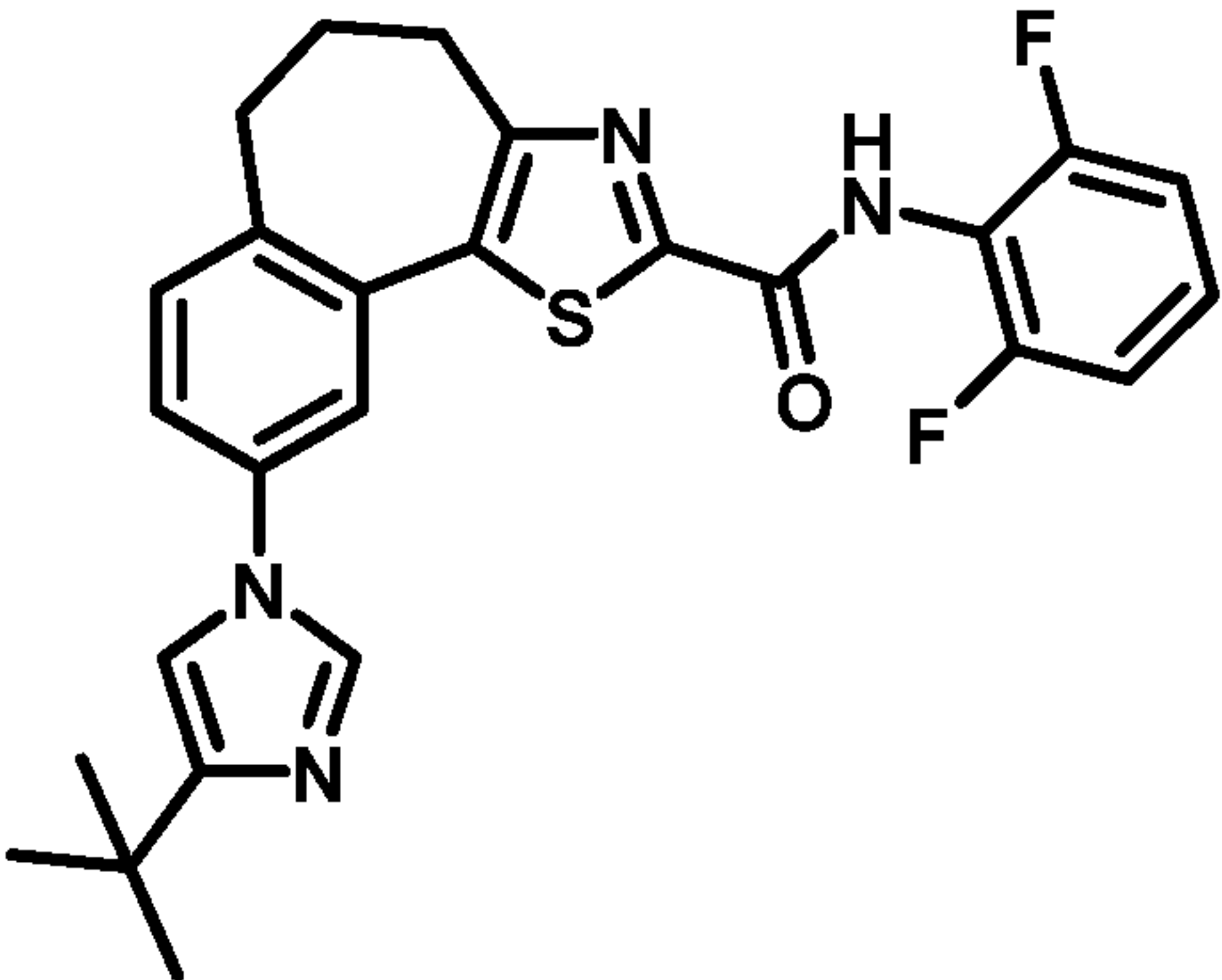
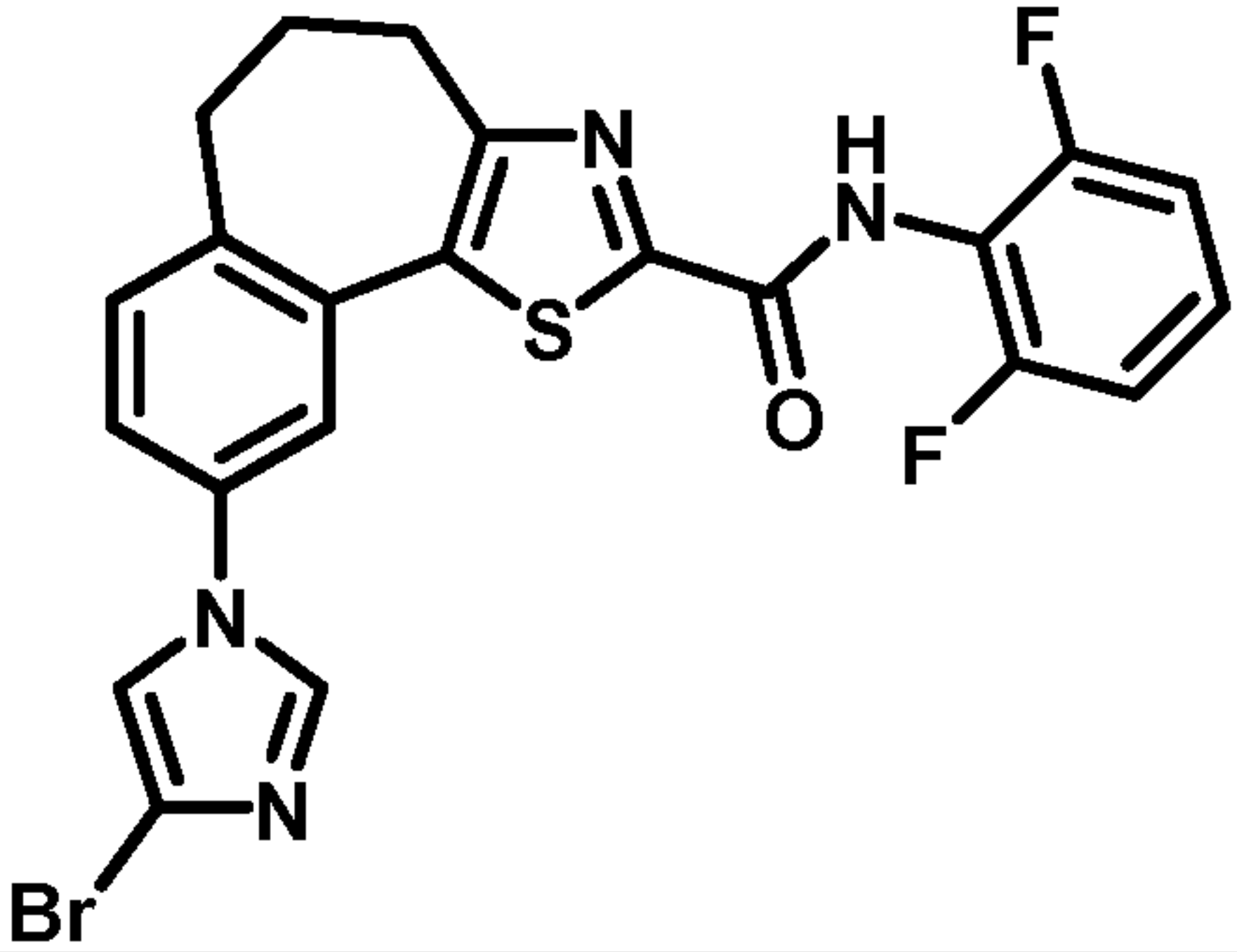
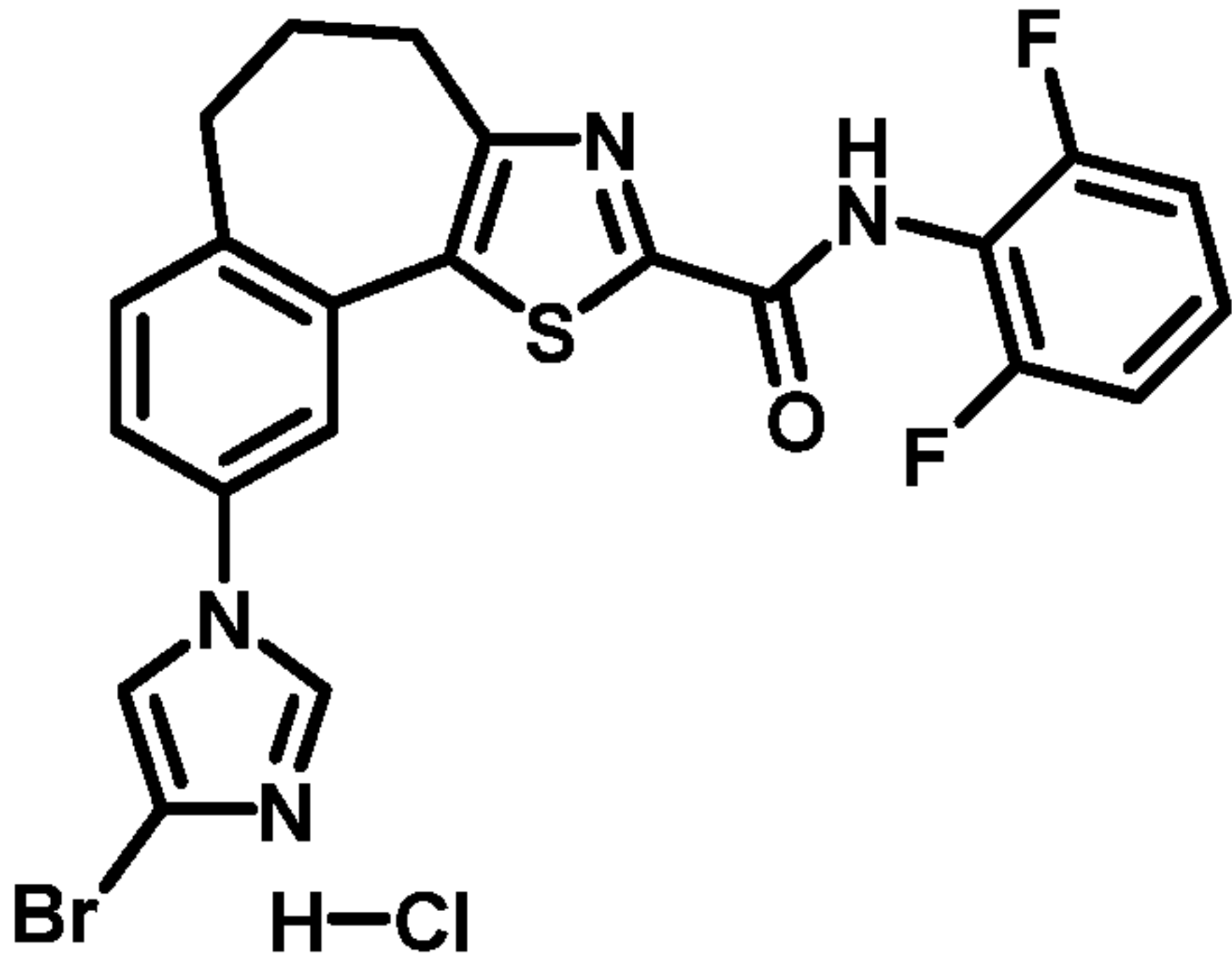
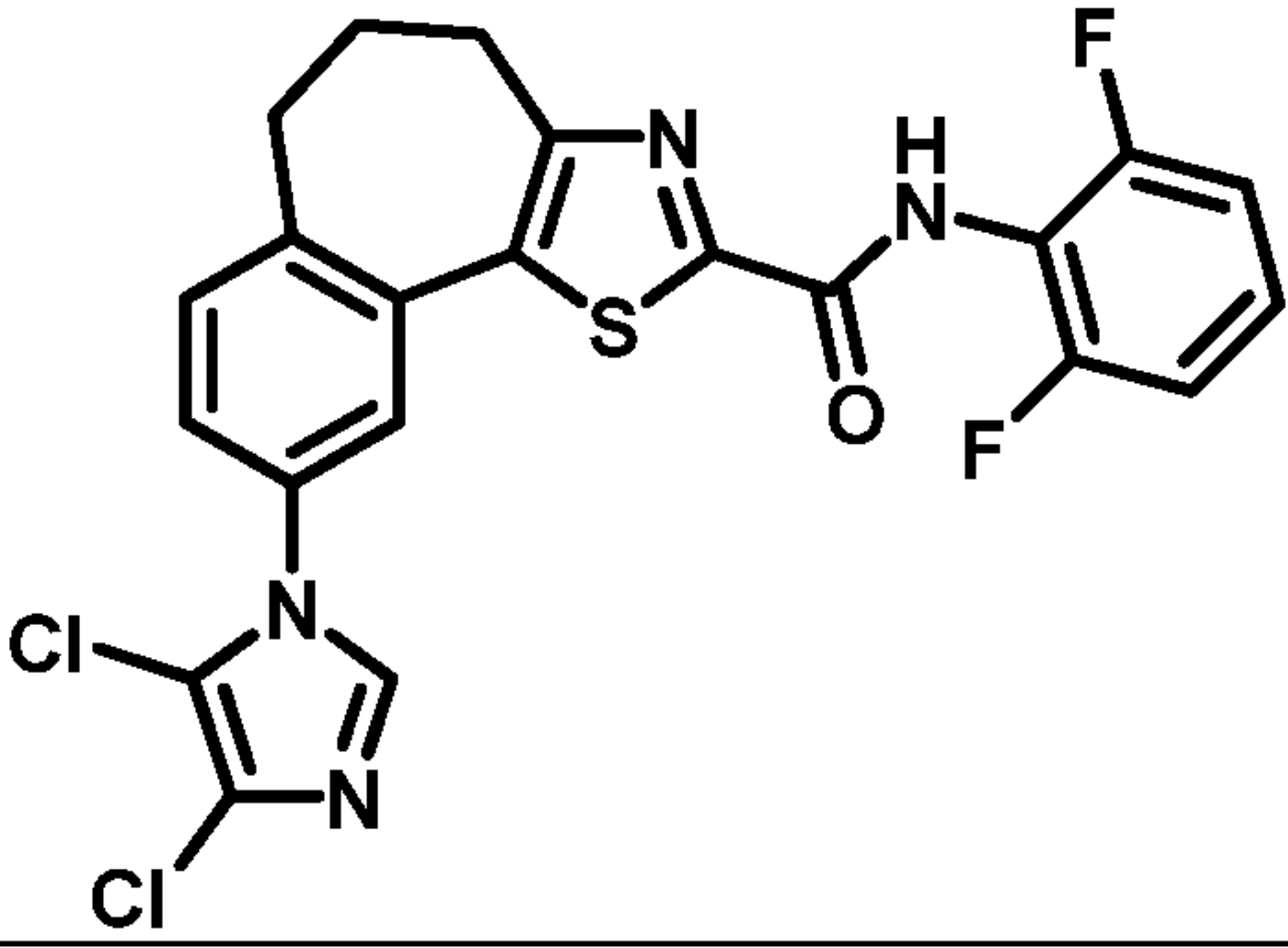
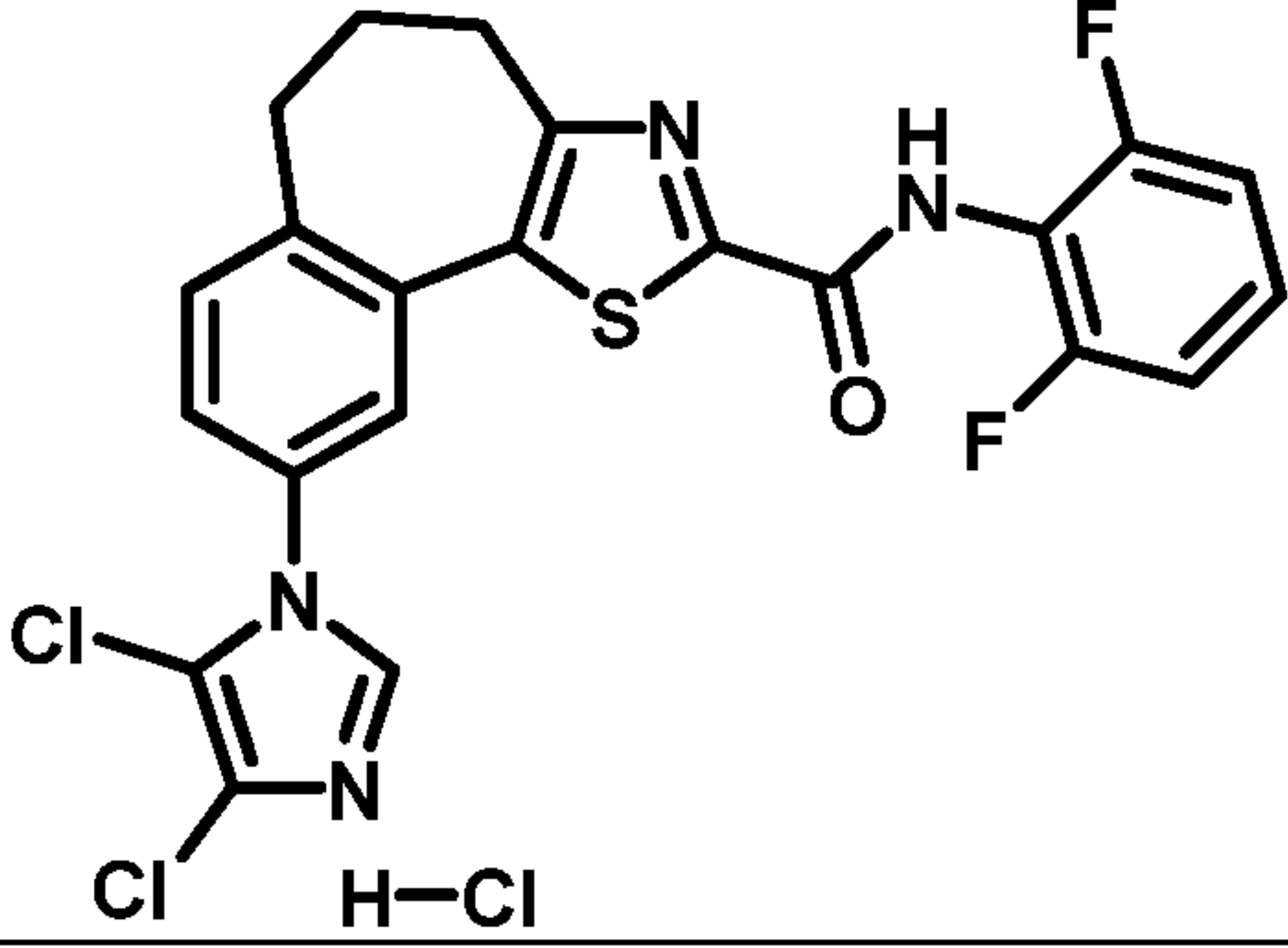
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124	 <chem>C1=CN=C(C=C1N2C=CC=C(C2)C3C=CC(=C3)S4C(=N2)C(=S4)C(=O)NC5=C(F)C(F)=CC(F)=C5)C6=CC=CC=C6</chem>
125	 <chem>ClC1=CN=C(C=C1N2C=CC=C(C2)C3C=CC(=C3)S4C(=N2)C(=S4)C(=O)NC5=C(F)C(F)=CC(F)=C5)C6=CC=CC=C6</chem>
126	 <chem>C1=CN=C(C=C1N2C=CC=C(C2)C3C=CC(=C3)S4C(=N2)C(=S4)C(=O)NC5=C(F)C=CC(F)=C5F)C6=CC=CC=C6</chem>
127	 <chem>ClC1=CN=C(C=C1N2C=CC=C(C2)C3C=CC(=C3)S4C(=N2)C(=S4)C(=O)NC5=C(F)C=CC(F)=C5F)C6=CC=CC=C6</chem>
128	 <chem>C1=CN=C(C=C1N2C=CC=C(C2)C3C=CC(=C3)S4C(=N2)C(=S4)C(=O)NC5=CC(F)=CC(F)=C5)C6=CC=CC=C6</chem>

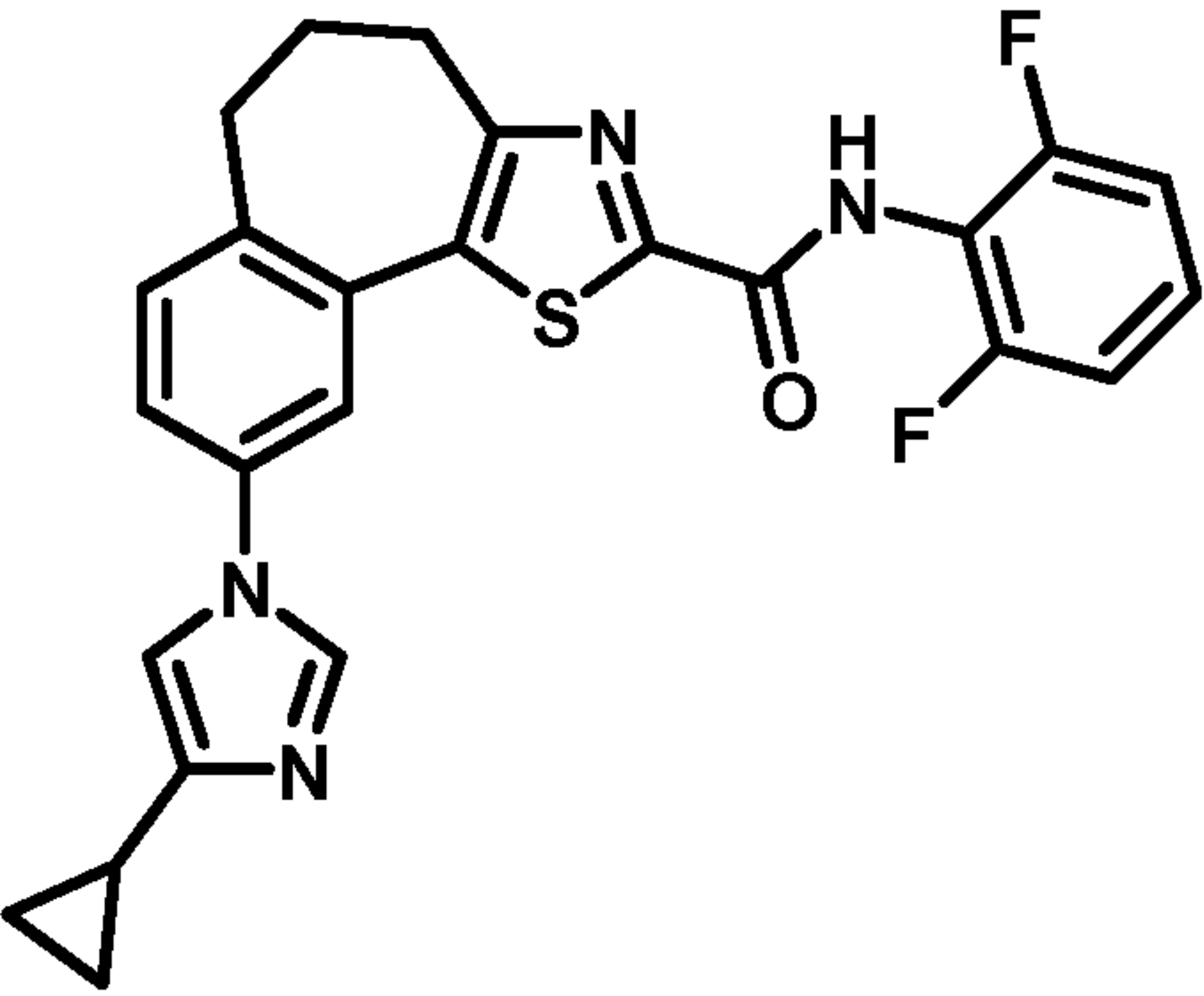
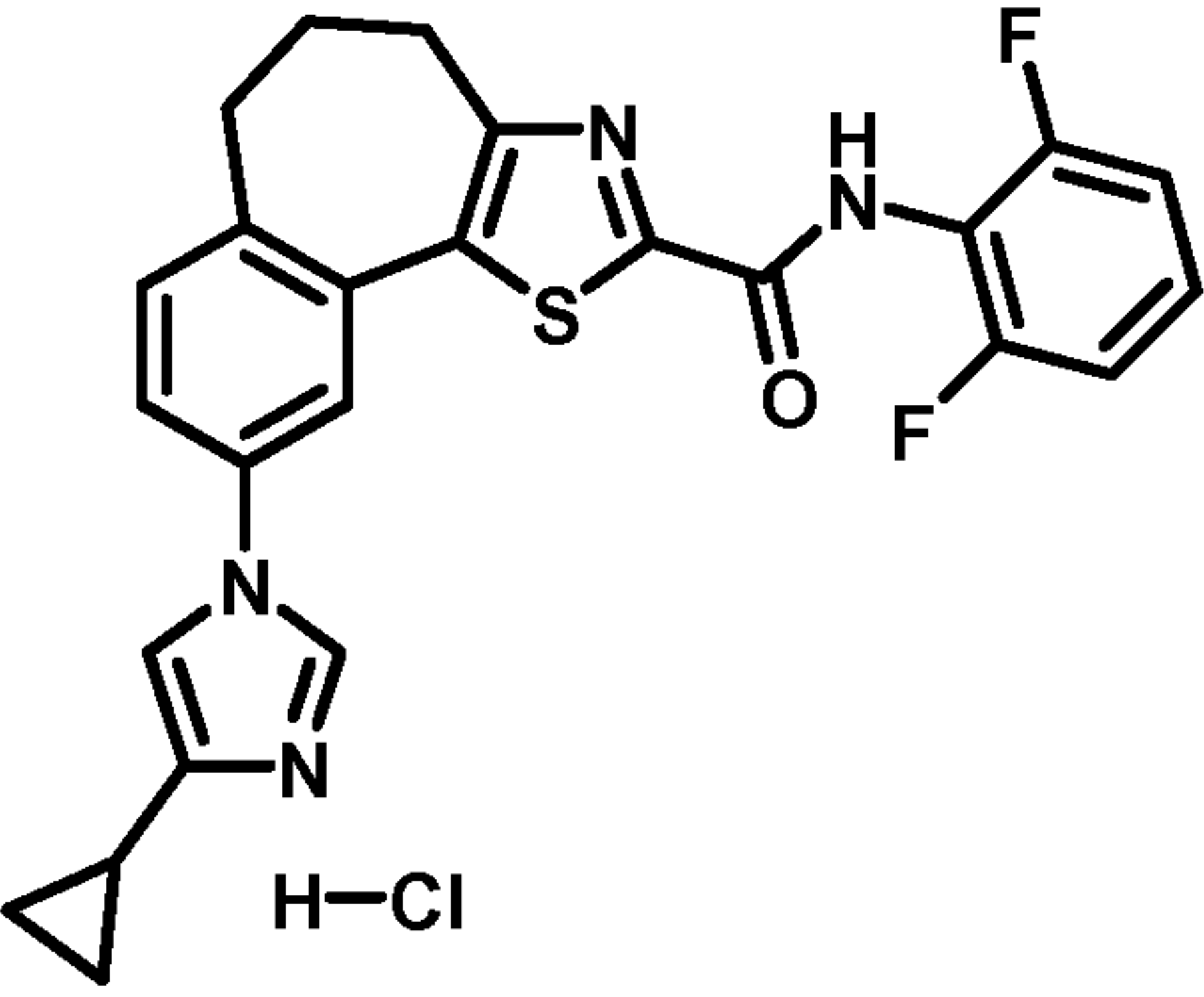
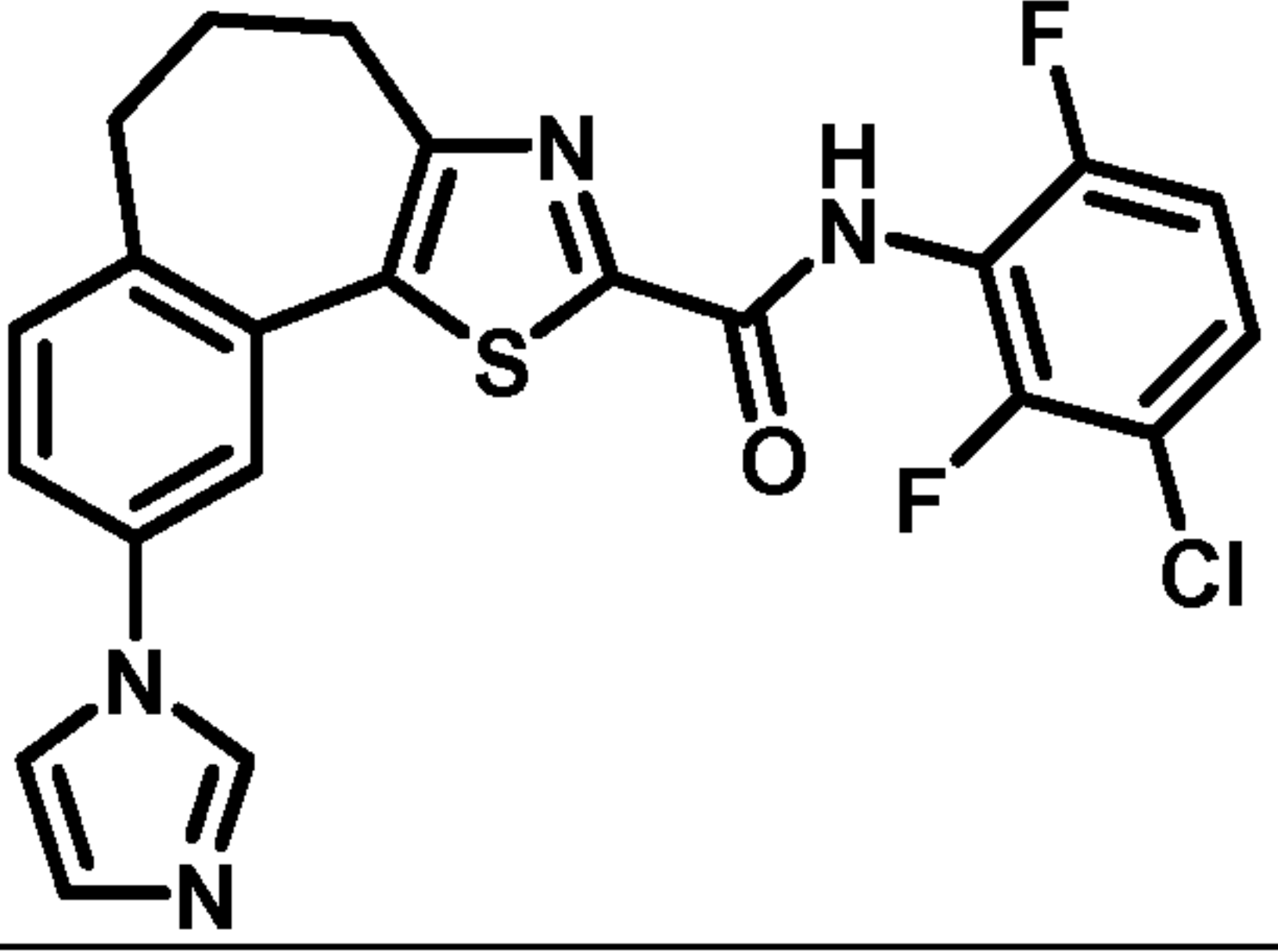
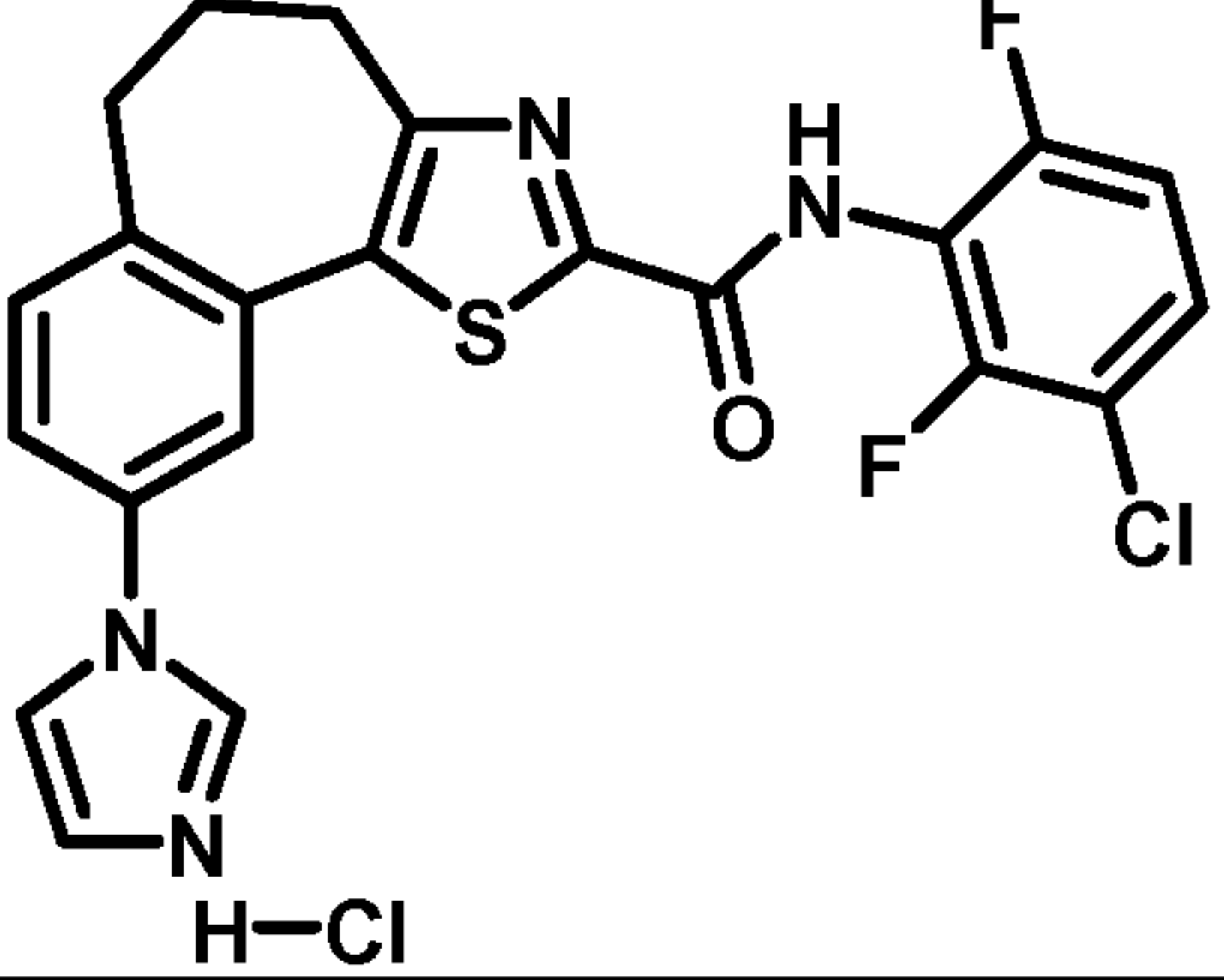
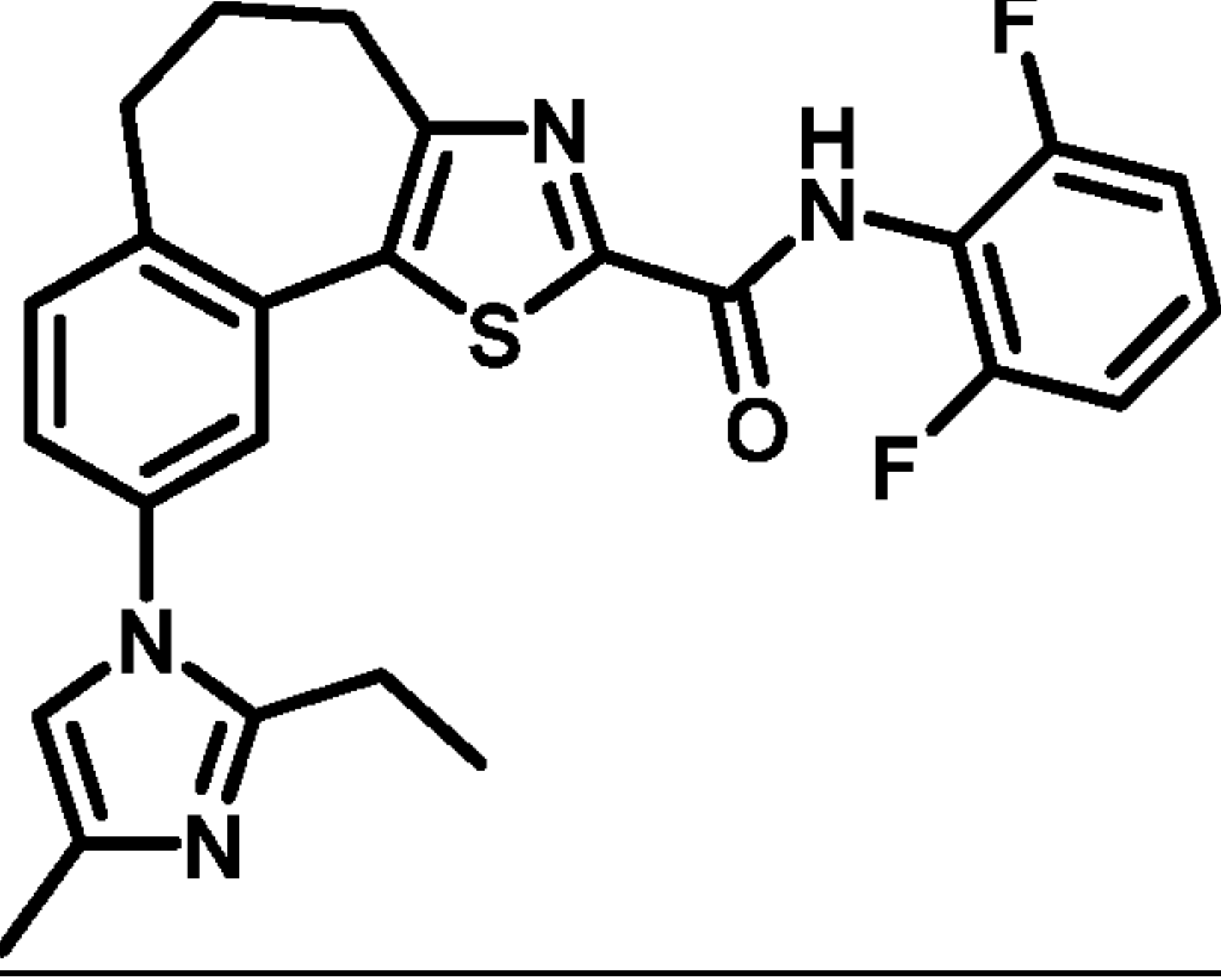
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131	 H-Cl
132	
133	 H-Cl
134	

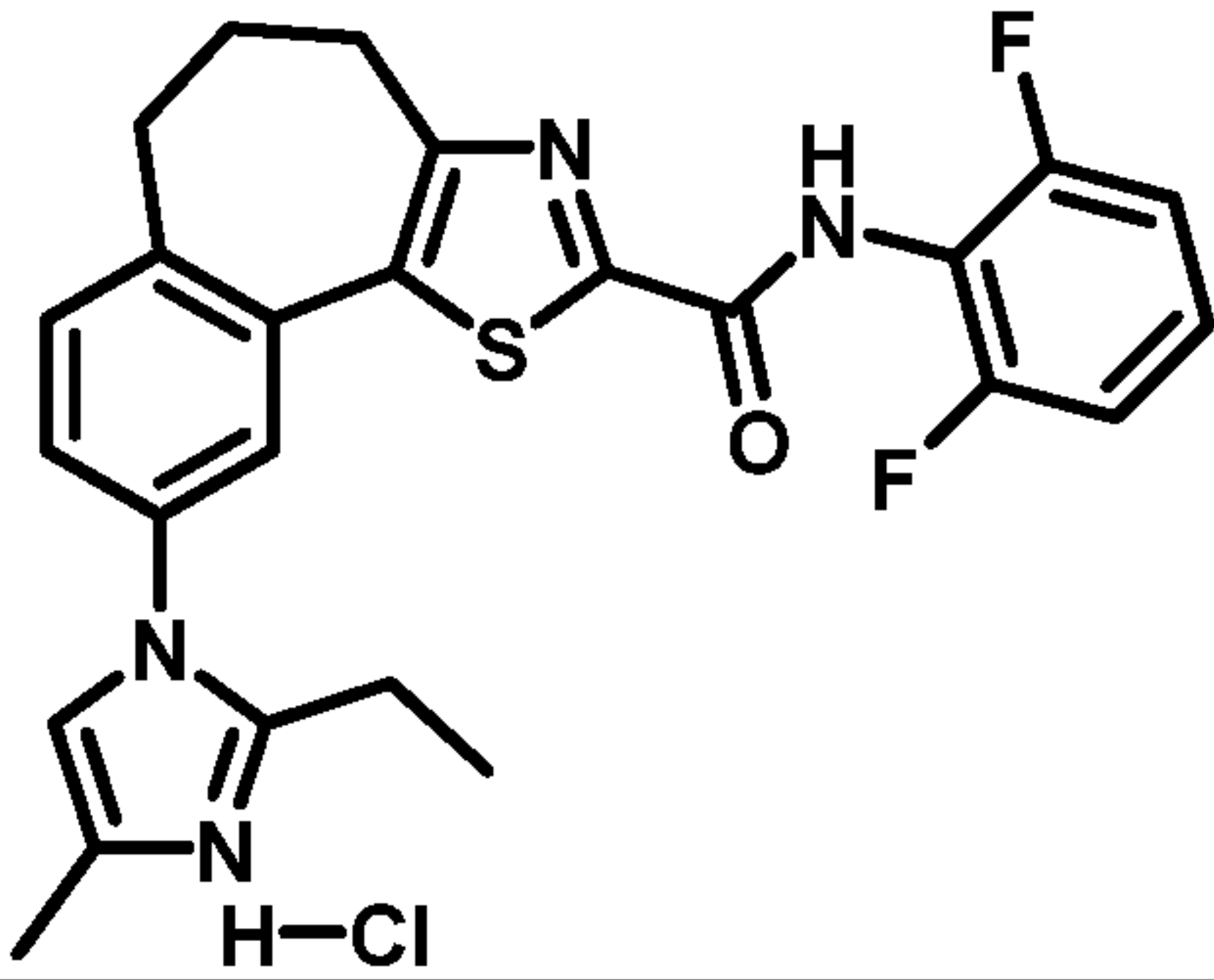
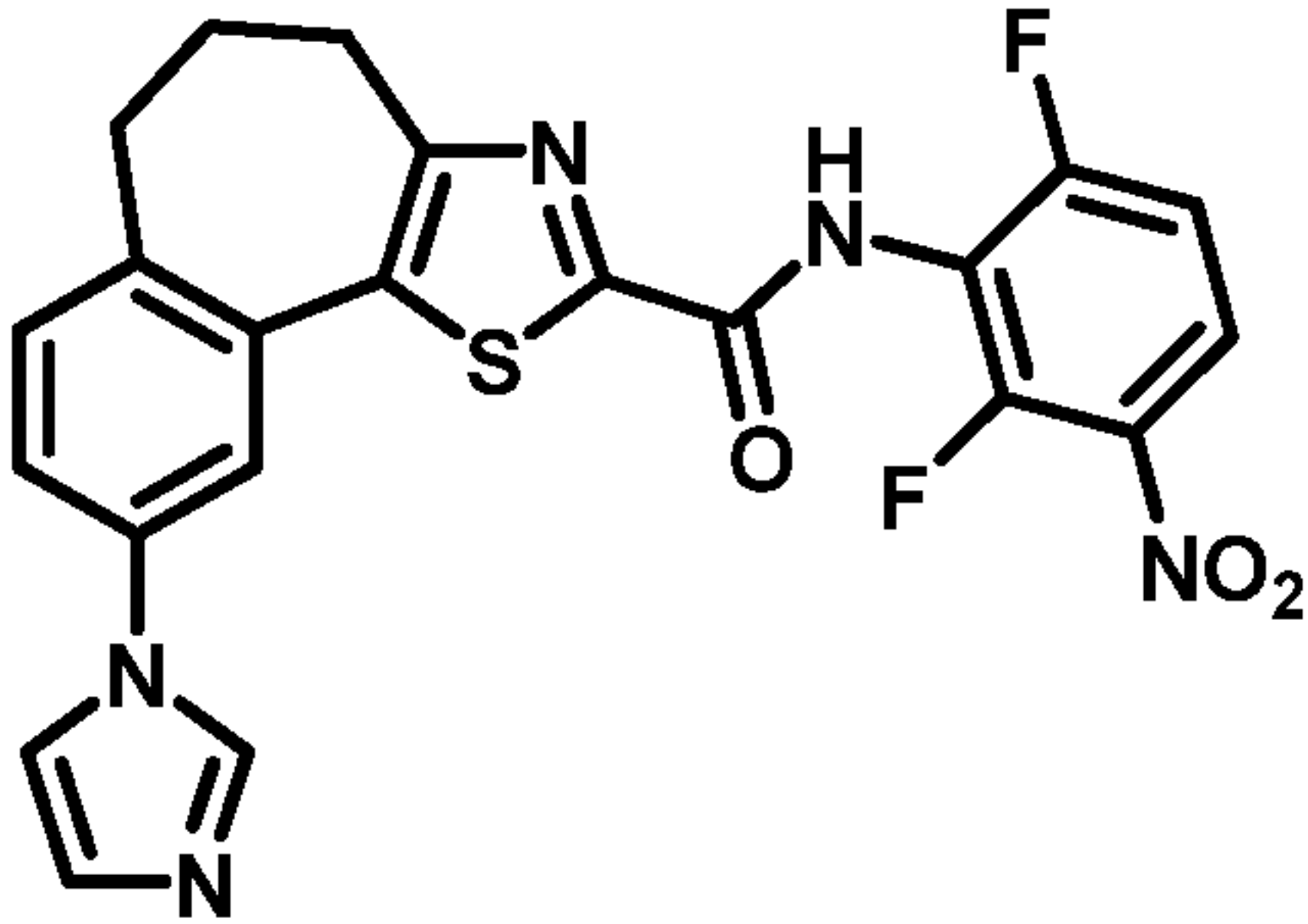
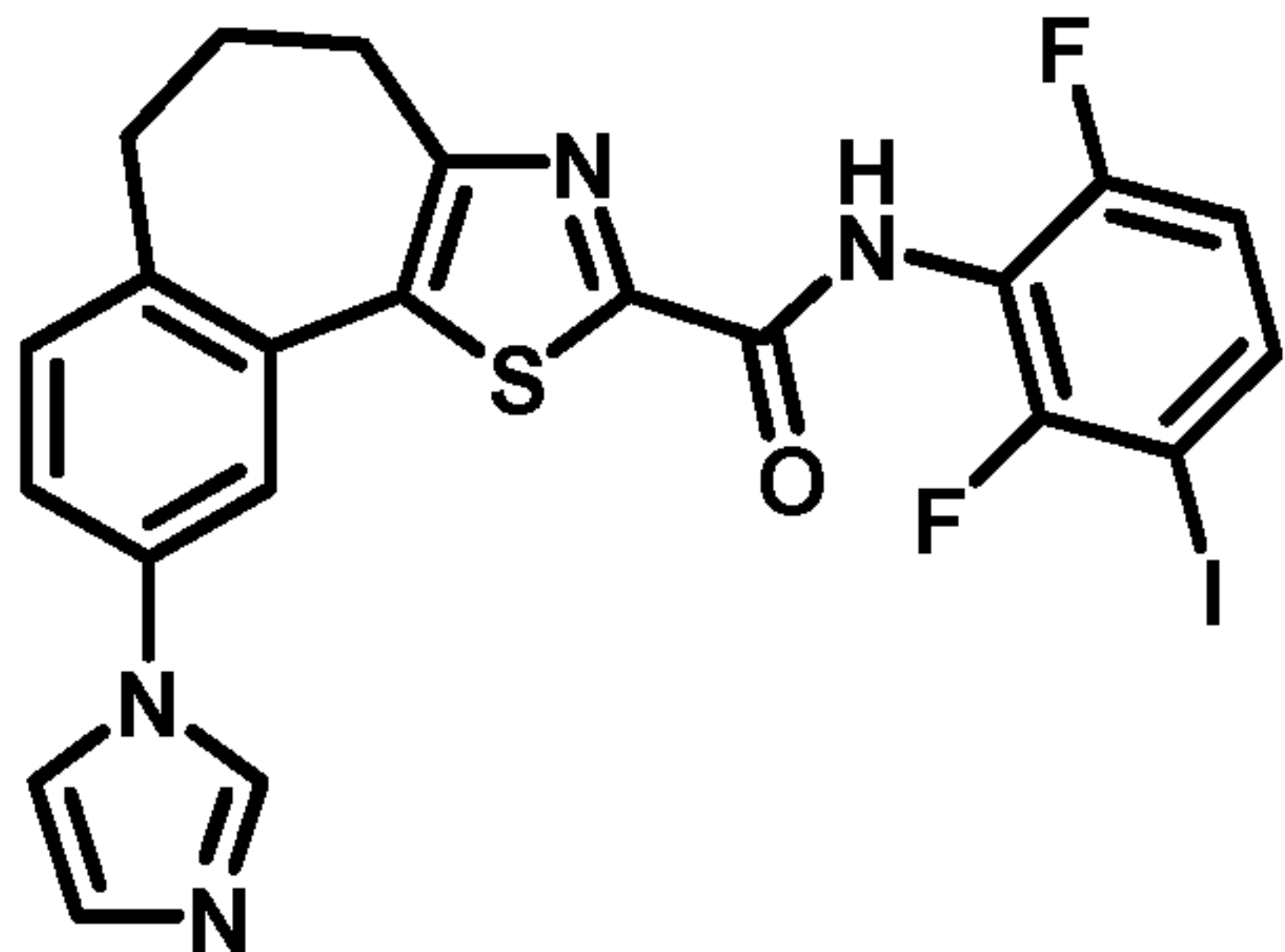
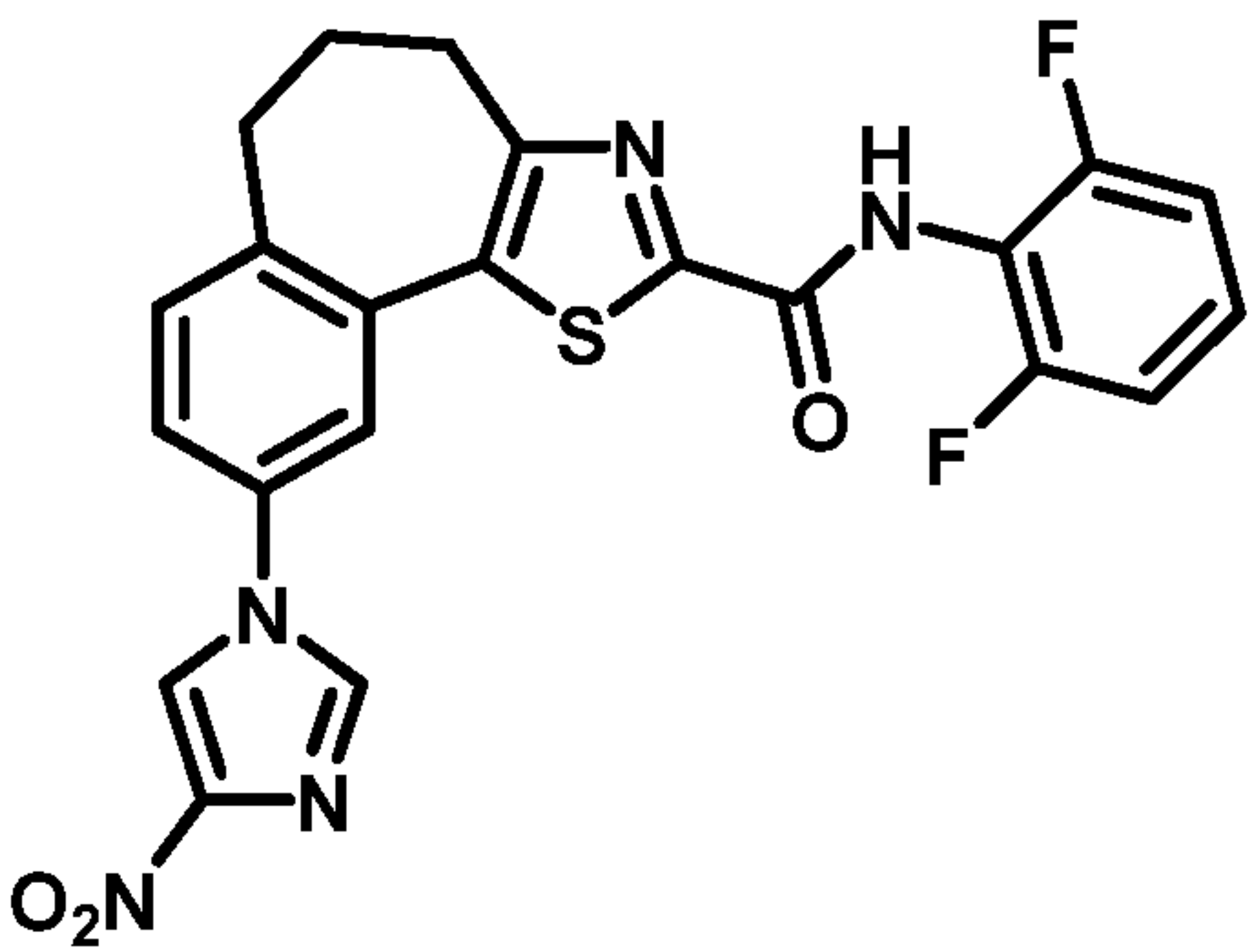
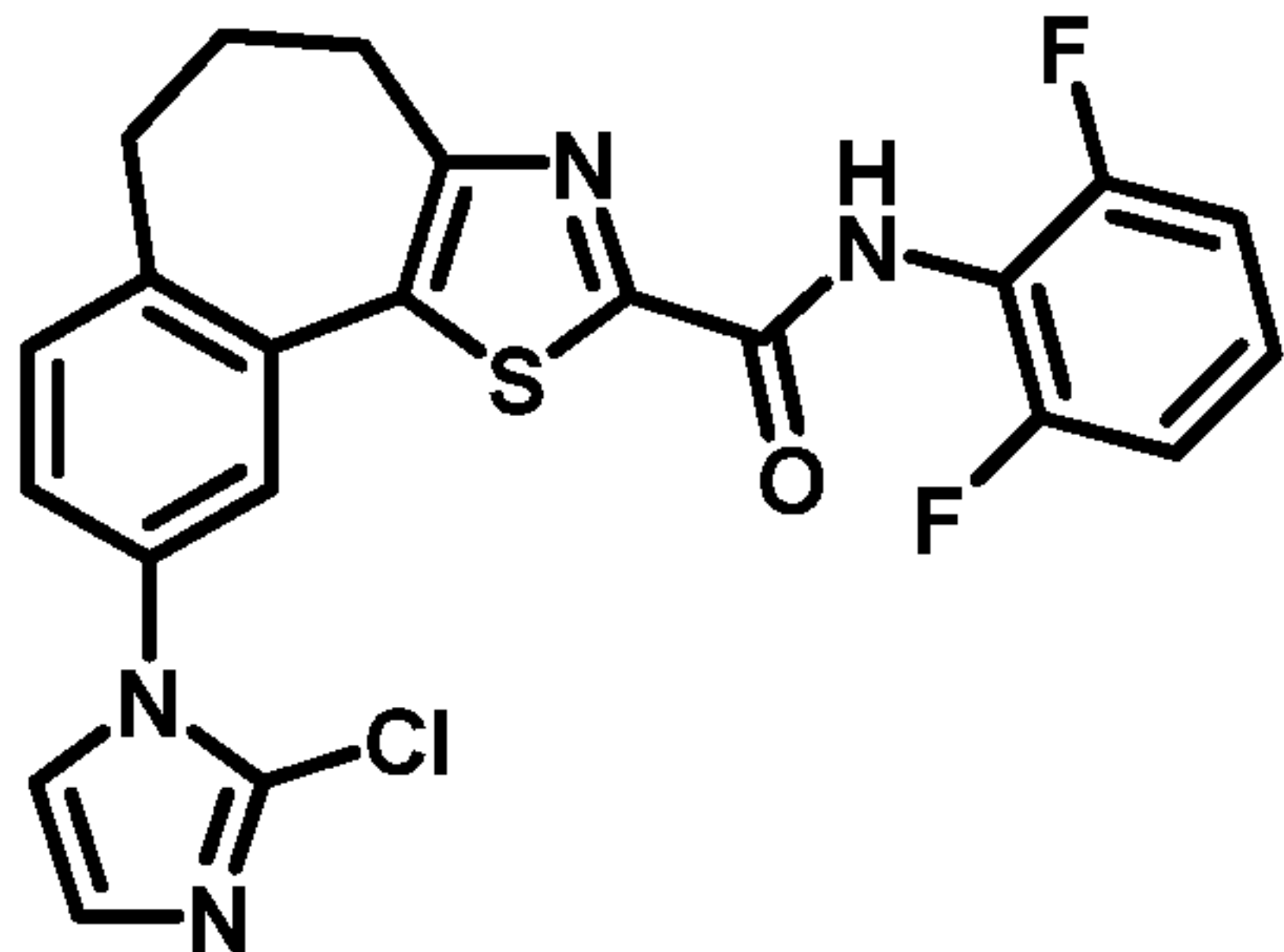
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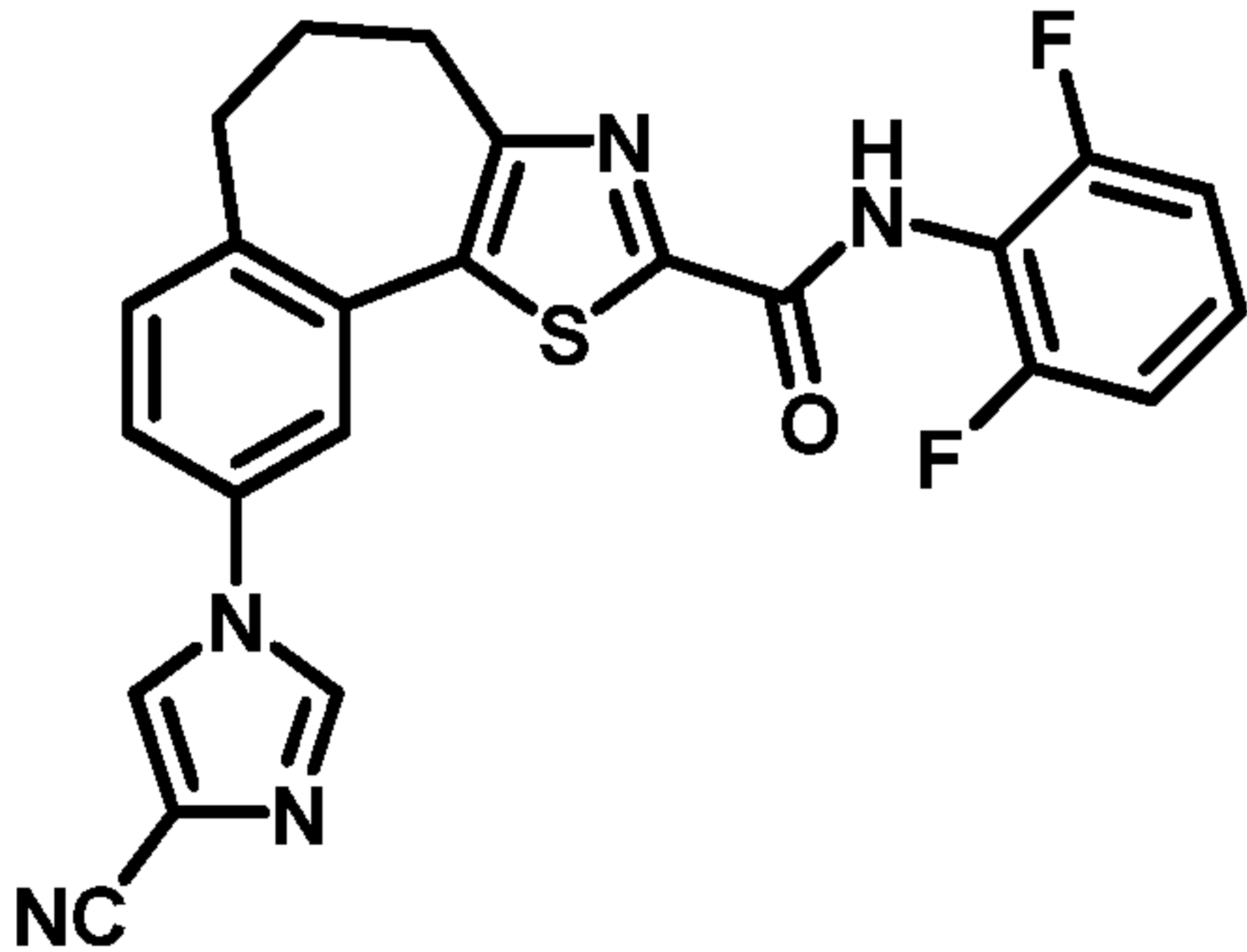
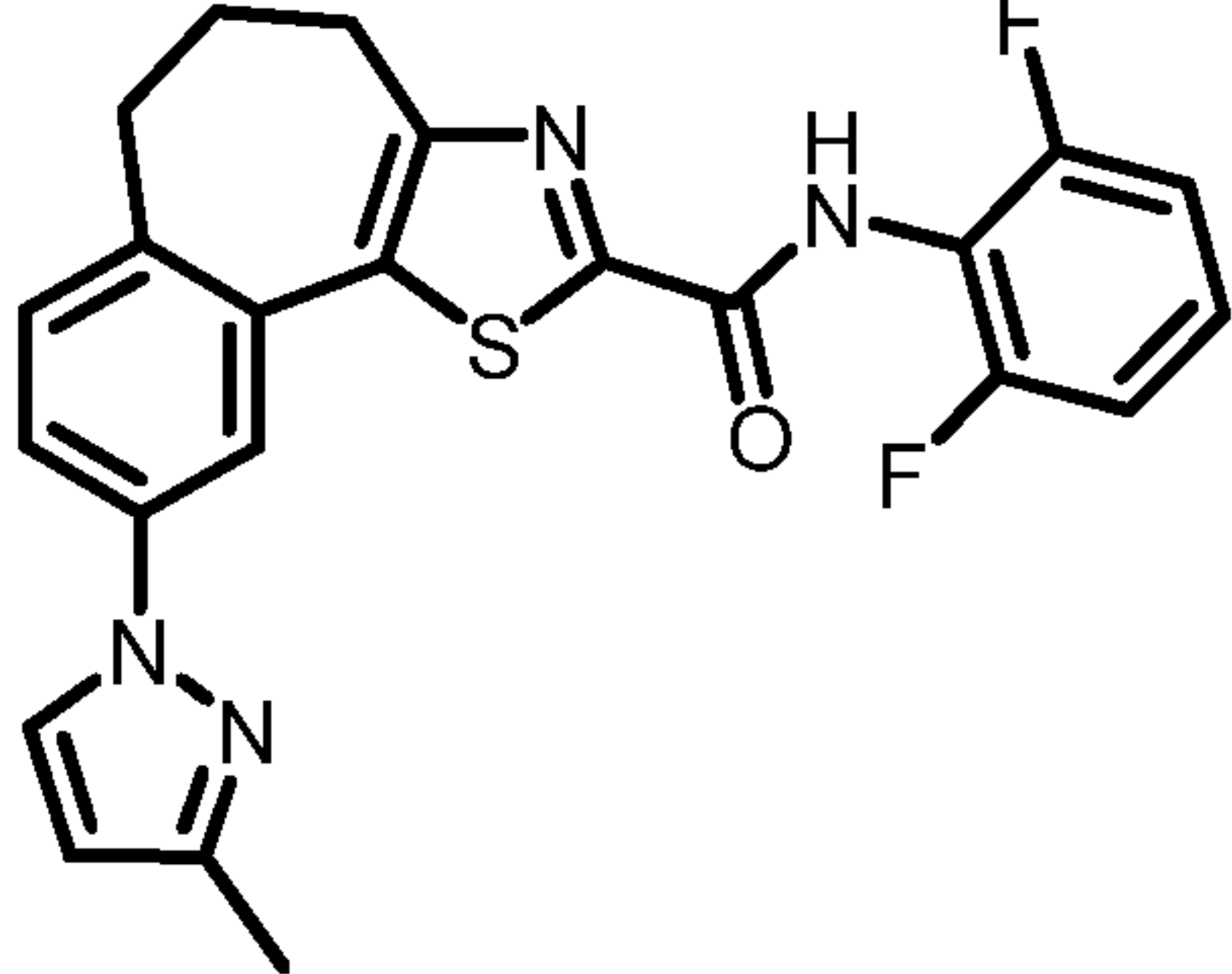
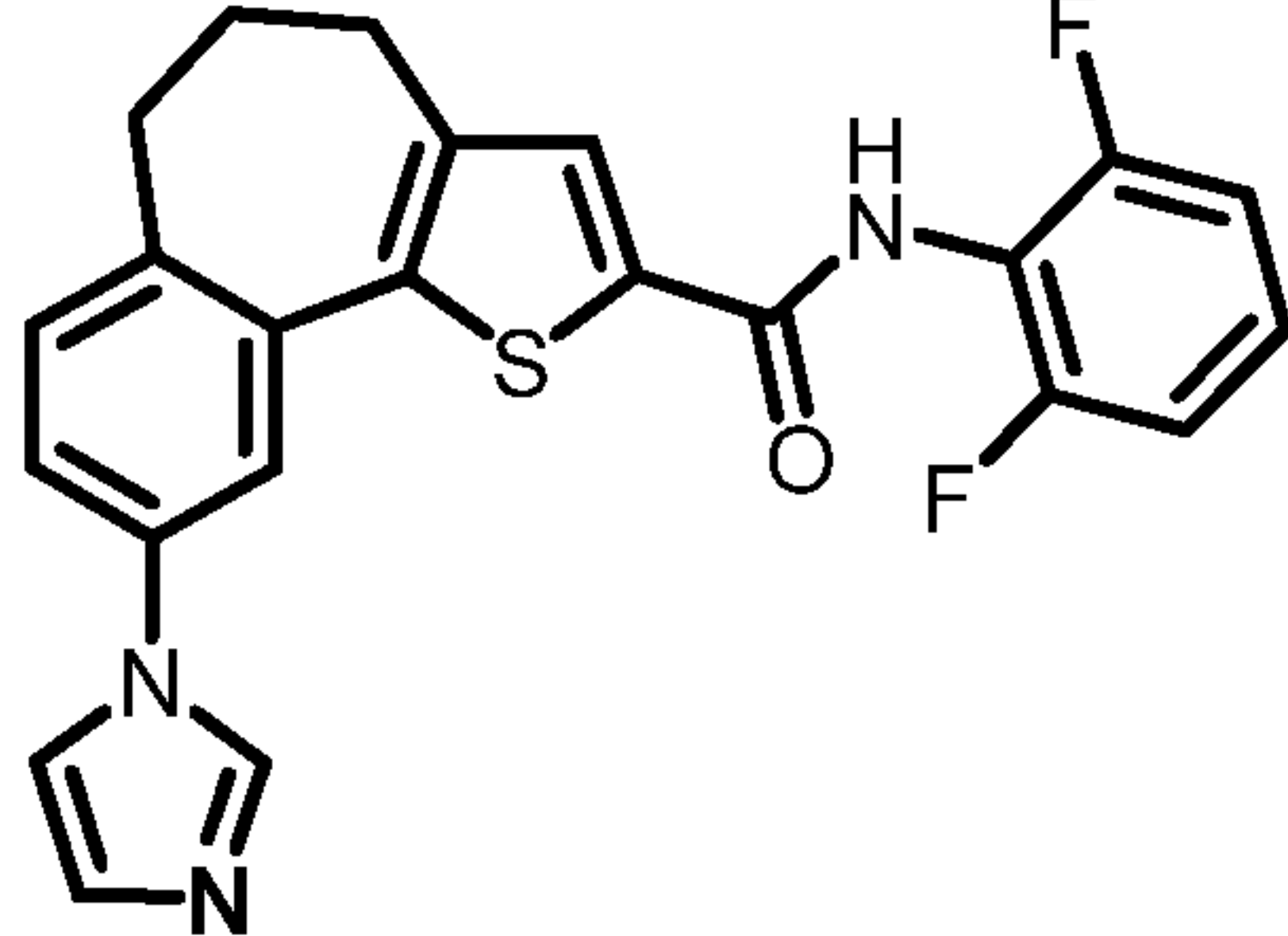
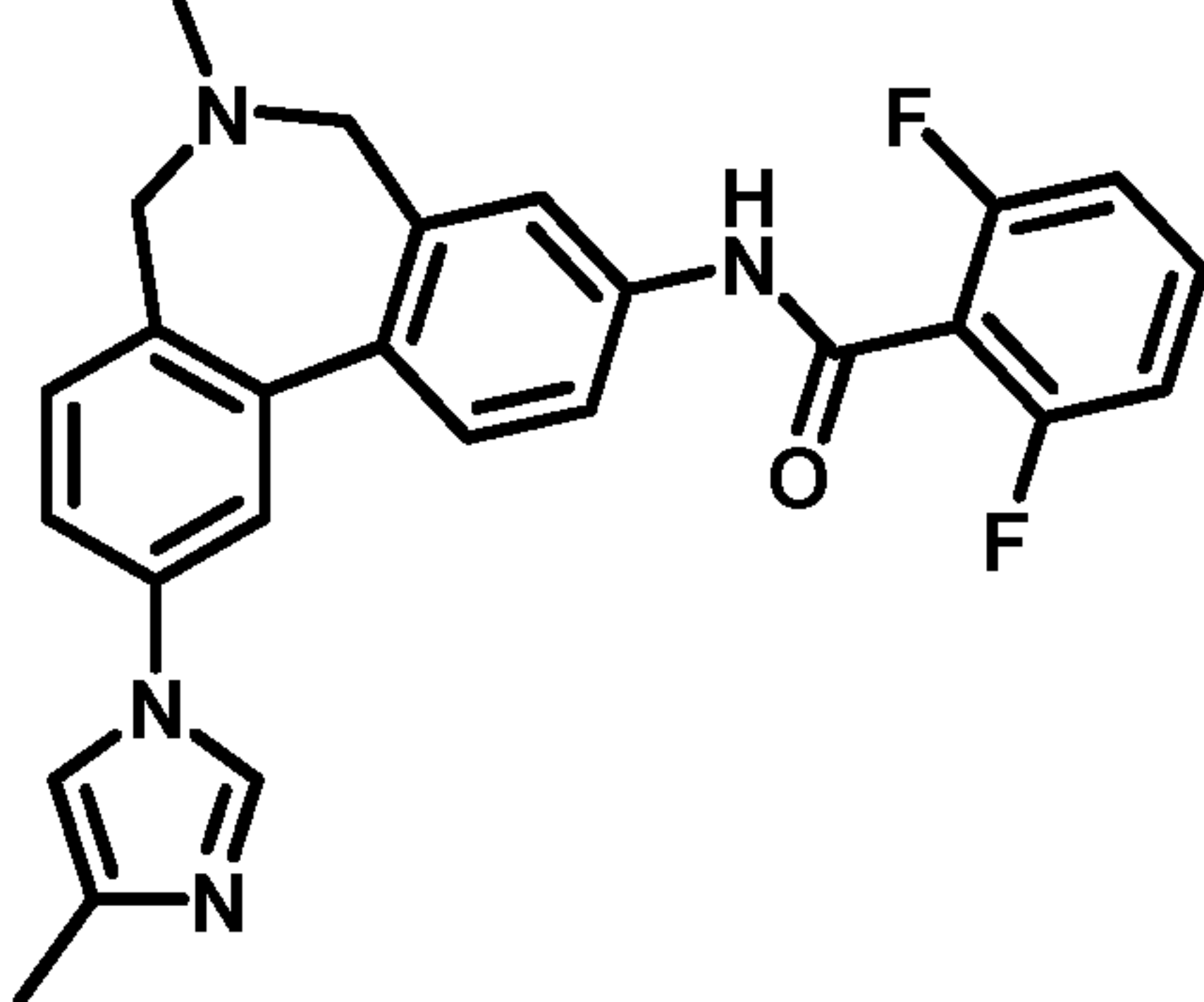
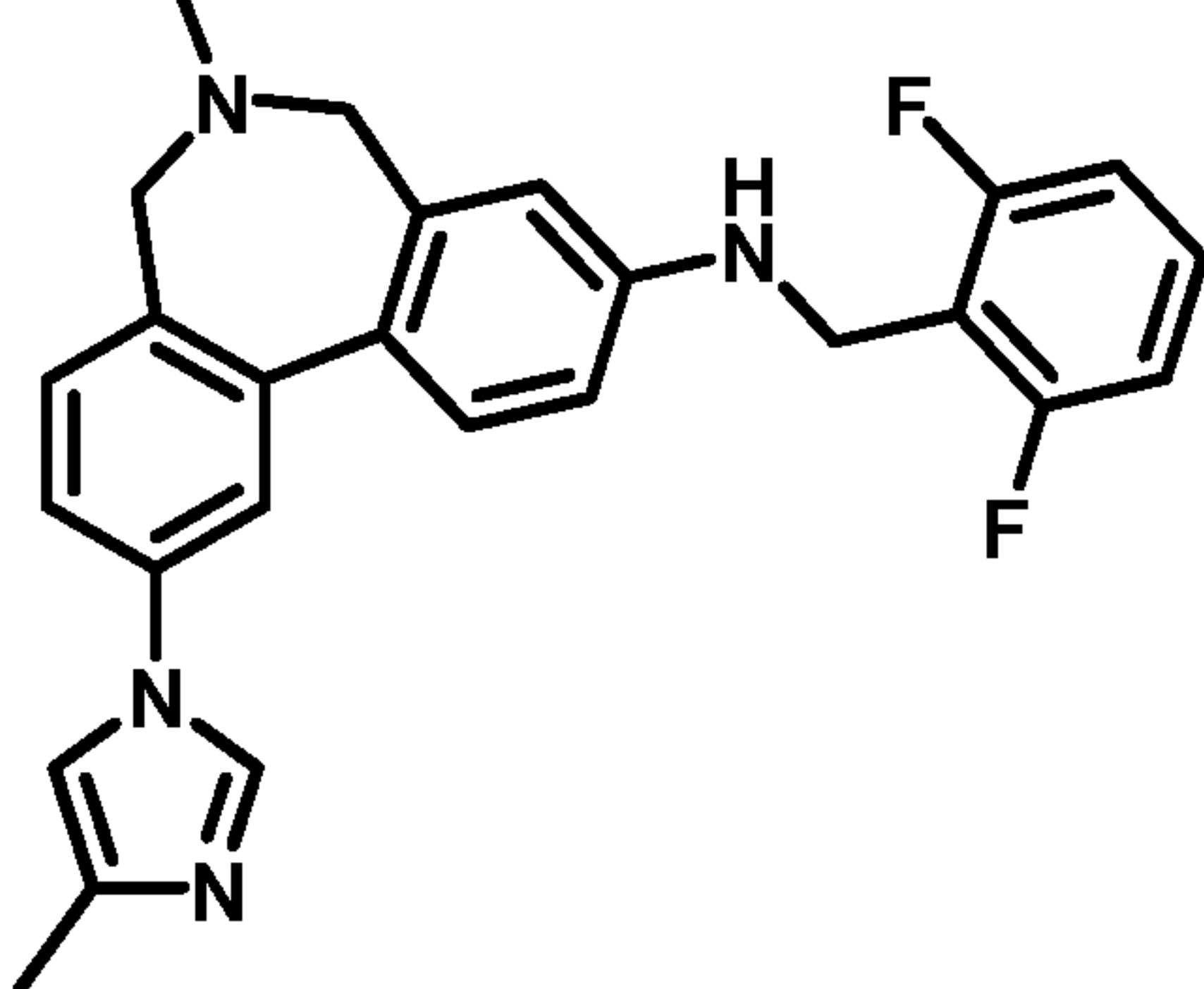
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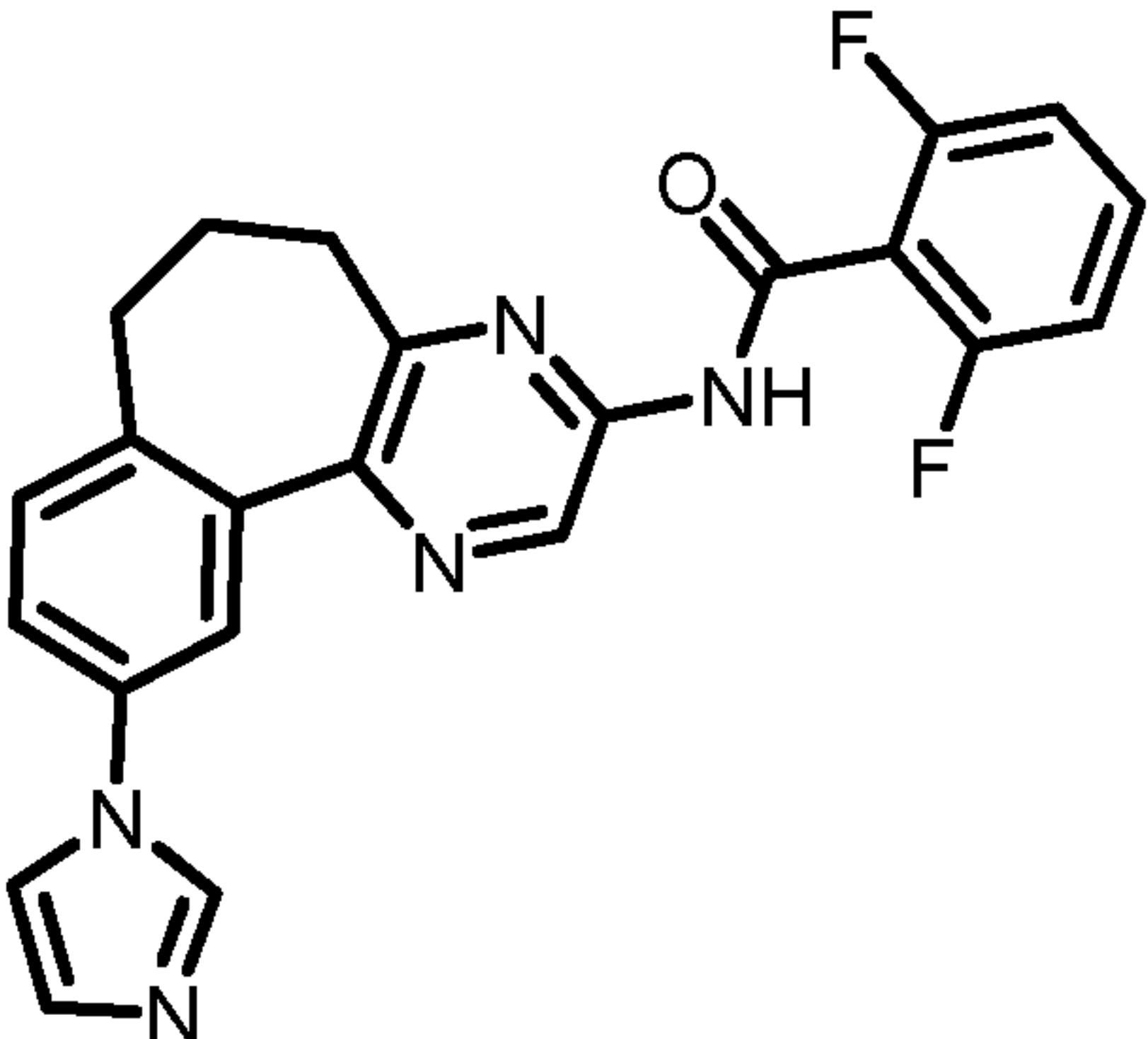
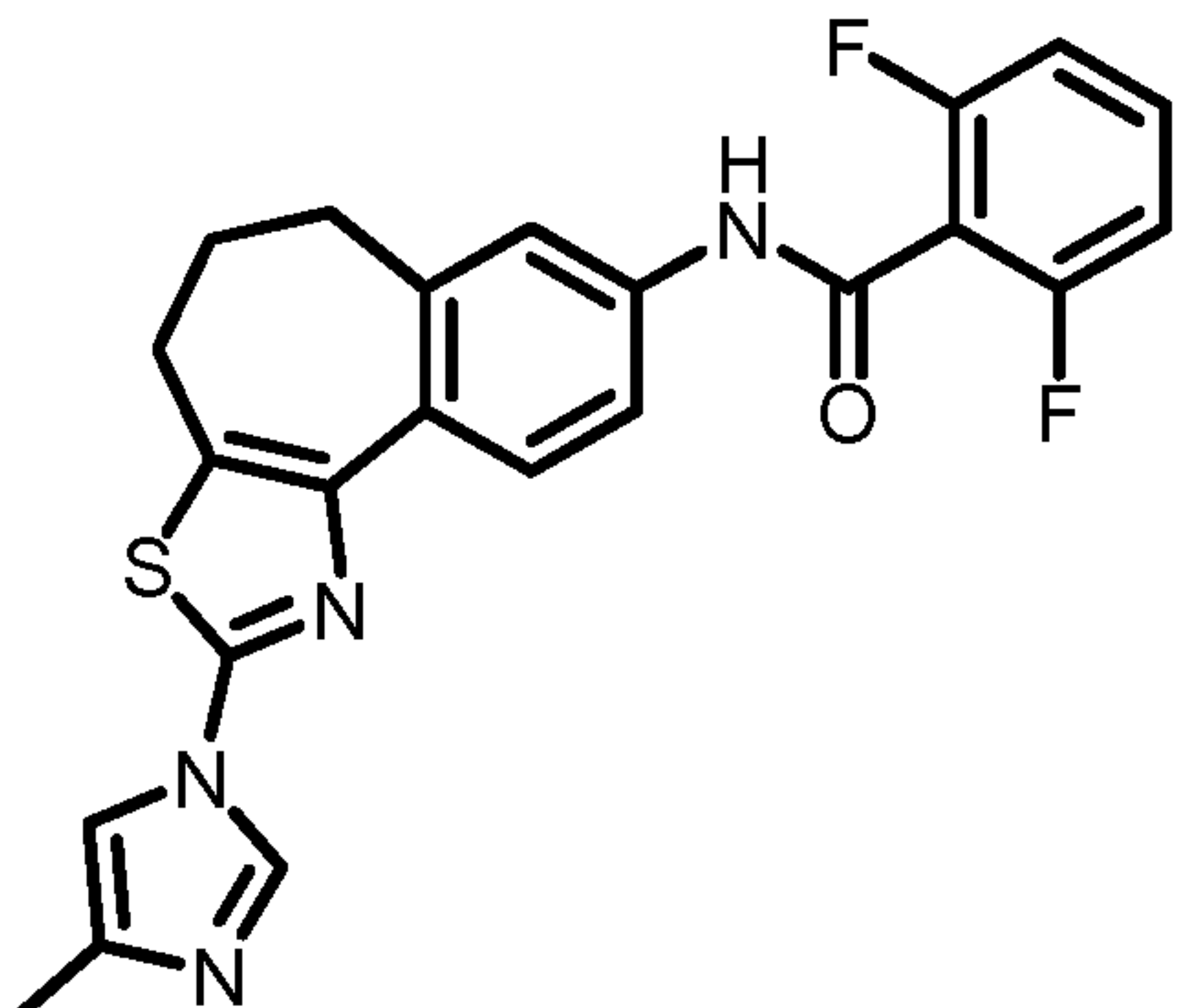
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149	 <chem>CC1(C)C=CN(C1)c2ccc(cc2)N3C4=CC=CC=C4S=C5N(C(=O)Nc6cc(F)cc(F)cc6)C=C53</chem>
150	 <chem>BrC1=CN(C=C1)c2ccc(cc2)N3C4=CC=CC=C4S=C5N(C(=O)Nc6cc(F)cc(F)cc6)C=C53</chem>
151	 <chem>BrC1=CN(C=C1)c2ccc(cc2)N3C4=CC=CC=C4S=C5N(C(=O)Nc6cc(F)cc(F)cc6)C=C53.Cl</chem>
152	 <chem>ClC1=CN(C(Cl)=C1)c2ccc(cc2)N3C4=CC=CC=C4S=C5N(C(=O)Nc6cc(F)cc(F)cc6)C=C53</chem>
153	 <chem>ClC1=CN(C(Cl)=C1)c2ccc(cc2)N3C4=CC=CC=C4S=C5N(C(=O)Nc6cc(F)cc(F)cc6)C=C53.Cl</chem>

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159	 <chem>CC1=CNC(C1)c2ccc(cc2)C3=NC(=S/C(=O)Nc4cc(F)cc(F)c4)C3</chem>
160	 <chem>O=[N+]([O-])c1cc(F)c(NC(=O)c2nc3ccccc3s2)cc1F</chem>
161	 <chem>Ic1cc(F)c(NC(=O)c2nc3ccccc3s2)cc1F</chem>
162	 <chem>[O-][N+](=O)c1cc2nc(NC(=O)c3nc4ccccc4s3)cc2cc1</chem>
163	 <chem>Clc1cc2nc(NC(=O)c3nc4ccccc4s3)cc2cc1</chem>

164	 <chem>N#Cc1cn[nH]1c2ccc3c(c2)sc(cc34C5=CC=CC=C5N4)C(=O)Nc6cc(F)c(F)cc6</chem>
165	 <chem>Cc1cn[nH]1c2ccc3c(c2)sc(cc34C5=CC=CC=C5N4)C(=O)Nc6cc(F)c(F)cc6</chem>
166	 <chem>c1cn[nH]1c2ccc3c(c2)sc(cc34C5=CC=CC=C5N4)C(=O)Nc6cc(F)c(F)cc6</chem>
167	 <chem>Cc1cn[nH]1c2ccc3c(c2)nc4cc5c(c3)ccc(NC(=O)c6cc(F)c(F)cc6)c5</chem>
168	 <chem>Cc1cn[nH]1c2ccc3c(c2)nc4cc5c(c3)ccc(NC(=O)Cc6cc(F)c(F)cc6)c5</chem>

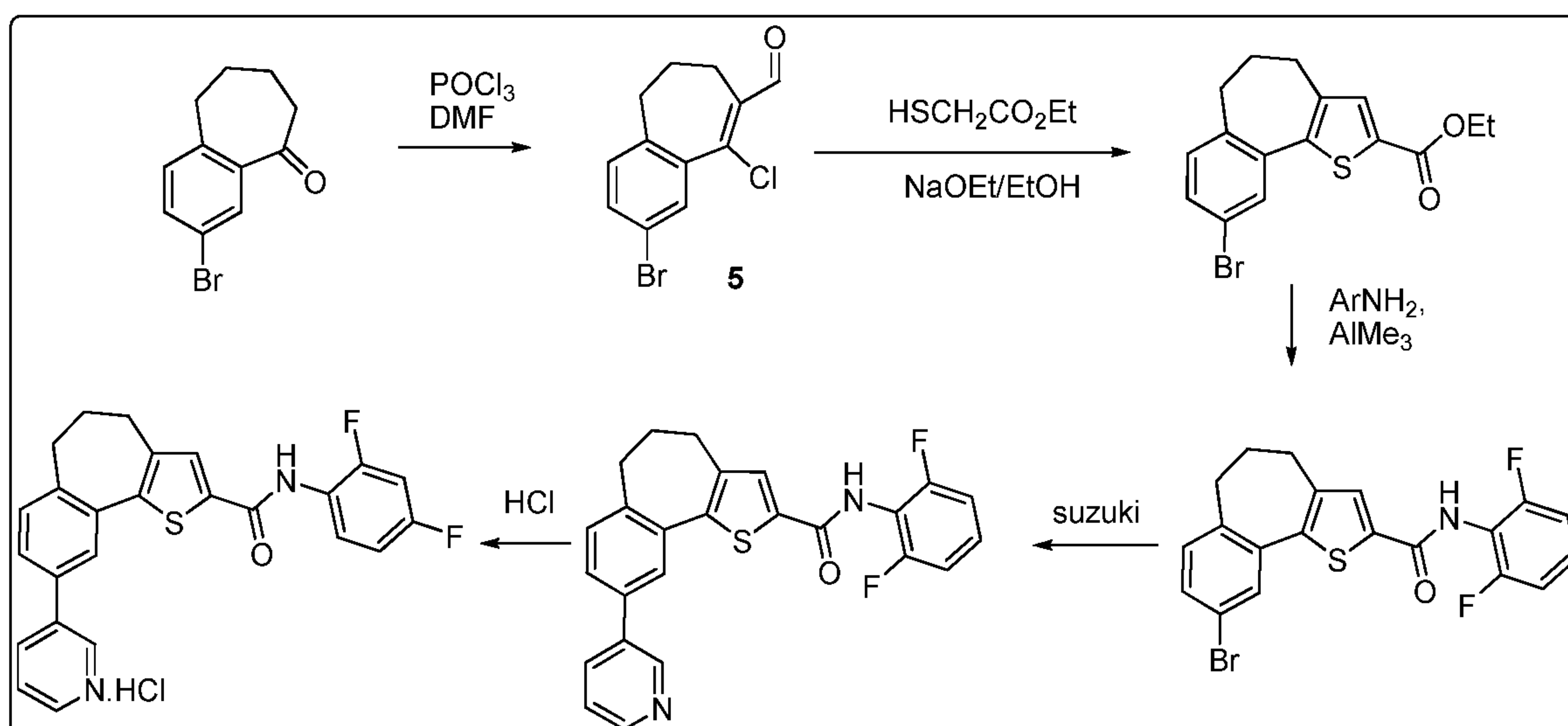
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METHODS FOR MAKING COMPOUNDS OF THE INVENTION

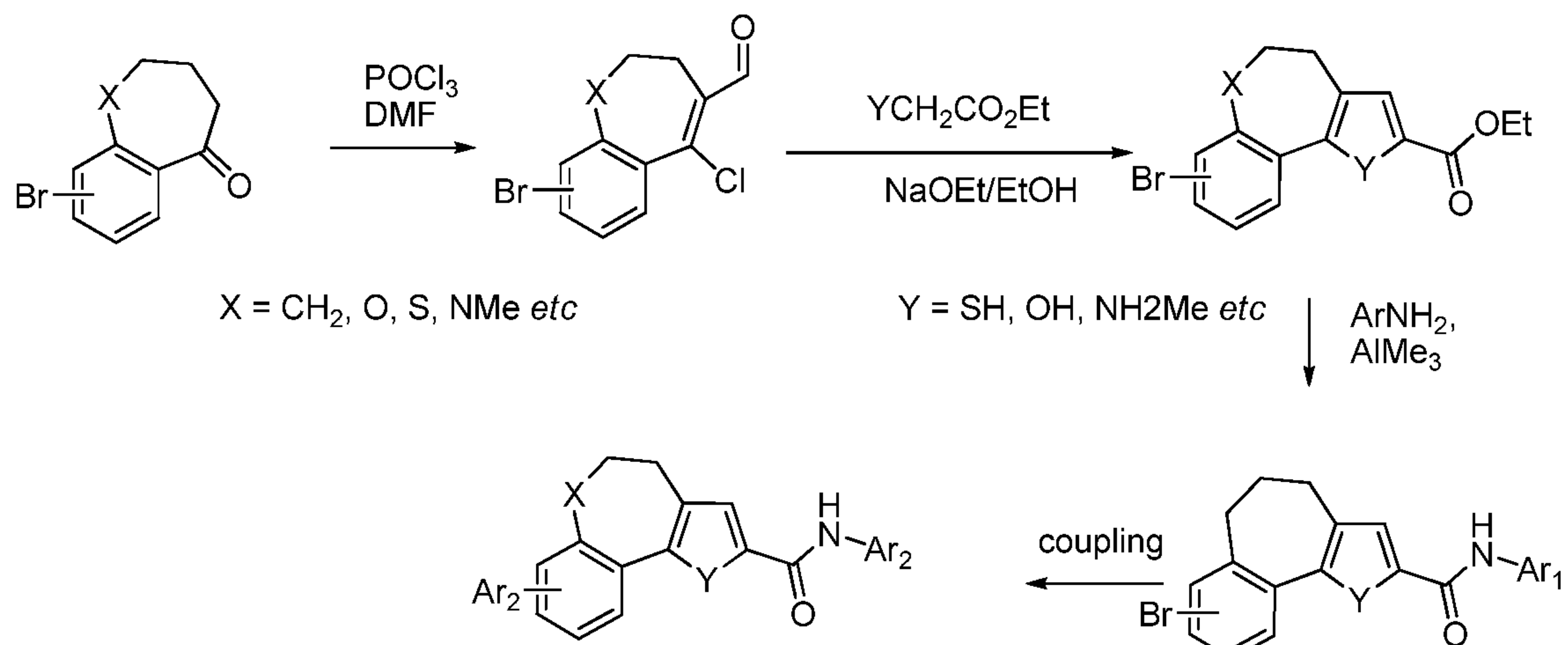
Compounds of the invention can be obtained via standard, well-known synthetic methodology, see e.g., March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992.

Compounds of the invention can also be prepared as in US Application No. 11/861,278, filed September 25, 2007, which is incorporated by reference in its entirety herein. In particular, compounds of the invention can be obtained by the following reaction schemes.

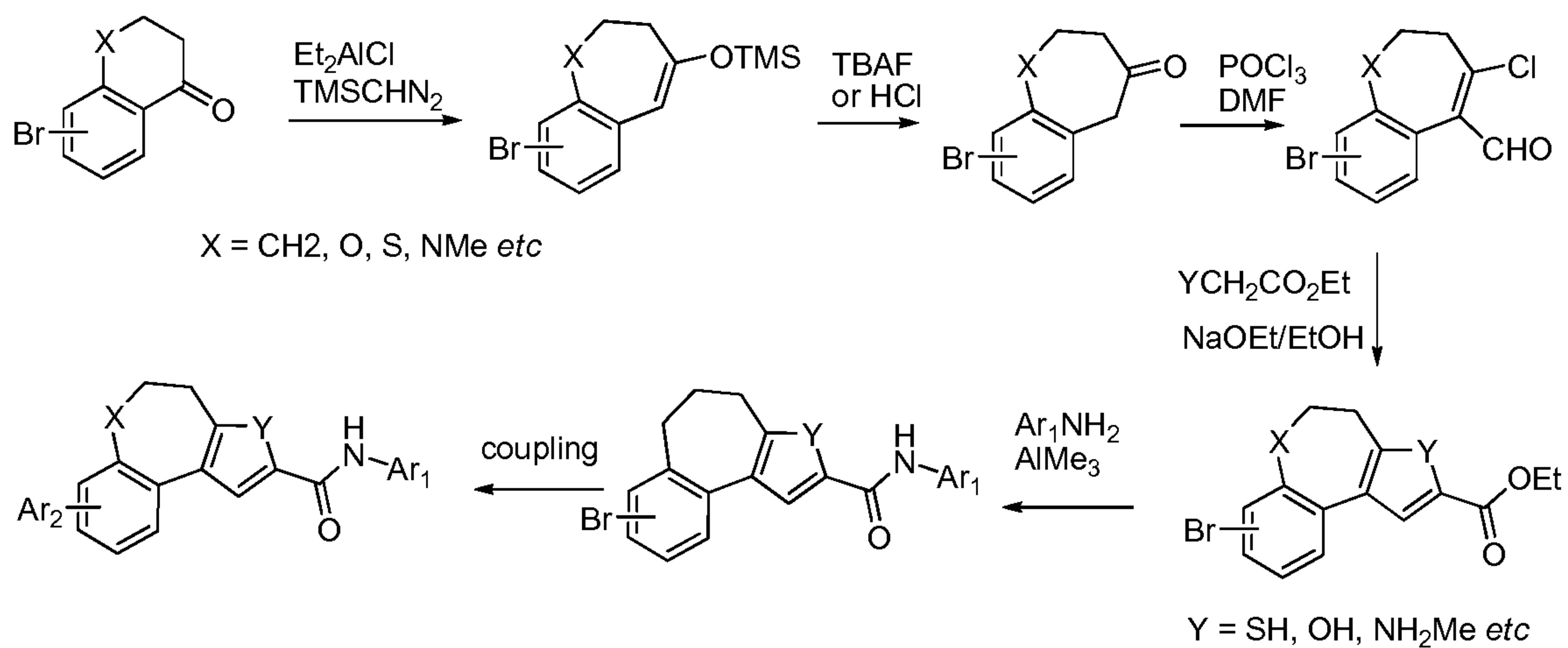
Scheme 1:



Scheme 2:

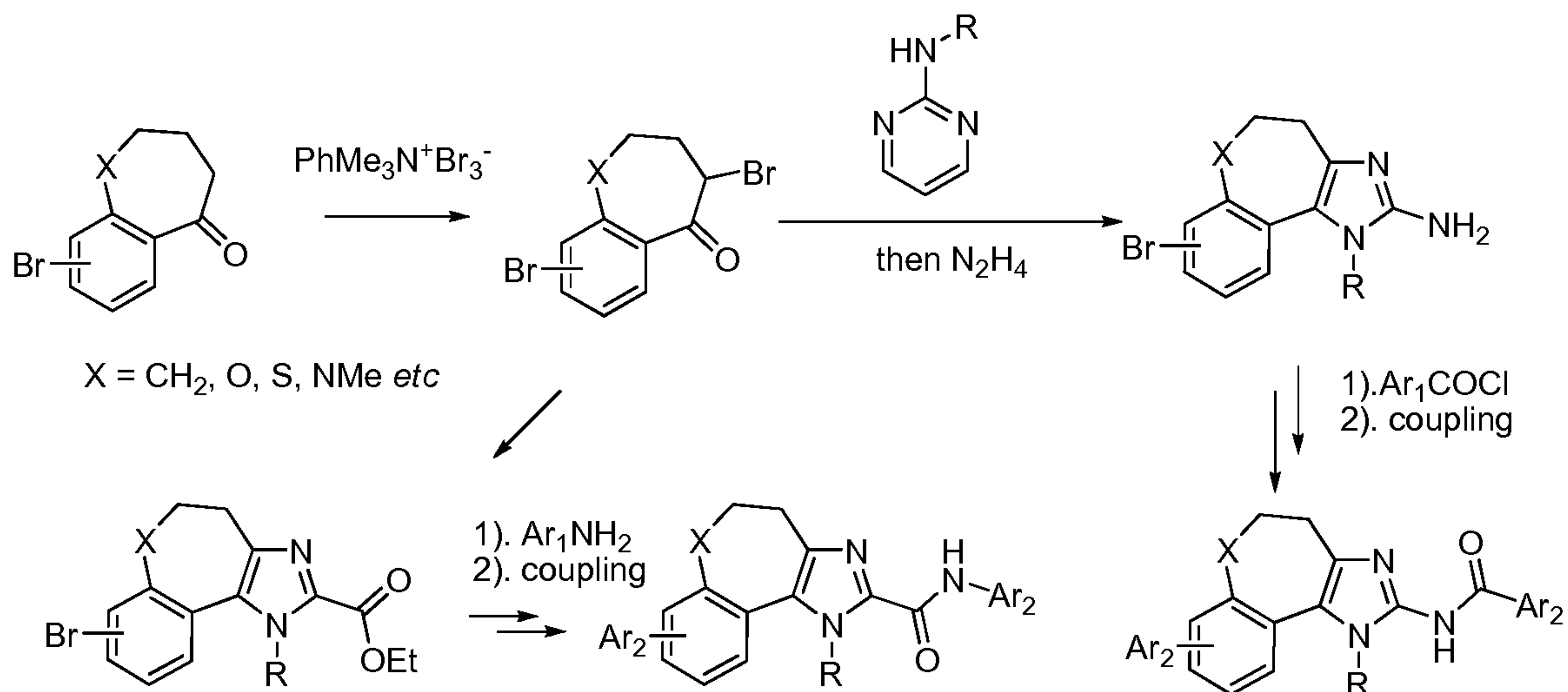


Scheme 3:

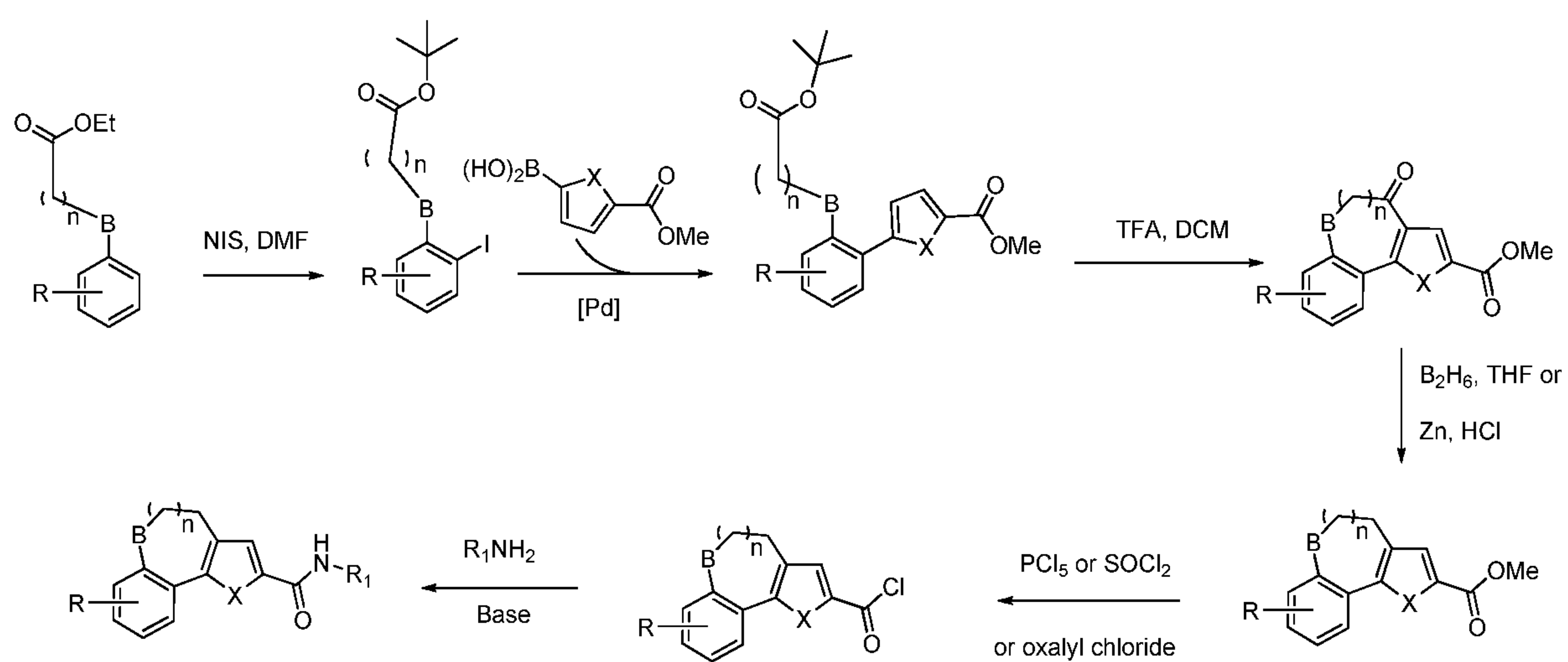


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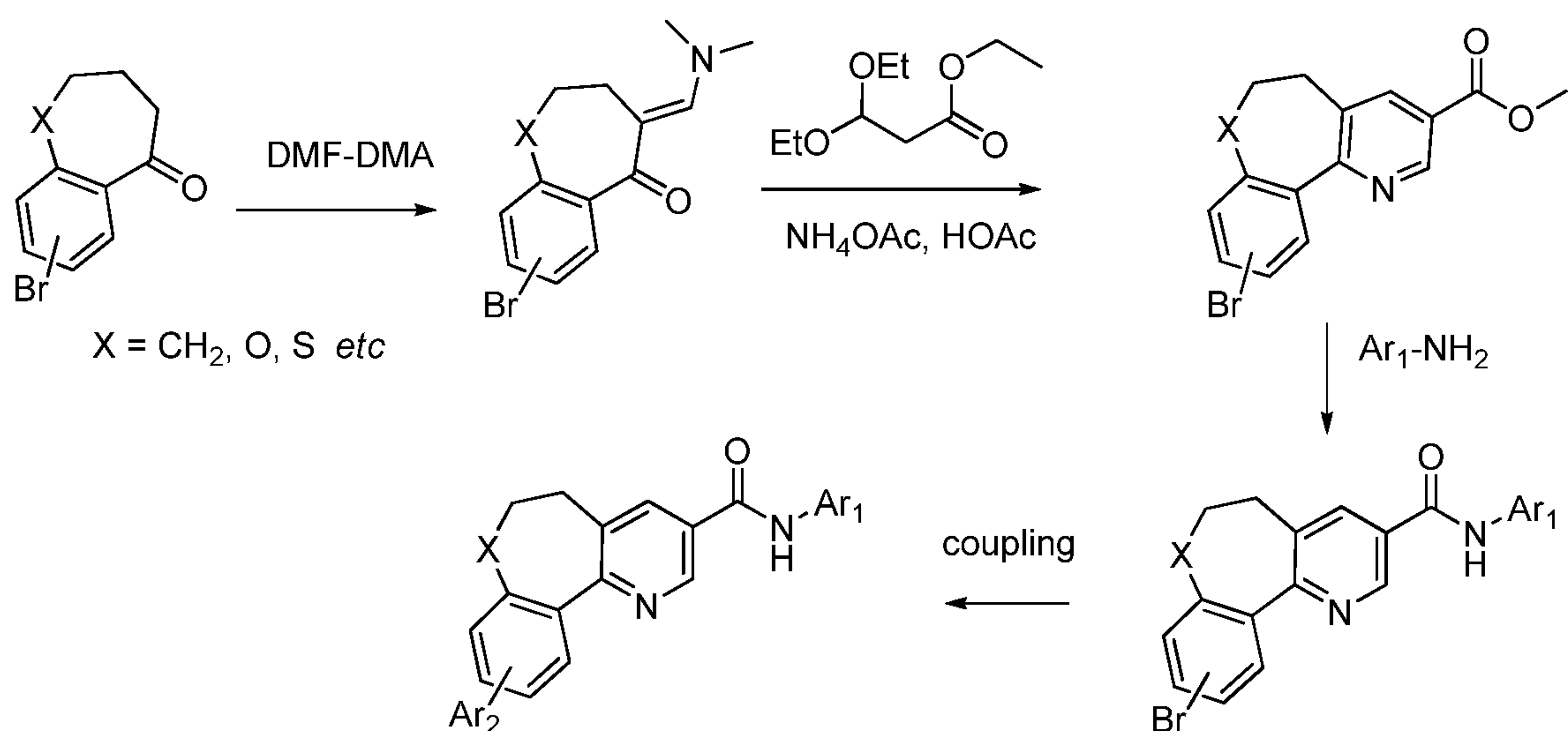
Scheme 4:



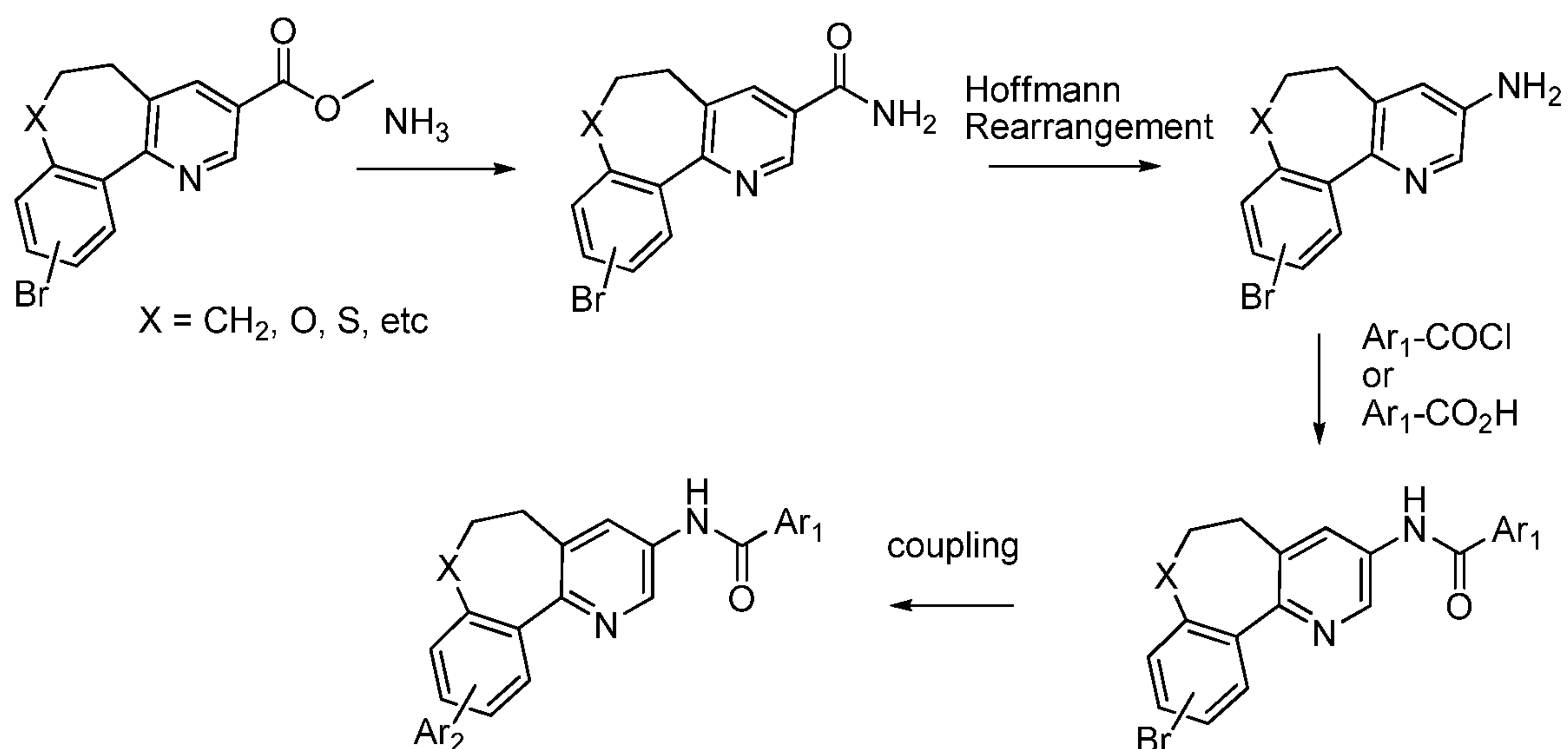
Scheme 5:



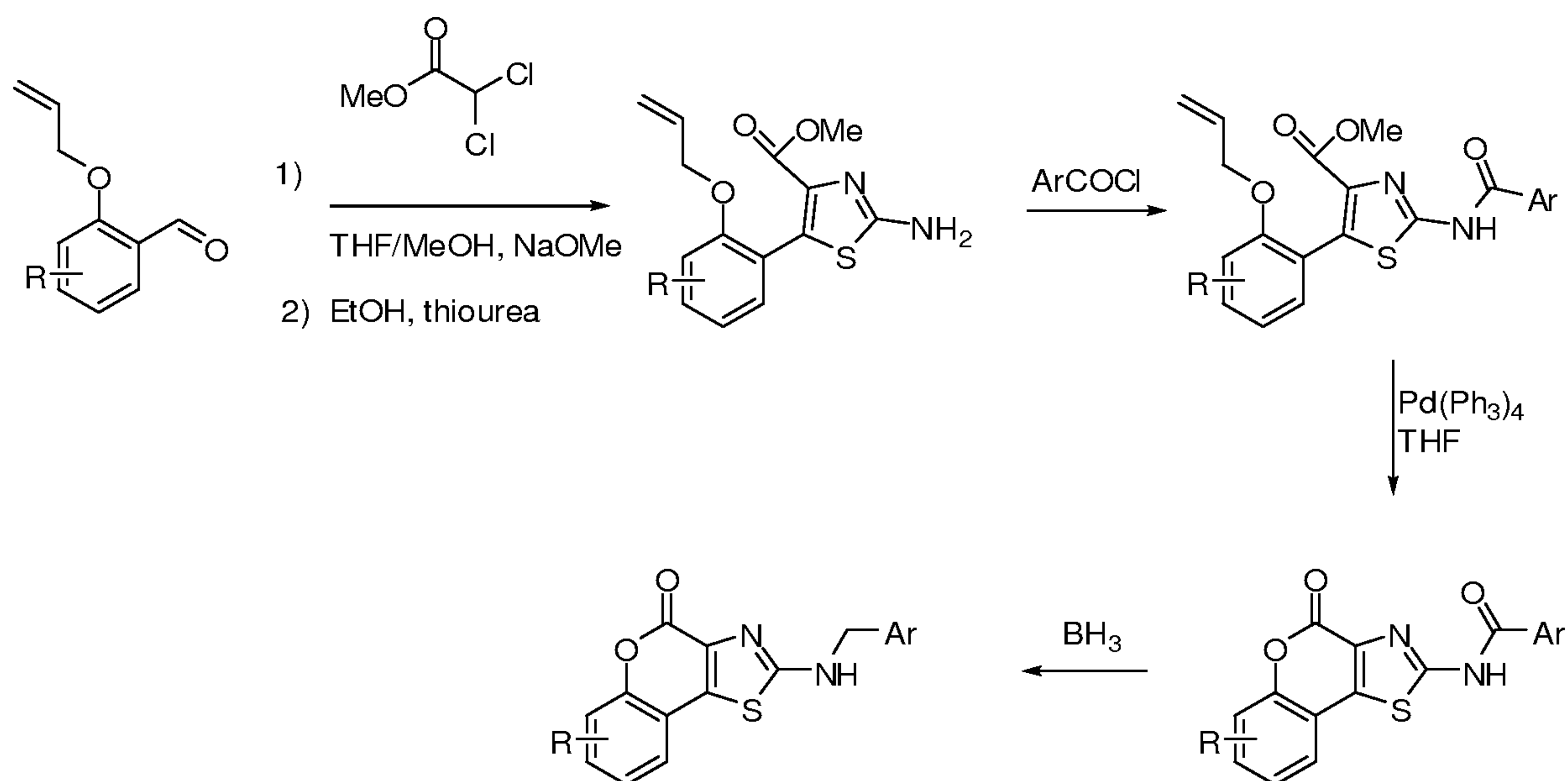
Scheme 6:



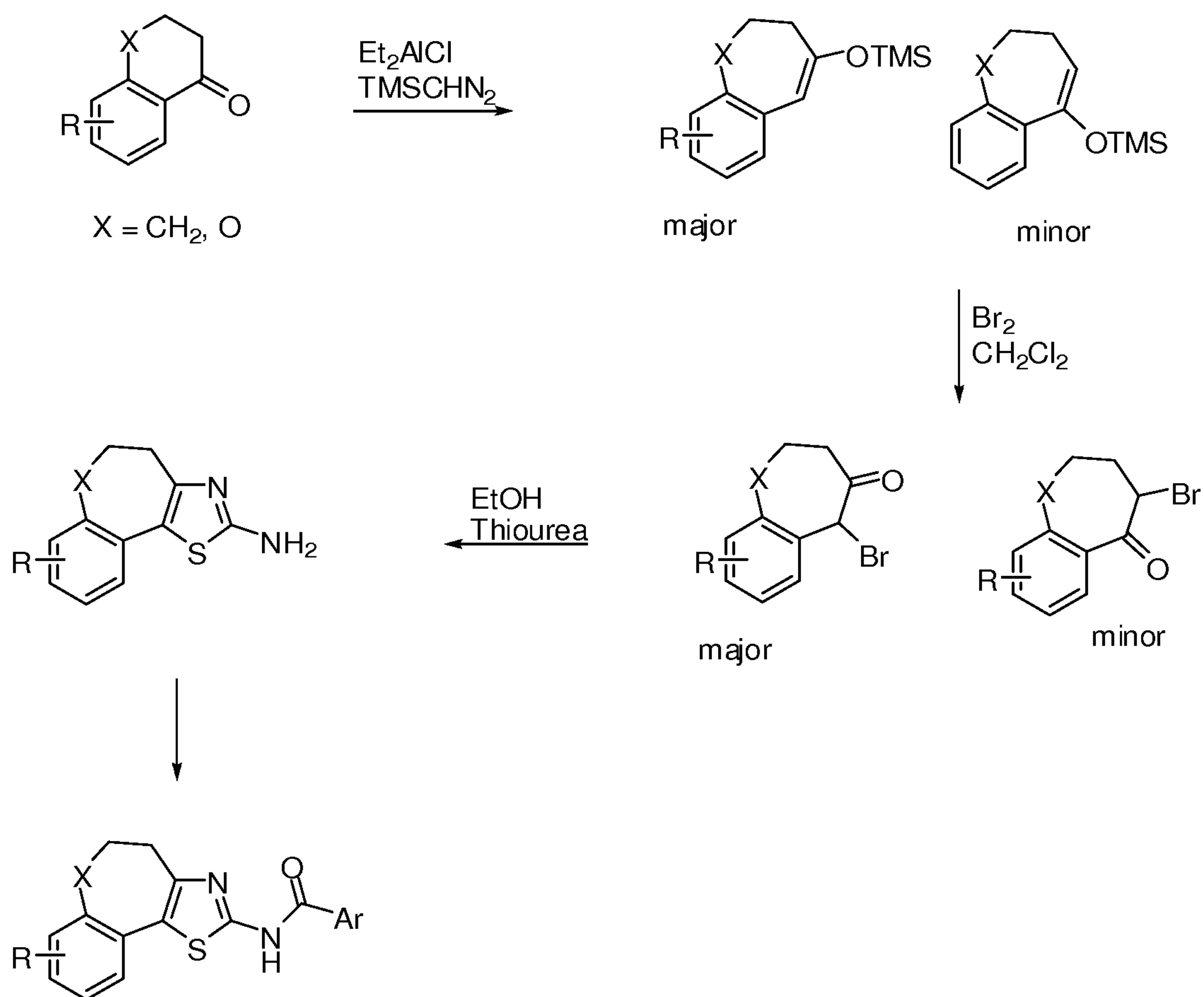
Scheme 7:



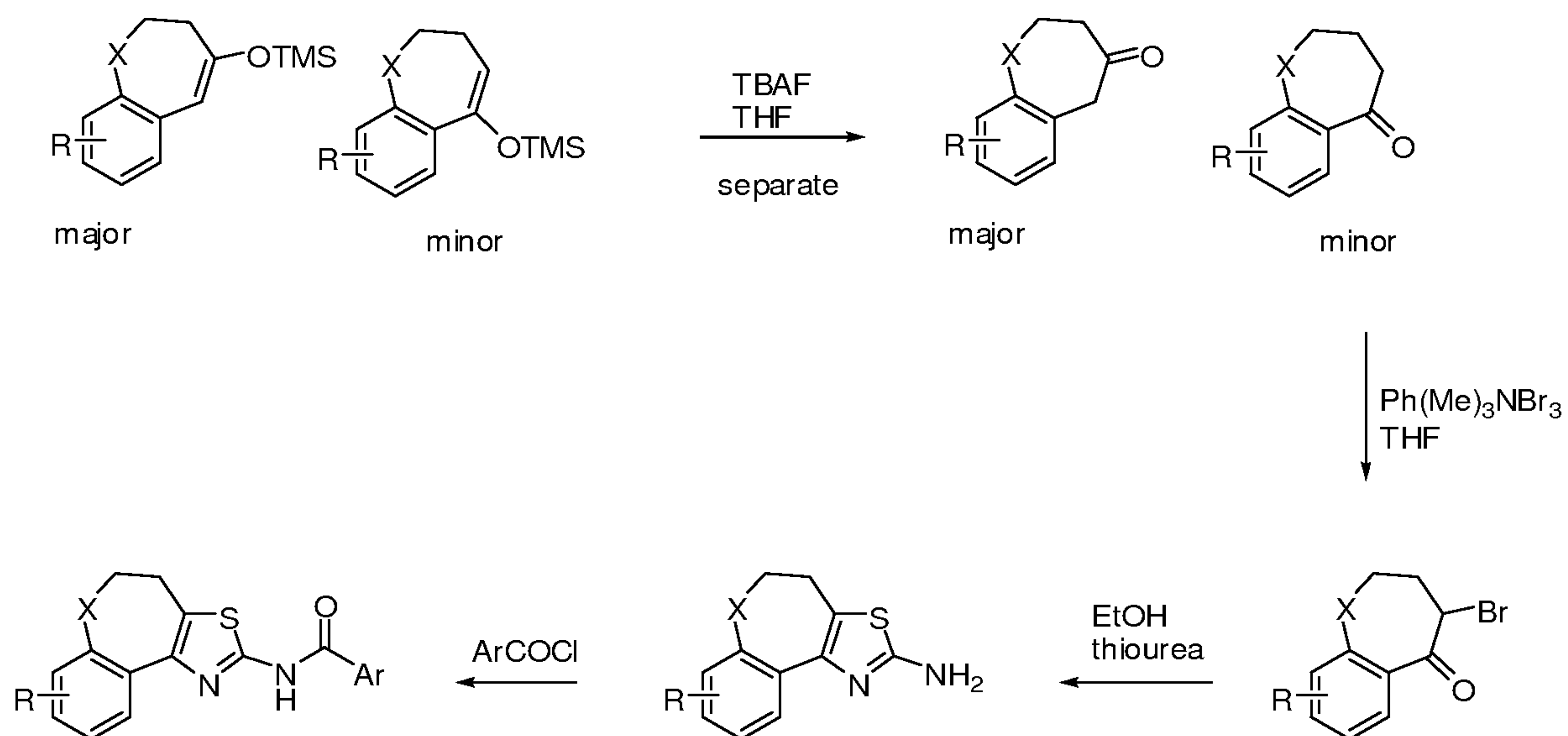
Scheme 8:



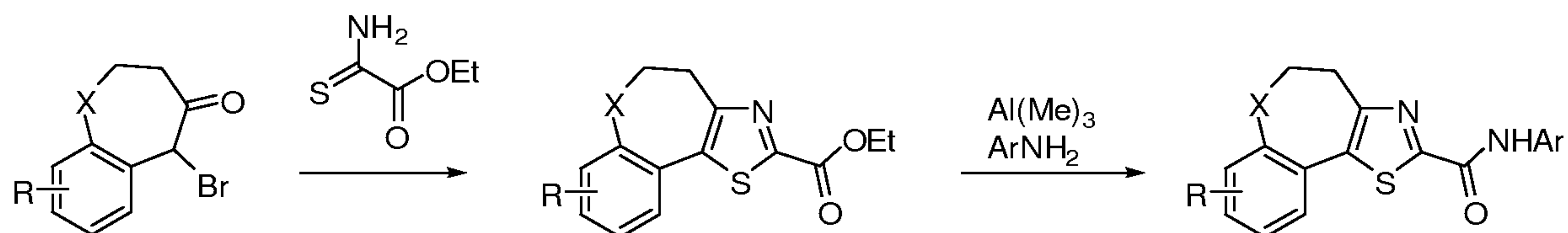
Scheme 9:



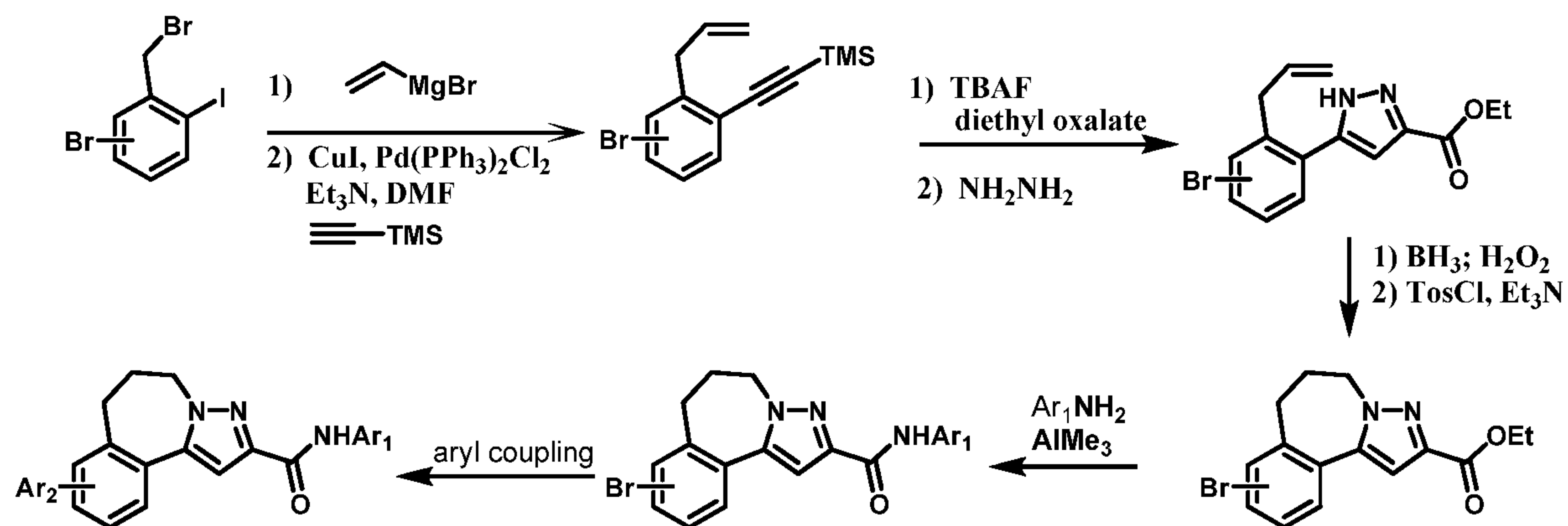
Scheme 10:



Scheme 11:

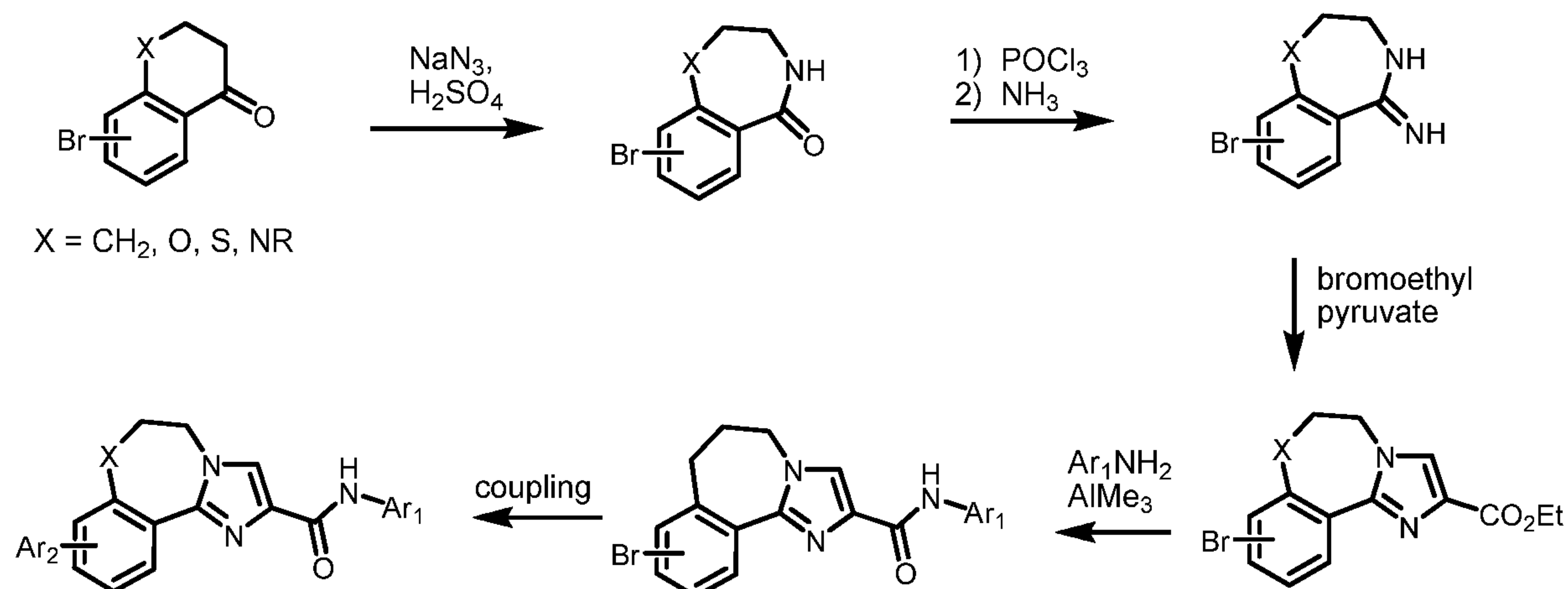


Scheme 12:

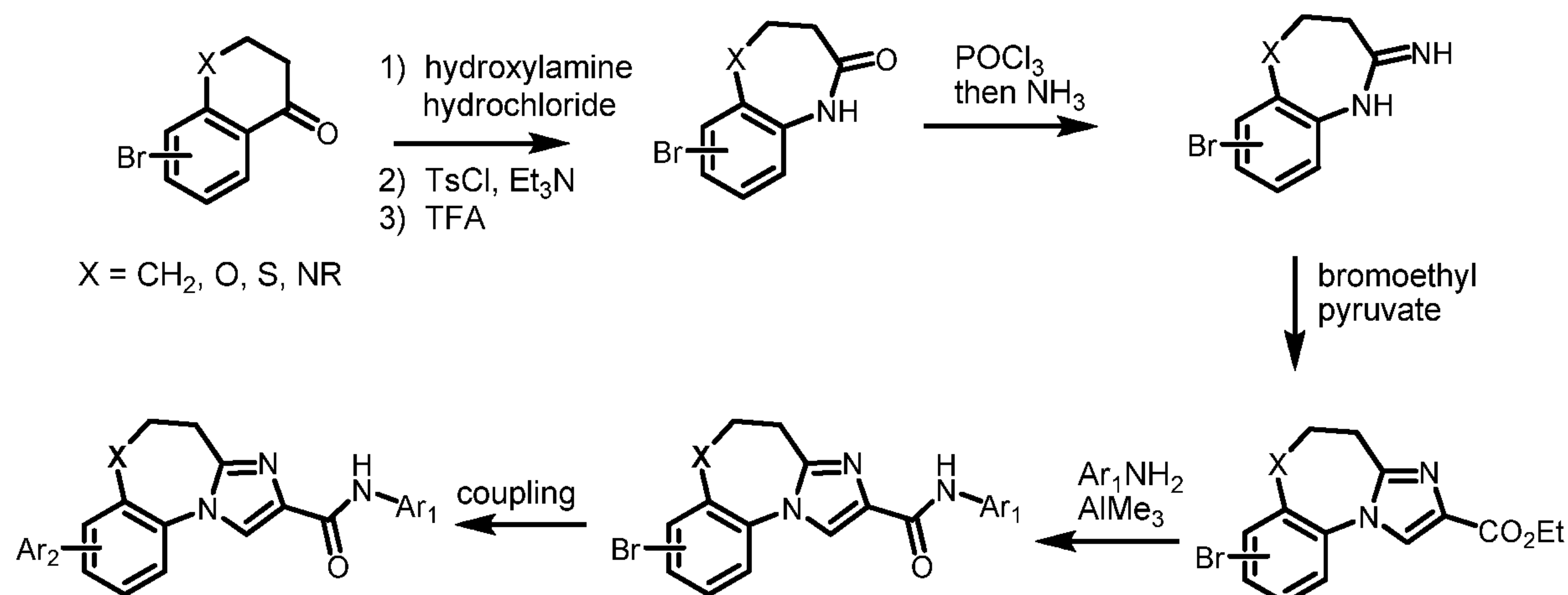


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Scheme 13:

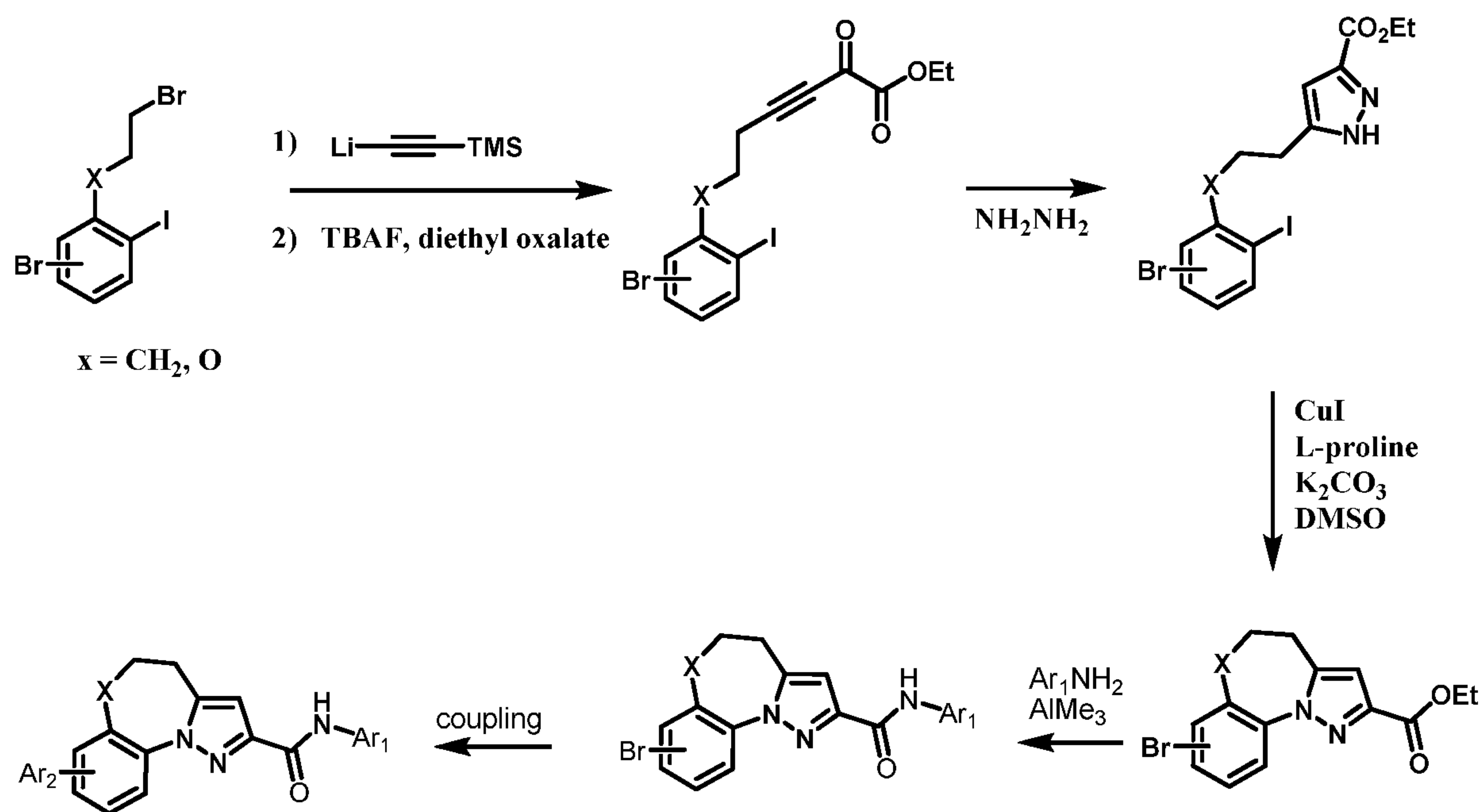


Scheme 14:



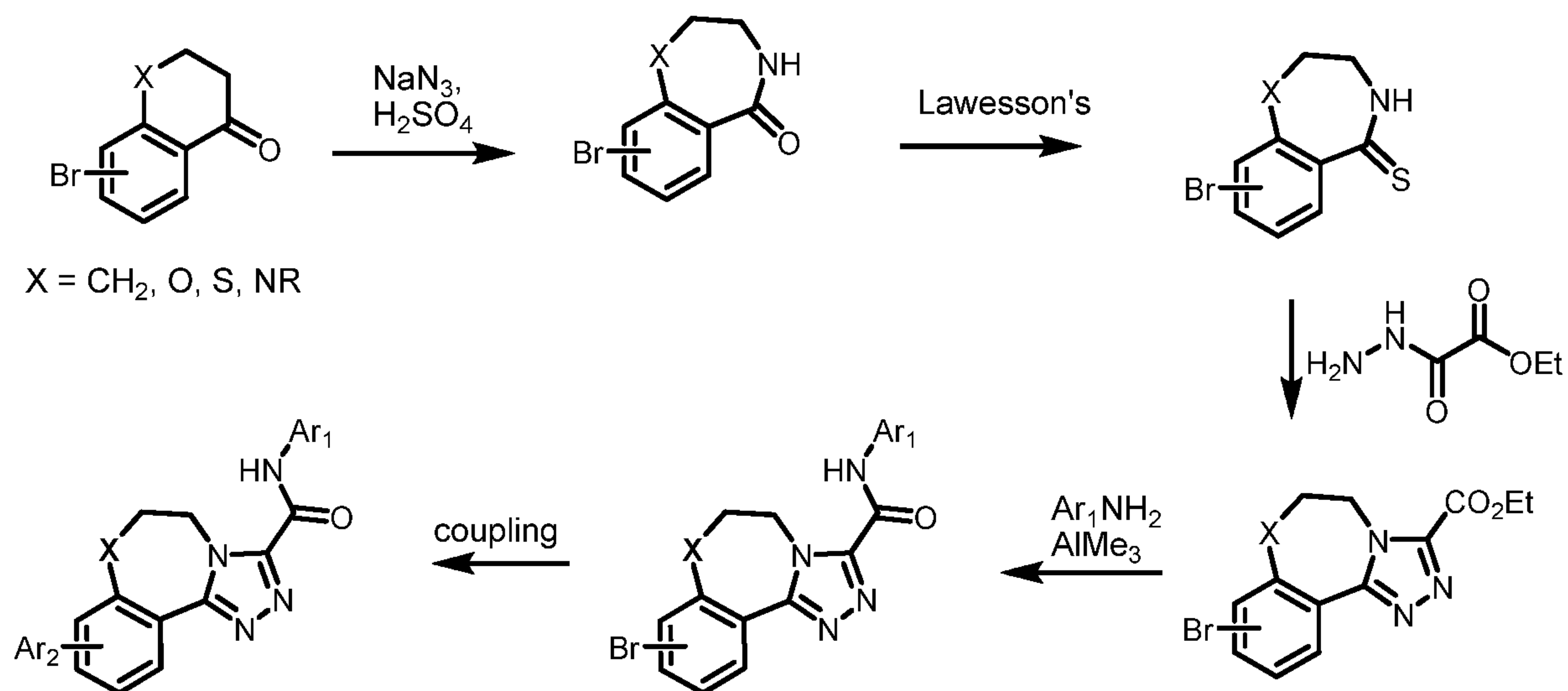
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Scheme 15:

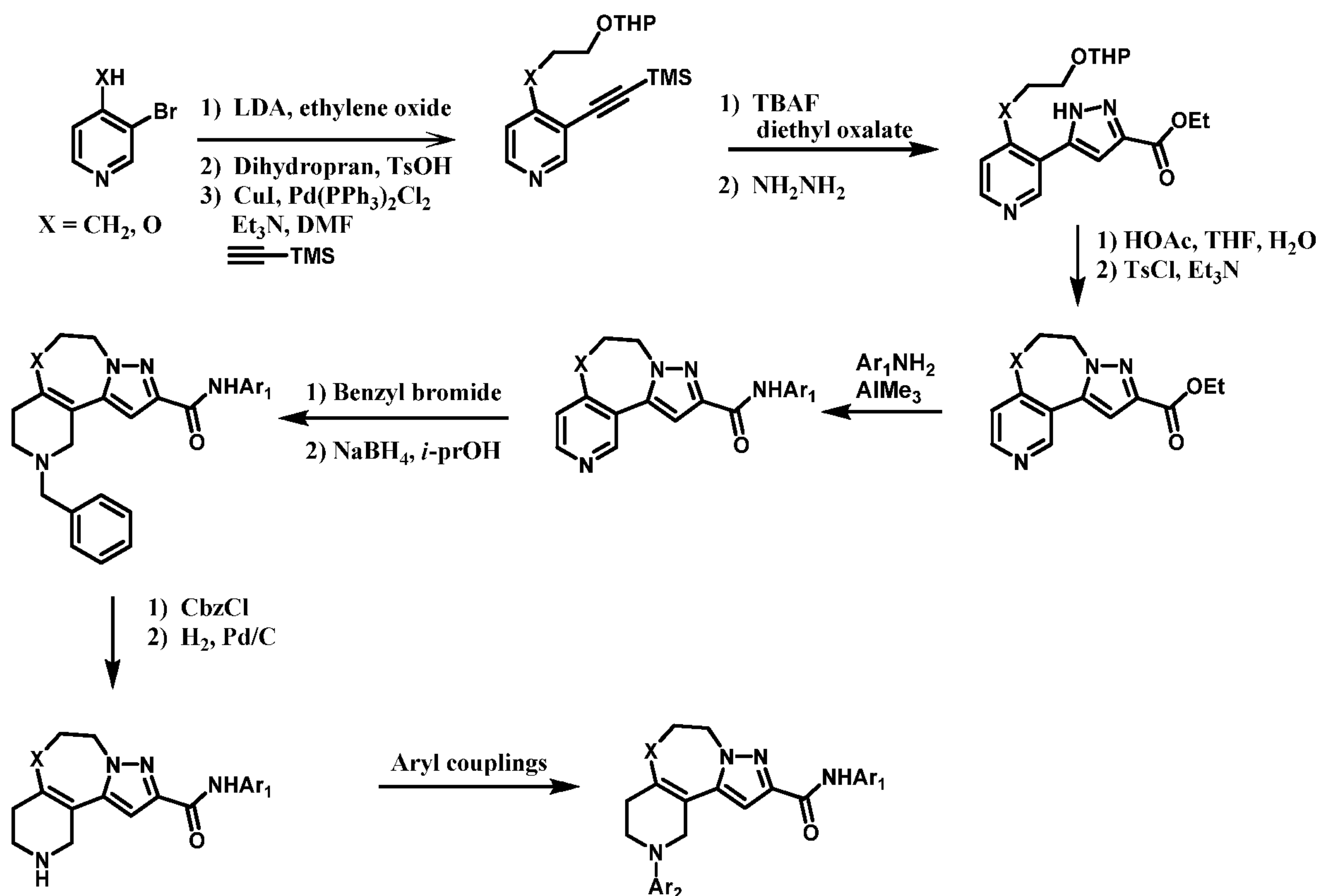


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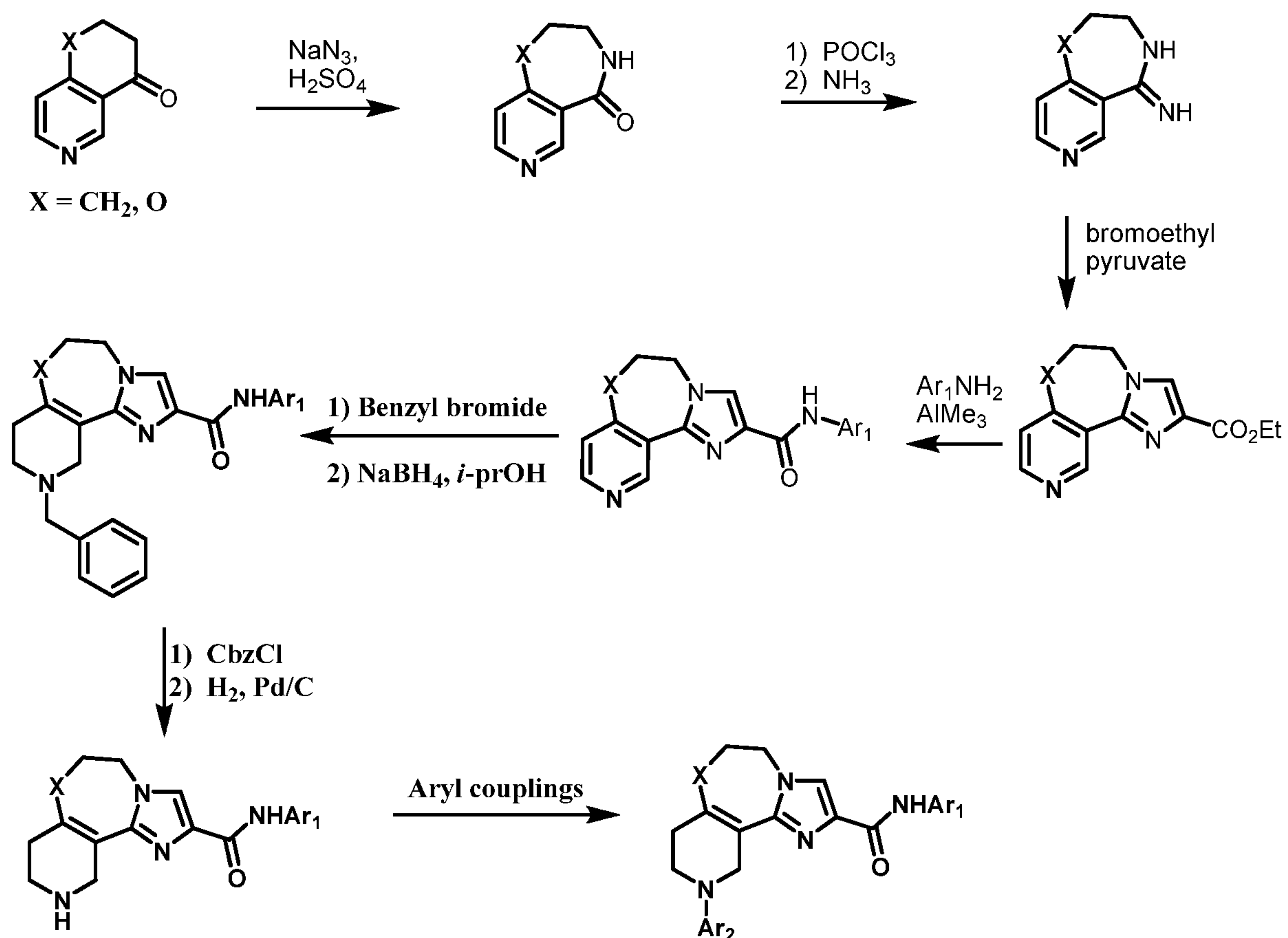
Scheme 16:



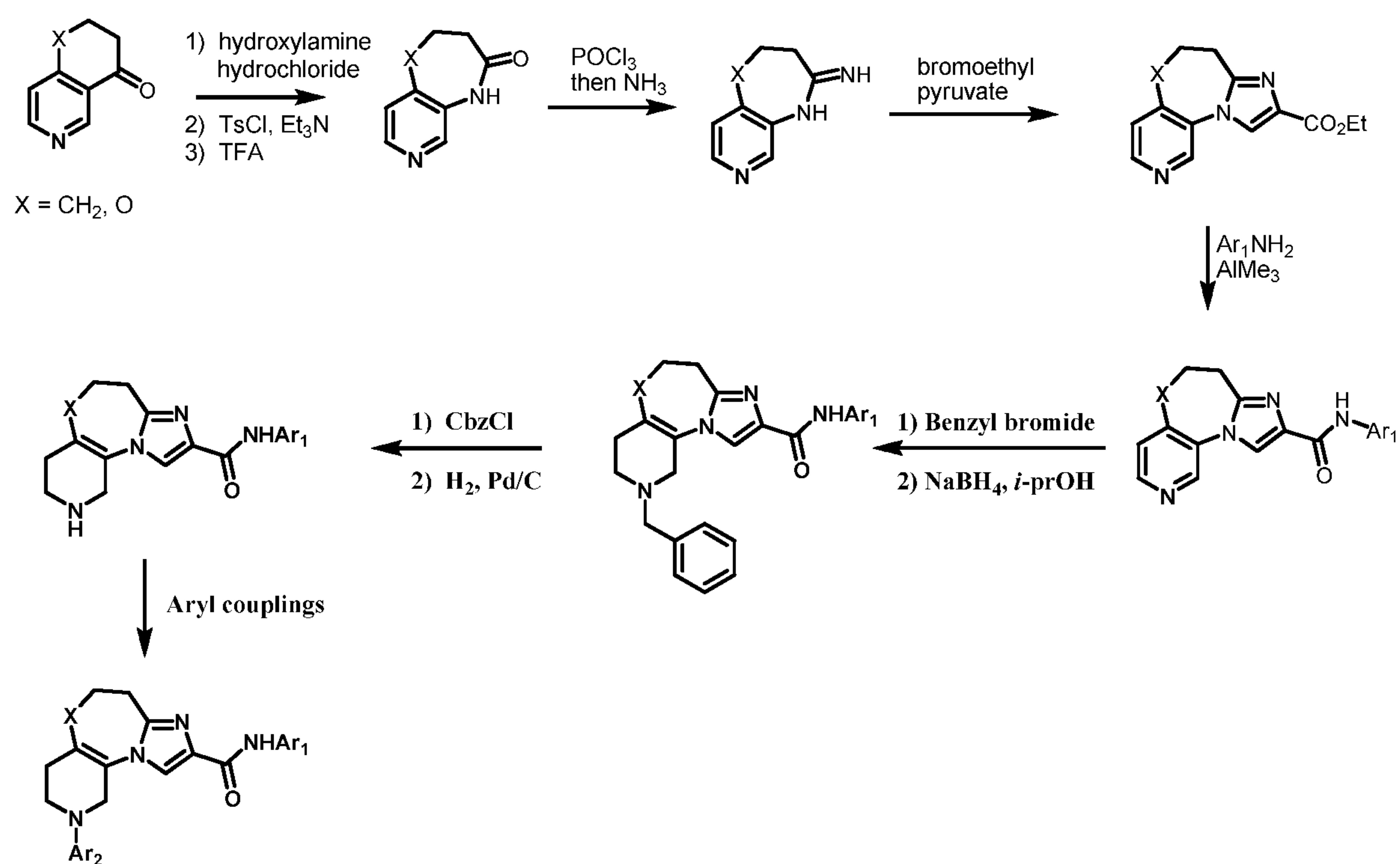
Scheme 17:



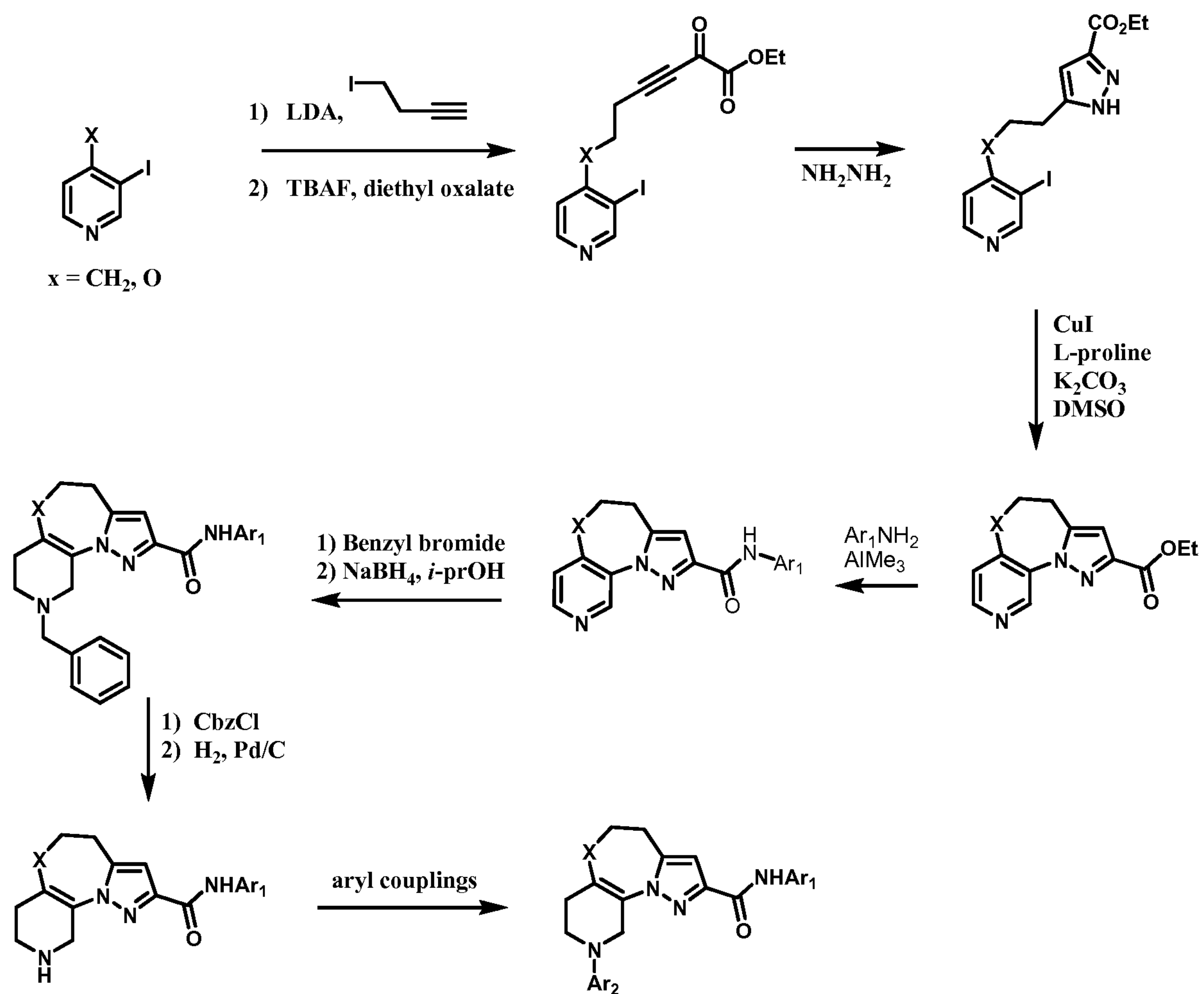
Scheme 18:



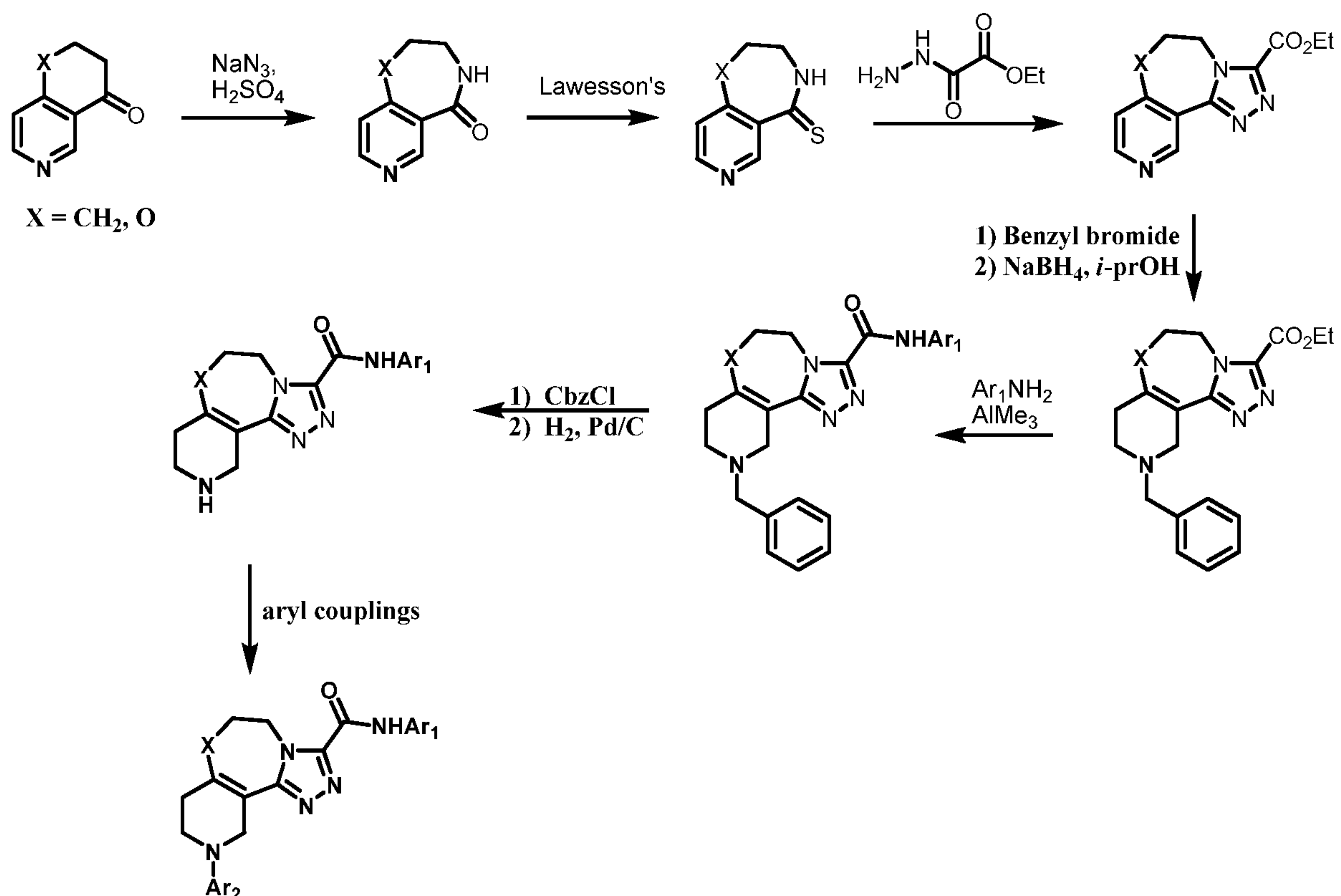
Scheme 19:



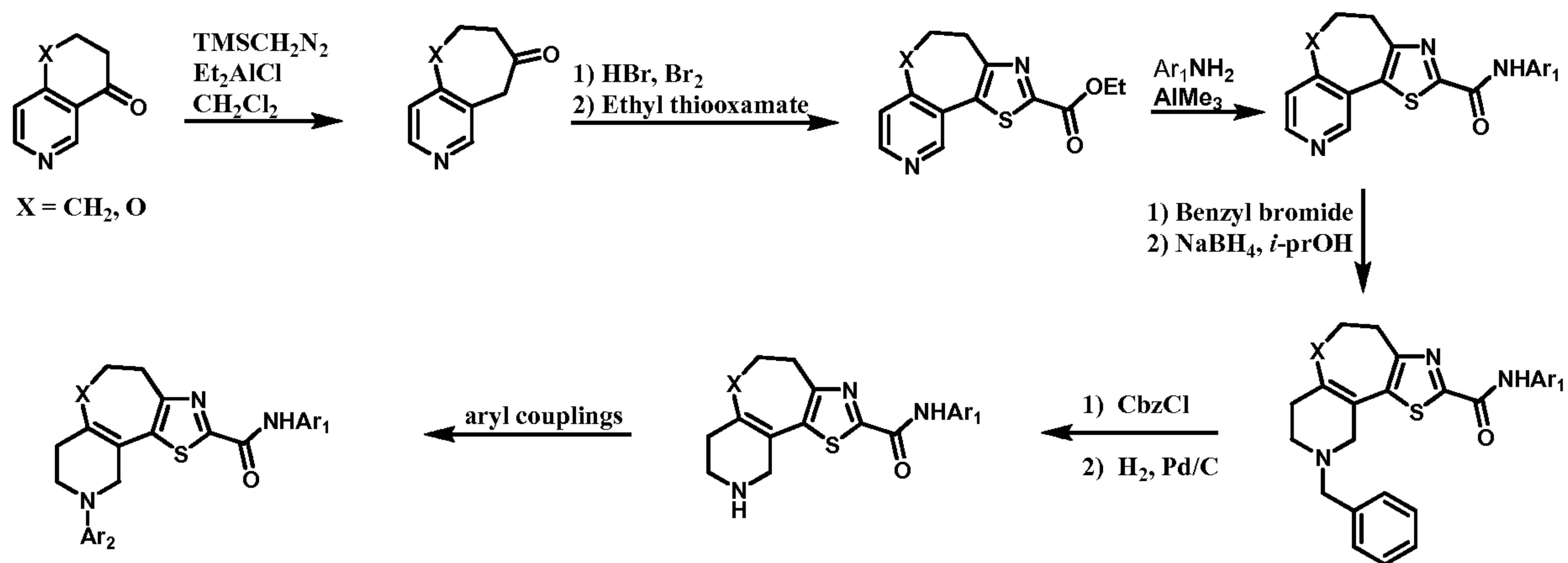
Scheme 20:



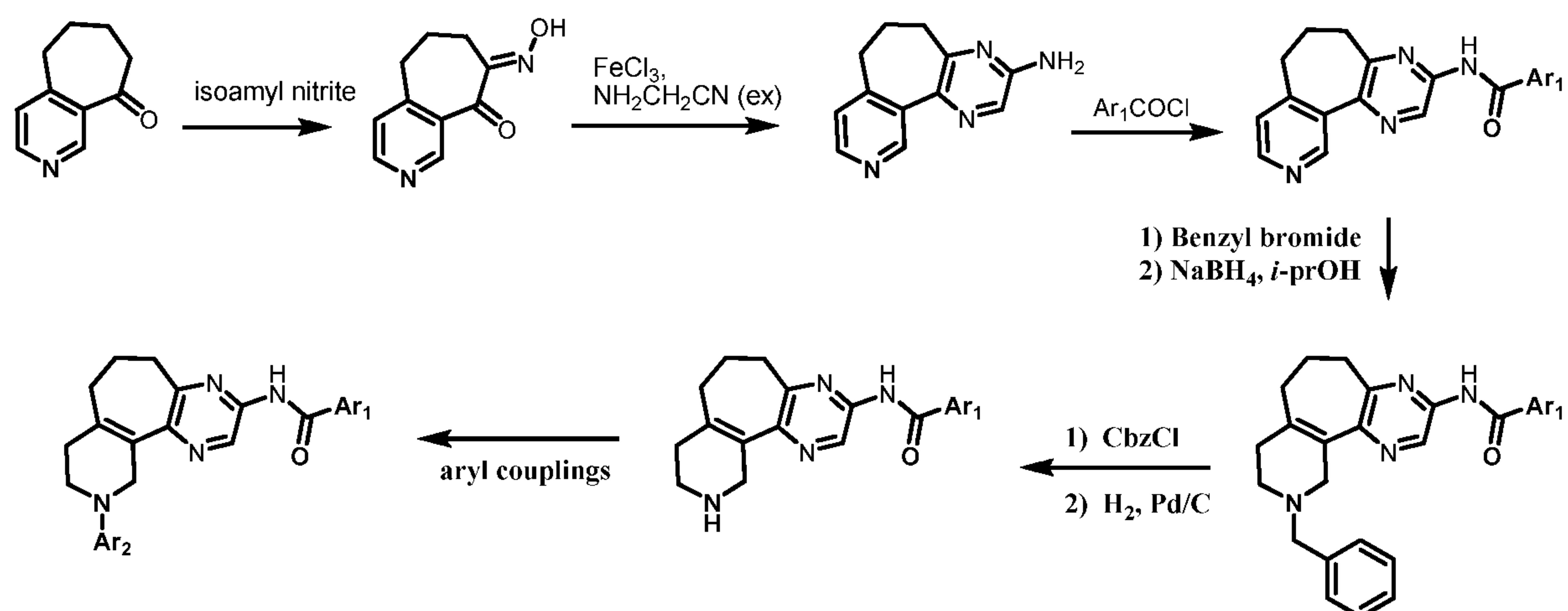
Scheme 21:



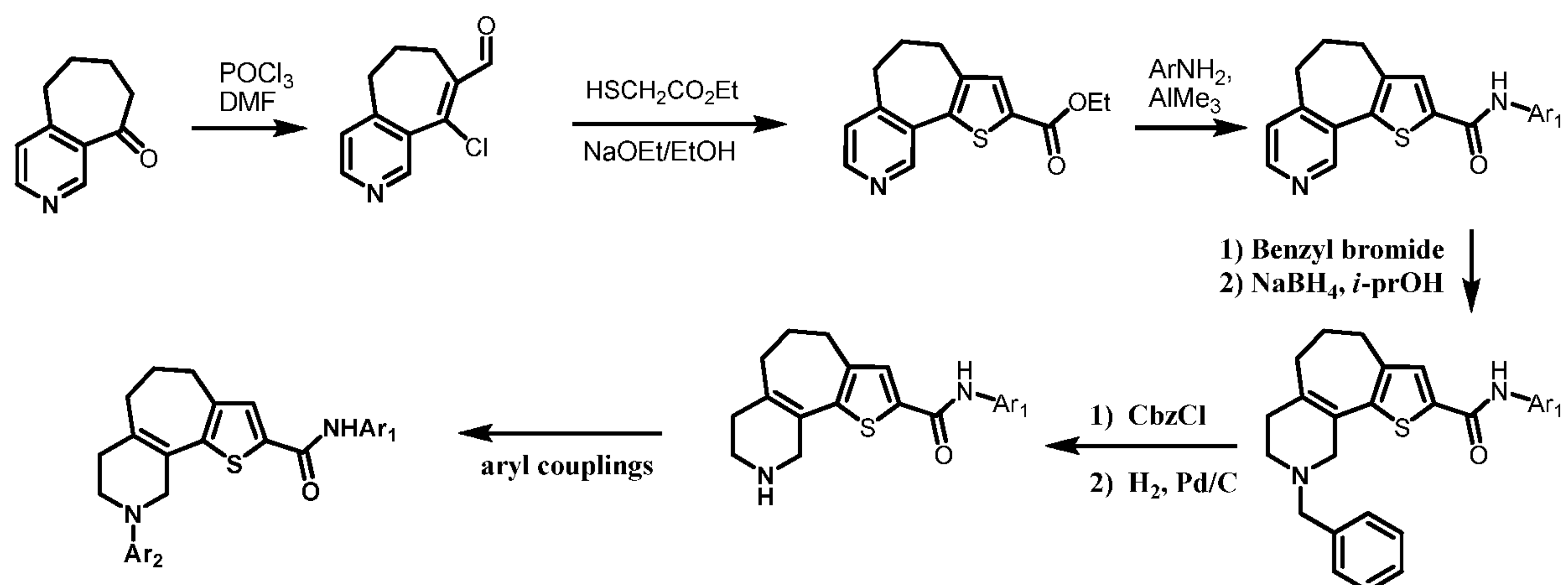
Scheme 22:



Scheme 23:

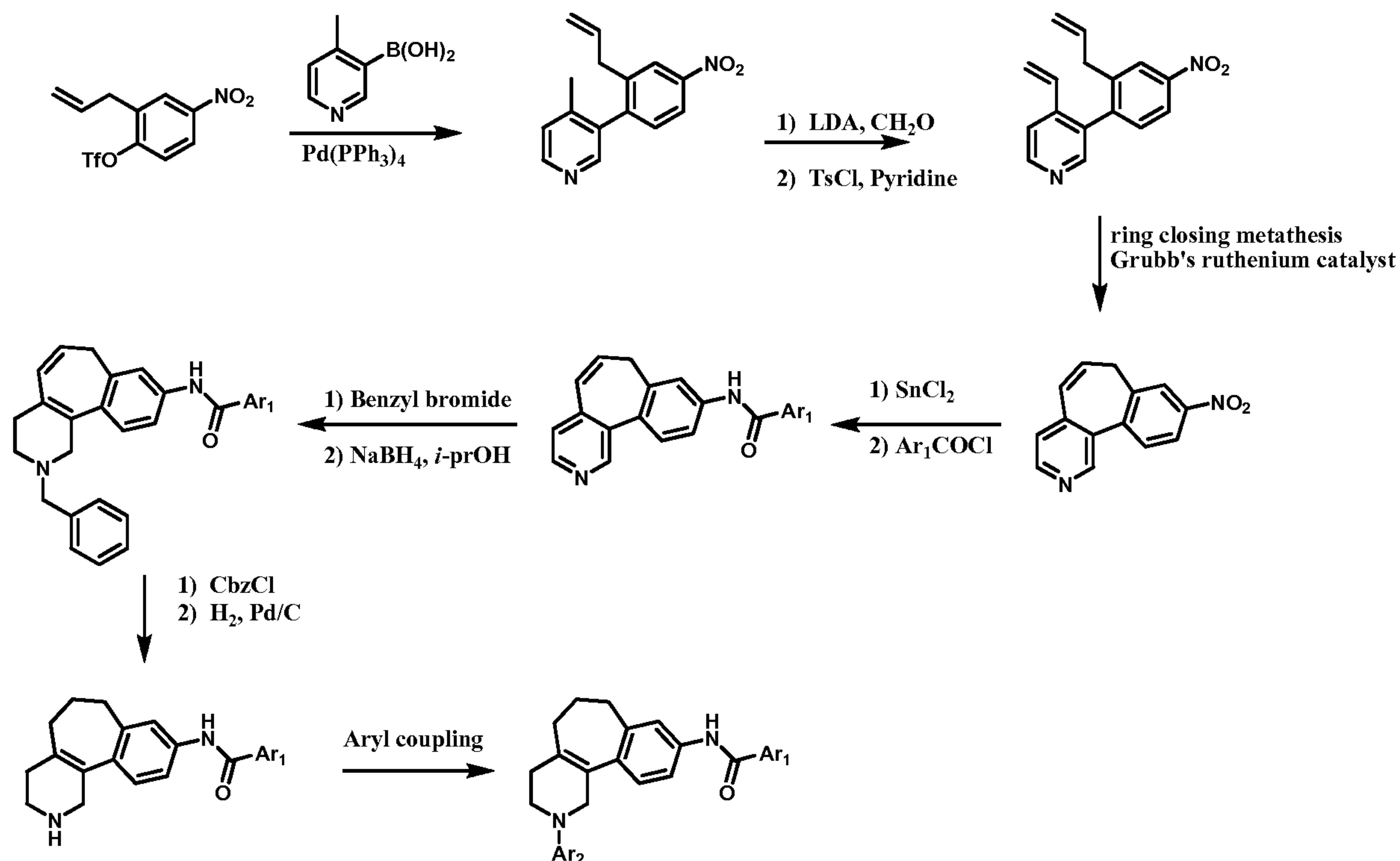


Scheme 24:



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Scheme 25:



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 NF κ B) 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 (IA), (I) through (XXX) or Tables 1-3, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of any one of formulas (IA), (I) through (XXX) or Tables 1-3, or a pharmaceutically acceptable salt 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.

5 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 (IA), (I) through (XXX), or Tables 1-3, or pharmaceutically acceptable salts 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

15 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt thereof, optionally in combination with one or more additional active agents.

25 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.

35 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.

5 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
10 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
15 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
20 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. Pharmacopia (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
25 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
30 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,
35 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt 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 (IA), (I) through (XXX), or Tables 1-3, or a pharmaceutically acceptable salt thereof can range from about 1 mg to about 5000 mg per day, preferably in an amount from about 50 mg to about 1500 mg per day, more preferably from about 75 mg to about 1000 mg per day. It is within the skill of the art to determine the appropriate dose and dosage form for a given patient.

ORAL DOSAGE FORMS

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art.

See generally, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

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

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

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

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

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

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

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algin, 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 any one of formulas (IA), (I) through (XXX), or Tables 1- 3, or a pharmaceutically acceptable salt thereof, in spheroids which further comprise microcrystalline cellulose and, optionally, hydroxypropylmethyl-cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

A specific controlled-release formulation of this invention comprises from about 6% to about 40% a compound of any one of formulas (IA), (I) through (XXX), or Tables 1-3 by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

PARENTERAL DOSAGE FORMS

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

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

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

TRANSDERMAL, TOPICAL, AND MUCOSAL DOSAGE FORMS

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

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA.

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

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

COMBINATION THERAPY

The methods for immunosuppression or for treating or preventing inflammatory conditions and immune disorders in a patient in need thereof can further comprise administering to the patient being administered a compound of this invention, an effective amount of one or more other active agents. Such active agents may include those used conventionally for immunosuppression or for inflammatory

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

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

In one embodiment relating to autoimmune and inflammatory conditions, the other therapeutic agent may be a steroid or a non-steroidal anti-inflammatory agent. Particularly useful non-steroidal anti-inflammatory agents, include, but are not limited to, aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, 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-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, 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. Molinoff and Raymond W. Ruddon eds., 9th ed 1996) and

Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

5 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, tripeleminamine, brompheniramine, hydroxyzine, cyclizine, meclizine, cyproheptadine, phenindamine, acrivastine, azelastine, levocabastine, and mixtures thereof. For a more
10 detailed description of antihistamines, see Goodman & Gilman's *The Pharmacological Basis of Therapeutics* (2001) 651-57, 10th ed).

Immunosuppressive agents include glucocorticoids, corticosteroids (such as Prednisone or Solumedrol), T cell blockers (such as cyclosporin A and FK506), purine analogs (such as azathioprine
15 (Imuran)), pyrimidine analogs (such as cytosine arabinoside), alkylating agents (such as nitrogen mustard, phenylalanine mustard, busulfan, and cyclophosphamide), folic acid antagonists (such as aminopterin and methotrexate), antibiotics (such as rapamycin, actinomycin D, mitomycin C, puramycin, and chloramphenicol), human IgG, antilymphocyte globulin (ALG), and antibodies (such as anti-CD3 (OKT3), anti-CD4 (OKT4), anti-CD5, anti-CD7, anti-IL-2 receptor, anti-alpha/beta TCR,
20 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,
25 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
30 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
35 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

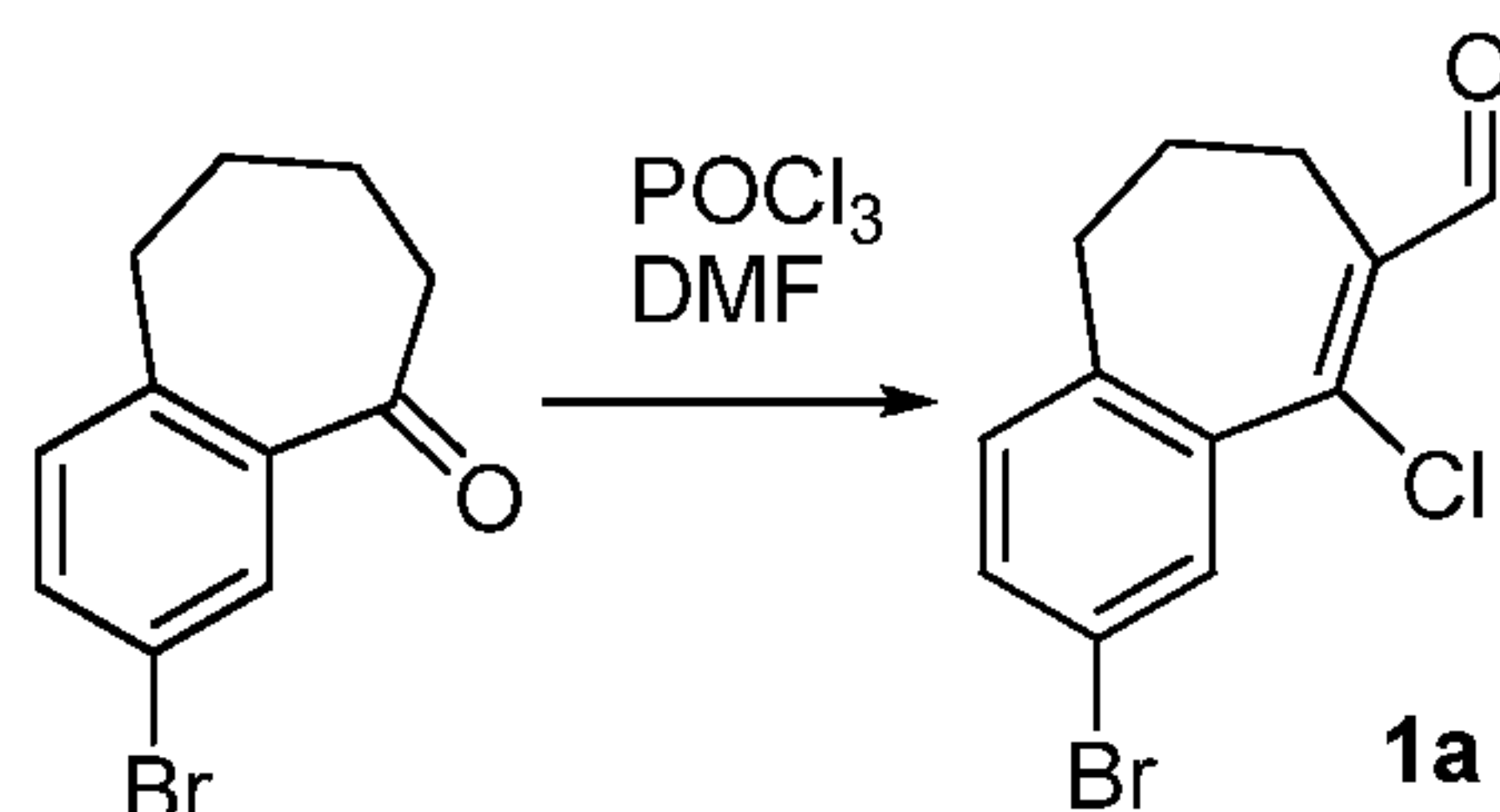
Without wishing to be bound by theory, it is believed that the compounds of this invention inhibit CRAC ion channels, thereby inhibiting production of IL-2 and other key cytokines involved with inflammatory and immune responses. The examples that follow demonstrate these properties.

MATERIALS AND GENERAL METHODS

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^1H -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.

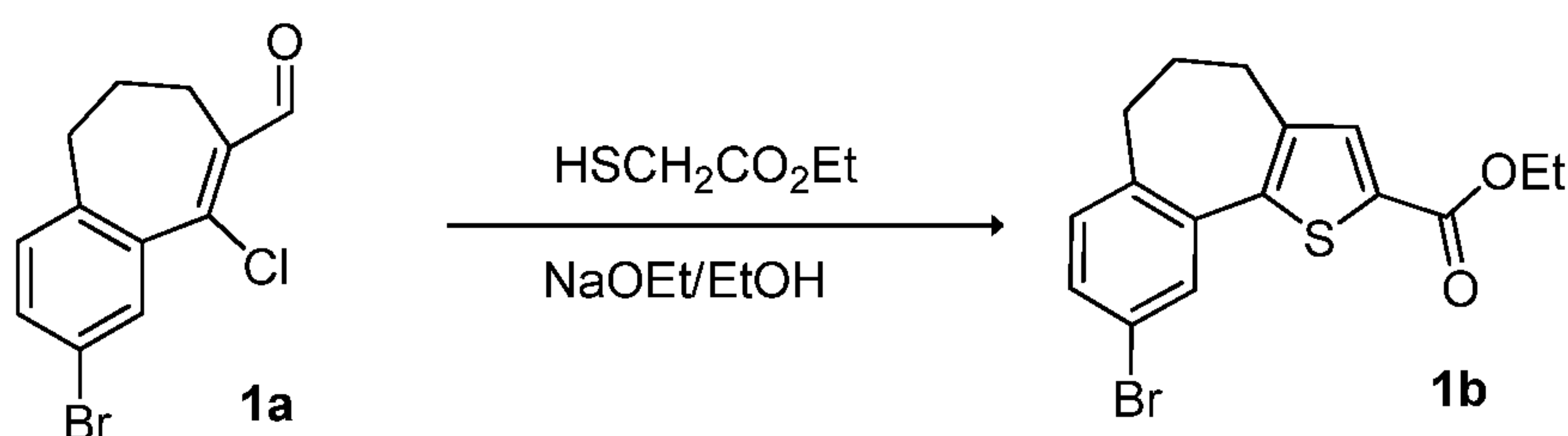
Patch clamp experiments were performed in the tight-seal whole-cell configuration at 21-25°C. High resolution current recordings were acquired by a computer-based patch clamp amplifier system (EPC-9, HEKA, Lambrecht, Germany). Patch pipettes had resistances between 2-4 M Ω after filling with the standard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

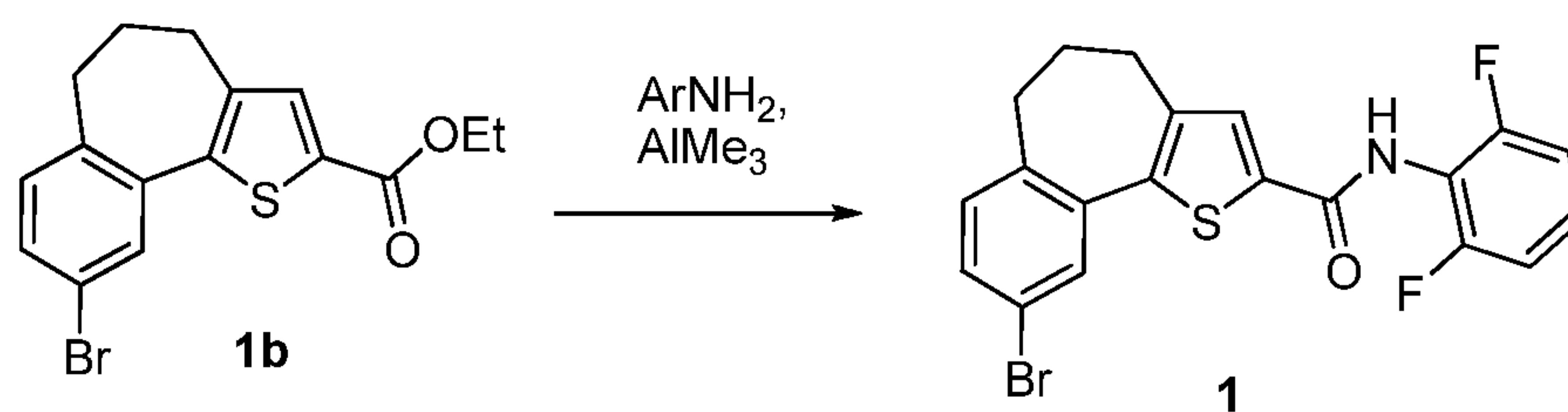
5 POCl₃ (2.0 mmol, 306 mg) was added dropwise to 2 mL of dry DMF under N₂ at 0°C with stirring. After addition, the solution was stirred at 0°C for 5 min. A solution of 8-Bromo-1-benzosuberone (2.0 mmol, 478 mg) in 1.0 mL of dry DMF was added dropwise to the resulting solution at 0°C. The mixture was stirred at 0°C for 30 min, and then heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and poured into an aq. solution of NaOAc. The mixture was extracted with Et₂O (3
10 times), and the organic phase was dried (Na₂SO₄) and concentrated under vacuum. Flash chromatography of the residue on silica gel (eluted with 0-100% EtOAc in hexanes) gave 485 mg (85%) of compound 1a as yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 10.37 (s, 1H), 7.64 (s, 1H), 7.37-7.19 (m, 2H), 2.60-2.55 (m, 2H), 2.24-2.08 (m, 4H). MS (ESI) [M+H⁺]: 287, 285.



15 Into a solution of NaOEt (1.2 mmol, 82 mg) in 10 mL of dry EtOH was added ethyl mercaptoacetate (1.2 mmol, 144 mg) at 0°C. The mixture was stirred at 0°C for 30 min. Then a solution of 2-bromo-9-chloro-6,7-dihydro-5H-benzo[7]annulene-8-carbaldehyde (1a) (1.0 mmol, 285 mg) prepared above in 1 mL of EtOH was added dropwise over 5 min at 0°C. The mixture was stirred at rt
20 for 2 hours, then boiled for 30 minutes, cooled and concentrated. The residue was dissolved with CH₂Cl₂; the solution was washed with saturated NH₄Cl and brine, dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (eluted with 0-30% EtOAc in hexanes) gave 328 mg (78%) of compound 1b as a white solid.

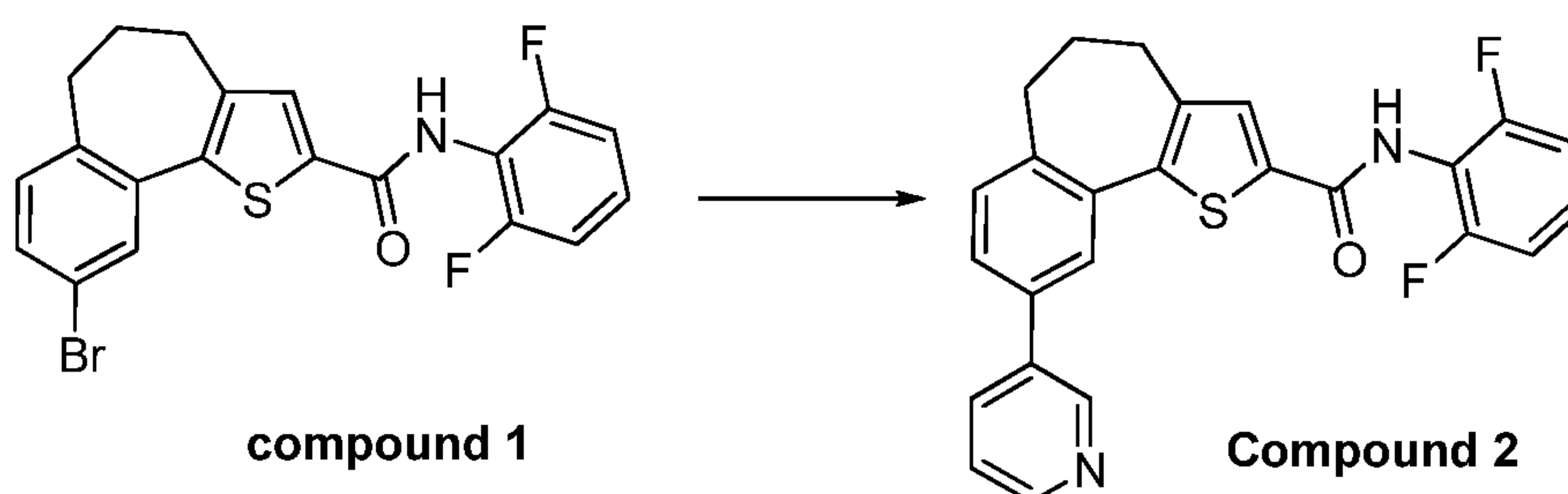
25 ¹H NMR (400 MHz, CDCl₃) δ 7.62-1.17 (m, 3), 4.36 (q, J = 7.0 Hz, 2H), 2.65-2.57 (m, 4H), 2.24-2.17 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H). MS (ESI) [M+H⁺]: 353, 351.



Into a solution of compound 1b (105 mg, 0.30 mmol) 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 CH₂Cl₂ (2X). The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-30% EtOAc in hexanes) gave 97 mg (75%) of Compound 1 as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.61-7.15 (m, 5), 7.02-6.96 (t, J = 8.0 Hz, 2H), 2.69-2.61 (m, 4H), 2.27-2.22 (m, 2H). MS (ESI) [M+H⁺]: 436, 434.

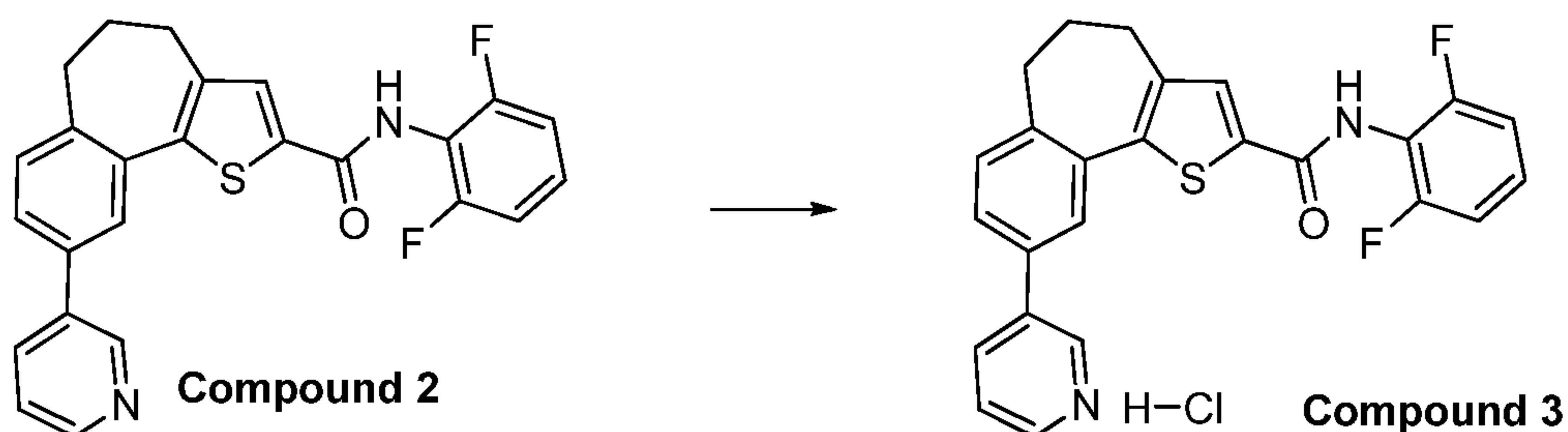
Compound 2:



A mixture of compound 1 (43 mg, 0.10 mmol), 3-pyridinylboronic acid (20 mg, 0.16 mmol), and Pd(Ph₃)₄ (23.0 mg, 0.02 mmol) in EtOH (1 mL) was degassed by vacuum/N₂-filled method (4X). The mixture was heated to 85 °C overnight, cooled to room temperature, concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-30% EtOAc in hexanes) gave 37 mg (85%) of compound 2 as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.87-7.20 (m, 9 H), 7.02-6.96 (t, J = 8.0 Hz, 2H), 2.75-2.66 (m, 4H), 2.35-2.25 (m, 2H). MS (ESI) [M+H⁺]: 433.

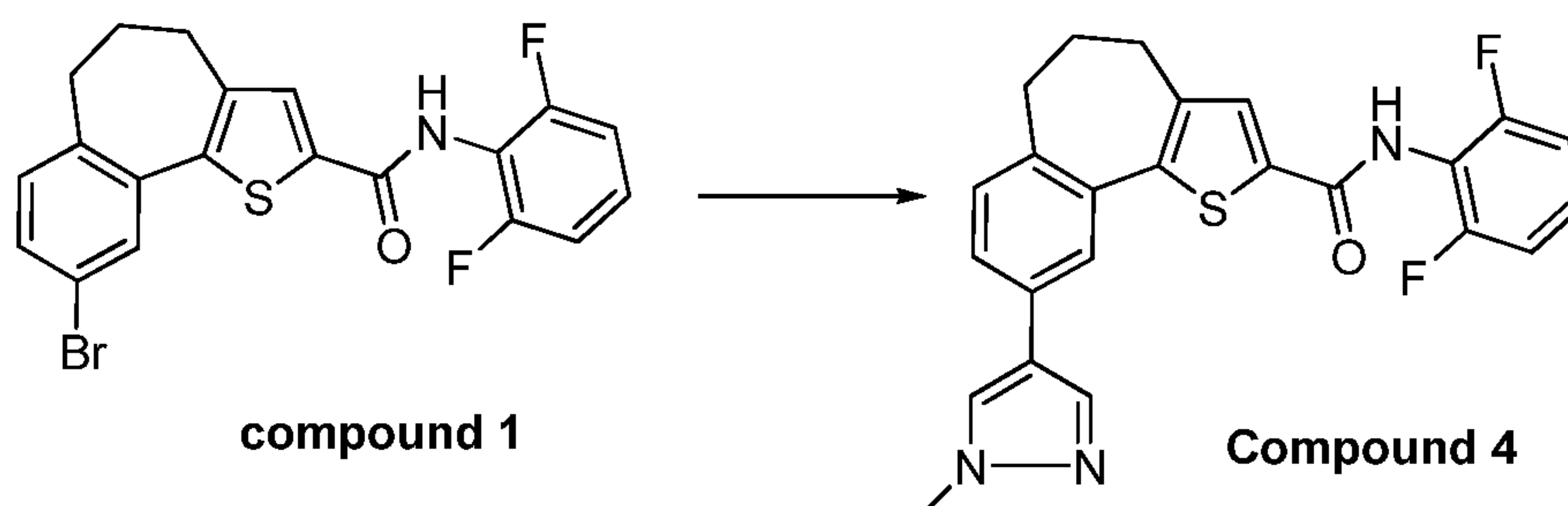
Compound 3:



Into a solution compound 2 (20mg) in CH₂Cl₂ (1.0 mL) at room temperature was added a solution of 2M HCl in Et₂O (0.05 mL, 0.1 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 Et₂O and dried to give 21 mg of compound 3 as a white solid.

5 MS (ESI) [M-Cl]: 433

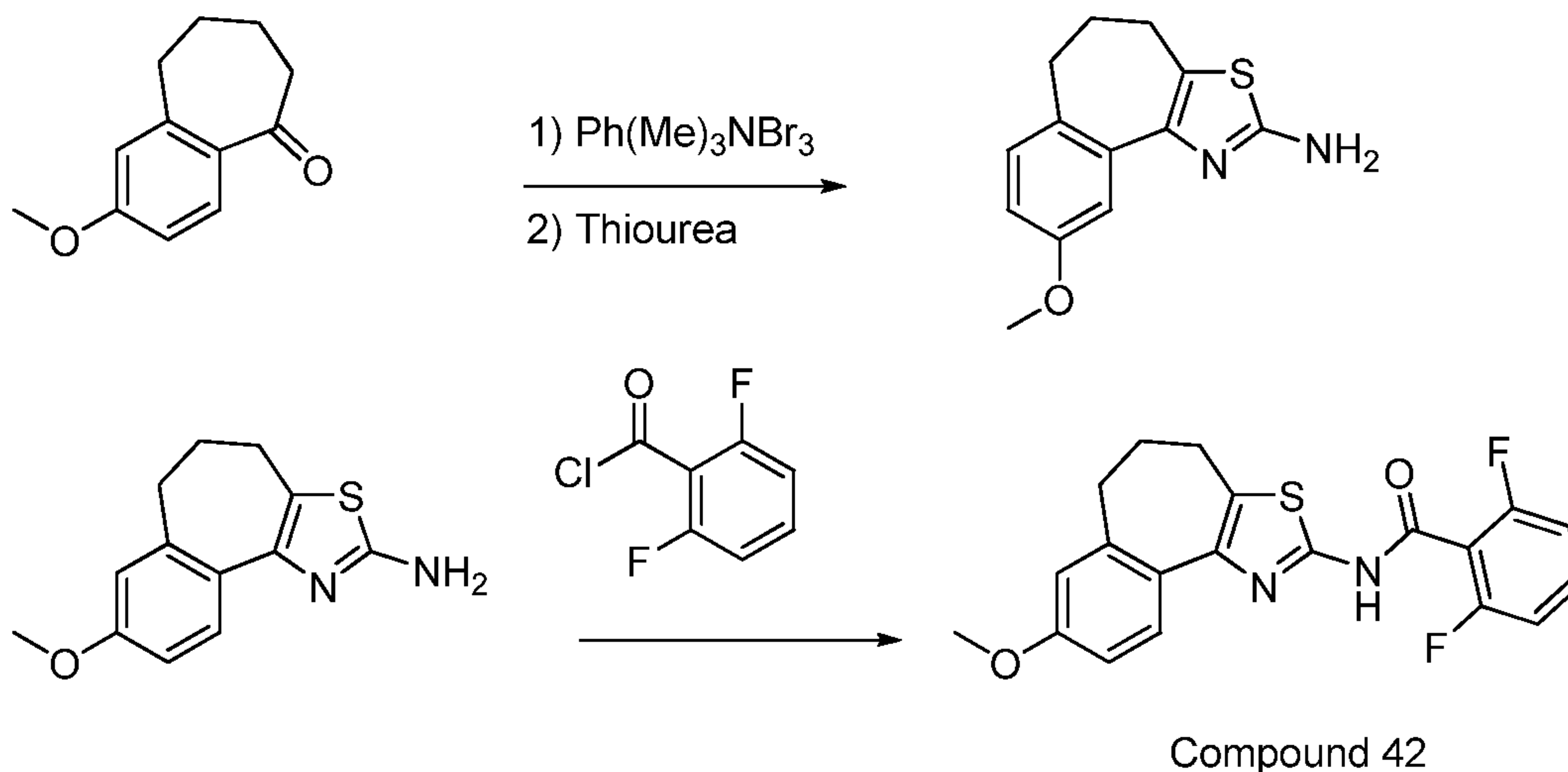
Compound 4:



Compound 4 was prepared from compound 1 and 1-methyl-1H-4-pyrazolylboronic acid as described for the preparation of Compound 2.

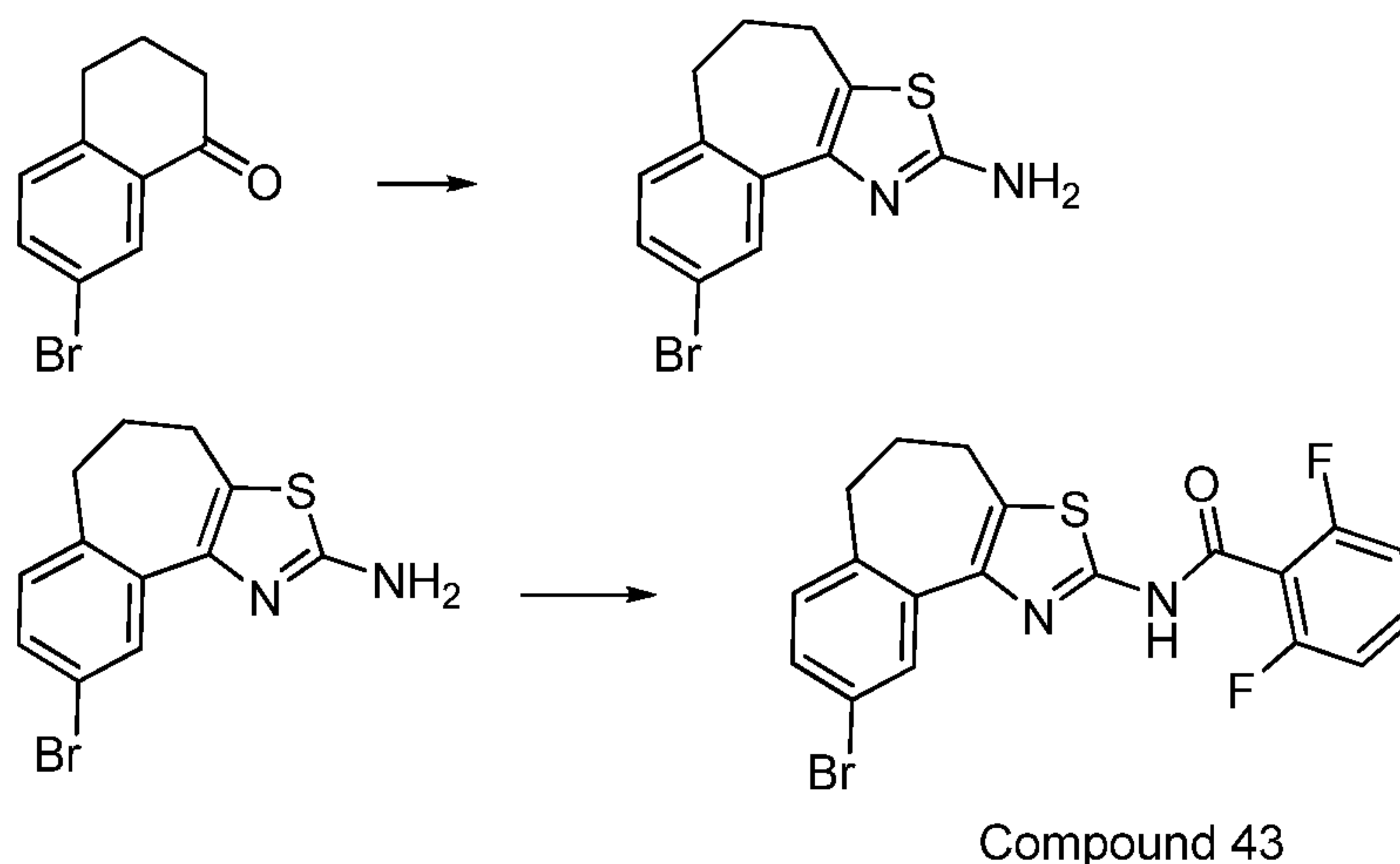
¹H NMR (400 MHz, CDCl₃) δ 7.77-7.19 (m, 7H), 7.01-7.97 (t, 2H, J = 8.0 Hz), 3.95 (s, 3H), 2.70-2.65 (m, 4H), 2.28-2.21 (m, 2H). MS (ESI) [M+H⁺]: 436.

Compound 42:



¹H NMR (300 MHz, CDCl₃) δ 11.3 (br s, 1H, NH), 7.69 (d, J = 8.5 Hz, 1H), 7.34-7.26 (m, 1H), 6.78 (t, J = 8.2 Hz, 2H), 6.76 (dd, J = 8.2, 2.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 3.84 (s, 3H), 2.93 (t, J = 7.2 Hz), 2.66-2.62 (m, 2H), 2.18-2.10 (m, 2H). MS (ESI) [M+H⁺]: 387.

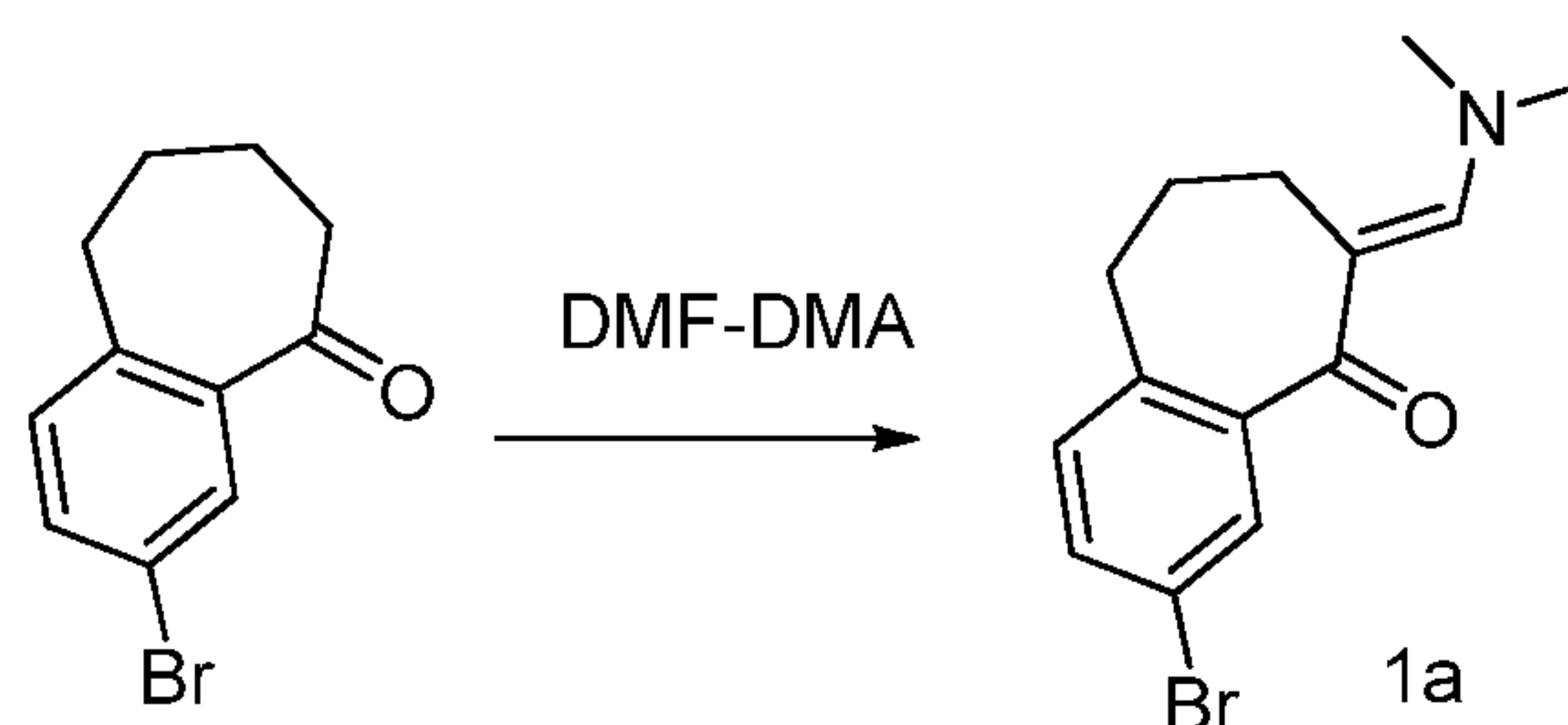
Compound 43:



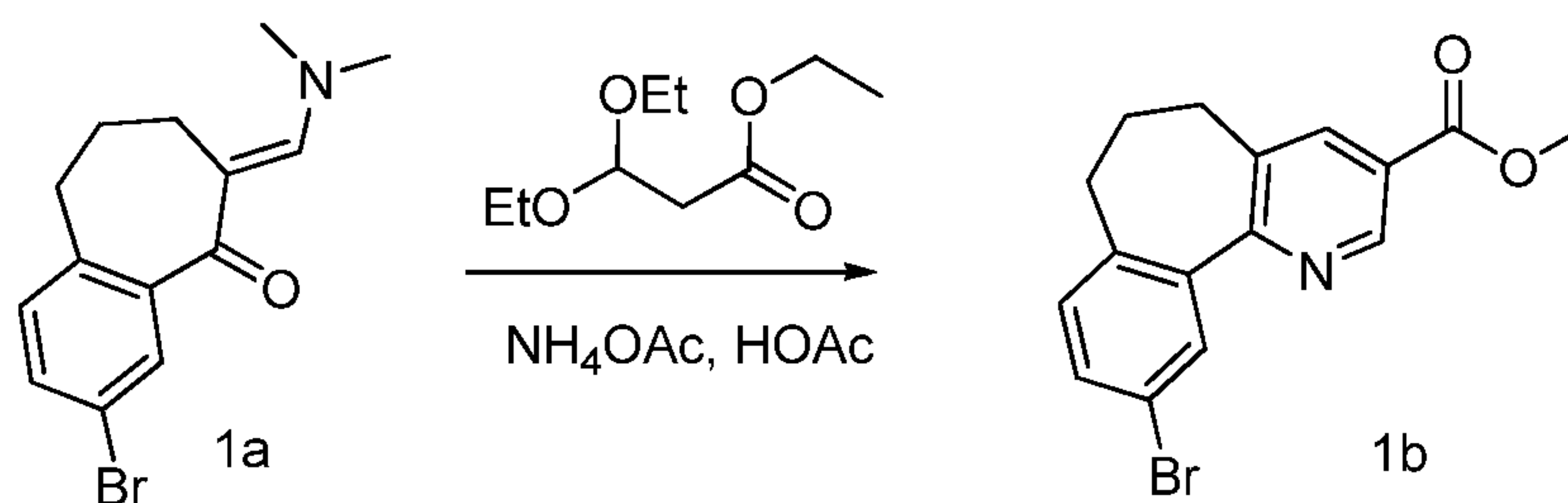
Compound 43 was prepared similarly to Compound 42.

¹H NMR (300 MHz, CDCl₃) δ 10.7 (brs, 1H, NH), 7.98 (d, *J* = 1.9 Hz, 1H), 7.28, 7.26 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.84 (t, *J* = 8.2 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.70-2.66 (m, 2H), 2.20-2.11 (m, 2H). MS (ESI) [M+H⁺]: 437, 435.

Compound 44:



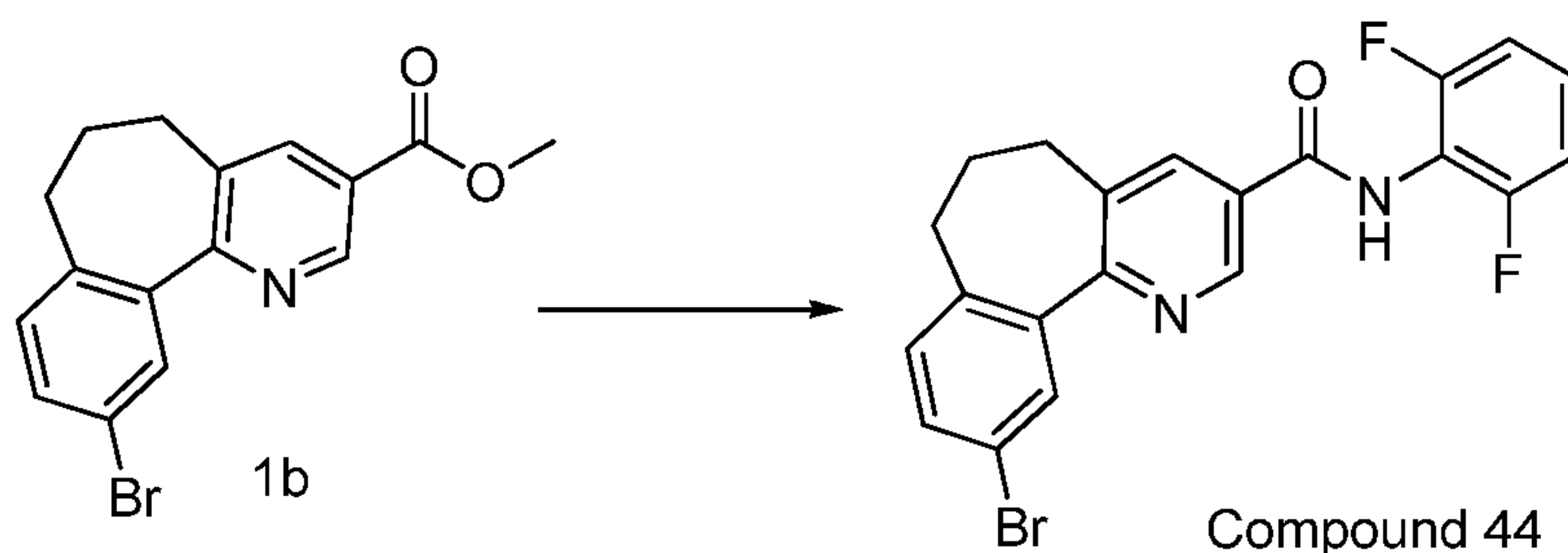
3-bromo-6-((dimethylamino)methylene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1a). A solution of 8-bromo-1-benzosuberone (2.0 mmol, 478 mg) in 1.0 mL of DMF dimethylacetal was heated at 90°C for 1 hour under N₂. After cooling to room temperature, the reaction mixture was diluted with 10 mL of CH₂Cl₂. The solution was washed with water, dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel to give 550 mg (93%) of **1a** as a solid. MS (ESI) [M+H⁺]: 296, 294.



The mixture of **1a** (130 mg, 0.44 mmol), NH₄OAc (77 mg, 1.0 mmol) and ethyl 3,3-diethoxypropanoate (100 mg, 0.53 mmol) in 1.0 mL of HOAc was sealed under N₂ and heated to 150°C for overnight. After

cooling to room temperature, the solvent was removed, and the residue was dissolved in 10 mL of EtOAc; the solution was washed with NaHCO₃ and brine, dried (Na₂SO₄) and concentrated. Flash chromatography of the residue on silica gel (eluted with 0-100% EtOAc in hexanes) gave 24 mg (16%) of pyridine **1b** as a white solid.

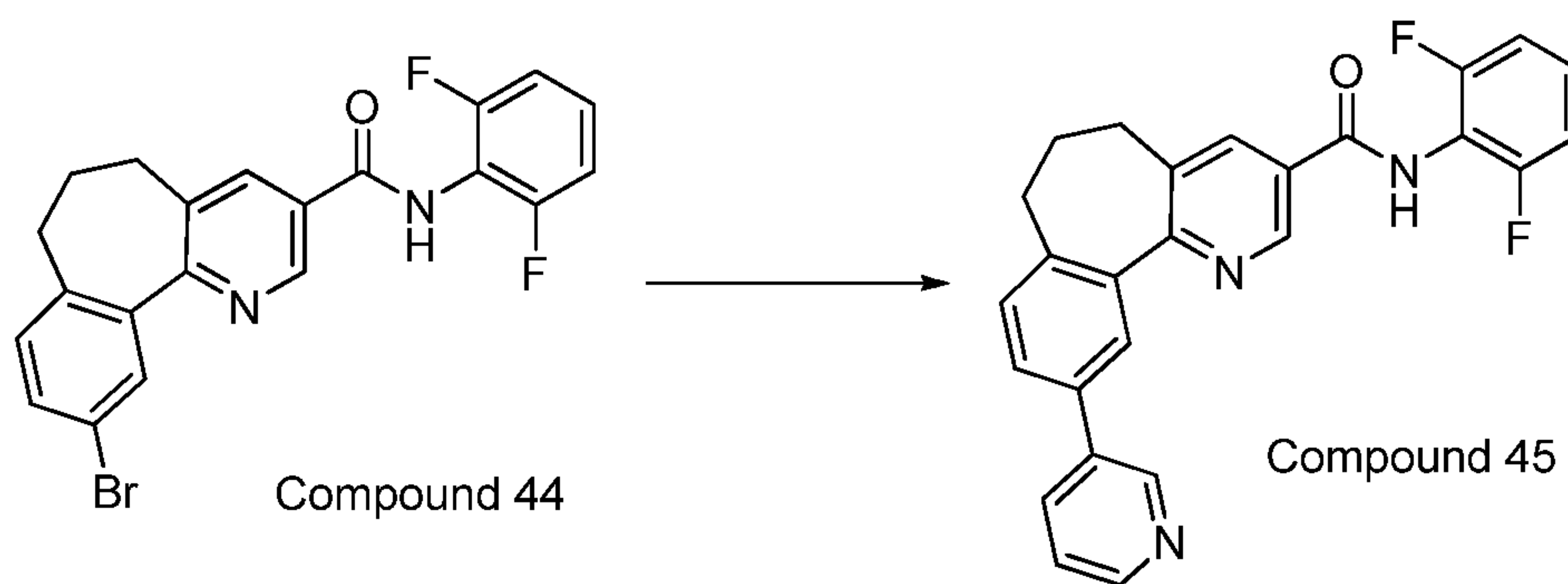
5 MS (ESI) [M+H⁺]: 348, 346.



Into a solution of compound **1b** (24 mg) and 2,6-difluoroaniline (14 mg) in toluene (1 mL) at room temperature was added a solution of 2M trimethylaluminum in hexane (0.1 mL). The mixture was heated to 90°C for 2 hours, cooled to room temperature, poured over ice, basified with 2N NaOH, extracted with CH₂Cl₂ (2X). The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-100% EtOAc in hexanes) gave 18 mg of Compound **44** as a white solid.

MS (ESI) [M+H⁺]: 431, 429

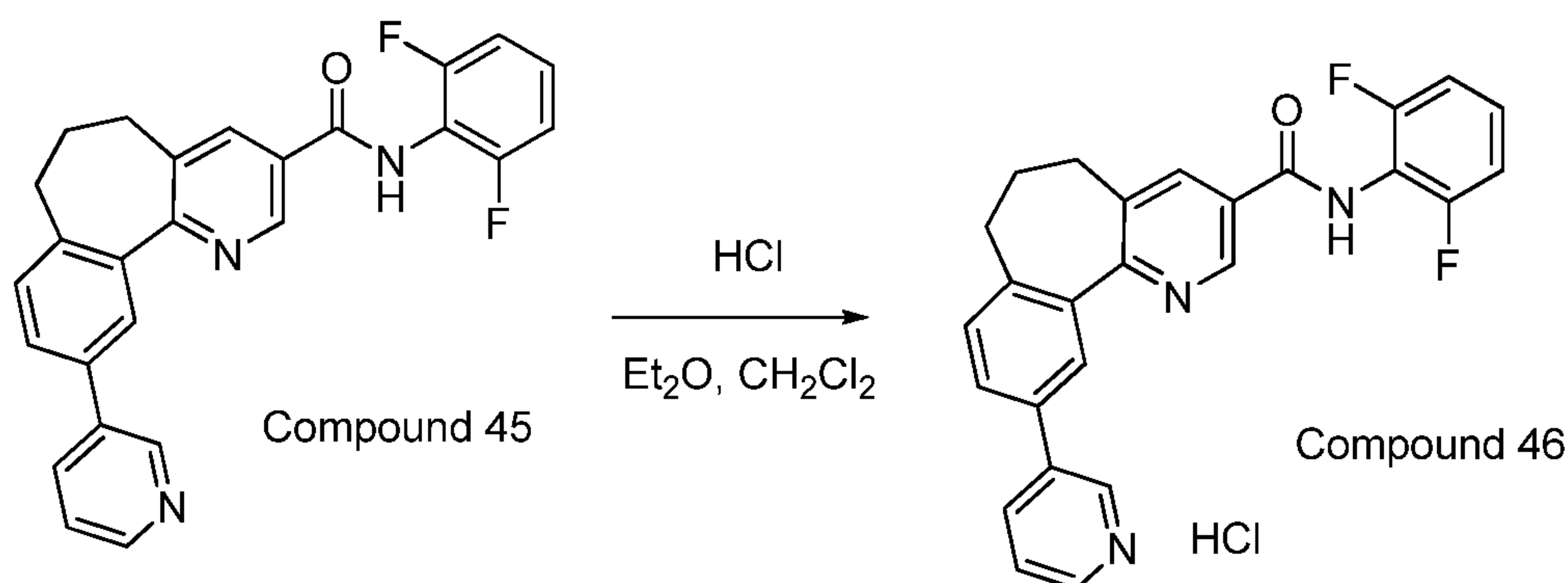
15 Compound 45:



A mixture of Compound **44** (15 mg), 3-pyridinylboronic acid (15 mg), and Pd(Ph₃)₄ (10 mg) in EtOH (1 mL) was degassed by vacuum/N₂-filled method (4X). The mixture was heated to 85°C overnight, cooled to room temperature, concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-10% MeOH in CH₂Cl₂) gave 10 mg of Compound **45** as a solid.

¹H NMR (400 MHz, CDCl₃) δ 9.15 (s, 1H), 8.93 (s, 1H), 8.59 (s, 1H), 8.17-7.20 (m, 8H), 7.03 (t, *J* = 8.0 Hz, 2H), 2.67-2.56 (m, 4H), 2.36-2.29 (m, 2H). MS (ESI) [M+H⁺]: 428

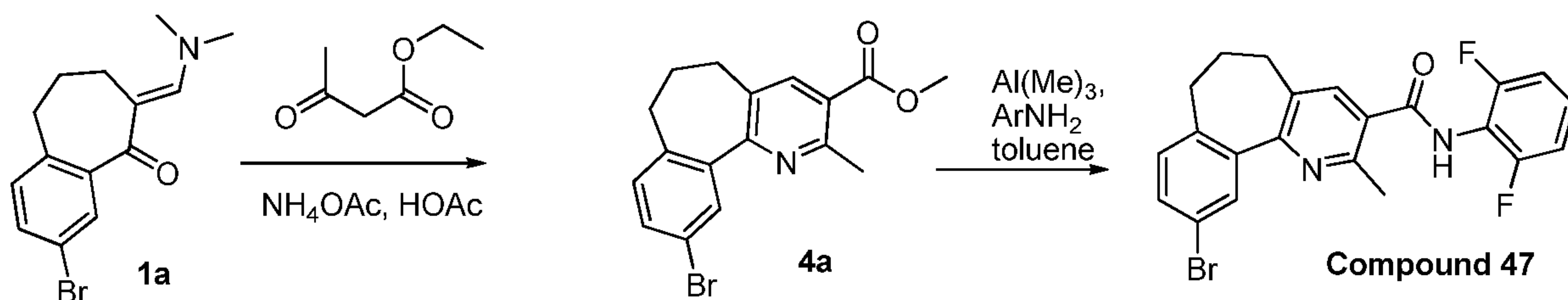
25 Compound 46:



Into a solution of Compound **45** (5 mg) in CH_2Cl_2 (0.5 mL) at room temperature was added a 1.1 equivalent of HCl in Et_2O . The mixture was stirred at room temperature for 10 minutes. Solvent and excess reagent was removed under reduced pressure. The solid was washed with Et_2O and dried to give 5 mg of Compound **46** as a white solid.

^1H NMR (400 MHz, $\text{CDCl}_3+\text{CD}_3\text{OD}$) δ 9.40-7.48 (m, 11H), 7.06 (t, $J = 8.0$ Hz, 2H), 2.83 (m, 2H), 2.74 (m, 2H), 2.50 (m, 2H). MS (ESI) $[\text{M}-\text{Cl}^-]$: 428

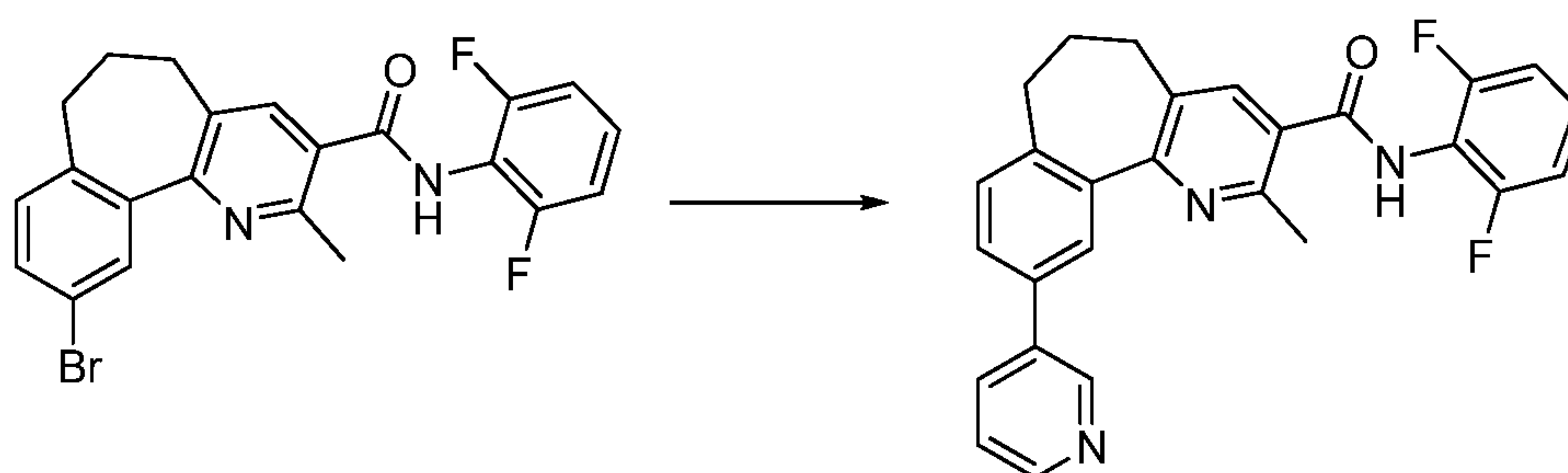
Compound 47:



Compound **47** was prepared from **1a** and ethyl acetoacetate in two steps similarly as described for the preparation of Compound **44**.

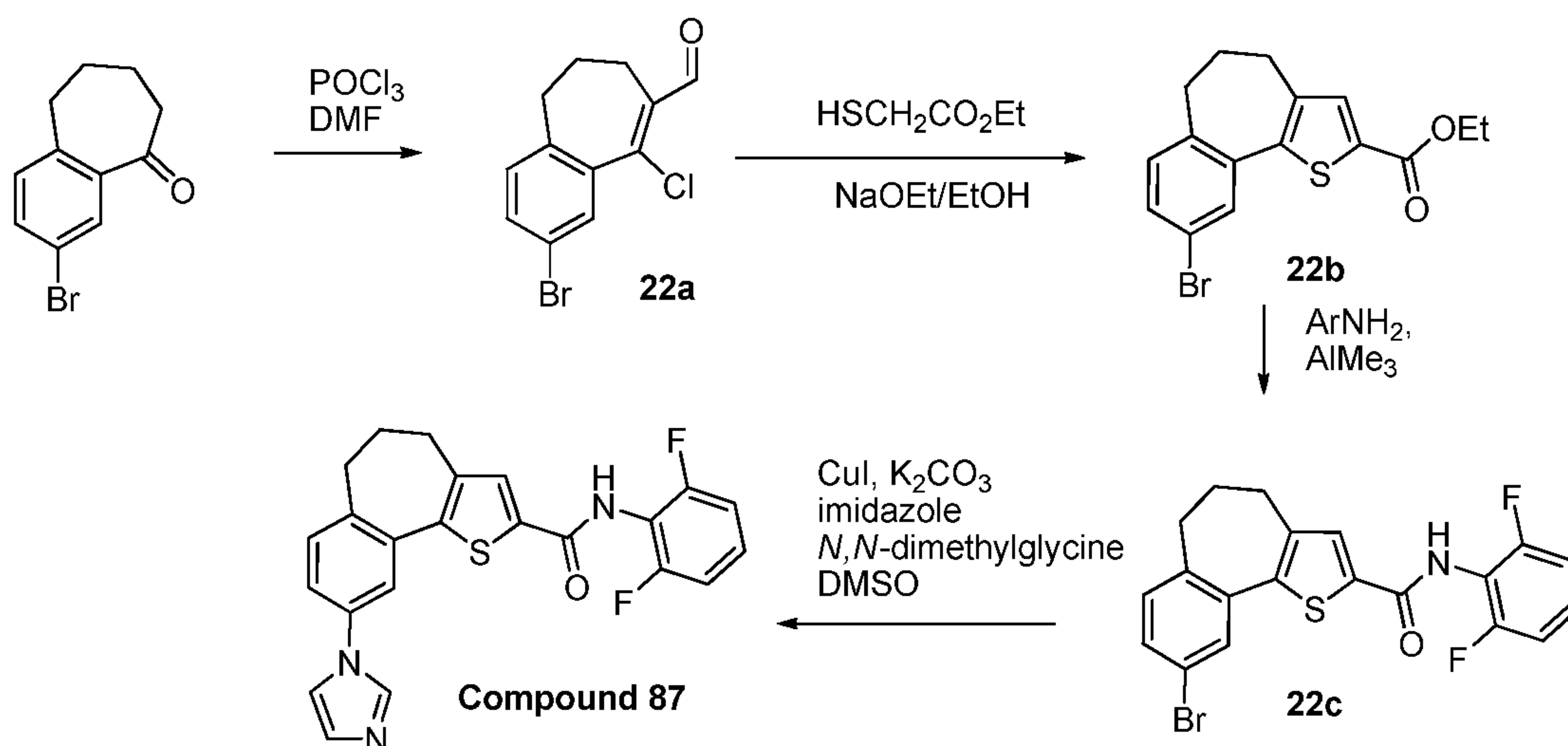
MS (ESI) $[\text{M}+\text{H}^+]$: 445, 443

Compound 48:



Compound **48** was prepared from Compound **47** similarly as described for the preparation of Compound **45**.

^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 7.86-7.28 (m, 9H), 7.04 (t, $J = 8.0$ Hz, 2H), 2.86 (s, 3H), 2.65-2.61 (m, 2H), 2.43-2.39 (m, 2H), 2.23-2.17 (m, 2H). MS (ESI) $[\text{M}+\text{H}^+]$: 442

Compound 87:

POCl₃ (2.0 mmol, 306 mg) was added dropwise to 2 mL of dry DMF under N₂ at 0°C with stirring.

After addition, the solution was stirred at 0°C for 5 min. A solution of

3-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2.0 mmol, 478 mg) in 1.0 mL of dry DMF was added drop wise to the resulting solution at 0°C. The mixture was stirred at 0°C for 30 min, and then heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and poured into an aq. solution of NaOAc. The mixture was extracted with Et₂O (3 X). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-100% EtOAc in hexanes) gave 485 mg (85%) of **22a** as yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 10.37 (s, 1H), 7.64 (s, 1H), 7.37-7.19 (m, 2H), 2.60-2.55 (m, 2H), 2.24-2.08 (m, 4H). MS (ESI) [M+H⁺]: 287, 285.

Into a solution of NaOEt (1.2 mmol, 82 mg) in 10 mL of dry EtOH was added ethyl mercaptoacetate (1.2 mmol, 144 mg) at 0°C. The mixture was stirred at 0°C for 30 min. A solution of

2-bromo-9-chloro-6,7-dihydro-5H-benzo[7]annulene-8-carbaldehyde (**22a**) (1.0 mmol, 285 mg) in 1 mL of EtOH was added drop wise over 5 min at 0°C. The mixture was stirred at room temperature for 2 hours, then at reflux for 30 minutes, cooled to room temperature, and concentrated. The residue was taken up with CH₂Cl₂. The resulting solution was washed with a solution of saturated NH₄Cl and brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica gel (eluted with 0-30% EtOAc in hexanes) to give **22b** (328 mg, 78%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.62-7.17 (m, 4), 4.36 (q, *J* = 7.0 Hz, 2H), 2.65-2.57 (m, 4H), 2.24-2.17 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H). MS (ESI) [M+H⁺]: 353, 351.

Into a solution of compound **22b** (105 mg, 0.30 mmol) 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

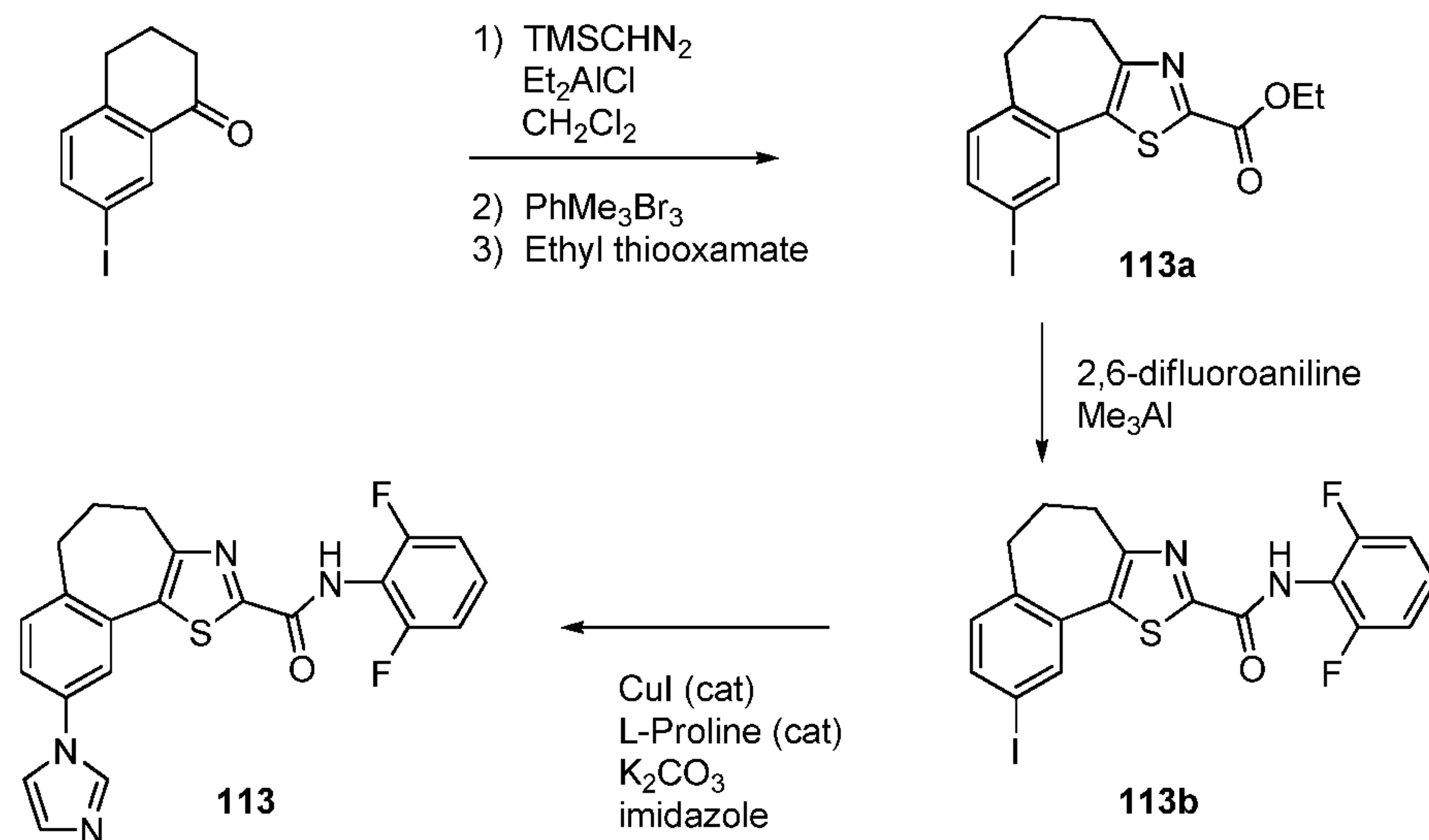
ice, basified with 2N NaOH, extracted with CH₂Cl₂. The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-30% EtOAc in hexanes) **22c** gave (97 mg, 75%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.61-7.15 (m, 5), 7.02-6.96 (t, *J* = 8.0 Hz, 2H), 2.69-2.61 (m, 4H), 2.27-2.22 (m, 2H). MS (ESI) [M+H⁺]: 436, 434.

Into a solution of aryl bromide **22c** (40 mg) in 1 mL of DMSO was added imidazole (10 mg), CuI (5 mg), *N,N*-dimethylglycine (7 mg), K₂CO₃ (25 mg). Under N₂ the mixture was sealed and heated to 110°C for 40 hrs. After cooling to room temperature, the mixture was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc twice, and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue on silica gel (eluted with 0-20% of MeOH in CH₂Cl₂) gave Compound 87 (17 mg) as a white solid.

¹H NMR (400 MHz, CDCl₃+CD₃OD) δ 7.70-7.20 (m, 8 H), 7.01 (t, *J* = 8.0 Hz, 2H), 2.75-2.66 (m, 4H), 2.35-2.25 (m, 2H). MS (ESI) [M+H⁺]: 422.

Compound 113:



Into a solution of 7-iodo-3,4-dihydronaphthalen-1(2H)-one (4.25g, 15.6 mmol) in dichloromethane (160 mL) at 0°C was added a solution of 1M Et₂AlCl in hexane (17.0 mL, 17.0 mmol). Into the resulting mixture a solution of 2M TMSCHN₂ in ether (8.0 mL, 16.0 mmol) was added slowly (vigorous N₂ release was observed). The mixture was stirred at 0°C for 15 minutes. Ice was added. The mixture was acidified with a solution of 3M HCl. The resulting mixture was extracted with dichloromethane (2X). The combined extracts were washed with water and dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was taken up in THF (80 mL). The mixture was cooled to 0°C. Into the reaction mixture phenyltrimethylammonium tribromide (6.02g, 16.0 mmol) was added. The mixture was stirred at 0°C for 30 minutes then at room temperature for 1 hour. The

reaction mixture was quenched by addition of a solution of 10% NaHSO₃. The mixture was stirred at room temperature for 15 minutes, extracted with dichloromethane (2X). The combined extracts were washed with water and dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was taken up in ethanol (20.0 mL). Ethyl thiooxamate (2.13g, 16.0mmol) was added. The mixture was stirred at room temperature overnight. A solution of saturated NaHCO₃ was added. The mixture was extracted with dichloromethane (2X). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with a solution of 1:9, EtOAc:hexanes) to give **113a** (2.85g).

MS (ESI) [M+H⁺]: 400.

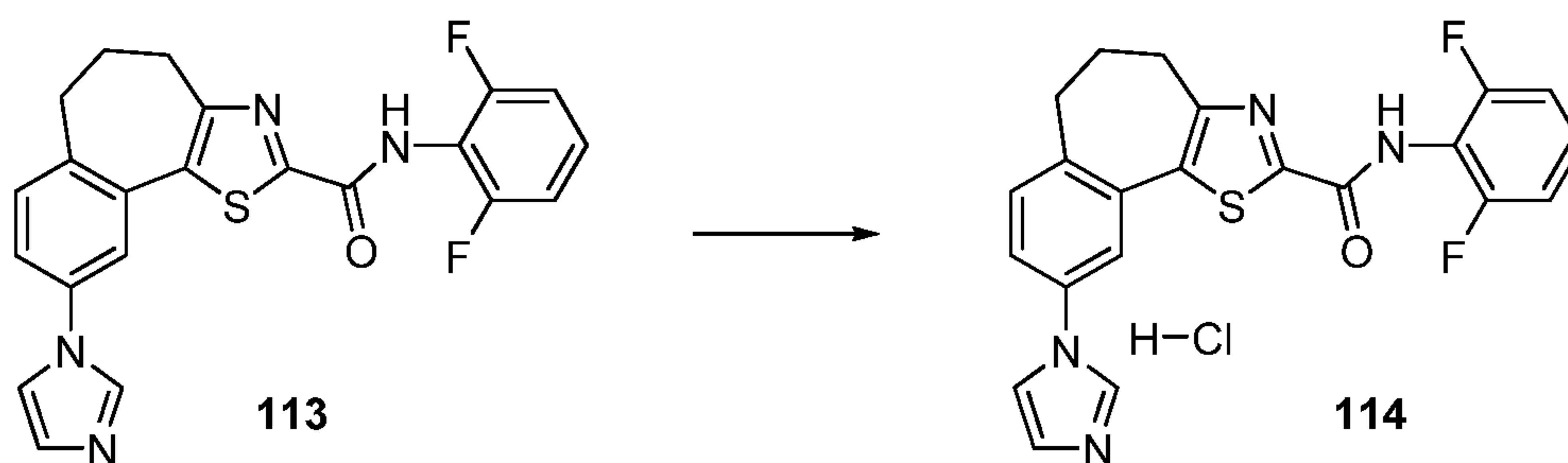
Into a solution of **113a** (2.0g, 5.0 mmol) and 2,6-difluoroaniline (774mg, 6.0mmol) in toluene (20.0mL) at 0 °C was added a solution of 2M Me₃Al in toluene (3.0 mL). The mixture was stirred at room temperature for 15 minutes the heated to 80 °C for 4 hours. Into the reaction mixture, ice was added. The resulting solution was acidified with a solution of 3N HCl, extracted with dichloromethane (2X). The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with a solution of 1:9, EtOAc:hexanes) to give **113b** (2.11g).

MS (ESI) [M+H⁺]: 483.

A mixture of compound **113b** (50.0 mg, 0.10 mmol), CuI (4.0mg, 0.02 mmol), L-proline (4.6 mg, 0.04mmol), imidazole (14.0 mg, 0.2mmol) and K₂CO₃ (28.0 mg, 0.2 mmol) was degassed by vacuum/N₂-filled method (2X). Into the degassed mixture DMSO was added (0.5 mL). The reaction mixture was again degassed, sealed and heated to 90 °C overnight, cooled to room temperature, diluted with water. The resulting mixture was extracted with dichloromethane (2X). The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **113** (29 mg).

MS (ESI) [M+H⁺]: 423.

Compound 114:



Into a solution of compound **113** (20 mg, 0.04 mmol) in dichloromethane (1.0 mL) at room temperature was added a solution of 2N HCl in ether (0.2 mL). The mixture was stirred at room temperature for 10 minutes. The solvents and excess HCl were removed under reduced pressure. The residue was washed with ether and dried to give compound **114** (21 mg).

5 MS (ESI) [M-Cl⁻]: 423.

Compound 115:

Compound **115** was prepared similarly as described for the preparation of compound **113** using **113b** and 2-methyl imidazole.

10 MS (ESI) [M+H⁺]: 437.

Compound 116:

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

MS (ESI) [M-Cl⁻]: 437.

15

Compound 117:

Compound **117** was prepared similarly as described for the preparation of compound **113** using **113b** and 4-methyl imidazole.

MS (ESI) [M+H⁺]: 437.

20

Compound 118:

Compound **118** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 437.

25

Compound 119:

Compound **119** was prepared similarly as described for the preparation of compound **113** using **113b** and pyrazole.

MS (ESI) [M+H⁺]: 437.

30

Compound 120:

Compound **120** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 437.

Compound 121:

35

Compound **121** was prepared similarly as described for the preparation of compound **113** using **113b** and 1,3,4-triazole.

MS (ESI) [M+H⁺]: 424.

Compound 122:

Compound **122** was prepared similarly as described for the preparation of compound **113** using **113a** and 2,4-difluoroaniline.

MS (ESI) [M+H⁺]: 423.

Compound 123:

Compound **123** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 423.

Compound 124:

Compound **124** was prepared similarly as described for the preparation of compound **113** using **113a** and 2,3,4-trifluoroaniline.

MS (ESI) [M+H⁺]: 441.

Compound 125:

Compound **125** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 441.

Compound 126:

Compound **126** was prepared similarly as described for the preparation of compound **113** using **113a** and 2,3,6-trifluoroaniline.

MS (ESI) [M+H⁺]: 441.

Compound 127:

Compound **127** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 441.

Compound 128:

Compound **128** was prepared similarly as described for the preparation of compound **113** using **113a** and 2,4,5-trifluoroaniline.

MS (ESI) [M+H⁺]: 441.

Compound 129:

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

MS (ESI) [M-Cl⁻]: 441.

Compound 130:

Compound **130** was prepared similarly as described for the preparation of compound **113** using **113a** and 2,4,6-trifluoroaniline.

MS (ESI) [M+H⁺]: 441.

Compound 131:

Compound **19** was prepared similarly as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 441.

Compound 132:

Compound **132** was prepared similarly as described for the preparation of compound **113** using **113a** and 4-amino-3-picoline.

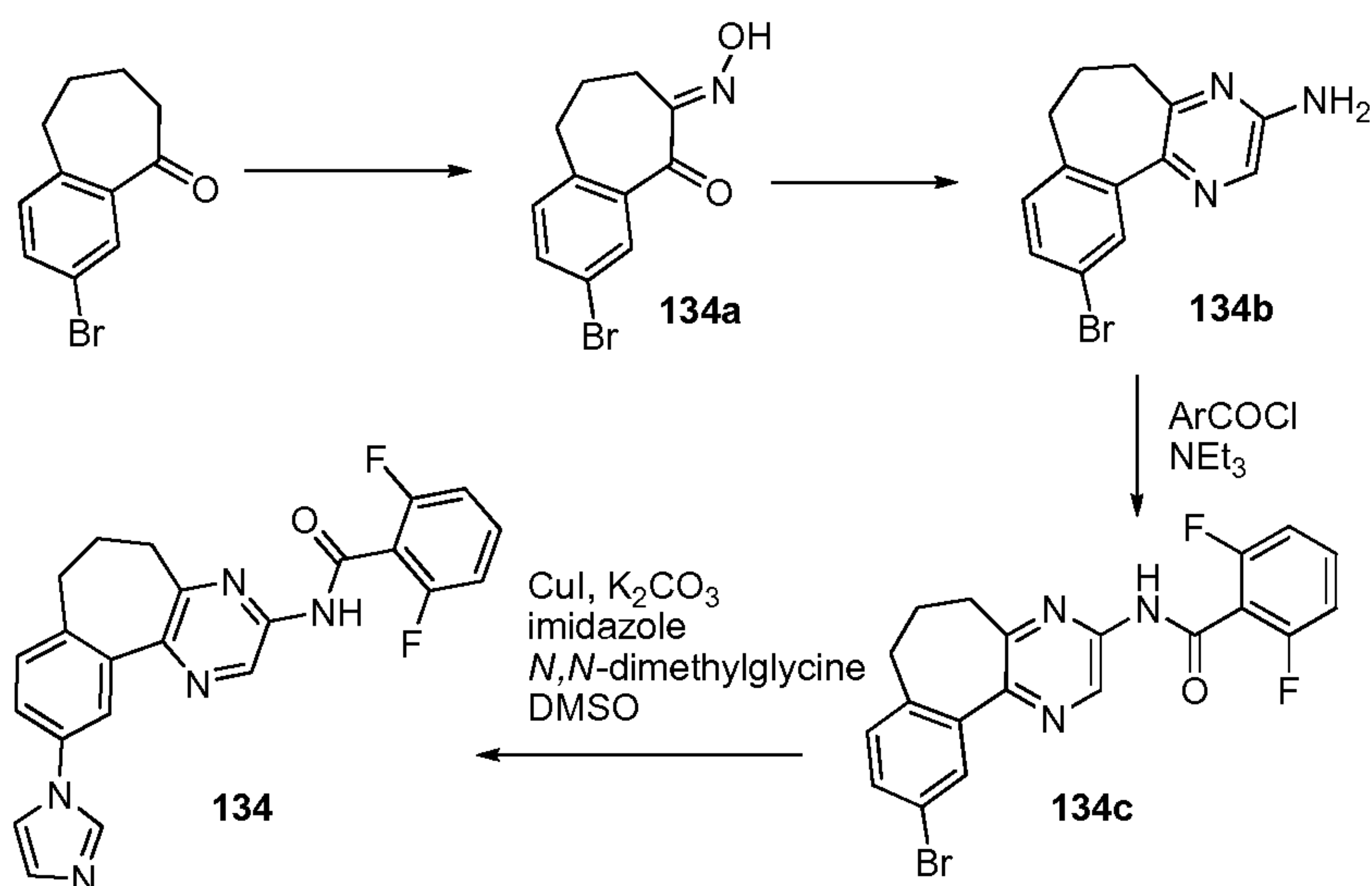
MS (ESI) [M+H⁺]: 402.

Compound 133:

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

MS (ESI) [M-HCl-Cl⁻]: 402.

Compound 134:



Into the solution of NaOMe (810 mg, 15 mmol) in 50 mL of MeOH was added

3-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2.39 g, 10 mmol) and isopentyl nitrite (1.48 mL, 11 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was taken up in CH₂Cl₂, washed with H₂O. The

aqueous layer was neutralized with 1N aqueous HCl and extracted with CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), filtered and concentrated. The residue was recrystallized from CH₂Cl₂/hexanes to give **134a** (2.1 g, 80%) as a yellow solid.

MS (ESI) [M+H⁺]: 270, 268

5

Into the solution of aminoacetonitrile hydrochloride (1.38 g, 15 mmol) in 10 mL of MeOH at room temperature were added 4N aqueous NaOH (16 mmol), **134a** (670 mg, 2.5 mmol) and ferric chloride (407 mg, 2.5 mmol). The resulting mixture was stirred at reflux for overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The residue was partitioned between CH₂Cl₂ and water. The aqueous phase was basified with 2N aqueous NaOH and extracted with CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography on silica gel to give **134b** (150 mg) as a white solid.

MS (ESI) [M+H⁺]: 292, 290

15

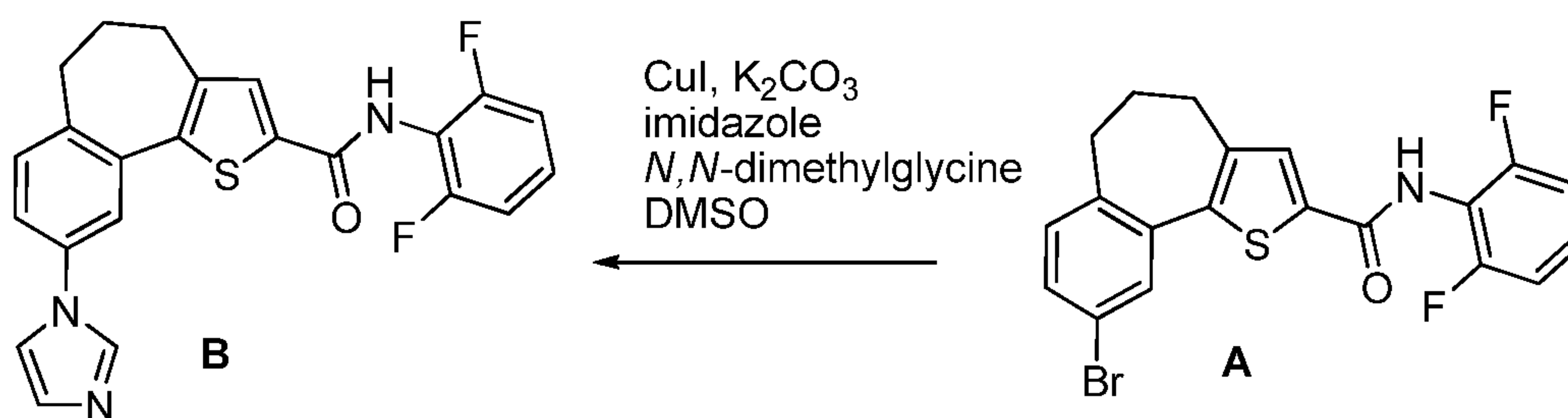
Into a solution of **134b** (146 mg, 0.5 mmol), NEt₃ (202 mg, 2 mmol), and catalytic amount of DMAP in 5 mL of CH₂Cl₂ at room temperature was added 2,6-difluorobenzoylchloride (176 mg, 1 mmol). The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in 5 mL of MeOH. K₂CO₃ (100 mg) was added. The mixture was stirred at 60°C for 1 hour, diluted with CH₂Cl₂, washed with water, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with 0-50% EtOAc in hexanes) to give **134c** (178 mg, 83% yield).

¹H NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H, NH), 8.45 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.51-7.44 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 2H), 2.66 (m, 2H), 2.55 (m, 2H), 2.34 (m, 2H). MS (ESI) [M+H⁺]: 432, 430

25

Compound 134 was prepared from **134c** similarly to that described below.

MS (ESI) [M+H⁺]: 418



30

Into a solution of aryl bromide **A** (40 mg) in 1 mL of DMSO was added imidazole (10 mg), CuI (5 mg), *N,N*-dimethylglycine (7 mg), K₂CO₃ (25 mg). Under N₂ the mixture was sealed and heated to 110°C for

40 hrs. After cooling to room temperature, the mixture was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc twice, and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue on silica gel (eluted with 0-20% of MeOH in CH₂Cl₂) gave compound **B** (17 mg) as a white solid.

5 ¹H NMR (400 MHz, CDCl₃+CD₃OD) δ 7.70-7.20 (m, 8 H), 7.01 (t, *J* = 8.0 Hz, 2H), 2.75-2.66 (m, 4H), 2.35-2.25 (m, 2H). MS (ESI) [M+H⁺]: 422.

Compound 139:

10 Into a solution of compound **113** (10.0 mg) in CH₂Cl₂ (1.0 mL) was added excess methyl iodide (0.1 mL). The mixture was stirred at room temperature overnight. The solvent and excess reagent were removed under reduced pressure to give compound **139** (13.0 mg).

¹H NMR (400 MHz, CDCl₃) δ 10.70 (s, 1H), 8.58 (s, 1H), 7.90 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.71 (d, *J* = 2.2, 1H), 7.66 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.33-7.26 (m, 1H), 7.05 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.51 (s, 3H), 3.14-3.08 (m, 2H), 2.87-2.84 (m, 2H), 2.31-2.25 (m, 2H). MS (ESI) [M-I]: 437

15

Compound 140:

Compound **140** was prepared similarly as described for the preparation of compound **113** using **113b** and 4-formyl imidazole.

20 ¹H NMR (400 MHz, CDCl₃) δ 9.95 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.58 (s, 1H), 7.50-7.06 (series of m, 4H), 7.04 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.16-3.13 (m, 2H), 2.89-2.86 (m, 2H), 2.35-2.28 (m, 2H). MS (ESI) [M+H⁺]: 451

Compound 141:

25 Into a solution of compound **140** (10.0 mg) in THF (1.0 mL) at room temperature was added drop wise a solution of 3M MeMgBr in ether (0.1 mL, 0.3 mmol). The mixture was stirred at room temperature for 15 minutes, quenched with addition of ice, extracted with CH₂Cl₂ (2X). The combined extracts were dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give compound **141** (8 mg).

30 ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 7.81 (s, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 8.0, 1H), 7.31-7.26 (m, 2H), 7.20 (s, 1H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.95 (q, *J* = 6.4 Hz, 1H), 3.15-3.11 (m, 2H), 2.86-2.83 (m, 2H), 2.32-2.26 (m, 2H), 1.60 (d, *J* = 6.4 Hz, 3H). MS (ESI) [M+H⁺]: 451

Compound 142:

35 Into a solution of compound **140** (10.0 mg) in MeOH (1.0 mL) at room temperature was added tosylmethyl isocyanide (20.0 mg, 0.10 mmol), and potassium carbonate (14.0 mg, 0.10 mmol). The mixture was stirred at room temperature overnight, diluted with CH₂Cl₂, washed with water (2X). The

organic was dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica to give compound **142** (6 mg).

^1H NMR (400 MHz, CDCl_3) δ 8.61 (s, 1H), 7.91 (d, $J = 1.2$ Hz, 1H), 7.88 (s, 1H), 7.57 (d, $J = 1.2$, 1H), 7.55 (d, $J = 2.4$, 1H) 7.43 (s, 1H), 7.41 (s, 1H), 7.36-7.26 (series of m, 2H), 7.03 (dd, $J = 8.0$, 8.0 Hz, 2H), 3.16-3.12 (m, 2H), 2.88-2.85 (m, 2H), 2.34-2.27 (m, 2H). MS (ESI) $[\text{M}+\text{H}^+]$: 490

Compound 143:

Compound **143** was prepared from **142** as described for the preparation of compound **114**.

MS (ESI) $[\text{M}-\text{Cl}^-]$: 490

Compound 144:

Into a solution of compound **141** (10.0 mg) and excess diethylamine (10.0 mg) in CH_2Cl_2 (1.0 mL) and acetic acid (2 drops) was added excess $\text{Na}(\text{OAc})_3\text{BH}$ (20.0 mg). The mixture was stirred at room temperature overnight, quenched with addition of a solution of saturated NaHCO_3 , extracted with CH_2Cl_2 (3X). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica to give **144** (7.0 mg).

MS (ESI) $[\text{M}+\text{H}^+]$: 508

Compound 145:

Compound **145** was prepared from compound **113a** similarly as described for the preparation of compound **113**.

^1H NMR (400 MHz, CDCl_3) δ 9.29 (s, 1H), 8.46 (d, $J = 8.4$ Hz, 1H), 7.87 (s, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 7.49 (d, $J = 8.0$, 1H), 7.33-7.20 (series of m, 5H), 3.16-3.12 (m, 2H), 2.88-2.85 (m, 2H), 2.34-2.27 (m, 2H). MS (ESI) $[\text{M}+\text{H}^+]$: 439

Compound 146:

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

MS (ESI) $[\text{M}-\text{Cl}^-]$: 439

Compound 147:

Compound **147** was prepared similarly as described for the preparation of compound **113** using compound **113b** and 4-ethylimidazole.

MS (ESI) $[\text{M}+\text{H}^+]$: 451

Compound 148:

Compound **148** was prepared from compound **147** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 451

Compound 149:

5 Compound **149** was prepared similarly as described for the preparation of compound **113** using compound **113b** and 4-*tert*-Butylimidazole.

¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H), 7.79 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.37-7.26 (series of m, 3H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.98 (d, *J* = 2.0, 1H), 3.13-3.10 (m, 2H), 2.85-2.82 (m, 2H), 2.32-2.25 (m, 2H), 1.37 (s, 9H).

10 MS (ESI) [M+H⁺]: 479

Compound 150:

Compound **150** was prepared similarly as described for the preparation of compound **113** using **113b** and 4-bromoimidazole.

15 ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.33-7.22 (series of m, 3H), 7.04 (dd, *J* = 8, 8 Hz, 2H), 3.15-3.11 (m, 2H), 2.87-2.84 (m, 2H), 2.32-2.25 (m, 2H).

MS (ESI) [M+H⁺]: 503

Compound 151:

20 Compound **151** was prepared from compound **150** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 503, 505

Compound 152:

25 Compound **152** was prepared similarly as described for the preparation of compound **113** using **113b** and 4,5-dichloroimidazole.

¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33-7.26 (series of m, 2H), 7.01 (dd, *J* = 8, 8 Hz, 2H), 3.17-3.14 (m, 2H), 2.90-2.87 (m, 2H), 2.34-2.28 (m, 2H). MS (ESI) [M+H⁺]: 491

30 Compound 153:

Compound **153** was prepared from compound **152** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 491

Compound 154:

35 Compound **154** was prepared similarly as described for the preparation of compound **113** using **113b** and 4-cyclopropylimidazole.

¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H), 7.72 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.36-7.26 (series of m, 4H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.13-3.10 (m, 2H), 2.84-2.81 (m, 2H), 2.34-2.25 (m, 2H), 1.95-1.87 (m, 1H), 0.92-0.82 (m, 4H). MS (ESI) [M+H⁺]: 463

5 Compound 155:

Compound **155** was prepared from **154** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 463

Compound 156:

10 ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 7.67 (s, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.32-7.26 (m, 2H), 7.11 (s, 1H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.17-3.13 (m, 2H), 2.89-2.86 (m, 2H), 2.34-2.25 (m, 2H). MS (ESI) [M+H⁺]: 457

Compound 157:

15 Compound **157** was prepared from compound **156** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 457

Compound 158:

20 Compound **158** was prepared similarly as described for the preparation of compound **113** using **113b** and 2-ethyl-4-methylimidazole.

¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.32-7.24 (m, 2H), 7.18 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.73 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.16-3.13 (m, 2H), 2.88-2.85 (m, 2H), 2.70-2.64 (m, 2H), 2.29 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). MS (ESI) [M+H⁺]: 465

25

Compound 159:

Compound **159** was prepared from **158** as described for the preparation of compound **114**.

MS (ESI) [M-Cl⁻]: 465

30 Compound 160:

Into a solution of compound **113** (50.0 mg, 0.12 mmol) in concentrated H₂SO₄ (2.0 mL) at 0°C was added slowly K₂NO₃ (17.0 mg, 0.12 mmol). The mixture was stirred at room temperature for 1 hour. Into the reaction mixture ice and a solution of 2N NaOH were added. The neutralized solution was extracted with CH₂Cl₂ (3X). The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica to give compound **160** (45.0 mg).

35

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.91 (s, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz,

1H), 7.41-7.28 (series of m, 3H), 7.05 (dd, $J = 8.0, 8.0$ Hz, 2H), 3.17-3.14 (m, 2H), 2.90-2.87 (m, 2H), 2.35-2.29 (m, 2H). MS (ESI) $[M+H^+]$: 468

Compound 161:

5 Into a solution of compound **113** (43.0 mg, 0.10 mmol) in concentrated H_2SO_4 (1.0 mL) at room temperature was added NIS (23.0 mg, 0.10 mmol). The mixture was stirred at room temperature for 1 day. Into the reaction mixture was poured over ice. The icy slurry was neutralized with a solution of 2N NaOH. The neutralized solution was extracted with CH_2Cl_2 (2X). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica to give
10 compound **161** (45.0 mg).

^1H NMR (400 MHz, $CDCl_3+CD_3OD$) δ 7.89 (s, 1H), 7.72-7.67 (m, 1H), 7.52 (d, $J = 2$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.35-7.26 (series of m, 3H), 7.22 (s, 1H), 6.89 (dd, $J = 8.0, 8.0$ Hz, 1H), 3.15-3.10 (m, 2H), 2.87-2.82 (m, 2H), 2.32-2.26 (m, 2H). MS (ESI) $[M+H^+]$: 549

15 Compound 162:

Compound **162** was prepared similarly as described for the preparation of compound **113** using **113b** and 4-nitroimidazole.

MS (ESI) $[M+H^+]$: 468

20 Compound 153:

Into a solution of compound **113** (50.0 mg, 0.12 mmol) in THF (2.0 mL) at $-78^\circ C$ was added a solution of 1.6M n-BuLi in hexane (0.2 mL, 0.32 mmol). The mixture was stirred at $-78^\circ C$ for 30 minutes. Into the reaction mixture, a solution NCS (27.0 mg, 0.2 mmol) in THF (1.0 mL) was added. The cooling bath was removed. The reaction mixture was kept at $0^\circ C$ for 30 minutes, re-cooled to $-78^\circ C$. A solution
25 of saturated ammonium chloride was added. Additional water was added. The mixture was 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 to give compound **163** (28 mg).

^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.51 (d, $J = 2.4$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.31-7.25 (series of m, 3H), 7.13 (d, $J = 1.6$ Hz, 1H), 7.10 (d, $J = 1.6$ Hz, 1H), 7.03 (dd, $J = 8.0, 8.0$ Hz, 2H),
30 3.17-3.13 (m, 2H), 2.89-2.86 (m, 2H), 2.34-2.29 (m, 2H). MS (ESI) $[M+H^+]$: 457

Compound 164:

Into a solution of compound **140** (20.0 mg, 0.044 mmol) in ethanol (1.0 mL) and water (2 drops) was added hydroxylamine hydrochloride (4.0 mg, 0.058 mmol). The mixture was stirred at room
35 temperature for 2 hours. The solvent was removed under reduced pressure. The residue was taken up in toluene and again concentrated to dryness. The resulting oxime was taken up in THF (2.0 mL). DIC

was added. The resulting solution was heated to 60 °C overnight, cooled to room temperature and concentrated under reduced pressure. The residue was purified on silica to give **164** (8.0 mg).

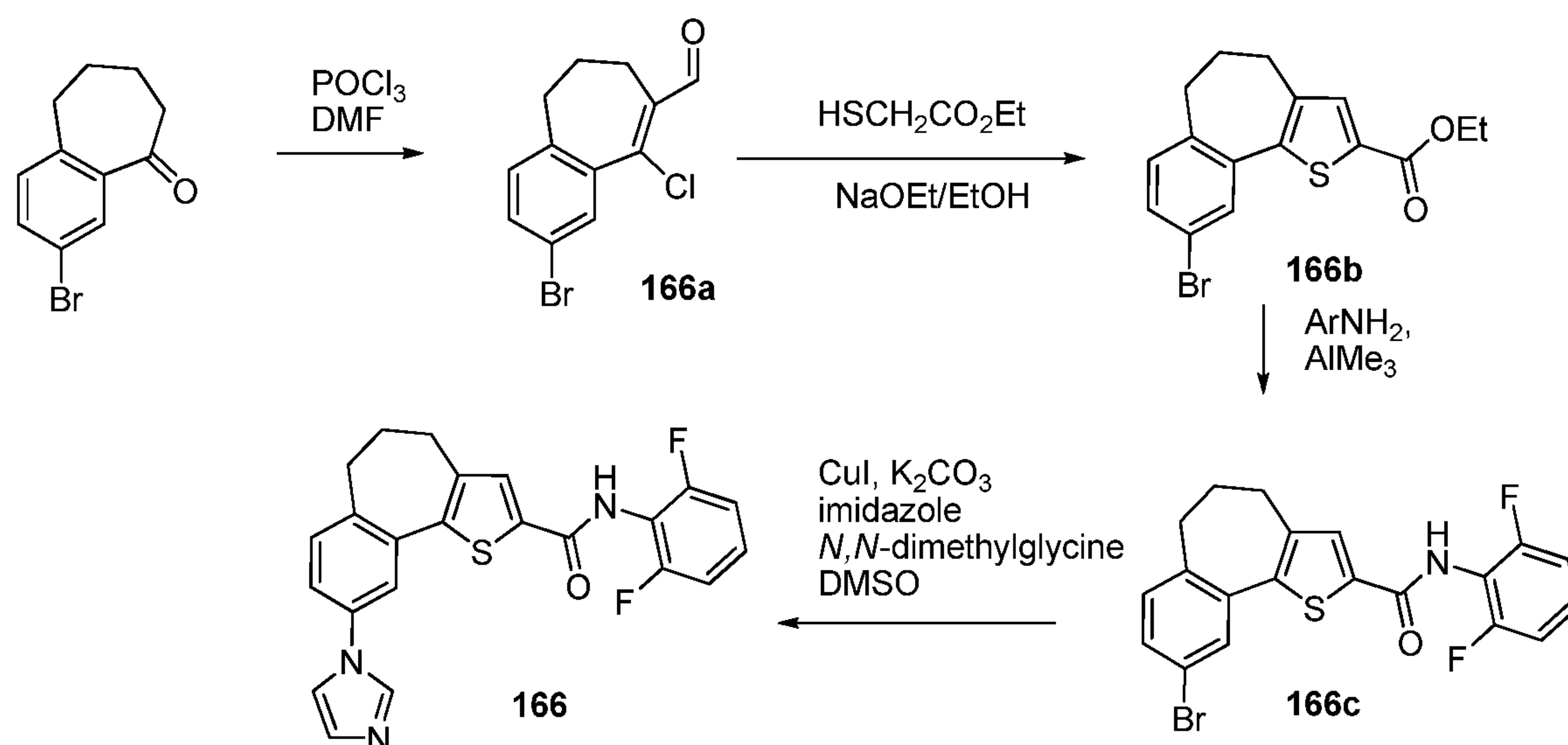
¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.50 7.87 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32-7.26 (series of m, 3H), 7.03 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.16-3.12 (m, 2H), 2.89-2.86 (m, 2H), 2.34-2.27 (m, 2H). MS (ESI) [M+H⁺]: 448.

Compound 165:

Compound **165** was prepared from compound **113b** and 3-methylpyrazole similarly as described for the preparation of compound **113**.

MS (ESI) [M+H⁺]: 437

Compound 166:



POCl₃ (2.0 mmol, 306 mg) was added dropwise to 2 mL of dry DMF under N₂ at 0 °C with stirring.

After addition, the solution was stirred at 0 °C for 5 min. A solution of

3-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2.0 mmol, 478 mg) in 1.0 mL of dry DMF was added drop wise to the resulting solution at 0 °C. The mixture was stirred at 0 °C for 30 min, and then heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and poured into an aq. solution of NaOAc. The mixture was extracted with Et₂O (3 X). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-100% EtOAc in hexanes) gave 485 mg (85%) of **166a** as yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 10.37 (s, 1H), 7.64 (s, 1H), 7.37-7.19 (m, 2H), 2.60-2.55 (m, 2H), 2.24-2.08 (m, 4H).

MS (ESI) [M+H⁺]: 287, 285.

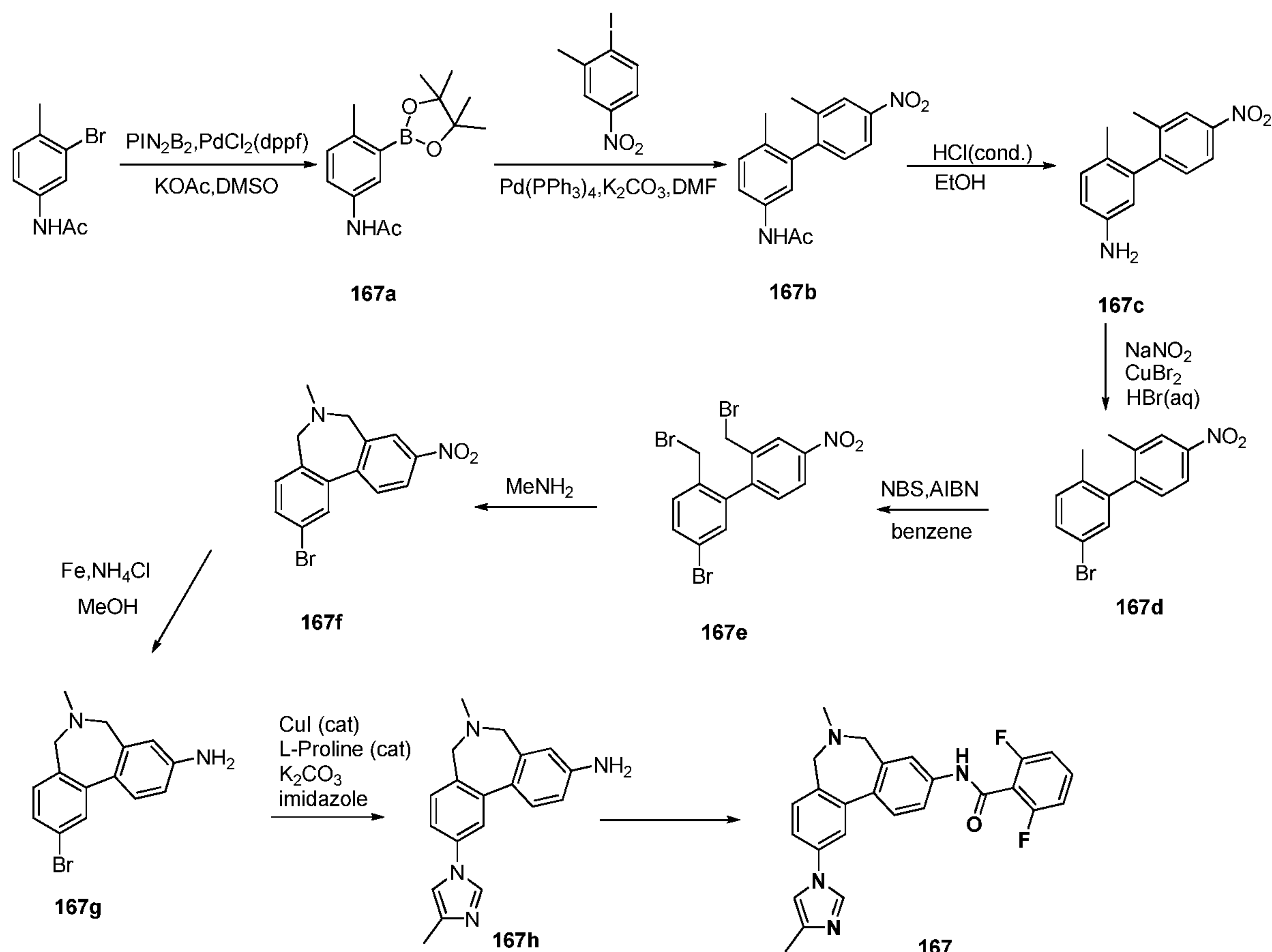
Into a solution of NaOEt (1.2 mmol, 82 mg) in 10 mL of dry EtOH was added ethyl mercaptoacetate

(1.2 mmol, 144 mg) at 0°C. The mixture was stirred at 0°C for 30 min. A solution of **166a** (1.0 mmol, 285 mg) in 1 mL of EtOH was added drop wise over 5 min at 0°C. The mixture was stirred at room temperature for 2 hours, then at reflux for 30 minutes, cooled to room temperature, and concentrated. The residue was taken up with CH₂Cl₂. The resulting solution was washed with a solution of saturated NH₄Cl and brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica gel (eluted with 0-30% EtOAc in hexanes) to give **166b** (328 mg, 78%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.17 (m, 4), 4.36 (q, *J* = 7.0 Hz, 2H), 2.65-2.57 (m, 4H), 2.24-2.17 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H). MS (ESI) [M+H⁺]: 353, 351.

Into a solution of compound **166b** (105 mg, 0.30 mmol) 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 CH₂Cl₂. The combined extracts were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (eluted with 0-30% EtOAc in hexanes) gave **166c** (97 mg, 75%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.15 (m, 5), 7.02-6.96 (t, *J* = 8.0 Hz, 2H), 2.69-2.61 (m, 4H), 2.27-2.22 (m, 2H). MS (ESI) [M+H⁺]: 436, 434.

Into a solution of **166c** (40 mg) in 1 mL of DMSO was added imidazole (10 mg), CuI (5 mg), *N,N*-dimethylglycine (7 mg), K₂CO₃ (25 mg). Under N₂ the mixture was sealed and heated to 110°C for 40 hrs. After cooling to room temperature, the mixture was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc twice, and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue on silica gel (eluted with 0-20% of MeOH in CH₂Cl₂) gave compound **166** (17 mg) as a white solid. ¹H NMR (400 MHz, CDCl₃+CD₃OD) δ 7.70-7.20 (m, 8 H), 7.01 (t, *J* = 8.0 Hz, 2H), 2.75-2.66 (m, 4H), 2.35-2.25 (m, 2H). MS (ESI) [M+H⁺]: 422.

Compound 167:



Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed N-(3-bromo-4-methylphenyl)acetamide (57.0 g, 0.25 mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (76.0 g, 0.29 mol), DMSO (500 mL), $\text{PdCl}_2(\text{dppf})$ (10.8 g, 12.3 mmol) and KOAc (68 g, 680.0 mmol). The resulting solution was allowed to react, with stirring, for 45 hr at 90°C. The reaction progress was monitored by LCMS. The reaction was then quenched by the addition of 1000 mL of water. The resulting solution was extracted with ethyl acetate (3x800 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with ethyl acetate:petroleum ether, 1:20). The product was further purified by precipitation with ether. The solids were collected by filtration to provide **167a** (32.0 g, 44%) as a yellow solid. MS (ESI) $[\text{M}+\text{H}^+]$: 276.

Into a degassed mixture of **167a** (33.6 g, 116 mmol), 1-iodo-2-methyl-4-nitrobenzene (63.1 g, 228 mmol), and potassium carbonate (50.0 g, 0.360 mol) in DMF (600 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (4.16 g, 3.53 mmol). The reaction mixture was heated to 90°C under nitrogen for 6 hr. The reaction mixture was cooled to room temperature, quenched by the addition of water (600 mL). The resulting solution was extracted with ethyl acetate (3x600 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with ethyl acetate:petroleum ether, 1:10) to give **167b** (25.0 g, 72%) as a yellow solid. LCMS calc. for

C₁₆H₁₆N₂O₃: 284; found: 285 (M + H).

Into a solution of **167b** (28.5 g, 90.3 mmol) in EtOH (200 mL) was added concentrated HCl (20 mL). The reaction mixture was heated to reflux for 2 hours, cooled to room temperature, and concentrated under reduced pressure. The crude mixture was diluted with water (200 mL), basified with K₂CO₃,
5 extracted with ethyl acetate (3x200 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with dichloromethane) to give **167c** (22.0 g, 94%) as a yellow solid. LCMS calc. for C₁₄H₁₄N₂O₂: 242; found: 243 (M + H).

10 Into a solution of **167c** (22.0 g, 86.0 mmol) in concentrated hydrobromic acid (250 mL) at 0°C was added drop wise a solution of NaNO₂ (9.30 g, 130 mmol) in H₂O (100 mL). The resulting solution was stirred at 0°C for 10 minutes. Into the reaction mixture a solution of CuBr (19.3 g, 132 mmol) in concentrated hydrobromic acid (50 mL) was added drop wise. The mixture was heated to 60°C for 30 min. The reaction was quenched by the addition of water (500 mL). The resulting solution was
15 extracted with ethyl acetate (3x500 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel to give **167d** (16.0 g, 58%) as a yellow solid. LCMS calc. for C₁₄H₁₂BrNO₂: 305; found: 306 (M + H).

20 Into a solution of **167d** (16.0 g, 50.0 mmol), in benzene (300 mL) were added NBS (17.8 g, 98.0 mmol) and AIBN (1.64 g, 9.80 mmol). The resulting solution was heated to reflux for 8 hours, cooled to room temperature, washed with water (3x200 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified on silica gel (eluted with petroleum ether) to give compound **167e** (6.0 g, 25%) as a yellow solid. LCMS calc. for C₁₄H₁₀Br₃NO₂: 461; found: 462 (M + H).

25 Into a solution of **167e** (6.0 g, 12 mmol,) in toluene (50 mL) was added a solution of 30% methylamine in ethanol (6.30 g, 60.0 mmol). The resulting solution was stirred at room temperature for 4 hours and then warmed to 40°C for 16 hours. The reaction was quenched by the addition of water (100 mL). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified silica gel (eluted
30 with ethyl acetate:petroleum ether, 1:1) to give compound **167f** (3.3 g, 77%) as a yellow solid. LCMS: (ES, m/z): Calcd for C₁₅H₁₃BrN₂O₂: 332; found: 333 (M + H).

35 Into a solution of **167f** (3.00 g, 8.67 mmol) in ethanol (30 mL) and acetic acid (1 mL) was added iron powder (1.12 g, 17.5 mmol, 2.20 equiv, 98%) in portions over 10 minutes, while the temperature was maintained at reflux. The reaction mixture was heated to reflux for an additional 30 minutes, cooled to

room temperature and concentrated under reduced pressure. The residue was taken up in water (50 mL).

The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified silica gel (eluted with dichloromethane:methanol, 200:1) to give **167g** (1.3g, 48%) as a yellow solid.

5 MS (ESI) [M+H⁺]: 303; ¹H NMR (300 HMz, CD₃OD): δ 7.60 (s, 1H), 7.45 (d, 1H), 7.28 (m, 2H), 6.84 (d, 1H), 6.77 (s, 1H), 3.35 (s, 4H), 2.46 (s, 3H).

Compound **167h** was prepared from compound **167g** and 4-methylimidazole similarly as described for the preparation of compound **113**.

10 MS (ESI) [M+H⁺]: 305.

Into a solution of compound **167h** (10.0 mg, 0.033 mmol) in CH₂Cl₂ (1.0 mL) at 0°C was added a 1M solution of 2,6-difluorobenzoyl chloride in CH₂Cl₂ drop wise. The reaction completion was frequently monitored by TLC. Upon reaction completion, methanol (1.0 mL) was added. The resulting mixture was concentrated under reduced pressure. The residue was purified on silica (eluted initially with CH₂Cl₂ then with MeOH: CH₂Cl₂, 1:9) to give compound **167** (11.0 mg).

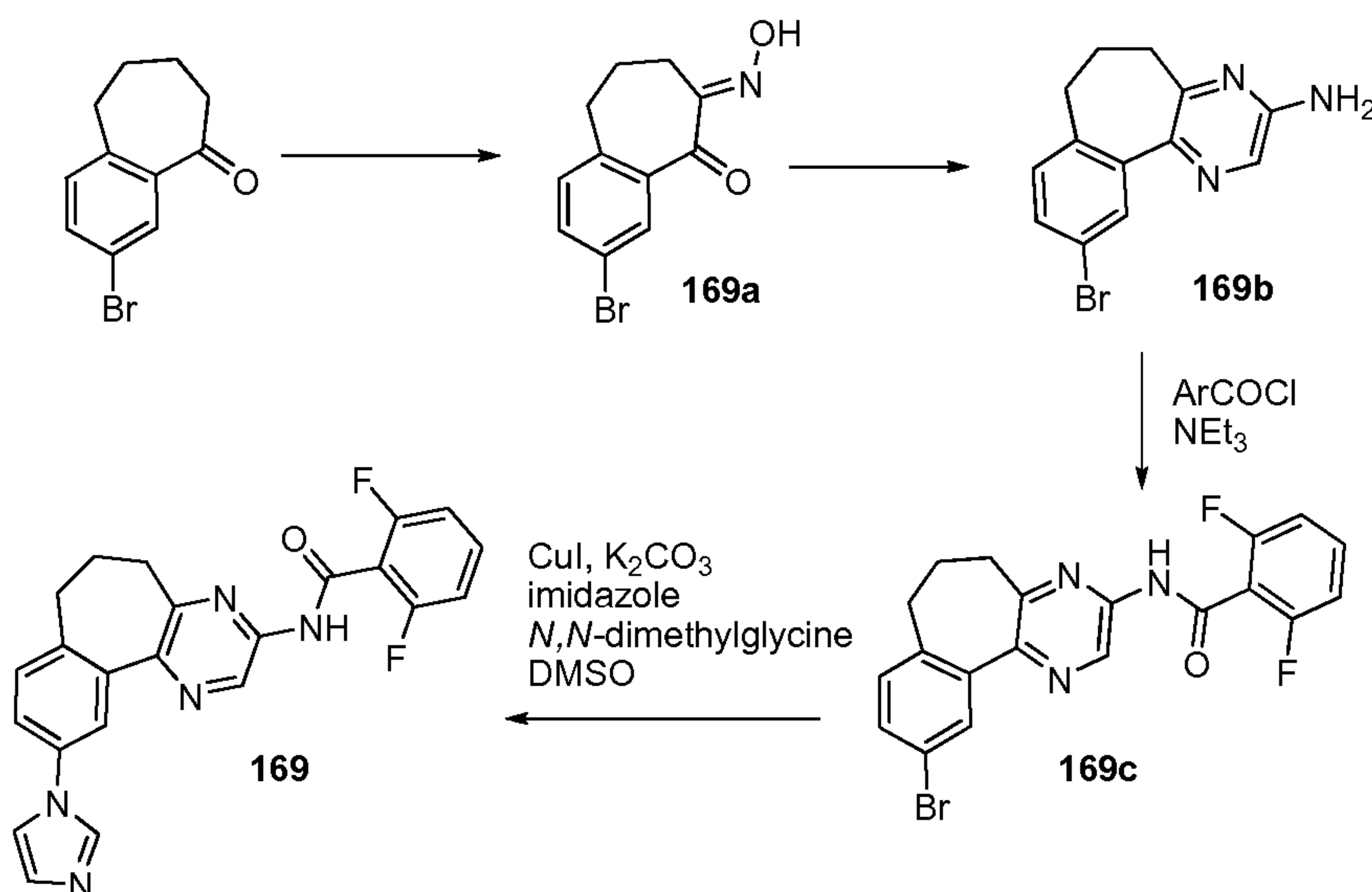
15 MS (ESI) [M+H⁺]: 445

Compound 168:

20 Into a solution of compound **167h** (10.0 mg, 0.033 mmol) and 2,6-difluorobenzaldehyde (5.0 mg, 0.035 mmol) in CH₂Cl₂ (2.0 mL) and acetic acid (2 drops) as added excess Na(OAc)₃BH (20.0 mg). The mixture was stirred at room temperature overnight, quenched with addition of water, extracted with CH₂Cl₂ (3X). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified silica gel to give compound **168** (3.0 mg).

25 MS (ESI) [M+H⁺]: 431

Compound 169:



Into the solution of NaOMe (810 mg, 15 mmol) in 50 mL of MeOH was added

3-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2.39 g, 10 mmol) and isoamyl nitrite (1.48 mL, 11 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ then washed with H₂O. The aqueous layer was neutralized with 1N aqueous HCl and extracted with CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), filtered and concentrated. The residue was recrystallized from

CH₂Cl₂:hexanes to give **169a** (2.1 g, 80%) as a yellow solid.

MS (ESI) [M+H⁺]: 270, 268.

Into the solution of aminoacetonitrile hydrochloride (1.38 g, 15 mmol) in 10 mL of MeOH at room temperature were added solution of 4N aqueous NaOH (4.0 mL, 16 mmol), **169a** (670 mg, 2.5 mmol) and ferric chloride (407 mg, 2.5 mmol). The resulting mixture was stirred at reflux overnight. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure.

The residue was partitioned between CH₂Cl₂ and water. The aqueous phase was basified with 2N aqueous NaOH and extracted with CH₂Cl₂. The combined organic phases were dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography on silica gel to give **169b** (150 mg) as a white solid.

MS (ESI) [M+H⁺]: 292, 290

Into a solution of **169b** (146 mg, 0.5 mmol), NEt₃ (202 mg, 2 mmol), and catalytic amount of DMAP in CH₂Cl₂ (5.0 mL) at room temperature was added 2,6-difluorobenzoyl chloride (176 mg, 1 mmol). The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in MeOH (5.0 mL). K₂CO₃ (100 mg) was added. The mixture was stirred at 60°C for 1 hour, diluted with CH₂Cl₂, washed with water, dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica (eluted with 0-50% EtOAc in hexanes) to give **169c** (178 mg, 83% yield).

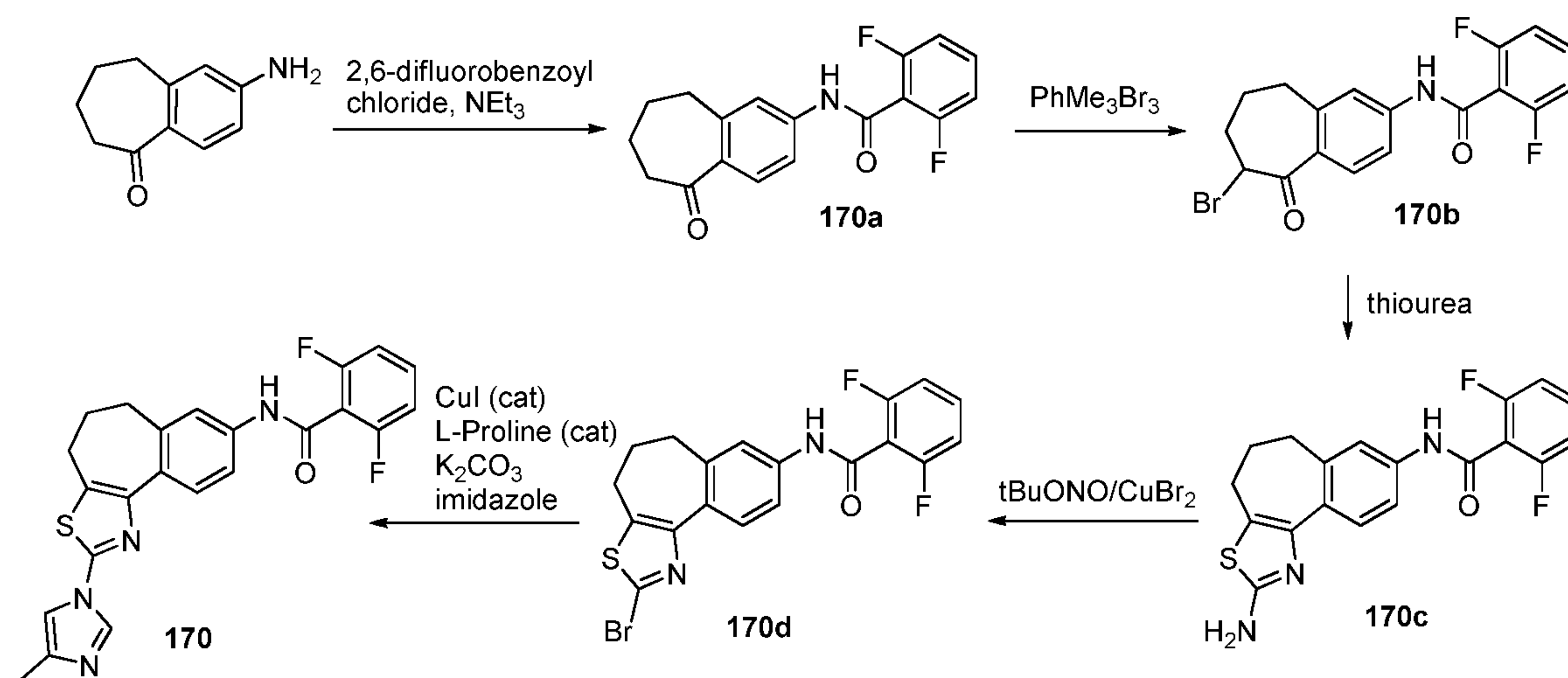
^1H NMR (400 MHz, CDCl_3) δ 9.64 (s, 1H, NH), 8.45 (s, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 7.51-7.44 (m, 2H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.04 (t, $J = 8.0$ Hz, 2H), 2.66 (m, 2H), 2.55 (m, 2H), 2.34 (m, 2H).

MS (ESI) $[\text{M}+\text{H}^+]$: 432, 430

5 Into a solution of **169c** (40 mg) in DMSO (1.0 mL) was added imidazole (10 mg), CuI (5 mg), *N,N*-dimethylglycine (7 mg) and K_2CO_3 (25 mg). Under N_2 the mixture was sealed and heated to 110°C for 40 hrs. After cooling to room temperature, the mixture was partitioned between EtOAc and H_2O . The aqueous phase was extracted with EtOAc (2X). The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel (eluted with 0-20% of MeOH in CH_2Cl_2) to give compound **169** (17 mg) as a white solid.

MS (ESI) $[\text{M}+\text{H}^+]$: 418

Compound 170:



15 Into a solution of 7-amino-1-benzosuberone (350 mg, 2 mmol), NEt_3 (303 mg, 3 mmol), and catalytic amount of DMAP in 5 mL of CH_2Cl_2 at room temperature was added 2,6-difluorobenzoylchloride (352 mg, 2 mmol). The mixture was stirred at room temperature overnight, concentrated under reduced pressure. The residue was taken up in 5 mL of MeOH. K_2CO_3 (200 mg) was added. The mixture was stirred at 60°C 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 0-50% EtOAc in hexanes) to give **170a** (560 mg, 89% yield).

MS (ESI) $[\text{M}+\text{H}^+]$: 316

25 Into a solution of **170a** (469 mg, 1.48 mmol) in THF (10 mL) at 0°C was added phenyltrimethylammonium tribromide (564 mg, 1.50 mmol) in small portions. The mixture was stirred at 0°C for 30 minutes then at room temperature overnight. The reaction mixture was quenched by addition of an aqueous solution of saturated NaHCO_3 . The mixture was stirred at room temperature for

15 minutes, extracted with dichloromethane (2X). The combined extracts were washed with water and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica (eluted with 0-50% EtOAc in hexanes) to give **170b** (560 mg).

MS (ESI) $[\text{M}+\text{H}^+]$: 396, 394.

5

Into a solution of **170b** (200 mg, 0.5 mmol) in 2-PrOH (5.0 mL) at room temperature was added thiourea (152 mg, 2.00 mmol). The mixture was heated in a sealed tube under N_2 at 120°C for 1 hour, cooled to room temperature. The solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 , washed with aqueous NaHCO_3 and brine, then dried (Na_2SO_4), filtered and concentrated.

10 The residue was purified on silica (eluted with 0-100% EtOAc in hexanes) to give **170c** (150 mg) as white solid.

MS (ESI) $[\text{M}+\text{H}^+]$: 372

15 Into a stirred solution of *t*-BuONO (0.036 mL, 31 mg, 0.30 mmol) and CuBr_2 (55 mg, 0.25 mmol) in CH_3CN (5.0 mL) was added drop wise a solution of **170c** (83 mg, 0.22 mmol) in a 1:1 solution of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1.0 mL). The mixture was stirred at room temperature for 2 hr, diluted with EtOAc (10.0 mL). The EtOAc solution was washed with H_2O , with saturated NaHCO_3 then with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified on silica (eluted with 0-100% EtOAc in hexanes) to give **170d** (64 mg) as white solid.

20 MS (ESI) $[\text{M}+\text{H}^+]$: 437, 435

Compound **170** was prepared from **170d** similarly as described for the preparation of compound **169**.

MS (ESI) $[\text{M}+\text{H}^+]$: 437

25 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 $2.5 \mu\text{g/mL}$) 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

30 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.

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

Compound #	IC ₅₀ (nM)
1, 2, 113, 114, 126, 127, 134	≤ 30
91, 117, 118, 119, 121, 130, 131	30 < IC ₅₀ ≤ 100
45, 46, 48, 120, 122, 123, 128, 132, 133	100 < IC ₅₀ ≤ 250
115, 124, 125, 129	250 < IC ₅₀ ≤ 500
116	500 < IC ₅₀ ≤ 1000
42, 43	> 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) RBL cells

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% CO₂. 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 Elektronik, 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; MgCl₂ 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; CaCl₂ 10mM;

Glucose 5.5mM; KCl 5.4mM; KH_2PO_4 0.4mM; $\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$ 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) Jurkat cells

Cells

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

Extracellular Solution

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

Intracellular Pipette Solution

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

Patch-clamp recordings

Patch-clamp experiments are performed in the tight-seal whole-cell configuration at 21-25 °C.

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

Data analysis

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

3) Primary T Cells

Preparation of Primary T Cells

Primary T cells are obtained from human whole blood samples by adding 100 μL 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,
5 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
10 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
20 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,
25 resuspended in 5 ml of incomplete RPMI, and counted using a hemocytometer.

Cell migration assay:

Aliquots of each T cell preparation are labeled with Calciem AM (TefLabs) and suspended at a concentration of 2.4×10^6 /ml in HEPES-buffered Hank's Balanced Salt Solution containing 1.83 mM
30 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
35 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.

5

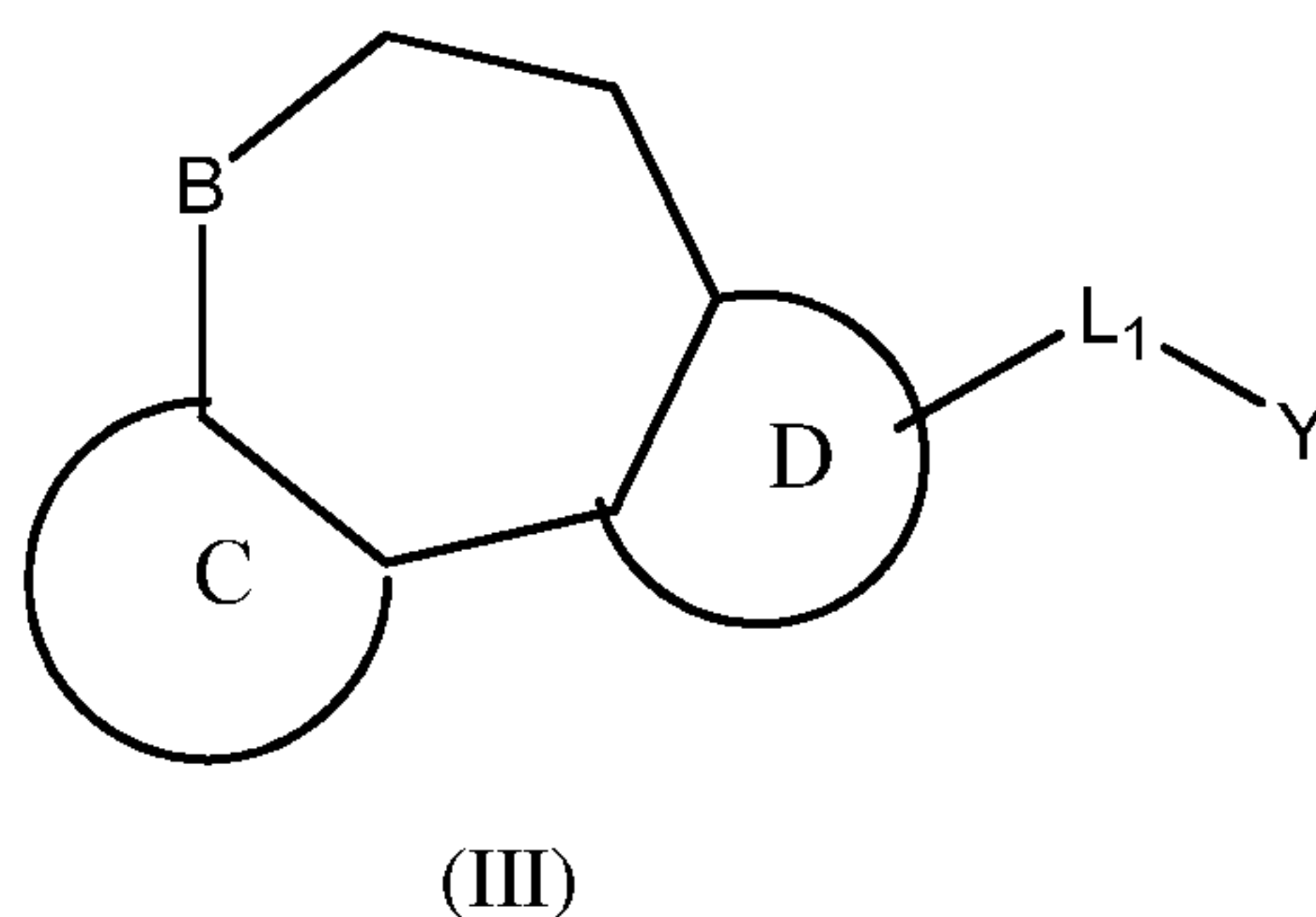
Compounds of the invention are expected to inhibit chemotactic response of T cells.

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.

10

WE CLAIM:

1. A compound represented by formula (III):



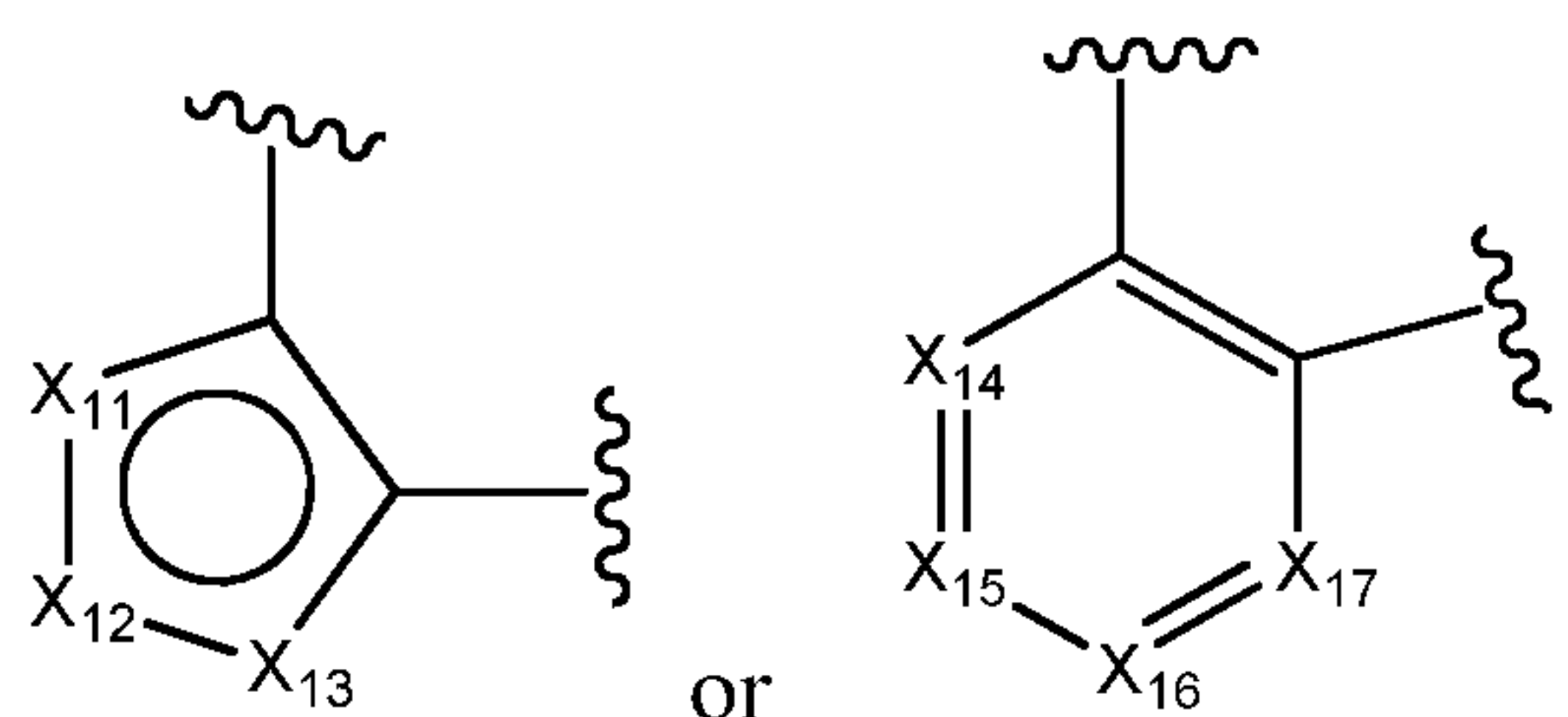
or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

Ring C is selected from



each of X_{11} , X_{12} and X_{13} are independently selected from $-\text{C}(\text{R}^a)-$, $-\text{C}(\text{R}^a)_2-$, $-\text{S}-$, $-\text{O}-$, $-\text{N}-$, or $-\text{N}(\text{R}^b)-$;

each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-\text{C}(\text{R}^a)-$ and $-\text{N}-$;

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

each R^b is independently $-\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl,

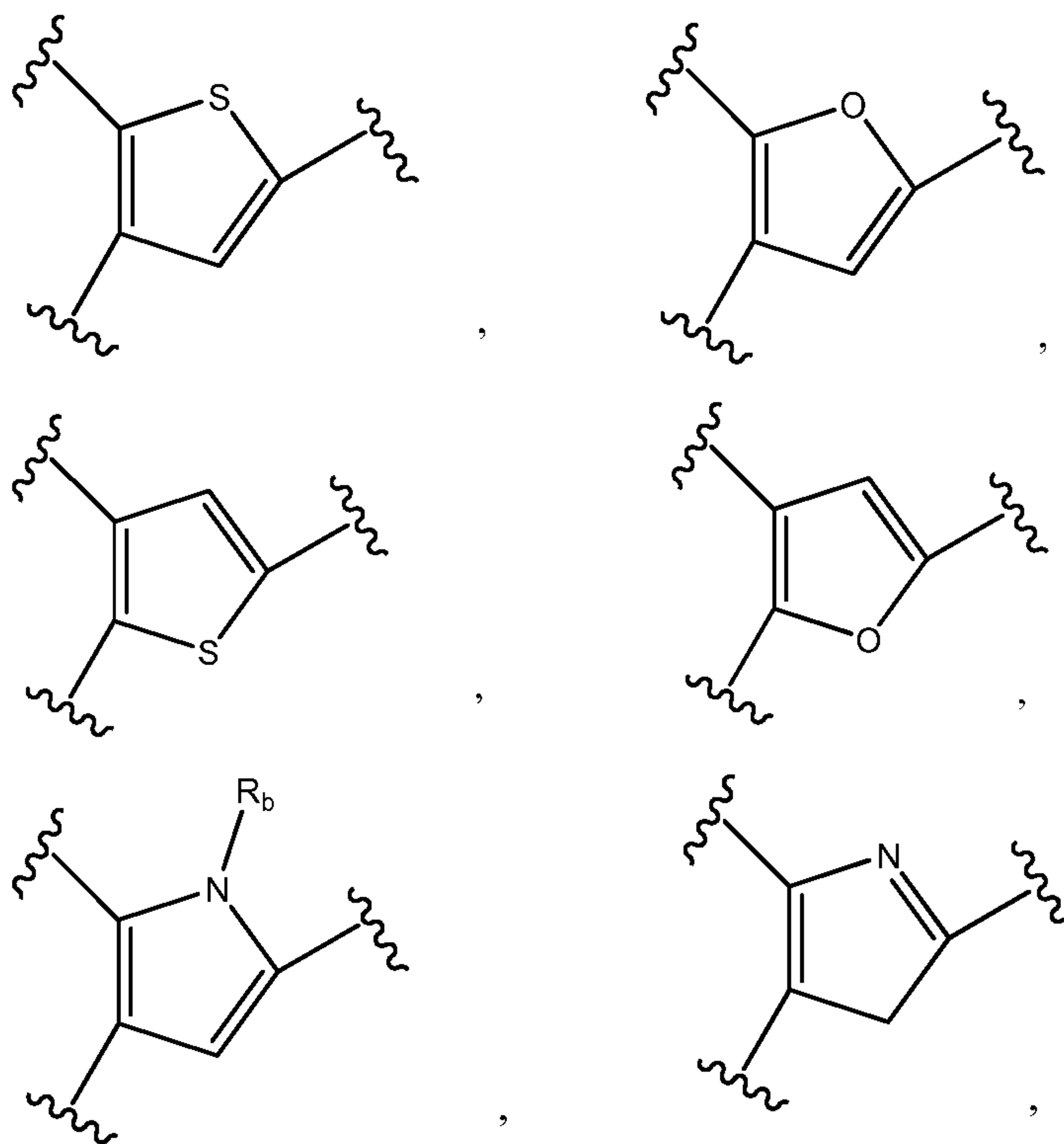
an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, $-\text{C}(\text{O})\text{R}_4$, or $-\text{C}(\text{O})\text{OR}_4$;

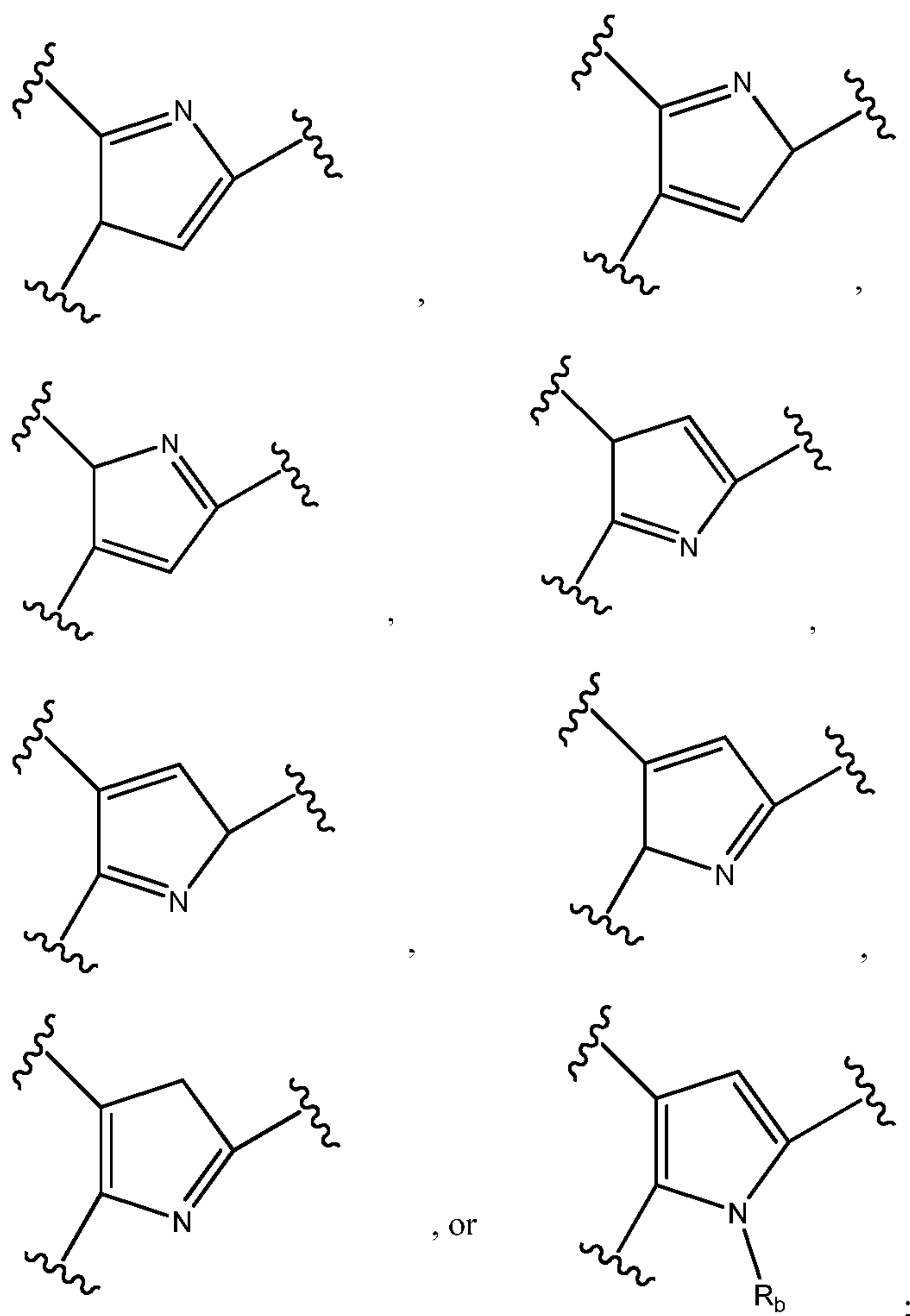
R_1 and R_2 , for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

p is 0, 1, or 2; and

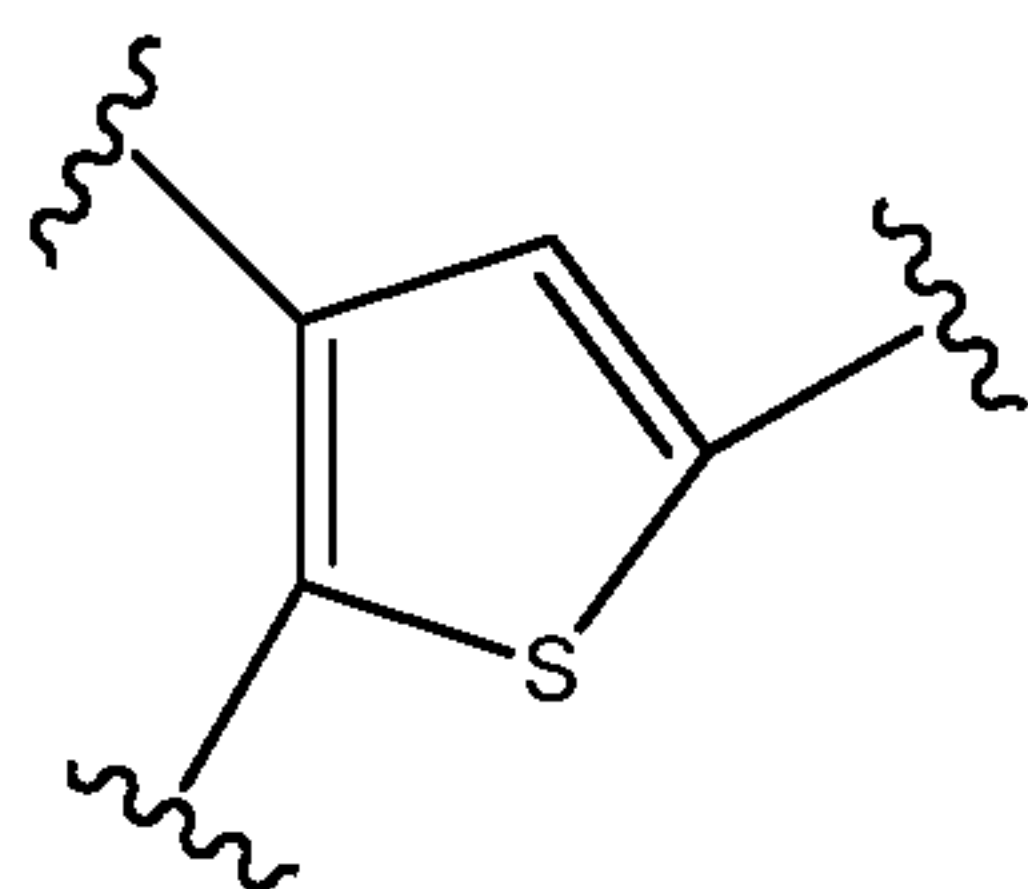
Ring D is selected from:





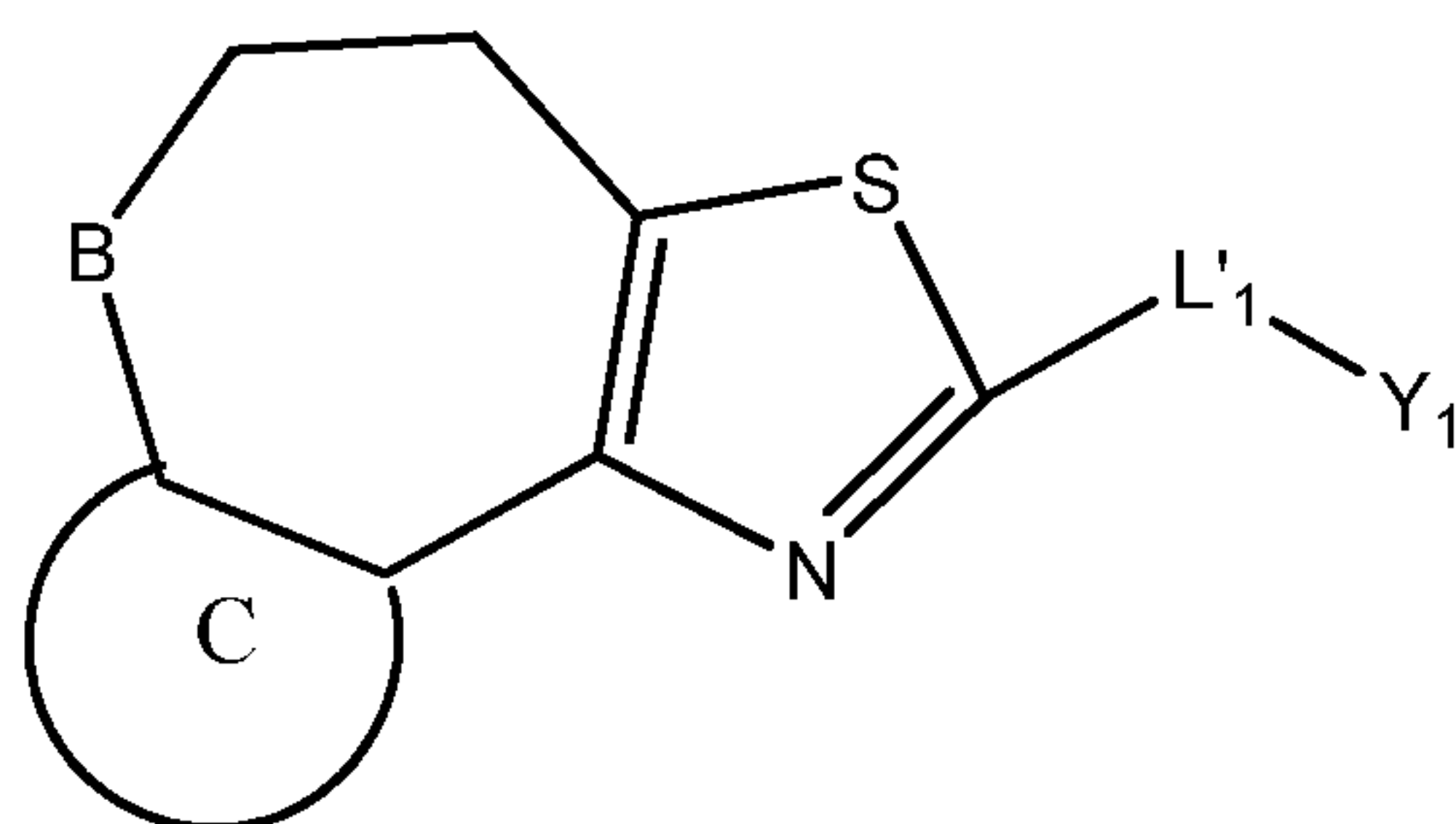
with the proviso that the compound is not 4H-thieno[3,2-d][1]benzazine-2-carboxamide, 6-[4-[[[1,1'-biphenyl]]-2-ylcarbonyl)amino]benzoyl]-N-cyclopropyl-5,6-dihydro-.

2. The compound of Claim 1, wherein Ring D is



3. The compound of Claim 2, wherein R_{34} is selected from the group consisting of Br, Cl, cyano, CF_3 , $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-N(CH_3)_2$, $-OCH_3$, $-C(O)NH_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.
4. The compound of Claim 3, wherein B is $-CH_2-$.

5. A compound represented by formula (IV):



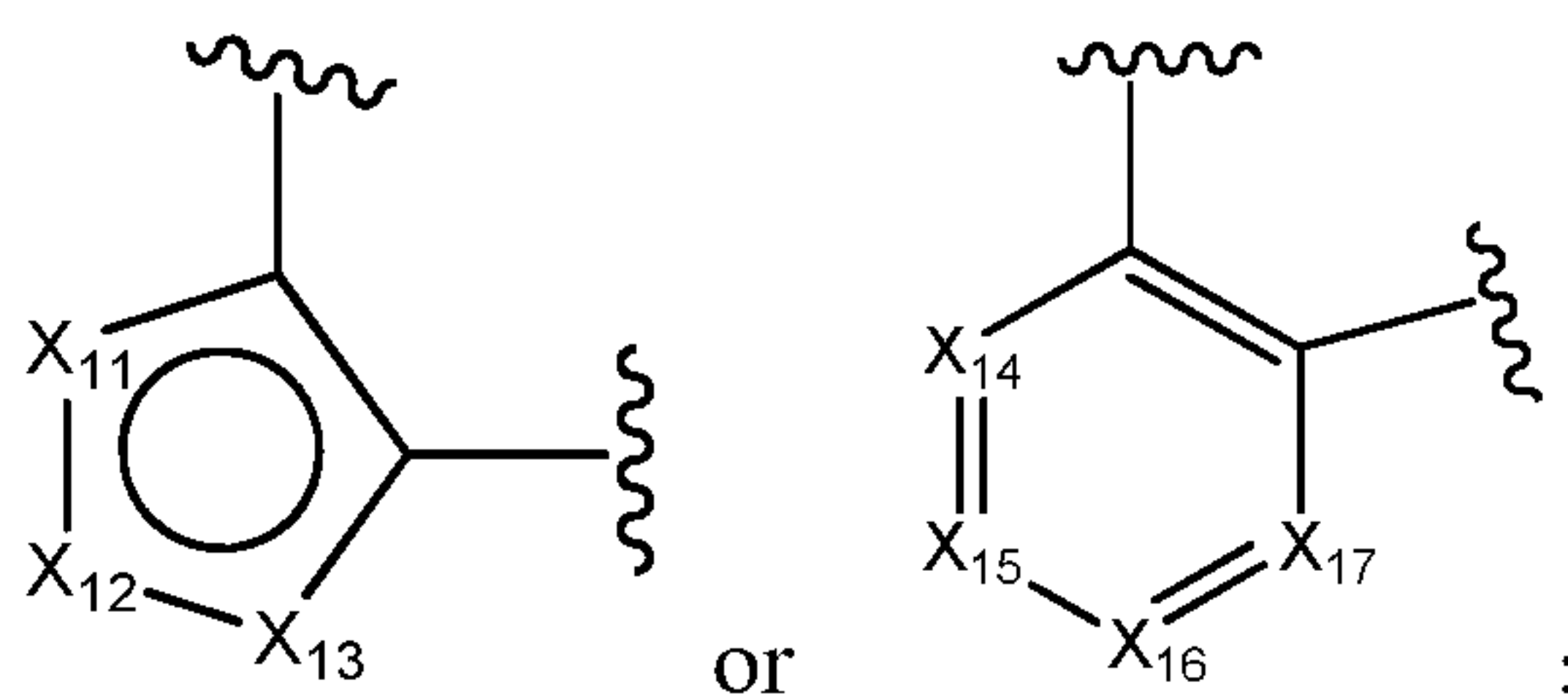
(IV)

or a pharmaceutically acceptable salt thereof, wherein:

L'_1 is $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y_1 is a 5 or 6 membered aromatic ring optionally substituted with C1-C4 alkyl, halo, or C1-C4 alkoxy, an optionally substituted 5 or 6 membered heteroaromatic ring, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl;

Ring C is selected from



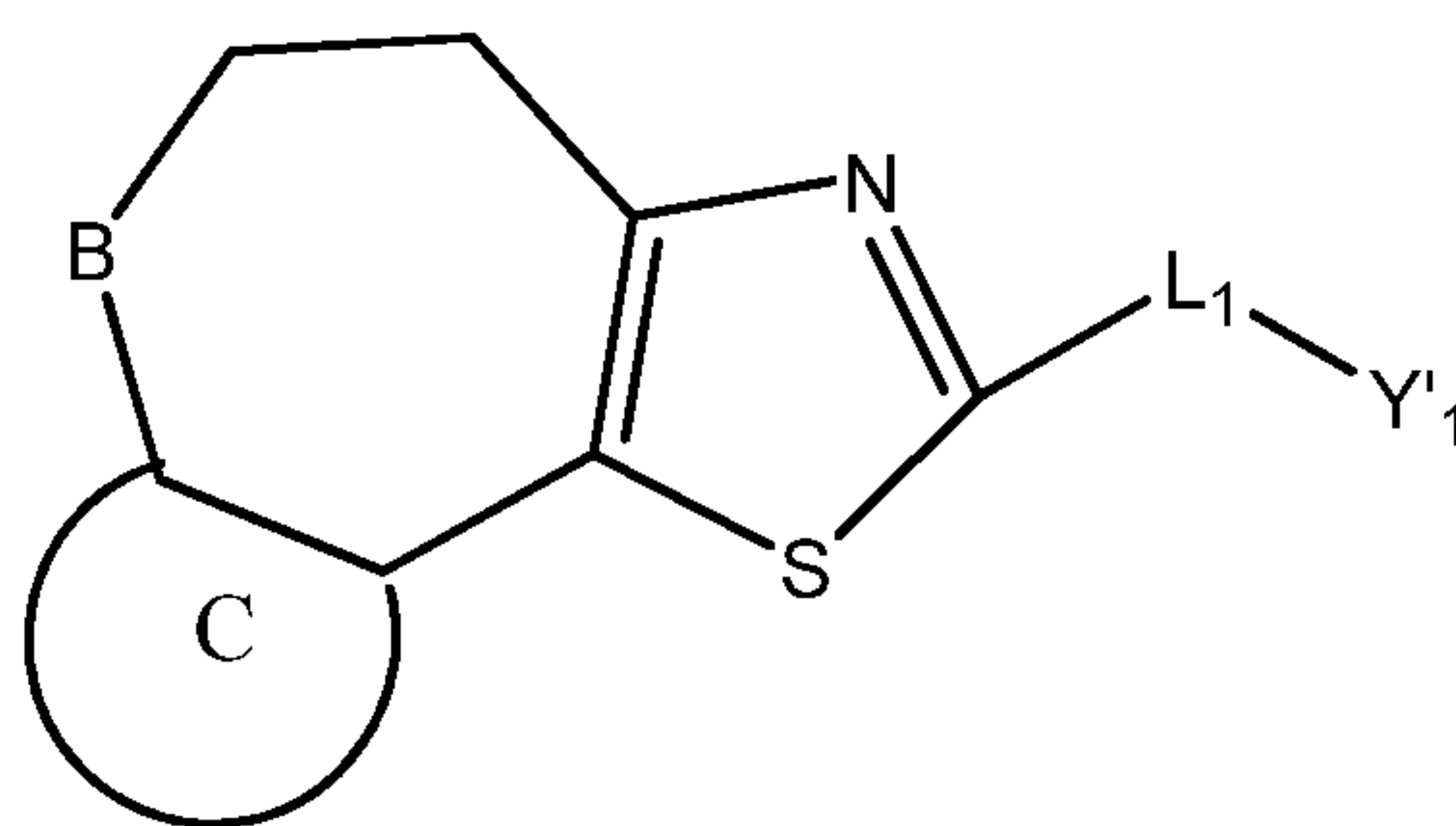
each of X_{11} , X_{12} and X_{13} are independently selected from $-\text{C}(\text{R}^a)-$, $-\text{C}(\text{R}^a)_2-$, $-\text{S}-$, $-\text{O}-$, $-\text{N}-$, or $-\text{N}(\text{R}^b)-$; and

each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-\text{C}(\text{R}^a)-$ and $-\text{N}-$;

with the proviso that when B is $-\text{CH}_2-$ or $-\text{NC}(\text{O})\text{R}_4-$, and L'_1 is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{NHC}(\text{O})\text{NH}-$, then X_{14} , X_{15} , X_{16} , and X_{17} are not all $-\text{C}(\text{R}^a)-$; and

with the proviso that the compound is not 4H-benzo[6,7]cyclohepta[1,2-d]thiazole-2-carboxamide, 5,6-dihydro-N-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-.

6. A compound represented by formula (V):



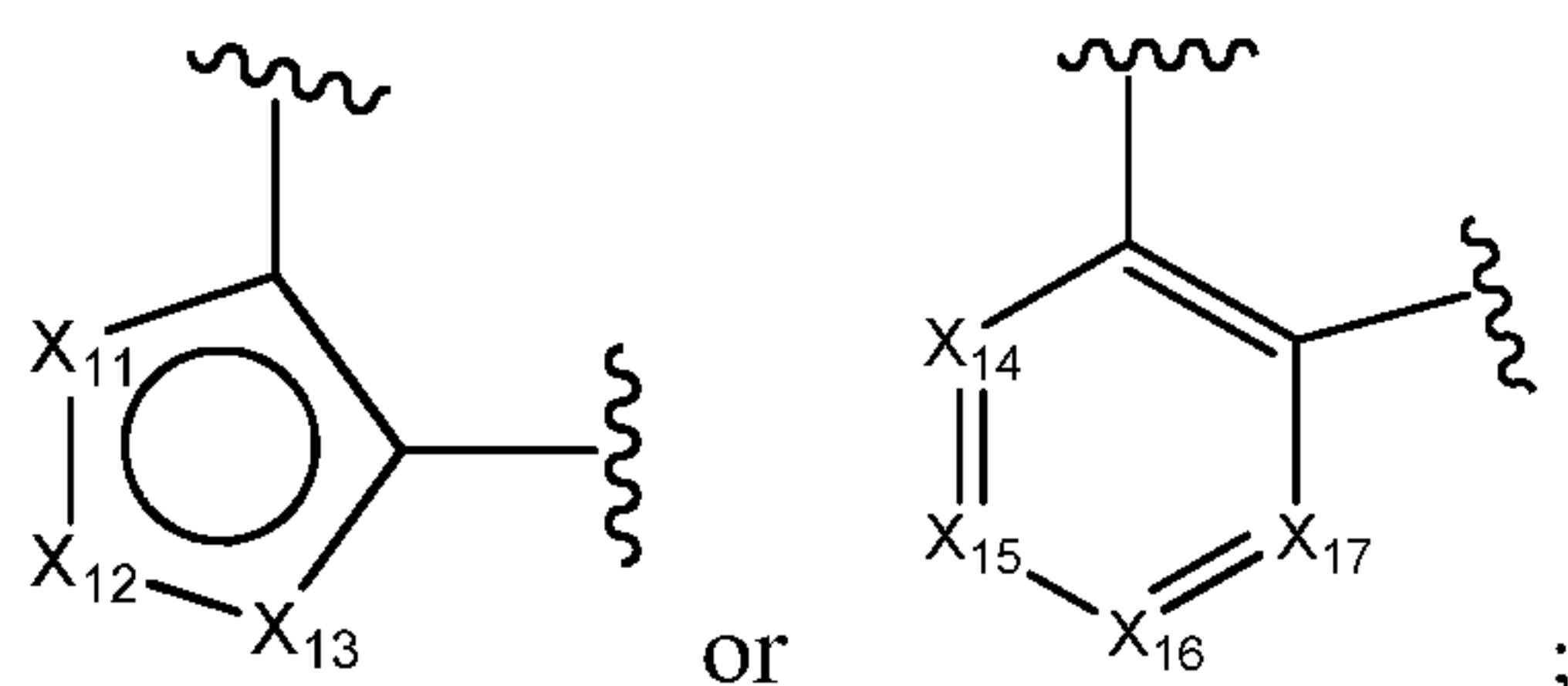
(V)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

Y'_1 is an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, or an optionally substituted cycloalkenyl;

Ring C is selected from

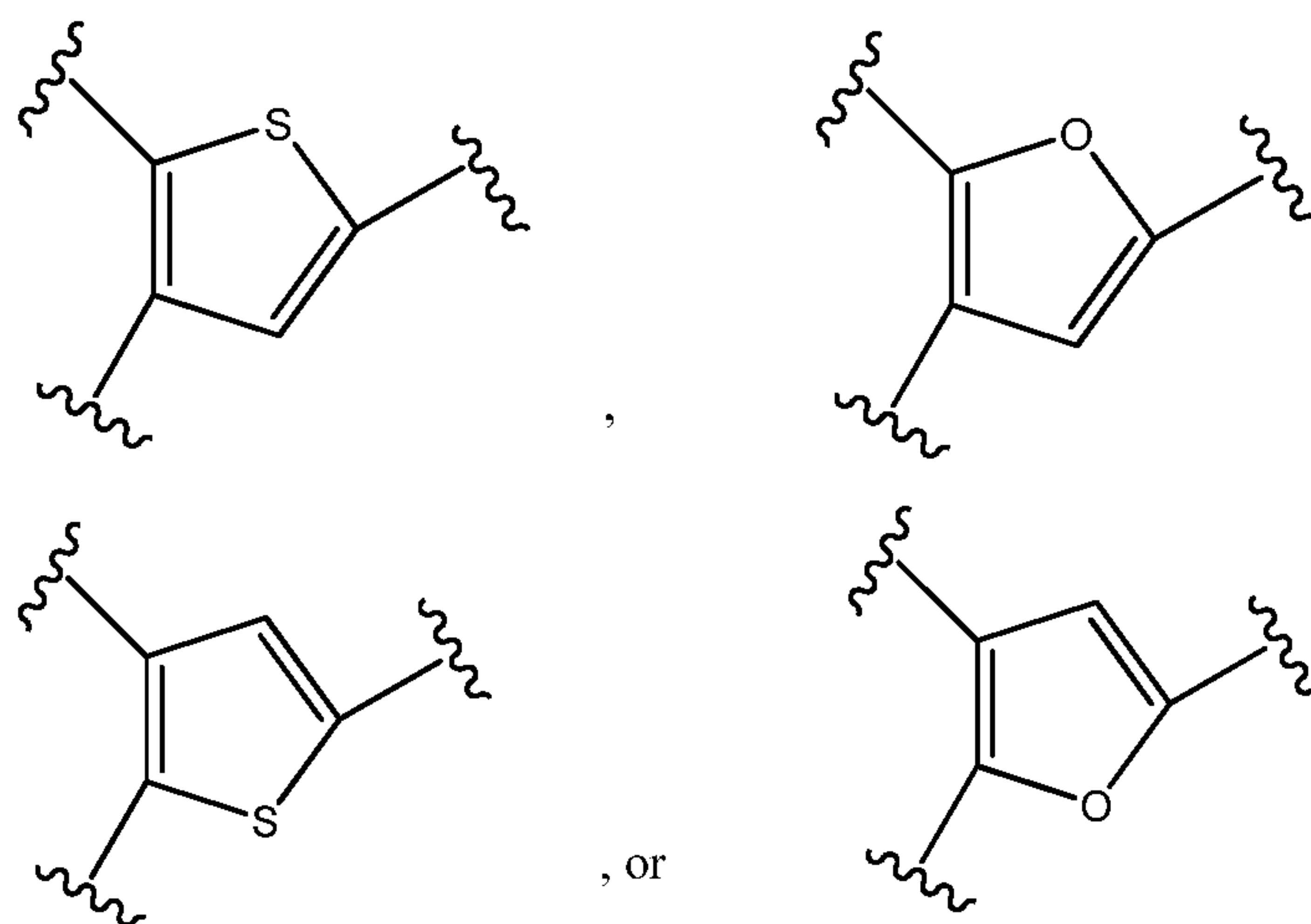


each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R^a)-$, $-C(R^a)_2-$, $-S-$, $-O-$, $-N-$, or $-N(R^b)-$; and

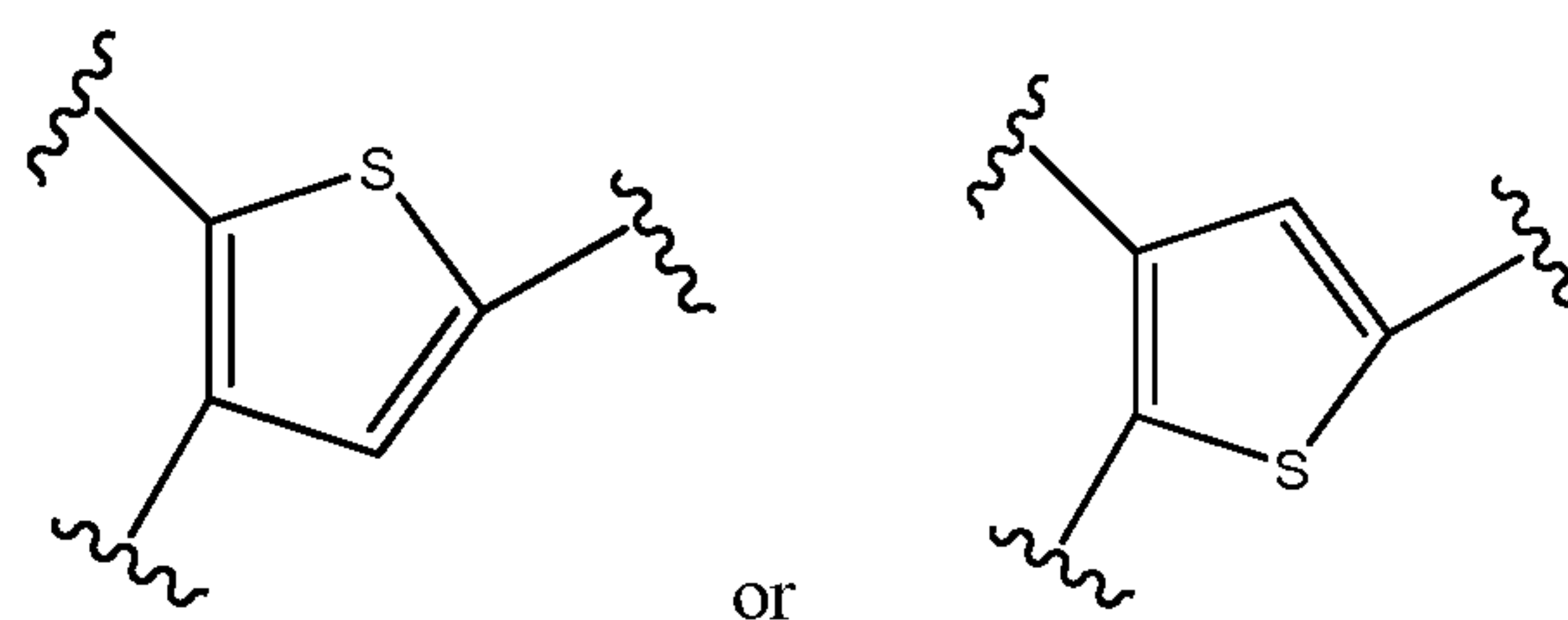
each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R^a)-$ and $-N-$;

with the proviso that when L_1 is $-NH-C(O)-$ and Y is methyl, then Ring C is not a pyrazole.

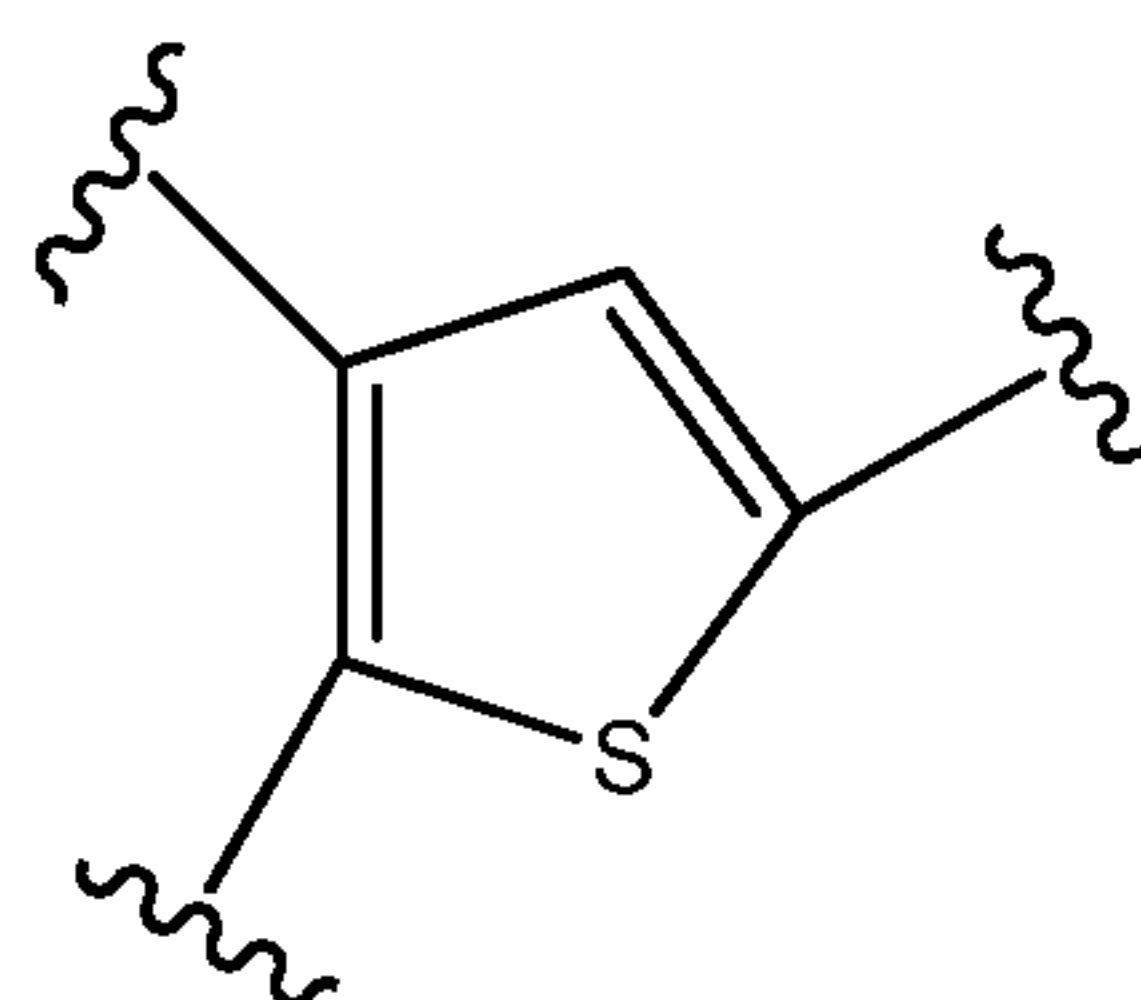
7. The compound of Claim 6, wherein Y'_1 is optionally substituted alkyl or optionally substituted cycloalkyl.
8. The compound of Claim 7, wherein Y'_1 is optionally substituted C3-C5 alkyl or optionally substituted C3-C6 cycloalkyl.
9. The compound of Claim 6, wherein Y'_1 is optionally substituted alkenyl or optionally substituted cycloalkenyl.
10. The compound of Claim 6, wherein Y'_1 is optionally substituted C3-C5 alkenyl or optionally substituted C3-C6 cycloalkenyl.
11. The compound of Claim 1 or 6, wherein Ring D is



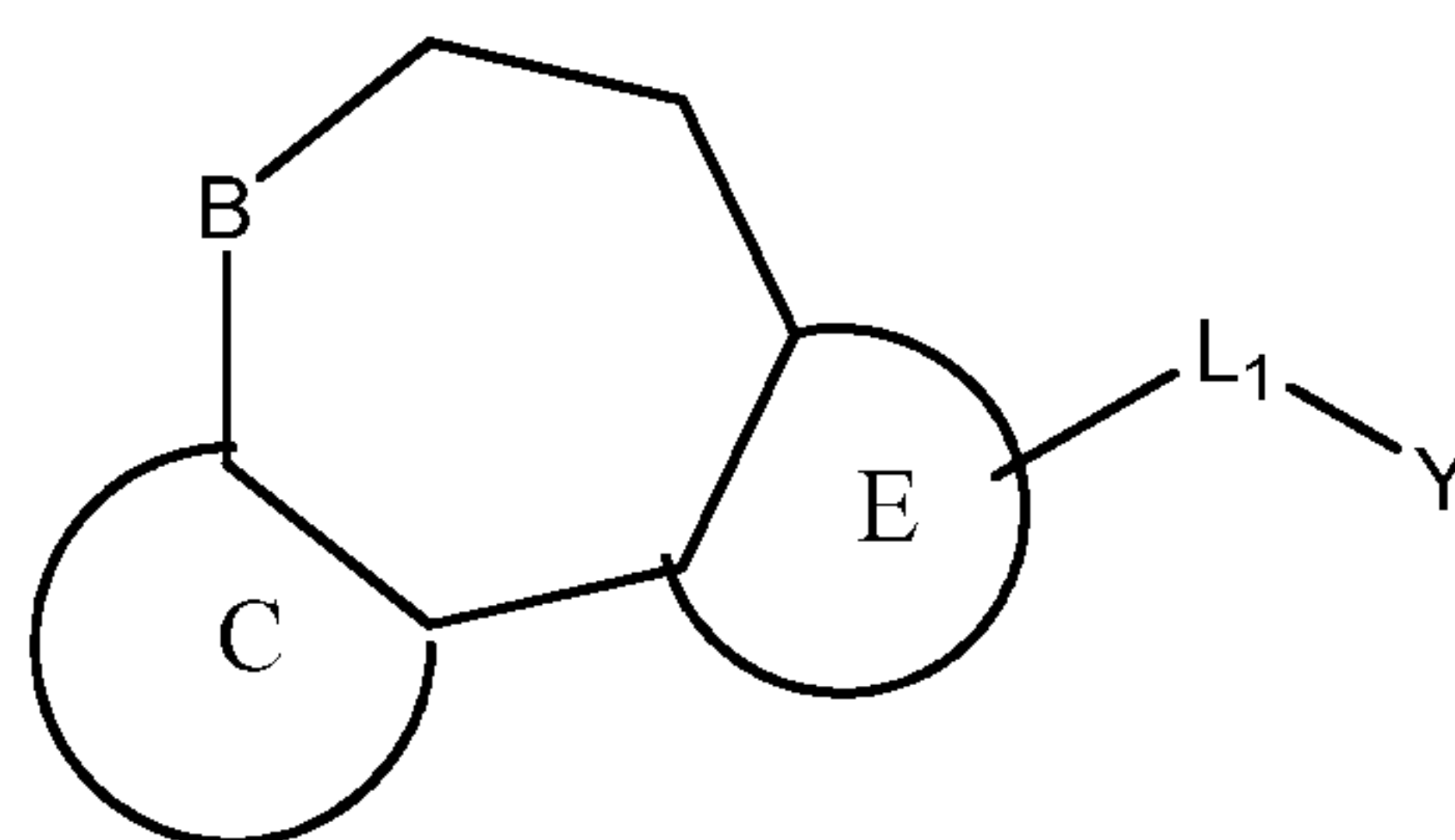
12. The compound of Claim 1 or 11, wherein Ring D is



13. The compound of Claim 1 or 12, wherein Ring D is



14. A compound represented by formula (VIII):



(VIII)

or a pharmaceutically acceptable salt thereof, wherein:

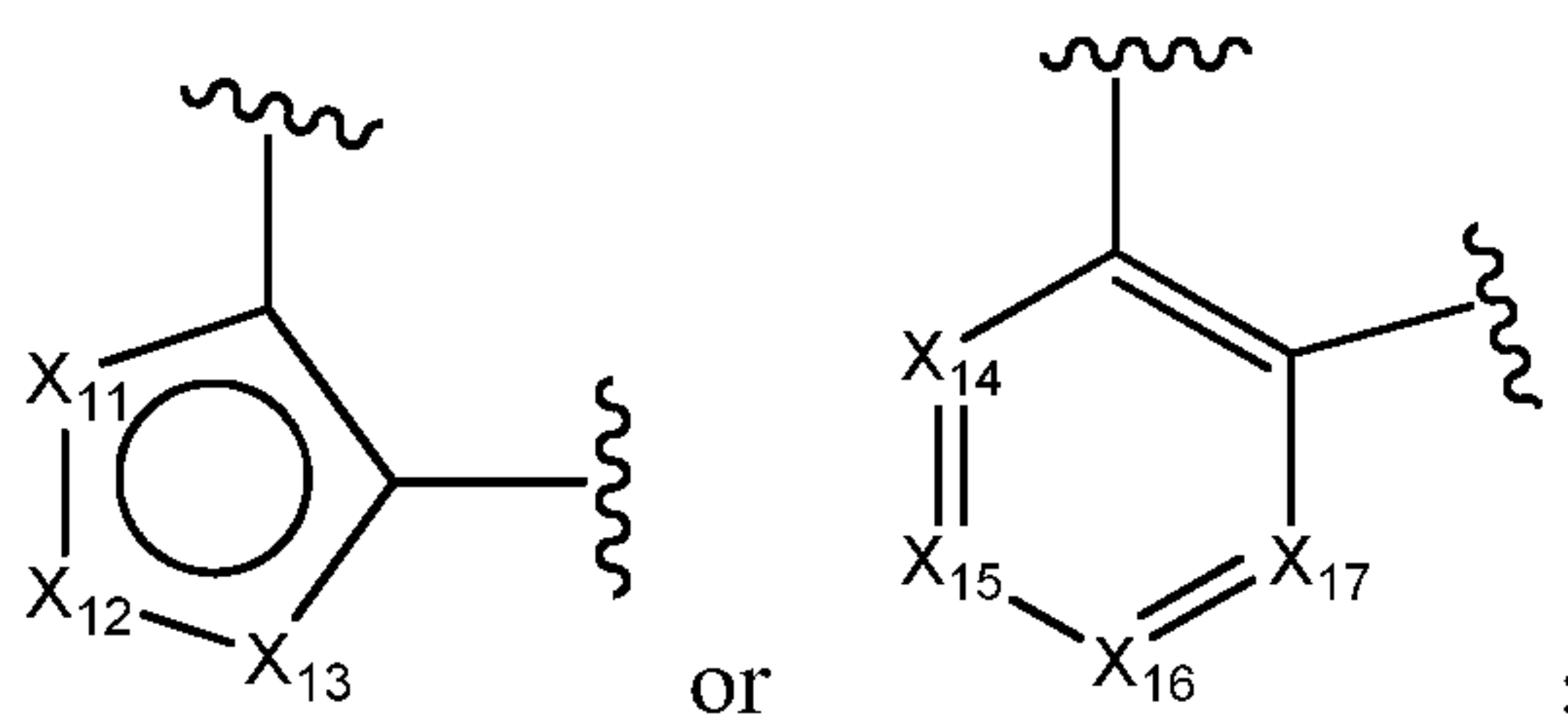
L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally

substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

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

Ring C is selected from



each of X_{11} , X_{12} and X_{13} are independently selected from $-C(R_a)-$, $-C(R_a)_2-$, $-S-$, $-O-$, $-N-$, or $-N(R_b)-$;

each of X_{14} , X_{15} , X_{16} , and X_{17} are independently selected from $-C(R_a)-$ and $-N-$;

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 $-C(O)OR_4$;

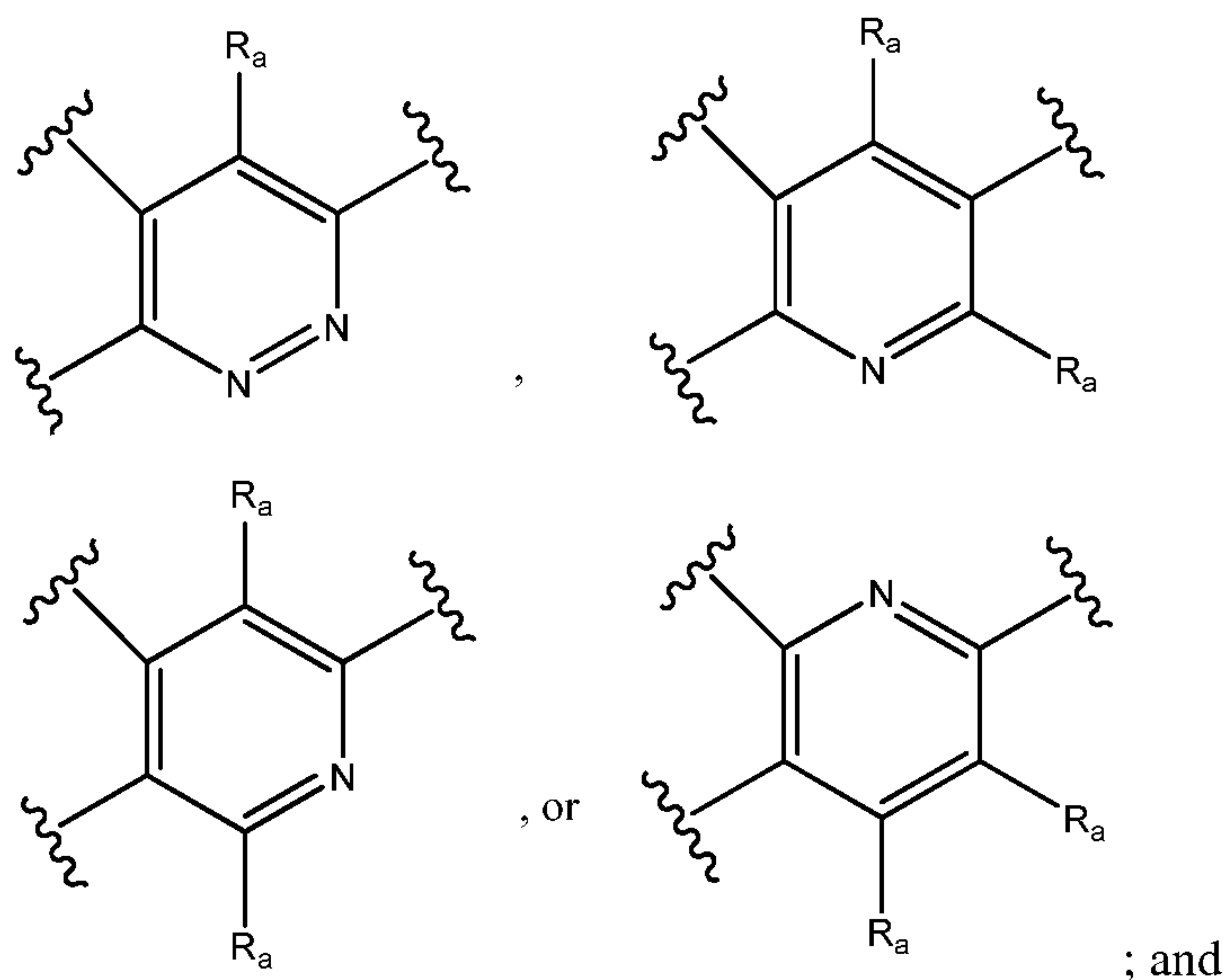
R_1 and R_2 , for each occurrence are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

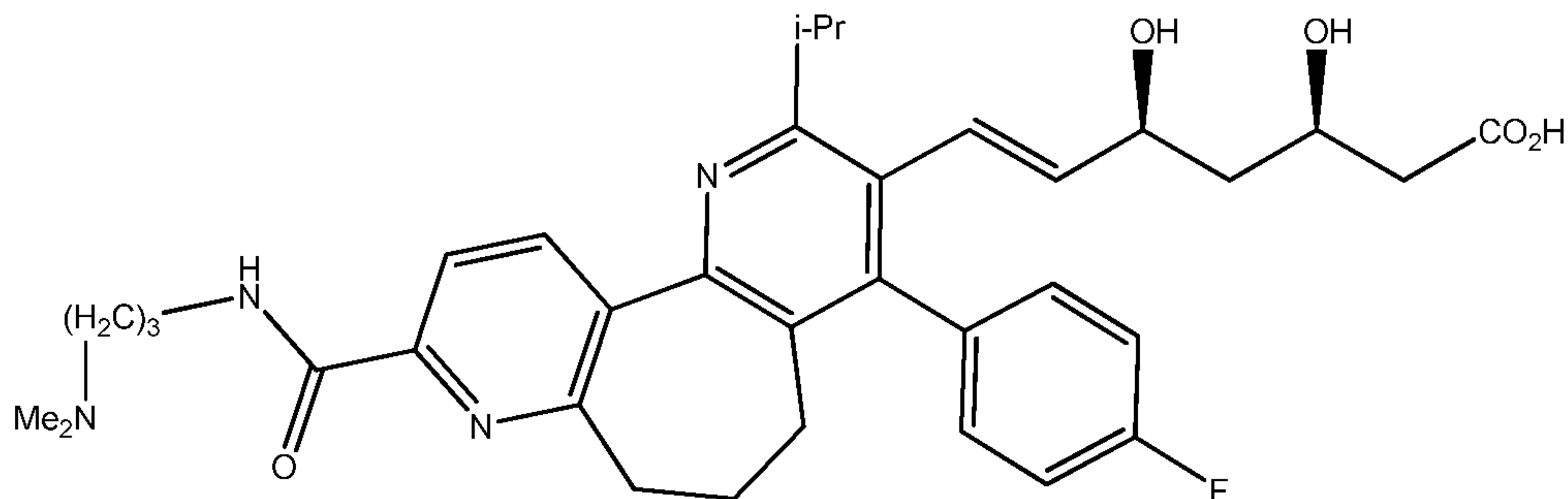
p is 0, 1, or 2; and

Ring E is selected from:



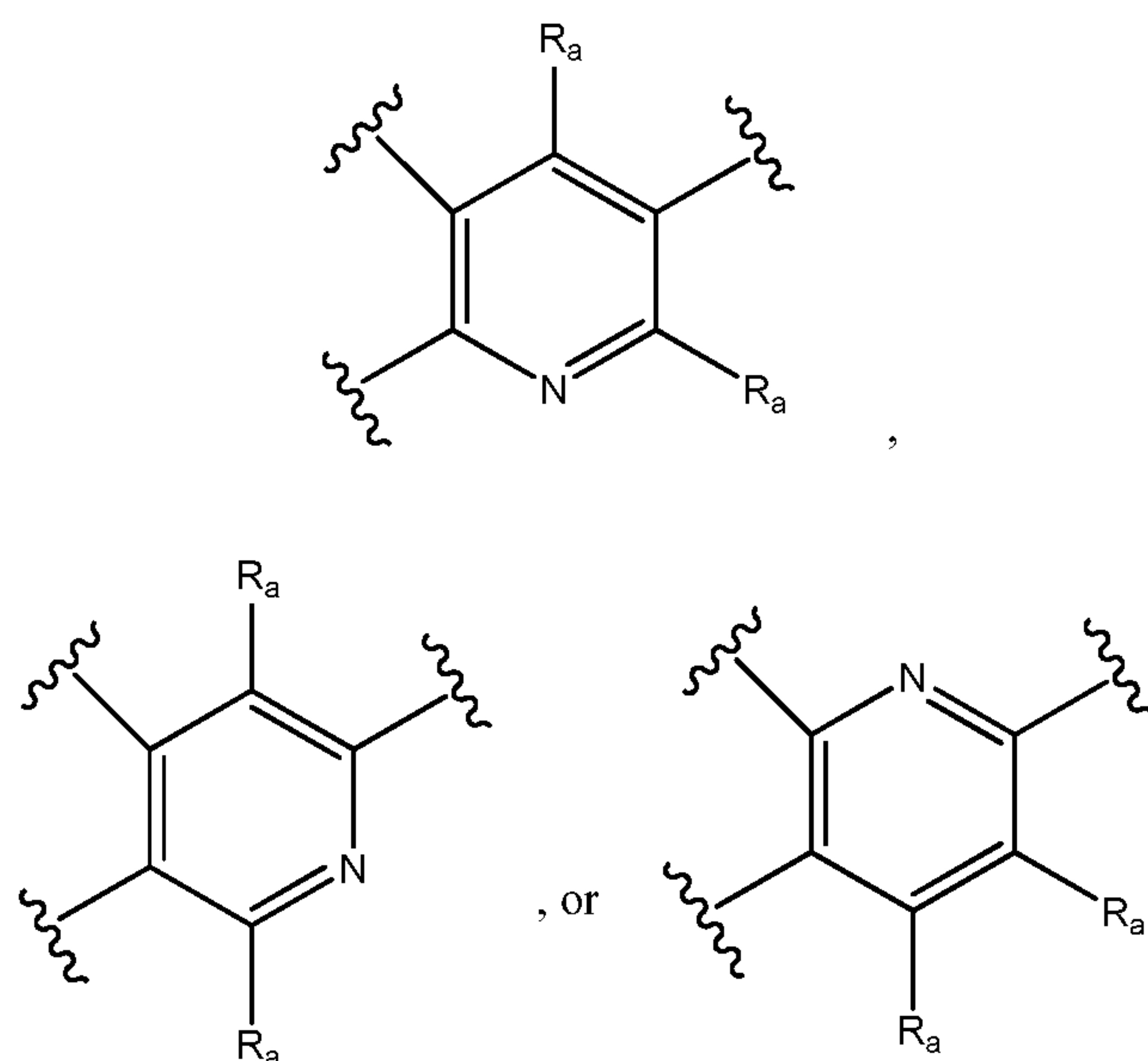
with the proviso that when Ring E is pyridazine, Y is an optionally substituted alkyl, and L'_1 is $-NH-CH_2-$, then Ring C is not a phenyl, an optionally substituted phenyl or a thiophene; and

with the proviso that the compound is not

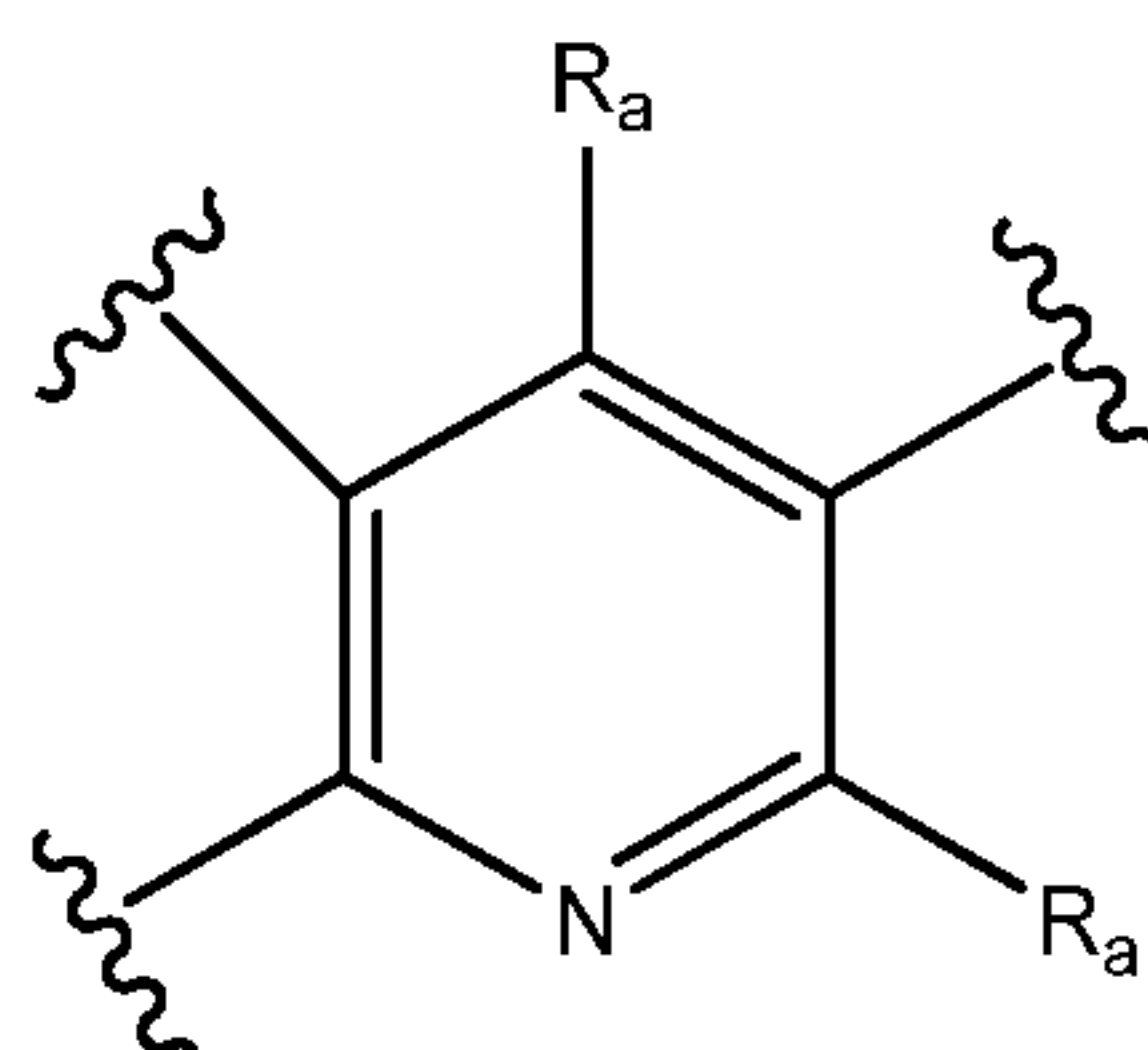


15. The compound of Claim 1, 5 or 14, wherein Y is an optionally substituted phenyl, an optionally substituted oxazolyl, an optionally substituted furanyl, an optionally substituted pyrazolyl, an optionally substituted pyridinyl, an optionally substituted pyridazinyl, an optionally substituted thiadiazolyl, or an optionally substituted thiophenyl.
16. The compound of Claim 1, 5 or 15, wherein Y is unsubstituted.
17. The compound of Claim 1, 5 or 15, wherein Y is a difluorophenyl.
18. The compound of Claim 1, 5 or 15, wherein Y is an optionally substituted thiadiazolyl.

19. The compound of Claim 1, 5 or 15, wherein Y is an optionally substituted thiophenyl.
20. The compound of Claim 1, 5 or 15, wherein Y is an optionally substituted pyridazinyl.
21. The compound of any one of Claims 18-20, wherein Y is substituted with one methyl group.
22. The compound of Claim 1, 5 or 15, wherein Y is optionally substituted alkyl or optionally substituted cycloalkyl.
23. The compound of Claim 1, 5 or 22, wherein Y is optionally substituted C3-C5 alkyl or optionally substituted C3-C6 cycloalkyl.
24. The compound of Claim 1 or 14, wherein Y is optionally substituted alkenyl or optionally substituted cycloalkenyl.
25. The compound of Claim 1 or 14, wherein Y is optionally substituted C3-C5 alkenyl or optionally substituted C3-C6 cycloalkenyl.
26. The compound of Claim 1 or 14, wherein Y is optionally substituted heterocyclyl.
27. The compound of Claim 14, wherein Ring E is

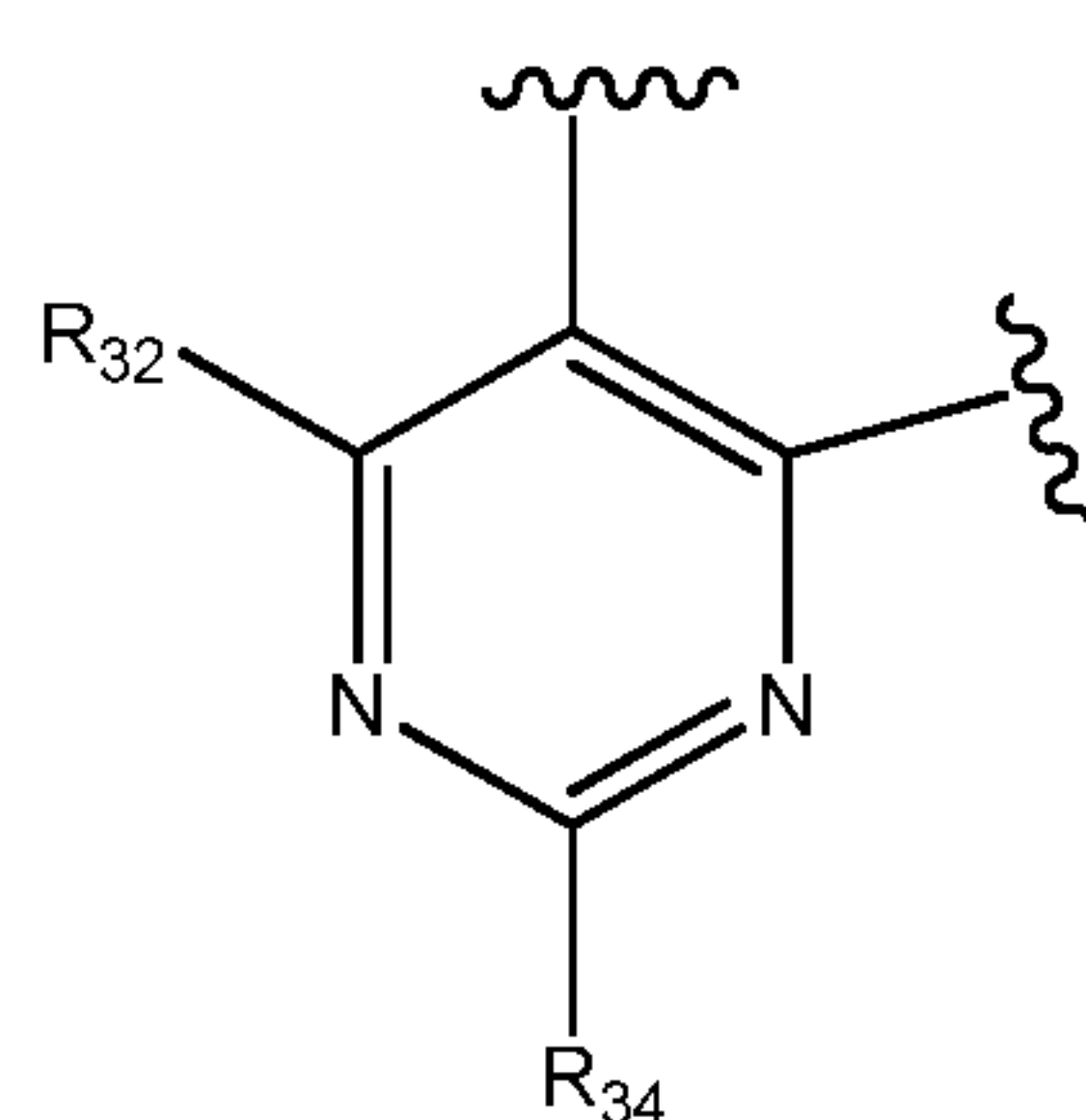
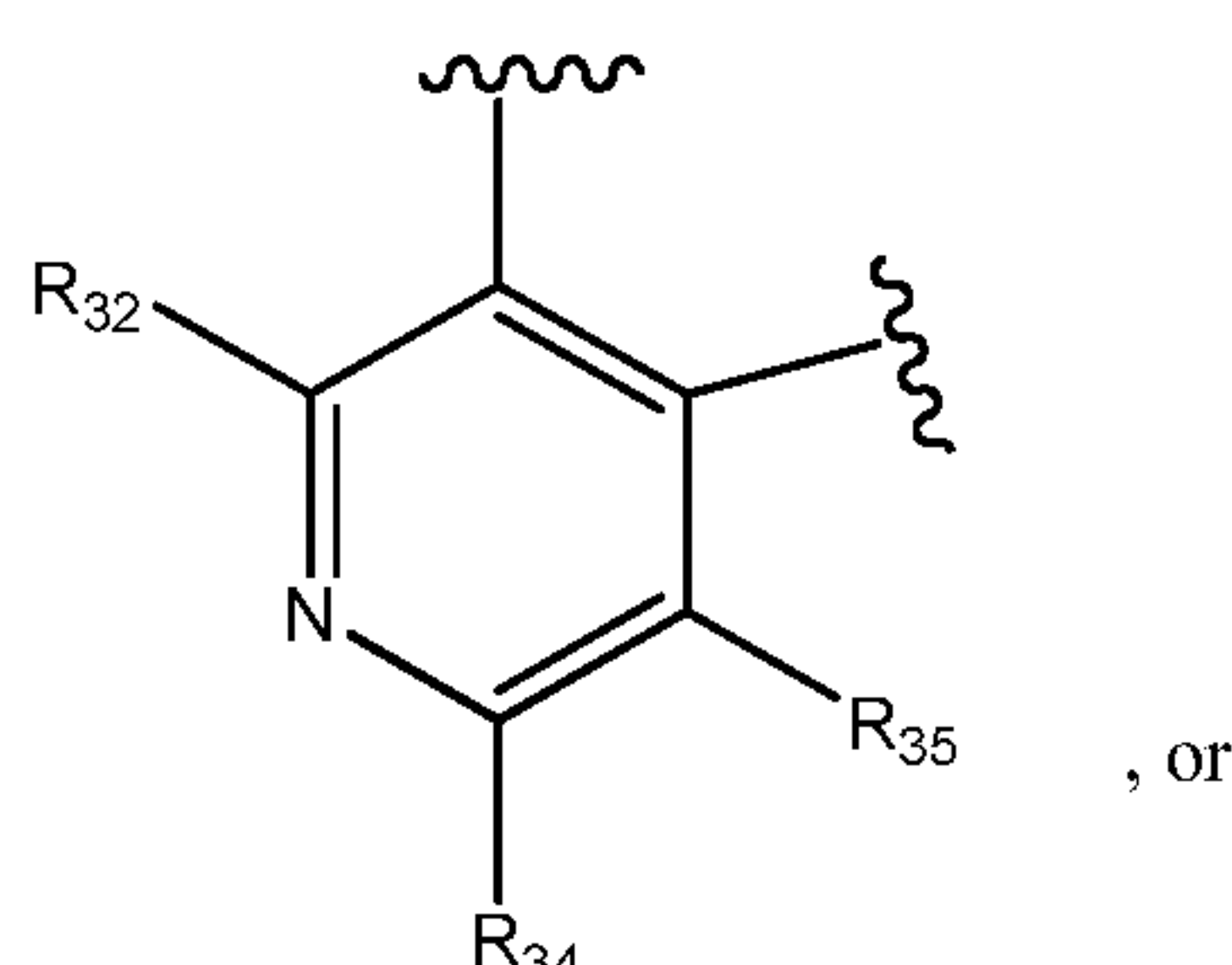
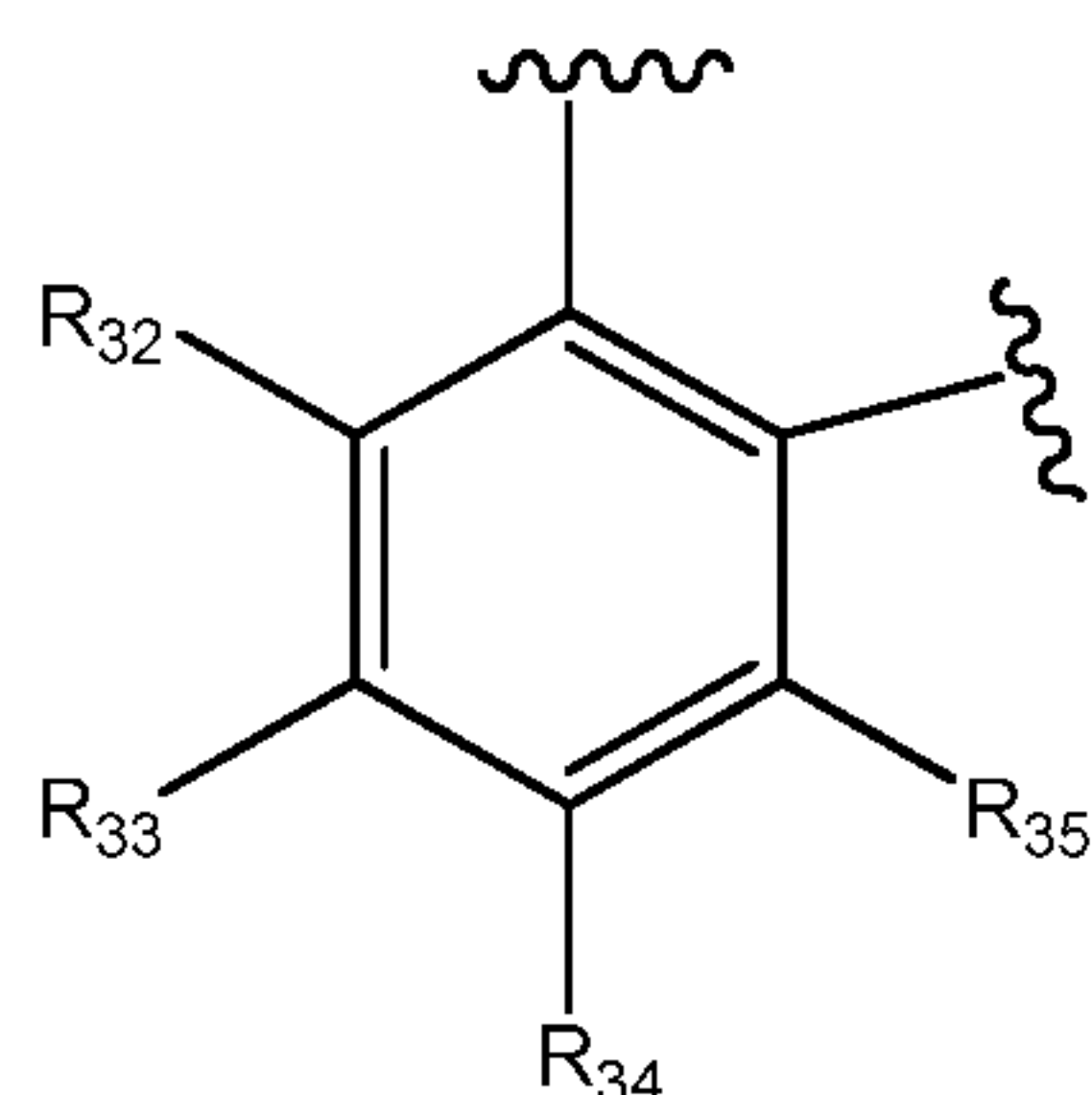
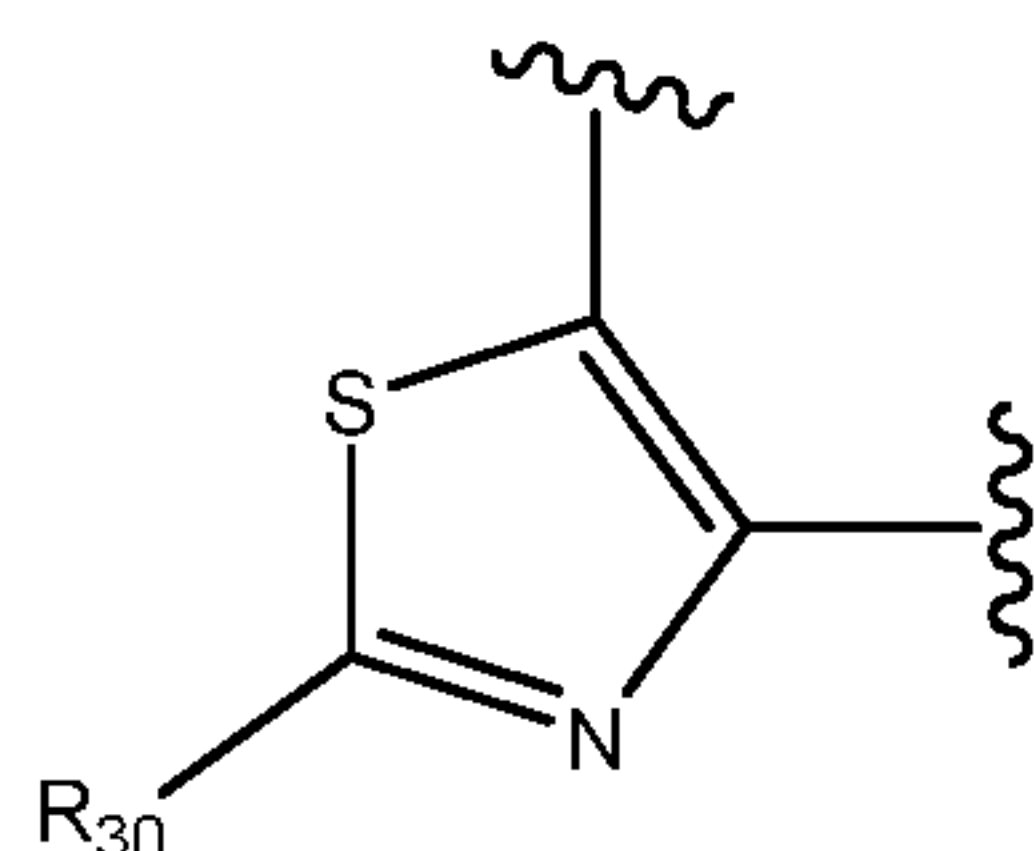
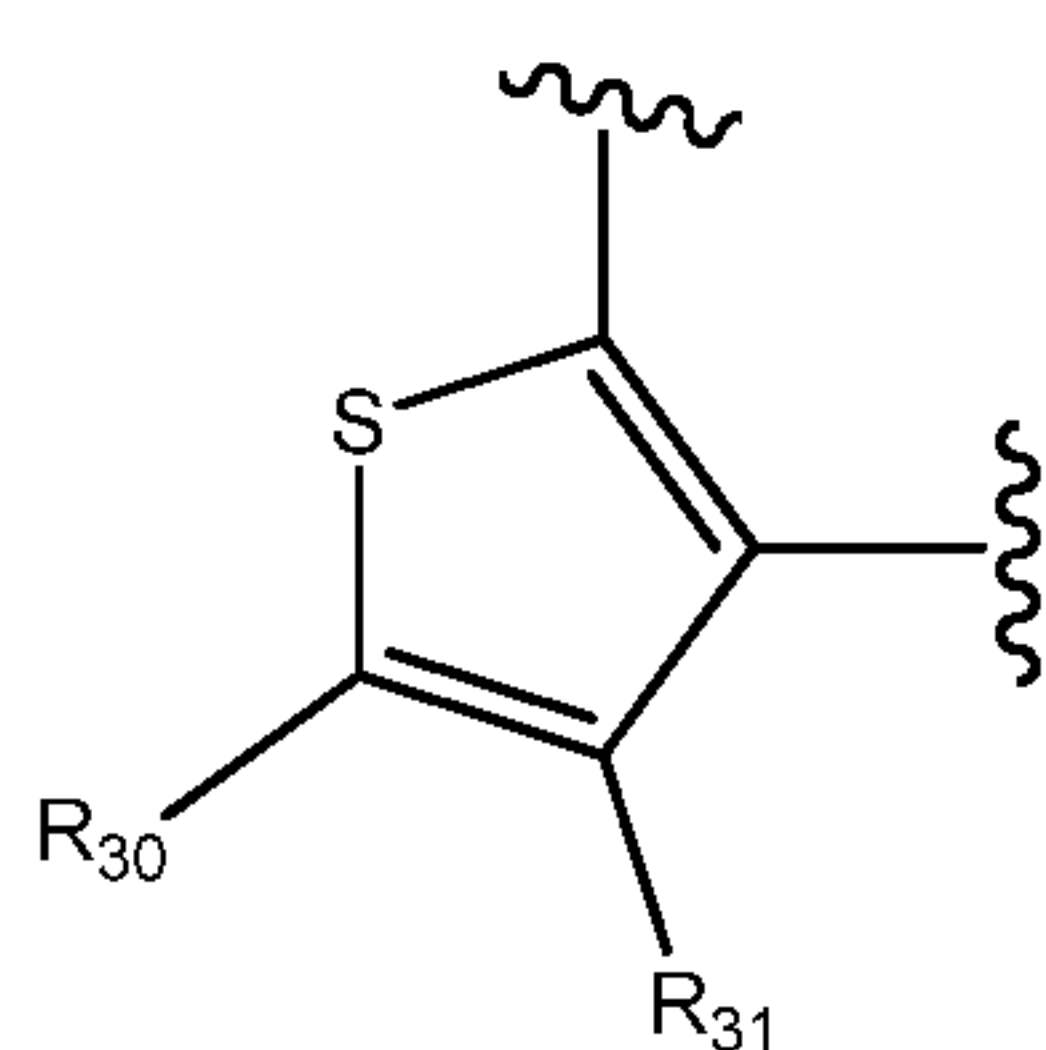


28. The compound of Claim 27, wherein Ring E is:



29. The compound of Claim 27 or Claim 28, wherein R_a is $-H$.

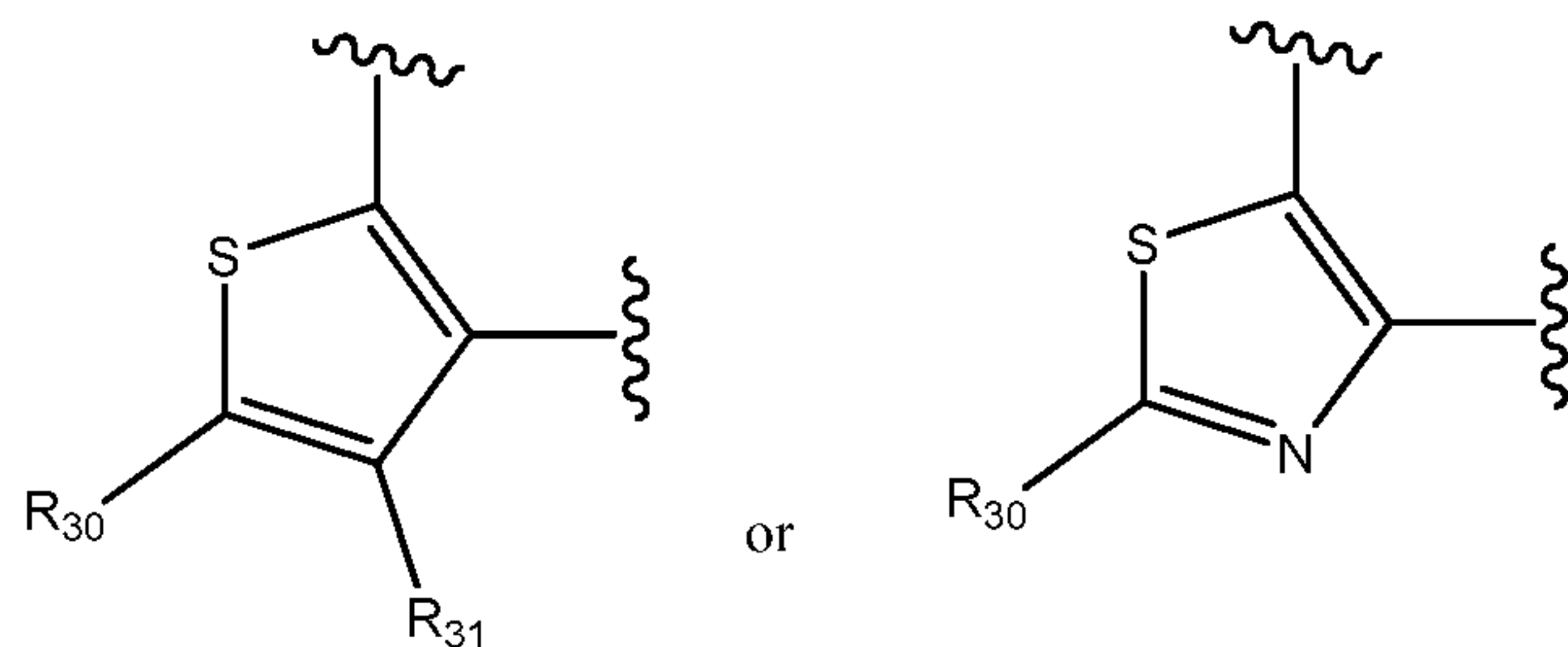
30. The compound of Claim 1, 5, 6 or 14, wherein Ring C is:



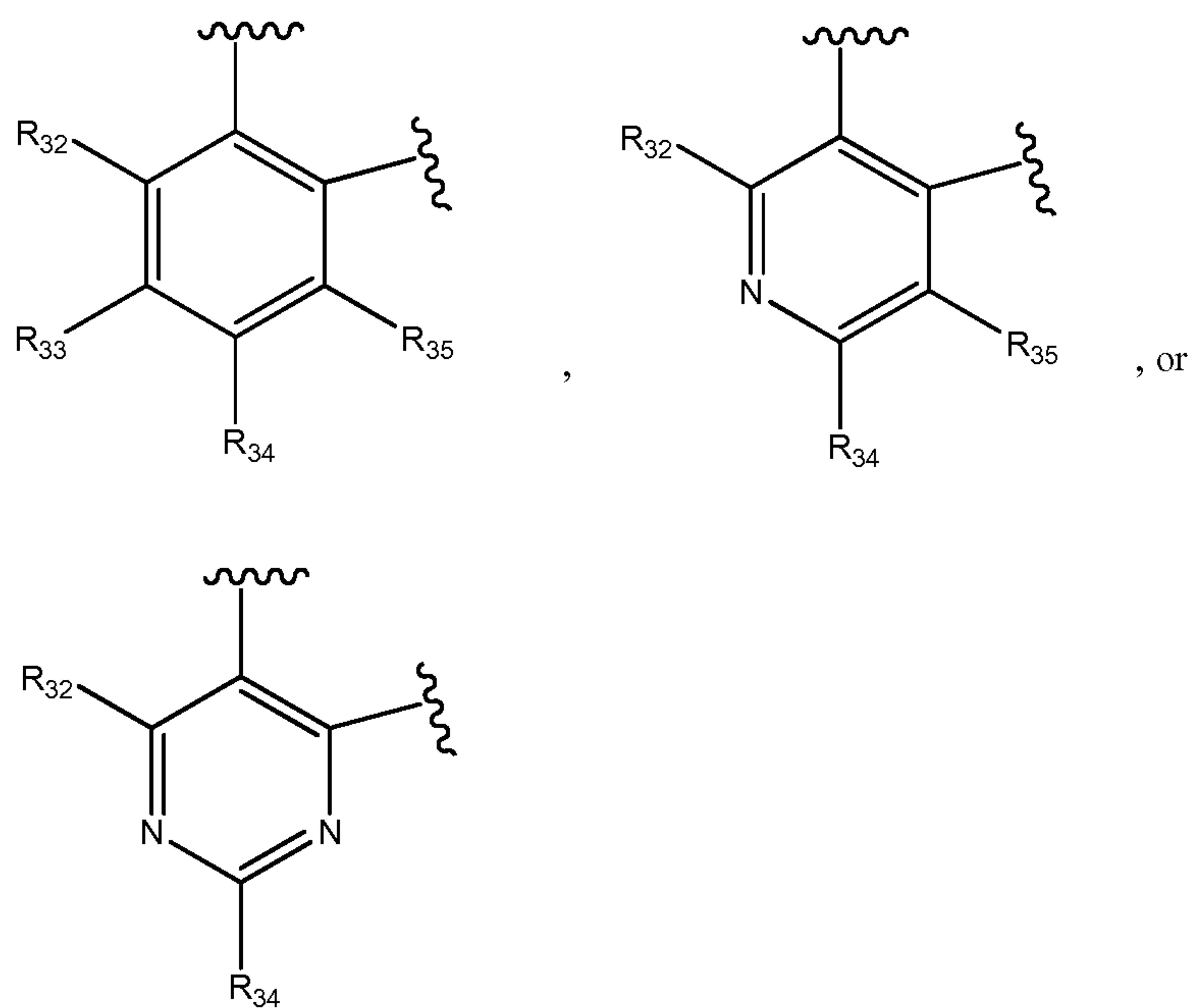
wherein each of R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , and R_{35} is independently selected from $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally 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



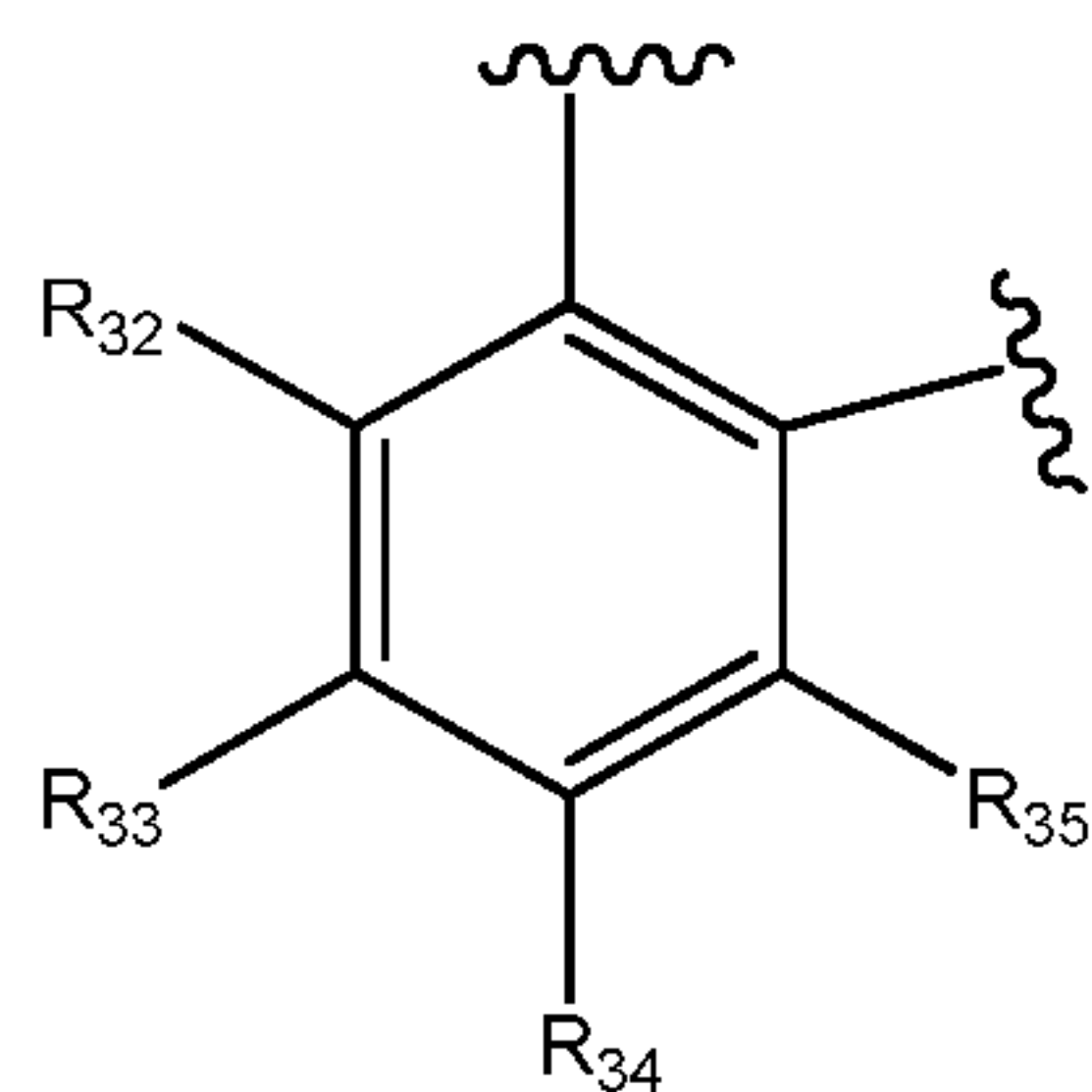
31. The compound of Claim 30, wherein Ring C is:



32. The compound of Claim 30, wherein Ring C is:



33. The compound of Claim 32, wherein Ring C is:



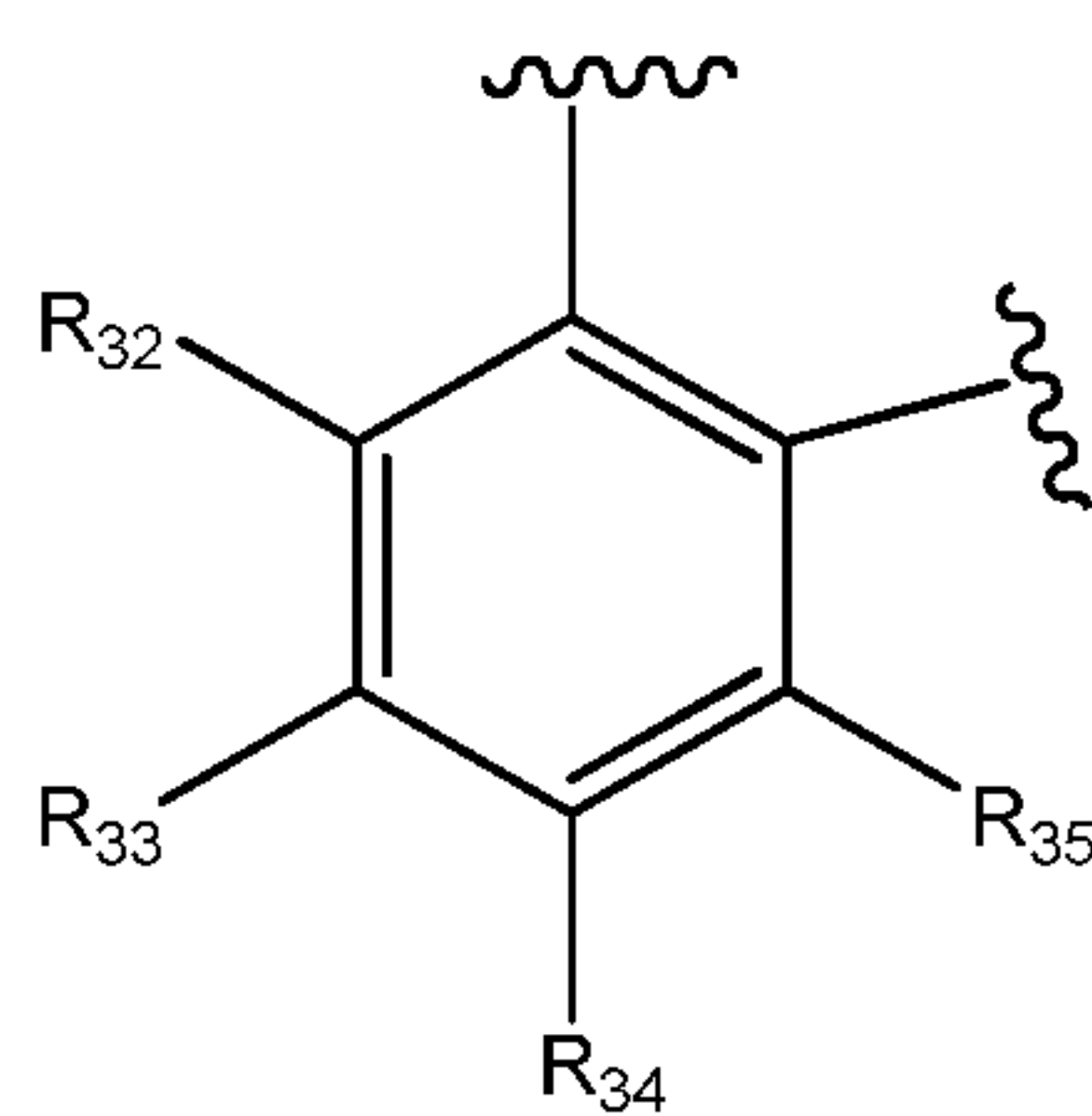
34. The compound of Claim 32 or 33, wherein R_{32} , R_{33} , and R_{35} are all $-\text{H}$.

35. The compound of Claim 34, wherein R_{34} is selected from the group consisting of halo, cyano, haloalkyl, $-\text{C}(\text{O})\text{OR}_4$, $-\text{NR}_1\text{R}_2$, $-\text{OR}_4$, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, or an optionally substituted 5 or

6-membered heteroaryl, wherein R_1 , R_2 and R_4 are lower alkyl.

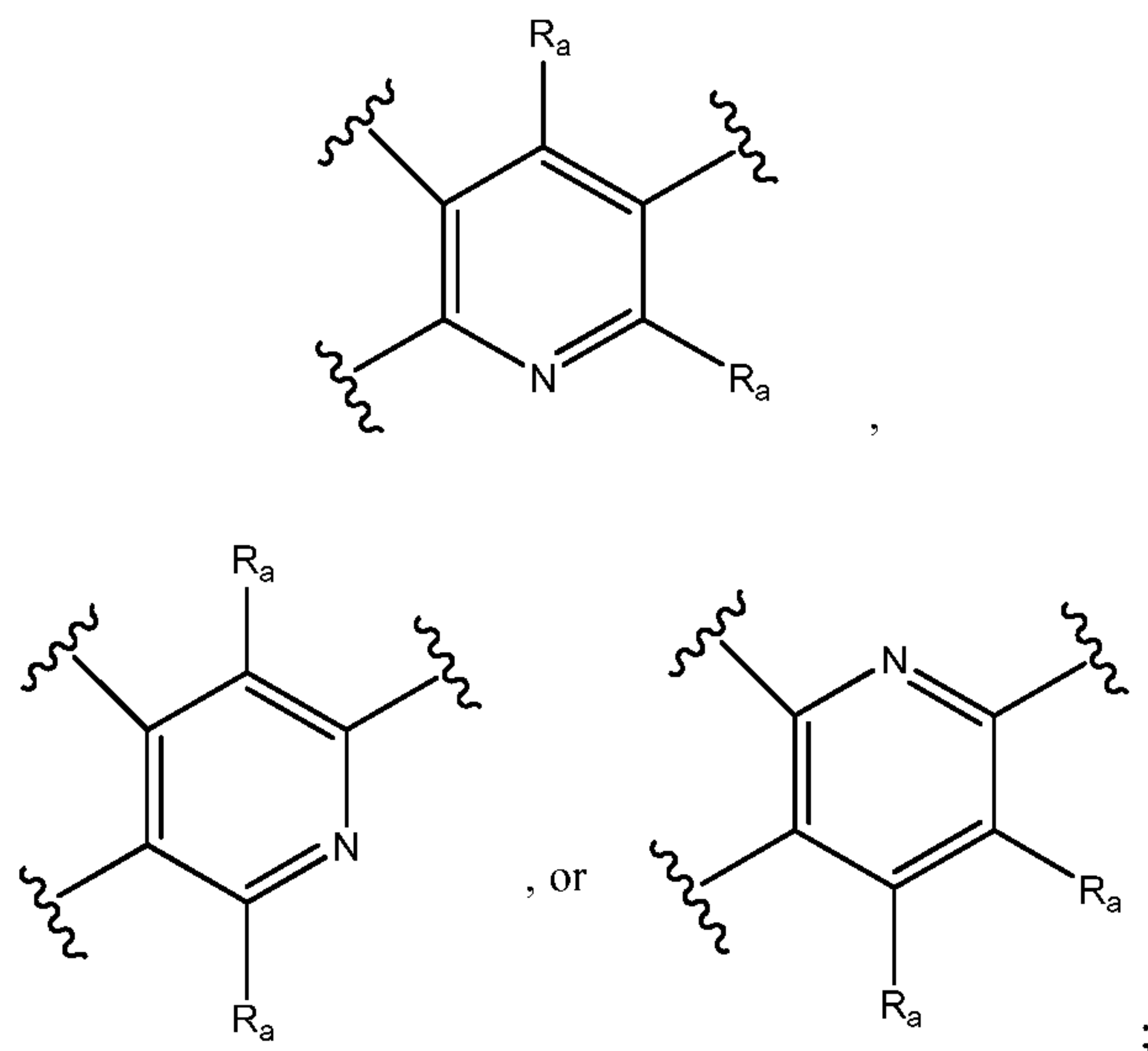
36. The compound of Claim 35, wherein R_{34} is selected from the group consisting of Br, Cl, cyano, CF_3 , $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-N(CH_3)_2$, $-OCH_3$, $-C(O)NH_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.
37. The compound of Claim 1, 5, 6 or 14, wherein each R^a is selected from the group consisting of halo, cyano, haloalkyl, $-C(O)OR_4$, $-NR_1R_2$, $-OR_4$, $-C(O)NR_1R_2$, or an optionally substituted 5 or 6-membered heteroaryl, wherein R_1 , R_2 and R_4 are lower alkyl.
38. The compound of Claim 37, wherein each R^a is selected from the group consisting of Br, Cl, cyano, CF_3 , $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-N(CH_3)_2$, $-OCH_3$, $-C(O)NH_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.
39. The compound of Claim 1, 5, 6 or 14, wherein L_1 is $-NH-C(O)-$ or $-C(O)-NH-$.
40. The compound of Claim 1, 5, 6 or 14, wherein B is $-CH_2-$, $-O-$, $-N(R^b)-$, wherein R^b is lower alkyl.
41. The compound of Claim 1 or 14, wherein:

Ring C is:



;

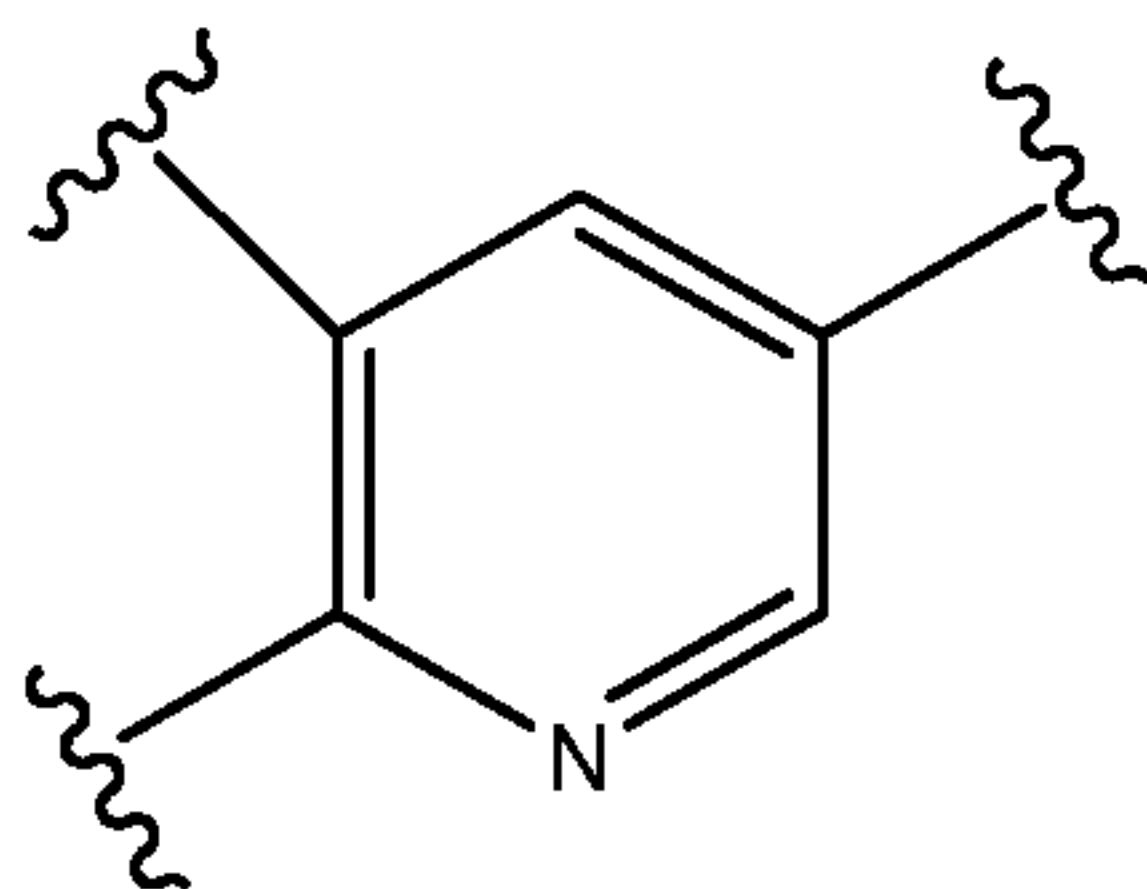
Ring E is



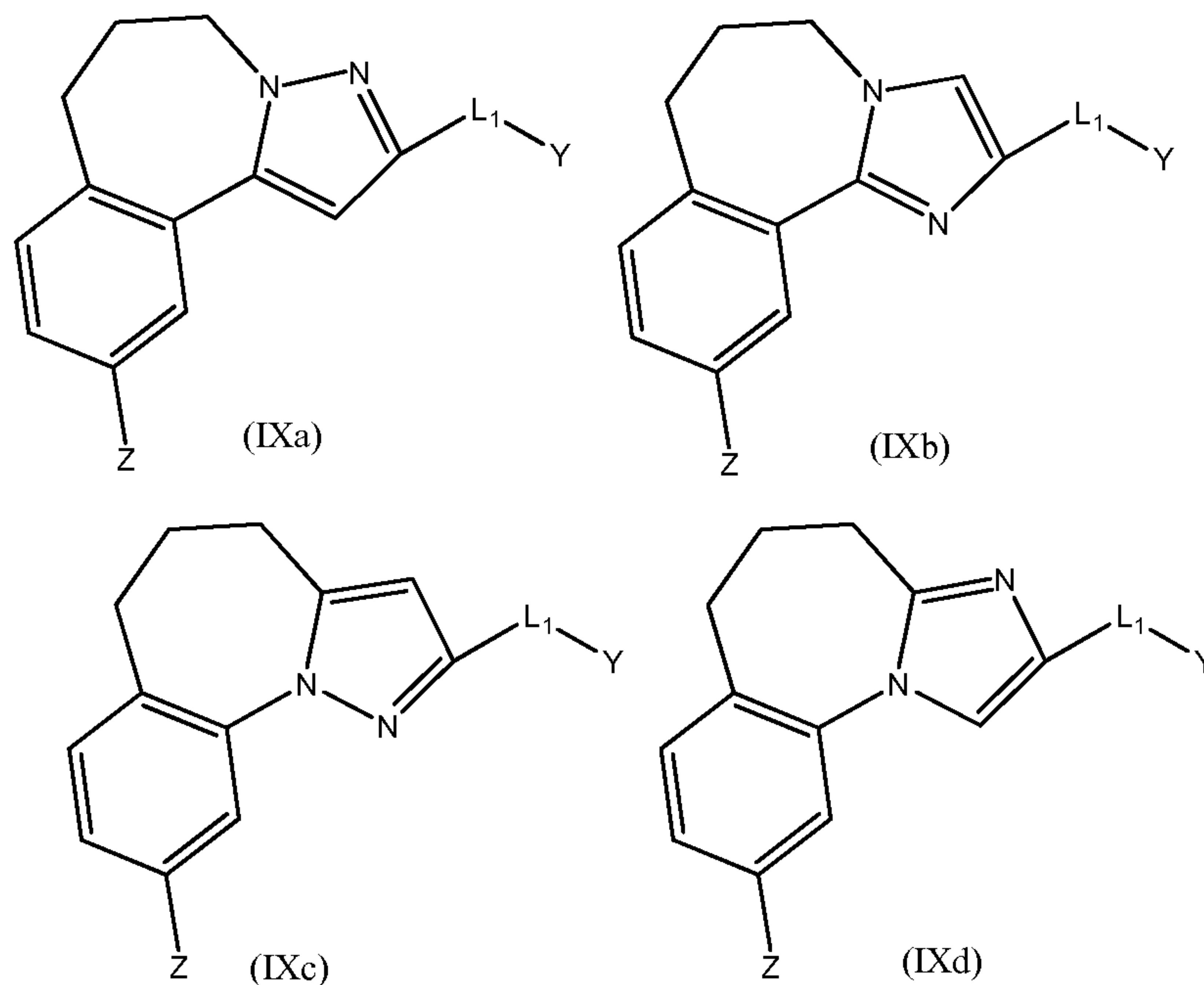
L_1 is $-\text{NH}-\text{C}(\text{O})-$ or $-\text{C}(\text{O})-\text{NH}-$; and

B is $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{R}^b)-$, wherein R^b is lower alkyl.

42. The compound of Claim 41, wherein R_{32} , R_{33} , and R_{35} are all $-\text{H}$.
43. The compound of Claim 42, wherein R_{34} is selected from the group consisting of halo, cyano, haloalkyl, $-\text{C}(\text{O})\text{OR}_4$, $-\text{NR}_1\text{R}_2$, $-\text{OR}_4$, $-\text{C}(\text{O})\text{NR}_1\text{R}_2$, or an optionally substituted 5 or 6-membered heteroaryl, wherein R_1 , R_2 and R_4 are lower alkyl.
44. The compound of Claim 43, wherein R_{34} is selected from the group consisting of Br, Cl, cyano, CF_3 , $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, an optionally substituted pyridine, an optionally substituted pyrazole, an optionally substituted thiazole, an optionally substituted oxazole, an optionally substituted imidazole, or an optionally substituted tetrazole.
45. The compound of Claim 40 or 44, wherein B is $-\text{CH}_2-$.
46. The compound of Claim 45, wherein Ring E is



47. A compound selected from the group consisting of:



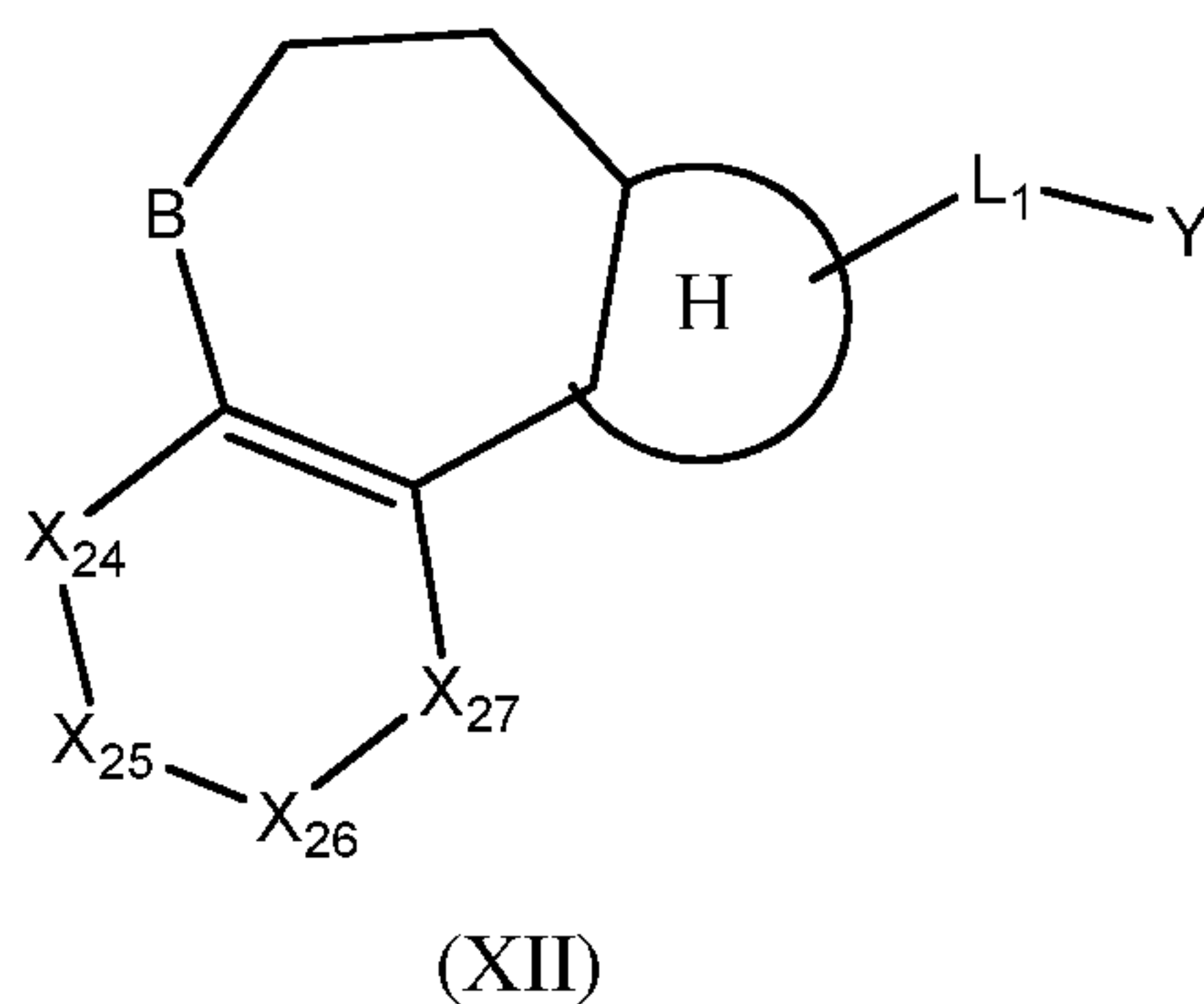
or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl; and

Z is a substituent.

48. A compound represented by formula (XII):



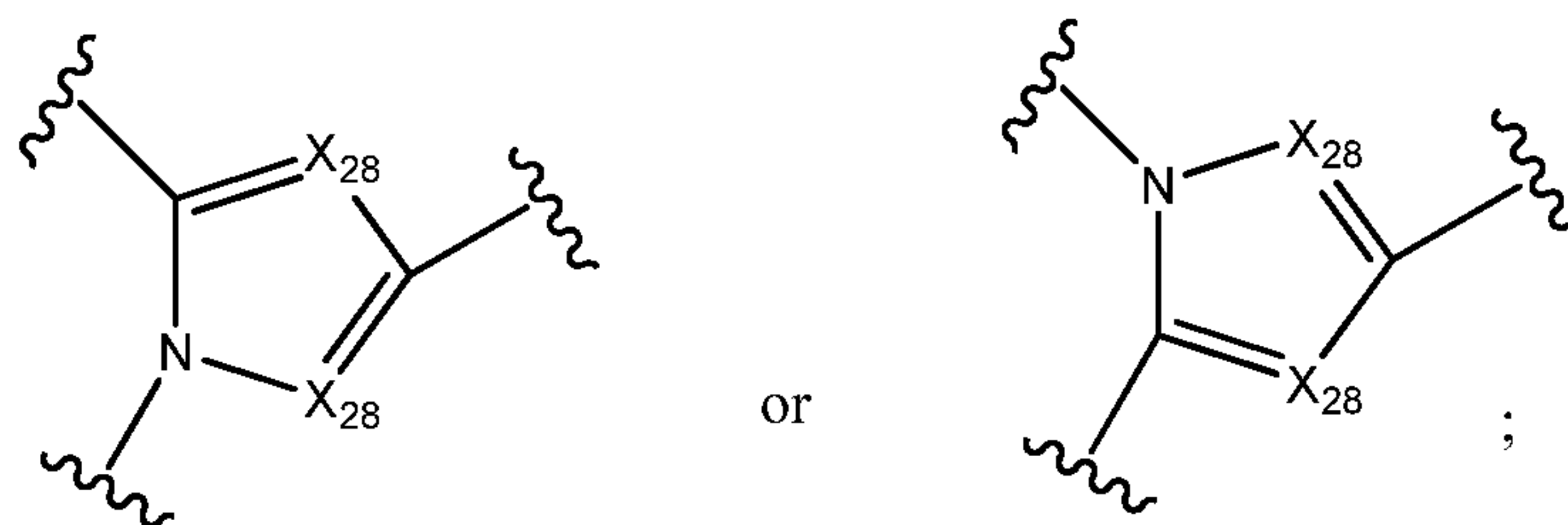
or a pharmaceutically acceptable salt thereof, wherein:

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

L_1 is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

Ring H is selected from:



X_{24} , X_{25} , X_{26} and X_{27} are each independently $-O-$, $-S-$, $-N(R^b)-$, or $-C(R^a)_2-$;

each X_{28} is independently $-N-$ or $-C(R^a)-$;

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 $-S(O)_pNR_1R_2$;

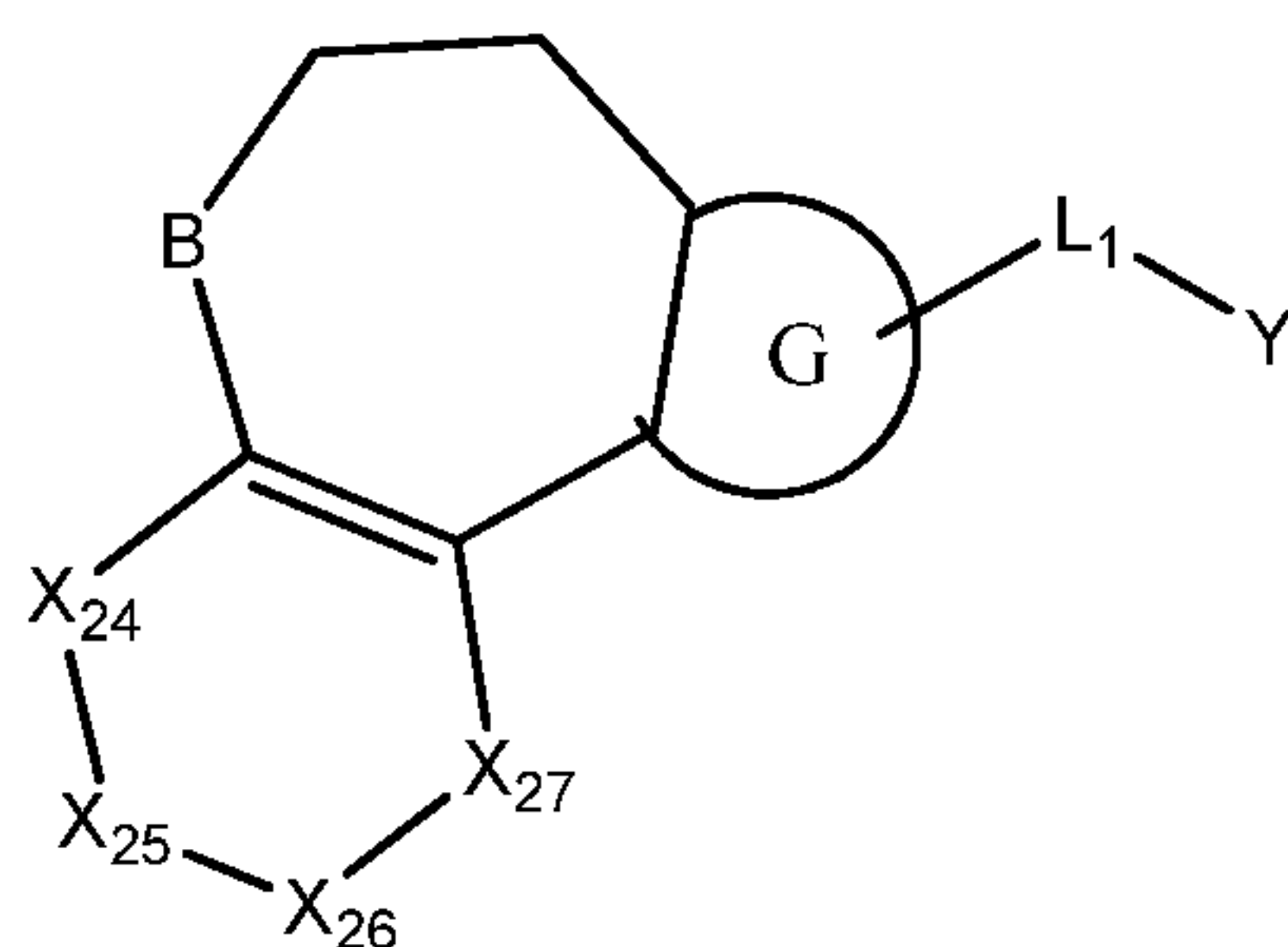
each R_b is independently $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted 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 are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 0, 1, or 2.

49. A compound represented by formula (XV):



(XV)

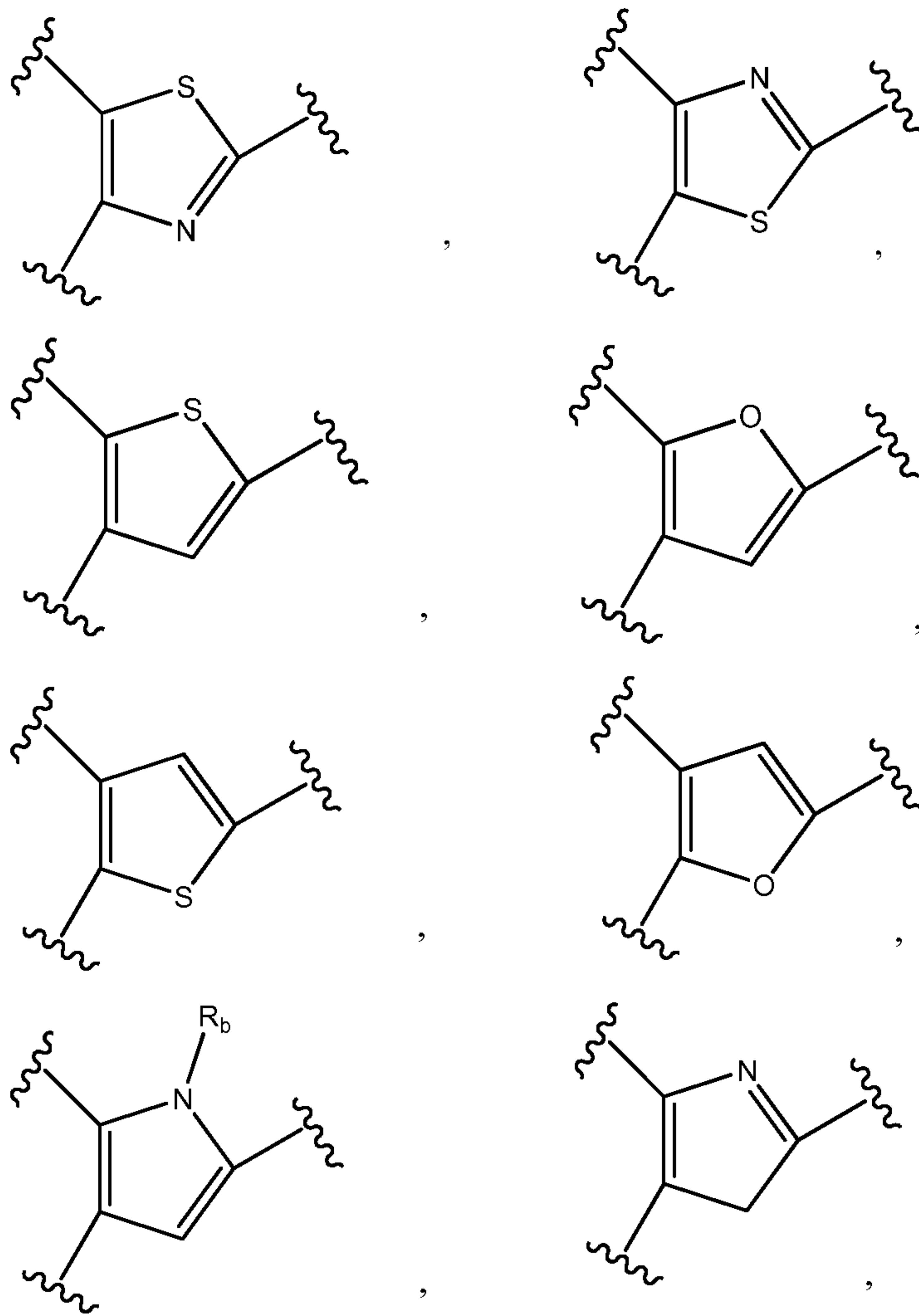
or a pharmaceutically acceptable salt thereof, wherein:

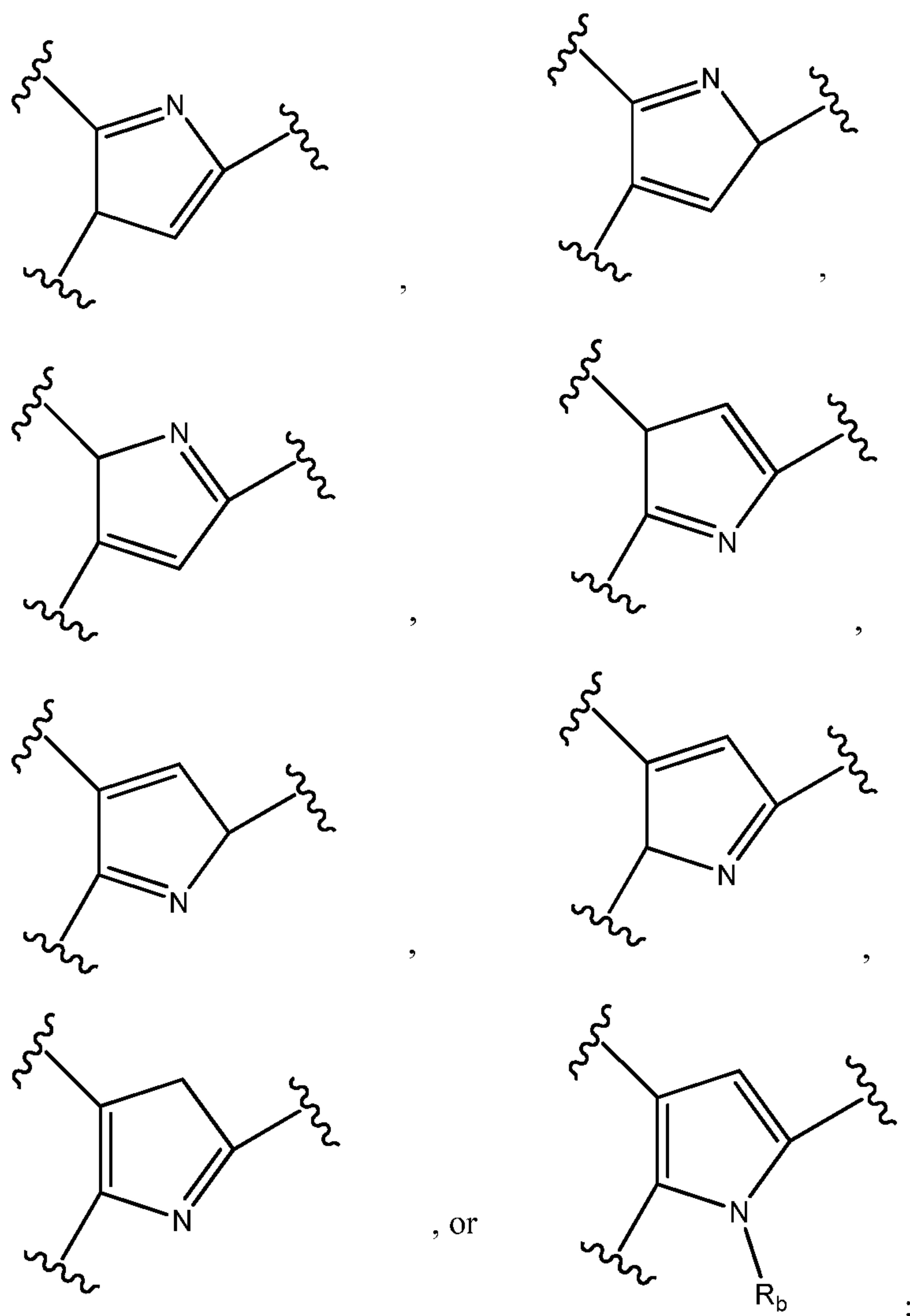
B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

L_1 is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, or $-\text{NHC}(\text{O})\text{NH}-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

Ring G is selected from:





X_{24} , X_{25} , X_{26} and X_{27} are each independently $-O-$, $-S-$, $-N(R^b)-$, or $-C(R^a)_2-$;

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 $-C(O)OR_4$;

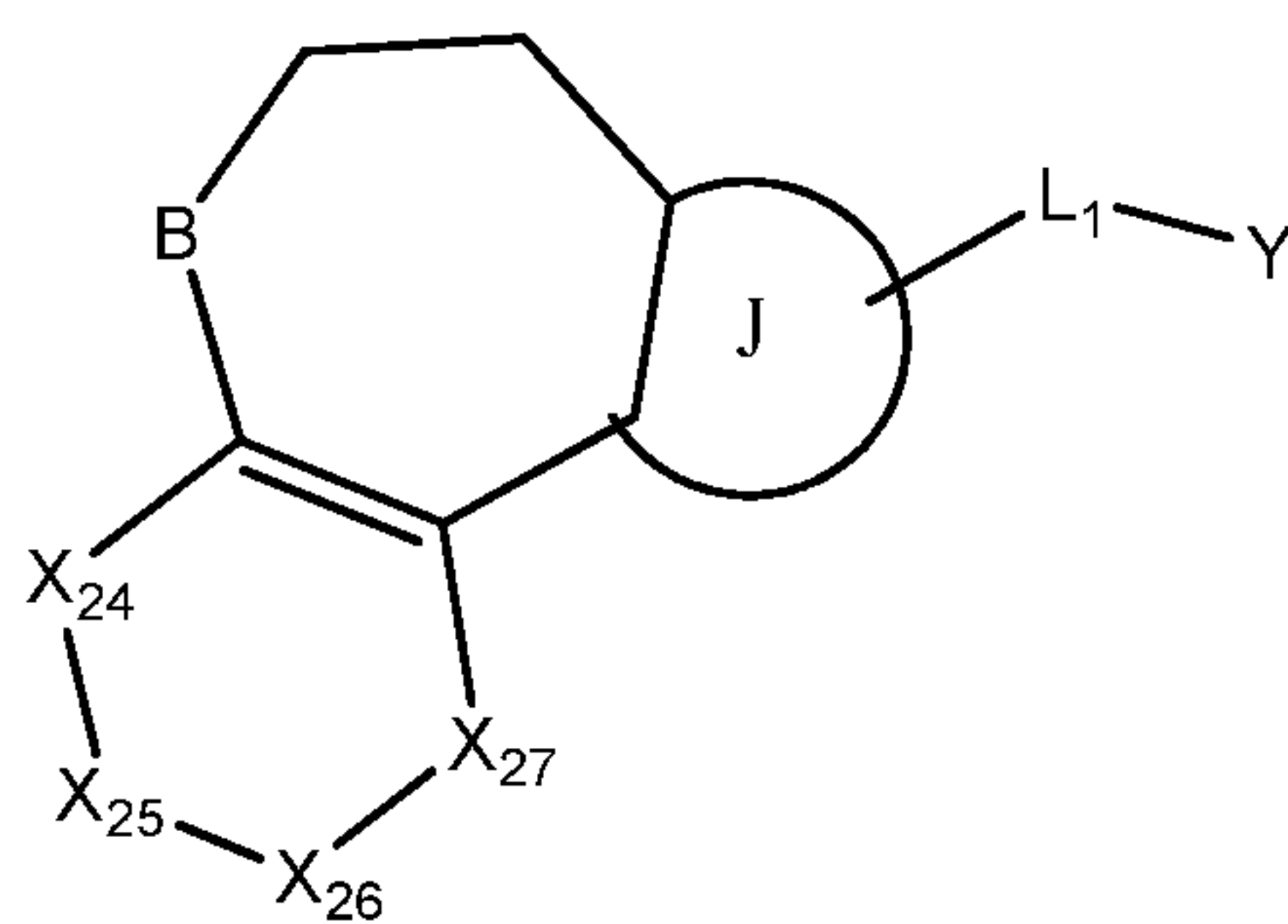
R_1 and R_2 , for each occurrence are, independently, H , an optionally substituted alkyl,

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

p is 0, 1, or 2.

50. A compound represented by formula (XIX):



(XIX)

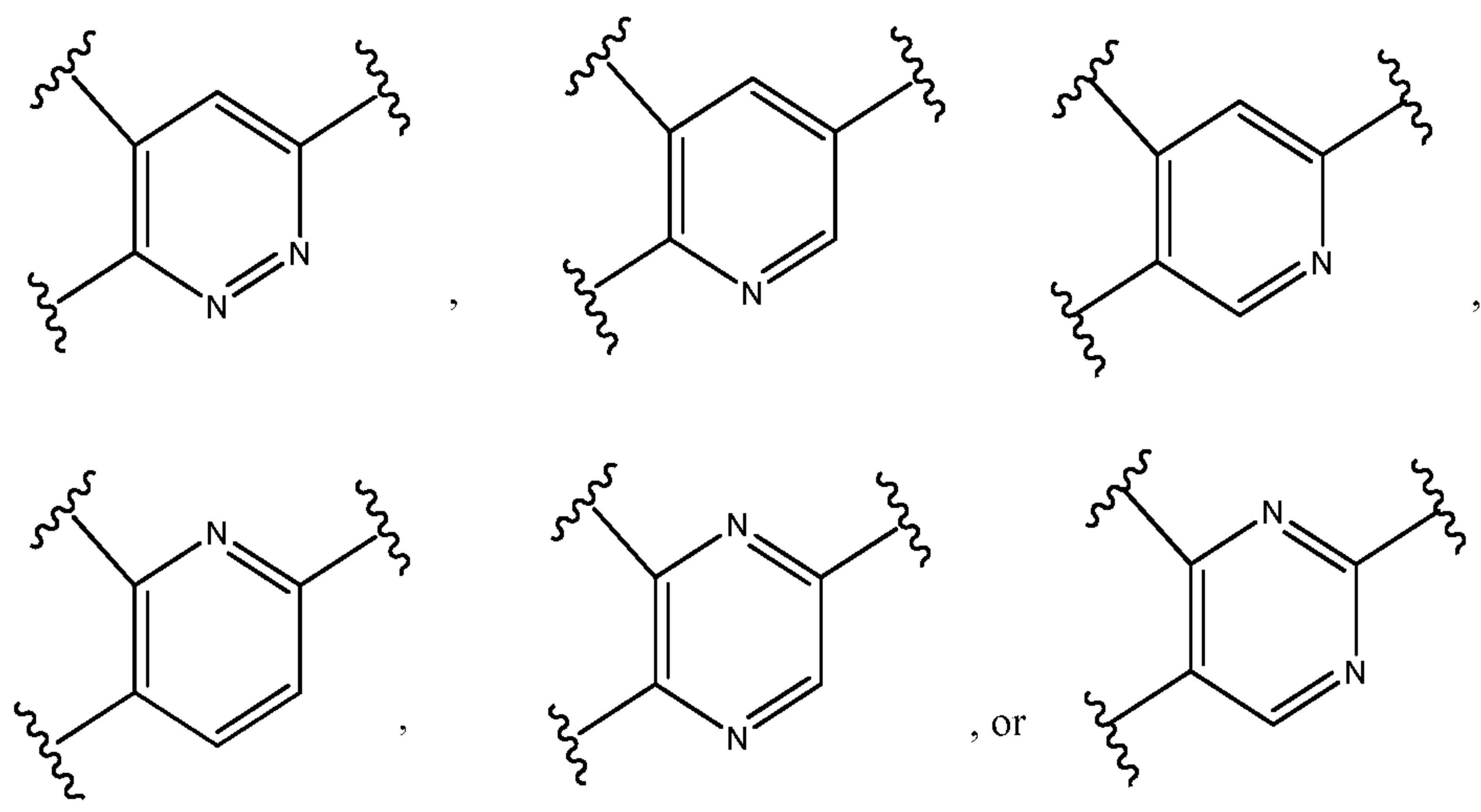
or a pharmaceutically acceptable salt thereof, wherein:

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

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

Ring J is:



X_{24} , X_{25} , X_{26} and X_{27} are each independently $-O-$, $-S-$, $-N(R^b)-$, or $-C(R^a)_2-$;

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 $-S(O)_pNR_1R_2$;

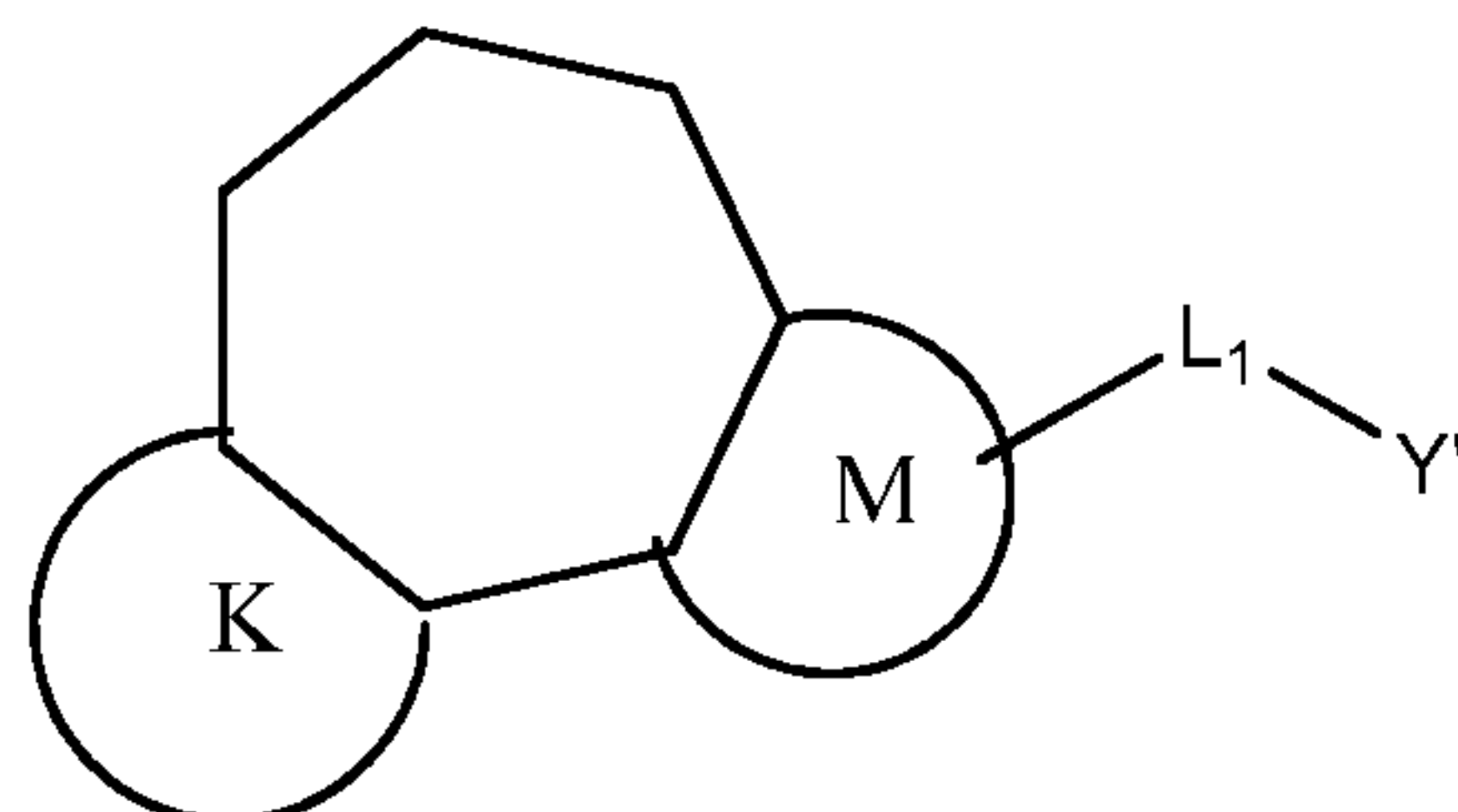
each R^b is independently $-H$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted 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 are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 0, 1, or 2.

51. A compound represented by formula (XX):



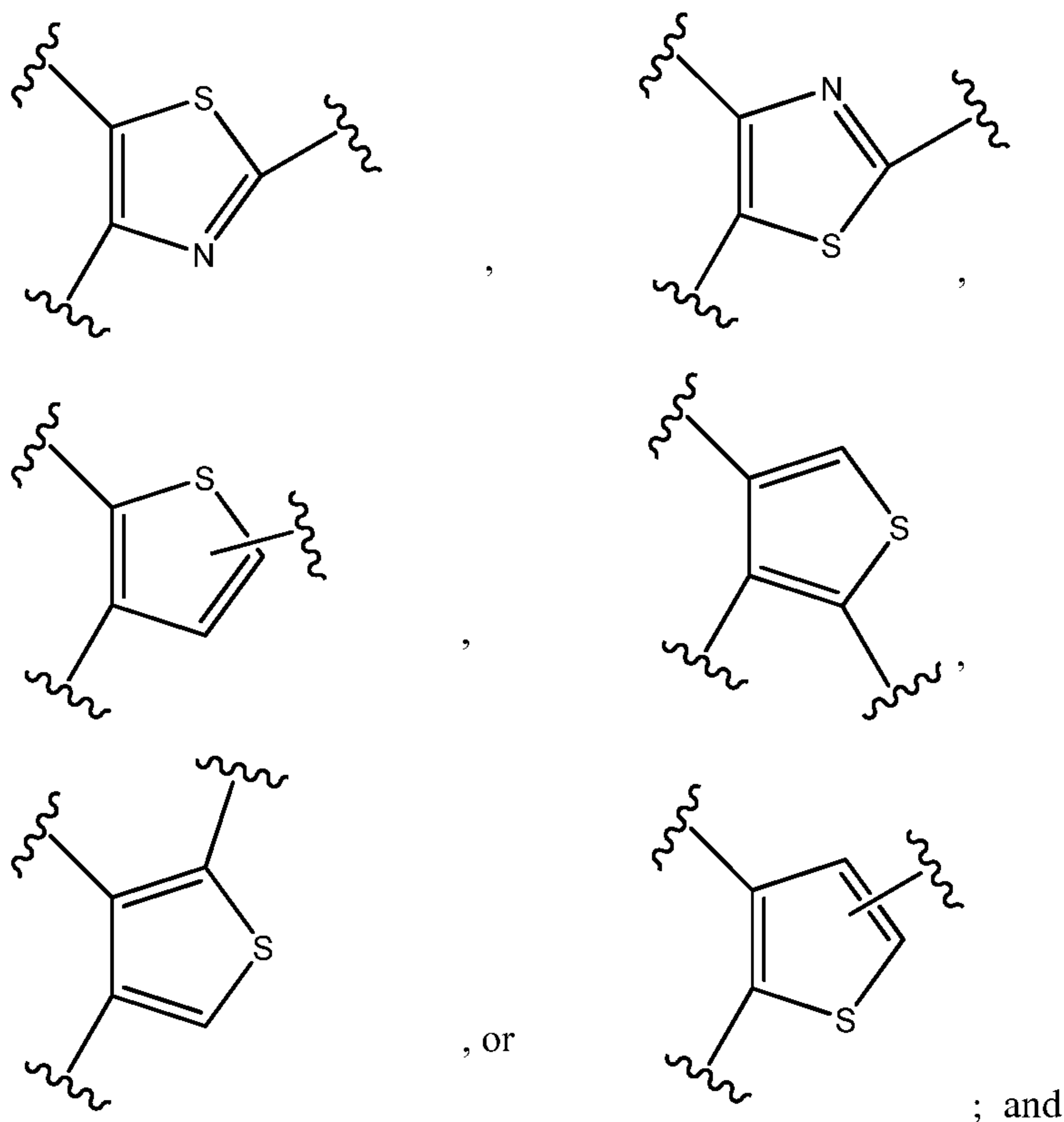
(XX)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

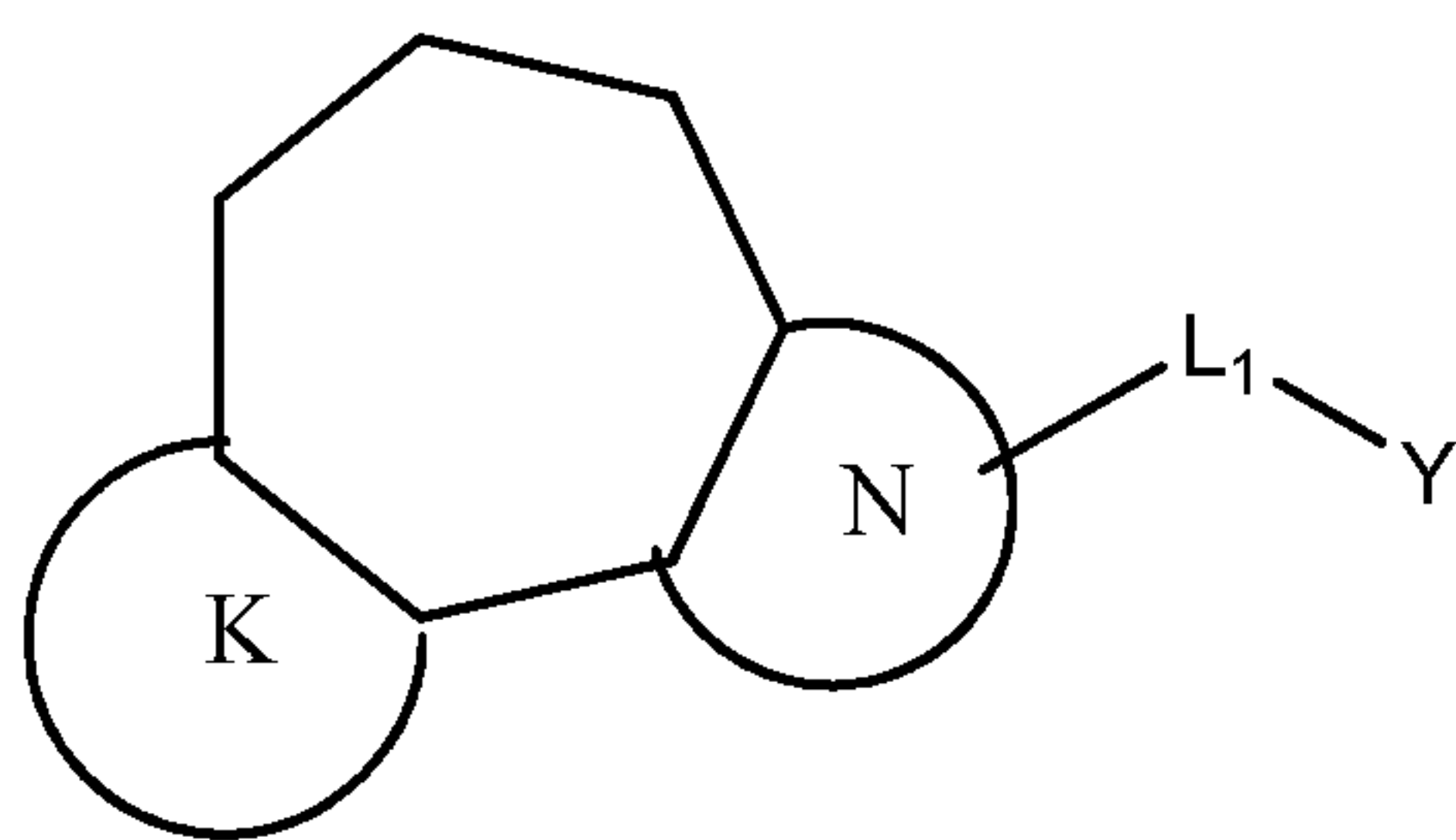
Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl;

Ring M is selected from:



Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

52. A compound represented by formula (XXI):



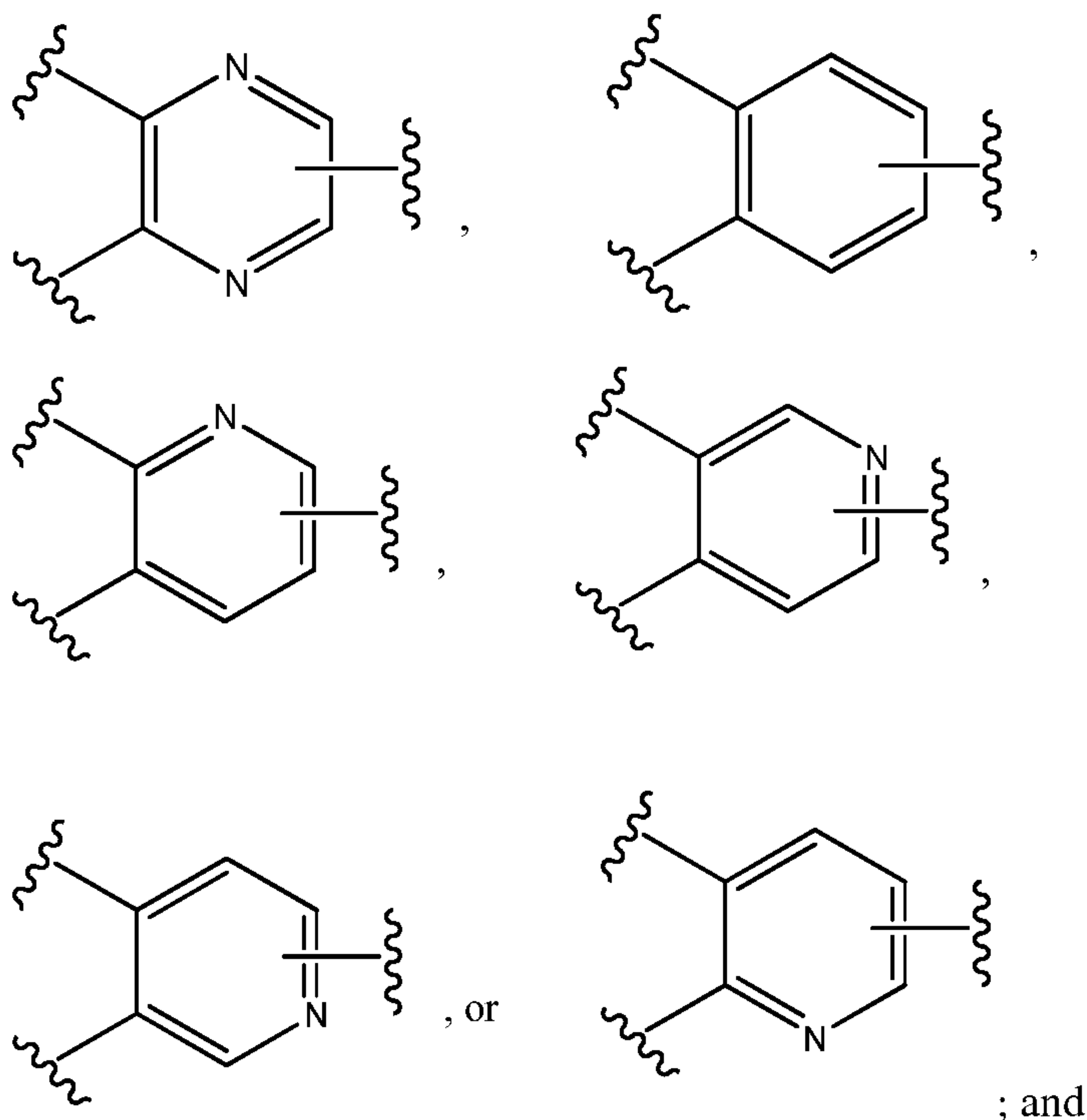
(XXI)

or a pharmaceutically acceptable salt thereof, wherein:

L_1 is $-NHCH_2-$, $-CH_2NH-$, $-NH-C(O)-$, $-C(O)-NH-$, or $-NHC(O)NH-$;

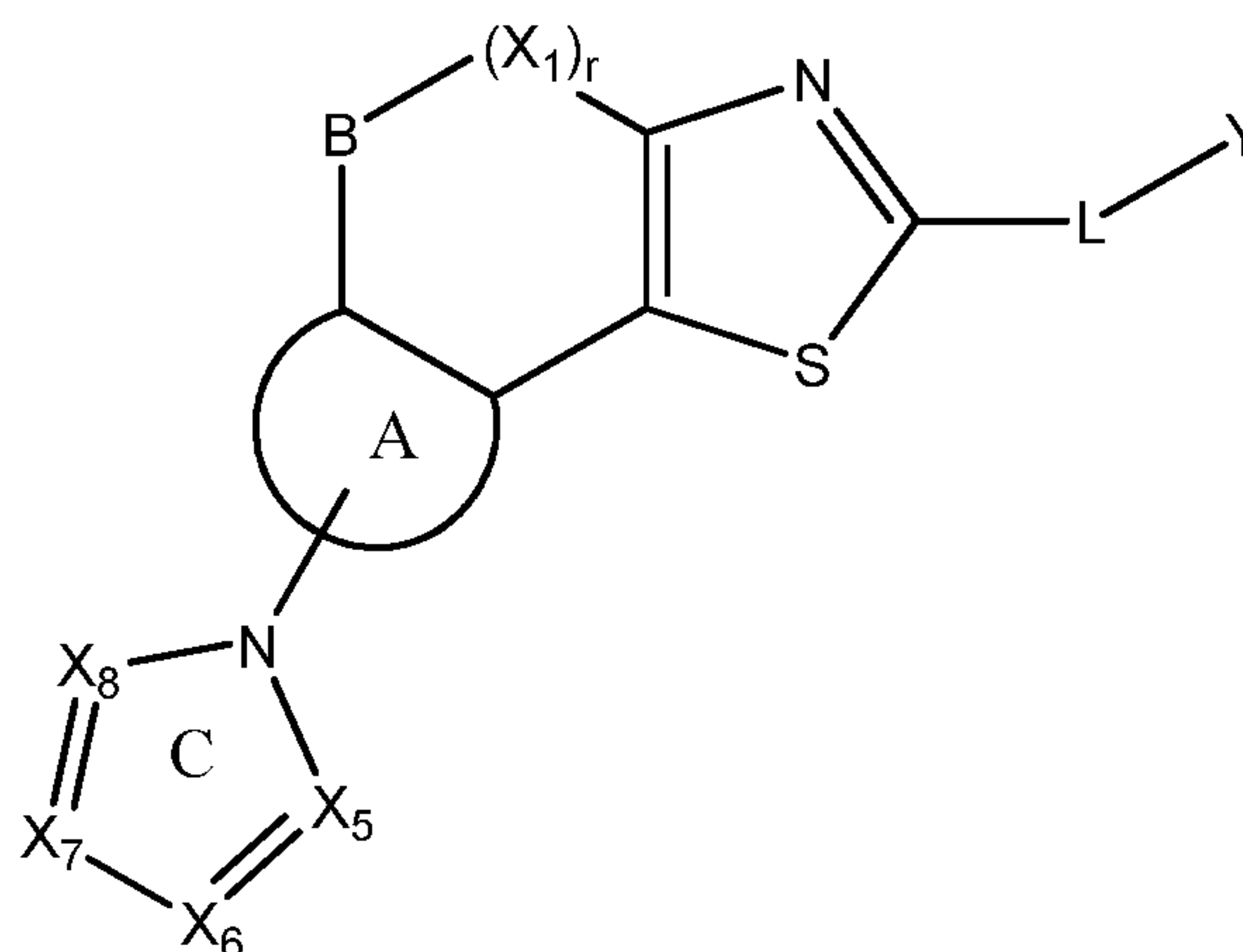
Y' is selected from the group consisting of an optionally substituted 5 or 6-membered aryl, an optionally substituted 5 or 6-membered heteroaryl, an optionally substituted C3-C5 alkyl, or an optionally substituted C3-C6 cycloalkyl;

Ring N is:



Ring K is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl, wherein the substituent is a 5 or 6-membered heteroaromatic ring with an optional substituent that contains 6 or fewer atoms, excluding any hydrogens.

53. A compound represented by formula (XXII):



(XXII)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl wherein the ring atoms are selected from the group consisting of C, S, O, or N, and wherein Ring A contains at least one C atom that is bonded to Ring C;

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 $-N(R^b)-$;

each of X_5 , X_6 , X_7 , and X_8 is independently $-N-$ or $-C(R^c)-$;

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 $-C(O)OR_4$;

each R^c 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, nitro, or cyano;

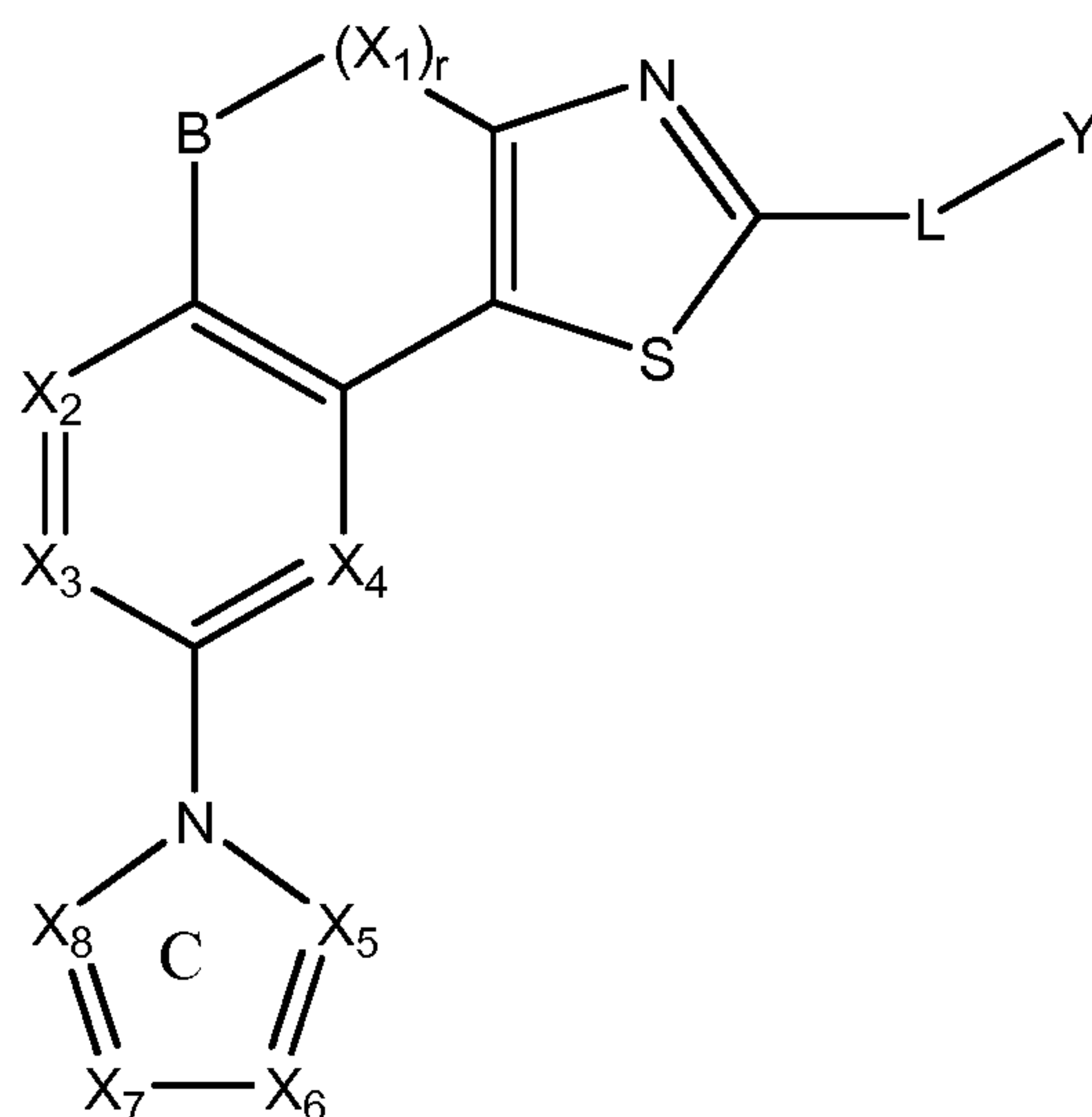
R_1 and R_2 , for each occurrence are, independently, H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

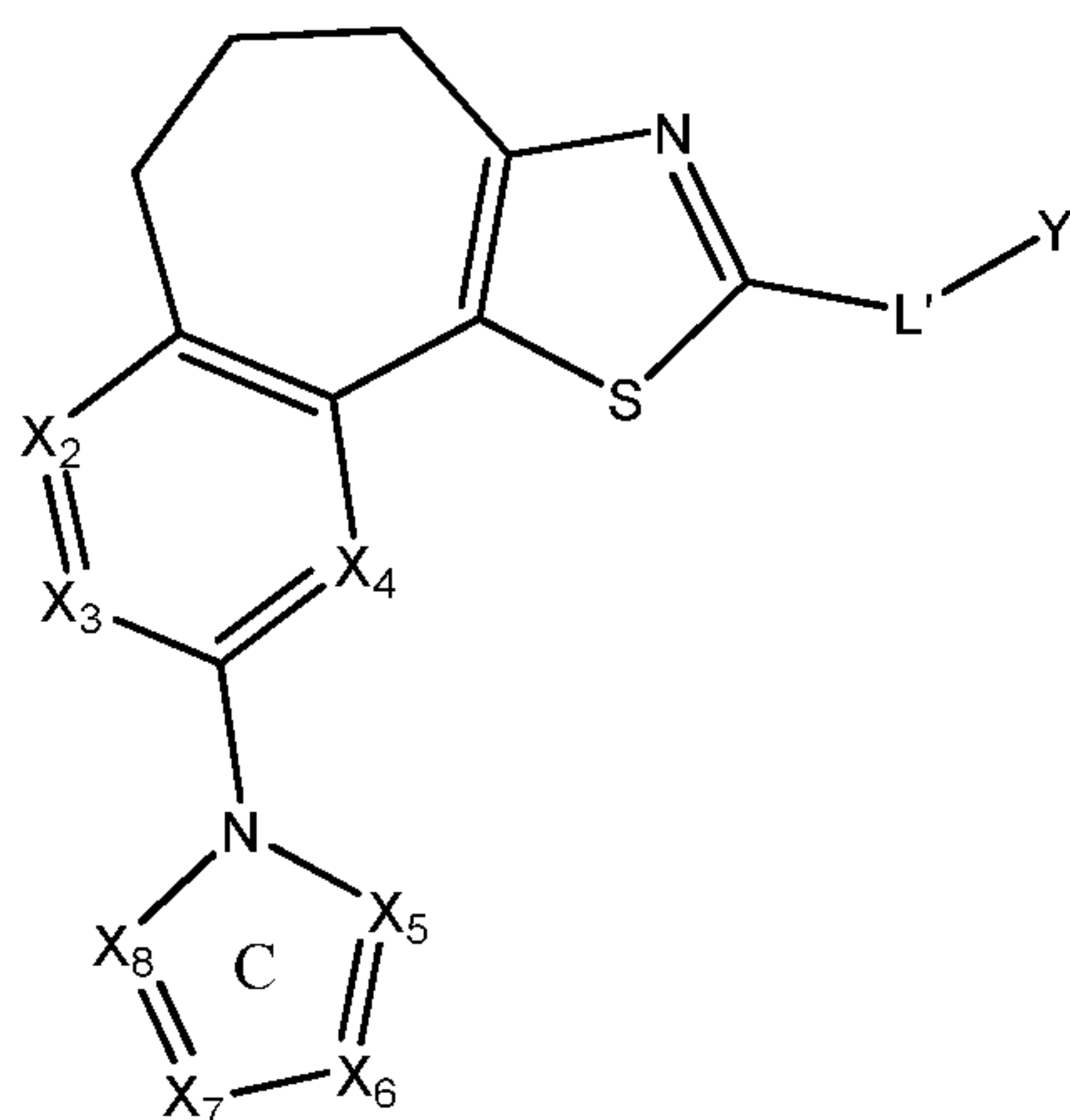
54. The compound of Claim 53, wherein the compound is represented by formula (XXIII):



(XXIII)

or a pharmaceutically acceptable salt thereof, wherein each of X_2 , X_3 , and X_4 is independently $-\text{CH}-$ or $-\text{N}-$.

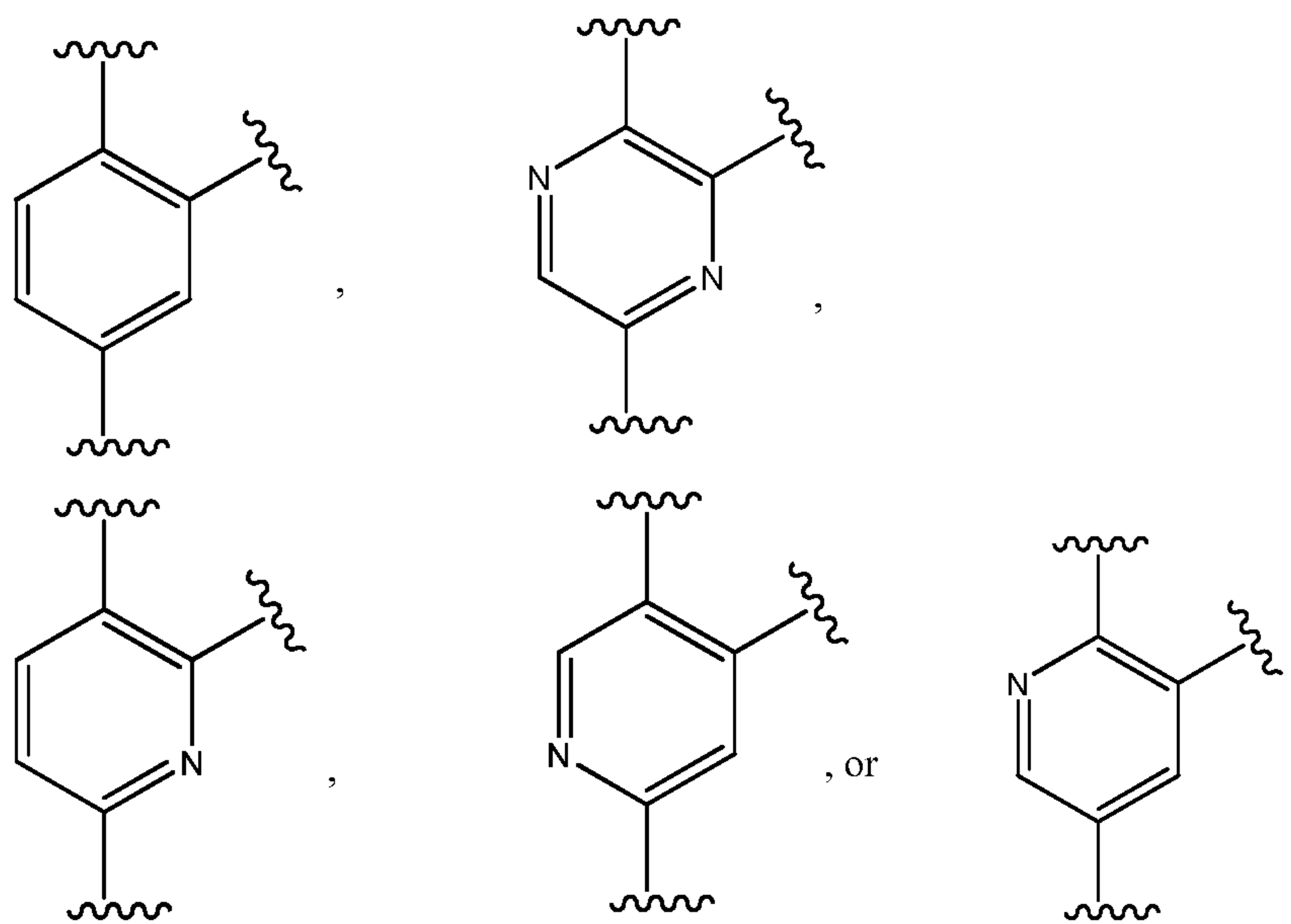
55. The compound of Claim 54, wherein the compound is represented by formula (XXIV):



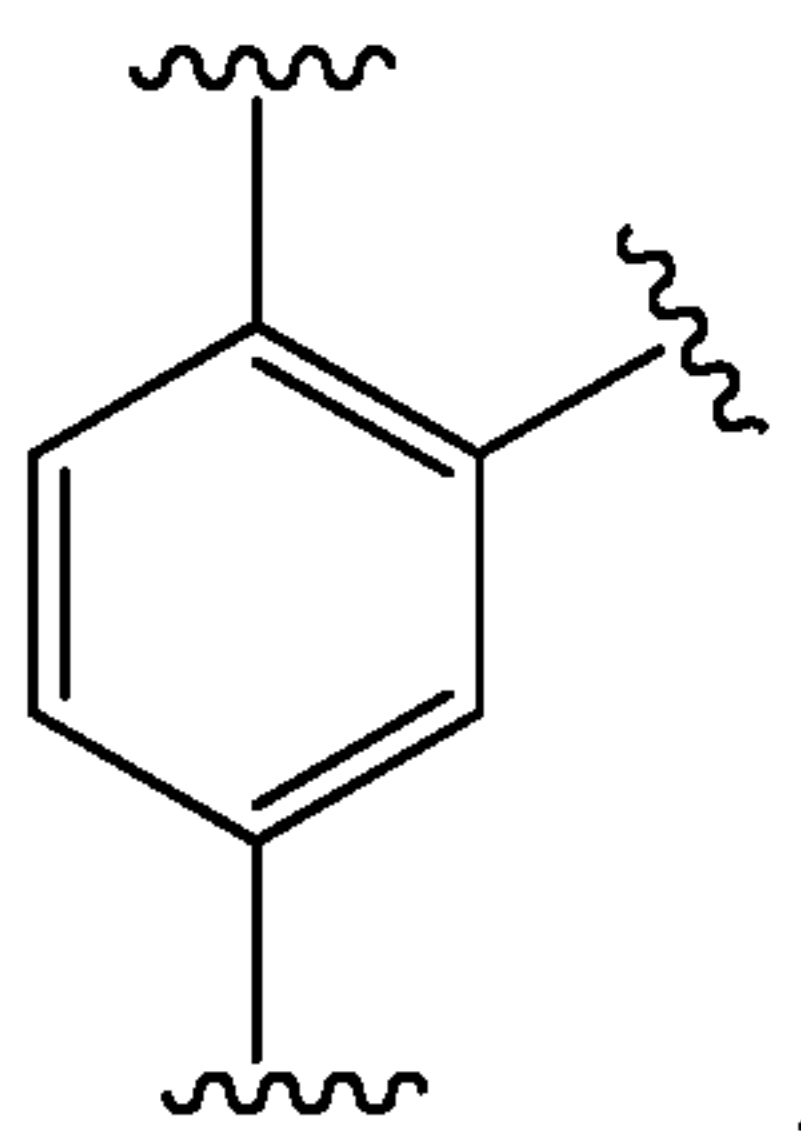
(XXIV)

or a pharmaceutically acceptable salt thereof, wherein L' is -NHCH₂-, -CH₂NH-, -NHC(O)NH-, -NH-C(O)-, or -C(O)-NH-.

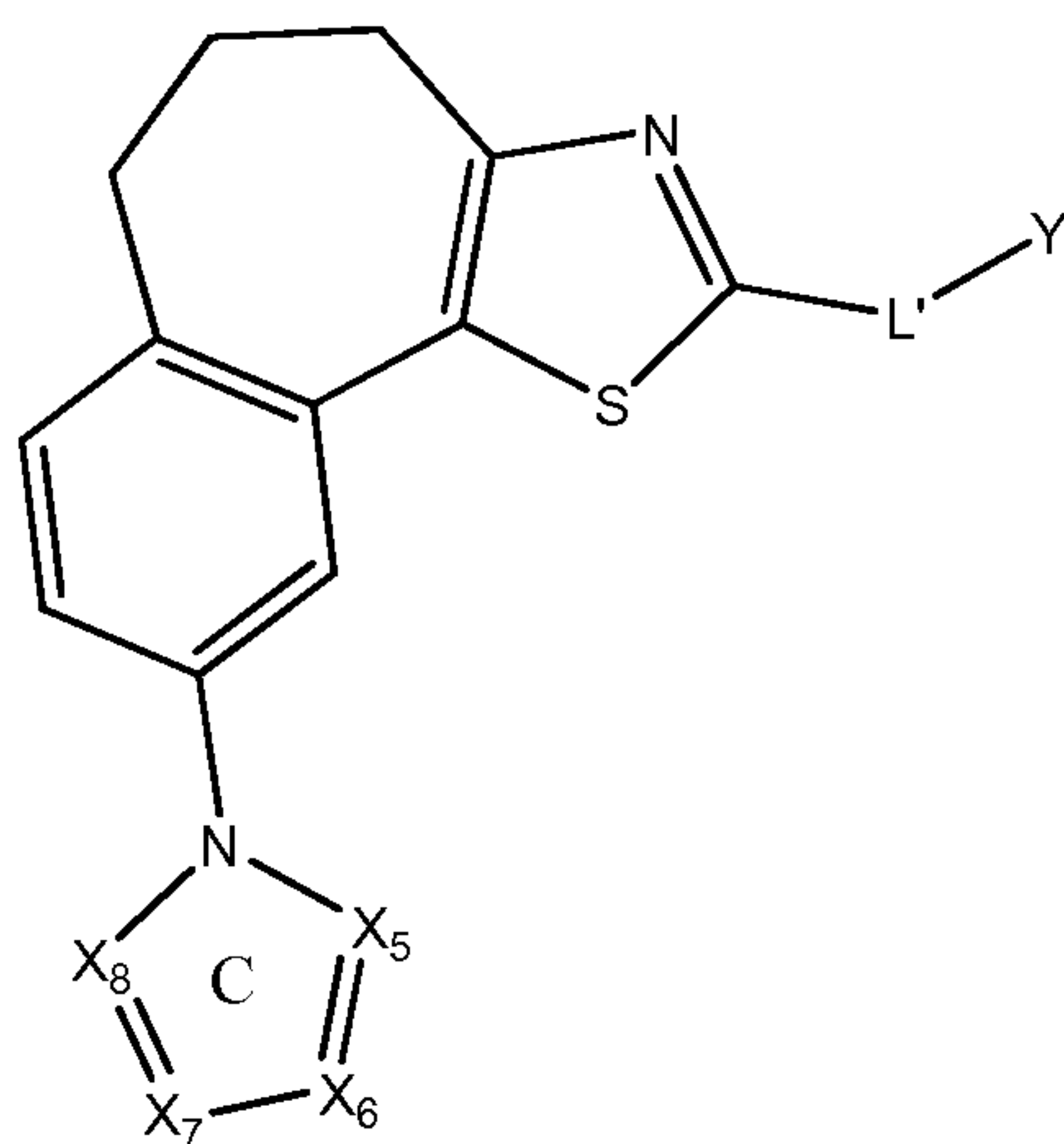
56. The compound of Claim 54 or 55, wherein the ring containing X₂, X₃, and X₄ is:



57. The compound of Claim 56, wherein the ring containing X₂, X₃, and X₄ is:



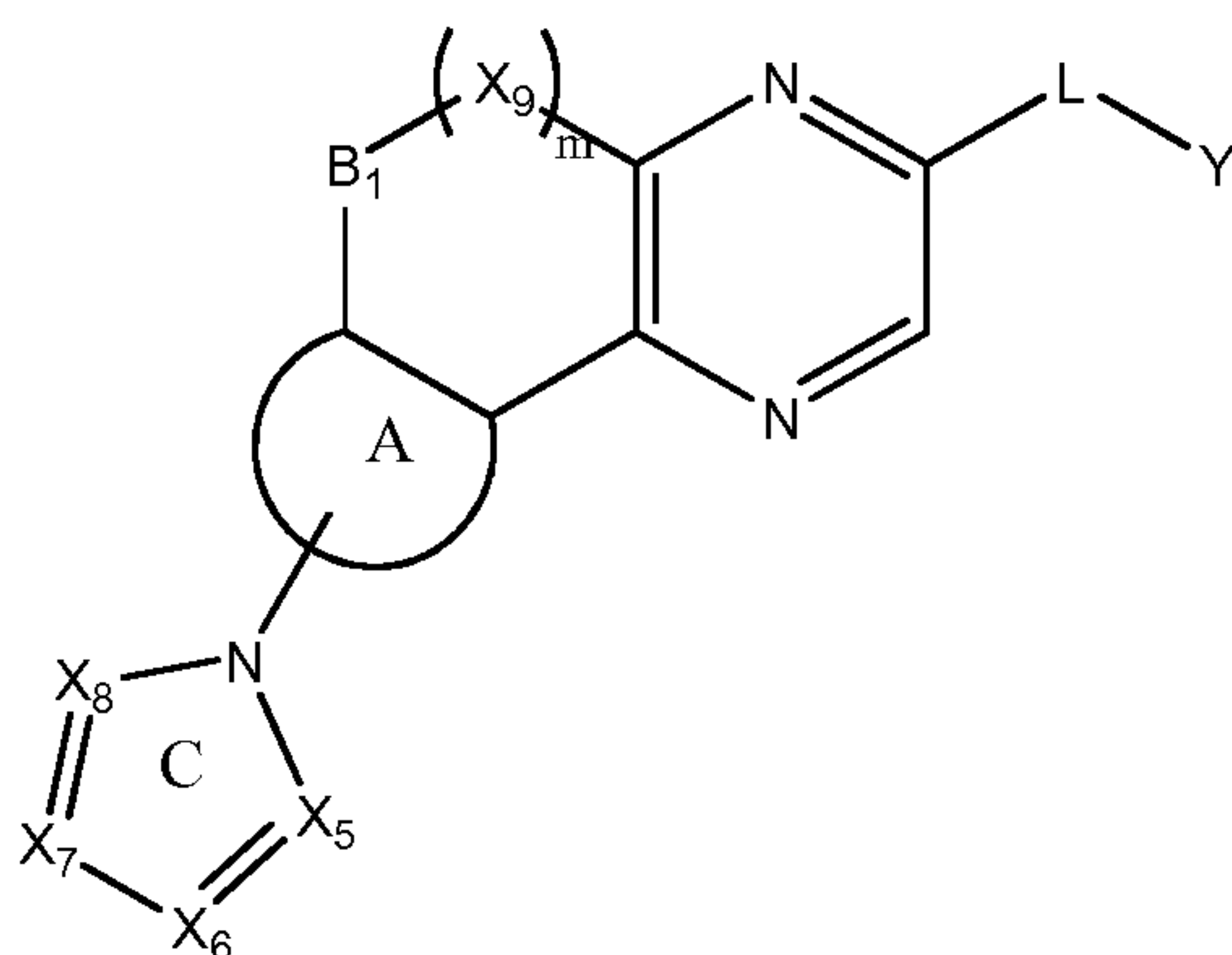
58. The compound of Claim 55, wherein the compound is represented by formula (XXV):



(XXV)

or a pharmaceutically acceptable salt thereof.

59. A compound represented by formula (XXVI):



(XXVI)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl wherein the ring atoms are selected from the group consisting of C, S, O, or N, and wherein Ring A contains at least one C atom that is bonded to Ring C;

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

B₁ is -C(R^a)₂-, -C(O)-; or -O-;

each of X₅, X₆, X₇, and X₈ is independently -N- or -C(R^c)-;

X₉ is -C(R^a)₂-;

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

each R^c is independently $-\text{H}$, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, a haloalkyl, halo, nitro, or cyano;

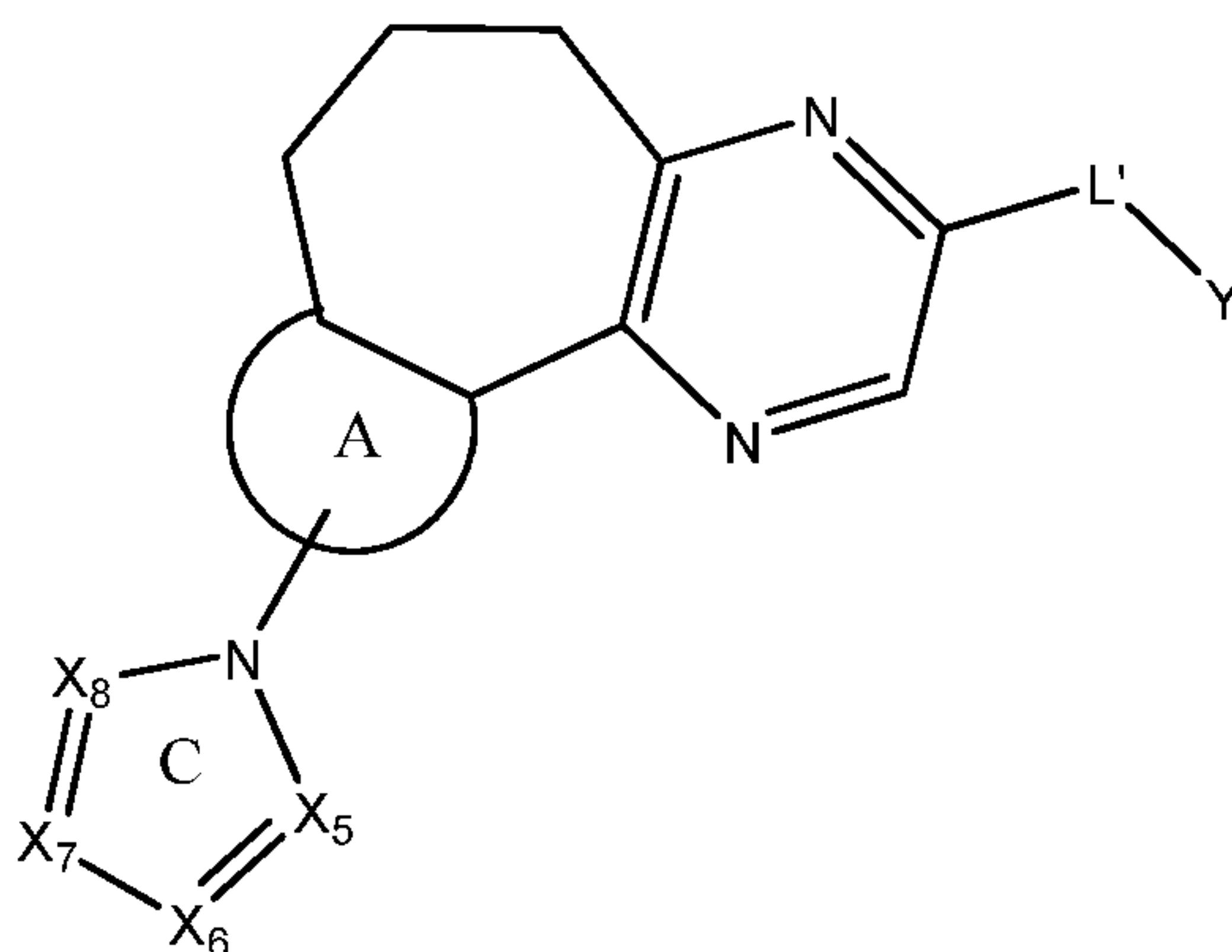
R_1 and R_2 , for each occurrence are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

p is 0, 1, or 2; and

m is 1 or 2.

60. The compound of Claim 59, wherein the compound is represented by formula (XXVII):

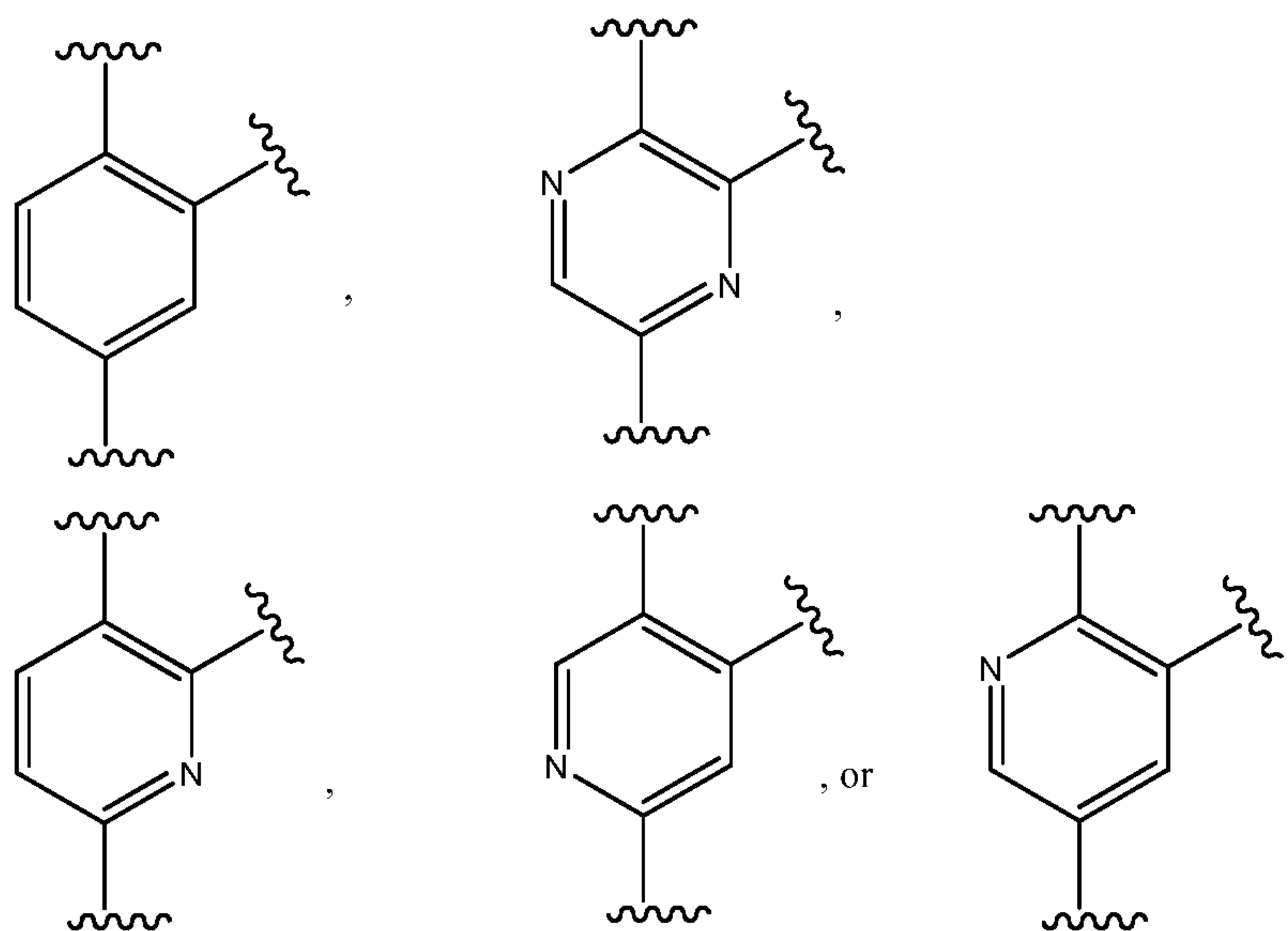


(XXVII)

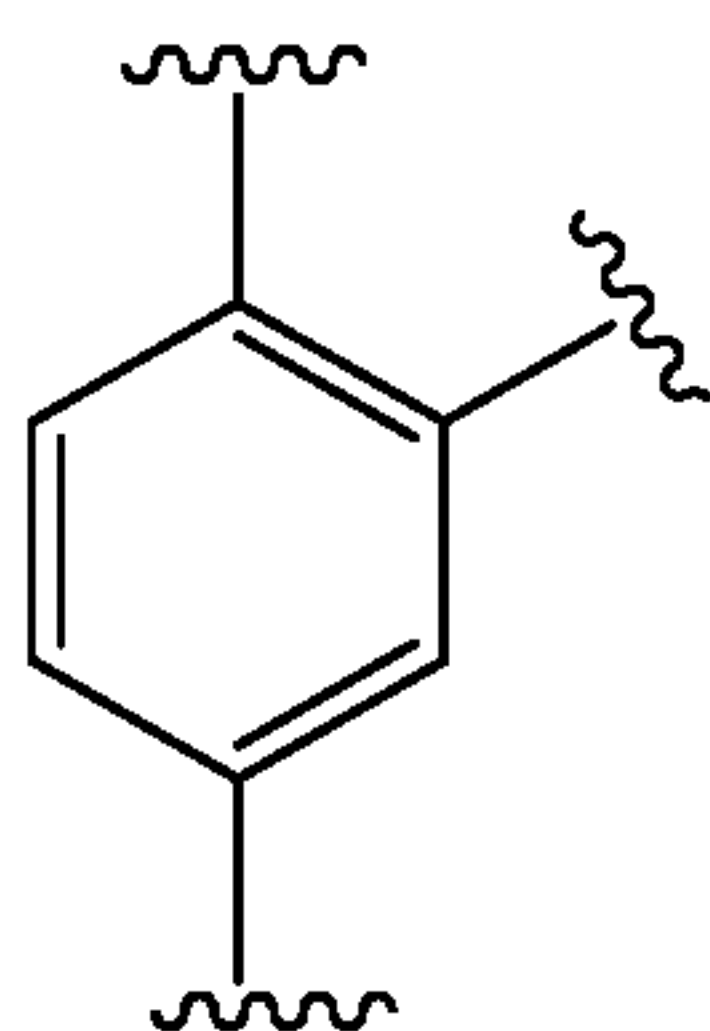
or a pharmaceutically acceptable salt thereof, wherein L' is $-\text{NHCH}_2-$, $-\text{CH}_2\text{NH}-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, or $-\text{C}(\text{O})-\text{NH}-$.

61. The compound of Claim 53, 59 or 60, wherein Ring A is selected from the group consisting of a monosubstituted phenyl, a monosubstituted pyrazinyl, a monosubstituted thiazolyl, a monosubstituted thienyl or a monosubstituted pyridyl.

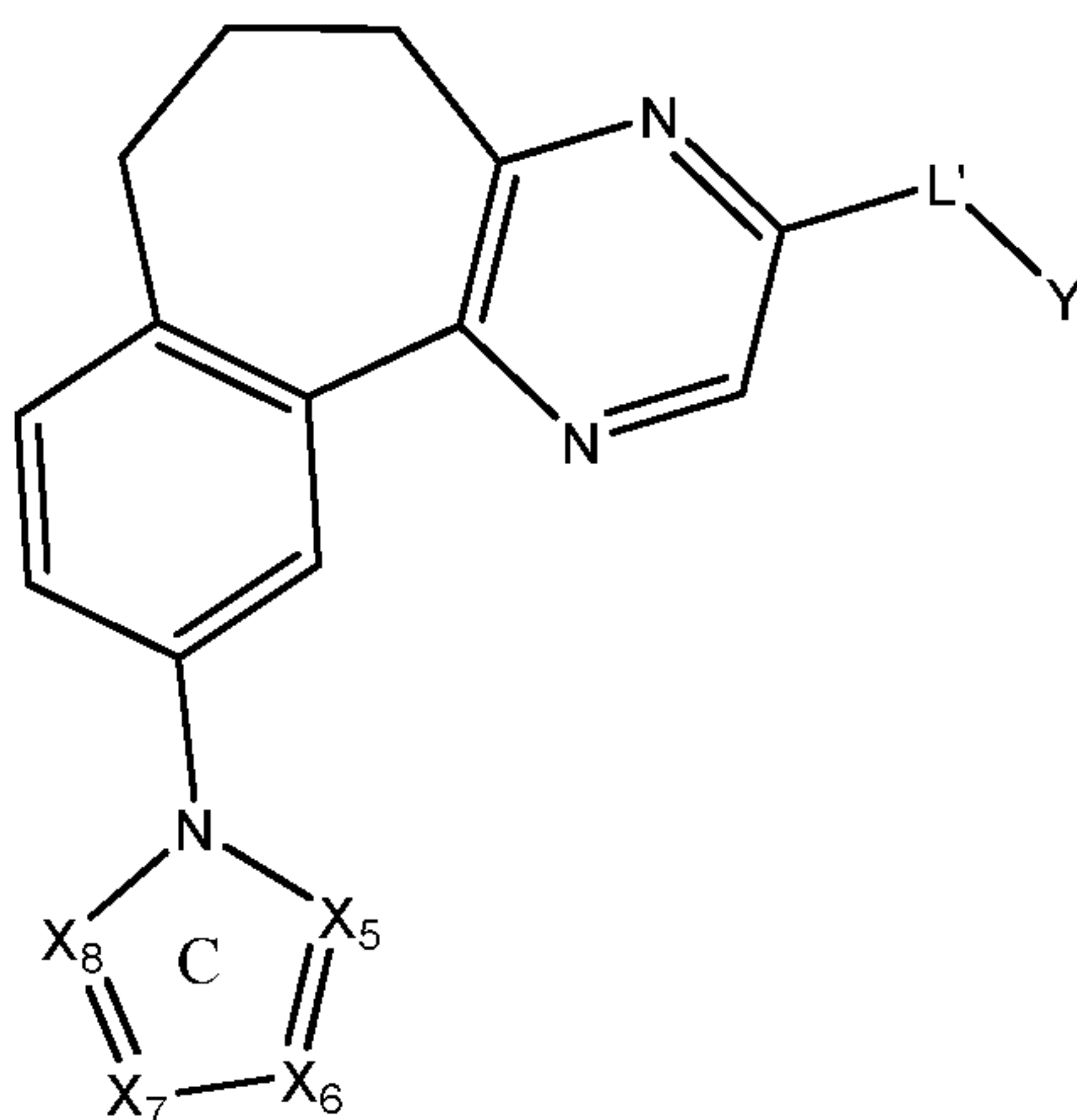
62. The compound of Claim 61, wherein Ring A is:



63. The compound of Claim 62, wherein Ring A is:



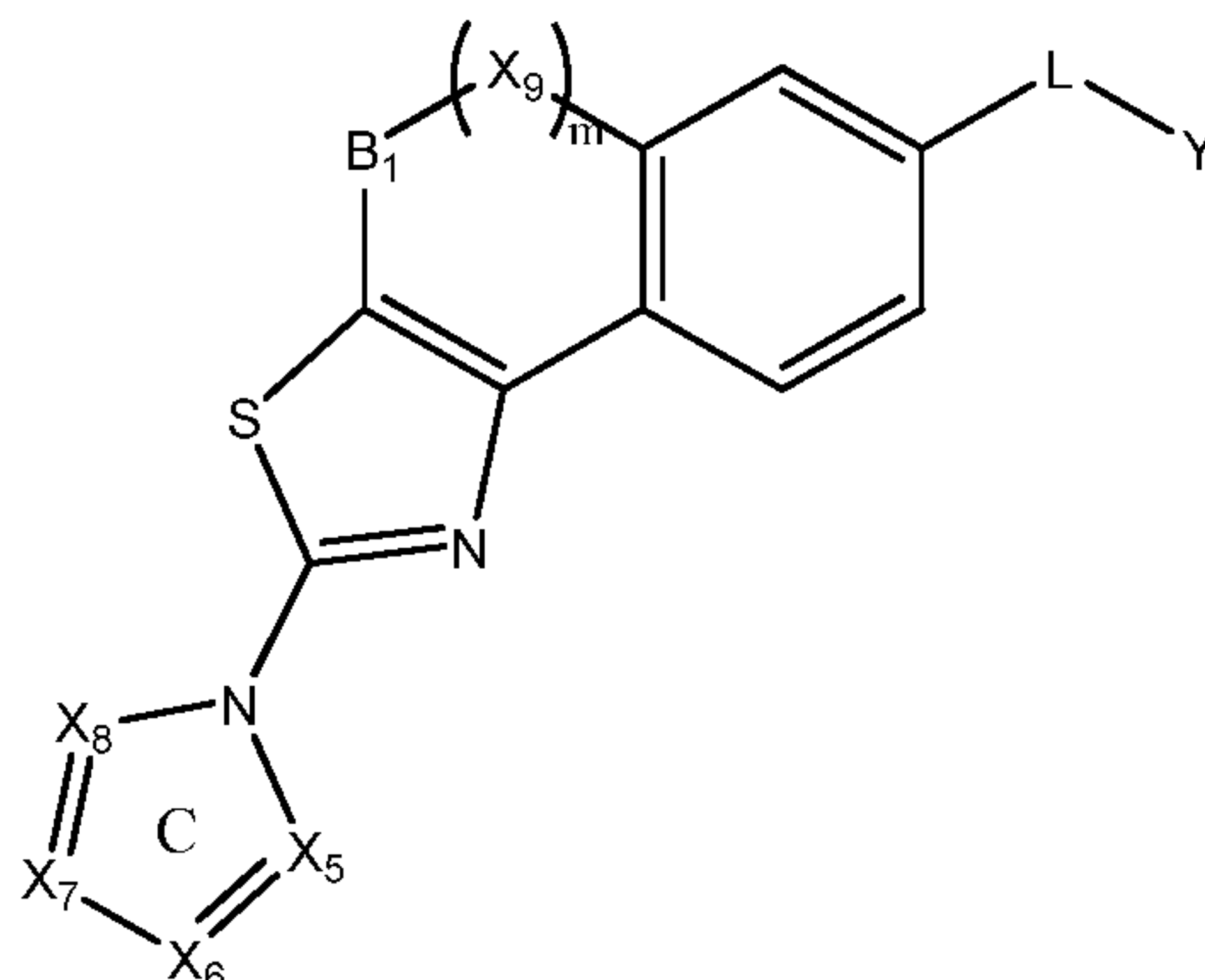
64. The compound of Claim 60, wherein the compound is represented by formula (XXVIII):



(XXVIII)

or pharmaceutically acceptable salt thereof.

65. A compound represented by formula (XXIX):



(XXIX)

or a pharmaceutically acceptable salt thereof, wherein:

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

B₁ is -C(R^a)₂-, -C(O)-; or -O-;each of X₅, X₆, X₇, and X₈ is independently -N- or -C(R^c)-;X₉ is -C(R^a)₂-;

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)NR₁R₂, -NR₄C(O)R₅, halo, -OR₄, cyano, nitro, haloalkoxy, -C(O)R₄, -NR₁R₂, -SR₄, -C(O)OR₄, -OC(O)R₄, -NR₄C(O)NR₁R₂, -OC(O)NR₁R₂, -NR₄C(O)OR₅, -S(O)_pR₄, or -S(O)_pNR₁R₂;

each R^c 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, nitro, or cyano;

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

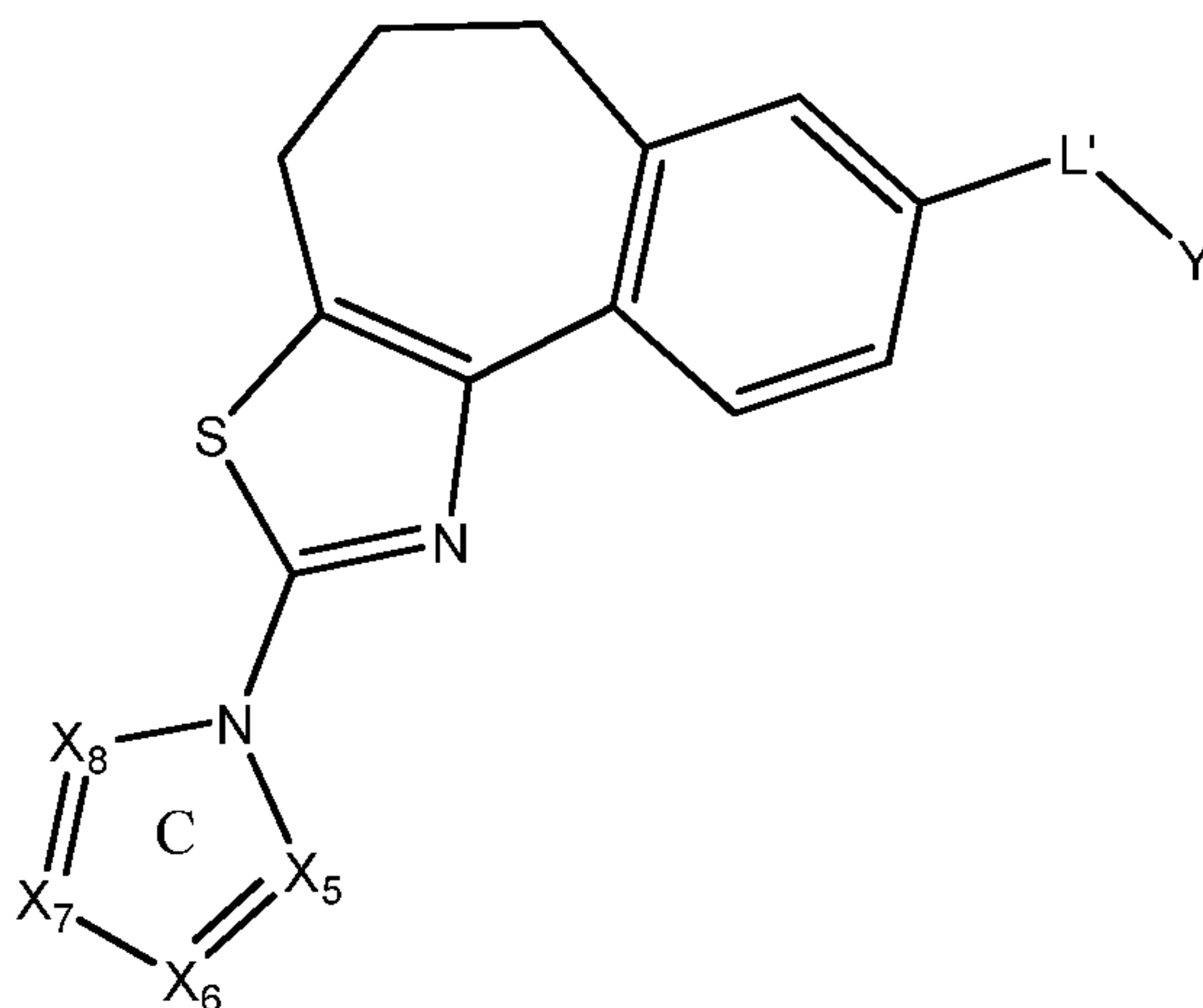
to which they are attached is optionally substituted heterocyclyl or optionally substituted heteroaryl;

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;

p is 0, 1, or 2; and

m is 1 or 2.

66. The compound of any one of Claims 53, 54, 59 or 65, wherein L is $-NHCH_2-$, $-CH_2NH-$, $-NHC(O)NH-$, $-NH-C(O)-$, or $-C(O)-NH-$.
67. The compound of any one of Claims 53, 54, 59 or 65, wherein B_1 is $-C(R^a)_2-$ or $-O-$.
68. The compound of Claim 65, wherein the compound is represented by formula (XXX):

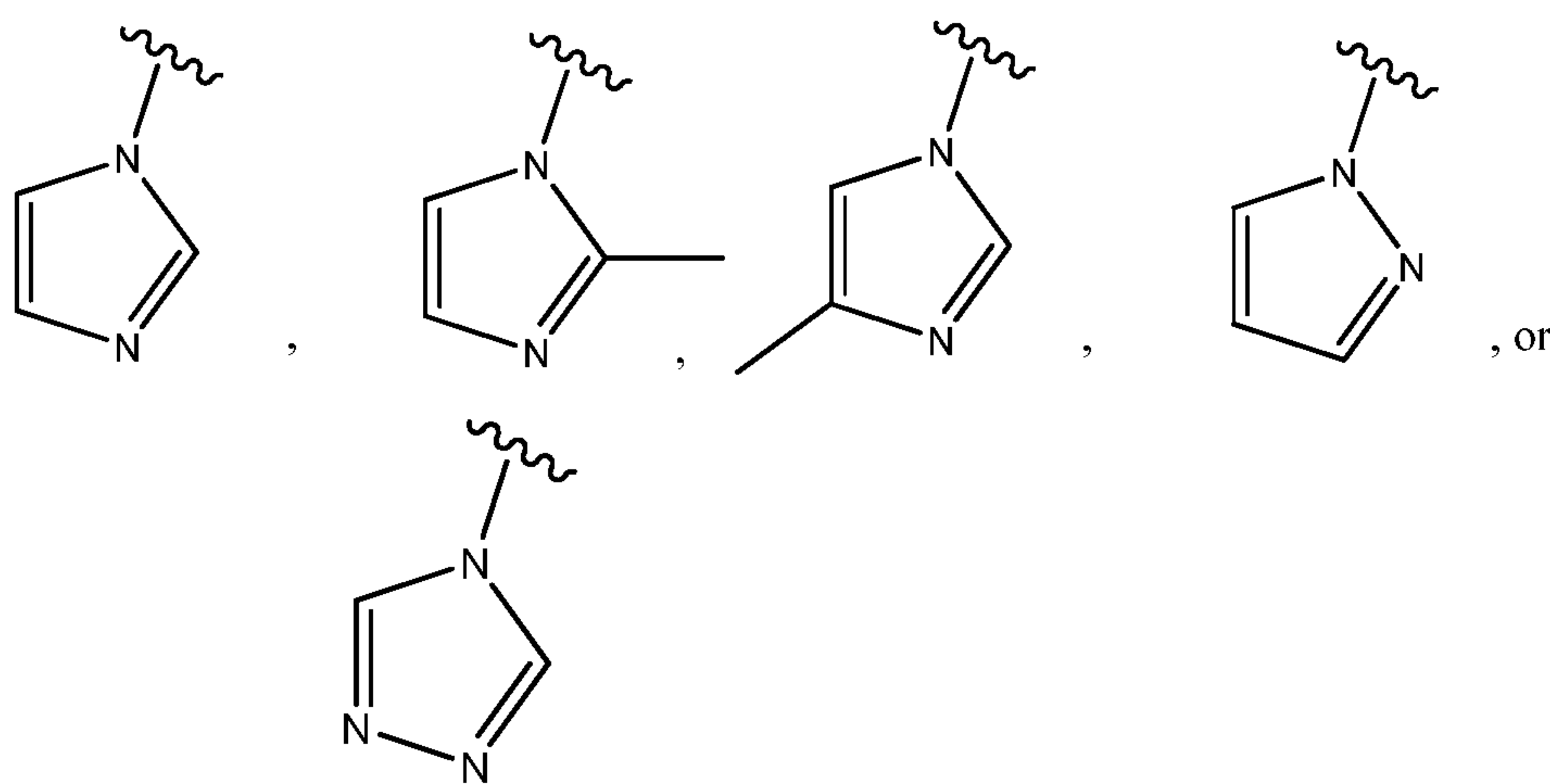


(XXX)

or pharmaceutically acceptable salt thereof, wherein L' is $-NHCH_2-$, $-CH_2NH-$, $-NHC(O)NH-$, $-NH-C(O)-$, or $-C(O)-NH-$.

69. The compound of any one of Claims 55, 58, 60, 64 or 68, wherein L' is $-NHCH_2-$, $-NH-C(O)-$, or $-C(O)-NH-$.
70. The compound of any one of Claims 53-55, 58-60, 64, 65 or 68, wherein Y is selected from the group consisting of an optionally substituted 5 or 6-membered aryl or an optionally substituted 5 or 6-membered heteroaryl.

71. The compound of Claim 1, 5, 14, 53-55, 58-60, 64, 65 or 68, wherein Y is an optionally substituted phenyl or an optionally substituted pyridinyl.
72. The compound of Claim 71, wherein Y is substituted with one to two substituents.
73. The compound of Claim 72, wherein the one to two substituents on Y are each independently a lower alkyl or a halo.
74. The compound of any one of Claims 53-55, 58-60, 64, 65 or 68, wherein Ring C is:



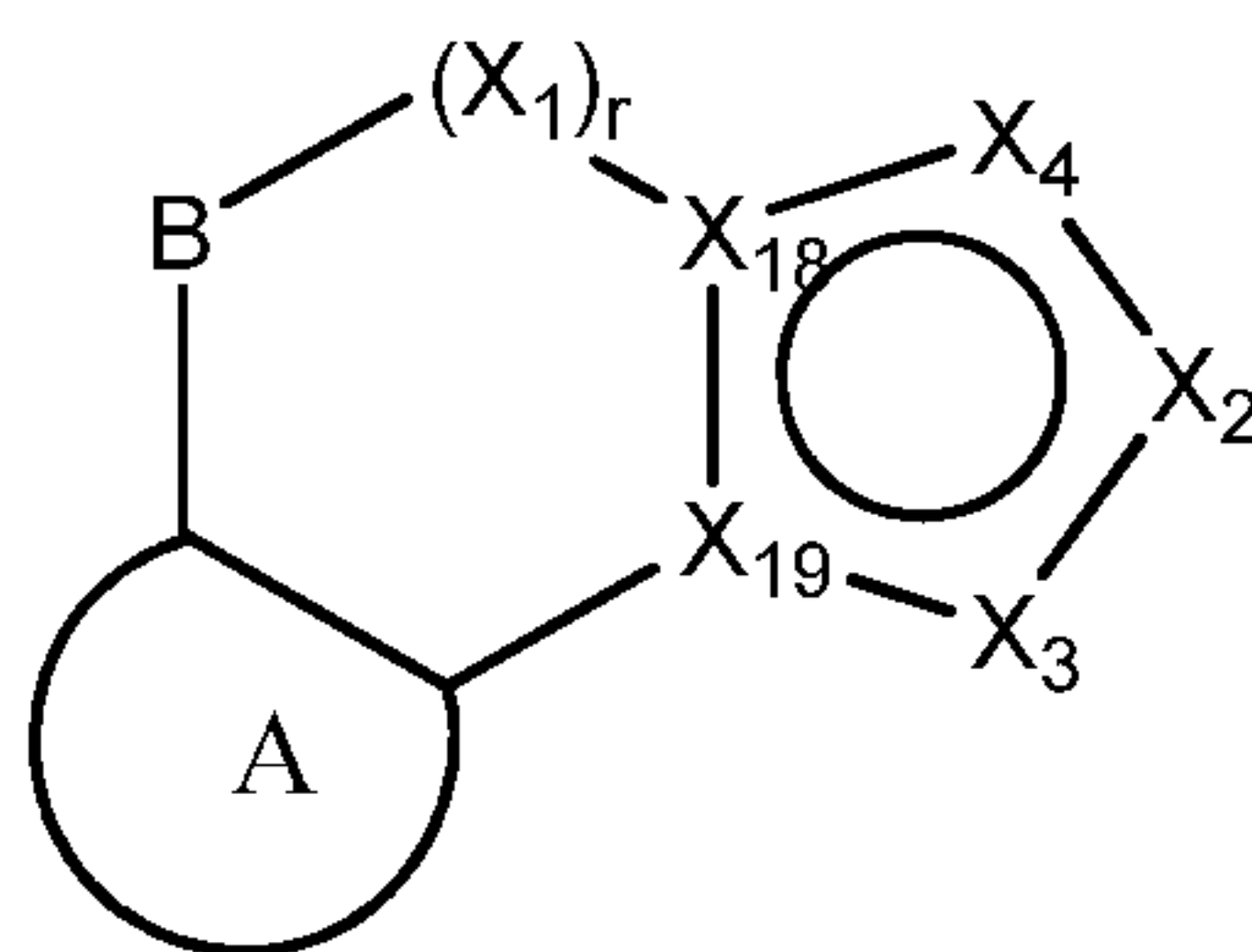
75. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of Claims 1 through 74, or a pharmaceutically acceptable salt thereof.
76. The pharmaceutical composition of Claim 75, further comprising one or more additional therapeutic agents.
77. The pharmaceutical composition according to Claim 76, wherein the additional therapeutic agent is selected from the group consisting of immunosuppressive agents, anti-inflammatory agents and suitable mixtures thereof.
78. The pharmaceutical composition of Claim 77, wherein the additional therapeutic agent is selected from the group consisting of steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and suitable mixtures thereof.

79. A method of inhibiting immune cell activation comprising administering to the cell a compound of any one of Claims 1 through 74.
80. The method of Claim 79, wherein immune cell activation is inhibited in a subject by administering the compound to the subject.
81. A method of inhibiting cytokine production in a cell, comprising administering to the cell a compound of any one of Claims 1 through 74.
82. The method of Claim 81, wherein cytokine production is inhibited in a subject by administering the compound to the subject.
83. The method of Claim 81, 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.
84. The method of Claim 83, wherein the cytokine is IL-2.
85. A method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to the cell a compound of any one of Claims 1 through 74.
86. The method of Claim 85, wherein T-cell and/or B-cell proliferation is inhibited in a subject by administering the compound to the subject.
87. A method for treating or preventing an immune disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 74.
88. The method of Claim 87, 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.

89. A method for treating or preventing an inflammatory condition in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 74.
90. The method according to Claim 89, 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 erythematoses; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer.
91. A method for suppressing the immune system of a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 74.
92. A method for treating or preventing an allergic disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Claims 1 through 74.
93. The method of Claim 92, 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.

94. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl ring wherein the ring atoms are selected from the group consisting of C, S, O, and N;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

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 $-N(R^b)-$;

one of X_2 , X_3 or X_4 is $-C(L-Y)-$ or $-C(R^a)(L-Y)-$ and the others are independently $-O-$, $-S-$, $-N-$, $-N(R^b)-$, $-C(R^a)_2-$, or $-C(R^a)-$, provided that when Y is an optionally substituted aryl or an optionally substituted heteroaryl, X_3 is $-S-$, and X_{18} and X_{19} are both $-C-$, then X_4 is not $-N-$;

each of X_{18} or X_{19} is independently $-N-$, $-C-$, or $-C(R^a)-$;

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,

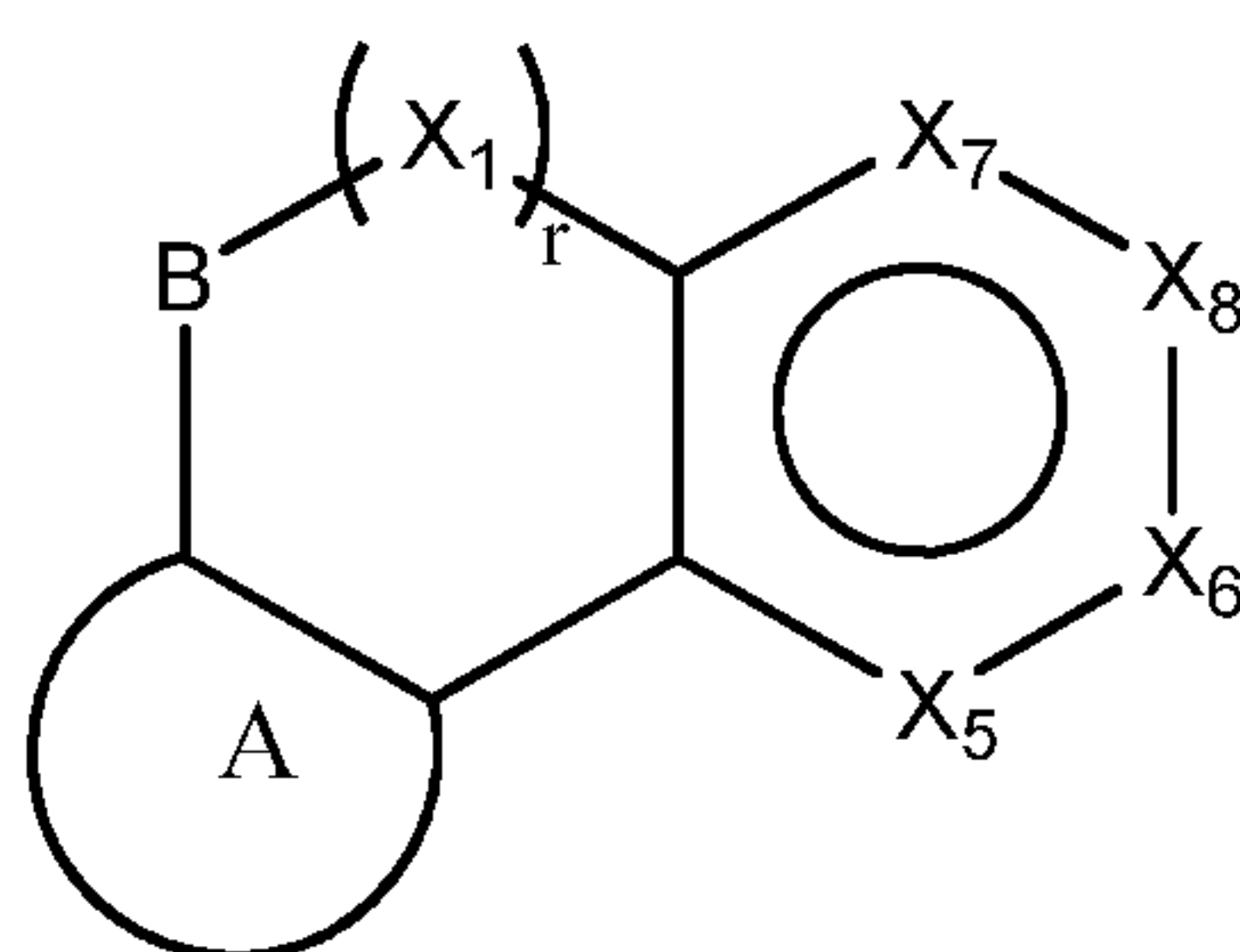
an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally 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.

95. The method of Claim 94, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.
96. The method of Claim 94, wherein the ion channel is a Ca^{2+} -release-activated Ca^{2+} channel (CRAC).
97. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted 5 or 6 membered aryl or an optionally substituted 5 or 6 membered heteroaryl ring wherein the ring atoms are selected from the group consisting of C, S, O, and N;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

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 $-N(R^b)-$;

one of X_5 , X_6 , X_7 , and X_8 is $-C(L-Y)-$ and the others are independently $-N-$ or $-CR^a-$, provided that when Y is an optionally substituted aryl or an optionally substituted heteroaryl, then X_5 and X_7 are not both $-N-$, when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is an optionally substituted phenyl or a 6-membered N-containing heteroaryl, then one of X_6 or X_7 is not $-N-$, and when Y is an optionally substituted aryl or an optionally substituted heteroaryl and Ring A is a N-containing heteroaryl, then at least one of X_5 , X_6 , and X_7 must be $-N-$;

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 $-C(O)OR_4$;

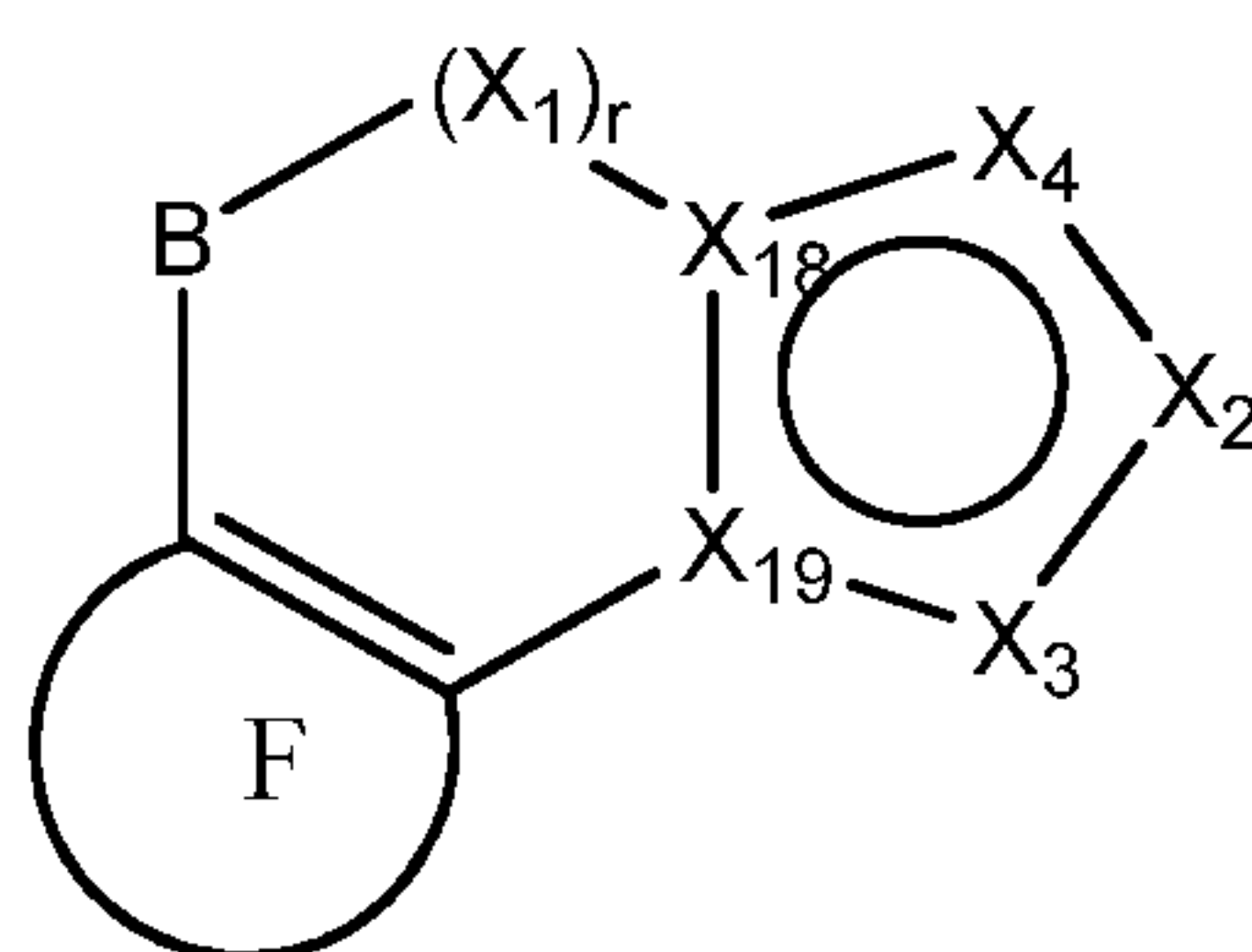
R_1 and R_2 , for each occurrence are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

98. The method of Claim 97, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.
99. The method of Claim 97, wherein the ion channel is a Ca^{2+} -release-activated Ca^{2+} channel (CRAC).
100. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of formula (X):



(X)

or a pharmaceutically acceptable salt thereof, wherein:

Ring F is an optionally substituted 5 or 6-membered non-aromatic ring containing atoms selected from the group consisting of C, S, O, and N;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

B is $-\text{C}(\text{R}^a)_2-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(\text{R}^b)-$;

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

one of X_2 , X_3 or X_4 is $-\text{C}(\text{L}-\text{Y})-$ or $-\text{C}(\text{R}^a)(\text{L}-\text{Y})-$ and the others are independently $-\text{O}-$, $-\text{S}-$, $-\text{N}-$, $-\text{N}(\text{R}^b)-$, $-\text{C}(\text{R}^a)_2-$, or $-\text{C}(\text{R}^a)-$;

each of X_{18} or X_{19} is independently $-\text{N}-$, $-\text{C}-$, or $-\text{C}(\text{R}^a)-$;

L is a linker;

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

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 $-C(O)OR_4$;

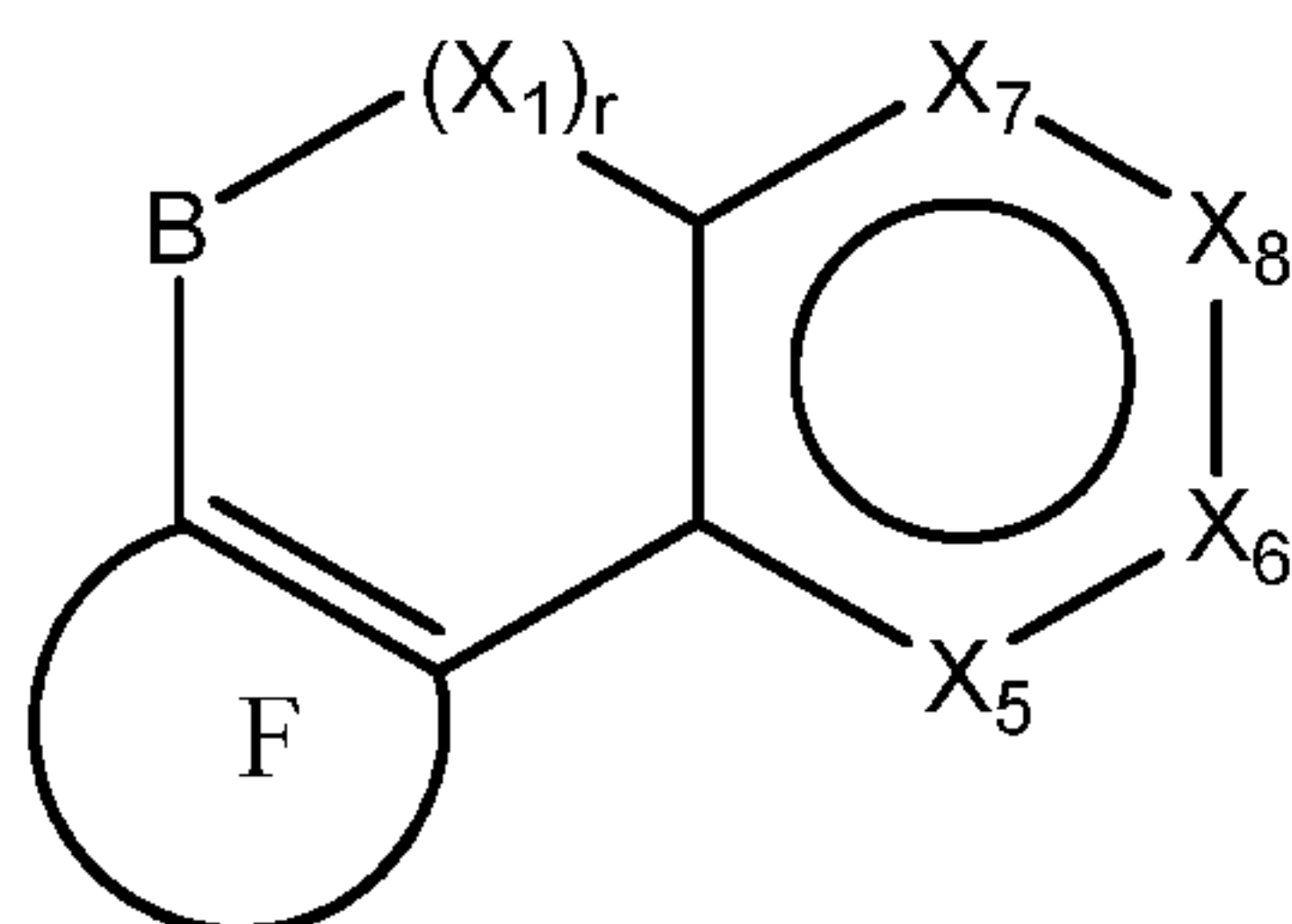
R_1 and R_2 , for each occurrence are, independently, H , an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted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

101. The method of Claim 100, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.
102. The method of Claim 100, wherein the ion channel is a Ca^{2+} -release-activated Ca^{2+} channel (CRAC).
103. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of formula (XVII):



(XVII)

or a pharmaceutically acceptable salt thereof, wherein:

Ring F is an optionally substituted 5 or 6-membered non-aromatic ring containing atoms selected from the group consisting of C, S, O, and N;

Y is an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted alkenyl, an optionally substituted cycloalkenyl, or an optionally substituted heterocyclyl;

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 $-N(R^b)-$;

one of X_5 , X_6 , X_7 , and X_8 is $-C(L-Y)-$ and the others are independently $-N-$ or $-CR^a-$;

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.

104. The method of Claim 103, wherein the ion channel is in a subject and it is modulated by administering the compound to the subject.
105. The method of Claim 103, wherein the ion channel is a Ca^{2+} -release-activated Ca^{2+} channel (CRAC).